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21. **EXPEDIENTE No.** 04-121724

54. **TÍTULO** ANTAGONISTAS DE RECEPTORES DE PEPTIDOS RELACIONADOS CON EL GEN DE CALCITONINA

51. **CLASIFICACIÓN INTERNACIONAL** A61K 31/519; A61K 31/496 A61K 31/497; A61P 11/06

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

**DOMICILIO** PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. **APODERADO** HECTOR GOMEZ MEJIA

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## 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<br>Dirección: P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000, Estados Unidos de América<br>Nacionalidad o Domicilio: Estados Unidos<br>Lugar de Constitución: Estados Unidos<br>Teléfono: Fax:<br>E-mail | **IDENTIFICACION**<br>C.C. ☐ NIT ☐<br>C.E. ☐ Otro ☐<br>Cual_____<br>Número _____ |
| **3 REPRESENTANTE O APODERADO** | Nombre: HECTOR GOMEZ MEJÍA<br>Dirección: Cra. 7 No. 16-56 Piso 9<br>Teléfono: 380-2200 Fax: 380-2700<br>E-mail: | **IDENTIFICACION**<br>C.C. ☒ NIT ☐<br>C.E. ☐ Otro ☐<br>Cual_____<br>Número 22720 TP 19436 |
| **4 INVENTOR (ES) (72)** | Nombre: Prasad V. Chaturvedula, Ling Chen, Rita Civiello, Charles Mark Conway, Andrew P. Degnan, Gene M. Dubowchik, Xiaojun Han, George N. Karageorge, Guanglin Luo, John E. Macor, Graham Poindexter, Shikha Vig<br>Dirección: Lancaster Way, Cheshire, CT 06410, US; 193 McCormick Lane, Middletown, CT 06457, US; 90 Cow Hill Road, Killingworth, CT 06419, US; 825 Farmington Drive, Cheshire, CT 06410, US; 123 York Street, Apt. 22-P, New Haven, CT 06511, US; 65 Spring Street, Middlefield, CT 06455, US; 65 Ridgecrest Drive, Cheshire, CT 06410, US; 34 Fox Run Road, Portland, CT 06480, US; 135 Devonshire Lane, Madison, CT 06443, US; 644 Moose Hill Road, Guilford, CT 06437, US; 15 Fox Hollow Road, Old Saybrook, CT 06475, US; 15 Park Place, Durham, CT 06422, Estados Unidos de América (Respectivamente)<br>Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente) | |

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**10** **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $422.000
- [ ] 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)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] 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** [illegible]

NOMBRE: HECTOR GOMEZ MEJIA

FIRMA:

C.C. 72720 de Bogotá T.P. 19436 del C.S.J.

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

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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)*: CHATURVEDULA, Prasad, V. [US/US]; 190 Lancaster Way, Cheshire, CT 06410 (US). CHEN, Ling [CN/US]; 193 McCormick Lane, Middletown, CT 06457 (US). CIVIELLO, Rita [US/US]; 90 Cow Hill Road, Killingworth, CT 06419 (US). CONWAY, Charles, Mark [US/US]; 825 Farmington Drive, Cheshire, CT 06410 (US). DEGNAN, Andrew, P. [US/US]; 123 York Street, Apt. 22-P, New Haven, CT 06511 (US). DUBOWCHIK, Gene, M. [US/US]; 65 Spring Street, Middlefield, CT 06455 (US). HAN, Xiaojun [CN/US]; 65 Ridgecrest Drive, Cheshire, CT 06410 (US). KARAGEORGE, George, N. [US/US]; 34 Fox Run Road, Portland, CT 06480 (US). LUO, Guanglin [CN/US]; 135 Devonshire Lane, Madison, CT 06443 (US). MACOR, John, E. [US/US]; 644 Mosse Hill Road, Guilford, CT 06437 (US). POINDEXTER, Graham [US/US]; 15 Fox Hollow Road, Old Saybrook, CT 06475 (US). VIG, Shikha [IN/US]; 15 Park Place, Durham, CT 06422 (US).

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

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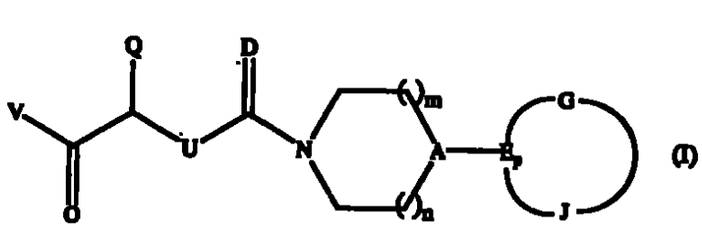
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(54) Title: CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS



(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 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.

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# 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 (Aahina 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

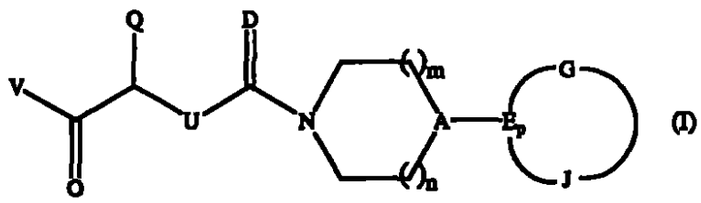
innervate (e.g., Williamson et al. *Cephalalgia* 1997 17:518-24). Since facial arteries are also innervated by the trigeminal nerve, other models study changes in facial blood flow induced by electrical trigeminal activation (e.g., Escott et al. *Brain Res* 1995 669:93). Alternatively, other peripheral 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 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-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, 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 $(S^y)_sR^3$; and

Q" is $NH(S^y)_sR^3$, $NHC(O)(S^y)_sR^3$, $NHC(O)O(S^y)_sR^3$ or $NHC(O)NH(S^y)_sR^3$;

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", 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, $C_{3-7}$cycloalkyl, 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 $(S^y)_s R^3$ 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, $(C_{1-4}\text{alkylene})_{0-1}R^{4'}$

$R^{4'}$ 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, $(C_{1-3}\text{alkyl})_{0-2}$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, 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

$R^1$ 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, $C_{1-6}$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.

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, dihydrobenzthiazolonyl, 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.

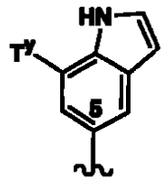
According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein $R^3$ is $R^{3a}$ and $R^{3a}$ is dihydrobenzoxazolyl, benzotriazolyl, indolyl, halonitrophenyl, halopyrimidine, halopurinyl, $C_{1-3}$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 $R^{3b}$.

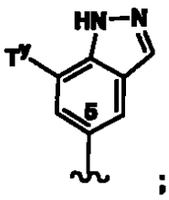
According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein $R^3$ is $R^{3b}$ and $R^{3b}$ is

1H-Indol-5-yl



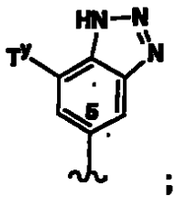
;

1H-Indazol-5-yl



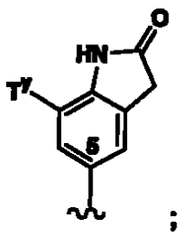
;

1H-Benzotriazol-5-yl



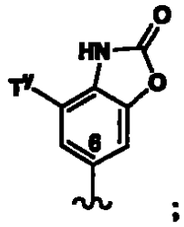
;

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



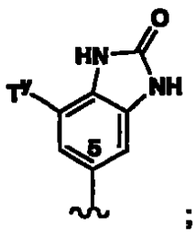
;

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



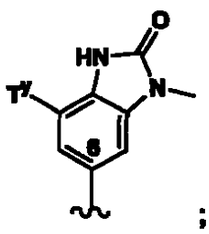
;

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



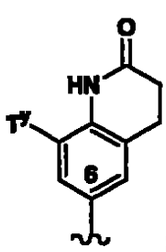
;

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



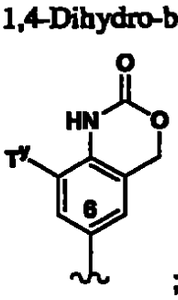
;

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



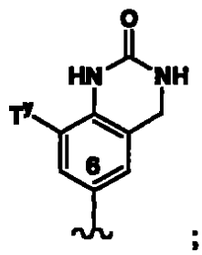
;

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



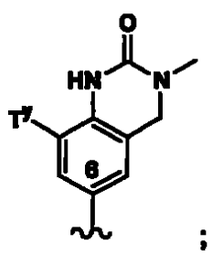
;

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



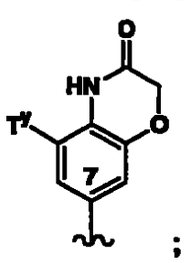
;

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 $R^3$ is$R^{3b}$ 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 $R^3$ 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, 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 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. Inhibition 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.

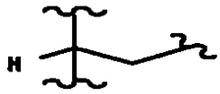
An embodiment or aspect which depends from another embodiment or aspect, will describe only the variables having values or provisos that differ from the embodiment or aspect from which it depends. If for example a dependent

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 $\pi$ 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 74$^{th}$ 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.

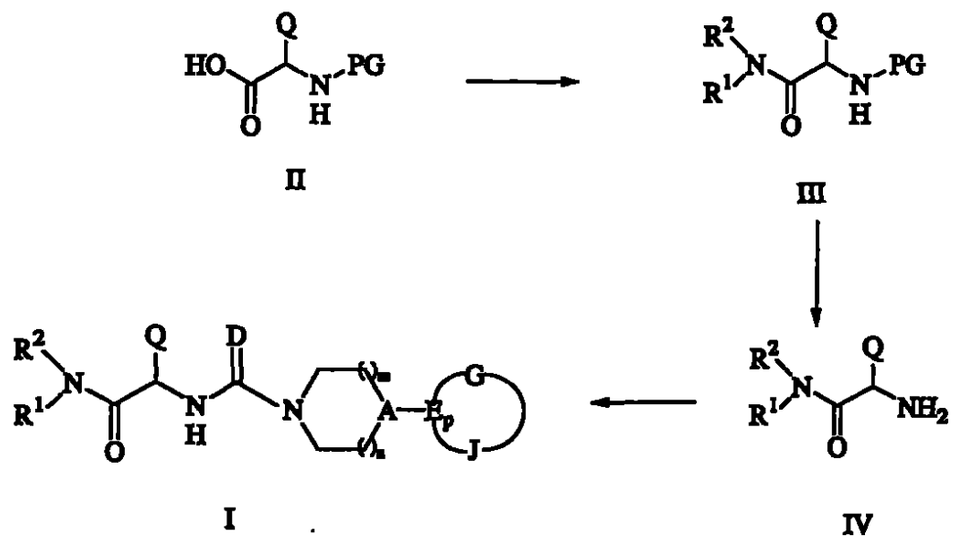
The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. The compounds of this invention may also be administered 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

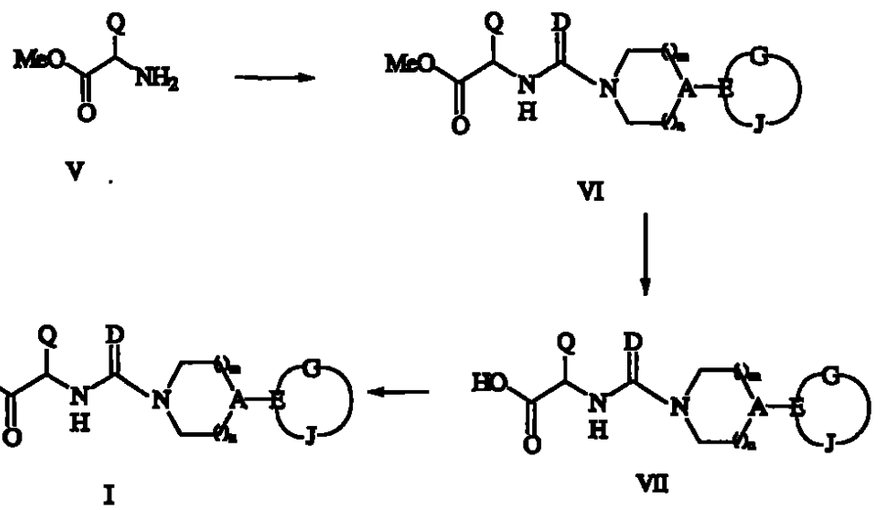
Compounds of the present invention may be synthesized according to the general schemas provided below. Variables provided in the schema below are defined in accordance with the description of compounds of the above Formula unless otherwise specified. The compounds of the present invention may be prepared 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.

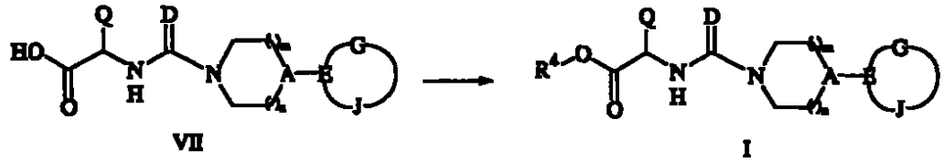
Scheme 2. Synthesis of Formula I Compounds



V VI VII I

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

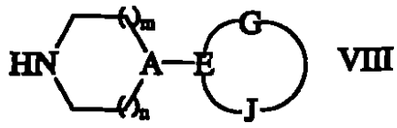


VII I

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.

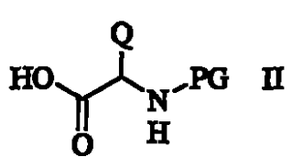
Preparation of $HNR^1R^2$ and Formula VIII amines

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

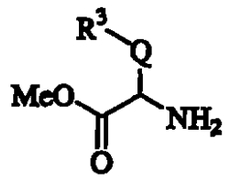



VIII

Preparation of Formula II and Formula V amino acids



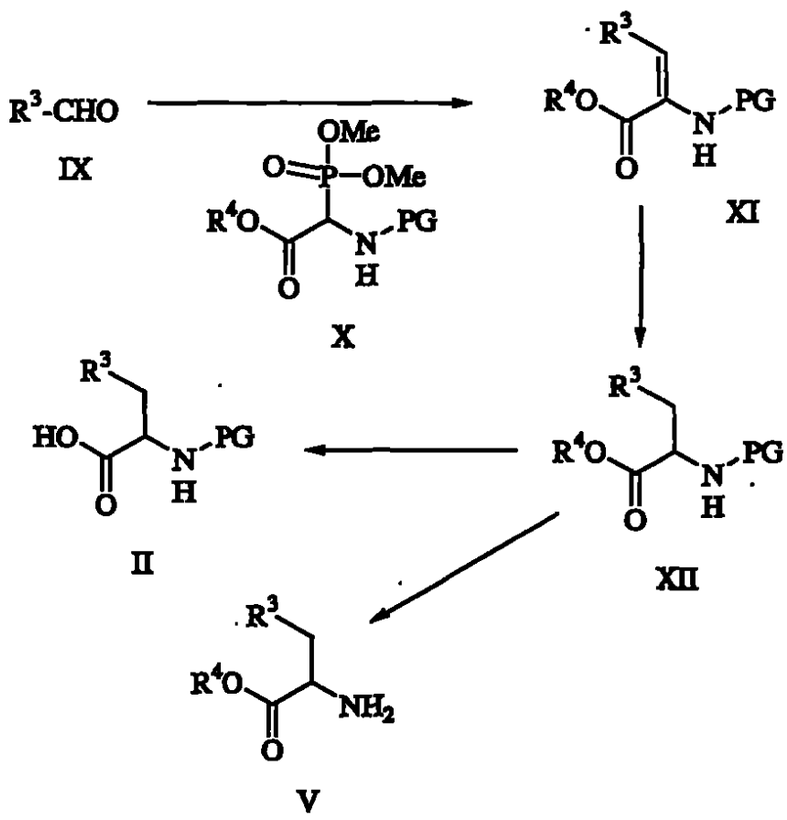

II




V

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

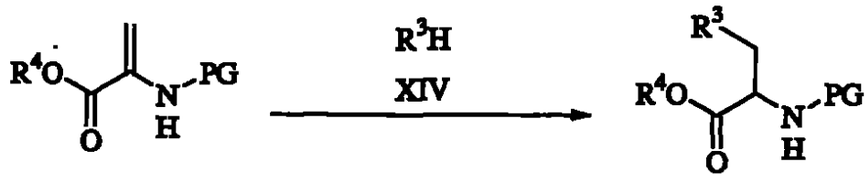
Scheme 4. Synthesis of Formula II and Formula V Compounds




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

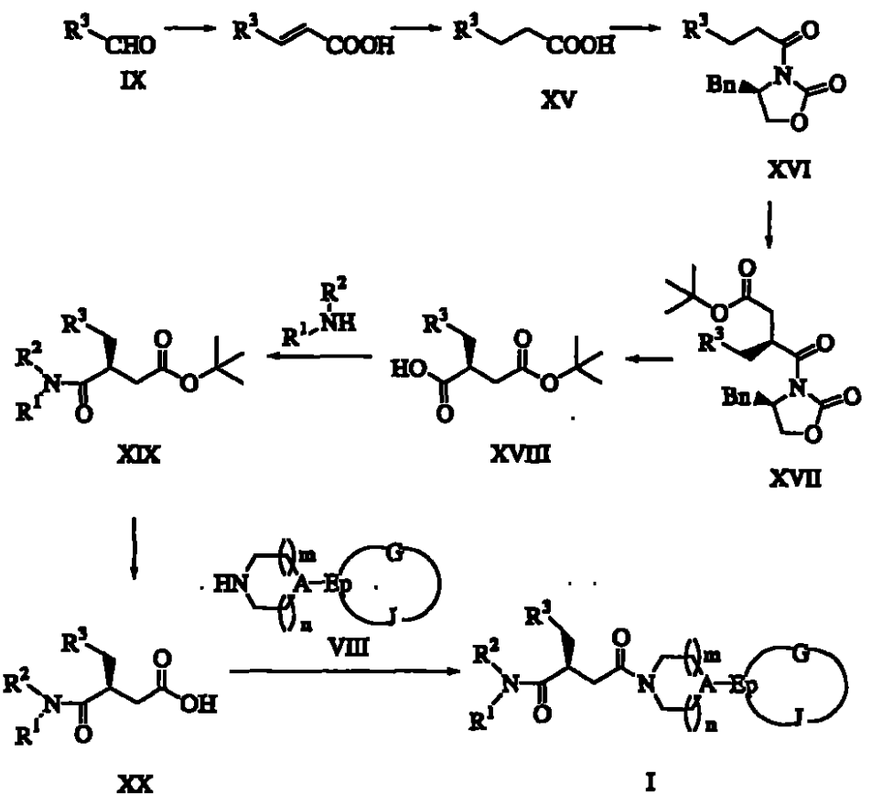



XIII XII

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.

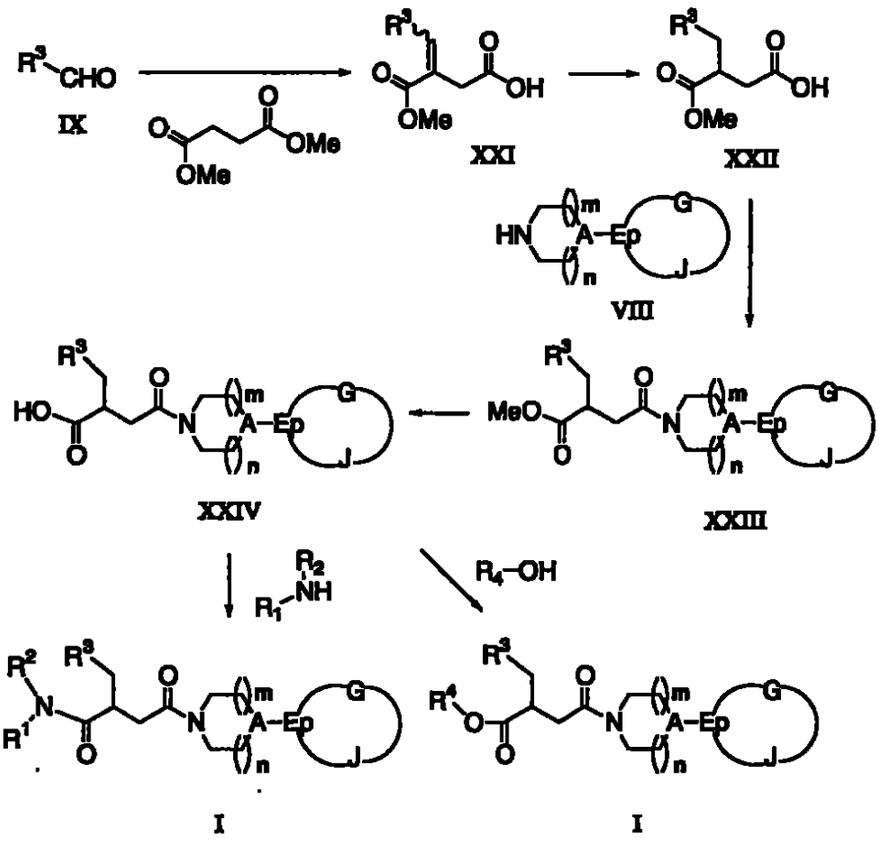
Other compounds of Formula I may be prepared according to Scheme 6 or Scheme 7. It may also be possible to use variations of said schemes to prepare the compounds of the present inventions, said variations known to those of ordinary skill in the art.

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.

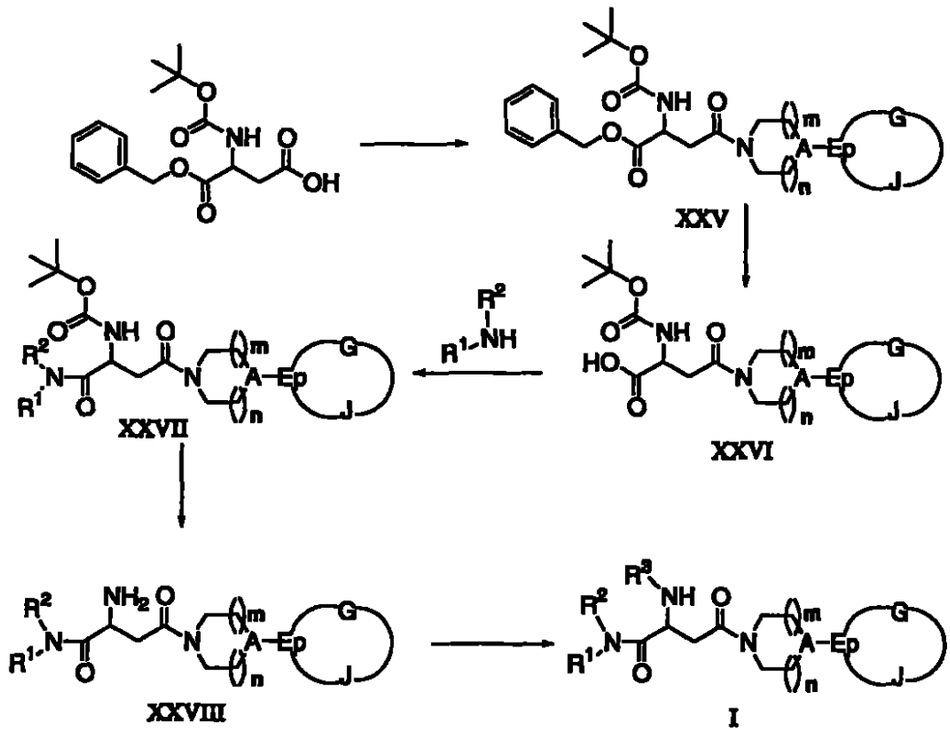
Scheme 7. Synthesis of Formula I Compounds




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.

Scheme 8. Synthesis of Formula I Compounds

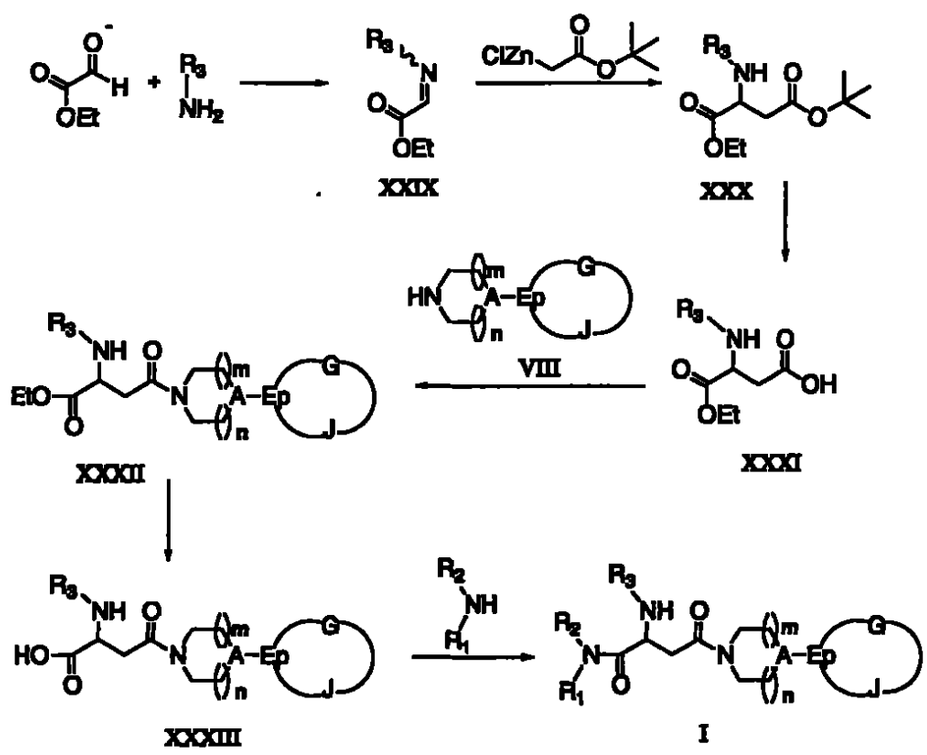



The synthesis described in Scheme 8 begins with a commercially available N-*tert*-butyloxycarbonyl-L-aspartic acid benzyl ester. Differently protected aspartic acid derivatives may also be used for synthetic convenience. The beta carboxyl group is coupled with amines of Formula VIII using standard peptide 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

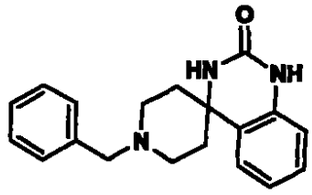



The synthesis described in Scheme 9 begins with an imine of Formula XXIX, prepared by condensation of ethyl glyoxalate and amines of formula $R^3$-$NH_2$. These are reacted with 2-*tert*-butoxy-2-oxoethylzinc chloride to give compounds of Formula XXX. Treatment wit strong acids removes the *tert*-butyl 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.

Ureidoamide Intermediates and Examples

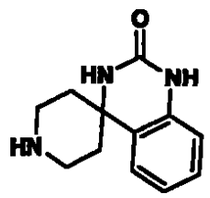
General. $^{1}H$- and $^{13}C$-NMR spectra were run on a Bruker 500 or 300 MHz instrument and chemical shifts were reported in ppm (δ) with reference to tetramethylsilane (δ = 0.0). All evaporations were carried out under reduced pressure. Unless otherwise stated, LC/MS analyses were carried out on a 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



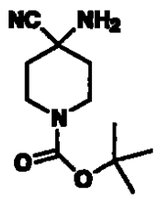

Polyphosphoric acid (113 g ) was heated to 100-110°C and stirred while 1-benzyl-piperidin-4-one (9.27 ml, 50 mmol) was added. Immediately afterwards, phenyl urea (9.55 g, 70. mmol) was added in portions small enough to avoid excessive foaming. The mixture was heated at 150-160°C overnight. Water (200 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 $(MH)^{+}$.

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



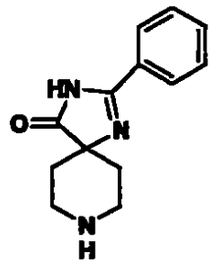
To a solution of 1-benzyl-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'(1'H)-quinazoline (1.00 g) in degassed methanol ( 50 ml ) and 6N hydrochloric acid (2.0 ml) was added 10% palladized charcoal (150 mg ). The mixture was shaken on a Parr apparatus under an atmosphere of hydrogen at 60 psi overnight. 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 $(MH)^+$.

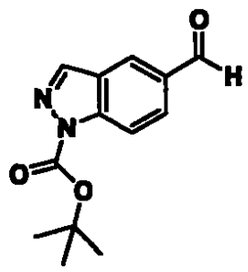
2-Phenyl-1,3,8-triaza-spiro[4.5]dec-1-en-4-one, hydrochloride




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.

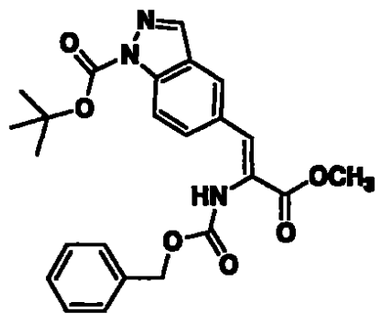
To a solution of 4-benzoylamino-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester (1.3 g, 4 mmol) in ethanol (10 mL) was added 6M sodium hydroxide (1.5 mL) followed by 30% hydrogen peroxide. The reaction mixture was then refluxed for 3 h. The reaction mixture was then diluted with water (30 mL), 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 $(MH)^+$.

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.

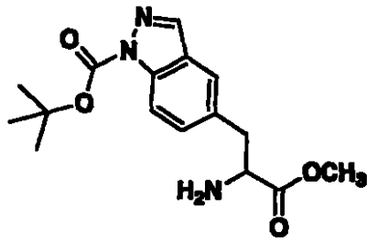
5-(2-Benzyloxycarbonylamino-2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester



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 minutes. 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 minutes. The reaction mixture

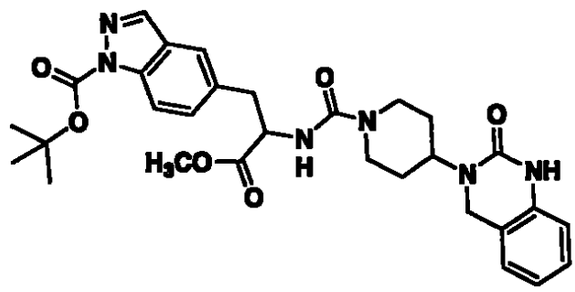
was stirred at -78°C for 4 h and then allowed to warm to room temperature overnight. The solvent was evaporated and the resulting residue subjected to flash column chromatography on silica gel (1:2 ethyl acetate/hexane) giving the title compound as a white foam (5.77 g, 85%). $^1$H-NMR ($CDCl_3$, 500 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



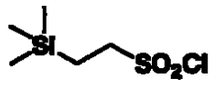
A mixture of 5-(2-benzyloxycarbonylamino-2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester (524 mg, 1.16 mmol) and 10% palladium on carbon (60 mg) in methanol (20 mL) was shaken for 4.5 h under 50 psi hydrogen gas using a Parr hydrogenator. The reaction mixture was evacuated and 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 minutes 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 $(MH)^+$.

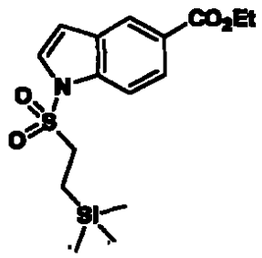
2-Trimethylsilanyl-ethanesulfonyl chloride



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).

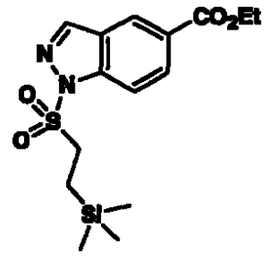
1-(2-Trimethylsilanyl-ethanesulfonyl)-1*H*-indole-5-carboxylic acid ethyl ester




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 $(MH)^+$.

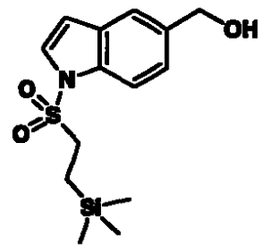
Similarly prepared:

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



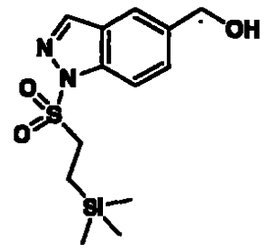
$^1$H-NMR ($CDCl_3$, 500 MHz) δ 8.51 (s, 1H), 8.34 (s, 1H), 8.21 (dd, J = 8.9, 1.5 Hz, 1H), 8.12 (d, J = 9.2 Hz, 1H), 3.96 (s, 3H), 3.42 – 3.39 (m, 2H), 0.86 – 0.82 (m, 2H), -0.02 (s, 9H). $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ 166.4, 143.1, 141.2, 130.1, 126.5, 125.0, 124.2, 112.9, 52.5, 51.3, 9.8, -2.1.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

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



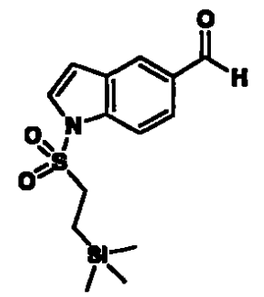
A solution of diisobutylaluminum hydride (82.9 mL, 1M in toluene, 82.9 mmol) was added slowly at 0°C to the solution of 1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indole-5-carboxylic acid ethyl ester (8.81g, 25.9 mmol) in toluene (200mL). After it was stirred at 0°C for 45 min, the reaction was quenched 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 $(MH)^+$.

[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

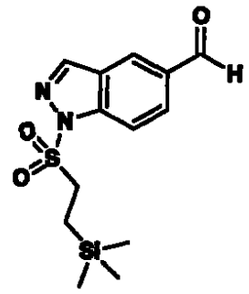


A solution of [1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-yl]-methanol (2.1g, 6.74 mmol) in methylene chloride (30 mL) was added at 0°C to a mixture of activated manganese dioxide (22g, azeotropically dried with toluene (2x)) and

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 $(MH)^+$.

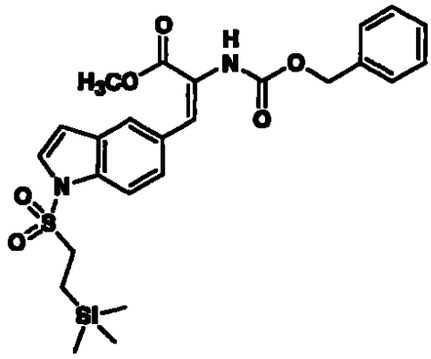
Similarly prepared:

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

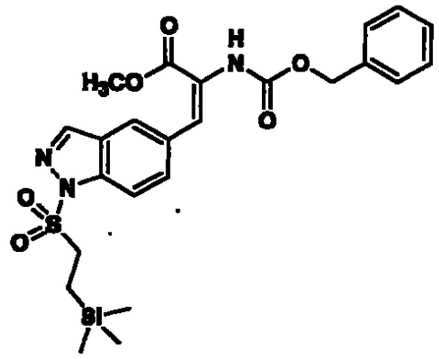


1,1,3,3-Tetramethylguanidine (0.68 mL, 5.43 mmol) was added at room temperature to a solution of N-(benzyloxycarbonyl)-α-phophonoglycine trimethyl ester (1.88g, 5.69 mmol) in tetrahydrofuran (40 mL). The mixture was stirred at room temperature for 15 min and cooled to –78°C, and a solution of 1-(2-

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 $(MH)^+$.

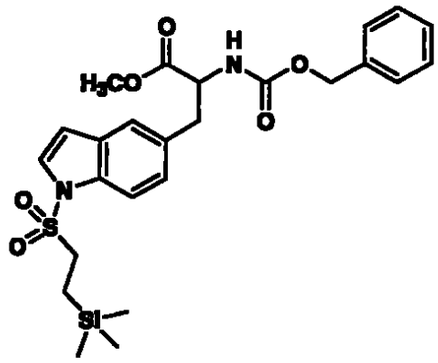
Similarly prepared:

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($CO_2$Me)(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 $(MH)^+$.

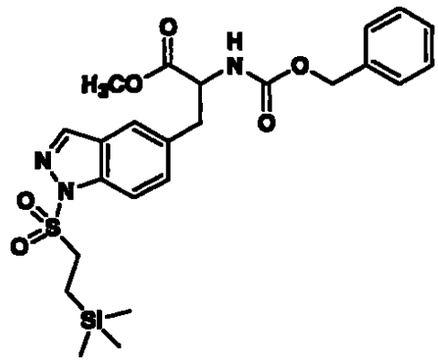
(±)-2-Amino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-yl]-propionic acid methyl ester



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 $(MH)^+$.

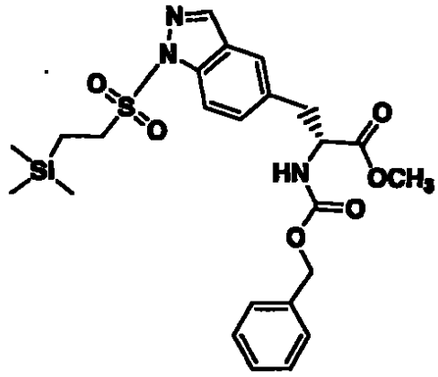
Similarly prepared:

(±)-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 $(MH)^+$.

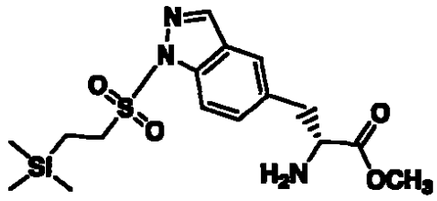
(*R*)-2-Benzyloxycarbonylamino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester



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 $(MH)^+$.

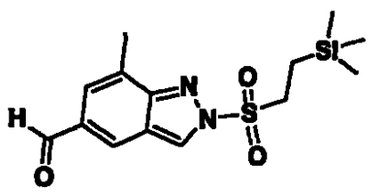
(*R*)-2-Amino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester



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),

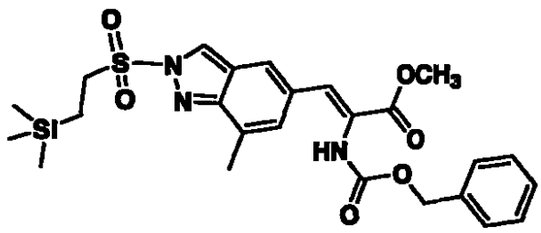
7.59 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 3.72 (s, 3H), 3.38-3.32 (m, 2H), 3.21 (dd, J = 13.9, 5.1 Hz, 1H), 2.98 (dd, J = 13.9, 7.9 Hz, 1H), 0.91-0.85 (m, 2H), -0.02 (s, 9H). Mass spec.: 384 $(MH)^+$

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).

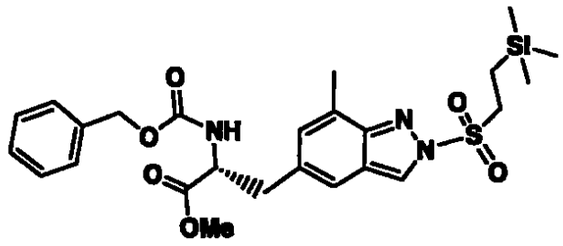
2-Benzyloxycarbonylamino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-acrylic acid methyl ester



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 $(MH)^+$.

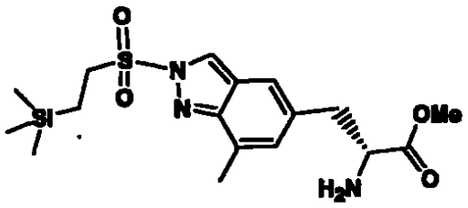
(*R*)-2-Benzyloxycarbonylamino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-propionic acid methyl ester




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 $(MH)^+$.

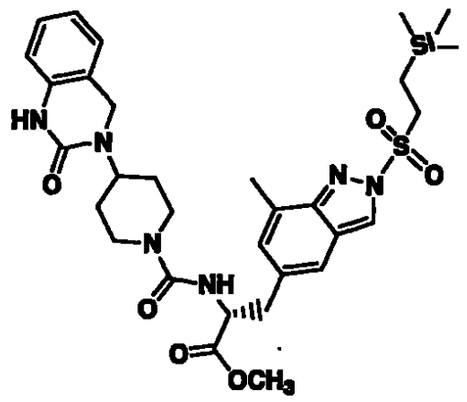
(*R*)-2-Amino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-propionic acid methyl ester




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 $(MH)^+$.

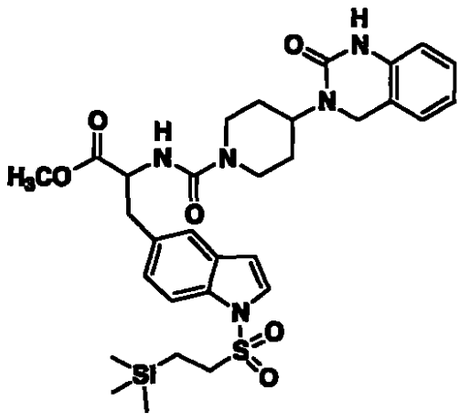
(*R*)-3-[7-Methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



A mixture of 2-amino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-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 minutes 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 $(MH)^+$.

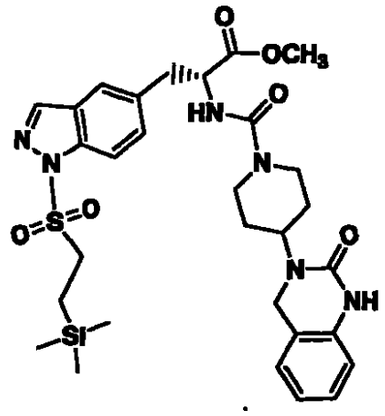
Similarly prepared:

(±)-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

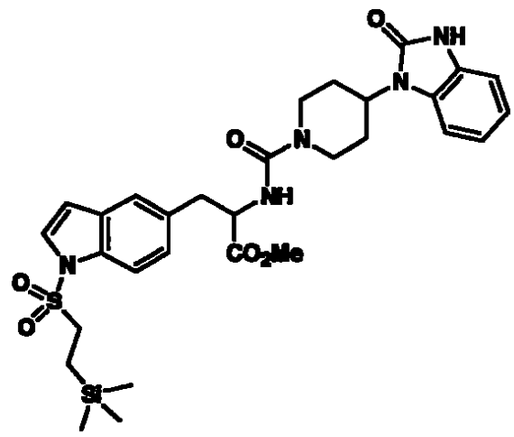


A solution of (*R*)-2-Amino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester (764 mg, 1.99 mmol), *N,N*-diisopropylethylamine (1.10 mL, 5.97 mmol) and disuccinimidylcarbonate (509 mg, 1.99 mmol) in methylene chloride (20 mL) was stirred for 40 min at room temperature. 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 $(MH)^+$.

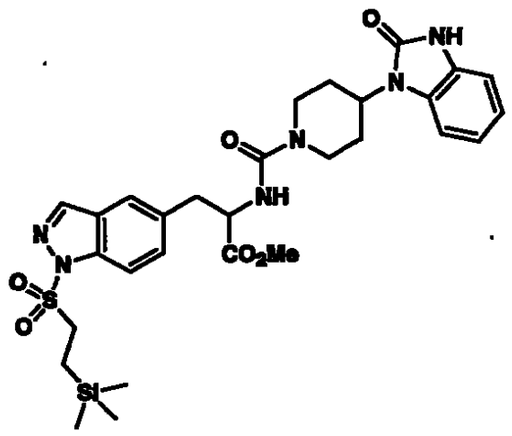
Similarly prepared:

(±)-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



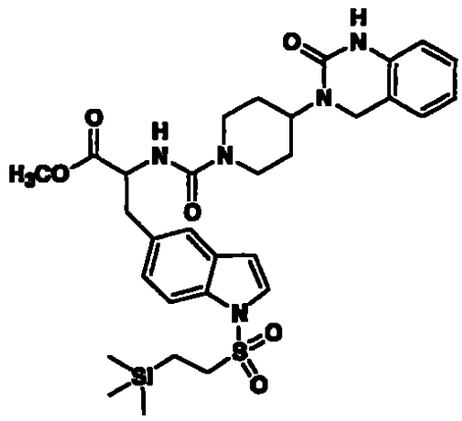

$^1$H-NMR ($CD_3CN$, 500 MHz) δ 9.78 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 3.7 Hz, 1H), 7.28 (dd, J = 8.5, 1.5 Hz, 1H), 7.10 – 7.08 (m, 1H), 7.05 – 7.03 (m, 1H), 6.99 – 6.97 (m, 2H), 6.70 (d, J = 3.7 Hz, 1H), 5.91 (d J = 7.9 Hz, 1H), 4.66 (q, J = 8.2 Hz, 1H), 4.45 – 4.39 (m, 1H), 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 $(MH)^+$.

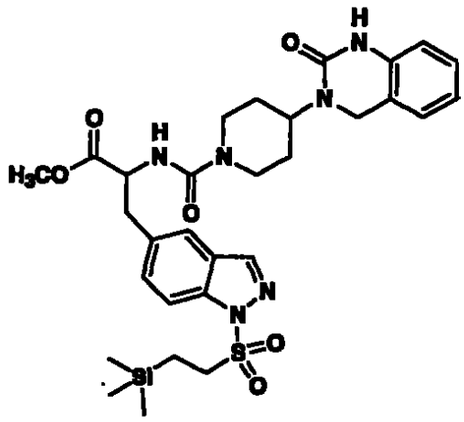
(±)-2-{[4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indol-5-yl]-propionic acid methyl ester



$^1$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 $(MH)^+$.

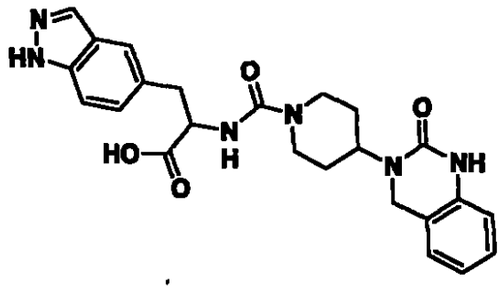
(±)-2-{[4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-yl]-propionic acid methyl ester



$^1$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 $(MH)^+$.

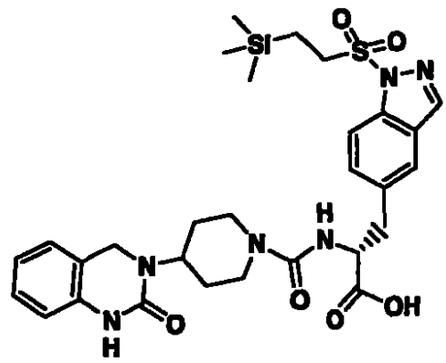
Example 1

(±)-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) in 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 $(MH)^+$.

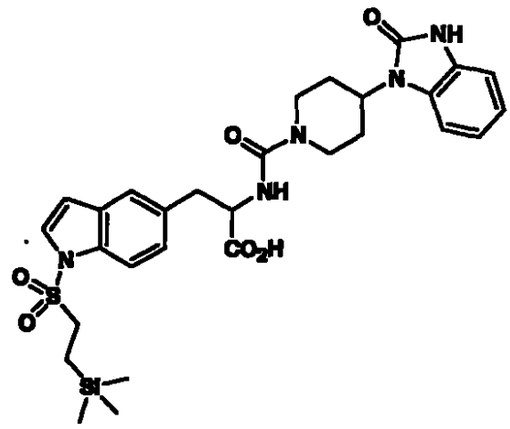
(*R*)-2-{[4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid



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 $(MH)^+$.

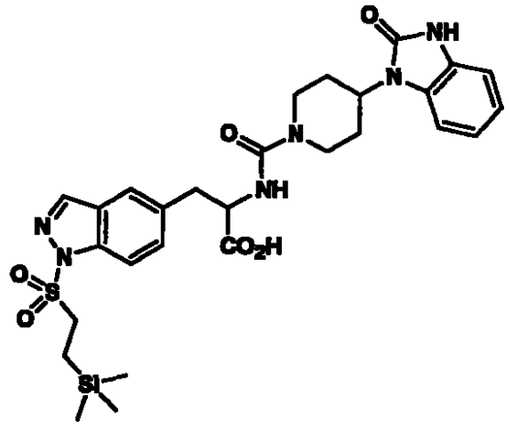
Similarly prepared:

(±)-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



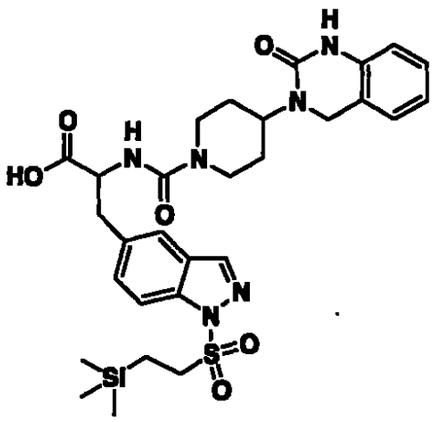
Mass spec. 612.25 $(MH)^+$.

(±)-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



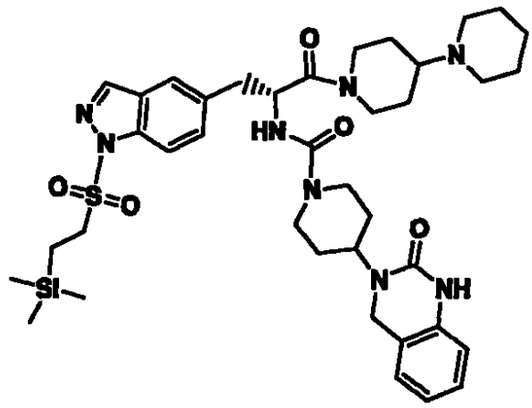
Mass spec. 613.26 $(MH)^+$.

(±)-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

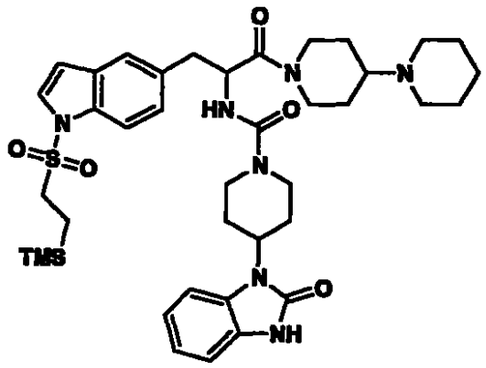


To a solution of (*R*)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid (554 mg, 0.88 mmol) and *N,N*-diisopropylethylamine (0.62 mL, 3.54 mmol) in methylene chloride (20 mL) was added a solution of 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 $(MH)^+$.

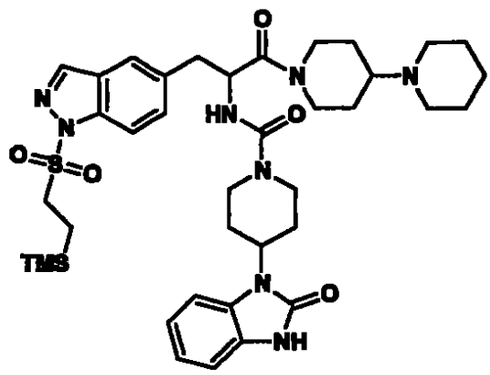
Similarly prepared:

(±)-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



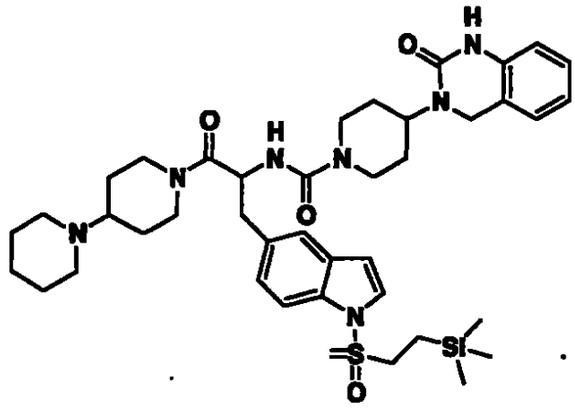

$^1$H-NMR ($CD_3CN$, 500 MHz) δ 9.42 (br s, 1H), 7.80 (d, J = 8.5 Hz, 0.6 H), 7.78 (d, J = 8.2 Hz, 0.4 H), 7.50 (s, 1H), 7.43 (t, J = 3.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 0.6 H), 7.23 (d, J = 8.5 Hz, 0.4 H), 7.10 – 7.07 (m, 1H), 7.02 – 6.95 (m, 3H), 6.69 (s, 0.4 H), 6.68 (s, 0.6 H), 5.88 (d, J = 8.5 Hz, 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



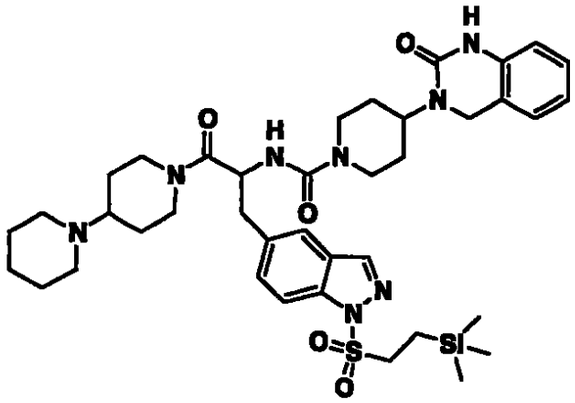
$^1$H-NMR ($CD_3CN$, 500 MHz) δ 9.67 (s, 1H), 8.32 (s, 1H), 7.96 (d, J = 8.7 Hz, 0.55 H), 7.93 (d, J = 8.6 Hz, 0.45 H), 7.70 (s, 1H), 7.51 (d, J = 8.6 Hz, 0.55 H), 7.47 (d, J = 8.8 Hz, 0.45 H), 7.08 – 7.05 (m, 1H), 7.03 – 6.99 (m, 1H), 6.98 – 6.94 (m, 2H), 6.01 (d, J = 7.9 Hz, 0.45 H), 5.96 (d, J = 7.9 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 $(MH)^+$.

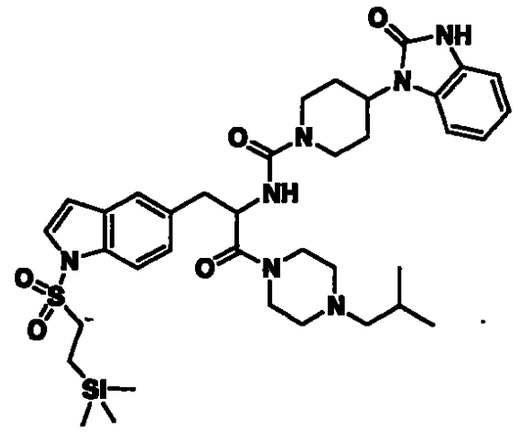
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-ylmethyl]-ethyl}-amide



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

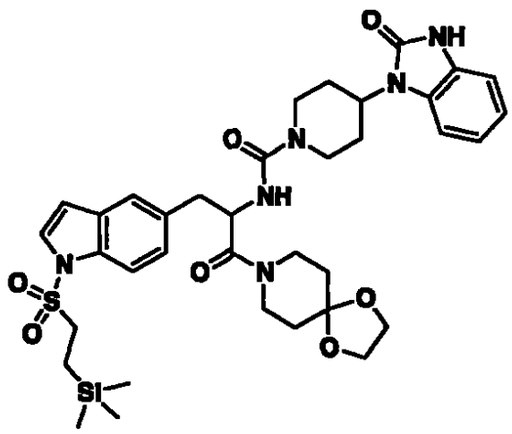
(m, 4H), 1.41 – 1.34 (m, 4H), 1.06 – 1.01 (m, 1H), 0.80 –0.75 (m, 2H), -0.07 (s, 9H). Mass spec.: 777.40 $(MH)^+$.

(±)-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



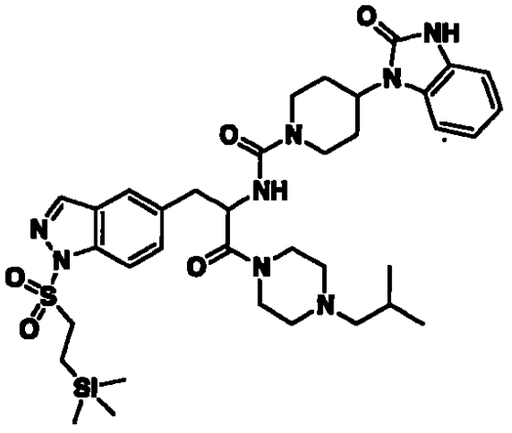
$^1$H-NMR ($CD_3CN$, 500 MHz) δ 9.75 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.12 - 7.09 (m, 1H), 7.04 – 7.02 (m, 1H), 7.00 – 6.97 (m, 2H), 6.72 (d, J = 3.7 Hz, 1H), 5.97 (d, J = 8.2 Hz, 1H), 5.01 (dd, J = 14.6, 7.2 Hz, 1H), 4.40 – 4.34 (m, 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 $(MH)^+$.

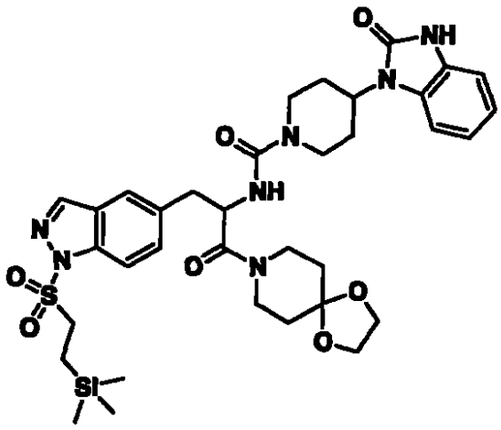
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid {2-(4-isobutyl-piperazin-1-yl)-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-ylmethyl]-ethyl}-amide



$^1$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 $(MH)^+$.

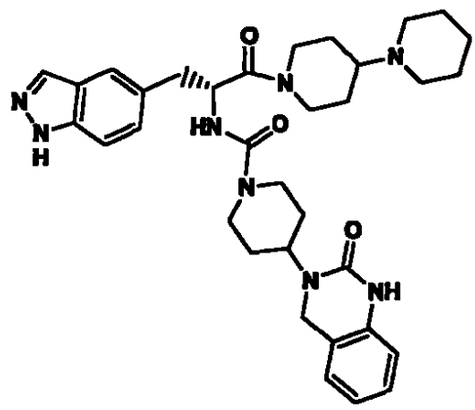
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid {2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-ylmethyl]-ethyl}-amide



$^1$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 ( )

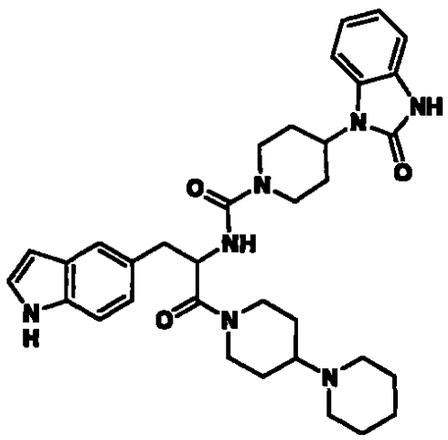


A solution of (*R*)-4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide (568 mg, 0.73 mmol) and cesium fluoride (1.11 g, 7.31 mmol) was heated at 80°C in acetonitrile (50 mL) for 4.5 hours. 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

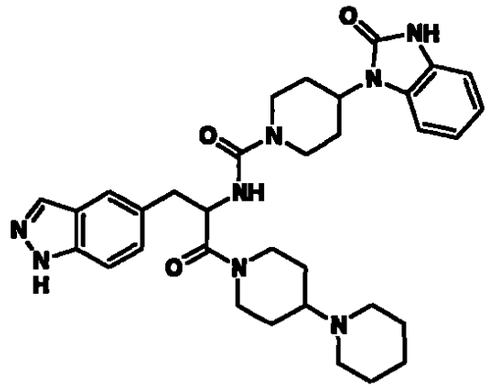
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(1*H*-indol-5-ylmethyl)-2-oxo-ethyl]-amide



$^1$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

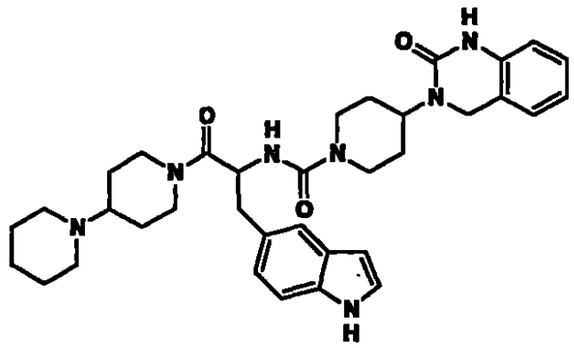


$^1$H-NMR (DMSO-$d_6$, 500 MHz) δ 10.70 (s, 1H), 8.22 (d, J = 8.2 Hz, 0.6H), 8.11 (s, 0.4H), 8.00 (s, 0.6H), 7.89 (d, J = 9.1 Hz, 0.4 H), 7.62 – 7.57 (m, 1H), 7.50 – 7.43 (m, 1H), 7.30 – 7.26 (m, 1H), 7.14 – 7.08 (m, 1H), 6.99 – 6.95 (m, 2H), 6.85 (br s, 1H), 4.89 – 4.80 (m, 1H), 4.45 – 4.31 (m, 2H),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

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

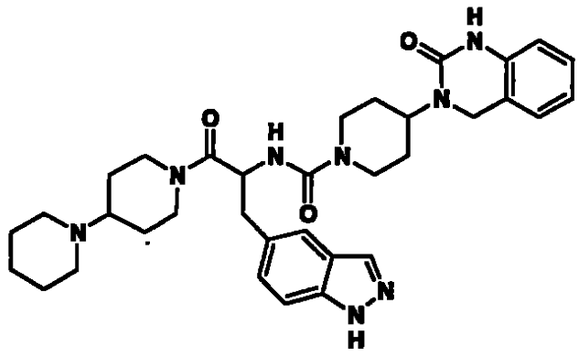
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(1H-indol-5-ylmethyl)-2-oxo-ethyl]-amide



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

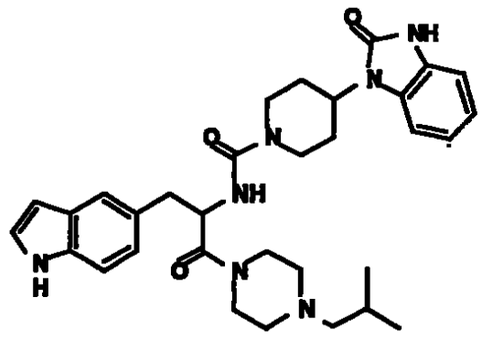
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



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

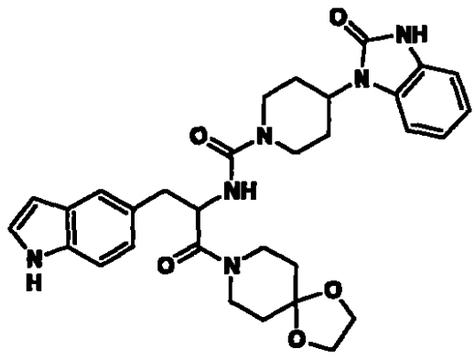
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [1-(1H-indol-5-ylmethyl)-2-(4-isobutyl-piperazin-1-yl)-2-oxo-ethyl]-amide



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

Example 8

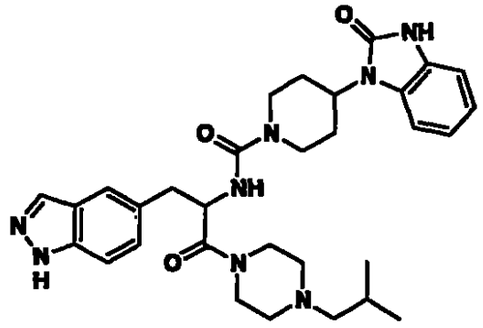
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-1-(1H-indol-5-ylmethyl)-2-oxo-ethyl]-amide



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

Example 9

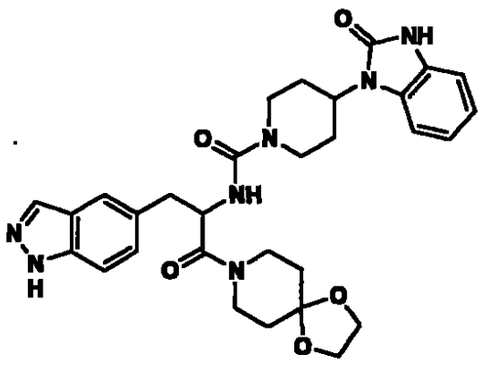
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [1-(1H-indazol-5-ylmethyl)-2-(4-isobutyl-piperazin-1-yl)-2-oxo-ethyl]-amide



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

Example 10

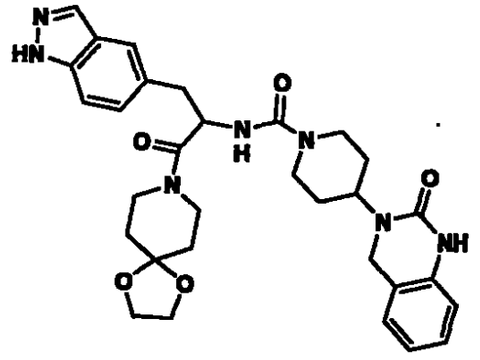
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-1-(1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



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

Example 11

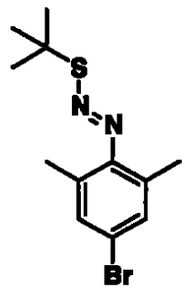
(±)-4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-1-(1*H*-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



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 hours 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),

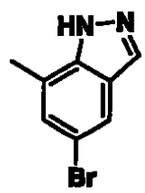
3.60-3.56 (m, 1H), 3.48-3.43 (m, 1H), 3.22-3.17 (m, 1H), 3.11 (d, J = 6.7 Hz, 2H), 2.90-2.85 (m, 2H), 2.68-2.60 (m, 4H), 1.67-1.61 (m, 2H), 1.54-1.49 (m, 2H). Mass spec.: 588 $(MH)^+$.

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



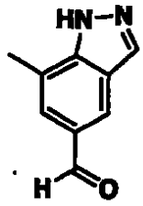
4-Bromo-2,6-dimethylaniline (20.00 g, 100 mmol) was ground to a powder with a mortar and pestle and then suspended in 24% hydrochloric acid (41 mL). The stirred mixture was cooled to -20°C and treated with sodium nitrite (7.24 g, 1.05 equiv) in water (16 mL), dropwise over 40 min while the temperature 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 $(MH)^+$.

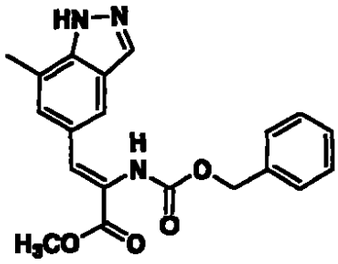
7-methylindazole-5-carboxaldehyde




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

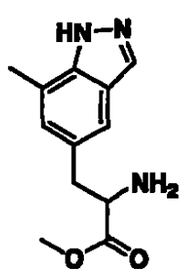
suspension was extracted with ethyl acetate (3 x 150 mL). The combined organic phases were washed with brine, dried (magnesium sulfate) and evaporated to give the product as a light-tan solid (3.01 g, 65%). $^1$H-NMR ($CDCl_3$, 500 MHz) δ 2.63 (3H, s), 7.73 (1H, s), 8.12 (1H, s), 8.25 (1H, s), 10.03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

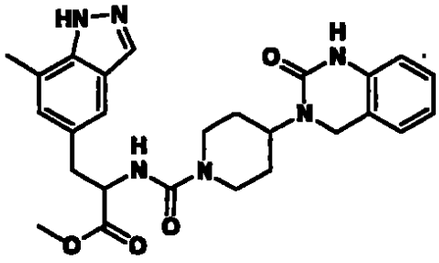
(±)-2-Amino-3-(7-methyl-1H-indazol-5-yl)-propionic acid methyl ester



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 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

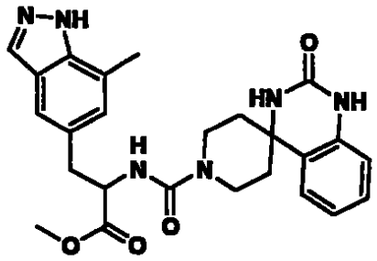


A stirred solution of (±)-2-amino-3-(7-methyl-1H-indazol-5-yl)-propionic acid methyl ester (162.9 mg, 0.698 mmol) in methylene chloride (3 mL) at room temperature was treated with carbonyl diimidazole (113.2 mg, 1 equiv). After 1.5 h at room temperature, 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (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 (DMF-$d_7$, 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

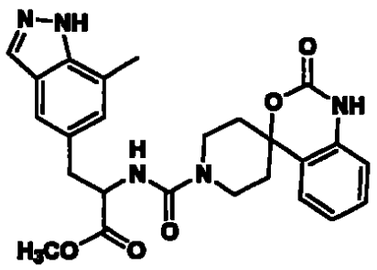
3-(7-Methyl-1H-indazol-5-yl)-2-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-(1H)-quinazoline)carbonyl amino]-propionic acid methyl ester



$^1$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 $(MH)^+$.

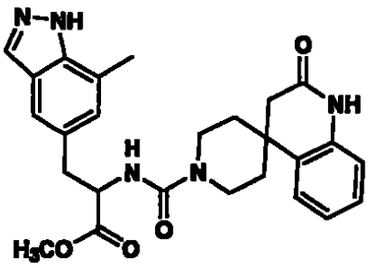
Example 14

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



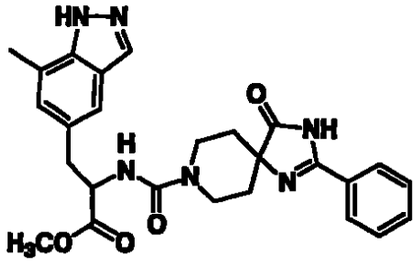
Mass spec.: 478.15 $(MH)^+$.

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 $(MH)^+$.

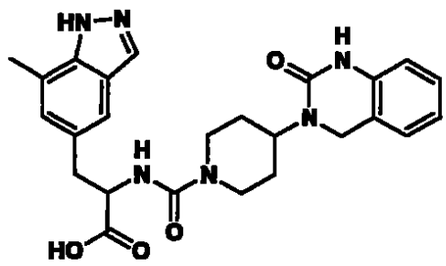
3-(7-Methyl-1H-indazol-5-yl)-2-[2'-phenyl-1',3',8'-triaza-spiro(4',5')deo-1-ene-8-carbonyl amino]-propionic acid methyl ester



$^1$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

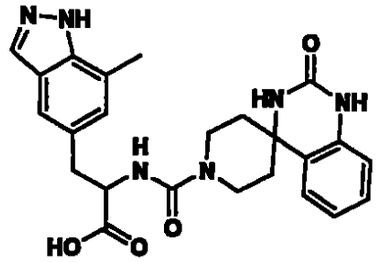
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



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 $(MH)^+$.

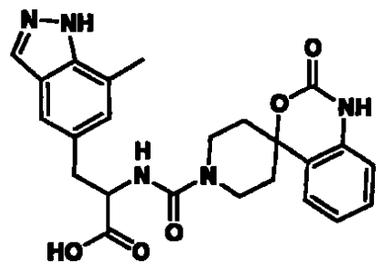
Similarly prepared:

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



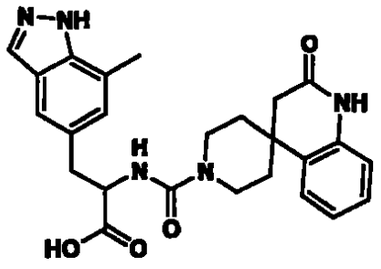
$^1$H-NMR (DMSO-$d_6$) δ 1.58 (4H, m), 2.46 (3H, s), 3.00-3.23 (3H, m), 3.78-3.91 (3H, m), 3.88 (2H, m) 4.28 (1H, s), 6.70 (1H, d), 6.75-6.85 ( 3H, m), 7.04 (1H, d), 7.11 (1H, m) 7.18 (1H, s), 7.96 (1H, s), 13.02 (1H, m). Mass spec.: 463.09 $(MH)^+$.

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



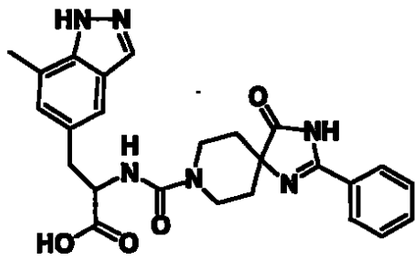
$^1$H-NMR (DMSO-$d_6$) δ 1.63-1.98 (4H, m), 2.46 (3H, s, 7-Me was overlapped with DMSO), 2.98-3.32 (4H, m), 3.90 (2H, m), 4.28 (1H, m), 6.78 (1H, d ), 6.87 (2H, m), 6.96 (1H, m), 7.05 (1H, s), 7.24 (1H, m), 7.41 (1H, s), 7.96 (1H, s),10.22 (1H, s) 12.42 (1H, br. ) 13.02 (1H, m). Mass spec.: 464.07 $(MH)^+$.

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 $(MH)^+$.

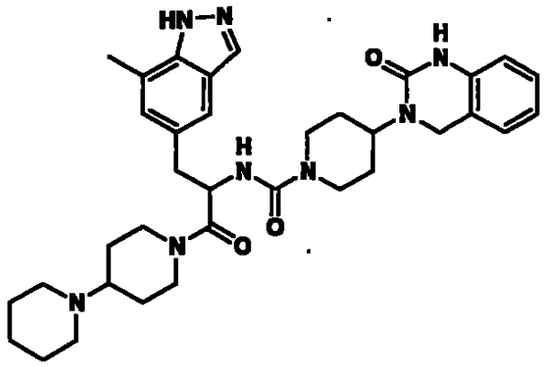
3-(7-Methyl-1H-indazol-5-yl)-2-[2'-phenyl-1',3',8'-triaza-spiro(4',5')deo-1-ene-8-carbonyl amino]-propionic acid



$^1$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



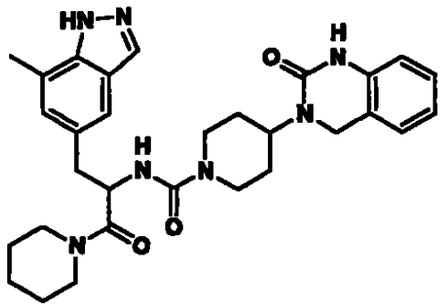
A stirred solution of (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid (65.7 mg, 0.138 mmol) in 2:1 dimethylformamide/methylene chloride (1.5 mL) at 0°C was treated with 4-(1-piperidyl)-piperidne (46.5 mg, 2 equiv), diisopropylethylamine (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

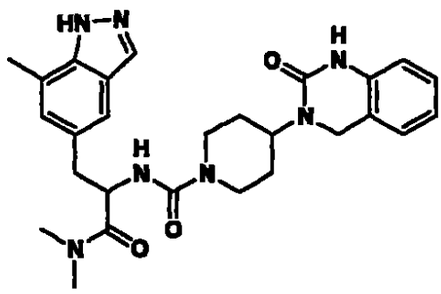
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide



$^1$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

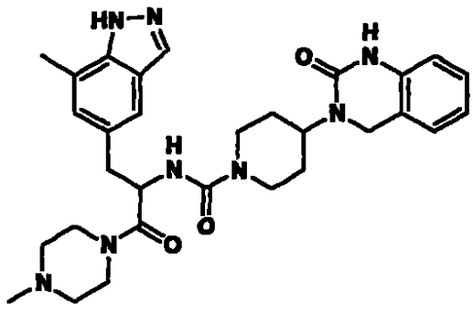
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-dimethylcarbamoyl-2-(7-methyl-1H-indazol-5-yl)-ethyl]-amide



$^1$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

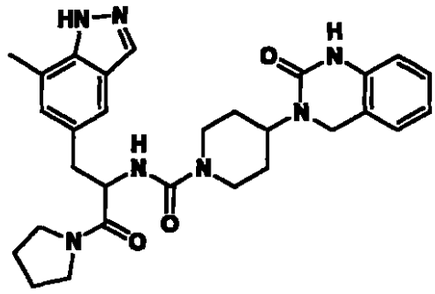
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide



$^1$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

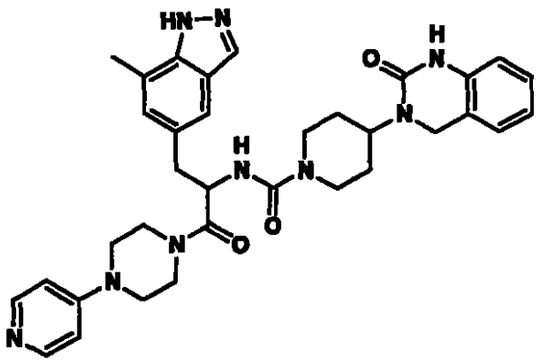
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-pyrrolidin-1-yl-ethyl]-amide



$^1$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

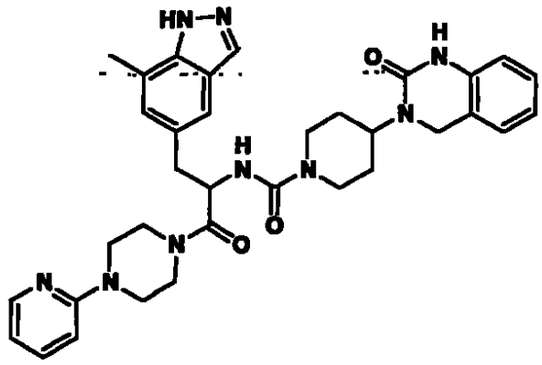
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



$^1$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

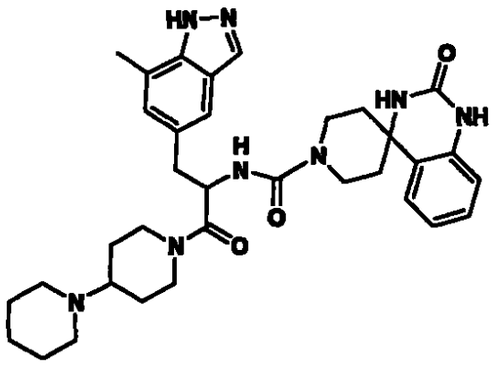
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-(4-pyridin-2-yl-piperazin-1-yl)-ethyl]-amide



$^1$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

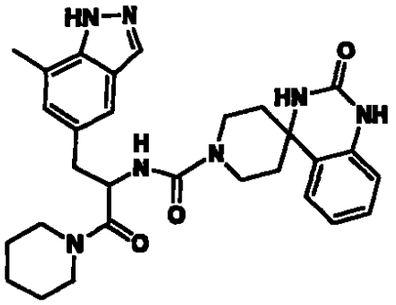
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide



$^1$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

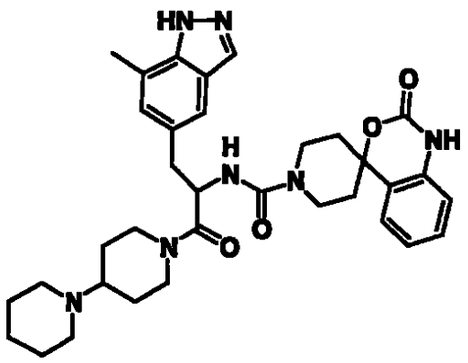
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-(1-piperidinyl)-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide



$^1$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

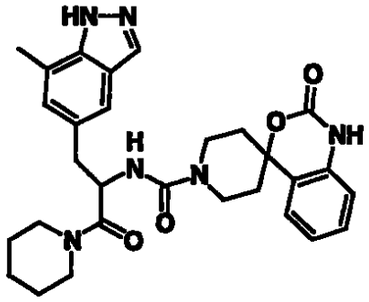
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-1',2'-dihydro-2'--oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



$^1$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

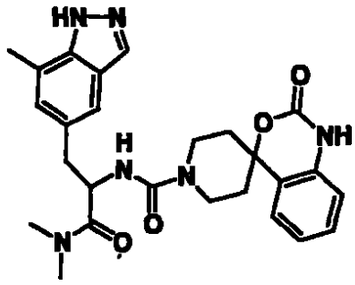
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-(1-piperidinyl)-2-oxoethyl]-1',2'-dihydro-2'--oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



$^1$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

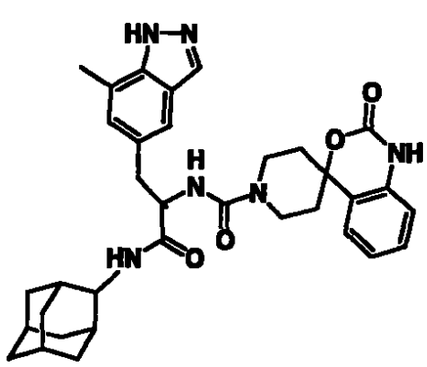
(±)-[1-Dimethylcarbamoyl-2-(7-methyl-1H-indazol-5-yl)-ethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



$^1$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

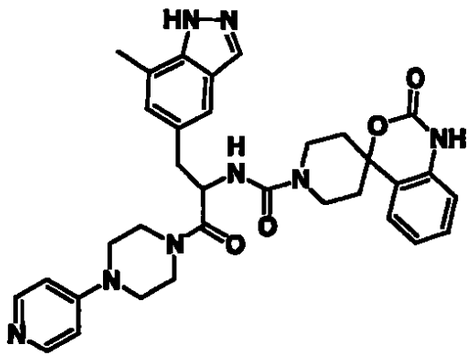
(±)-[1-(2-adamantyl-carbamoyl)-2-(7-methyl-1H-indazol-5-yl)-ethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



$^1$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

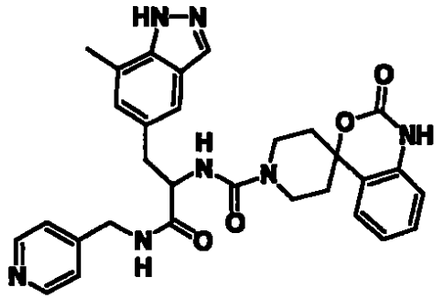
(±)-1',2'-Dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



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

Example 30

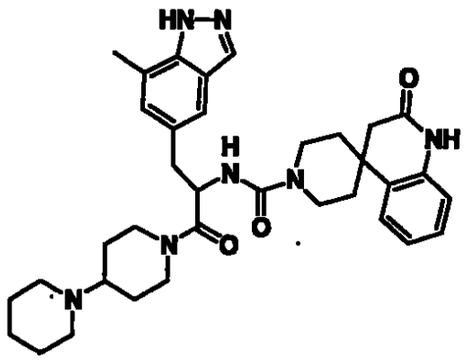
(±)-1',2'-Dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine-1-carboxylic acid {2-(7-methyl-1H-indazol-5-yl)-1-[(pyridin-4-ylmethyl)-carbamoyl]-ethyl}-amide



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

Example 31

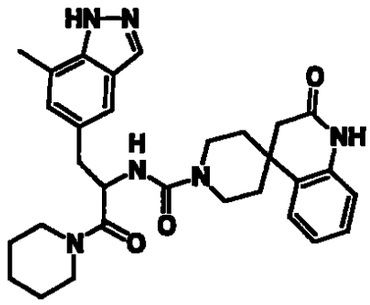
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]3',4'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinoline]-1-carboxamide



$^1$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

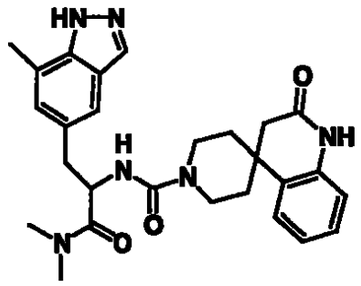
(±)- 1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-piperidinyl]-2-oxoethyl]3',4'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinoline]-1-carboxamide



$^1$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

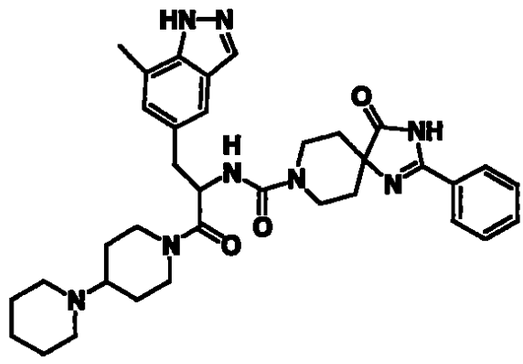
(±)-[1-Dimethylcarbmoyl-2-(7-methyl-1H-indazol-5-yl)-ethy]l-3',4'-dihydro -2'-oxospiro- [piperidine-4,4'-(1H)-quinoline]-1-carboxamide



$^1$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

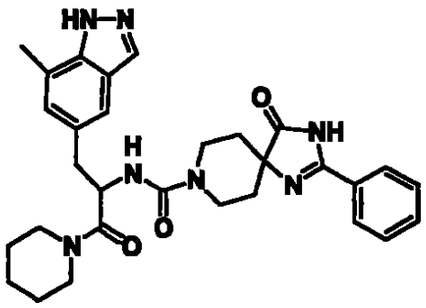
(±)-4-Oxo-2-phenyl-1,3,8-triaza-spiro[4,5]dec-1-ene-8-carboxylic acid{1-(7-methyl-1H-indazol-5- yl methyl)-2-[1,4]bipiperidinyl-1'-yl-2-oxo-ethyl}-amide



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

Example 35

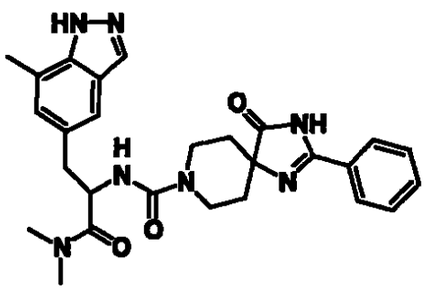
(±)-4-Oxo-2-phenyl-1,3,8-triaza-spiro[4,5]dec-1-ene-8-carboxylic acid{1-(7-methyl-1H-indazol-5- yl methyl)-2-[1-piperidinylyl]-2-oxo-ethyl}-amide



$^1$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

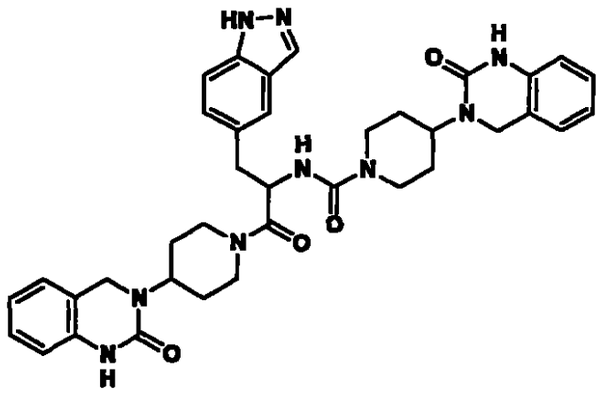
(±)-4-Oxo-2-phenyl-1,3,8-triaza-spiro[4,5]dec-1-ene-8-carboxylic acid[1-dimethylcarbamoyl -2-(7-methyl-1H-indazol-5- yl)-ethyl]amide



$^1$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

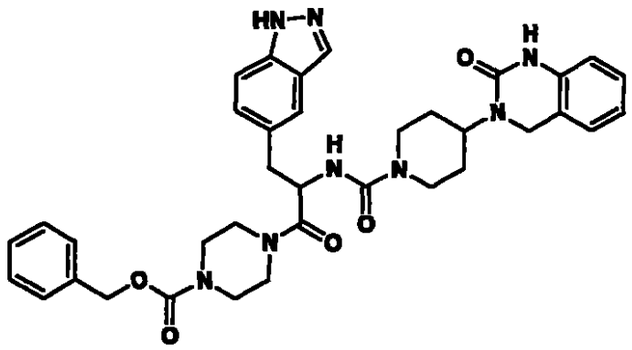
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid {1-(1H-indazol-5-ylmethyl)-2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-amide



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

Example 38

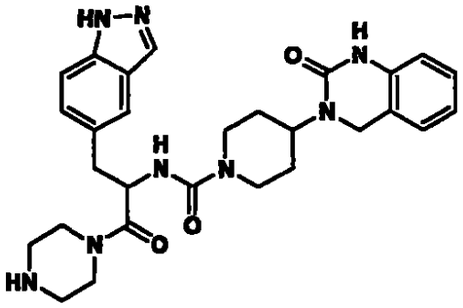
4-(3-(1H-Indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionyl)-piperazine-1-carboxylic acid benzyl ester



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

Example 39

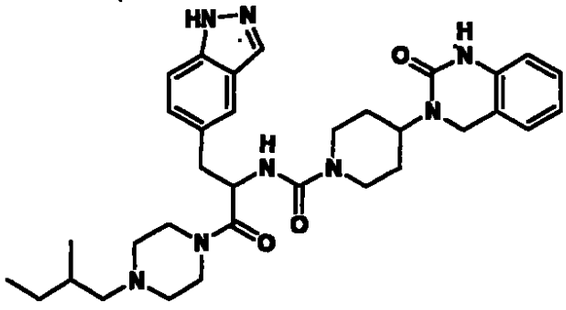
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(1H-indazol-5-ylmethyl)-2-oxo-2-piperazin-1-yl-ethyl]-amide



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

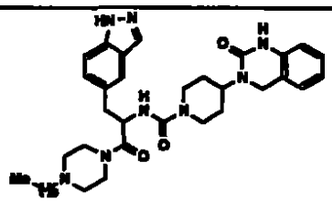
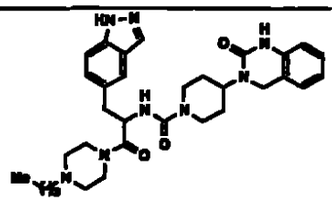
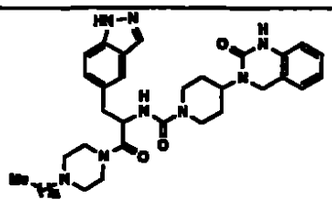


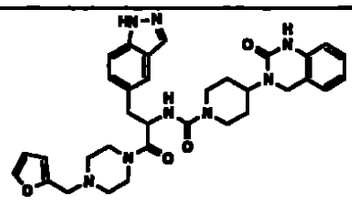
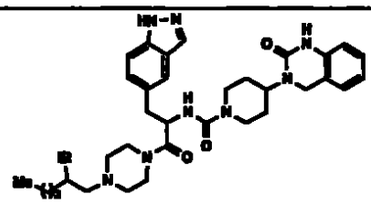
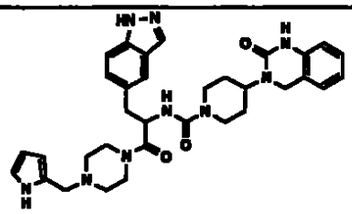
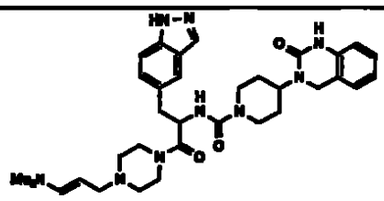
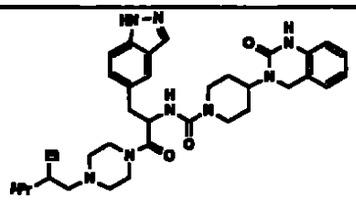
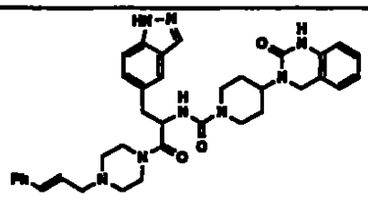
A stirred solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(1H-indazol-5-ylmethyl)-2-oxo-2-piperazin-1-yl-ethyl]-amide (100 mg, 0.188 mmol) in methanol (25 mL) was treated with 2-methyl-butyraldehyde (0.03 ml, 0.376 mmol). After 1h at room temperature, sodium triacetoxyborohydride (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$(MH)^+$.

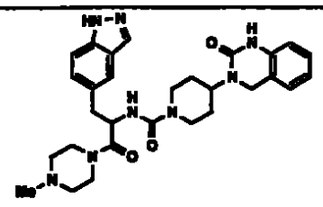
General Experimental Procedure for the Preparation of Examples 40b-40k.

The appropriate aldehyde (0.04 mmol) was added to a solution of Example 39 piperazine (0.02 mmol) in MeOH (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 MeOH and an ammonia/MeOH solution. The ammonia/MeOH 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.

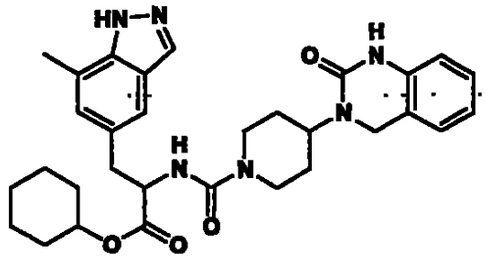
| Example No. | Structure | HPLC Retention time (min) | Mass spec $(MH)^+$ |
|---|---|---|---|
| 40b |  | 2.62 | 629 |
| 40c |  | 1.41 | 587 |
| 40d |  | 1.27 | 573 |

| Example No. | Structure | HPLC Retention time (min) | Mass spec $(MH)^+$ |
|---|---|---|---|
| 40e |  | 1.74 | 611 |
| 40f |  | 1.89 | 643 |
| 40g |  | 1.48 | 610 |
| 40h |  | 2.19 | 614 |
| 40i |  | 2.36 | 629 |
| 40j |  | 1.66 | 647 |

| Example No. | Structure | HPLC Retention time (min) | Mass spec $(MH)^+$ |
|---|---|---|---|
| 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

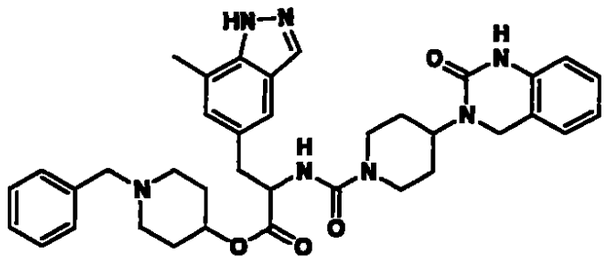


To a stirred solution of (±) –2-amino-3-(7-methyl- 1H-indazol-5-yl)-propinic acid (20 mg, 0.042 mmoles), 4-(dimethylamino)pyridine (2.5 mg, 0.02 mmoles), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (33 mg, 0.17 mmoles) in methylene chloride (2 mL) and dimethylforamide (1 mL), was 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

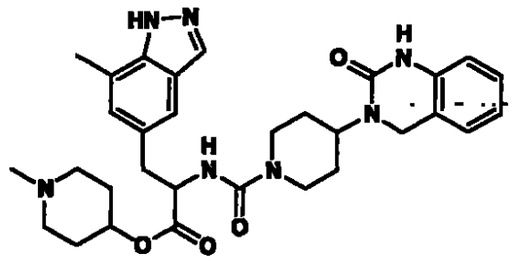
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-benzyl-piperidin-4-yl ester



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

Example 41c

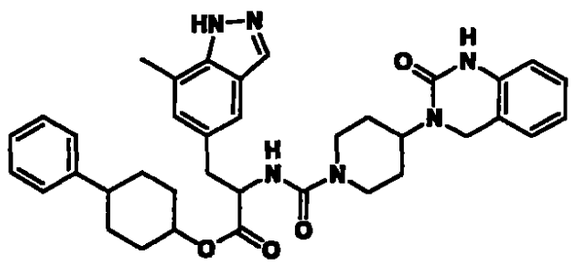
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester



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

Example 41d

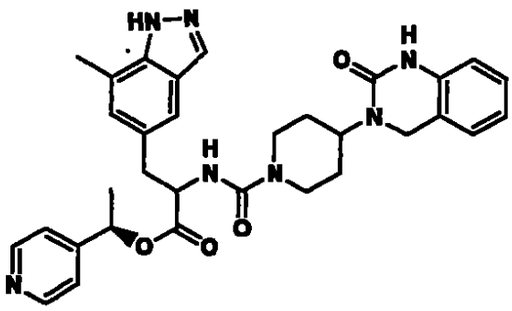
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester



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

Example 41e

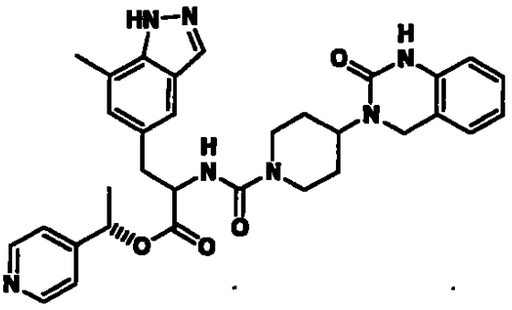
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid (R)-1-pyridin-4-yl-ethyl ester



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

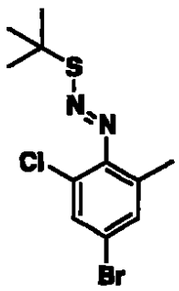
Example 41f

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 $(MH)^+$.

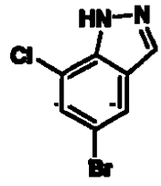
4-Bromo-2-chloro-6-methylphenyldiazo-t-butyl sulfide



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

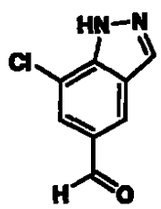
temperature was maintained below -5°C. After a further 30 min at -5°C to -20°C, the mixture was buffered to ca. pH 5 with solid sodium acetate. This mixture (kept at ca. -10°C) was added in portions to a stirred solution of t-butyl thiol (2.06 mL, 1 equiv.) in ethanol (18.5 mL) at 0°C over ca. 10 min. 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 $(MH)^+$.

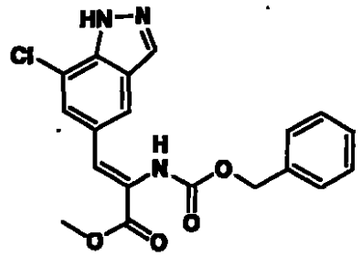
7-Chloroindazole-5-carboxaldehyde




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 $(MH)^+$.

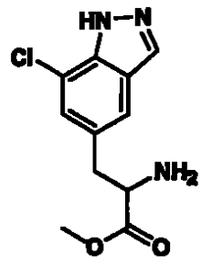
2-Benzyloxycarbonylamino-3-(7-chloro-1H-indazol-5-yl)-acrylic acid methyl ester




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 $(MH)^+$.

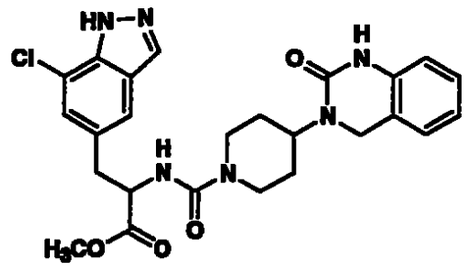
(±)-2-Amino-3-(7-chloro-1H-indazol-5-yl)-propionic acid methyl ester



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

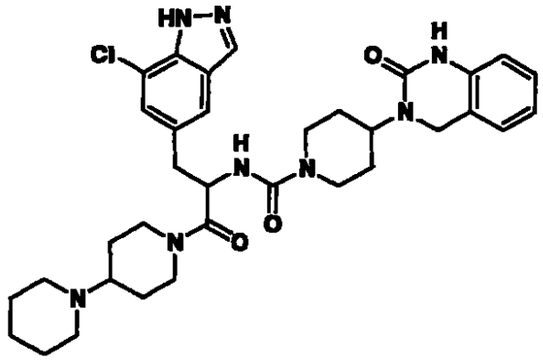


A stirred solution of (±)-2-amino-3-(7-chloro-1H-indazol-5-yl)-propionic acid methyl ester (78 mg, 0.31 mmol) in tetrahydrofuran (2 mL) at 0°C was treated with

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

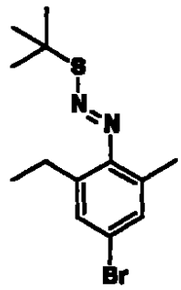
solution was stirred 30 minutes and concentrated. The product was purified by column chromatography to give 14.7 mg (77%, 2 steps). $^1$H-NMR ($CDCl_3$, 500 MHz) δ 1.30-1.60 (m, 8H), 1.65-1.88 (m, 5H), 2.14 (m, 1H), 2.23 (m, 1H), 2.30-2.70 (m, 7H), 2.80-3.20 (m, 5H), 3.94 (d, *J*=13.4, 13.1, 1H), 4.10-4.30 (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

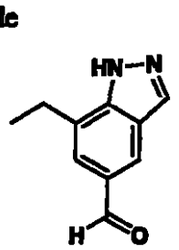
sodium nitrite (2.27 g, 1.05 equiv.) in water (5 mL), dropwise over 10 min while the temperature was maintained below -5°C. After a further 30 min at -5°C to -20°C, the mixture was buffered to ca. pH 5 with solid sodium acetate. This mixture (kept at ca. -10°C) was added in portions to a stirred solution 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



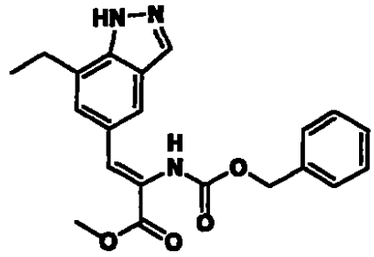

To a stirred solution of potassium t-butoxide (33.6 g, 10 equiv.) in DMSO (200 mL) was added a solution of 4-bromo-2-ethyl-6-methylphenyldiazo-t-butyl sulfide (9.4 g, 30 mmol) in DMSO (100 mL) via cannula. The mixture was stirred vigorously for 1 h. The reaction mixture was then carefully poured into 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



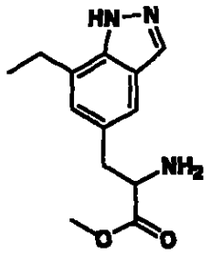
5-Bromo-7-ethyl-1H-indazole (2.0 g, 8.9 mmol) and sodium hydride (226 mg, 1.1 equiv.) were weighed into a flame-dried round-bottom flask containing a magnetic stir bar. Under a nitrogen atmosphere at room temperature, dry tetrahydrofuran (60 mL) was added. The mixture was stirred at room temperature 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 $(MH)^+$.

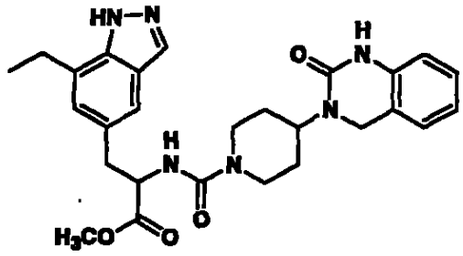
(±)-2-Amino-3-(7-ethyl-1H-indazol-5-yl)-propionic acid methyl ester



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

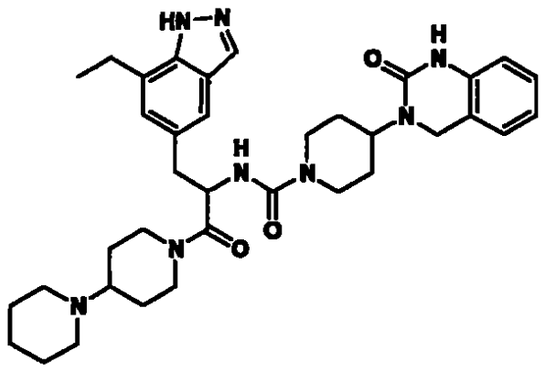


A stirred solution of (±)-2-amino-3-(7-ethyl-1H-indazol-5-yl)-propionic acid methyl ester (100 mg, 0.41 mmol) in tetrahydrofuran (2 mL) at 0°C was treated with carbonyl diimidazole (66 mg, 1 equiv). The reaction was stirred for 5 min, warmed to room temperature, stirred for 15 min, and then treated with 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

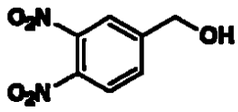
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



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),

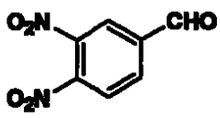
4.57 (m, 2H), 5.10-5.24 (m, 1H), 5.67 (d, *J*=8.2, 0.6H), 5.74 (d, *J*=7.9, 0.4H), 6.67 (d, *J*=7.9, 1H), 5.67 (d, *J*=8.2, 0.6H), 5.74 (d, *J*=7.9, 0.4H), 6.67 (d, *J*=7.9, 1H), 6.93 (dd, *J*=7.6, 7.3, 1H), 6.96 (s, 0.4H), 7.03 (dd, *J*=7.0, 6.7, 1H), 7.09 (m, 1.6H), 7.15 (dd, *J*=7.0, 6.7, 1H), 7.31 (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



$BH_3$-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).

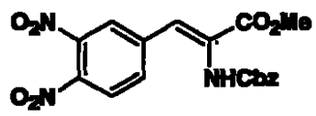
3,4-Dinitro-benzaldehyde



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.

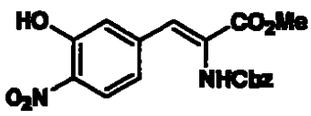
2-Benzyloxycarbonylamino-3-(3,4-dinitro-phenyl)-acrylic acid methyl ester




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).

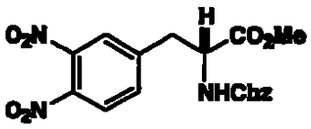
Similarly prepared:

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).

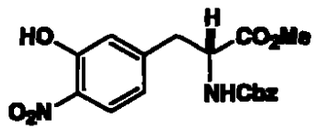
(R)-2-Benzyloxycarbonylamino-3-(3,4-dinitro-phenyl)-propionic acid methyl ester




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 × 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).

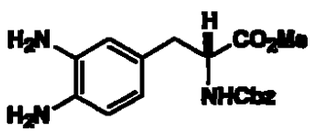
Similarly prepared:

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



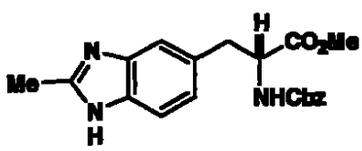

$^1$H-NMR ($CDCl_3$, 500 MHz) δ 7.97 (d, J = 9.0 Hz, 1H), 7.36 – 7.30 (m, 5H), 6.90 (s, 1H), 6.71 (d, J = 8.5 Hz, 1H), 5.29 (d, j = 7.0 Hz, 1H), 5.11 (d, J = 12.5 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.68 (dd, j = 13.0, 6.0 Hz, 1H), 3.74 (s, 3H), 3.20 (dd, j = 13.5, 5.0 Hz, 1H), 3.05 (dd, J = 13.5, 6.0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

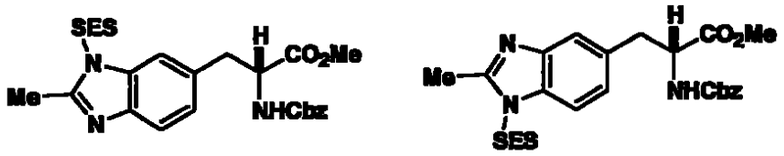


A solution of (R)-2-benzyloxycarbonylamino-3-(3,4-diamino-phenyl)-propionic acid methyl ester-acetic acid (640 mg) in acetic acid (8 mL) was heated at 130°C for 4h. The mixture was then poured into water and cooled to 0°C. The pH was adjusted to 8 by gradual addition of solid sodium bicarbonate. The 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 brownish 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



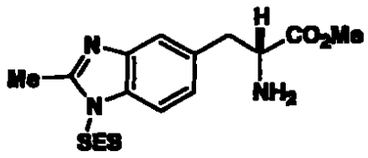

To a suspension of (R)-2-benzyloxycarbonylamino-3-(2-methyl-1H-benzoimidazol-5-yl)-propionic acid methyl ester (533 mg, 1.96 mmol), and sodium carbonate in acetonitrile (20 mL) was added neat 2-trimethylsilanyl-ethanesulfonyl chloride all at once. The mixture was stirred at room temperature overnight.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

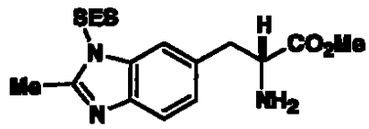
3.17 (m, 2H), 2.79 (s, 3H), 0.92 – 0.83 (m, 2H), -0.02 (s, 4.5 H), -0.05 (s, 4.5H). Mass spec.: 532.26 $(MH)^+$.

(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



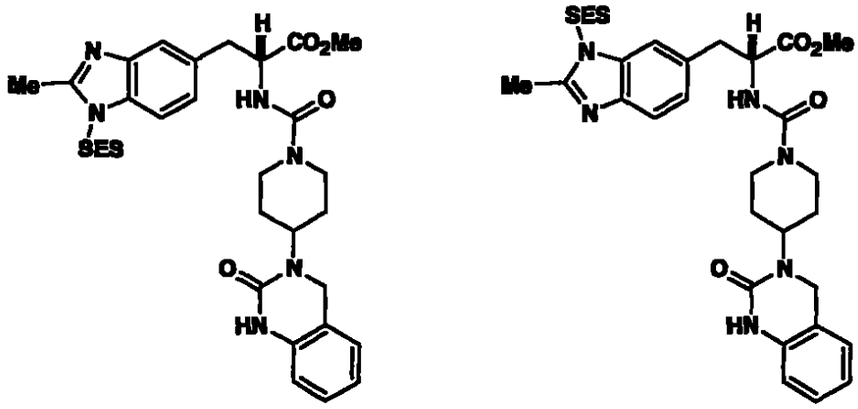




A methanol (50 mL) suspension of (R)-2-benzyloxycarbonylamino-3-[2-methyl-3-(2-trimethylsilanyl-ethanesulfonyl)-3H-benzoimidazol-5-yl]-propionic acid methyl ester and (R)-2-Benzyloxycarbonylamino-3-[2-methyl-1-(2-trimethylsilanyl-ethanesulfonyl)-1H-benzoimidazol-5-yl]-propionic acid methyl ester (1:1 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

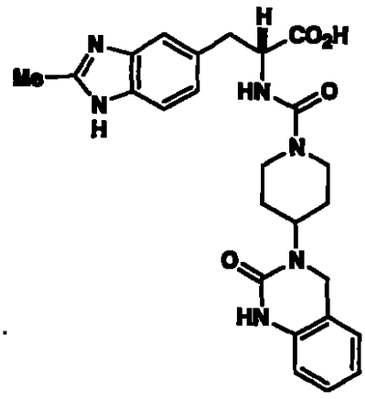
and

(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 $(MH)^+$.

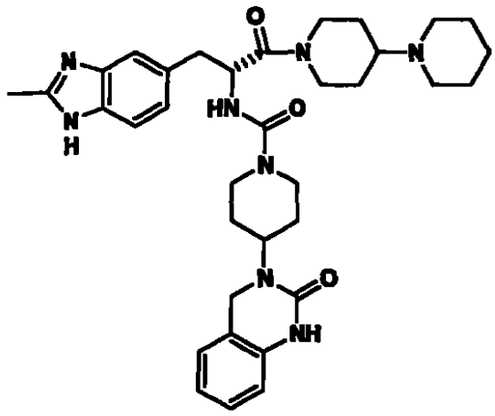
(R)-3-(2-Methyl-1H-benzoimidazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



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 $(MH)^+$.

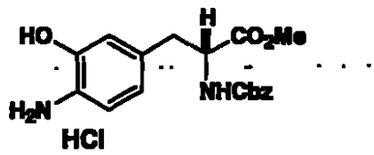
Example 46

(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



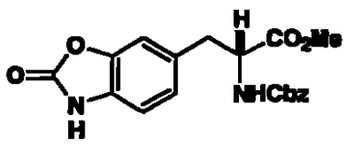
Prepared as described above for (*R*)-4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide. Purified by silica gel chromatography using methylene chloride:methanol:triethylamine (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



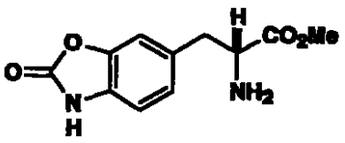

Powdered iron (3.7 g, 66.4 mmol) and ammonium chloride (5.9 g, 111 mmol) were added at 0°C to a solution of (R)-2-benzyloxycarbonylamino-3-(3-hydroxy-4-nitro-phenyl)-propionic acid methyl ester (2.07 g, 5.53 mmol) in degassed 1:1 methanol/water (400 mL). The resulting mixture was stirred at room temperature 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 $(MH)^+$.

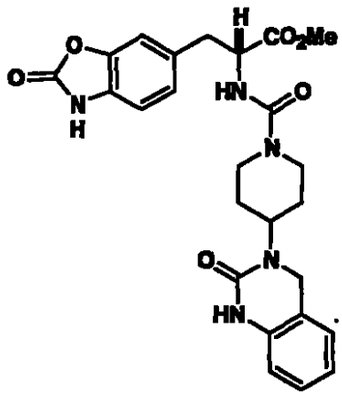
(R)-2-Amino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



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.

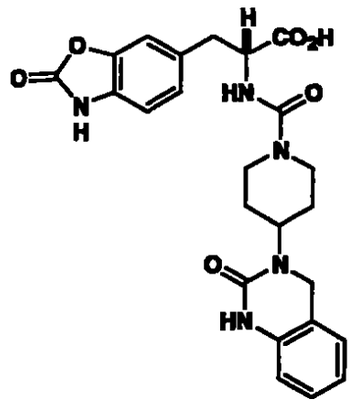
Solvents were removed *in vacuo* to afford the title compound. $^1$H-NMR ($CD_3OD$, 500 MHz) δ 8.41 (br s, 2H), 7.17 (s, 1H), 7.09 (br s, 2H), 4.32 (s, 1H), 3.83 (s, 3H), 3.33 (s, 1H), 3.30 (s, 1H), 3.22 (s, 1H). Mass spec.: 237.20 $(MH)^+$.

(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 $(MH)^+$.

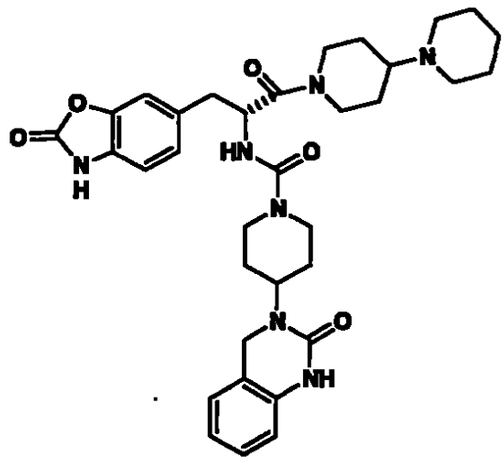
(R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



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

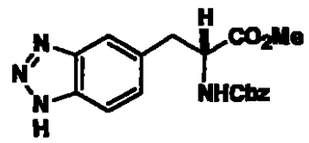
(R)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide



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-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide. The crude product was purified by silica gel chromatography using methylene

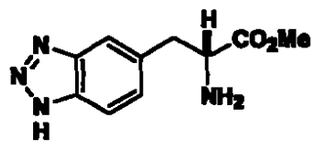
chloride:methanol:triethylamine (93:5:2) as eluent to give a white solid. This was dissolved in ethyl acetate (60 mL) and washed with a 1:1 sat. sodium bicarbonate/brine twice and dried over sodium sulfate. After filtration, solvents were removed to afford the title compound as a white solid (70%). $^1$H-NMR ($CD_3OD$, 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 $(MH)^+$.

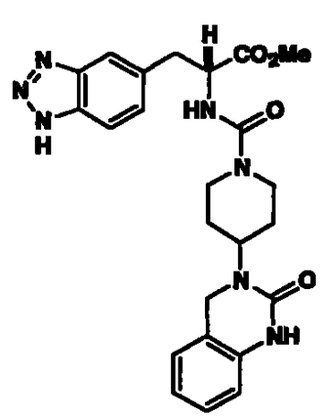
(R)-2-Amino-3-(1H-benzotriazol-5-yl)-propionic acid methyl ester



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

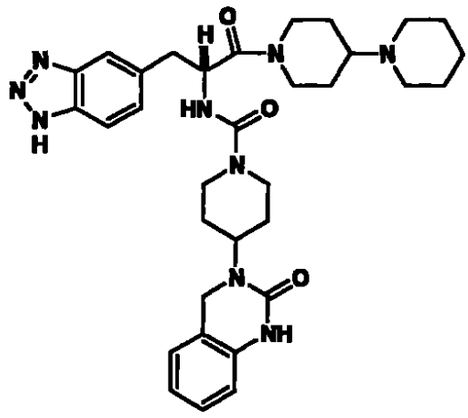


Prepared as described above for (*R*)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester except that carbonyl diimidazole was used in place of *N,N*-disuccinimidyl carbonate (DSC). $^1$H-NMR ($CD_3OD$, 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 $(MH)^+$.

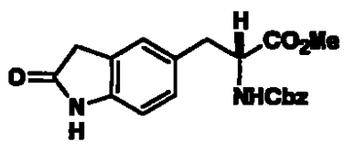
Example 49

(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



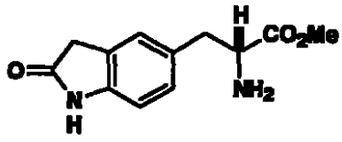
Prepared as described above for (*R*)-4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide. Purified by silica gel chromatography using methylene chloride/methanol/triethylamine (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



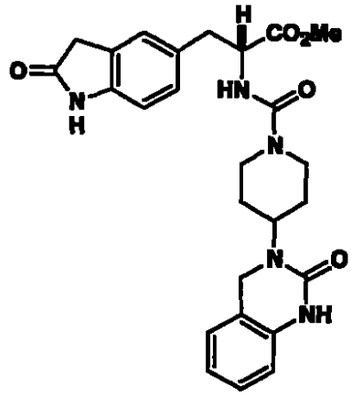
$PyHBr_3$ (1.28 g, 4.02 mmol) was added in small portions over 30 min to a solution of (R)-2-benzyloxycarbonylamino-3-(1*H*-indol-5-yl)-propionic acid methyl ester (0.47 g, 1.34 mmol) in *t*-butanol (10 mL) while the reaction temperature was maintained between 25-30°C. The resulting mixture was stirred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

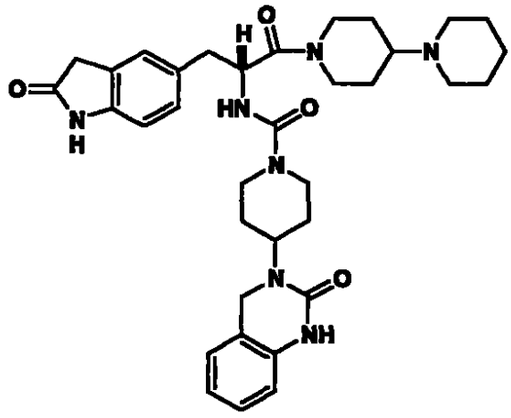
(R)-3-(2-Oxo-2,3-dihydro-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



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 $(MH)^+$.

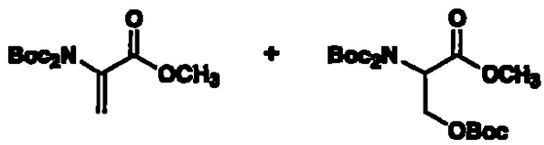
Example 50

(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 $(MH)^+$.

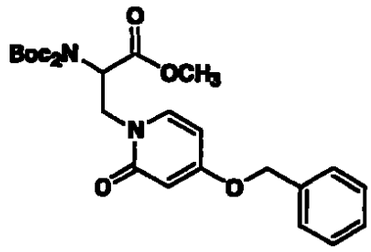
2-(Di-*tert*-butoxycarbonylamino)-acrylic acid methyl ester



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

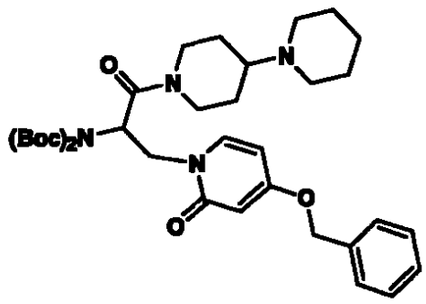
mixture of the title compound and 2-(di-*tert*-butoxycarbonylamino)-3-*tert*-butoxycarbonyloxy-propionic acid methyl ester. As it was later found that both react with secondary amines to give the same products, the mixture was used without separation. 2-(Di-*tert*-butoxycarbonylamino)-acrylic acid methyl 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 $(MH)^+$.

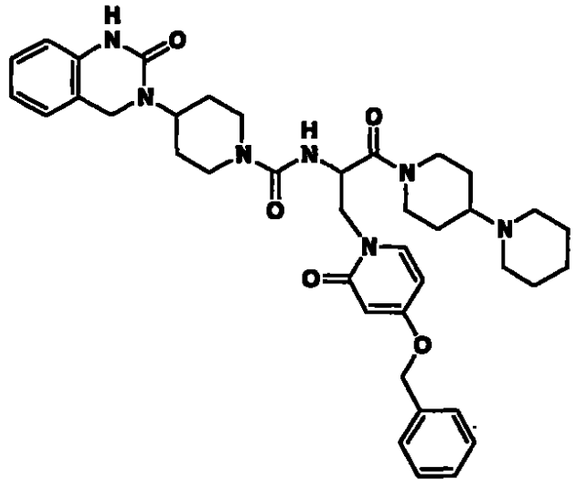
(±)-4-Benzyloxy-1-[3-[1,4']bipiperidinyl-1'-yl-2-(di-*tert*-butoxycarbonylamino)-3-oxo-propyl]-1H-pyridin-2-one




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 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

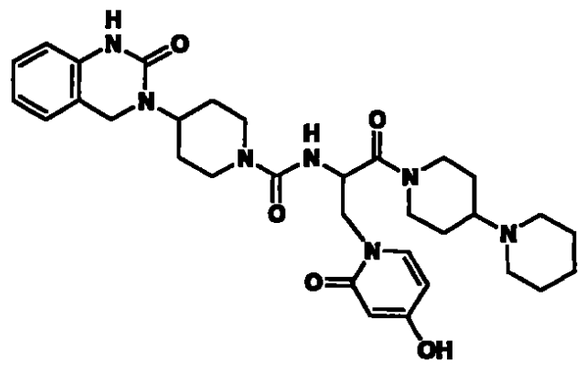
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-benzyloxy-2-oxo-2H pyridin-1-ylmethyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-amide



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 $(MH)^+$.

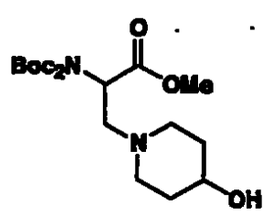
Example 52

(±)-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 $(MH)^+$.

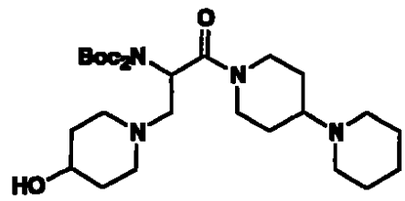
(±)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-hydroxy-piperidin-1-yl)-propionic acid methyl ester



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

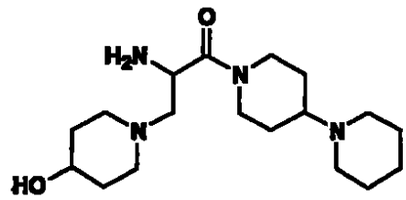
equiv). A gentle stream of nitrogen was placed over the reaction while it stirred overnight. The crude oil which resulted was dissolved in ethyl acetate, washed with water, then brine, dried over magnesium sulfate, and concentrated to give 1.38 g (quant.) as an oil which was used without purification. 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 $(MH)^+$.

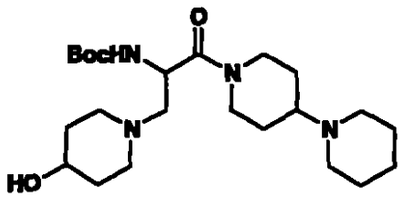
(±)-2-Amino-1-[1,4']bipiperidinyl-1'-yl-3-(4-hydroxy-piperidin-1-yl)-propan-1-one



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

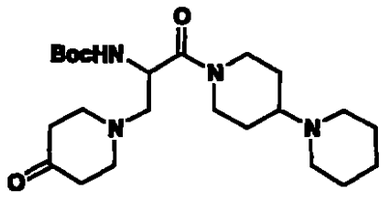
removed and the reaction stirred for 30 min. The reaction was concentrated to afford the product as its trifluoroacetic acid salt (400 mg, quant.) which was used without purification. Mass spec.: 339.46 $(MH)^+$.

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



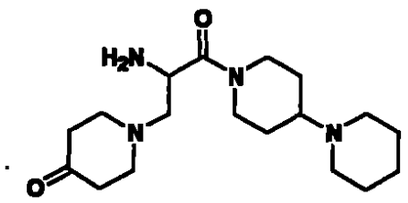

To a solution 2-amino-1-[1,4']bipiperidinyl-1'-yl-3-(4-hydroxy-piperidin-1-yl)-propan-1-one (trifluoroacetic acid salt, 300 mg, 0.58 mmol) and diisopropylethylamine (0.30 mL, 4 equiv) in tetrahydrofuran (5 mL) was added di-*tert*-butyl-dicarbonate (128 mg, 1 equiv). The resulting solution was stirred 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 $(MH)^+$.

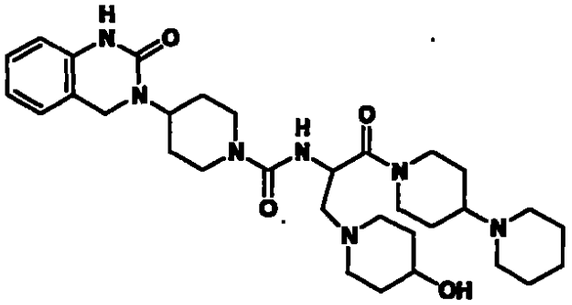
(±)-1-(2-Amino-3-[1,4']bipiperidinyl-1'-yl-3-oxo-propyl)-piperidin-4-one



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 $(MH)^+$.

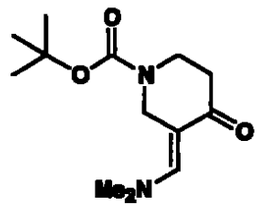
Example 53

(±)-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



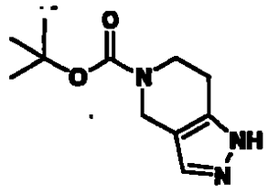
To a solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-hydroxy-piperidin-1-ylmethyl)-2-oxo-ethyl]-amide (3 trifluoroacetic acid salt, 200 mg, 0.39 mmol) in methylene chloride (5 mL) at 0°C was added diisopropylethylamine (0.27 mL, 3.9 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



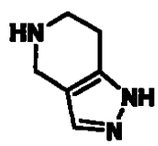
4-Oxo-piperidine-1-carboxylic acid *tert*-butyl ester (10 g, 50 mmol) was dissolved in dimethyl formamide dimethylacetal (50 mL) and heated to reflux for 1.25 h. The solution was cooled, concentrated, and purified by flash chromatography to give 2.55 g (19%). Mass spec.: 255.16 $(MH)^+$.

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 $(MH)^+$.

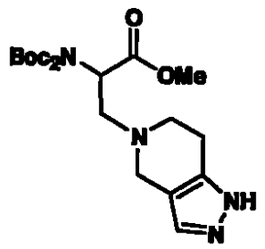
4,5,6,7-Tetrahydro-1H-pyrazolo[4,3-c]pyridine



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

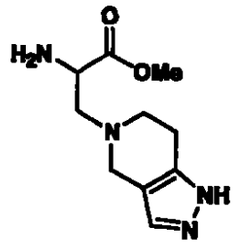
as needed by dissolving the salt in water, loading it onto an SCX column, flushing with methanol, and then eluting with 2 M ammonia in methanol.

(±)-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, *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 $(MH)^+$.

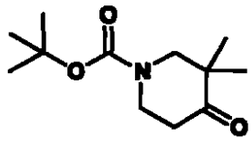
(±)-2-Amino-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester




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,

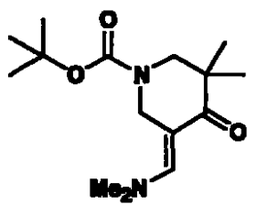
redissolved in methanol, and passed onto a column of strong cation exchange resin. After flushing with methanol, the product was removed from the column by eluting with 2 M ammonia in methanol to afford the product as its free base (275 mg, 95%). $^1$H-NMR ($CDCl_3$, 500 MHz) δ 2.71 (dd, *J*=12.8, 8.6, 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, 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 $(M+Na)^+$.

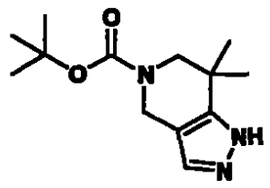
5-Dimethylaminomethylene-3,3-dimethyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester



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.

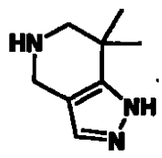
$^1$H-NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 6H), 1.45 (s, 9H), 3.06 (s, 6H), 3.37 (m, 2H), 4.57 (m, 2H), 7.41 (bs, 1H).

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



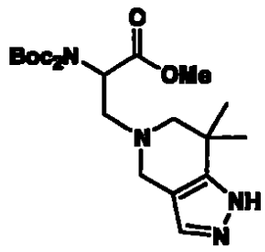
To a solution of 5-dimethylaminomethylene-3,3-dimethyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (6.35 g, 22 mmol) in methanol (15 mL) was added hydrazine hydrate (1.2 mL, 1.1 equiv). The solution was stirred at room temperature overnight and concentrated to give 5.3 g (94%) which was used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

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



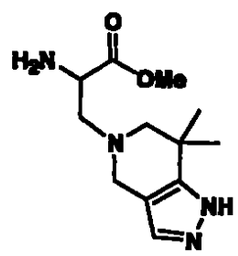
To a solution of 7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester (5.3 g, 21 mmol) in methylene chloride (10 mL) at 0°C was added trifluoroacetic acid (5 mL). The reaction was allowed to warm to room temperature, stirred 15 min, and treated with additional 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 $(MH)^+$.

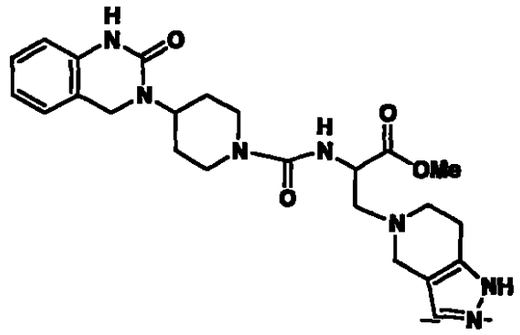
(±)-2-Amino-3-(7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester




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 $(MH)^+$.

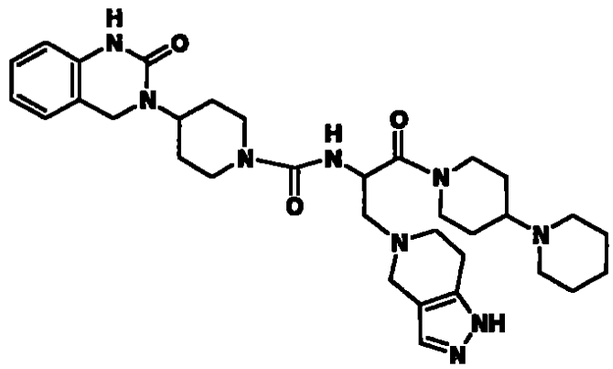
(±)-2-{[4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester



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

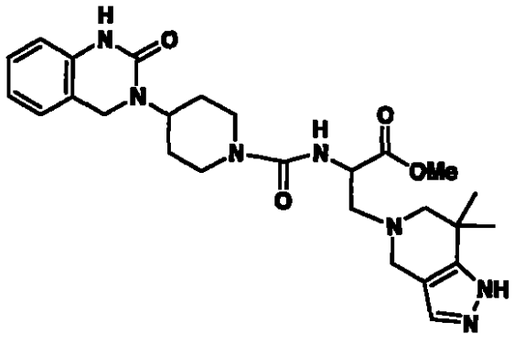
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-ylmethyl)-ethyl]-amide



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 minutes 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

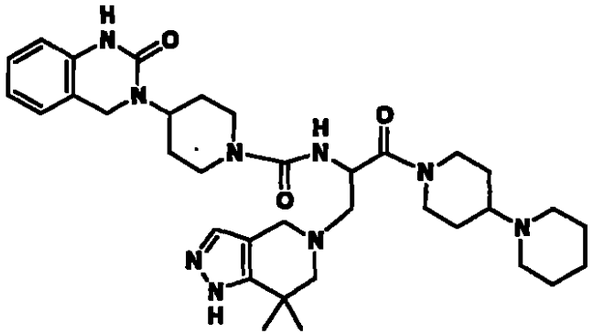
(±)-3-(7,7-Dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



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

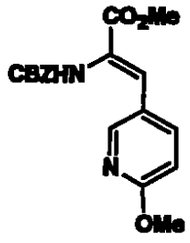
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-ylmethyl)-2-oxo-ethyl]-amide



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 $(MH)^+$.

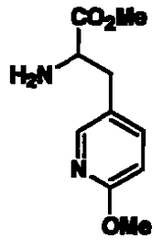
2-Benzyloxycarbonylamino-3-(6-methoxy-pyridin-3-yl)-acrylic acid methyl ester




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

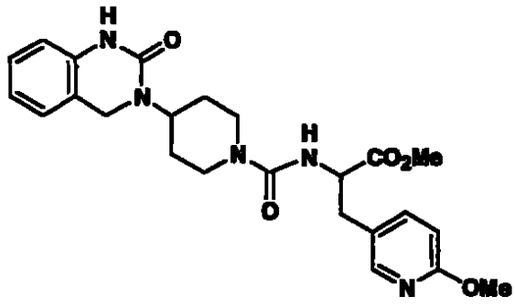
were in turn washed with brine, dried over magneaium sulfate, and concentrated to give 2.63 g (quant.) which was used without purification. Mass spec.: 343.08 $(MH)^+$.

(±)-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 $(MH)^+$.

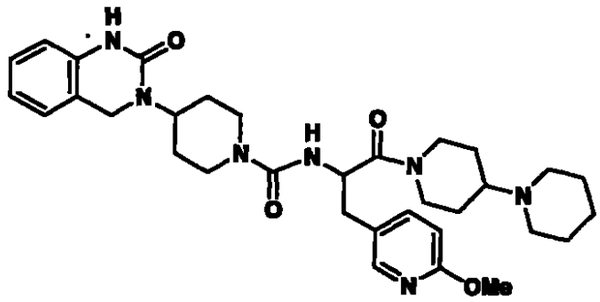
(±)-3-(6-Methoxy-pyridin-3-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



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 $(MH)^+$.

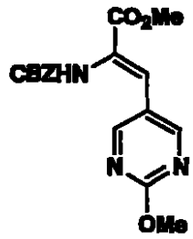
Example 57

(±)-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)phosphinic 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 $(MH)^+$.

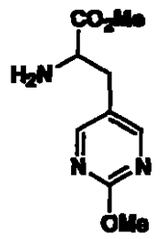
2-Benzyloxycarbonylamino-3-(2-methoxy-pyrimidin-5-yl)-acrylic acid methyl ester



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

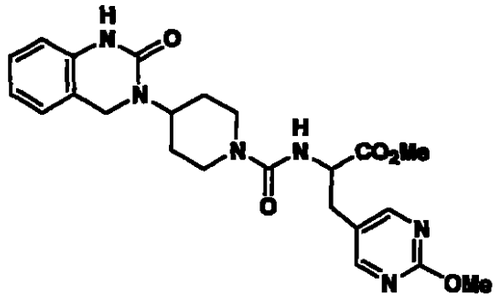
and stirred 1 h. The reaction was quickly poured into a sep funnel containing ethyl acetate and water. Brine was added to aid in separation of the layers. The aqueous was extracted with ethyl acetate (3X) which were in turn washed with brine, dried over magnesium sulfate, and concentrated. The crude 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

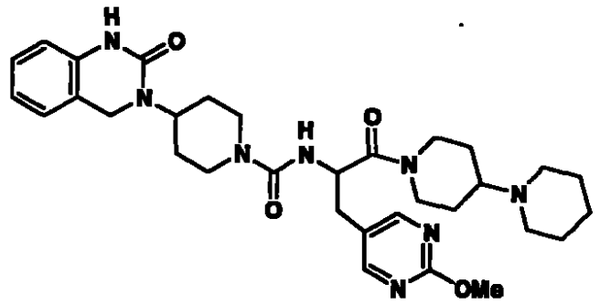


To a solution of 2-Amino-3-(2-methoxy-pyrimidin-5-yl)-propionic acid methyl ester (125 mg) and diisopropylethylamine (0.3 mL) in methylene chloride (2 mL, 0°C) was added *N,N'*-disuccinimidyl carbonate (155 mg). After 30 min, 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (120 mg) in methylene chloride (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 $(MH)^+$.

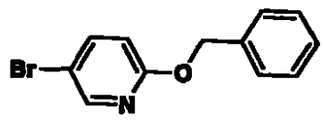
Example 58

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

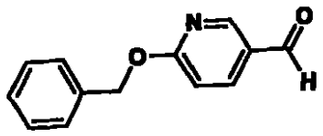
2-Benzyloxy-5-bromo-pyridine



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

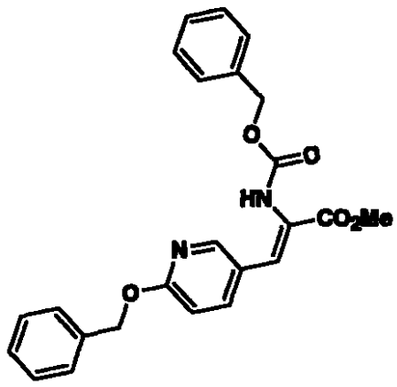
washed with water, then brine, dried over magnesium sulfate, and concentrated to give 1.9 g (85%) which was used without purification. Mass spec.: 264.25 $(MH)^+$.

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 $(MH)^+$.

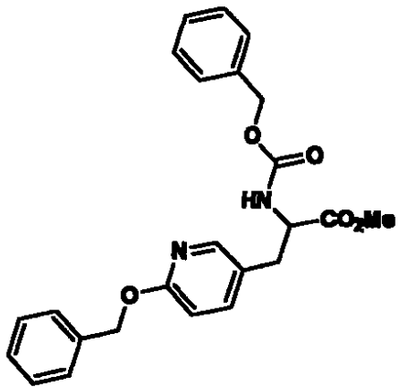
2-Benzyloxycarbonylamino-3-(6-benzyloxy-pyridin-3-yl)-acrylic acid methyl ester



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

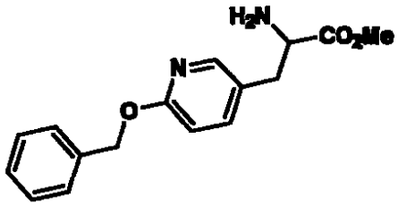
extracted with diethyl ether (2x), washed with brine, dried over magnesium sulfate, and concentrated to give 0.98 g (quant.) as an oil which was used without purification. Mass spec.: 419.32 $(MH)^+$.

(±)-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%).

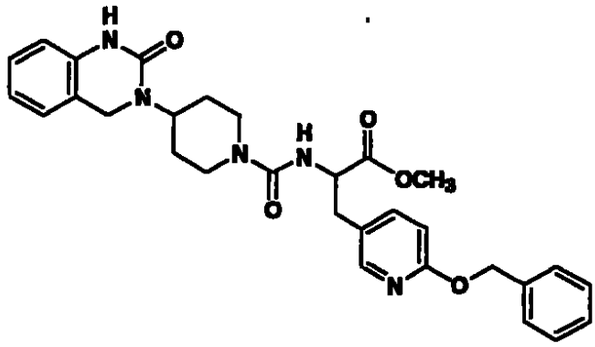
(±)-2-Amino-3-(6-benzyloxy-pyridin-3-yl)-propionic acid methyl ester




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 $(MH)^+$.

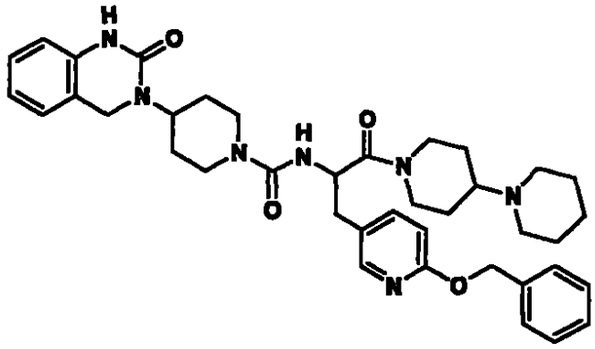
(±)-3-(6-Benzyloxy-pyridin-3-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



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

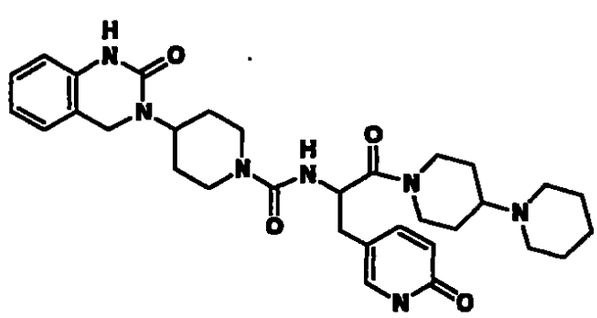


To a stirred solution of 3-(6-benzyloxy-pyridin-3-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl

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)phoshinic 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 $(MH)^+$.

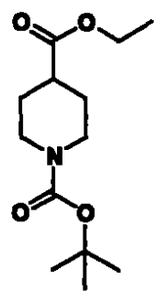
Example 60

(±)-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



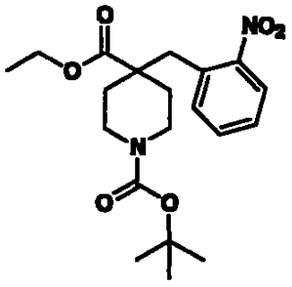
A flask was charged with 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(6-benzyloxy-pyridin-3-ylmethyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-amide (27 mg, 0.04 mmol), palladium on charcoal (10%, 4 mg), and methanol (1 mL). The flask was flushed with nitrogen, then hydrogen, 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. $^1$H 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 $(M+Na)^+$.

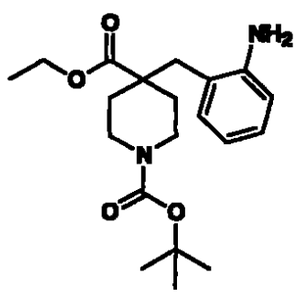
4-(2-Nitro-benzyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester



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

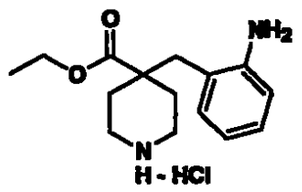
final product was purified from the complex reaction mixture by way of column chromatography on silica gel (eluent – hexanes – ethyl acetate 4:1) to give the desired product (1.61 g, 13%) as brown oil. Mass spec.: 415.38 $(M+Na)^+$.

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



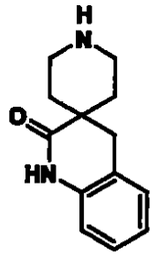
A mixture of 4-(2-nitro-benzyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (1.61 g, 4.102 mmol) and 10% palladium on charcoal (0.10 g) in ethanol (190 mL) was hydrogenated at 50 psi overnight. The resultant mixture was filtered through a plug of celite, and the filtrate concentrated 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



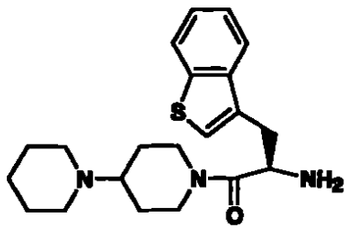
To a solution of 4-(2-amino-benzyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (1.29 g, 4.102 mmol) in dichloromethane (15 mL) was added a 4.0M solution of hydrogen chloride in dioxane (5 mL). The resulting solution was stirred at room temperature overnight. The concentration 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

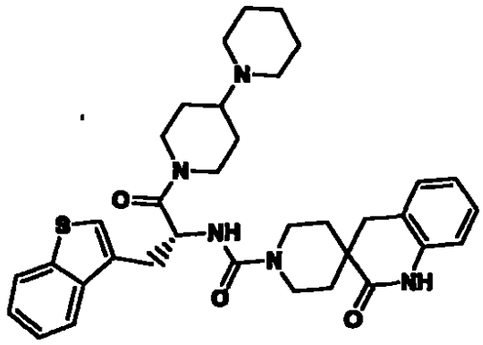


To a well stirred solution of 3-benzo[b]thiophen-3-yl-(2R)-2-*tert*-butoxycarbonylamino-propionic acid (1.0 g, 3.1 mmol) in methylene chloride (30 mL) at room temp was added 4-piperidinopiperidine (573 mg, 3.4 mmol), triethylamine (1.3 mL, 9.3 mmol) followed by 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (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

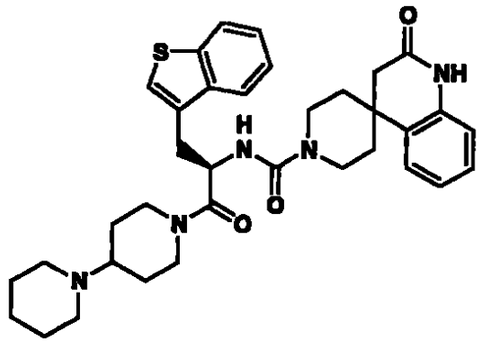
(R)-1-Oxo-3,4-benzo-2,9-diaza-spiro [5.5] undec-3-ene-9-carboxylic acid (1–benzo [*b*] thiophen-3-ylmethyl-2-[1,4'] bipiperidinyl-1'-yl-2–oxo-ethyl)-amide



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

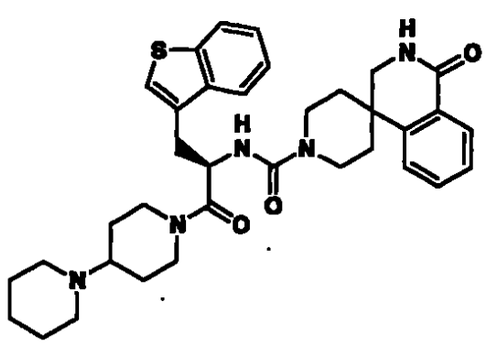
N-[(1R)-1-(Benzo[b]thien-3-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-3',4'-dihydro-2-oxospiro-[piperidine-4,4'(1H)-quinoline]-1-carboxamide



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 $(MH)^+$.

Example 63

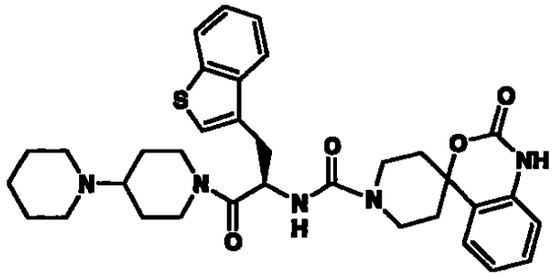
N-[(1R)-1-(Benzo[b]thien-3-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-2',3'-dihydro-1-oxospiro-[piperidine-4,4'(1H)-isoquinoline]-1-carboxamide



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

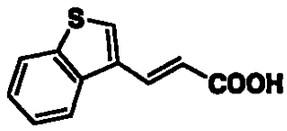



Prepared as described for (R)-1-oxo-3,4-benzo-2,9-diaza-spiro [5.5] undec-3-ene-9-carboxylic acid (1–benzo [*b*] thiophen-3-ylmethyl-2-[1,4'] bipiperidinyl-1'-yl-2–oxo-ethyl)-amide from 1,2-dihydro-2-oxospiro-[4H-3,1-benzoxazine-4,4'-piperidine (prepared as described in Takai, et al.; Chem. Pharm. Bull. 1985, 33, 1129-1139) to give the title compound (76%). Mass spec.: 616 $(MH)^+$. $R_f$= 1.42.

94

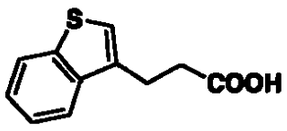
Succinate Intermediates and Examples

3-Benzo[b]thiophen-3-yl-acrylic acid



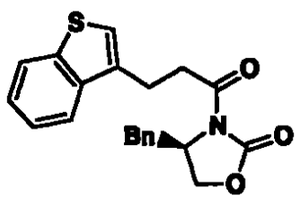

A suspension of 1-benzothiophene-3-carbaldehyde (4.9 g, 0.03 mol), malonic acid (6.6 g, 0.06 mol) and piperidine (1 mL) in 100 mL anhydrous pyridine was heated at 110°C overnight. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was taken up in 100 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



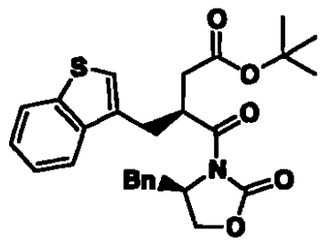

A suspension of 3-benzo[b]thiophen-3-yl-acrylic acid: (5.6 g, 0.027 mol) and 10% Pd/C (600 mg) in 1:1 methanol/ethyl acetate (50 mL) was hydrogenated in a Parr apparatus at 50 psi overnight. The mixture was filtered and concentrated to give the crude product without further purification (ca.100% conversion). Mass spec.: 205(MH)$^-$.

3-(3-Benzo[b]thiophen-3-yl-propionyl)-4(R)-benzyl-oxazolidin-2-one



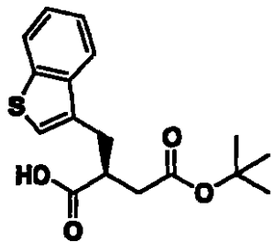
To a solution of 3-benzo[b]thiophen-3-yl-propionic acid (2.1g, 0.010 mol), triethylamine (4.12 g, 0.040 mol) in anhydrous tetrahydrofuran (100 mL) at 0°C was added pivaloyl chloride (1.38 mL, 0.011 mol). After stirring for 1.5 h at 0°C, lithium chloride (0.475 g, 0.011 mol) and (*R*)-4-benzyl-2-oxazolidinoe (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



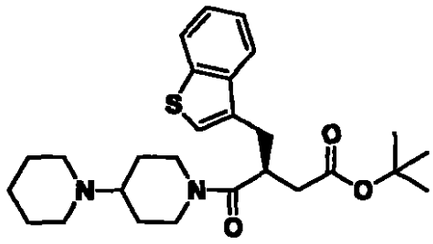

To a solution of 3-(3-benzo[b]thiophen-3-yl-propionyl)-4-benzyl-oxazolidin-2-one (3.35 g, 9.18 mmol) in 100 mL anhydrous tetrahydrofuran at –78°C was added lithium diisopropyl amide in tetrahydrofuran (6.1 mL, 11.01 mmol) and the reaction mixture was stirred for 30 min Following addition of *t*-butyl 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



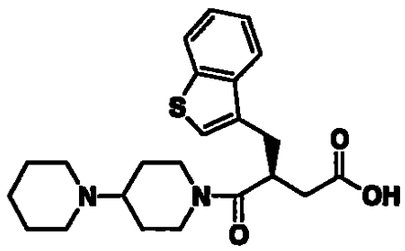
To a stirred solution of 3-benzo[b]thiophen-3-ylmethyl-4-(4-benzyl-2-oxo-oxazolidin-3-yl)-4-oxobutyric acid *tert*-butyl ester (2.15 g, 4.49 mmol) in tetrahydrofuran (50 mL) and water (30 mL) at 0°C was added 30 % aqueous hydrogen peroxide (1 mL) followed by lithium hydroxide (0.2155 g, 8.98 mmol). The 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.

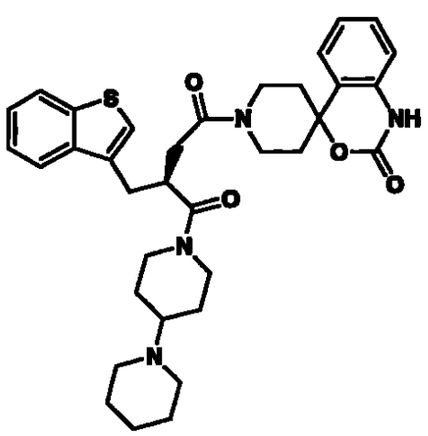
3(S)-Benzo[b]thiophen-3-ylmethyl-4-[1,4']bipiperidinyl-1'-yl-4-oxo-butyric acid



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

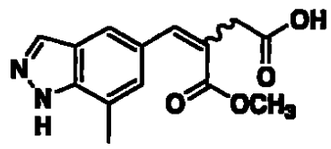
1-[1,4']Bipiperidinyl-1'-yl-2-(3(S)-Benzo[b]thiophen-3-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



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

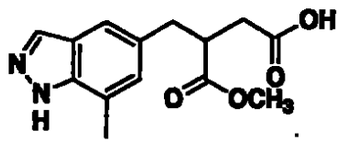
methanol/methylene chloride, to give the desired product in 60% yield. LC/MS: $t_R$=1.34 min, 615.45 $(MH)^+$.

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 $(MH)^+$.

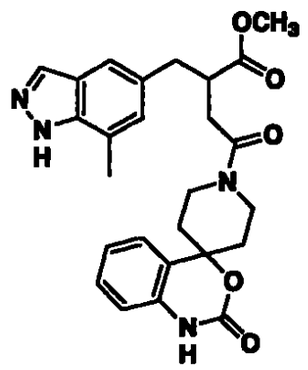
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-succinic acid 1-methyl ester



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

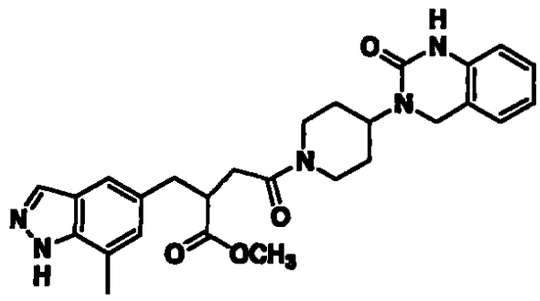


A solution of 2-(7-methyl-1H-indazol-5-ylmethyl)-succinic acid 1-methyl ester (0.2253 g, 0.82 mmol), 1,2-dihydro-2-oxospiro-4H-3,1-dihydro-benzoxazine-4'4-piperidine (0.1938 g, 0.89 mmol) and triethylamine (0.099 g, 0.98 mmol) in methylene chloride (15 mL) was treated with 3-(diethoxyphosphoryloxy)-1,2,3-benzotriain-4(3H)-one (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:

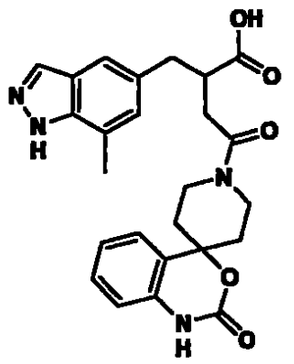
Example 67

(±)-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 $(MH)^+$.

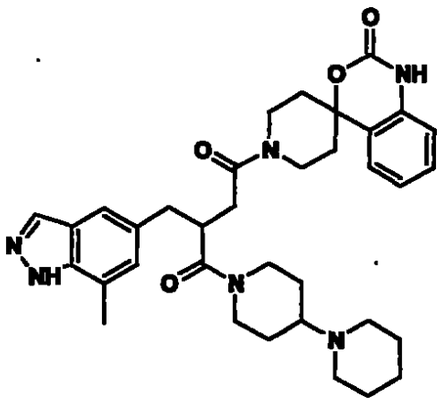
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid



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

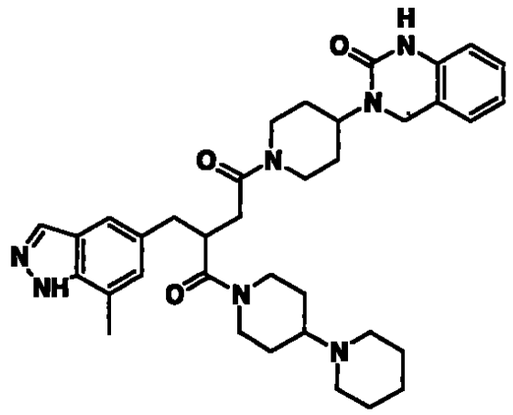


A solution of 2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid (0.020 g, 0.04 mmol), piperidylpiperidine (0.0087 g, 0.05 mmol) and triethylamine (0.09 g, 0.08 mmol) in methylene chloride (5 mL) at room temperature was treated with 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

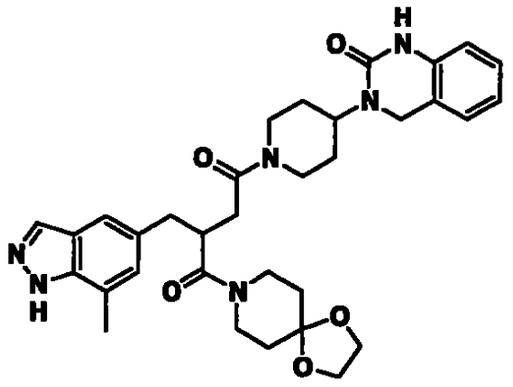
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



$^1$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

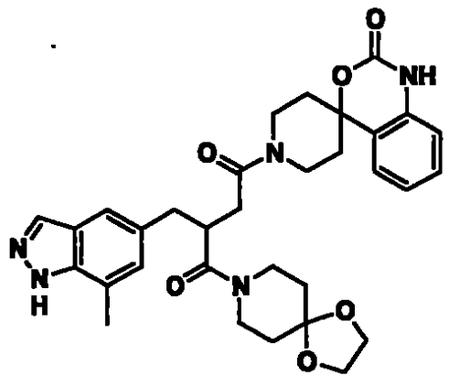
(±)-1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-(7-methyl-1H-indazol-5- ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



$^1$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

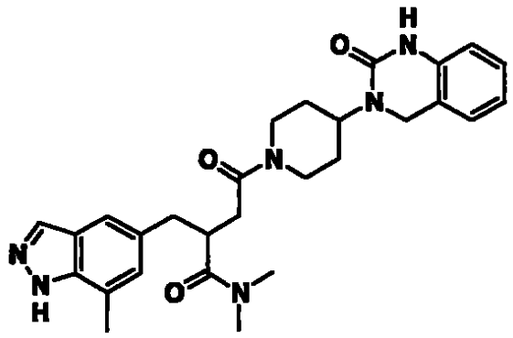
(±)-1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-(7-methyl-1H-indazol-5- ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



$^1$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

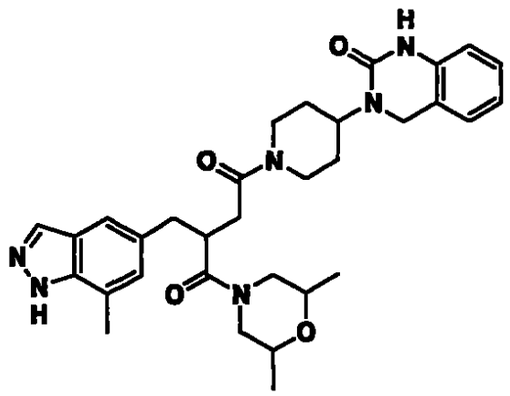
(±)-*N,N*-Dimethyl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyramide



LC/MS: $t_R$=1.36 min, 525.35 $(M+Na)^+$.

Example 73

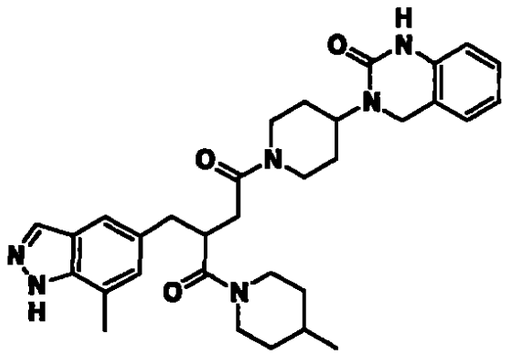
(±)-1-(2,6-Dimethyl-morpholin-4-yl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: $t_R$=1.41 min, 573.39 $(MH)^+$.

Example 74

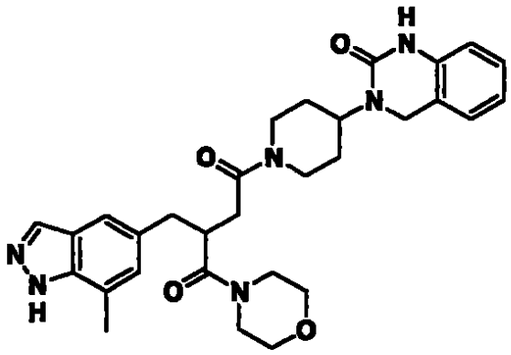
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-1-(4-methyl-piperidin-1-yl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



$^1$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

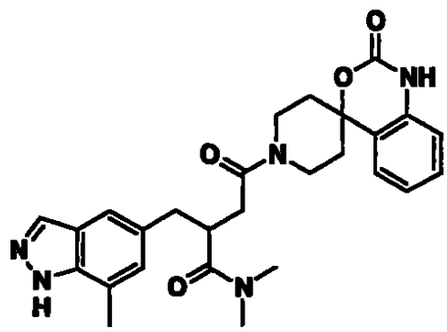
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-1-morpholin-4-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: $t_R$=1.32 min, 545.42 $(MH)^+$.

Example 76

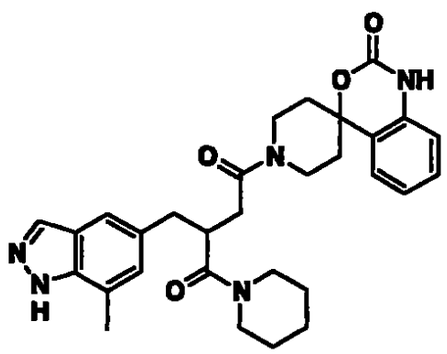
(±)-*N,N*-Dimethyl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyramide



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

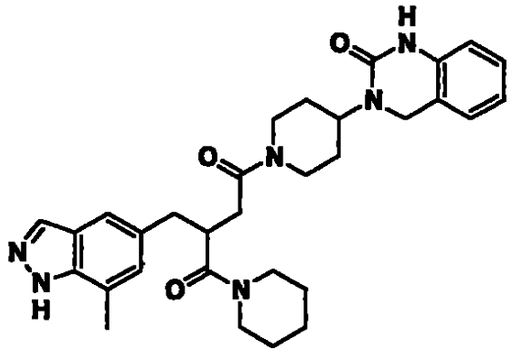


$^1$H-NMR (400 MHz, $CDCl_3$) δ 9.26 - 9.01 (1H, m), 8.09 (1H, s), 7.42 - 6.89 (7H, m), 4.56 (1H, m), 3.84 (1H, m), 3.65 (3H, m), 3.30 (2H, m), 3.05 (3H, m), 2.81 (1H, m),

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

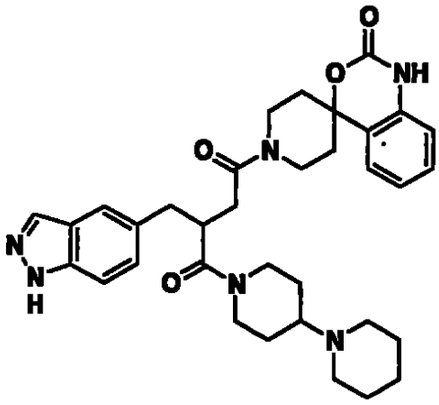
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-1-piperidin-1-yl-butane-1,4-dione



$^1$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

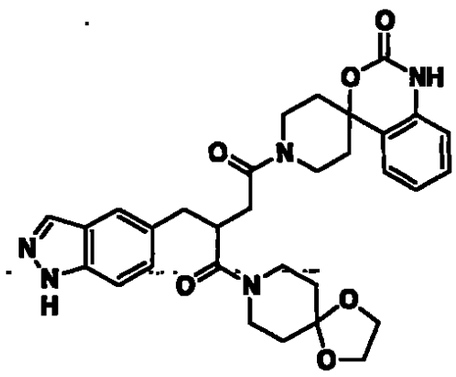
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



$^1$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

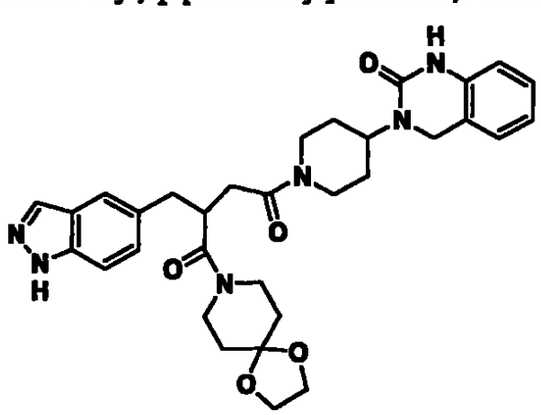
(±)-1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-(1H-indazol-5- ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



LC/MS: $t_R$=1.25 min, 574.25 $(MH)^+$.

Example 81

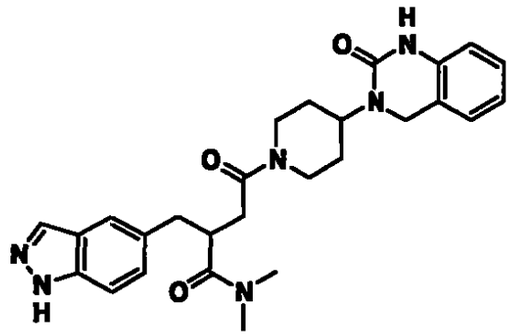
(±)-1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-(1H-indazol-5-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: $t_R$=1.34 min, 587.38 $(MH)^+$.

Example 82

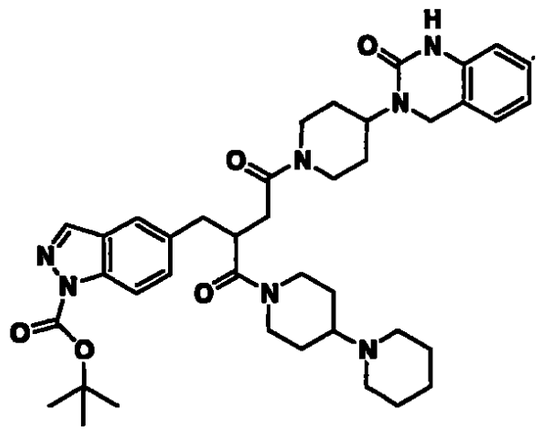
(±)-2-(1H-Indazol-5-ylmethyl)-N,N-dimethyl-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyramide



LC/MS: $t_R$=1.28 min, 489.33 $(MH)^+$.

Example 83

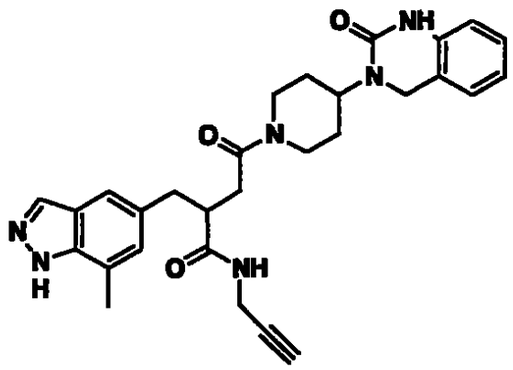
(±)-5-{2-([1,4']Bipiperidinyl-1'-carbonyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyl}-indazole-1-carboxylic acid *tert*-butyl ester



LC/MS: $t_R$=1.47 min, 742.55 $(M+Na)^+$.

Example 84

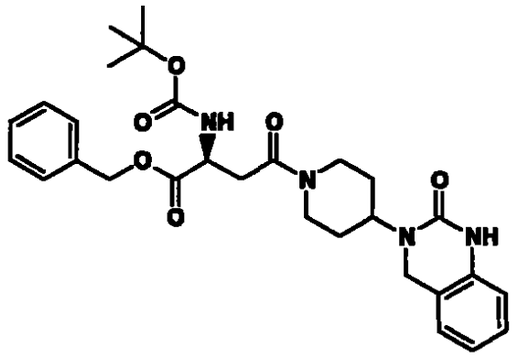
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-N-prop-2-ynyl-butyramide



*LC/MS*: $t_R$=1.33 min, 535.32 $(M+Na)^+$.

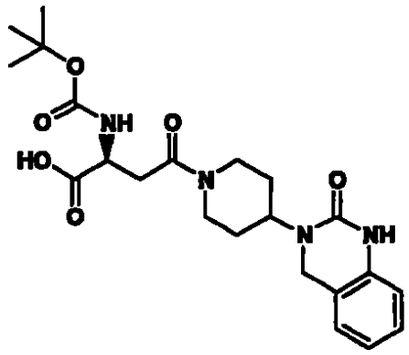
Aspartate Intermediates and Examples

(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 $(M+Na)^+$.

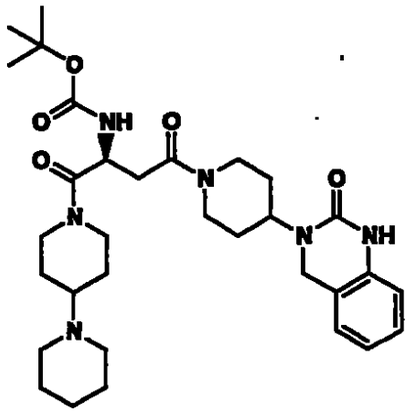
(L)-2-*tert*-Butoxycarbonylamino-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid



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

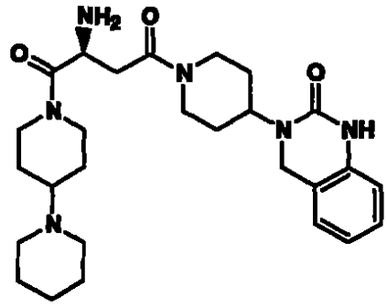
(L)-{1-([1,4']Bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-carbamic acid *tert*-butyl ester



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 $(MH)^+$.

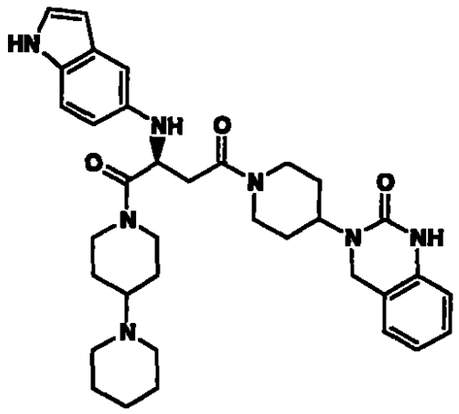
(L)-2-Amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione




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

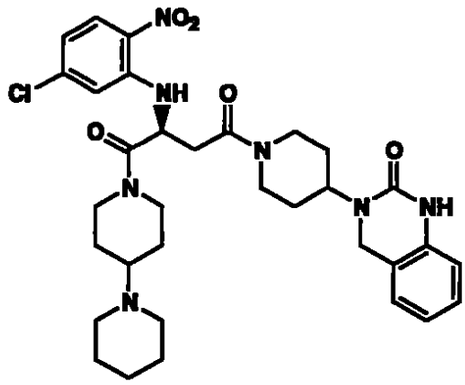
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(1H-indol-5-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



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

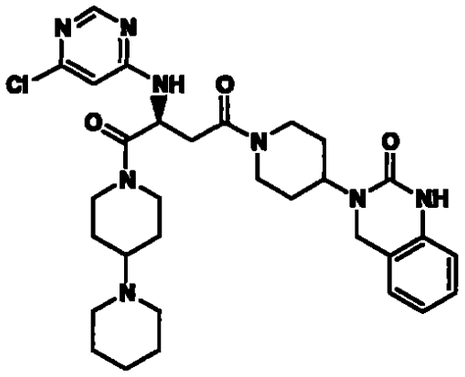
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(5-chloro-2-nitro-phenylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



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



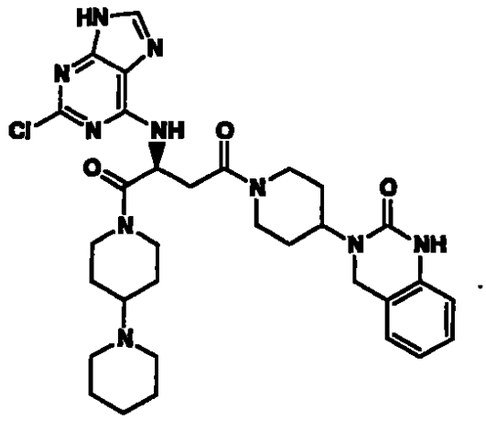
A mixture of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (22.3 mg, 0.045 mmol) and 4, 6-dichloropyrimidine (16 mg, 0.095 mmol) in 2-propanol (0.5 mL) in a microwavable vial was heated at 130°C under microwave irradiation for 40 min. 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

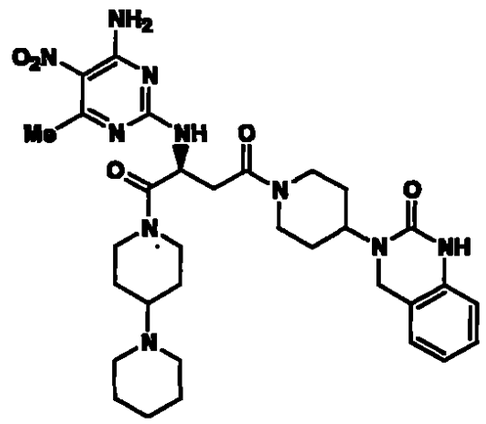
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-chloro-9H-purin-6-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: $t_R$ = 1.10 min, 649 $(MH)^+$.

Example 90

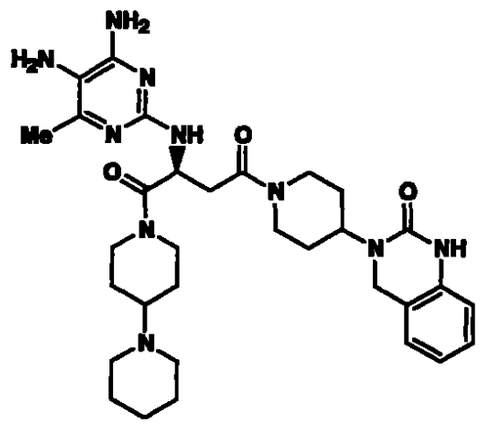
(L)-2-(4-Amino-6-methyl-5-nitro-pyrimidin-2-ylamino)-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: $t_R$ = 1.12 min, 649 $(MH)^+$.

Example 91

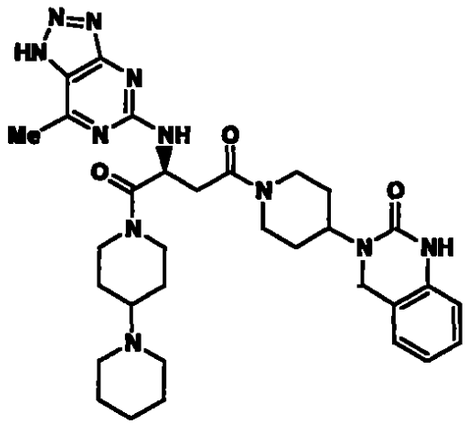
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(4,5-diamino-6-methyl-pyrimidin-2-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



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



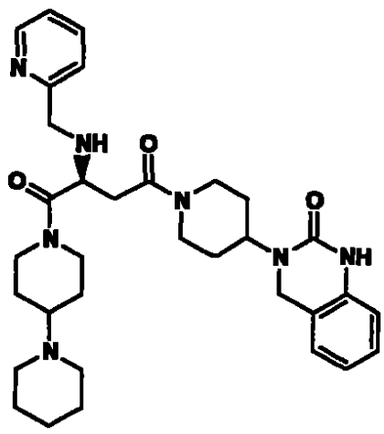
To a stirred solution of 1-[1,4']bipiperidinyl-1'-yl-2-(4,5-diamino-6-methyl-pyrimidin-2-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (10.6 mg, 0.0125 mmol) in acetic acid (1.5 mL) was added sodium nitrite (24 mg) followed by a few drops of water. The resulting light yellow solution 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

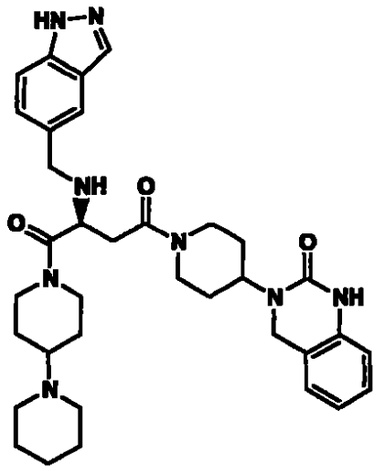
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-((2'-pyridyl)-methyl-amino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: $t_R$ = 0.87 min, 588 $(MH)^+$.

Example 94

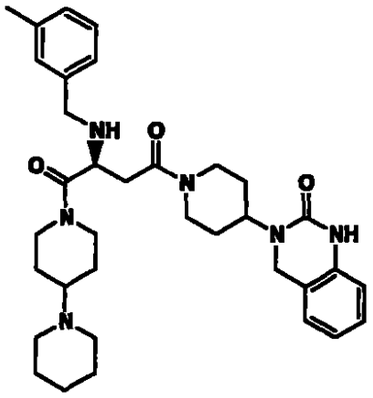
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-((5'-indazolyl)-methyl-amino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: $t_R$ = 0.92 min, 626 $(MH)^+$.

Example 95

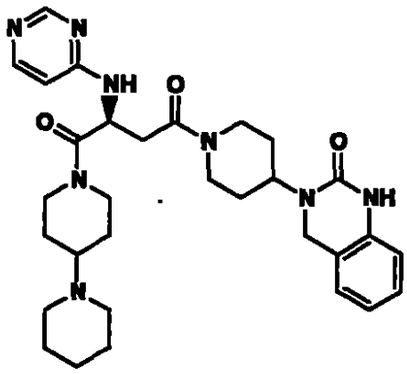
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-((3'-methyl-phenyll)-methyl-amino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: $t_R$ = 1.08 min, 600 $(MH)^+$.

Example 96

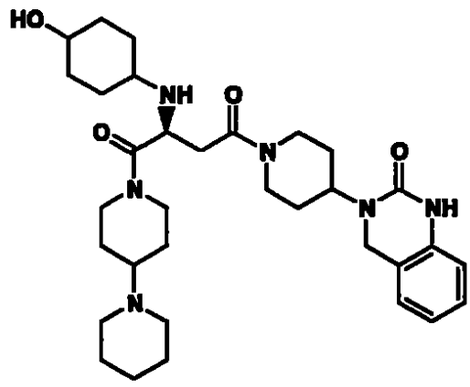
(L)-1-[1,4']Bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-2-(pyrimidin-4-ylamino)-butane-1,4-dione



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

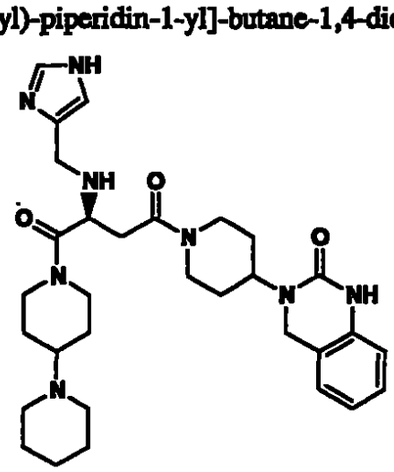
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(4-hydroxy-cyclohexylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



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

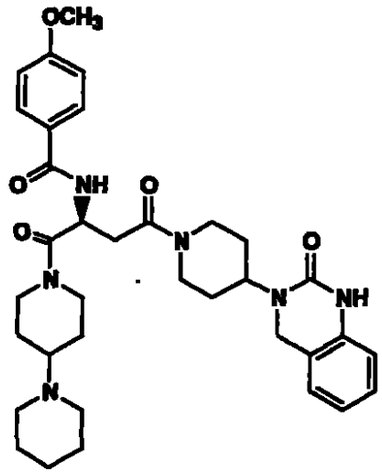
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-[(1H-imidazol-4-ylmethyl)-amino]-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



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

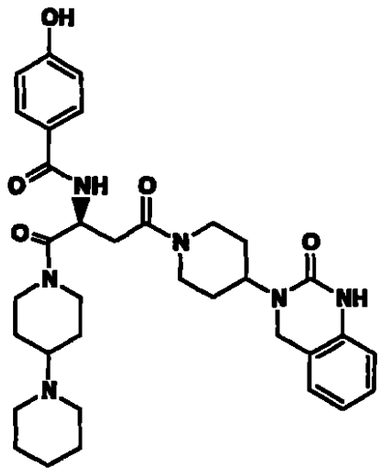



To a stirred mixture of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (91.5 mg, 0.184 mmol) and *p*-anisoyl chloride (34.6 mg, 0.203 mmol) in methylene chloride was

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

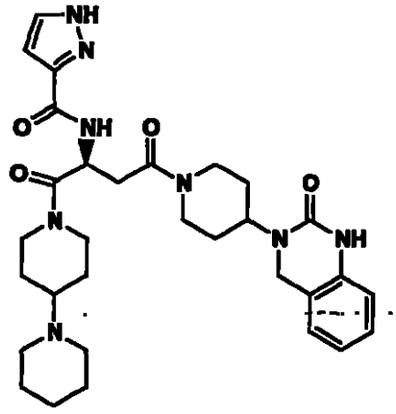



A stirred solution of *N*-{1-([1,4']bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-4-methoxy-benzamide solution in methylene chloride (69 mg) was treated with boron tribromide (1M in methylene chloride, 0.6 mL), dropwise at room temperature. The resulting 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 $(MH)^+$.

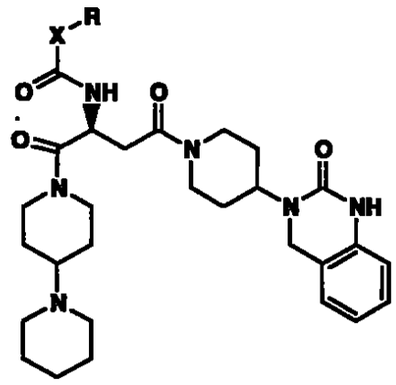
Example 101

(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) 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 $(MH)^+$.

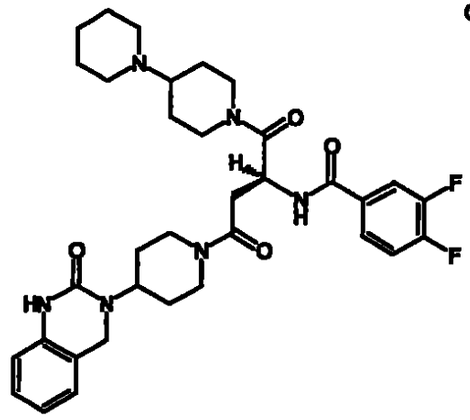
General procedure for the synthesis of Examples 102-134:

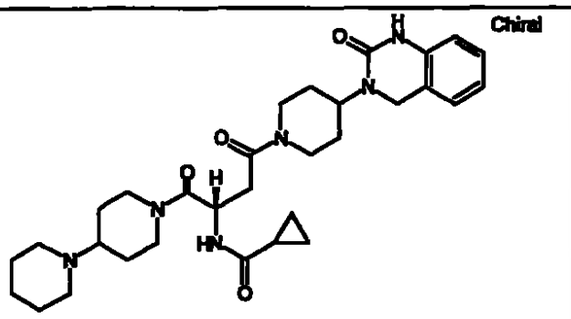
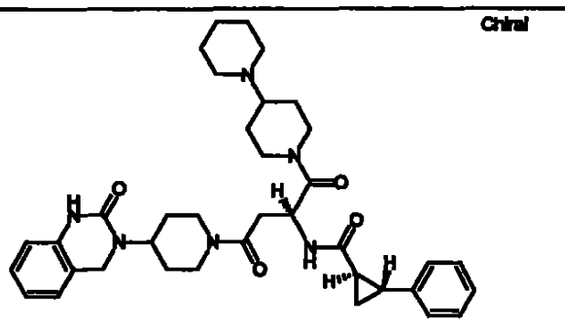
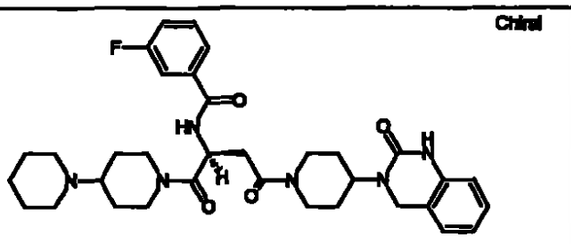
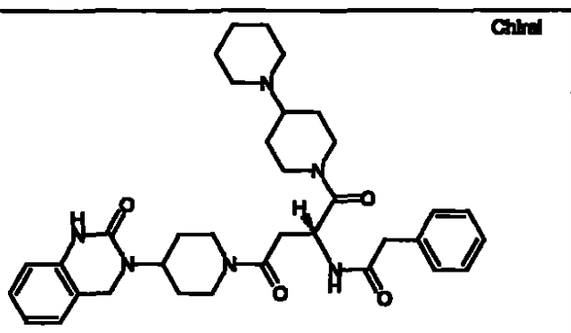


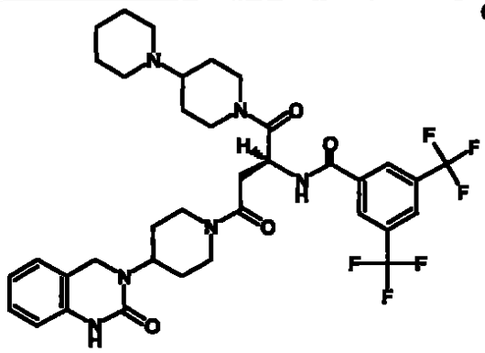
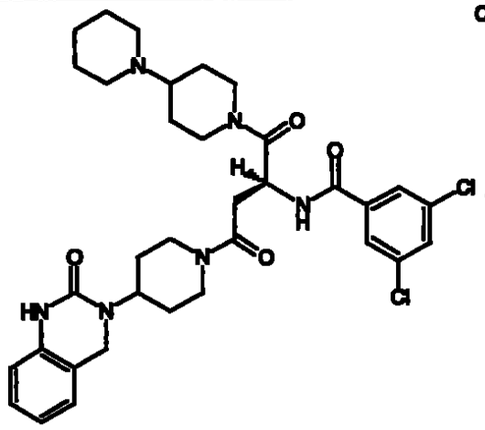
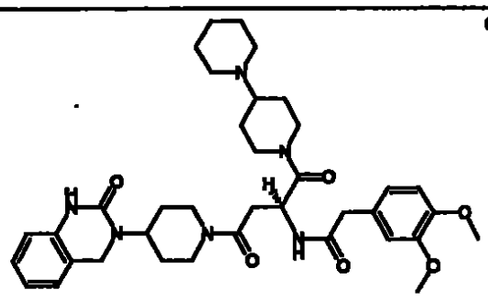
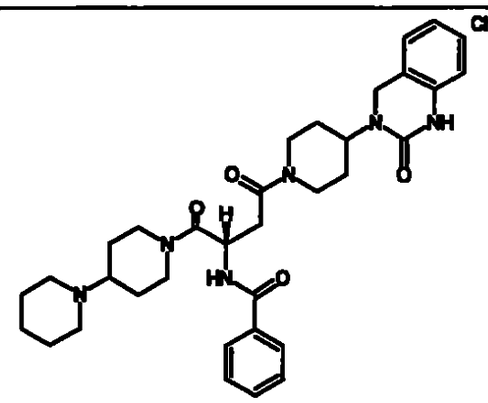
X = C, O

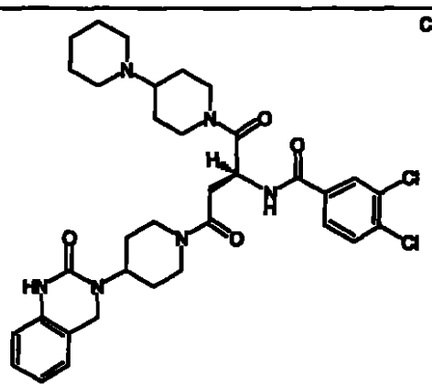
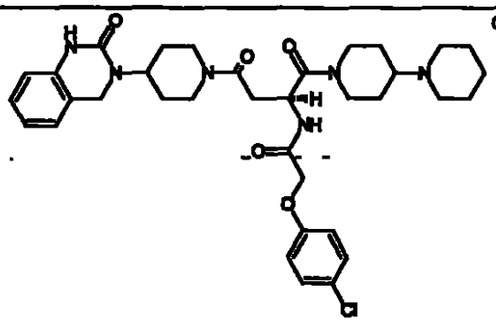
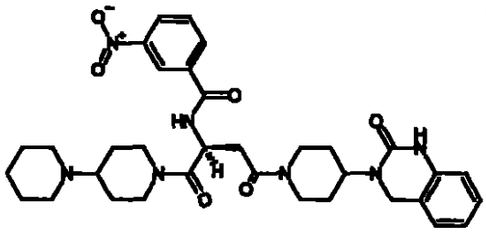
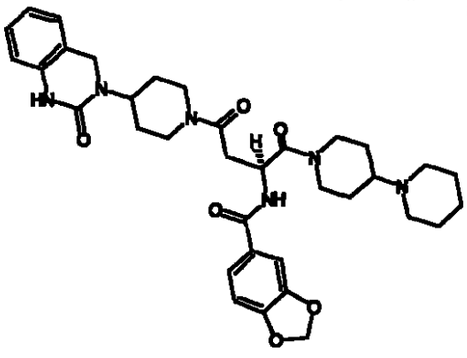
The starting amine, 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione, was dispersed in a 96-well mini-reactor (ca. 10 mg each) in 1 mL dichloroethane. Individual acyl chlorides (ca. 2 equiv.) were added followed by a resin-bound solid-phase 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.

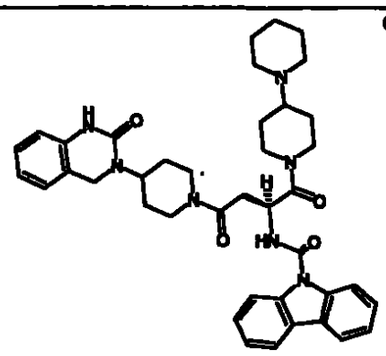
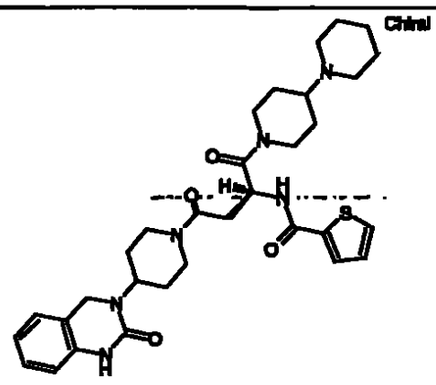
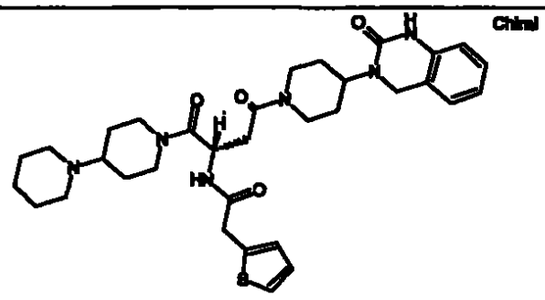
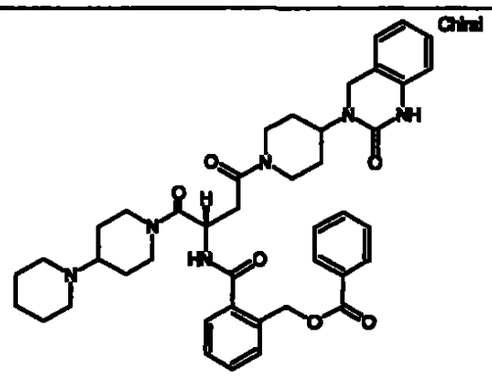
Table 2. Amides and Carbamates

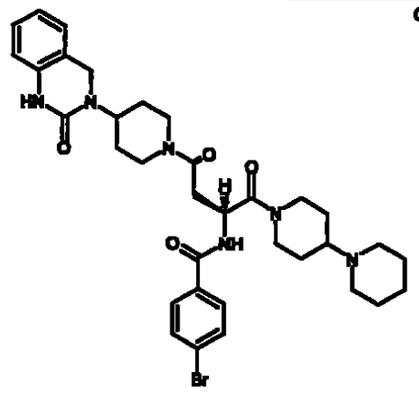
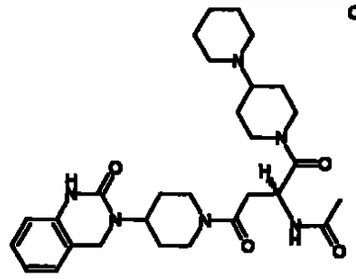
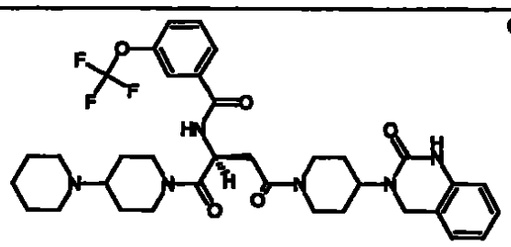
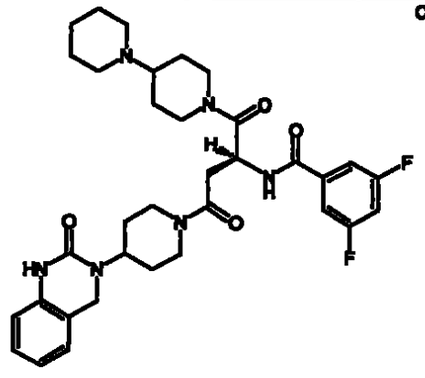
| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 102 |  Chiral | 1.84 | 637.38 |

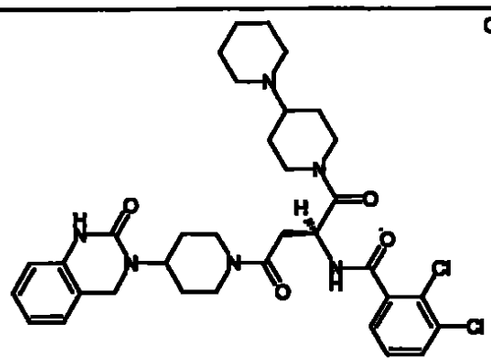
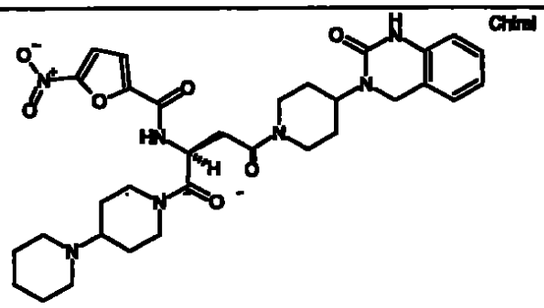
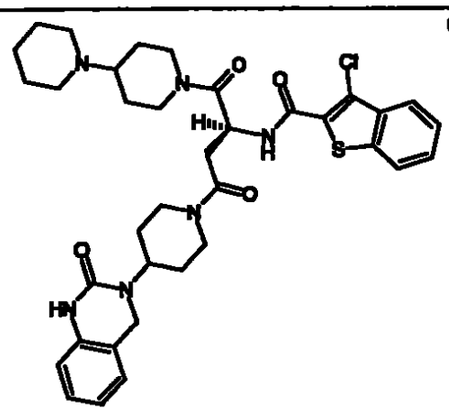
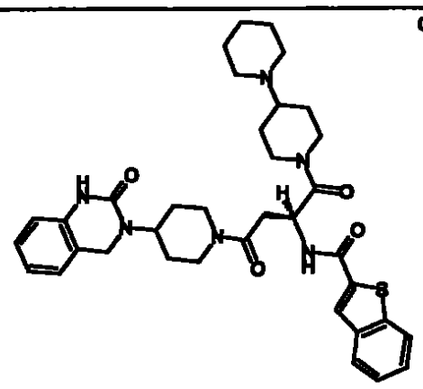
| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 103 |  Chiral | 1.39 | 565.45 |
| 104 |  Chiral | 1.89 | 641.46 |
| 105 |  Chiral | 1.73 | 619.42 |
| 106 |  Chiral | 1.62 | 615.41 |

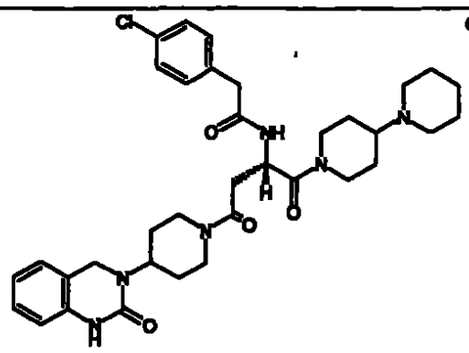
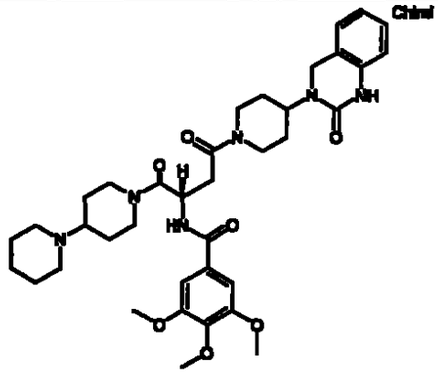
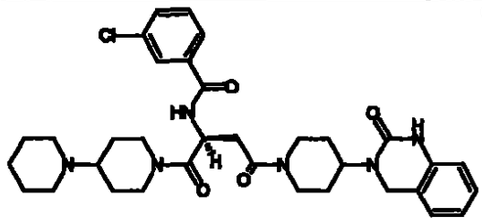
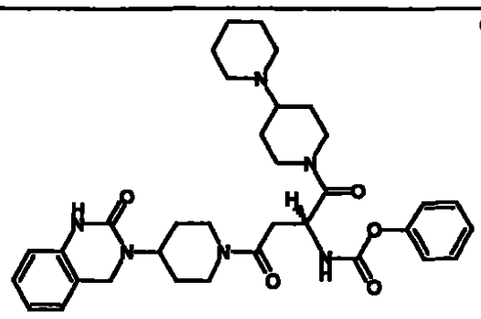
| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 107 |  | 2.25 | 737.37 |
| 108 |  | 2.12 | 669.3 |
| 109 |  | 1.59 | 675.46 |
| 110 |  | 1.62 | 601.43 |

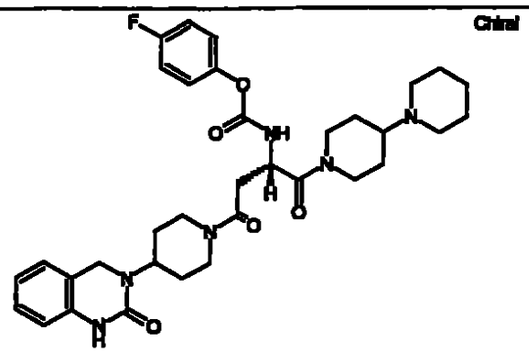
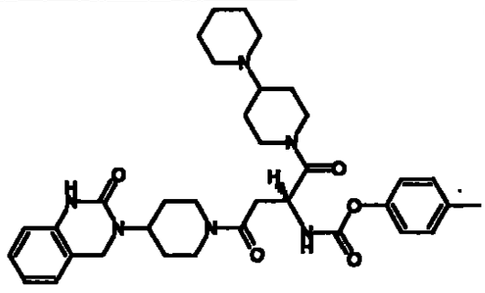
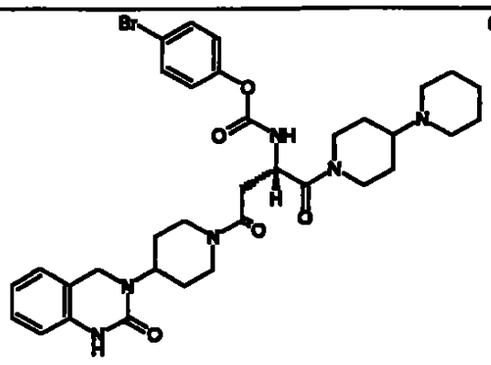
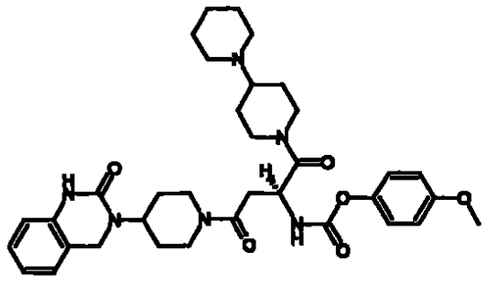
| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 111 |  Chiral | 2.09 | 669.33 |
| 112 |  Chiral | 1.91 | 665.36 |
| 113 |  Chiral | 1.68 | 646.37 |
| 114 |  Chiral | 1.66 | 645.4 |

| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 115 |  | 2.14 | 690.45 |
| 116 |  | 1.59 | 607.39 |
| 117 |  | 1.59 | 621.4 |
| 118 |  | 2.01 | 735.43 |

| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 119 |  | 1.92 | 679.32 |
| 120 |  | 1.22 | 537.4 |
| 121 |  | 2.03 | 685.4 |
| 122 |  | 1.79 | 637.38 |

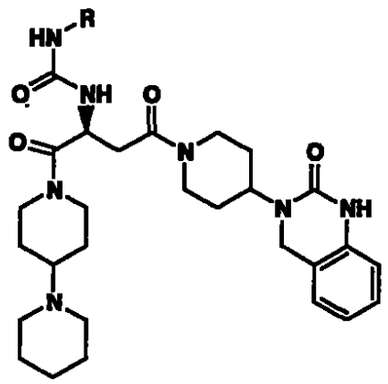
| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 123 |  Chiral | 1.84 | 669.3 |
| 124 |  Chiral | 1.53 | 636.35 |
| 125 |  Chiral | 2.04 | 691.35 |
| 126 |  Chiral | 1.89 | 657.35 |

| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 127 |  | 1.86 | 649.39 |
| 128 |  | 1.67 | 691.42 |
| 129 |  | 1.84 | 635.38 |
| 130 |  | 1.69 | 617.42 |

| Example | Structure | HPLC $t_R$ (min) | MS (M+) |
|---|---|---|---|
| 131 |  | 1.74 | 635.38 |
| 132 |  | 1.84 | 631.44 |
| 133 |  | 1.94 | 695.28 |
| 134 |  | 1.7 | 647.41 |

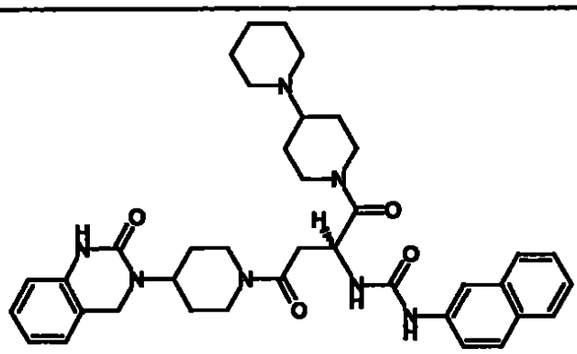
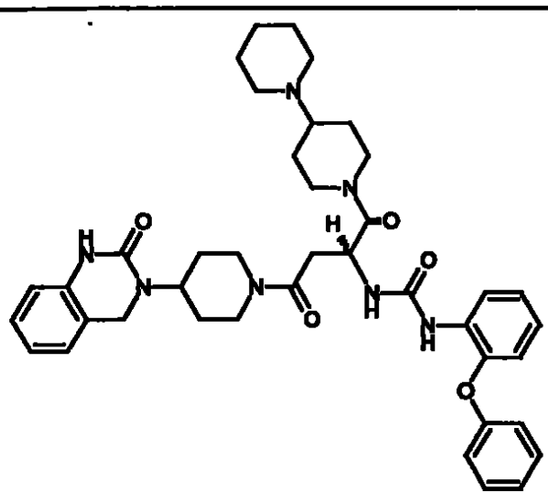
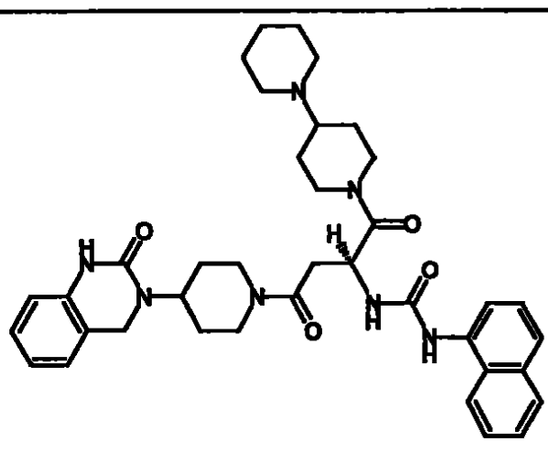
113

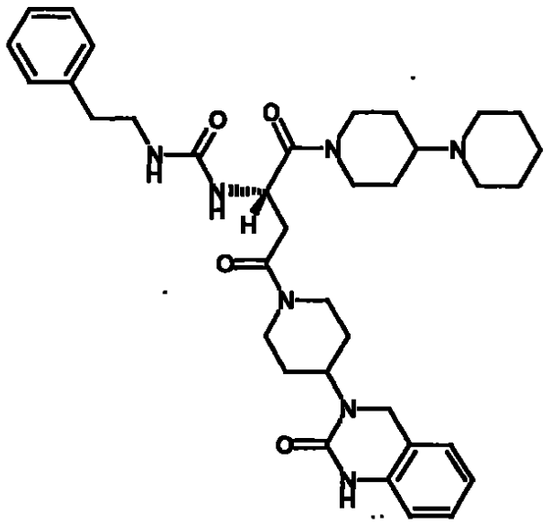
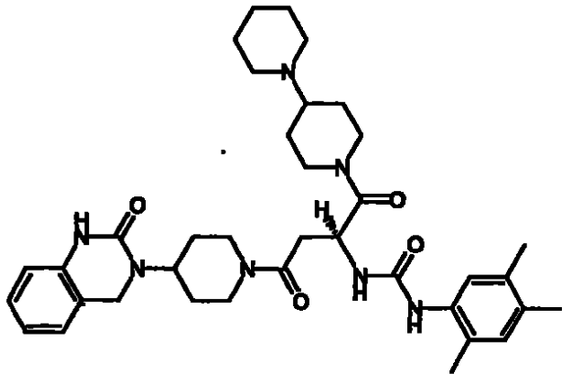
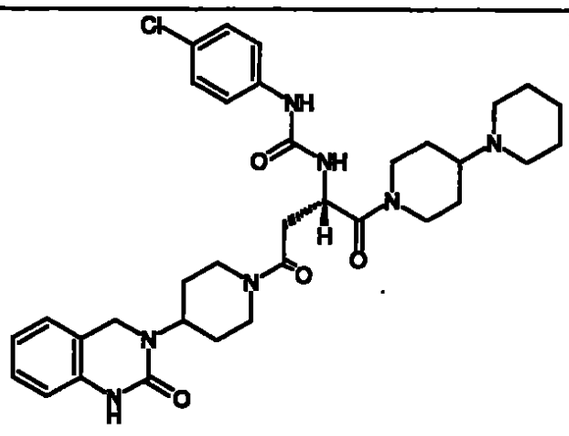
General procedure for the synthesis of Examples 135-200:

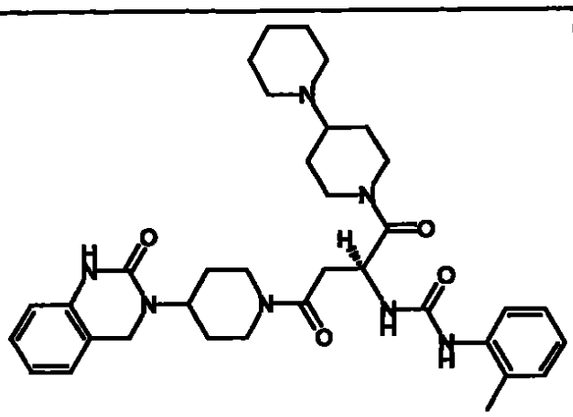
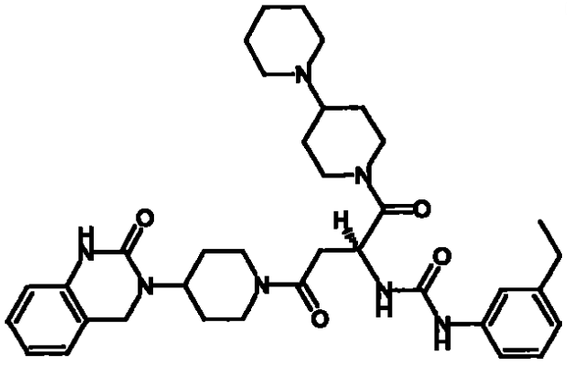
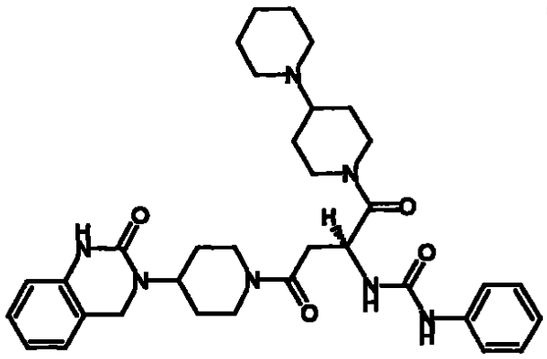
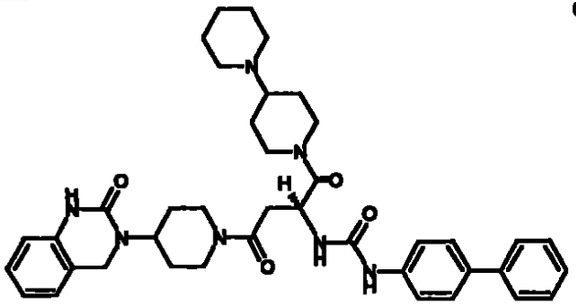


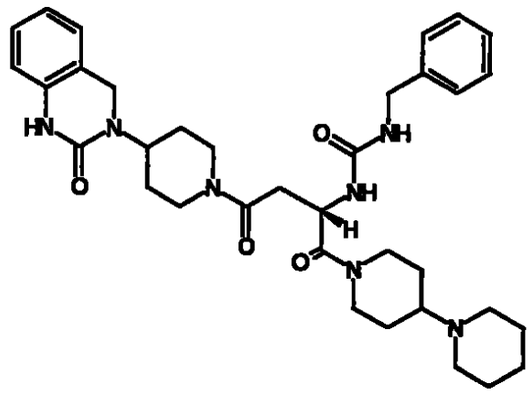
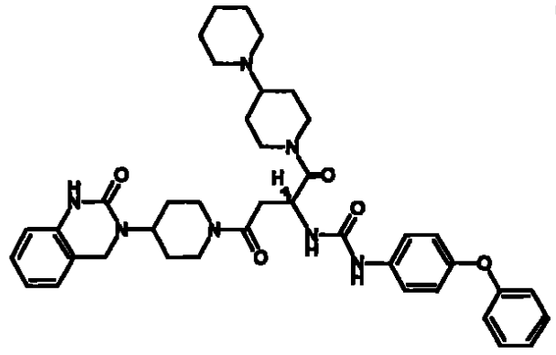
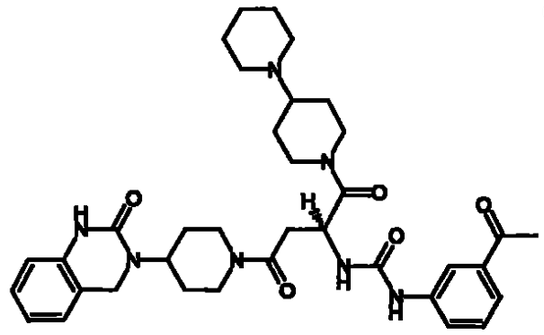
The starting amine, 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione, was dispersed in a 96-well mini-reactor (ca. 10 mg in each well) in dichloroethane (1 mL). Individual isocyanates (ca. 2 equiv) were added to individual wells. The block 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.

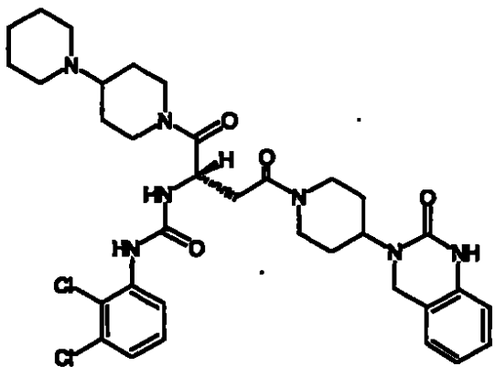
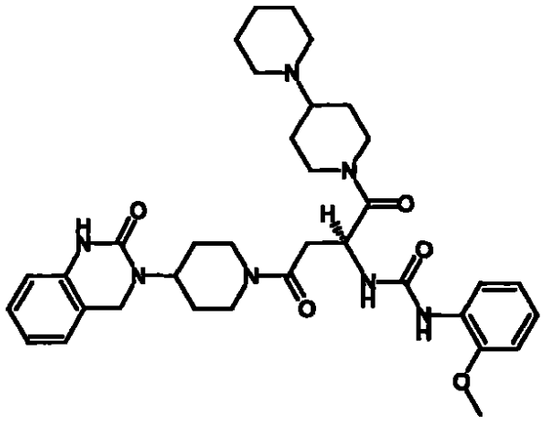
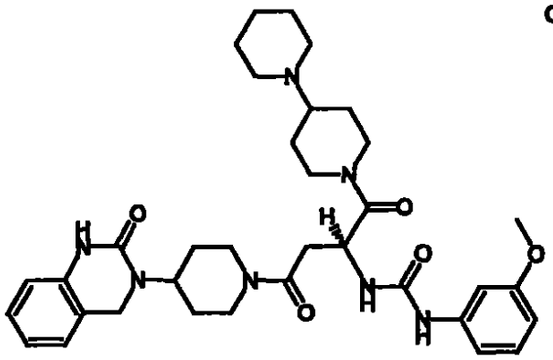
Table 3. Ureas

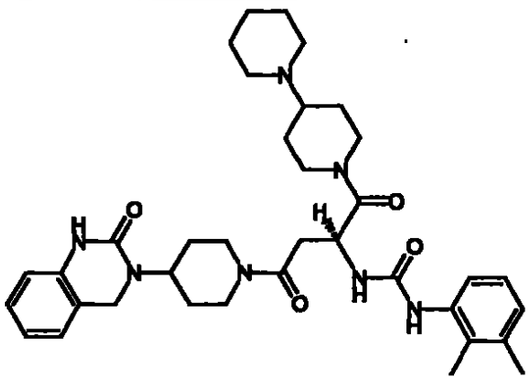
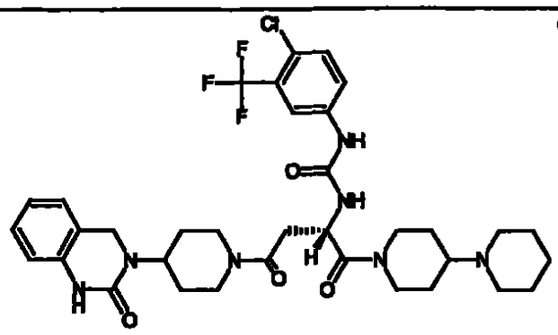
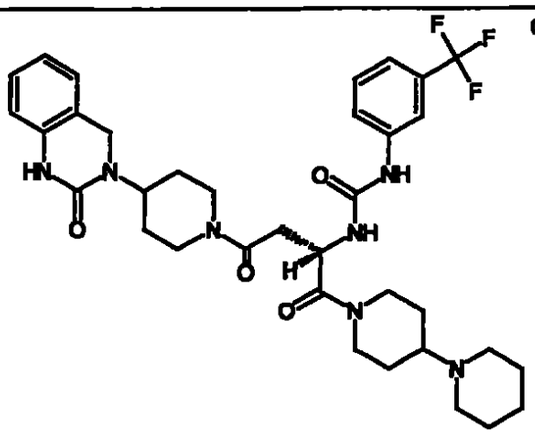
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 135 | Chiral  | 1.43 | 665.84 |
| 136 | Chiral  | 1.56 | 707.88 |
| 137 | Chiral  | 1.39 | 665.84 |

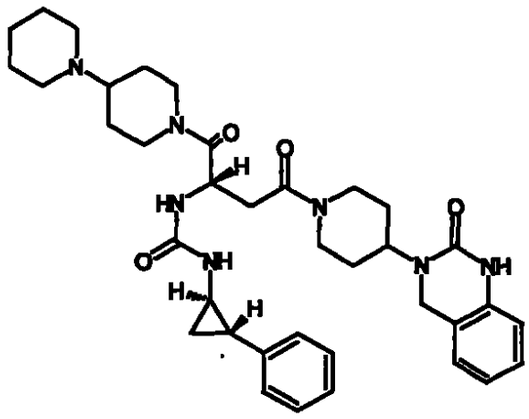
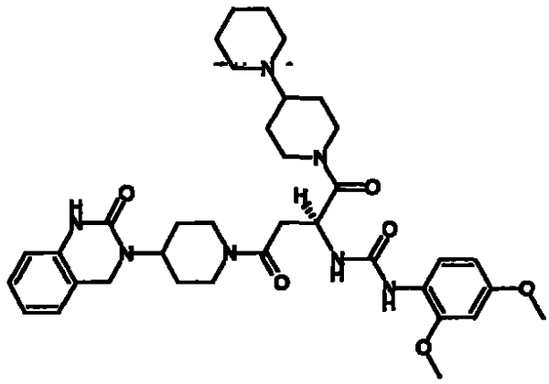
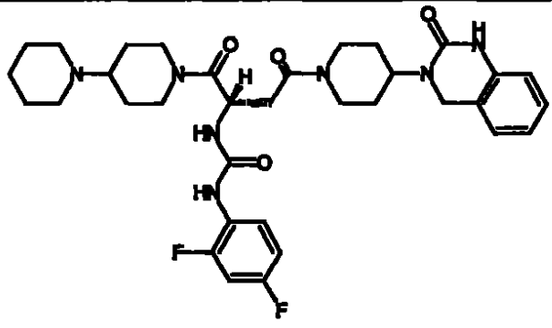
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 138 | Chiral  | 1.3 | 643.83 |
| 139 | Chiral  | 1.44 | 657.86 |
| 140 | Chiral  | 1.42 | 650.22 |

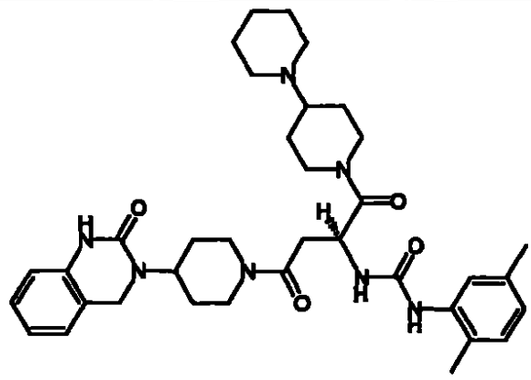
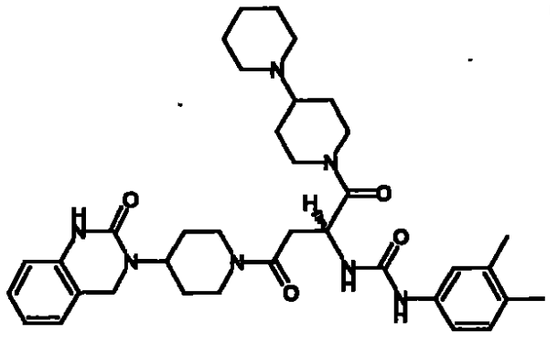
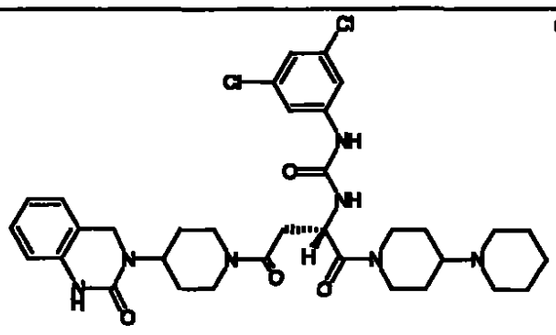
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 141 | Chiral  | 1.26 | 629.81 |
| 142 | Chiral  | 1.41 | 643.83 |
| 143 | Chiral  | 1.24 | 615.78 |
| 144 | Chiral  | 1.53 | 691.88 |

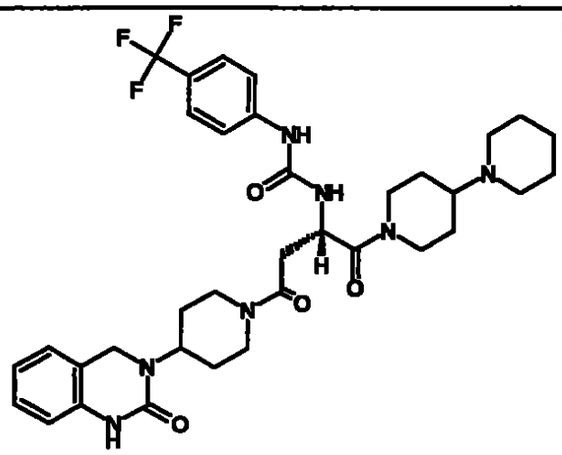
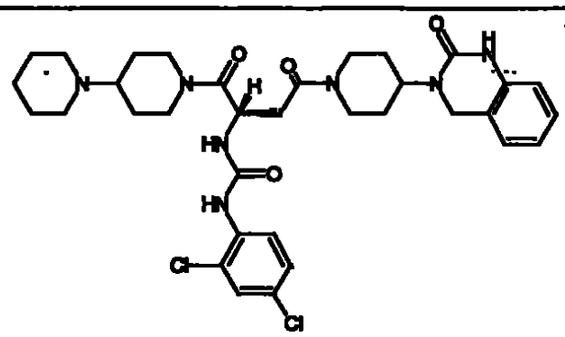
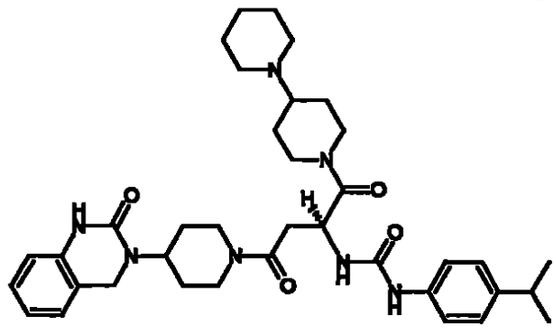
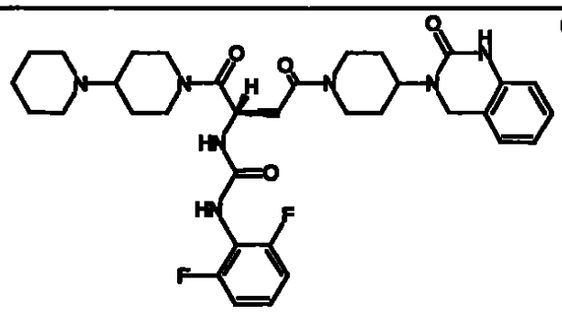
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 145 |  Chiral | 1.21 | 629.81 |
| 146 |  Chiral | 1.52 | 707.88 |
| 147 |  Chiral | 1.19 | 657.82 |

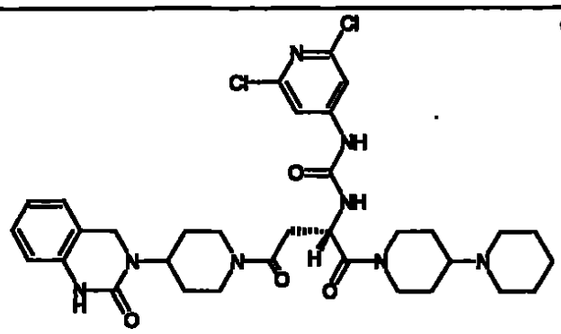
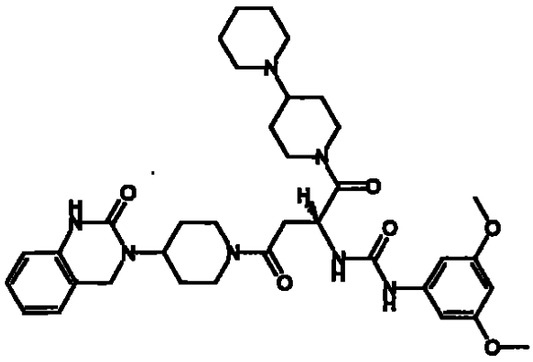
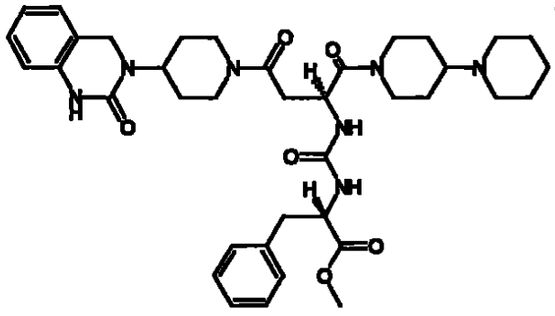
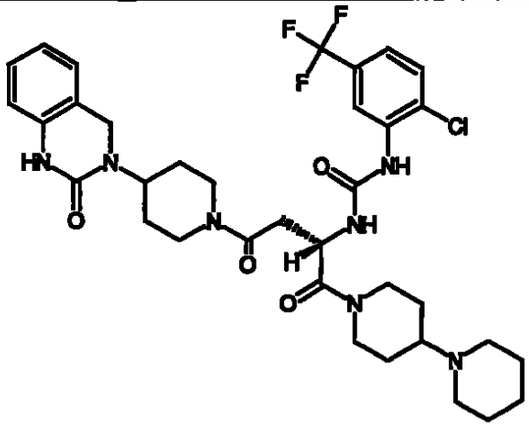
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 148 | Chiral  | 1.44 | 684.67 |
| 149 | Chiral  | 1.3 | 645.81 |
| 150 | Chiral  | 1.24 | 645.81 |

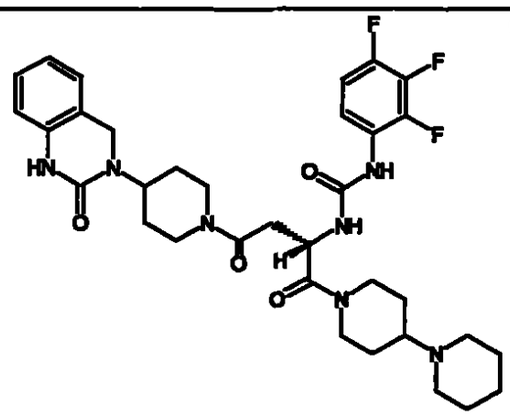
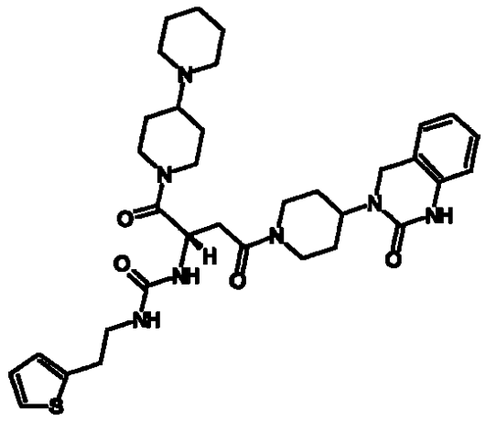
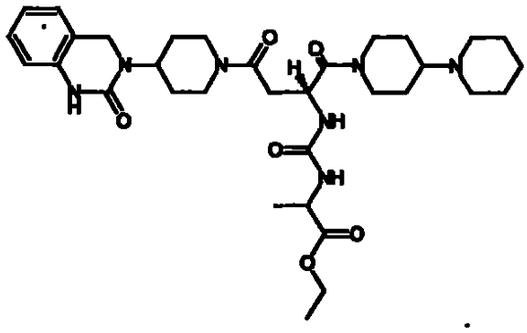
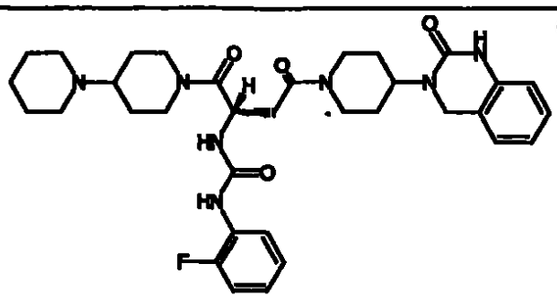
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 151 | Chiral  | 1.33 | 643.83 |
| 152 | Chiral  | 1.56 | 718.22 |
| 153 | Chiral  | 1.55 | 683.78 |

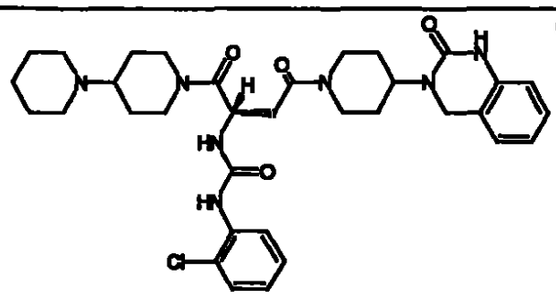
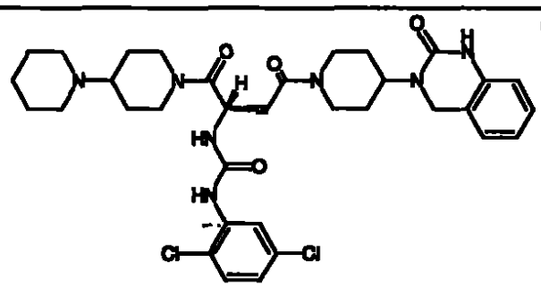
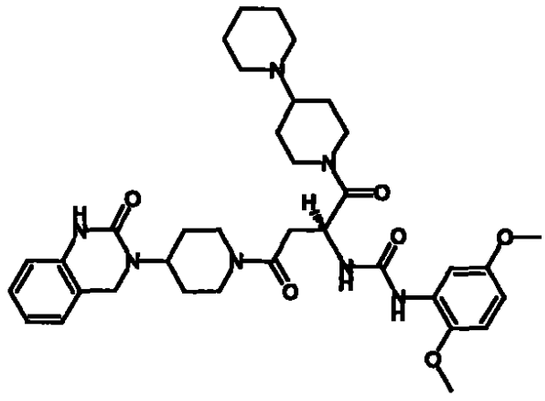
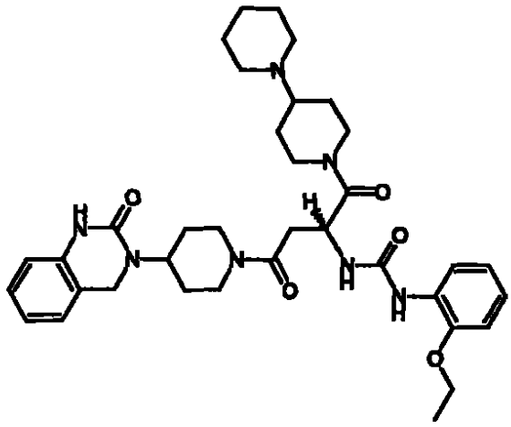
| Example | Structure | HPL C $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 154 | Chiral  | 1.37 | 655.84 |
| 155 | Chiral  | 1.27 | 675.83 |
| 156 | Chiral  | 1.26 | 651.76 |

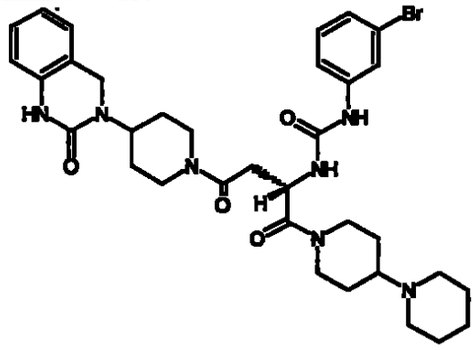
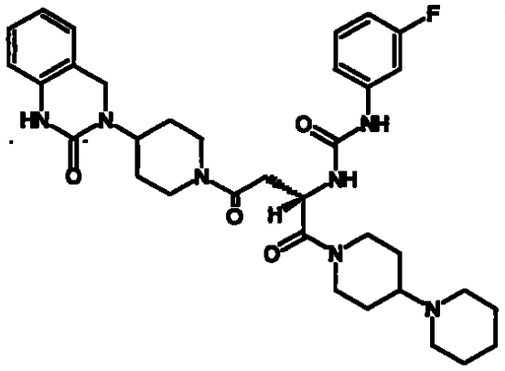
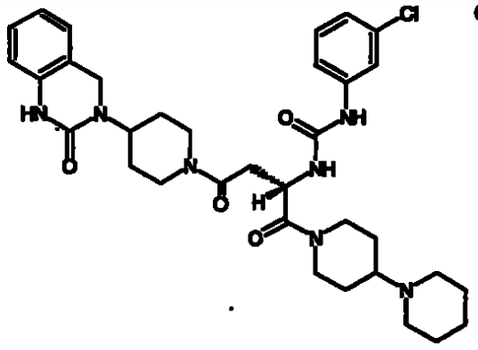
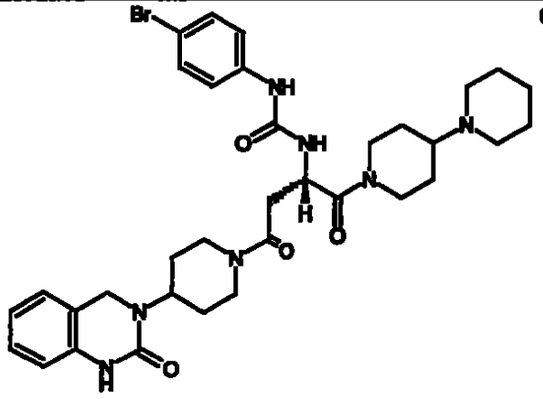
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 157 |  Chiral | 1.39 | 643.83 |
| 158 |  Chiral | 1.43 | 643.83 |
| 159 |  Chiral | 1.57 | 684.67 |

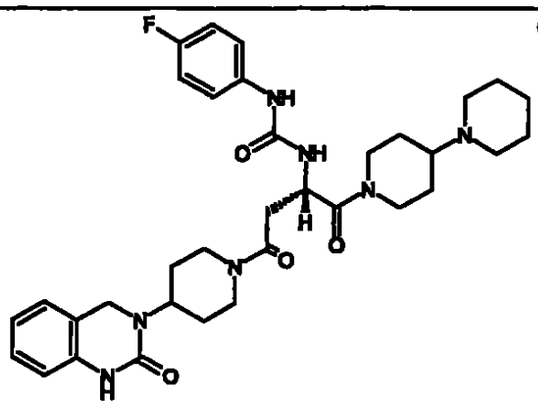
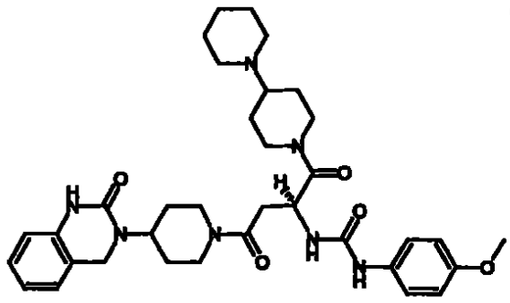
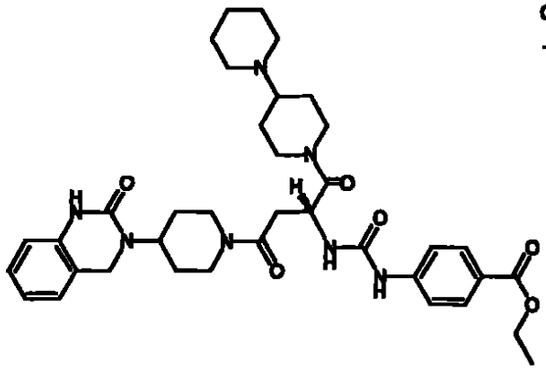
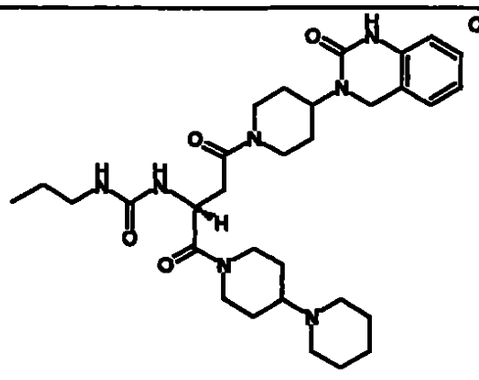
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 160 |  Chiral | 1.46 | 683.78 |
| 161 |  Chiral | 1.48 | 684.67 |
| 162 |  Chiral | 1.5 | 657.86 |
| 163 |  Chiral | 1.14 | 651.76 |

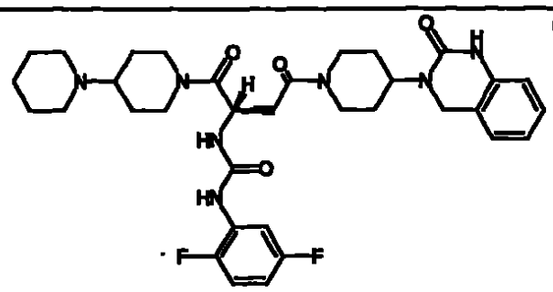
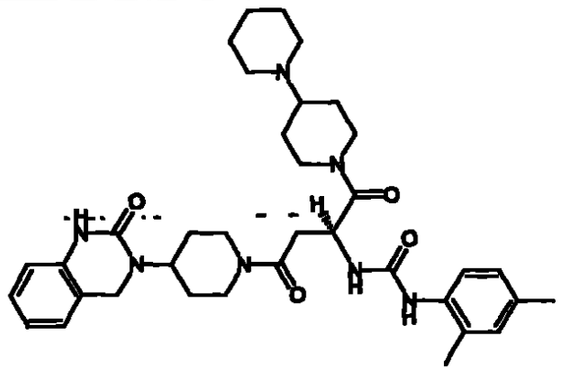
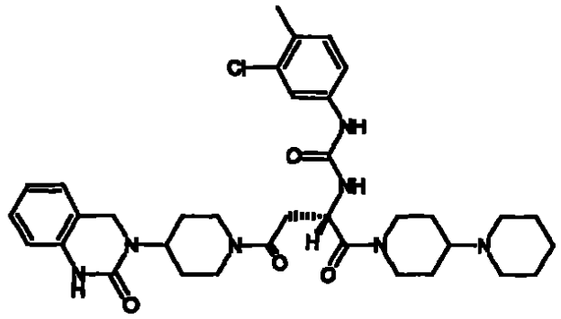
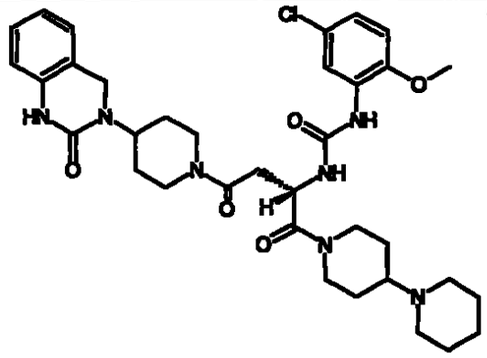
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 164 | Chiral  | 1.34 | 685.66 |
| 165 | Chiral  | 1.26 | 675.83 |
| 166 | Chiral  | 1.28 | 701.87 |
| 167 | Chiral  | 1.52 | 718.22 |

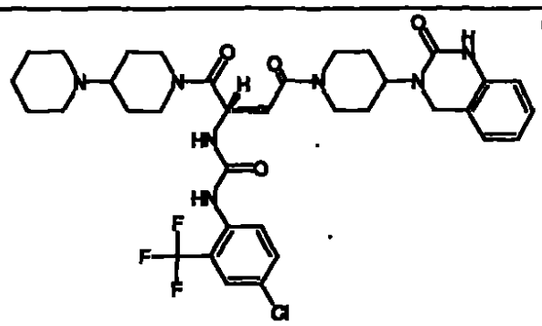
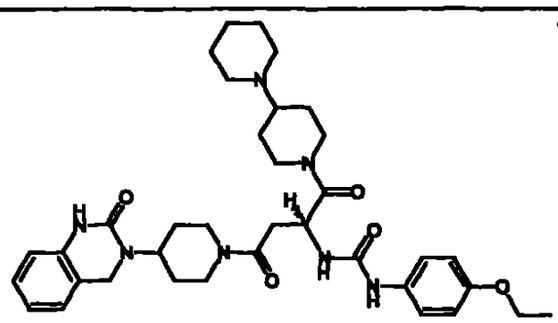
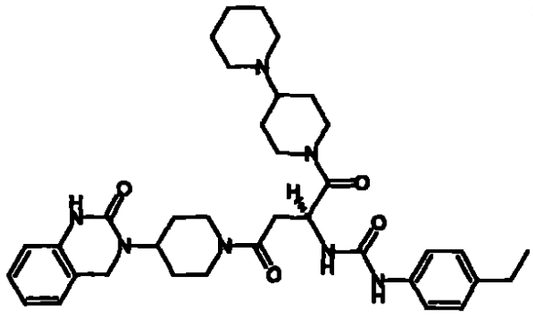
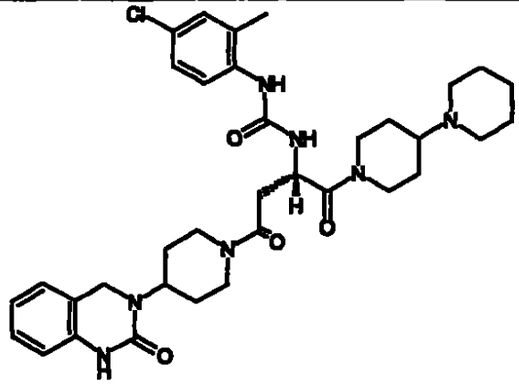
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 168 |  Chiral | 1.35 | 669.75 |
| 169 |  Chiral | 1.24 | 649.86 |
| 170 |  Chiral | 1.11 | 639.8 |
| 171 |  Chiral | 1.31 | 633.77 |

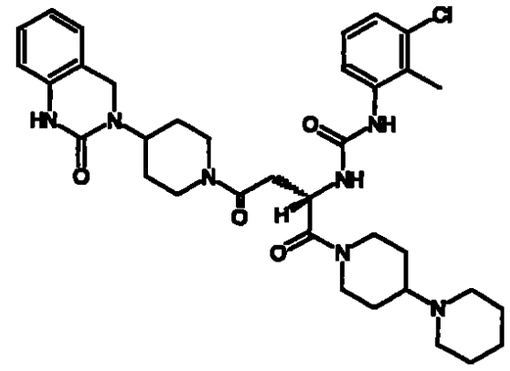
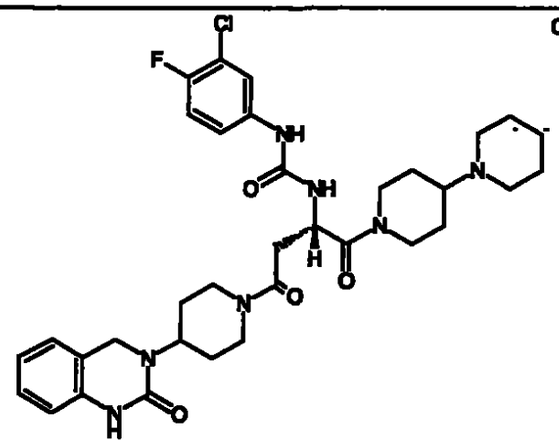
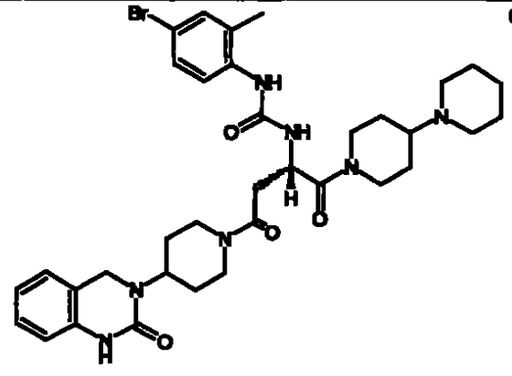
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 172 |  Chiral | 1.34 | 650.22 |
| 173 |  Chiral | 1.47 | 684.67 |
| 174 |  Chiral | 1.27 | 675.83 |
| 175 |  Chiral | 1.34 | 659.83 |

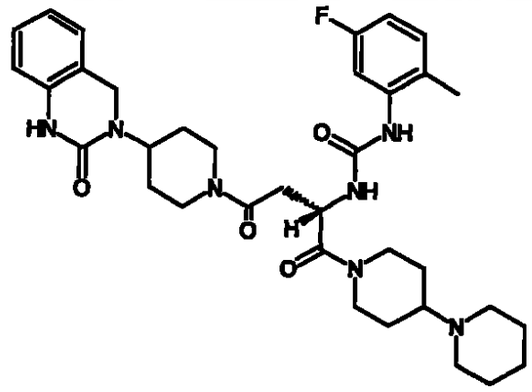
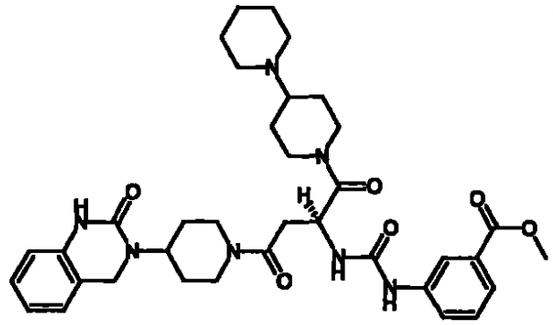
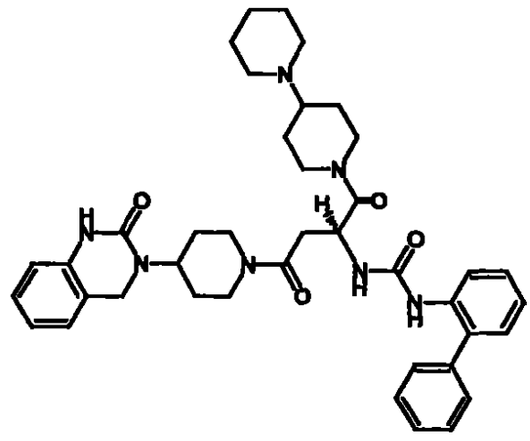
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 176 |  Chiral | 1.41 | 694.68 |
| 177 |  Chiral | 1.28 | 633.77 |
| 178 |  Chiral | 1.39 | 650.22 |
| 179 |  Chiral | 1.42 | 694.68 |

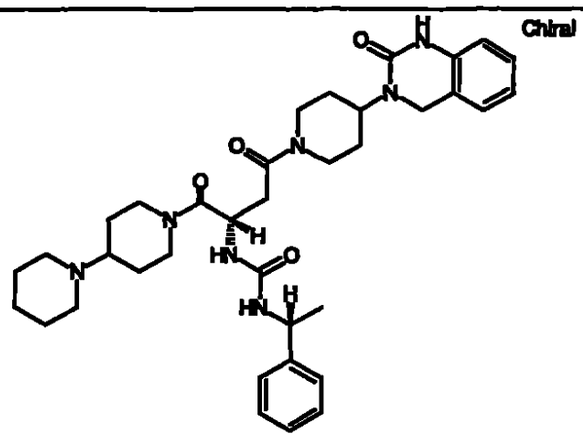
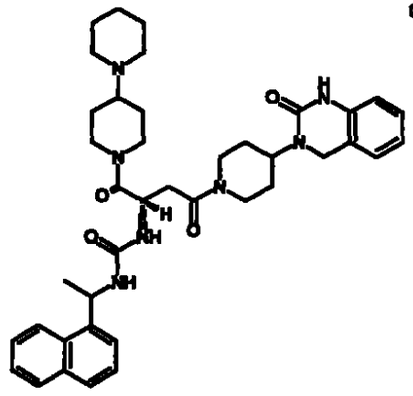
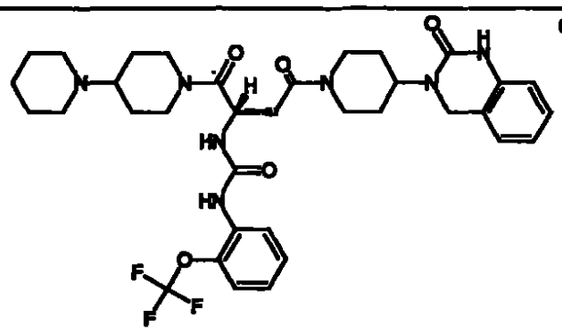
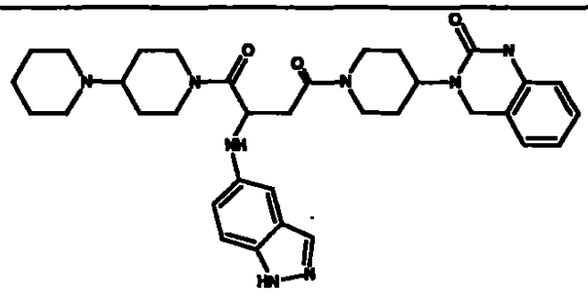
| Example | Structure | HPL C $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 180 |  Chiral | 1.26 | 633.77 |
| 181 |  Chiral | 1.19 | 645.81 |
| 182 |  Chiral | 1.34 | 687.84 |
| 183 |  Chiral | 1.08 | 581.76 |

| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 184 |  Chiral | 1.31 | 651.76 |
| 185 |  Chiral | 1.39 | 643.83 |
| 186 |  Chiral | 1.33 | 664.25 |
| 187 |  Chiral | 1.41 | 680.25 |

| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 188 |  Chiral | 1.48 | 718.22 |
| 189 |  Chiral | 1.28 | 659.83 |
| 190 |  Chiral | 1.41 | 643.83 |
| 191 |  Chiral | 1.41 | 664.25 |

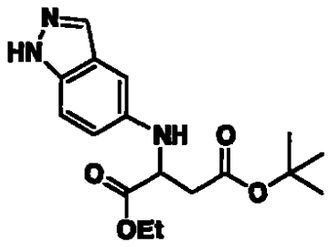
| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 192 |  Chiral | 1.41 | 664.25 |
| 193 |  Chiral | 1.41 | 668.21 |
| 194 |  Chiral | 1.45 | 708.71 |

| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 195 |  Chiral | 1.39 | 647.8 |
| 196 |  Chiral | 1.27 | 673.82 |
| 197 |  Chiral | 1.45 | 691.88 |

| Example | Structure | HPLC $t_R$ (min) | MS $(MH)^+$ |
|---|---|---|---|
| 198 |  Chiral | 1.26 | 643.83 |
| 199 |  Chiral | 1.45 | 693.89 |
| 200 |  Chiral | 1.4 | 699.78 |
| 201 |  | 0.917 | 613.54 |

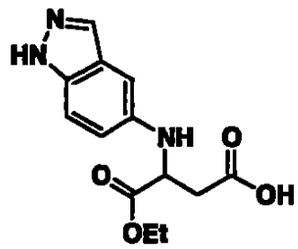
123

2-(1H-Indazol-5-ylamino)-succinic acid 4-*tert*-butyl ester 1-ethyl ester



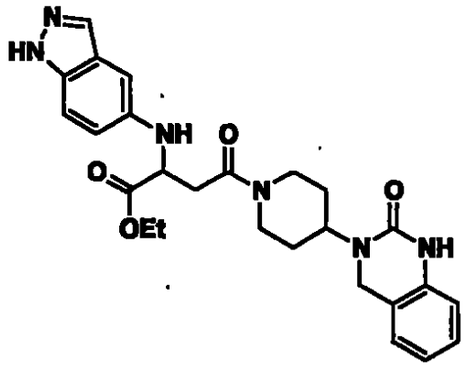
To a solution/suspension of 5-aminoindazole (1.01 g, 7.6 mmol) in tetrahydrofuran (20 mL) was added ethyl glyoxlate solution (ca. 50% in toluene, 1.7 mL, 1.1 equiv) in one portion followed by magnesium sulfate (4.6 g). The mixture was stirred at room temperature overnight (23 h) and then filtered and 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 $(MH)^+$.

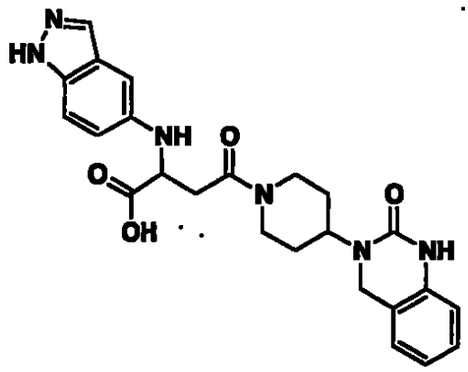
2-(1H-Indazol-5-ylamino)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid ethyl ester



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 $(MH)^+$.

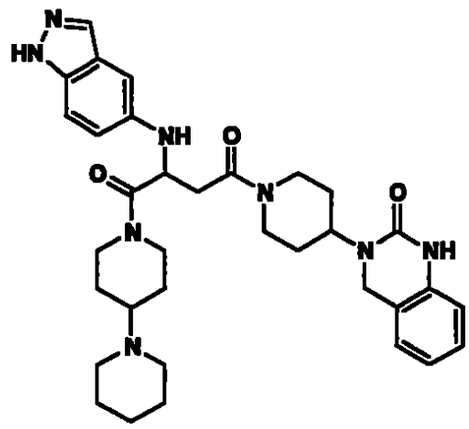
2-(1H-Indazol-5-ylamino)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid



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

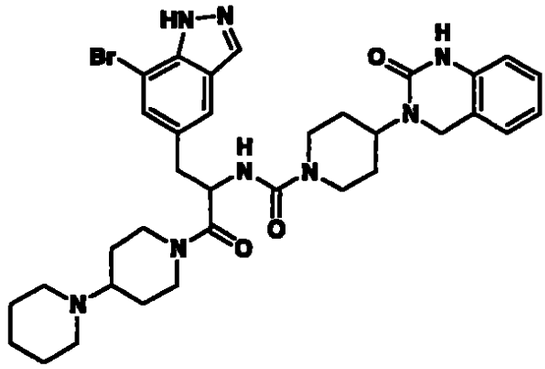
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(1H-indazol-5-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



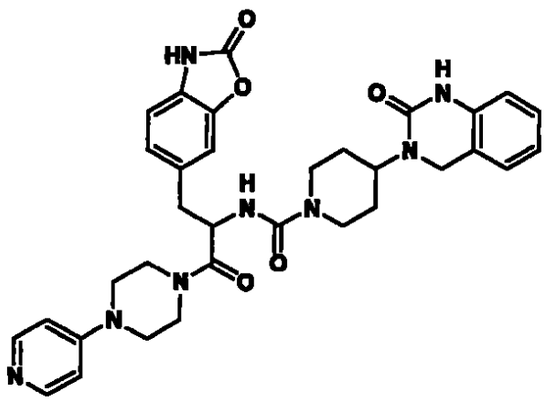
To a solution of 2-(1H-indazol-5-ylamino)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid ethyl ester (0.069 mmol) in dimethylformamide (0.5 mL) in a capped drum vial was added piperidinylpiperidine (14.3 mg, 0.076 mmol, 1.1 equiv), DEPBT (22.8 mg, 1.1 equiv) and triethylamine (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 $(MH)^+$.

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:

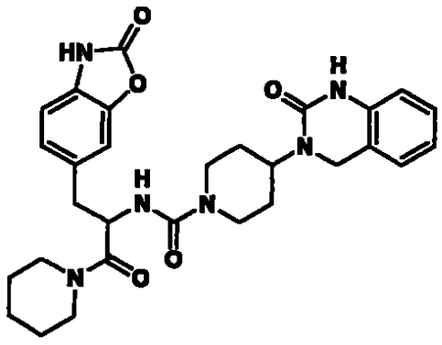
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-bromo-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



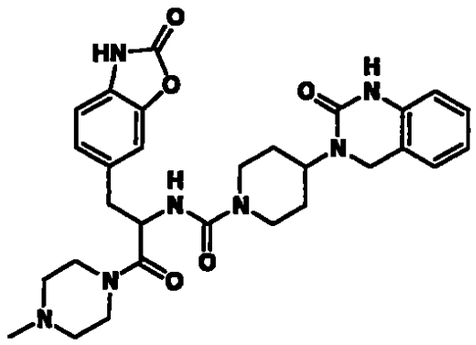
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



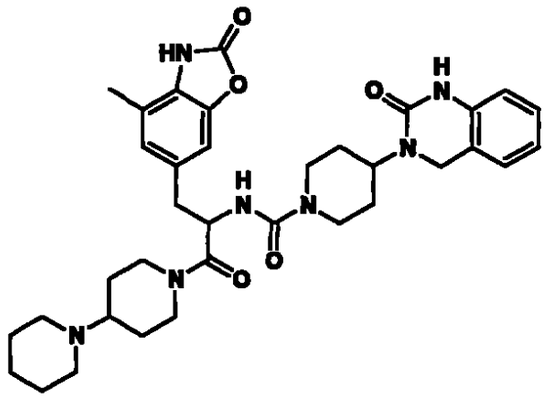
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-piperidin-1-yl-ethyl]-amide



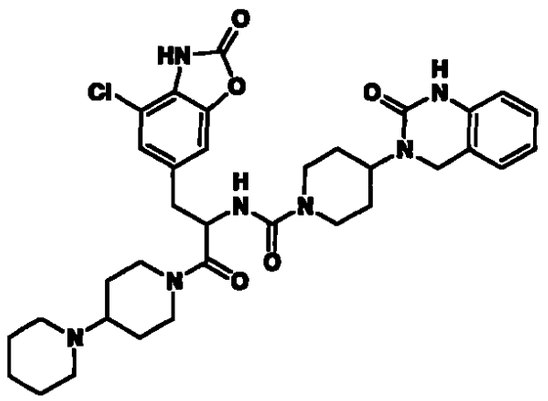
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide



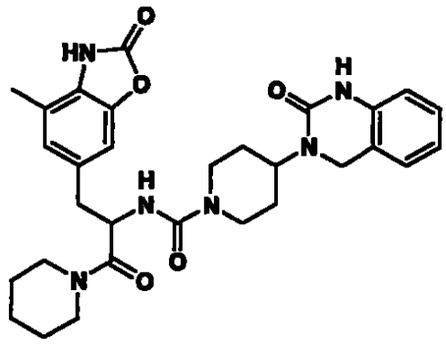
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



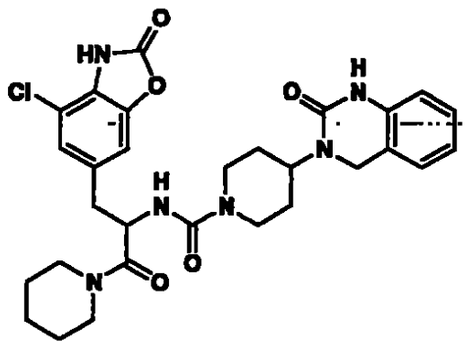
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



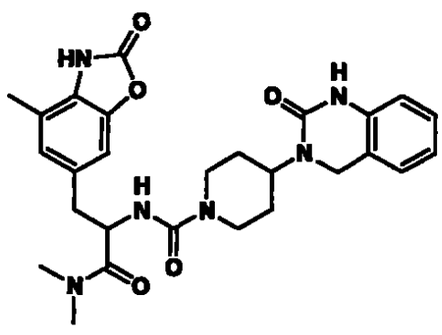
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide



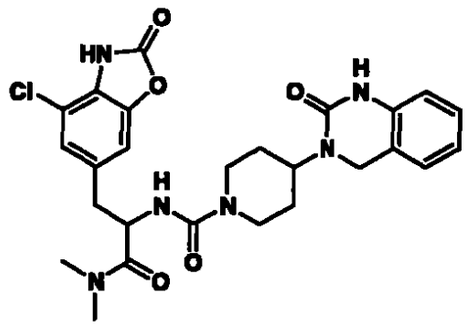
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide



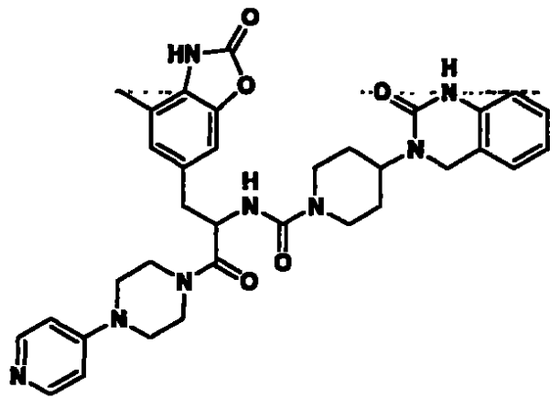
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-dimethylcarbamoyl-2-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl]-amide



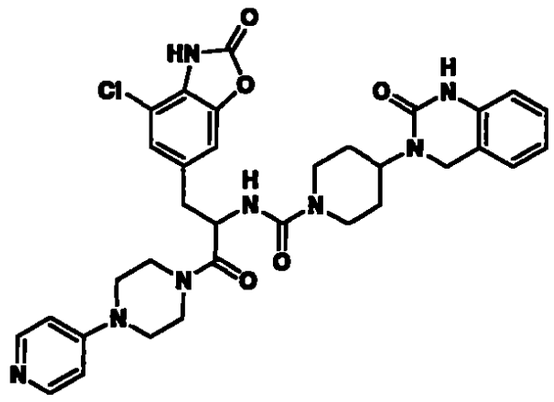
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-1-dimethylcarbamoyl-ethyl]-amide



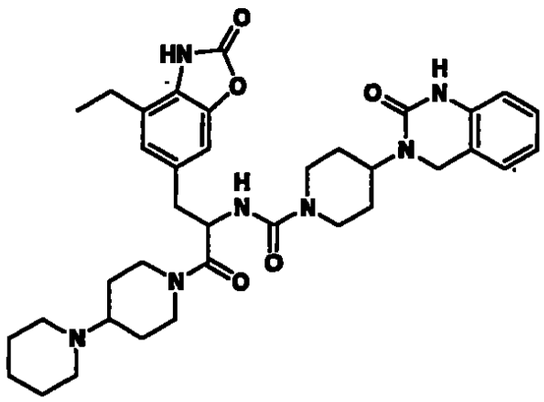
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



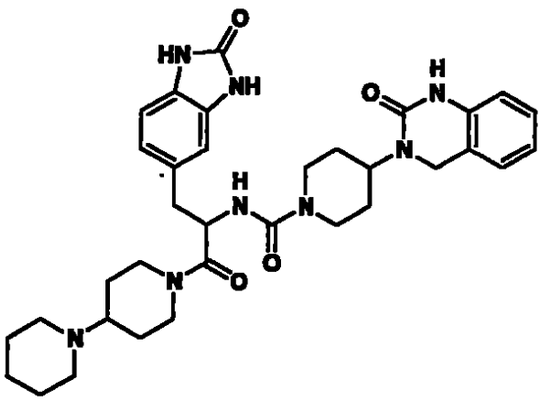
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



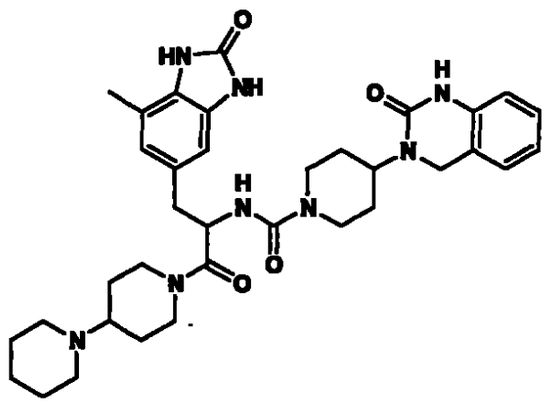
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-ethyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



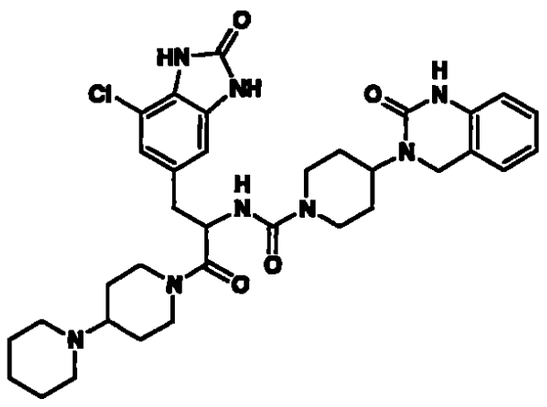
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-(2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-ethyl]-amide



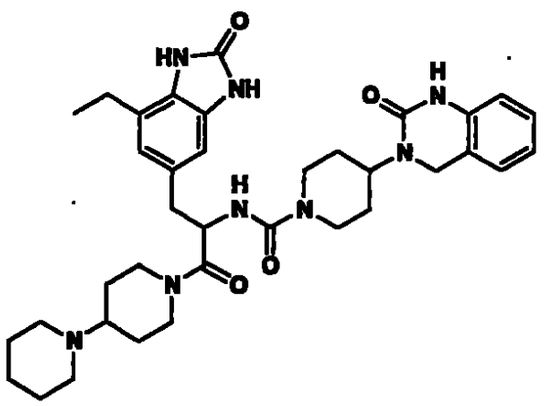
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



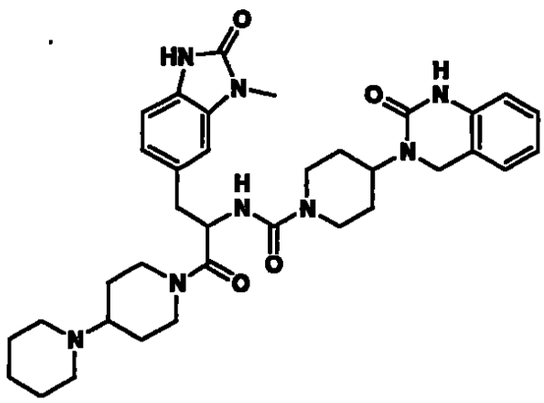
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



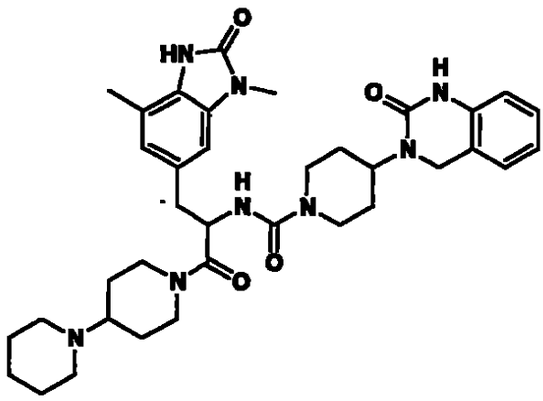
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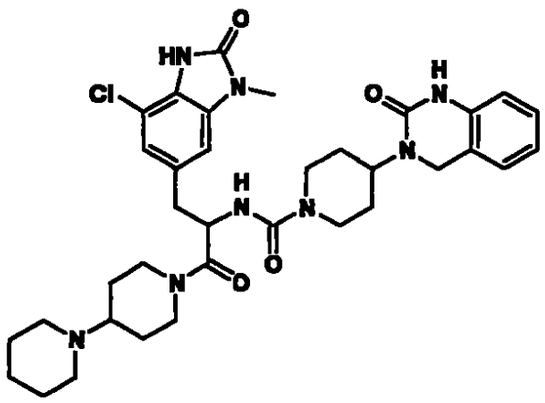
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



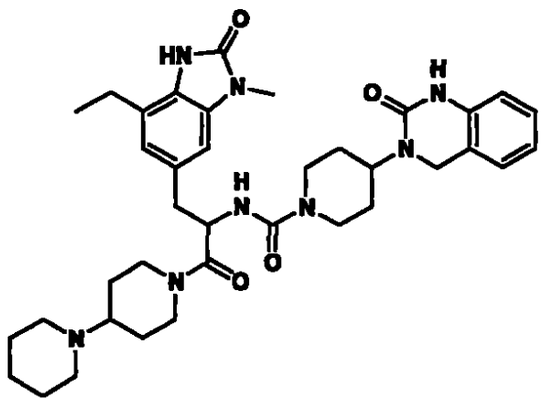
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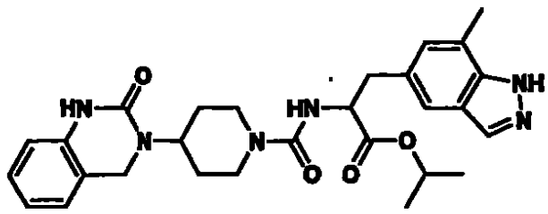
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



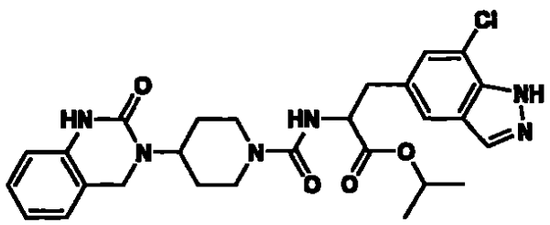
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



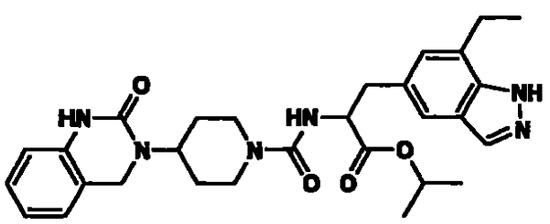
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester



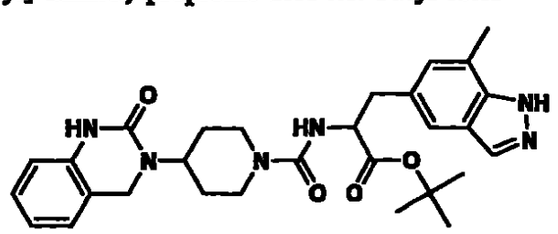
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester



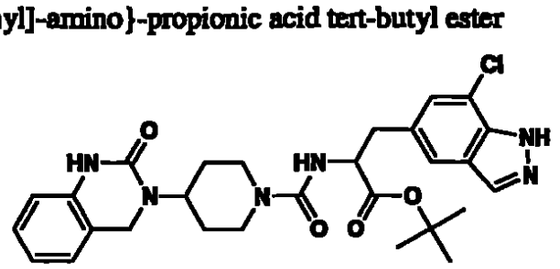
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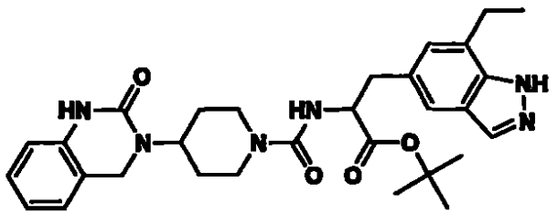
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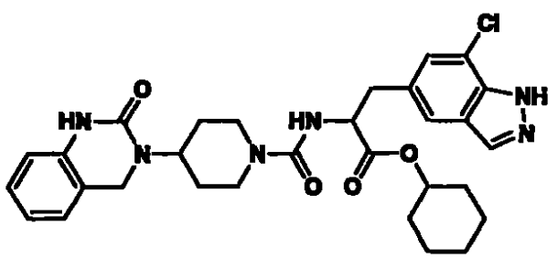
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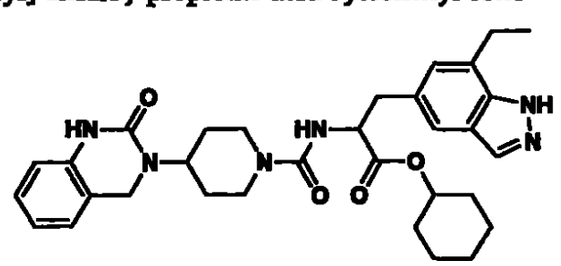
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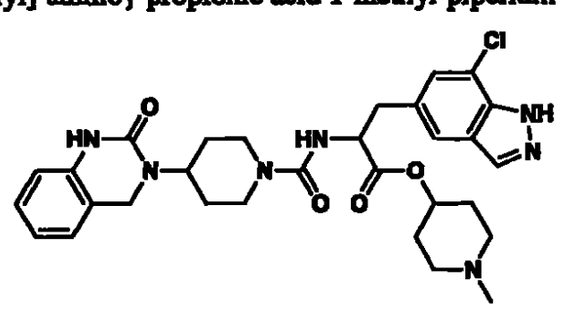
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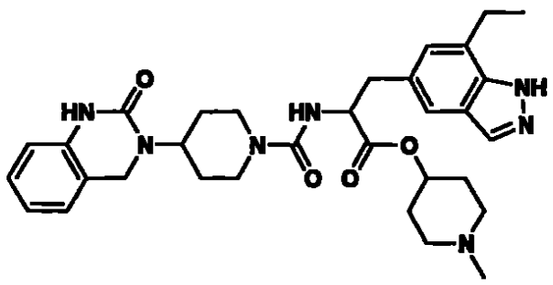
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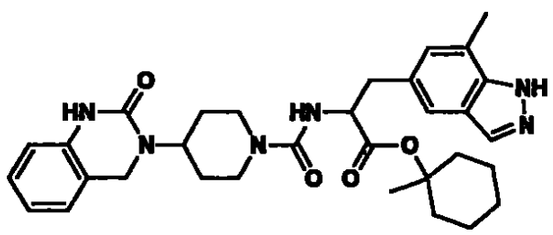
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester



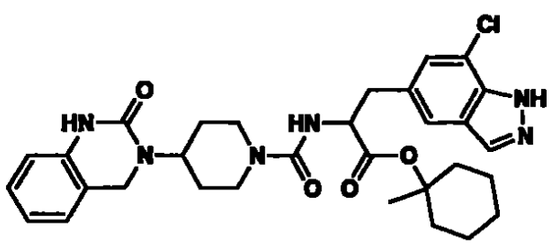
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester



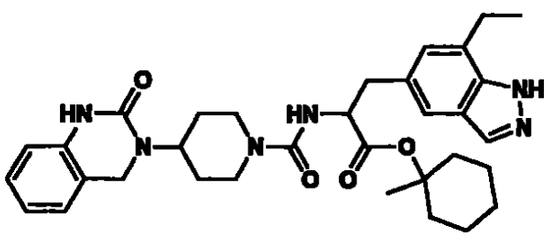
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester



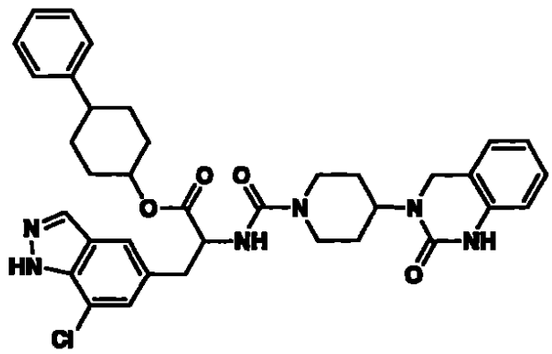
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester



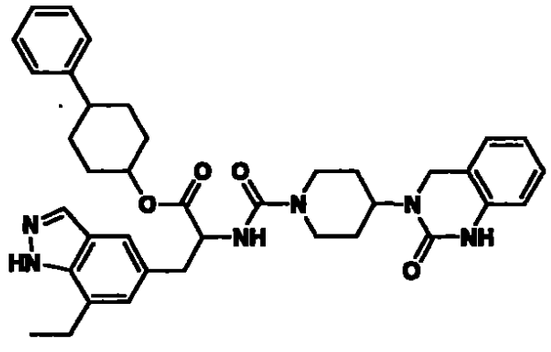
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester



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



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



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 two hours. 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 | * | * |

| Example # | CGRP binding[1] $IC_{50}$ (nM) | cAMP Function[2] $IC_{50}$ (nM) | Cerebral Artery[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 41e | A | * | * |
| 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 |

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| Example # | CGRP binding[1] $IC_{50}$ (nM) | cAMP Function[2] $IC_{50}$ (nM) | Cerebral Artery[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 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 | * |
| 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 | * | * |

| Example # | CGRP binding[1] $IC_{50}$ (nM) | cAMP Function[2] $IC_{50}$ (nM) | Cerebral Artery[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 98 | D | * | * |
| 99 | D | D | * |
| 100 | C | * | * |
| 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 | * | * |

| Example # | CGRP binding[1] $IC_{50}$ (nM) | cAMP Function[2] $IC_{50}$ (nM) | Cerebral Artery[3] $EC_{50}$ (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 | * | * |
| 148 | B | * | * |
| 149 | B | * | * |
| 150 | B | * | * |
| 151 | C | * | * |
| 152 | C | * | * |
| 153 | C | * | * |
| 154 | C | * | * |
| 155 | C | * | * |

| Example # | CGRP binding[1] $IC_{50}$ (nM) | cAMP Function[2] $IC_{50}$ (nM) | Cerebral Artery[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 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 | * | * |
| 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 | * | * |

| Example # | CGRP binding[1] $IC_{50}$ (nM) | cAMP Function[2] $IC_{50}$ (nM) | Cerebral Artery[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 185 | C | * | * |
| 186 | C | * | * |
| 187 | C | * | * |
| 188 | C | * | * |
| 189 | C | * | * |
| 190 | C | * | * |
| 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 minutes 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 |

| Example # | $K_b$(nM) | slope |
|---|---|---|
| 69 | 0.016 | 1 |
| 70 | | 0.71 |
| 71 | 2 | 0.87 |

See Figure 1. Schild Analysis.

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 desigined. 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 minutes 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 hαCGRP 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 hαCGRP(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 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.

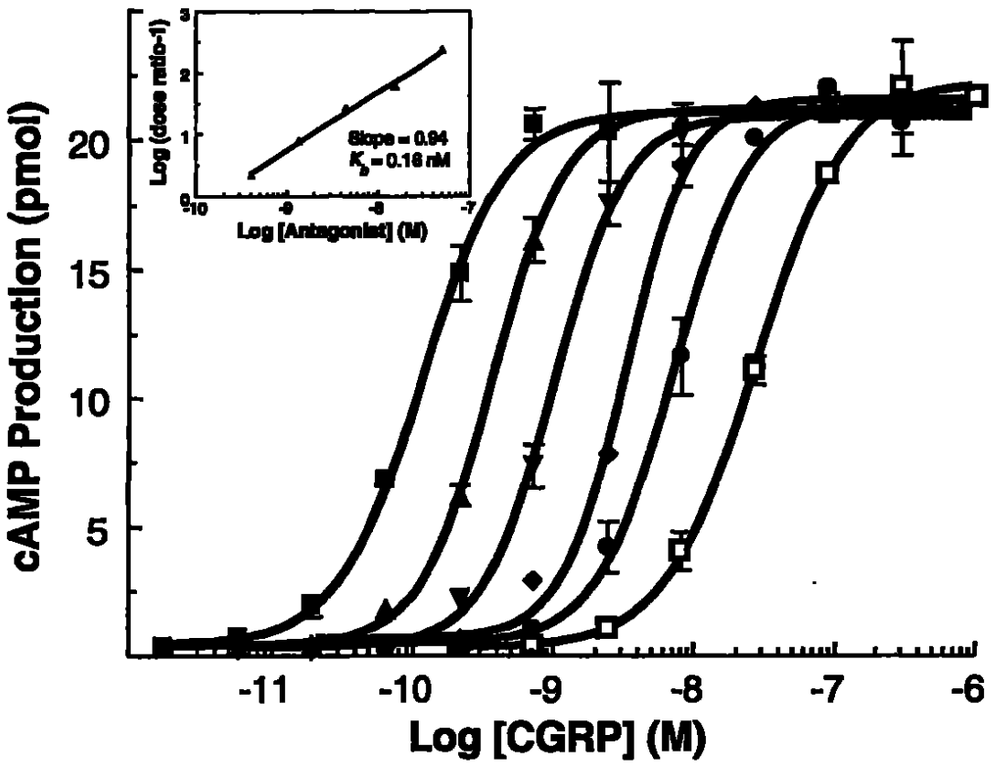
In the table below, results are denoted as follows: W ≤ 25%; 25% < X ≤ 50%; 50% < Y ≤ 75%; Z > 75%.

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%. | | | | |

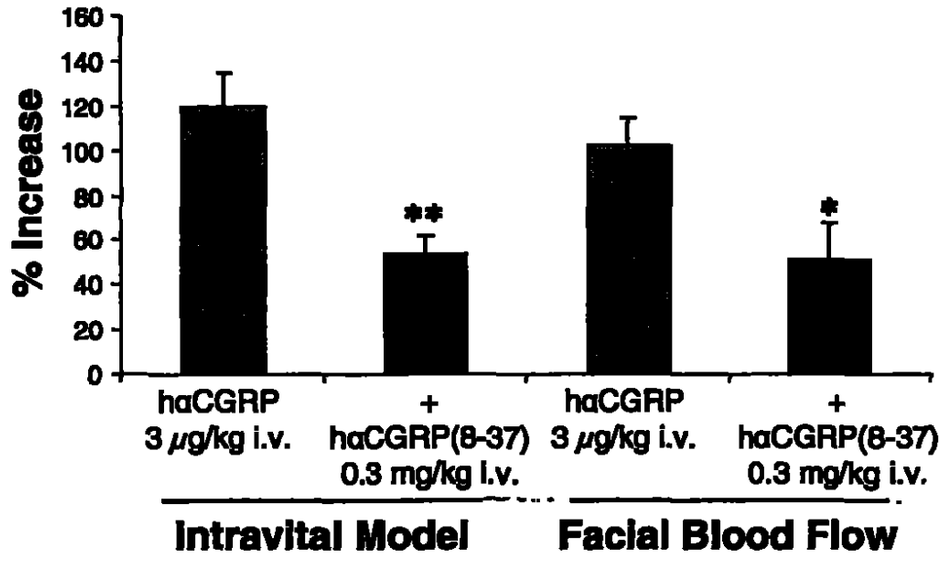
See Figure 5. Effect of CGRP Antagonist on Non-Human Primate Blood Pressure.

Figure 1. Schild Analysis




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




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

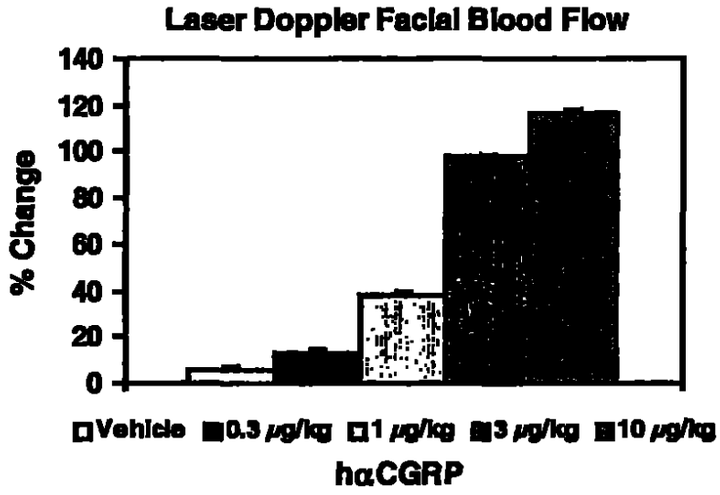
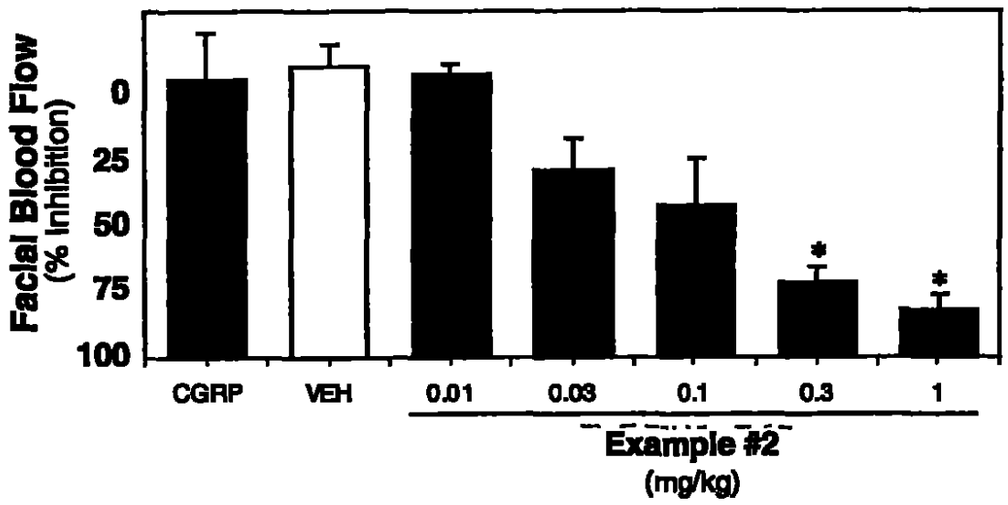


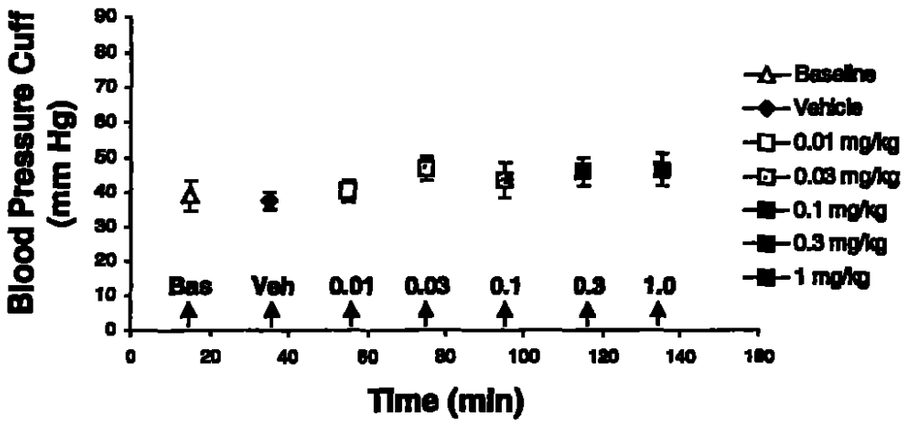
Figure 4. Inhibitition of CGRP-Induced Changes in Non-Human Primate Facial Blood Flow




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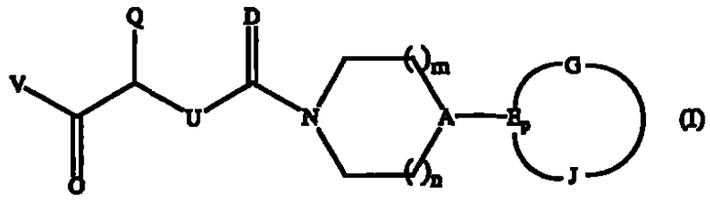
Figure 5. Effect of CGRP Antagonist on Non-Human Primate Blood Pressure.




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What is claimed is:

1. A compound according to Formula (I)



(I)

or a pharmaceutically acceptable salt or solvate 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-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, 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 $(S^y)_sR^3$; and

Q" is $NH(S^y)_sR^3$, $NHC(O)(S^y)_sR^3$, $NHC(O)O(S^y)_sR^3$ or $NHC(O)NH(S^y)_sR^3$;

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", 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-$C_{1-4}$alkylene-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, $C_{3-7}$cycloalkyl, 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".

2. A compound according to claim 1, wherein Q is Q' and $R^3$ is $R^{3b}$.
3. A compound according to claim 1, wherein Q is Q', $R^3$ is $R^{3a}$ and p is 0 such that G, J and A together form GJA".
4. A compound according to claims 2 or 3, wherein Q is Q' and U is $CH_2$.
5. A compound according to claims 2 or 3, wherein Q is Q' and U is NH.
6. A compound according to claim 1, wherein Q is Q".
7. A compound according to claim 6, wherein Q" is $NH(S^y)_sR^3$.
8. A compound according to claim 6, wherein Q" is $NHC(O)(S^y)_sR^3$.
9. A compound according to claim 6, wherein Q" is $NHC(O)O(S^y)_sR^3$.
10. A compound according to claim 6, wherein Q" is $NHC(O)NH(S^y)_sR^3$.
11. A compound according to claim 1, wherein V is $OR^4$.

12. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$.

13. A compound according to claim 1, wherein $R^4$ is H, $C_{1-6}$alkyl or $(C_{1-4}$alkylene$)_{0-1}R^{4'}$ and $R^{4'}$ is $C_{3-7}$cycloalkyl.

14. A compound according to claim 1, 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

$R^1$ 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.

14. A compound according to claim 1, wherein 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, 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.

15. A compound according to claim 1, 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.

16. A compound according to claim 1, 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.

16. A compound according to claim 1, 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.

17. A compound according to claim 1, 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.

18. A compound according to claim 1, 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.

19. A compound according to claim 1, 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.

20. A compound according to claim 1, wherein $R^3$ is $R^{3a}$ and $R^{3a}$ is substituted or unsubstituted 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.

21. A compound according to claim 1, wherein $R^3$ is $R^{3b}$ and $R^{3b}$ is substituted or unsubstituted 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.

22. A compound according to claim 1, wherein D is O and m and n are each 1.

23. A compound according to claim 1, wherein p is 1; and G, J and E together form $A^x$ or $A^y$.

24. A compound according to claim 1, wherein 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".

25. A compound according to claim 1, wherein 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'.

26. A compound according to claim 1, wherein 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".

27. A compound according to claim 1, 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.

28. A compound selected from the group consisting of (±)-3-(1*H*-Indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid;

(*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;

(±)-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;

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

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

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

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;

(±)-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-(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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

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

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

(±)- [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',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;

(±)-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;

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

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

(±)-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;

(±)-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;

(±)-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;

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;

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;

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;

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;

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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(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;

(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;

(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;

(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;

(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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(±)-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;

(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;

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;

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;

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;

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;

(±)-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;

(±)-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-[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;

(±)-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-(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-(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;

(±)-*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;

(±)-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;

(±)-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;

(±)-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;

(±)-*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;

(±)-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;

(±)-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-[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-(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;

(±)-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

(±)-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;

(±)-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;

(±)-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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

(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;

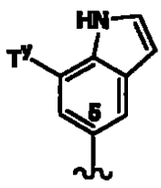
(L)-1H-Pyrazole-3-carboxylic acid {1-([1,4']bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-amide; and

(±)-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;

and pharmaceutically acceptable salts and solvates thereof.

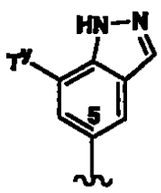
29. A compound according to claim 1 wherein $R^3$ is $R^{3b}$ and $R^{3b}$ is

1H-Indol-5-yl



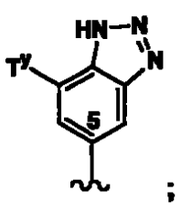
;

1H-Indazol-5-yl



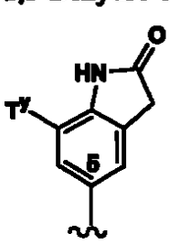
;

1H-Benzotriazol-5-yl



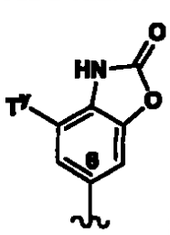
;

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



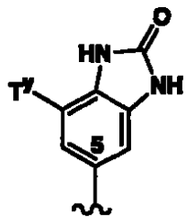
;

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



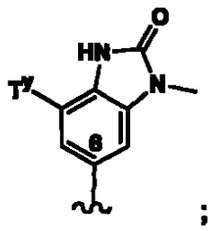
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1,3-Dihydro-benzoimidazol-2-on-5-yl



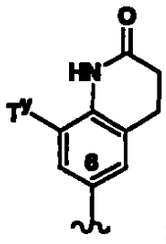
;

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



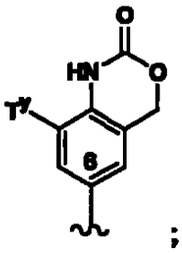
;

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



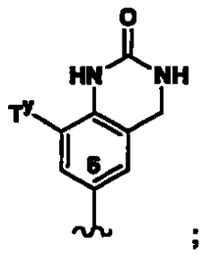
;

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



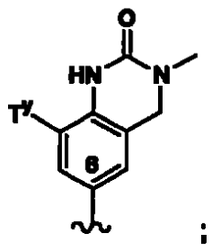
;

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



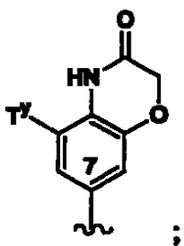
;

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.

30. 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 [2-[1,4']bipiperidinyl-1'-yl-1-(4-chloro-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-2-oxo-1-(2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-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-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-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-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;

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-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-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-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;

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;

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;

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-pyridin-4-yl-ethyl ester; and

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-pyridin-3-yl-ethyl ester

or pharmaceutically acceptable salts or solvates thereof.

31. A pharmaceutical composition comprising a compound according to claim 1.

32. A method of treating migraine in a patient in need thereof comprising the administration of an antimigraine effective amount of a pharmaceutical composition compriaing a compound according to claim 1.

33. 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.

34. 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.

35. 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.

36. 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.

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/16576

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07D 487/14, 487/22; A61K 31/517, 31/496, 31/4427; A61P 11/00, 11/06, 25/06
US CL : 544/284, 286, 336; 546/186, 193, 195, 199; 514/259, 252.14, 336, 337

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/284, 286, 336; 546/186, 193, 195, 199; 514/259, 252.14, 336, 337

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 6552,043 B1 (PATCHETT et al) 22 April 2003 (22.04.2003), see entire document especially formula I on column 1. | 1-36 |

☐ 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 |
|---|---|
| 09 September 2003 (09.09.2003) | 28 OCT 2003 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703)305-3230 | Authorized officer<br>Valerie Harris for<br>Veronica Hagen<br>Telephone No. (703)308-1235 |

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(71) Solicitante: *(para todos los Estados designados excepto US)*: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

(72) Inventores; e

(75) Inventores/Solicitantes *(únicamente para US)*: CHATURVEDULA, Prasad, V. [US/US]; 190 Lancaster Way, Cheshire, CT 06410 (US). CHEN, Ling [CN/US]; 193 McCormick Lane, Middletown, CT 06457 (US). CIVIELLO, Rita [US/US]; 90 Cow Hill Road, Killingworth, CT 06419 (US). CONWAY, Charles, Mark [US/US]; 825 Farmington Drive, Cheshire, CT 06410 (US). DEGNAN, Andrew, P. [US/US]; 123 York Street, Apt. 22-P, New Haven, CT 06511 (US). DUBOWCHIK, Gene, M. [US/US]; 65 Spring Street, Middlefield, CT 06455 (US). HAN, Xiaojun [CN/US]; 65 Ridgecrest Drive, Cheshire, CT 06410 (US). KARAGEORGE, George, N. [US/US]; 34 Fox Run Road, Portland, CT 06480 (US). LUO, Guanglin [CN/US]; 135 Devonshire Lane, Madison, CT 06443 (US). MACOR, John, E. [US/US]; 644 Moose Hill Road, Guilford, CT 06437 (US). POINDEXTER, Graham [US/US]; 15 Fox Hollow Road, Old Saybrook, CT 06475 (US). VIG, Shikha [IN/US]; 15 Park Place, Durham, CT 06422 (US).

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

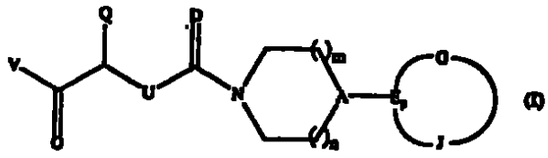
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(54) Título: ANTAGONISTAS DE RECEPTORES DE PEPTIDOS RELACIONADOS CON EL GEN DE CALCITONINA



(I)

(57) Resumen: La presente invención se refiere a compuestos de la fórmula (I) como antagonistas de receptores de péptidos relacionados con el gen de calcitonina ("receptor de CGRP"), a composiciones farmacéuticas que los comprenden, a métodos para identificarlos, a métodos de tratamiento que los utilizan y a su uso en la terapia para el tratamiento de la vasodilatación neurogénica, inflamación neurogénica, migraña y otros dolores de cabeza, lesión térmica, choque circulatorio, flujo repentino asociado con la menopausia, enfermedades inflamatorias de las vías áreas, tales como asma y enfermedad pulmonar obstructiva, crónica (COPD) y otras condiciones, el tratamiento de las cuales puede ser efectuado por el antagonismo de los receptores de CGRP.

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# ANTAGONISTAS DE RECEPTORES DE PEPTIDOS RELACIONAD S CON EL GEN DE CALCITONINA

## Campo de la Invención

La presente invención se refiere a antagonistas novedosos de molécula pequeña de receptores de péptidos relacionados con el gen de calcitonina ("receptor de CGRP"), a composiciones farmacéuticas que los comprenden, a métodos para identificarlos, a métodos de tratamiento que los utilizan y a su uso en la terapia para el tratamiento de la vasodilatación neurogénica, inflamación neurogénica, migraña, dolor de cabeza histamínico y otros dolores de cabeza, lesión térmica, choque circulatorio, flujo repentino asociado con la menopausia, enfermedades inflamatorias de las vías áreas, tales como asma, y enfermedad pulmonar obstructiva, crónica (COPD, por sus siglas en inglés) y otras condiciones, el tratamiento de las cuales puede ser efectuado por el antagonismo de los receptores de CGRP.

## Antecedentes de la Invención

El péptido relacionado con el gen de calcitonina (CGRP, por sus siglas en inglés) es un péptido de 37 aminoácidos de origen natural identificado primero en 1982 (Amara, S. G. y colaboradores, *Science* 1982, 298, 240-244). Dos formas del péptido son expresadas (αCGRP y βCGRP), las

cuales difieren por uno a tres aminoácidos en ratas y humanos, respectivamente. El péptido está distribuido ampliamente tanto en el sistema nervioso periférico (PNS, por sus siglas en inglés) como en el sistema nervioso central (CNS, por sus siglas en inglés), está localizado principalmente en neuronas sensoriales, aferentes y centrales y exhibe una variedad de efectos biológicos, que incluyen la vasodilatación.

Cuando es liberado de la célula, el CGRP se une a receptores específicos acoplados a la proteína G de la superficie celular y ejerce su acción biológica predominantemente por la activación de la adenilato-ciclasa intracelular (Poyner, D. R. y colaboradores, *Br J Pharmacol* 1992, *105*, 441-7; Van Valen, F. y colaboradores, *Neurosci Lett* 1990, *119*, 195-8). Dos clases de receptores de CGRP, $CGRP_1$ y $CGRP_2$, han sido propuestos en base a las propiedades antagónicas del fragmento peptídico CGRP(8-37) y la capacidad de análogos lineales del CGRP para activar los receptores de $CGRP_2$ (Juaneda, C. y colaboradores, *TiPS* 2000, *21*, 432-438). Sin embargo, existe una falta de evidencia molecular para el receptor de $CGRP_2$ (Brain, S. D. y colaboradores, *TiPS* 2002, *23*, 51-53). El receptor de $CGRP_1$ tiene tres componentes: (i) un receptor similar al receptor de calcitonina transmembrana 7 (CRLR, por sus siglas en inglés); (ii) la proteína modificadora de la actividad de receptores transmembrana

individual tipo uno (RAMP1); y (iii) la proteína componente de receptor intracelular (RCP, por sus siglas en inglés) (Evans B. N. y colaboradores, *J Biol Chem.* 2000, *275*, 31438-43). La RAMP1 es requerida para el transporte de CRLR a la membrana plasmática y para la unión de ligandos al receptor de CGRP (McLatchie, L. M. y colaboradores, *Nature* 1998, *393*, 333-339). La RCP es requerida para la transducción de señales (Evans B. N. y colaboradores, *J Biol Chem.* 2000, *275*, 31438-43). Existen diferencias específicas de especies conocidas en la unión de antagonistas de molécula pequeña al receptor de CGRP con afinidad típicamente mayor observada por el antagonismo del receptor humano que por otras especies (Brain, S. D. y colaboradores, *TiPS* 2002, *23*, 51-53). La secuencia de aminoácidos de RAMP1 determina la selectividad de especies, en particular, el residuo de aminoácido Trp74 es responsable del fenotipo del receptor humano (Mallee y colaboradores, *J Biol Chem* 2002, *277*, 14294-8).

Se requiere que los inhibidores a nivel de receptor para CGRP sean útiles en condiciones patofisiológicas donde ha ocurrido una activación excesiva de receptores de CGRP. Algunas de estas incluyen la vasodilatación neurogénica, inflamación neurogénica, migraña, dolor de cabeza histamínico y otros dolores de cabeza, lesión térmica, choque circulatorio, flujo repentino por menopausia y asma. La activación de receptores de CGRP ha sido implicada en la

patogénesis del dolor de cabeza por 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 en el suero de CGRP son elevados durante la migraña (Goadsby PJ y colaboradores, *Ann Neurol* 1990; 28: 183-7) y el tratamiento con fármacos anti-migraña regresa los niveles de CGRP a un estado normal acorde con el alivio del dolor de cabeza (Gallai V. y colaboradores, *Cephalalgia* 1995; 15: 384-90). Los individuos migrañosos exhiben niveles basales elevados de CGRP en comparación con los controles (Ashina M y colaboradores, Pain. 2000; 86(1-2): 133-8.2000). La infusión intravenosa de CGRP produce un dolor de cabeza duradero en los individuos migrañosos (Lassen LH y colaboradores, *Cephalalgia*. 2002 Feb; 22(1): 54-61). Los estudios preclínicos en perros y ratas reportan que el bloqueo sistémico de CGRP con el antagonista peptídico CGRP(8-37) no altera la hemodinámica sistémica, restante ni el flujo sanguíneo, regional (Shen, Y-T. y colaboradores, *J Pharmacol Exp Ther* 2001, 298, 551-8). De esta manera, los antagonistas de receptores de CGRP pueden presentar un tratamiento novedoso para la migraña que evita las desventajas cardiovasculares de la vasoconstricción activa asociada con agonistas no selectivos de 5-$HT_{1B/1D}$, "triptanos" (por ejemplo, sumatriptano).

Existen varios modelos de migraña in vivo que son

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conocidos en la bibliografía (véase De Vries, P. y colaboradores, *Eur J Pharmacol* 1999, *375*, 61-74). Algunos estimulan eléctricamente el ganglio trigeminal y miden la dilatación de los vasos intracraniales que inervan (por ejemplo, Williamson y colaboradores, *Cephalalgia* 1997 17:518-24). Puesto que las arterias faciales también son inervadas por el nervio trigeminal, otros modelos estudian los cambios en el flujo sanguíneo facial inducido por la activación trigeminal, eléctrica (por ejemplo, Escott y colaboradores, *Brain Res* 1995 669:93). Alternativamente, también son estudiados otros nervios periféricos (por ejemplo, safeno) y lechos vasculares (por ejemplo, el flujo sanguíneo abdominal) (por ejemplo, Escott y colaboradores, *Br JPharmacol* 1993 *110*, 772-6;). Se ha mostrado que todos los modelos son bloqueados mediante el tratamiento previo con el antagonista peptídico CGPR(8-37), un fragmento peptídico que tiene ausente los 1$^{os}$ siete residuos o por un antagonista de receptores de CGRP de molécula pequeña. En algunos casos, el CGRP exógeno ha sido utilizado como un estímulo. Sin embargo, todos estos modelos son procedimientos terminales, invasivos y ninguno ha mostrado el efecto abortivo clínicamente importante de invertir un incremento establecido en la dilatación arterial o el flujo sanguíneo incrementado utilizando el tratamiento posterior de un antagonista de receptores de CGRP. Williamson y colaboradores, Cephalalgia 1997 17:518-24 y Williamson y

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colaboradores, Cephalalgia. 1997 17:525-31: utilizaron *inter alia* el CGRP i.v. como un estímulo para incrementar el diámetro de arterias durales, intracraneal en ratas anestesiadas con pentobarb sódico empleando un procedimiento "vital", terminal que involucró la perforación para adelgazar el cráneo y la creación de una ventana craneal, cerrada para visualizar las arterias durales. El efecto fue bloqueado mediante el tratamiento previo con CGRP(8-37) i.v. Escott y colaboradores, *Brain Res* 1995 669:93; *inter alia* perforaron el cráneo de la rata y utilizaron eléctrodos cerebrales para estimular eléctricamente el glangio trigeminal y midieron el flujo sanguíneo facial con la técnica Laser Doppler en un procedimiento terminal en ratas anestesiadas con pentobarb sódico que involucra el bloqueo neuromuscular, intubación traqueal y ventilación artificial. El efecto fue bloqueado por el tratamiento con CGRP(8-37). Escott y colaboradores, *Br J Pharmacol* 1993 *110*, 772-6; *inter alia* utilizaron el CGRP intradérmico (i.d.) como el estímulo para incrementar el flujo sanguíneo en la piel abdominal de rata de animales anestesiados con pentobarb sódico equipados con venas yugulares, canuladas para el suministro de anestésico y de fármaco. El efecto fue bloqueado por el tratamiento previo con el CGRP(8-37) i.v.. Chu y colaboradores, *Neurosci Lett* 2001 *310*, 169-72, utilizaron *inter alia* el CGRP i.d. como el estímulo en ratas y midieron los cambios con la técnica Laser

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Doppler en el flujo sanguíneo en la piel de la espalda en un método terminal utilizando animales anestesiados con pentobarb sódico y con cánula traqueal; y mostraron el bloqueo mediante el tratamiento previo por liberación continua de CGRP(8-37) de bombas osmóticas implantadas subcutáneamente (s.c.). Hall y colaboradores, *Br J Pharmacol* 1995 *114*, 592-7 y Hall y colaboradores *Br Pharmacol* 1999 *126*, 280-4 *inter alia* utilizaron el CGRP tópico para incrementar el diámetro de arteriolas de los sacos de mejillas de hámster y el CGRP i.d. para incrementar el flujo sanguíneo en la piel dorsal de rata de animales anestesiados con pentobarb sódico equipados con venas yugulares, canuladas para el suministro de anestésico y fármaco. El efecto fue bloqueado por medio del tratamiento previo con CGPR(8-37) i.v. Doods y colaboradores, Br J Pharmacol. febrero de 2000; 129(3):420-3 *inter alia* perforaron el cráneo del tití (mono del Nuevo Mundo) y utilizaron electrodos cerebrales para producir la estimulación eléctrica del ganglio trigeminal y midieron el flujo sanguíneo facial en un procedimiento terminal, invasivo que involucra el bloqueo neuromuscular y la ventilación artificial de animales anestesiados con pentobarbital sódico. El incremento en el flujo fue bloqueado por el tratamiento previo de un antagonista de CGRP de molécula pequeña. Véase, también la patente WO 03/272252 "Isolated DNA Molecules Encoding Humanized Calcitonin Gene-Related Peptide Receptor,

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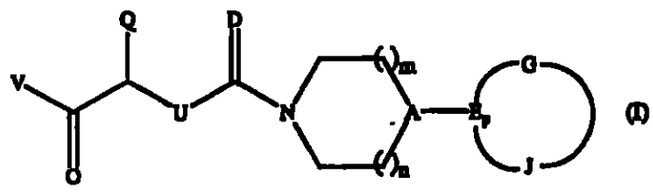
Related Non-Human Transgenic Animals and Assay Methods". De esta manera, el método de la presente invención, procedimiento que es *inter alia* un modelo de supervivencia no invasivo en primates, que mide los cambios inducidos por CGRP exógeno en el flujo sanguíneo facial y que demuestra los efectos del tratamiento previo y posterior de los antagonistas de CGRP peptídicos de molécula pequeña en titis anestesiados con isoflurano que respiran espontáneamente quienes se recuperan del procedimiento ofrece ventajas significantes.

Una variedad de antagonistas de receptores de CGRP de molécula pequeña, no peptídicos ha sido reportada recientemente. La patente WO 97/09046 y equivalentes describe *inter alia* compuestos relacionados con quinina y quinidina los cuales son ligandos, en particular antagonistas, del receptor de CGRP. Las patentes WO 98/09630 y WO 98/56779 y equivalentes describen *inter alia* compuestos de nitrobenzamida diversamente sustituidos como antagonistas de receptores de CGRP. Las patentes WO 01/32649, WO 01/49676 y WO 01/32648 y equivalentes describen *inter alia* una serie de 4-oxobutanamidas y derivados de ciclopropano relacionados como antagonistas de receptores de CGRP. Las patentes WO 00/18764, WO 98/11128 y WO 00/55154 y equivalentes describen *inter alia* bencimidazolinil-piperidinas como antagonistas para el receptor de CGRP. Aparte del CGRP, se ha descrito una

serie de antagonistas de somatostatina en las patentes WO 99/52875 y WO 01/25228 y equivalentes. Véase también las patentes norteamericanas Nos. 6,344,449, 6,313,097, 6,521,609, 6,552,043 y solicitudes relacionadas. De esta manera, los antagonistas de receptores de CGRP que son efectivos para el tratamiento de la inflamación neurogénica, migraña y otros trastornos serían grandemente ventajosos.

## Breve Descripción de la Invención

De esta manera, de acuerdo con una primera modalidad del primer aspecto de la presente invención, se proporcionan compuestos de la fórmula (I)



(I)

y sales y solvatos farmacéuticamente aceptables de los mismos en donde

V es $-N(R^1)(R^2)$ u $OR^4$;

$R^4$ es H, alquilo de 1 a 6 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono o $(\text{alquileno-}C_1\text{-}C_4)_{0\text{-}1}R^{4'}$

$R^{4'}$ es cicloalquilo de 3 a 7 átomos de carbono, 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 sustituido opcionalmente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de halo, ciano, alquilo de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, hidroxi, amino, cicloalquilo de 3 a 7 átomos de carbono, alquilamino de 1 a 3 átomos de carbono, dialquilamino de 1 a 3 átomos de carbono, (alquil-$C_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo; y

$R^{4'}$ contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del 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 de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, -alquilen-$C_1$-$C_6$-amino(alquilo-$C_1$-$C_3$)$_2$, cicloalquilo de 3 a 7 átomos de carbono, 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 sustituidos cada uno

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opcional e independientemente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de halo, ciano, alquilo de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, hidroxi, amino, cicloalquilo de 3 a 7 átomos de carbono, alquilamino de 1 a 3 átomos de carbono, dialquilamino 1 a 3 átomos de carbono, (alquilo-$C_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo;

$R^1$ y $R^2$ contienen opcional e independientemente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los heterociclos que comprenden $R^1$ y $R^2$;

en donde $L^1$ es interrumpido opcional e independientemente del átomo de nitrógeno al cual está unido por $L^2$, en donde $L^2$ es independientemente alquileno de 1

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a 3 átomos de carbono o alquilideno de 1 a 3 átomos de carbono; o

$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es azetidinilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piperazinilo, piperidinilo, morfolino o tiomorfolino;

en donde X es sustituido opcionalmente por Y, en donde Y es dioxolanilo, alquilo de 1 a 9 átomos de carbono, alquenilo de 2 a 9 átomos de carbono, alquinilo de 2 a 9 átomos de carbono, alquilamino de 1 a 4 átomos de carbono, dialquilamino de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, fenilo,

azetidinilo, furanilo, tienilo, pirrolilo, pirrolinilo, pirrolidinilo, pirrolidinonilo, imidazolilo, imidazolinilo, imidazolidinilo, imidazolidinonilo, pirazolilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piridilo, pirimidinilo, dihidrobencimidazolonilo, piperazinilo, piperidinilo, morfolino, benzotiazolilo, bencisotiazolilo o tiomorfolino;

y en donde X e Y son interrumpidos opcionalmente por Z, en donde Z es -NHC(O)O-, -NHC(O)NH-, $NC(O)NH_2$, -NH-, -alquileno- de 1 a 3 átomos de carbono, -alquileno- de 1 a 3 átomos de carbono, alquenilen-$C_1$-$C_3$-NHC(O)O-

alquileno de 1 a 3 átomos de carbono; y

sustituidos opcional e independientemente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de alquilo de 1 a 4 átomos de carbono, amino, alquilamino de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_6$-amino (alquilo-$C_1$-$C_3$)$_2$, (alquil-$C_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo;

X e Y contienen opcional e independientemente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los heterociclos que comprenden X e Y;

con la condición que si X es sustituido por Y, y si X

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e Y no son interrumpidos por Z, entonces X e Y comparten opcionalmente un átomo de carbono y juntos forman un radical espirocíclico;

Q es Q' o Q";

en donde

Q' es $(S^y)_sR^3$; y

Q" es $NH(S^y)_sR^3$, $NHC(O)(S^y)_sR^3$, $NHC(O)O(S^y)_sR^3$ o $NHC(O)NH(S^y)_sR^3$;

en donde $S^y$ es alquileno de 1 a 3 átomos de carbono o alquilideno de 1 a 3 átomos de carbono y s es 0 o 1;

U es $CH_2$ o NH;

con la condición que si Q es Q", entonces U es $CH_2$;

$R^3$ es $R^{3a}$ o $R^{3b}$

en donde

$R^{3a}$ es

(i) un heterociclo que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cinco de los mismos o diferentes heteroátomos

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seleccionados del grupo que consiste de O, N y S y el heterociclo contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los anillos fusionados;

(ii) un heterociclo de 4 a 6 miembros que contiene de uno a tres de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S, que contiene opcionalmente de 1 a 2 carbonilos, en donde el átomo de carbono del carbonilo es un miembro del heterociclo de 4 a 6 miembros;

(iii) cicloalquilo de 3 a 7 átomos de carbono;

(iv) carbazolilo, fluorenilo, fenilo, -O-fenilo, -O-alquilen-$C_1$-$C_4$-fenilo o naftilo; o

(v) alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$, $-C(O)O-R^{3'}$ o alquinilo de 2 a 7 átomos de carbono; y

en donde $R^{3a}$ es sustituido opcionalmente por 1 a 3 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilenfenilo de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_3$-OC(O)-fenilo, ciano, amino, nitro, halo, alquilo de 1 a 6 átomos de carbono, mono-bi-tri-haloalquilo de 1 a 3 átomos de carbono, mono-bi-tri-haloalquiloxi de 1 a 3 átomos de carbono, (alquil-$C_1$-$C_3$)$_{1-2}$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 de 1 a 6 átomos de carbono;

con la condición que si $R^{3a}$ es $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ o $-C(O)O-R^{3'}$, entonces $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ o $-C(O)O-R^{3'}$ no son sustituidos;

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$R^{3b}$ 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, 1-(1,1-dimetiletoxicarbonilo)-1H-indol-3-ilo, 4-imidazolilo, 1-metil-4-imidazolilo, 2-tienilo, 3-tienilo, tiazolilo, 1H-indazol-3-ilo, 1-metil-1H-indazol-3-ilo, benzo[b]fur-3-ilo, benzo[b]tien-3-ilo, piridinilo, quinolinilo o isoquinolinilo; sustituido opcionalmente en el esqueleto de carbono de 1 a 3 átomos de carbono por mono-, di- o trisustituido por átomos de flúor, cloro o bromo o por grupos alquilo de cadena recta o ramificada, grupos -cicloalquilo de 3 a 8 átomos de carbono, 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, dialquilaminocarbonilo, alcanoilo, ciano, tetrazolilo, fenilo, piridinilo, tiazolilo, furilo, trifluorometoxi, trifluorometiltio, trifluorometilsulfinilo o trifluorometilsulfonilo;

en donde los sustituyentes pueden ser los mismos o diferentes y los grupos benzoilo, benzoilamino y benzoilmetilamino mencionados anteriormente pueden ser sustituidos adicionalmente, a su vez, en el radical fenilo por un átomo de flúor, cloro o bromo o por un grupo alquilo, trifluorometilo, amino o acetilamino;

D es O, NCN o $NSO_2$-alquilo de 1 a 3 átomos de carbono;

A es C, N o CH;

m y n son independientemente 0, 1 o 2;

con la condición que

si m y n son 0, entonces A no es N;

si m es 2, entonces n no es 2; o

si n es 2, entonces m no es 2;

E es N, CH o C;

P es 0 o 1;

si p es 1, entonces G, J y E juntos forman $A^X$ o $A^Y$;

$A^X$ es un heterociclo fusionado que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cuatro de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S; y

que contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro del heterociclo fusionado;

$A^Y$ es un heterociclo de 4 a 6 miembros que contiene de uno a tres heteroátomos seleccionados del grupo que consiste de O, N y S; y

que contiene opcionalmente 1 a 2

carbonilos, en donde el átomo de carbono del carbonilo es un miembro del heterociclo de 4 a 6 miembros;

en donde $A^x$ y $A^y$ son sustituidos opcionalmente por alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, ciano, cicloalquilo de 3 a 7 átomos de carbono, fenilo, halofenilo, halo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, piridilo, pirimidinilo, piperidinilo, piperazinilo o morfolino; o

si p es 0, de tal manera que G y J sean unidos cada uno a A, entonces A es C, y G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen 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 que

$A^x$ no sea un heterociclo 1,3-diaza-fusionado; y

$A^y$ no sea un 1,3-diaza-heterociclo;

y con la condición adicional que

si Q es Q", entonces $R^3$ es $R^{3a}$; y

si Q es Q', entonces

$R^3$ es $R^{3b}$; o

$R^3$ es $R^{3a}$, p es 0 y G, J y A juntos forman GJA".

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y $R^3$ es $R^{3b}$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde Q es Q', $R^3$ es $R^{3a}$ y p es 0 de tal manera que G, J y A juntos forman GJA".

De acuerdo con otra modalidad del primer aspecto de

la presente invención, se proporcionan compuestos de acuerdo con 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y U es $CH_2$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de

1 a 3 átomos de carbono, s es 1 y U es $CH_2$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono, s es 1 y U es $CH_2$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y U es NH.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 NH.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono, s es 1 y U es NH.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono, s es 1 y U es NH.

De acuerdo con otra modalidad del primer aspecto de

la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde Q es Q".

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NH(S^y)_sR^3$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 es 0.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente

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invención en donde Q es Q" y Q" es $NHC(O)O(S^y)_sR^3$, $S^y$ es alquileno de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 3 átomos de carbono y s es 1.

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De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde V es $OR^4$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde V es $OR^4$ y $R^4$ es alquilo de 1 a 6 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde

V es $-N(R^1)(R^2)$ u $OR^4$;

$R^4$ es H, alquilo de 1 a 6 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, $(alquilen\text{-}C_1\text{-}C_4)_{0\text{-}1}R^{4'}$

$R^{4'}$ es cicloalquilo de 3 a 7 átomos de carbono, 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 sustituido opcionalmente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de halo, ciano, alquilo de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, hidroxi, amino, cicloalquilo de 3 a 7 átomos de carbono, alquilamino de 1 a 3 átomos de carbono, dialquilamino de 1 a 3 átomos de carbono, (alquil-$C_1$-$C_3$)$_{0-2}$ureido, fenilo o bencilo;

$R^{4'}$ contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del

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carbonilo es un miembro de la estructura de 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 de 1 a 6 átomos de carbono, -alquilen-$C_1$-$C_6$-amino(alquil-$C_1$-$C_3$)$_2$, cicloalquilo de 3 a 7 átomos de carbono, 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 sustituidos cada uno opcional e independientemente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de halo, ciano, alquilo de 1 a 4 átomos de carbono, haloalquilo de 1 a

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4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, hidroxi, amino, cicloalquilo de 3 a 7 átomos de carbono, alquilamino de 1 a 3 átomos de carbono, dialquilamino de 1 a 3 átomos de carbono, (alquil-$C_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo;

$R^1$ y $R^2$ contienen opcional e independientemente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los heterociclos que comprenden $R^1$ y $R^2$;

en donde $L^1$ es interrumpido opcionalmente del nitrógeno al cual está unido por $L^2$, en donde $L^2$ es alquileno de 1 a 3 átomos de carbono; o

$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es azetidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piperazinilo, piperidinilo, morfolino o tiomorfolino;

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en donde X es sustituido opcionalmente por Y, en donde Y es dioxolanilo, alquilo de 1 a 4 átomos de carbono, alquilamino de 1 a 4 átomos de carbono, dialquilamino de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, fenilo, azetidinilo, pirrolilo, pirrolinilo, pirrolidinilo, pirrolidinonilo, imidazolilo, imidazolinilo, imidazolidinilo, imidazolidinonilo, pirazolilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piridilo, pirimidinilo, dihidrobencimidazolonilo, piperazinilo, piperidinilo, morfolino, benzotiazolilo, bencisotiazolilo o tiomorfolino; y en donde X e Y son interrumpidos opcionalmente por Z, en donde Z es -NHC(O)O-, -NHC(O)NH-,

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$NC(O)NH_2$, -NH-, -alquileno- de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_3$-NHC(O)O-alquileno de 1 a 3 átomos de carbono; y

sustituidos opcional e independientemente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de alquilo de 1 a 4 átomos de carbono, amino, alquilamino de 1 a 3 átomos de carbono, alquilen-$C_1$-$C_6$-amino(alquil-$C_1$-$C_3$)$_2$, (alquil-$C_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo;

X e Y contienen opcional e independientemente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los heterociclos que comprenden X e Y;

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con la condición que si X es sustituido por Y, y si X e Y no son interrumpidos por Z, entonces X e Y comparten opcionalmente un átomo de carbono y juntos forman un radical espirocíclico.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^4$ es H, alquilo de 1 a 6 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono o (alquilen-$C_1$-$C_4$)$_{0-1}R^{4'}$; $R^{4'}$ es cicloalquilo de 3 a 7 átomos de carbono, 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 sustituido opcionalmente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de halo, ciano, alquilo de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono,

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hidroxi, amino, cicloalquilo de 3 a 7 átomos de carbono, alquilamino de 1 a 3 átomos de carbono, dialquilamino de 1 a 3 átomos de carbono, (alquil-$C_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^4$ es H, alquilo de 1 a 6 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono o (alquilen-$C_1$-$C_4$)$_{0-1}R^{4'}$; $R^{4'}$ es cicloalquilo de 3 a 7 átomos de carbono, 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^4$ es H, alquilo de 1 a 6 átomos de carbono o (alquilen-$C_1$-$C_4$)$_{0-1}R^{4'}$; $R^{4'}$ es cicloalquilo de 3 a 7 átomos de carbono.

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De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 consiste de H, alquilo de 1 a 6 átomos de carbono, -alquilen-$C_1$-$C_6$-amino(alquil-$C_1$-$C_3$)$_2$, cicloalquilo de 3 a 7 átomos de carbono, 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 átomo de nitrógeno al cual están unidos ,forman X,

en donde X es azetidinilo, pirrolinilo, pirrolidinilo, imidazolinilo,

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imidazolidinilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piperazinilo, piperidinilo, morfolino o tiomorfolino;

en donde X es sustituido por Y, en donde Y es dioxolanilo, alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono,, cicloalquilo de 3 a 7 átomos de carbono, fenilo, azetidinilo, pirrolilo, pirrolinilo, pirrolidinilo, pirrolidinonilo, imidazolilo, imidazolinilo, imidazolidinilo, imidazolidinonilo, pirazolilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piridilo, pirimidinilo, dihidrobencimidazolonilo, piperazinilo, piperidinilo, morfolino, benzotiazolilo, bencisotiazolilo o tiomorfolino;

y en donde X e Y comparten opcionalmente un átomo de

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carbono y juntos forman un radical espirocíclico.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 6 átomos de carbono, o

$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo o morfolino;

en donde X es sustituido por Y, en donde Y es dioxolanilo, alquilo de 1 a 4 átomos de carbono o piperidinilo;

y en donde X e Y comparten opcionalmente un átomo de carbono y juntos forman un radical espirocíclico.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 $L^1$ se selecciona del

grupo que consiste de H, alquilo de 1 a 6 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo o morfolino;

en donde X es sustituido por Y, en donde Y es dioxolanilo, alquilo de 1 a 4 átomos de carbono o piperidinilo;

y en donde X e Y comparten opcionalmente un átomo de carbono y juntos forman un radical espirocíclico.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo;

en donde X es sustituido por Y, en donde Y es piperidinilo.

De acuerdo con otra modalidad del primer aspecto de

la presente invención, se proporcionan compuestos de acuerdo con 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 átomo de nitrógeno al cual están unidos, forman X,

en donde X es morfolino;

en donde X es sustituido por Y, en donde Y es alquilo de 1 a 4 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo;

en donde X es sustituido por Y, en donde Y es alquilo de 1 a 4 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 átomo de nitrógeno al cual están unidos forman X,

en donde X es piperidinilo;

en donde X es sustituido por Y, en donde Y es dioxolanilo,

y en donde X e Y comparten un átomo de carbono y juntos forman un radical espirocíclico.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde X e Y no son interrumpidos por Z.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde X e Y no son interrumpidos por Z; y X e Y comparten un átomo de carbono y juntos forman un radical espirocíclico.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3a}$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3b}$.

De acuerdo con otra modalidad del primer aspecto de

la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es un heterociclo que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiéne de uno a cinco de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es un heterociclo que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cinco de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S y el heterociclo contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los anillos fusionados.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es un heterociclo que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cinco de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S y el heterociclo contiene opcionalmente

1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los anillos fusionados; en donde $R^{3a}$ es sustituido opcionalmente por 1 a 3 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_3$-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo de 1 a 3 átomos de carbono, mono-bi-tri-haloalquiloxi de 1 a 3 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, (alquil-$C_1$-$C_3$)$_{1-2}$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 de 1 a 6 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es un heterociclo de 4 a 6 miembros que contiene de uno a tres de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es un heterociclo de 4 a 6 miembros que contiene de uno a tres de los mismos o diferentes

heteroátomos seleccionados del grupo que consiste de O, N y S, que contiene opcionalmente 1 o 2 carbonilos, en donde el átomo de carbono del carbonilo es un miembro del heterociclo de 4 a 6 miembros.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es un heterociclo de 4 a 6 miembros que contiene de uno a tres de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S, que contiene opcionalmente 1 o 2 carbonilos, en donde el átomo de carbono del carbonilo es un miembro del heterociclo de 4 a 6 miembros; en donde $R^{3a}$ es sustituido opcionalmente por 1 a 3 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_3$-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo de 1 a 3 átomos de carbono, mono-bi-tri-haloalquiloxi de 1 a 3 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, (alquil-$C_1$-$C_3$)$_{1-2}$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 de 1 a 6 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de

la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es cicloalquilo de 3 a 7 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es cicloalquilo de 3 a 7 átomos de carbono; en donde $R^{3a}$ es sustituido opcionalmente por 1 a 3 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_3$-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo de 1 a 3 átomos de carbono, mono-bi-tri-haloalquiloxi de 1 a 3 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, (alquil-$C_1$-$C_3$)$_{1-2}$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 de 1 a 6 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es carbazolilo, fluorenilo, fenilo, -O-fenilo, -O-alquilen-$C_1$-$C_4$-fenilo o naftilo.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es carbazolilo, fluorenilo, fenilo, -O-fenilo, -O-alquilen-$C_1$-$C_4$-fenilo o naftilo; en donde $R^{3a}$ es sustituido opcionalmente por 1 a 3 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_3$-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo de 1 a 3 átomos de carbono, mono-bi-tri-haloalquiloxi de 1 a 3 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, (alquil-$C_1$-$C_3$)$_{1-2}$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 de 1 a 6 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^{3a}$ es alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$ o alquinilo de 2 a 7 átomos de carbono.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente

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invención en donde $R^{3a}$ es alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$ o alquinilo de 2 a 7 átomos de carbono; en donde $R^{3a}$ es sustituido opcionalmente por 1 a 3 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_3$-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo de 1 a 3 átomos de carbono, mono-bi-tri-haloalquiloxi de 1 a 3 átomos de carbono, alcoxi de 1 a 6 átomos de carbono, (alquil-$C_1$-$C_3$)$_{1-2}$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 de 1 a 6 átomos de carbono, con la condición que si $R^{3a}$ es $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ o $-C(O)O-R^{3'}$; entonces $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ o $-C(O)O-R^{3'}$ no son sustituidos.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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 de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, dihidroquinolinonilo, hidroquinolinonilo, quinolinilo, dihidroisoquinolinonilo, hidroisoquinolinonilo,

isoquinolinilo, dihidroquinazolinonilo, hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, bencimidazolilo, indazolilo, dihidrobencimidazolonilo, hidrobencimidazolonilo, bencimidazolinilo, dihidrobenztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzoxazolilo, benzotriazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo, benzotienilo, dihidrobenzofuranonilo, hidrobenzofuranonilo, benzofuranilo, benzdioxolanilo, 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; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3a}$ y $R^{3a}$ es fenilo, naftilo, indazolilo, bencimidazolinilo, dihidrobenzoxazolilo, benzotriazolilo, benzotienilo, benzdioxolanilo, dihidroindolonilo, indolilo, furanilo, tienilo, piridilo,

purinilo, carbazolilo, piperidinilo, triazolopirimidinilo, tetrahidropirazolopiridinilo; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3a}$ y $R^{3a}$ es dihidrobenztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo, benzotienilo, dihidrobenzofuranonilo, hidrobenzofuranonilo, benzofuranilo, dihidroindolonilo, hidroindolonilo, indolilo, indolizinilo, isoindolilo, indolinilo o indazolilo; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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, alquil-$C_1$-$C_3$-nitroaminopirimidina, triazolopirimidinilo, piridilo, indazolilo, fenilo o benzdioxolanilo; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

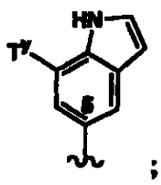
De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente

invención en donde $R^3$ es $R^{3a}$ y $R^{3a}$ es naftilo, fenil-O-fenilo o tienilo; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención, en donde $R^3$ es $R^{3b}$.

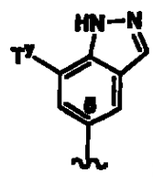
De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3b}$ y $R^{3b}$ es

1H-Indol-5-ilo



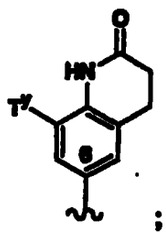
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1H-Indazol-5-ilo



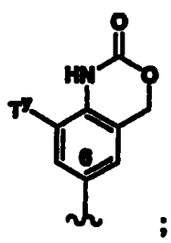
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1H-Benzotriazol-5-ilo



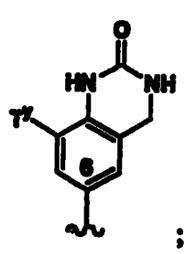
;

1,4-Dihidro-benzo[d][1,3]oxazin-2-ón-6-ilo



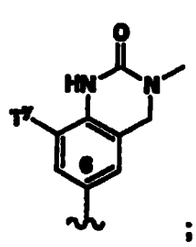
;

3,4-Dihidro-1H-quinazolin-2-on-6-ilo



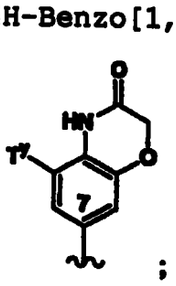
;

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 de 1 a 4 átomos de carbono, F, Cl, Br o nitrilo.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3b}$ y $R^{3b}$ es azetidinilo, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos d carbono, alquinilo de 2 a 6 átomos de carbono, dihidroquinolinonilo, hidroquinolinonilo, dihidroisoquinolinonilo, hidroisoquinolinonilo, dihidroquinazolinonilo, hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, bencimidazolilo, 1H-indazol-5-ilo, dihidrobencimidazolonilo, hidrobencimidazolonilo, bencimidazolinilo, dihidrobenztiazolonilo, 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; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3b}$ y $R^{3b}$ es dihidrobencimidazolonilo, hidrobencimidazolonilo, bencimidazolinilo, 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; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3b}$ y $R^{3b}$ es azetidinilo, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, dihidroquinolinonilo, hidroquinolinonilo, dihidroisoquinolinonilo, hidroisoquinolinonilo,

dihidroquinazolinonilo, hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, bencimidazolilo, 1H-indazol-5-ilo, dihidrobencimidazolonilo, hidrobencimidazolonilo, bencimidazolinilo, dihidrobenztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo, dihidrobenzofuranonilo, hidrobenzofuranonilo, benzdioxolanilo, dihidrobenzoxazolilo, benzotriazolilo, purinilo, carbazolilo, pirimidinilo, piperidinilo, piperazinilo o morfolino; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $R^3$ es $R^{3b}$ y $R^{3b}$ es azetidinilo, alquilo d 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, dihidroquinolinonilo, hidroquinolinonilo, dihidroisoquinolinonilo, hidroisoquinolinonilo, dihidroquinazolinonilo, hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, bencimidazolilo, 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; sustituido opcionalmente como se proporciona en la primera modalidad d l primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acu rdo cón 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, carbazolilo; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con 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, alquil-$C_1$-$C_3$-nitroaminopirimidinilo, triazolopirimidinilo, piridilo, 1H-indazol-5-ilo, fenilo o benzdioxolanilo.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo 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 S.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo 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 acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo 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 S.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde m y n son cada uno 1.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde D es O.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo

con la primera modalidad del primer aspecto de la pres nte invención en donde A es C.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde A es CH.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde A es N.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acu rdo con la primera modalidad del primer aspecto de la presente invención en donde E es N.

De acuerdo con otra modalidad del primer aspecto d la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde E es CH.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde E es C.

De acuerdo con otra modalidad del primer aspecto de la pres nte invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente

invención en donde los compuestos exhiben, como se describe en este texto, un valor $IC_{50}$ de unión a CGRP menor que 10 nM.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde los compuestos exhiben, como se describe en este texto, un valor $IC_{50}$ de unión a CGRP menor que 100 nM.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde los compuestos exhiben, como se describe en este texto, un valor $IC_{50}$ de unión a CGRP menor que 1000 nM.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 1; y G, J y E forman juntos $A^x$ o $A^y$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 1; y G, J y E forman juntos $A^x$.

De acuerdo con otra modalidad del primer aspecto d la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente

invención en donde p es 1; y G, J y E forman juntos $A^y$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $A^x$ es un heterociclo fusionado que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cuatro de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S; y que contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro del heterociclo fusionado.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $A^x$ es un heterociclo fusionado que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cuatro de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $A^x$ es un heterociclo fusionado que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cuatro de los

mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S y en donde $A^x$ es sustituido por fenilo.

De acuerdo con otra modalidad del primer aspecto d la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $A^x$ es un heterociclo fusionado descrito en es texto.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $A^y$ es un heterociclo de 4 a 6 miembros qu contiene de uno a tres heteroátomos seleccionados del grupo que consiste de O, N y S; y que contiene opcionalmente 1 a 2 carbonilos, en donde el átomo de carbono del carbonilo es un miembro del heterociclo de 4 a 6 miembros.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo 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 de uno a tres heteroátomos seleccionados del grupo que consiste de O, N y S.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde $A^y$ s un h terociclo d 4 a 6 miembros que

contiene de uno a tres heteroátomos seleccionados del grupo que consiste de O, N y S; y que contiene opcionalmente de 1 a 2 carbonilos, en donde el átomo de carbono del carbonilo es un miembro del heterociclo de 4 a 6 miembros; y en donde $A^y$ es sustituido por fenilo.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la pres nte invención en donde $A^y$ es un heterociclo de 4 a 6 miembros descrito en este texto.

De acuerdo con otra modalidad del primer aspecto d la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA' o GJA".

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA'.

De acuerdo con otra modalidad del primer aspecto de

la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA".

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA' y GJA' es $A^x$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acu rdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA' y GJA' es $A^y$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la present invención en dond p s 0, de tal manera qu G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de

anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA" y GJA" es $A^x$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema qu contienen A y en donde G, J y A juntos son GJA" y GJA" es $A^y$.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A forman juntos un heterociclo seleccionado 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, piperazinilo y morfolino; en donde el heterociclo es sustituido opcionalmente por alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, ciano, cicloalquilo de 3 a 7 átomos de carbono, fenilo, halofenilo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, piridilo, pirimidinilo, piperidinilo, piperazinilo o morfolino.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema qu contienen A y en donde G, J y A forman juntos un heterociclo seleccionado 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, piperazinilo y morfolino; en donde el heterociclo es sustituido opcionalmente por alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, ciano, cicloalquilo de 3 a 7 átomos de carbono, fenilo, halofenilo, furanilo, pirazolilo, pirazolinilo, pirazolidinilo, piridilo, pirimidinilo, piperidinilo, piperazinilo o morfolino.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A forman juntos un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidrobenzofuranonilo, dihidroindolonilo, indolinilo, pirazolinilo, pirazolidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, piperidinilo, piperazinilo y morfolino; en donde el heterociclo es sustituido opcionalmente por alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de

carbono, ciano, cicloalquilo de 3 a 7 átomos de carbono, fenilo, halofenilo, piperazinilo o morfolino.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A forman juntos un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidroquinoxalinonilo, dihidrobenzoxazinilo, hidrobenzoxazinilo, dihidrobenzoxazinonilo, dihidrobencimidazolonilo, dihidrobencimidazolilo, dihidro-Benztiazolonilo, dihidrobenztiazolilo, dihidrobenzotiofenonilo, dihidrobenzofuranonilo, dihidroindolonilo, indolinilo, pirazolinilo, pirazolidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, piperidinilo, piperazinilo y morfolino.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la pres nte inv nción en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de

anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A forman juntos un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidroquinoxalinonilo, dihidrobenzoxazinilo, hidrobenzoxazinilo y dihidrobenzoxazinonilo.

De acuerdo con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de acuerdo con la primera modalidad del primer aspecto de la presente invención en donde p es 0, de tal manera que G y J son unidos cada uno a A, luego G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A forman juntos un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidroquinoxalinonilo y dihidrobenzoxazinilo.

De acuerdo con varias modalidades de un segundo aspecto de presente invención, se proporcionan composiciones farmacéuticas que comprende los compuestos de la fórmula (I) como se define en este texto.

De acuerdo con varias modalidades de un tercer aspecto de la presente invención, se proporcionan métodos para tratar la inflamación (particularmente inflamación

neurogénica), dolor de cabeza (particularmente migraña), dolor, lesión térmica, choque circulatorio, diabetes, síndrome de Reynaud, insuficiencia arterial periférica, hemorragia subaracnoidea/craneal, crecimiento tumoral, flujo repentino asociado con la menopausia y otras condiciones, el tratamiento de las cuales puede efectuarse por el antagonismo del receptor de CGRP mediante la administración de composiciones farmacéuticas que comprenden los compuestos de la fórmula (I) como se define en este texto.

De acuerdo con varias modalidades de un cuarto aspecto de la presente invención, son los usos de los compuestos de la presente invención seleccionados del grupo que consiste de (a) regulación inmune de mucosa del intestino, (b) efecto protector contra la lesión anafiláctica, cardiaca, (c) estimulación o prevención de la estimulación de interleucina 1b (IL-1b) de la resorción del hueso, (d) modulación de la expresión de receptores de NK1 en neuronas espinales y (e) enfermedades inflamatorias de las vías áreas y enfermedad pulmonar, obstructiva, crónica, que incluye el asma. *Véase (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, Tongli 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, 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, Berlin, 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 and Pharmacotherapy, Faculty of Medicine, University of Pecs, Pecs, Hung. Current Medicinal Chemistry: Anti-Inflammatory & Anti-Allergy Agents (2003), 2(2), 191-218 todas incorporadas en este texto a manera de referencia.

De acuerdo con varias modalidades de un 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 inhibidores de COX-2, NSAIDS, aspirina, acetaminofeno, triptanos, ergotamina y cafeína para el tratamiento de la migraña.

De acuerdo con un sexto aspecto de la presente

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invención, se proporcionan métodos no terminales, *in vivo* para identificar compuestos anti-migraña.

De acuerdo la primera modalidad del sexto aspecto de la presente invención se proporciona un método no terminal, *in vivo* para identificar compuestos anti-migraña que comprende administrar un agonista de receptores de CGRP a un mamífero en una cantidad capaz de inducir un incremento el flujo, sanguíneo seguido por la administración de un compuesto de prueba en una cantidad capaz de invertir el incremento inducido por CGRP en el flujo sanguíneo, en donde el mamífero es un mamífero transgénico con RAMP1 humanizado que tiene Trp74 o un mamífero que expresa de manera endógena RAMP1 que tiene Trp74.

De acuerdo con otra modalidad del sexto aspecto de la presente invención, se proporciona un método no terminal, *in vivo* para identificar compuestos anti-migraña que comprende administrar a un mamífero un compuesto de prueba antes del suministro de un agonista de receptores de CGRP en donde el agonista de receptores de CGRP es administrado n una cantidad capaz de inducir un incremento en el flujo sanguíneo y en donde el compuesto de prueba es administrado en una cantidad capaz de suprimir el incremento inducido por CGRP en el flujo sanguíneo, en donde el mamífero es un mamífero transgénico con RAMP1 humanizado que tiene Trp74 o un mamífero que expresa de manera endógena la RAMP1 que tiene

Trp74.

De acuerdo con otra modalidad del sexto aspecto de la presente invención, se proporciona un método no terminal, *in vivo* para identificar compuestos anti-migraña que comprende administrar a un mamífero un agonista de receptores de CGRP en una cantidad capaz de inducir un incremento en el diámetro de arterias periféricas, seguido por la administración de un compuesto de prueba en una cantidad capaz de invertir el incremento inducido por CGRP en el diámetro de arterias periféricas, en donde el mamífero es un mamífero transgénico con RAMP1 humanizada que tiene Trp74 o un mamífero que expresa de manera endógena la RAMP1 que tiene Trp74.

De acuerdo con otra modalidad del sexto aspecto de la presente invención, se proporciona un método no terminal, in vivo para identificar compuestos anti-migraña que comprende administrar a un mamífero un compuesto de pru ba antes del suministro de un agonista de receptores de CGRP en donde el agonista de receptores de CGRP es administrado en una cantidad capaz de inducir un incremento en el diámetro de arterias periféricas y en donde el compuesto de prueba es administrado en una cantidad capaz de suprimir el incremento inducido por CGRP en el diámetro de arterias periféricas, en donde el mamífero es un mamífero transgénico con RAMP1 humanizada que tiene Trp74 o un mamífero que expresa de

manera endógena RAMP1 que tiene Trp74.

De acuerdo con otras modalidades del sexto aspecto de la presente invención, se proporcionan métodos no terminales, *in vivo* para identificar compuestos anti-migraña como se describe en este texto, en donde el flujo sanguíneo es el flujo sanguíneo facial.

De acuerdo con otras modalidades del sexto aspecto de la presente invención, se proporcionan métodos no terminales, *in vivo* para identificar compuestos anti-migraña como se describe en este texto, en donde el mamífero que expresa de manera endógena la RAMP1 que tiene Trp74 es un primate no humano.

De acuerdo con otras modalidades del sexto aspecto de la presente invención, se proporcionan métodos no terminales, *in vivo* para identificar compuestos anti-migraña como se describe en este texto, en donde el mamífero que expresa de manera endógena la RAMP1 que tiene Trp74 es un hombre.

De acuerdo con otras modalidades del sexto aspecto de la presente invención, se proporcionan métodos no terminales, *in vivo* para identificar compuestos anti-migraña como se describe en este texto, en donde el mamífero que expresa de manera endógena la RAMP1 que tiene Trp74 es un primate no humano y l primate no humano es un titi.

De acuerdo con otras modalidades del sexto aspecto

de la presente invención, se proporcionan métodos no terminales, *in vivo* para identificar compuestos anti-migraña como se describe en este texto en donde los compuestos anti-migraña son antagonistas de receptores de CGRP.

Otras modalidades de la presente invención pueden comprender una combinación adecuada de dos o más de las modalidades y/o aspectos descritos en este texto.

Aún otras modalidades de la presente invención pueden comprender un subconjunto adecuado de una modalidad y/o un aspecto descrito en este texto.

Todavía aún otras modalidades y aspectos de la invención serán aparentes de acuerdo con la descripción proporcionada a continuación.

## Breve Descripción de las Figuras

Figura 1. Análisis Schild.

La respuesta a la dosis de la producción de cAMP estimulada por CGRP en ausencia (cuadros rellenos) y presencia (todos los otros) de concentraciones crecientes (izquierda a derecha) del antagonista de CGRP, ejemplo 2. Esta insertado un diagrama Schild de la relación de dosis logarítmica menos 1 (eje Y) contra la concentración logarítmica del agonista, ejemplo 2 (eje X): Pendiente = 0.94, $K_b$ = 0.16 nM.

Figura 2. Validación Directa del Flujo Sanguín o Facial como Sustituto para la Dilatación de Arterias Intracraniales en la Rata.

El suministro intravenoso de hαCGRP i.v. induce incrementos porcentuales, comparables (100-120% de línea d base) en el diámetro de arterias del meníngeo intermedio y el flujo sanguíneo facial de rata (barras ralladas izquierda y derecha, respectivamente). El tratamiento previo con el antagonista peptídico CGRP(8-37) produce 50% de inhibición de la administración de HαCGRP i.v. subsecuente para ambas medidas (barras rellenas). El diámetro de arterias intracraneales y el flujo sanguíneo facial se midieron concurrentemente en cada animal (n = 5 ratas). Los datos son promedio ± sem * $p < 0.05$, ** $p < 0.01$ vs HαCGRP correspondiente, sola.

Figura 3. Respuesta a la Dosis para HαCGRP en el Flujo Sanguíneo Facial con la Técnica Laser Doppler n Primates no Humanos.

El suministro de HαCGRP induce un incremento dependiente de la dosis en el flujo sanguíneo facial con la técnica Laser Doppler en primates no humanos (por ejemplo, titi común). Los animales (n = 6) recibieron dosis crecientes HαCGRP en intervalos d 30 minutos. Los datos son % de cambio pico de la línea de base ± sem, con cada animal que sirve

como su propio control.

Figura 4. Inhibición de Cambios Inducidos por CGRP en el Flujo Sanguíneo Facial en Primates no Humanos.

El antagonista de CGRP novedoso, ejemplo 2 (barras rellenas) suministrado antes de HαCGRP (barra rallada), inhibe de manera dependiente de la dosis el incremento inducido por CGRP en el flujo sanguíneo facial con la técnica Laser Doppler. El vehículo (barra abierta) no tuvo efecto. Los datos son promedio ± sem (n = 5-6 primates por grupo). *p < 0.05 comparado con CGRP solo.

Figura 5. Efecto del Antagonista de CGRP Sobre la Presión Sanguínea en Primates no Humanos.

En contraste a la inhibición dependiente de la dosis del flujo sanguíneo facial en primates (véase figura 4), el ejemplo 2 tiene un efecto insignificante sobre la presión sanguínea (estudios paralelos en animales separados, n=6). Los animales recibieron dosis repetidas del ejemplo 2 en intervalos de 20 minutos. Los datos BP son promedio ± sem durante un periodo de 20 minutos medido por medio de un esfigmomanómetro.

## Descripción Detallada de la Invención

La descripción d la invención en este texto debe

considerarse en congruencia con las leyes y principios de la unión química. Por ejemplo puede ser necesario remover un átomo de hidrógeno a fin de acomodar un sustituyente en cualquier ubicación dada.

Como se utiliza en este texto, el término "heterocíclico" o "heterociclo" incluye radiales cíclicos que contienen uno o más heteroátomos (por ejemplo, O, N o S), los heterociclos incluyen aquellos que son aromáticos y aquellos que no lo son, es decir "alicíclicos", a menos que se especifique de otra manera.

Como se utiliza en este texto, el término "sistema bicíclico, fusionado" cuando se describe, por ejemplo, un sistema bicíclico 5.6-fusionado que contiene de 1 a 4 átomos de nitrógeno, incluye sistemas aromáticos y alicíclicos, por ejemplo indolizina, indol, isoindol, 3H-indol, indolina, indazol o bencimidazol.

Si un sustituyente es nombrado genéricament , entonces cualquiera y todas las especies de ese genero comprenden ese aspecto de la invención. Por ejemplo, un sustituyente nombrado genéricamente como "pirrolonilo" (el radical de "pirrolona", un pirrol que tiene un carbonilo) incluye pirrol-2-onilos en donde el carbonilo es adyacente al átomo de nitrógeno y pirrol-3-onilos en donde el carbonilo y el átomo de nitróg no ti nen un m tileno intermedio.

De manera similar, la presente invención comprende

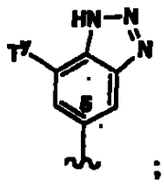
que un sustituyente puede ser unido en cualquiera y todos los puntos adecuados de unión en el sustituyente a menos que se especifique de otra manera.

Sin embargo, se debe entender que los compuestos incluidos por la presente invención son aquellos que son químicamente estables, es decir, los sustituyentes heteroalicíclicos de la presente invención no deben unirse de tal manera que un heteroátomo en el sustituyente heteroalicíclico sea alfa con respecto a un punto de unión en donde el punto de unión también sea un heteroátomo.

Una modalidad o aspecto, que depende de otra modalidad o aspecto, describirá solo las variables que tienen valores o condiciones que difieren de la modalidad o aspecto del cual depende. Por ejemplo, si una modalidad dependiente se dirige solo a $R^2$, entonces las variables y condiciones relacionadas con $R^2$ deben reflejar de que modalidad dependen.

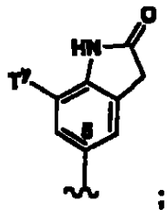
Si una variable es calificada con un valor de cero, entonces una unión que enlaza la variable ya no debe ser representada.

Como se utiliza en este texto, el término "alquileno" significa un alcano divalente, *es decir*, un alcano que tiene dos átomos de hidrógeno removidos del alcano (el átomo de hidrógeno removido de dos diferentes átomos de carbono cuando el alcano contiene más de un átomo de carbono), por ej mplo $-CH_2CH_2CH_2-$.



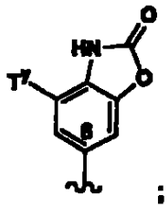
;

1,3-Dihidro-indol-2-on-5-ilo



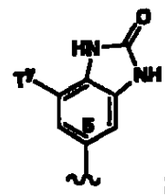
;

3H-Benzooxazol-2-on-6-ilo



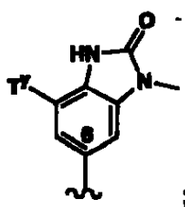
;

1,3-Dihidro-benzoimidazol-2-on-5-ilo



;

1-Metil-1,3-dihidro-benzoimidazol-2-on-6-ilo



;

3,4-Dihidro-1H-quinolin-2-on-6-ilo

que un sustituyente puede ser unido en cualquiera y todos los puntos adecuados de unión en el sustituyente a menos que se especifique de otra manera.

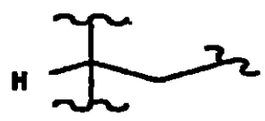
Sin embargo, se debe entender que los compuestos incluidos por la presente invención son aquellos que son químicamente estables, es decir, los sustituyentes heteroalicíclicos de la presente invención no deben unirse de tal manera que un heteroátomo en el sustituyente heteroalicíclico sea alfa con respecto a un punto de unión en donde el punto de unión también sea un heteroátomo.

Una modalidad o aspecto, que depende de otra modalidad o aspecto, describirá solo las variables que tienen valores o condiciones que difieren de la modalidad o aspecto del cual depende. Por ejemplo, si una modalidad dependiente se dirige solo a $R^2$, entonces las variables y condiciones relacionadas con $R^2$ deben reflejar de que modalidad dependen.

Si una variable es calificada con un valor de cero, entonces una unión que enlaza la variable ya no debe ser representada.

Como se utiliza en este texto, el término "alquileno" significa un alcano divalente, *es decir*, un alcano que tiene dos átomos de hidrógeno removidos del alcano (el átomo de hidrógeno removido de dos diferentes átomos de carbono cuando el alcano contiene más de un átomo de carbono), por ejemplo $-CH_2CH_2CH_2-$.

Como se utiliza en este texto, el término "alquilideno" significa un alcano que tiene dos átomos de hidrógeno removidos de un átomo de carbono en el alcano, *por ejemplo,*




Se debe entender que las designaciones de enlace doble alternante en el anillo de seis miembros de la estructura fusionada de 5,6-miembros representada en la fórmula (I) son relativas y presentan los electrones orbitales π sacados de su lugar del anillo.

Como se utiliza en este texto, el término "arilo" o "ar-" incluye fenilo o naftilo.

Como se utiliza en este texto, el término "heterociclico" o "heterociclo" incluye tanto heteroarilo como heteroalicíclico.

Como se utiliza en este texto, el término "halo" o "halógeno" incluye flúor, cloro, bromo y yodo y además significa que uno o más de los mismos o diferentes átomos de halógeno pueden ser sustituidos en un radical respectivo.

A menos que se especifique de otra manera, los hidrocarburos acíclicos tales como alquilo, alcoxi, alquenilo y alquinilo pueden ser de cadena recta o ramificada.

Se debe entender que la presente invención puede

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incluir cualquiera y todos los posibles estereoisómeros, isómeros geométricos, diastereoisómeros, enantiómeros, anómeros e isómeros ópticos, a menos que una descripción particular especifique de otra manera.

Como su utiliza en este texto, el término "Trp74" significa que el 74º residuo de RAMP1 es triptófano (Mallee y colaboradores, *J Biol Chem* 2002, *277*, 14294-8) incorporado por referencia en este texto.

Como su utiliza en este texto, el término "compuesto anti-migraña" incluye cualquier compuesto, péptido o fragmento peptídico (modificado o no modificado) capaz de revertir o atenuar la vasodilatación mediada por receptores de CGRP (por ejemplo, antagonistas de receptores de CGRP).

Como su utiliza en este texto, el término "compuesto de prueba" incluye cualquier compuesto, péptido o fragmento peptídico (modificado o no modificado) que se someta a prueba para determinar si es capaz de revertir o atenuar la vasodilatación mediada por receptores de CGRP (*por ejemplo*, antagonistas de receptores de CGRP putativos).

Como su utiliza en este texto, el término "agonista de receptores de CGRP" incluye cualquier compuesto, péptido o fragmento peptídico (modificado o no modificado) capaz de inducir la vasodilatación mediada por receptores de CGRP particularmente, *por ejemplo*, αCGRP o βCGRP; otros miembros de la familia de calcitonina, *por ejemplo*, adrenomedulina;

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fragmentos de CGRP N-terminales, *por ejemplo*, CGRP(1-12) CGRP(1-15) y CGRP(1-22); versiones de amida C-terminal (NH2) de CGRP, *por ejemplo*, CGRP(1-8+NH2), CGRP(1-13+NH2) o CGRP(1-14+NH2); y análogos de CGRP de origen no natural, *por ejemplo*, [Ala$^1$ψCH2NH)Cys$^2$]hCGRP el cual contiene un enlace pseudopeptídico entre Ala$^1$ y Cys$^2$. *Véase* 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. 31 de Enero de 2003; 110(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. Noviembre de 1989; 251(2):718-25 incorporadas en este texto a manera de referencia.

Los compuestos de esta invención pueden existir en la forma de sales farmacéuticamente aceptables. Estas sales pueden incluir sales de adición con ácidos inorgánicos tales como, por ejemplo, ácido clorhídrico y ácido sulfúrico y con ácidos orgánicos tales como, por ejemplo, ácido acético, ácido cítrico, ácido metanosulfónico, ácido toluensulfónico, ácido tartárico y ácido maleico. Además, en caso que los compuestos de esta invención contengan un grupo ácido, el

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grupo ácido puede existir en la forma de sales de metales alcalinos tales como, por ejemplo, una sal de potasio y una sal sódica; sales de metales alcalinotérreos tales como, por ejemplo, sal de magnesio y 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, una sal de sacarina o una sal de maleato puede ser de beneficio particular. Los compuestos de la presente invención pueden ser hidratados o no hidratados.

Los compuestos de esta invención pueden administrarse en formas de dosificación orales, tales como tabletas, cápsulas (cada una de las cuales incluye formulaciones de liberación sostenida y de liberación a través del tiempo), píldoras, polvos, gránulos, elixires, tinturas, suspensiones, jarabes y emulsiones. Los compuestos de esta invención también pueden administrase por vía intravenosa, intraperitoneal, subcutánea o intramuscular, todas utilizando las formas de dosificación bien conocidas para aquellas personas expertas en el campo farmacéutico. Los compuestos pueden administrarse solos, pero serán administrados generalmente con un portador farmacéutico seleccionado en base a la ruta de administración seleccionada y la práctica farmacéutica estándar. Los compuestos de esta invención también pueden administrarse en forma intranasal mediante el uso tópico de vehículos intranasales, adecuados o

mediante rutas transdérmicas, utilizando parches transdérmicos para la piel. Cuando los compuestos de esta invención son administrados por la ruta transdérmica, la dosificación será continua por todo el régimen de dosificación.

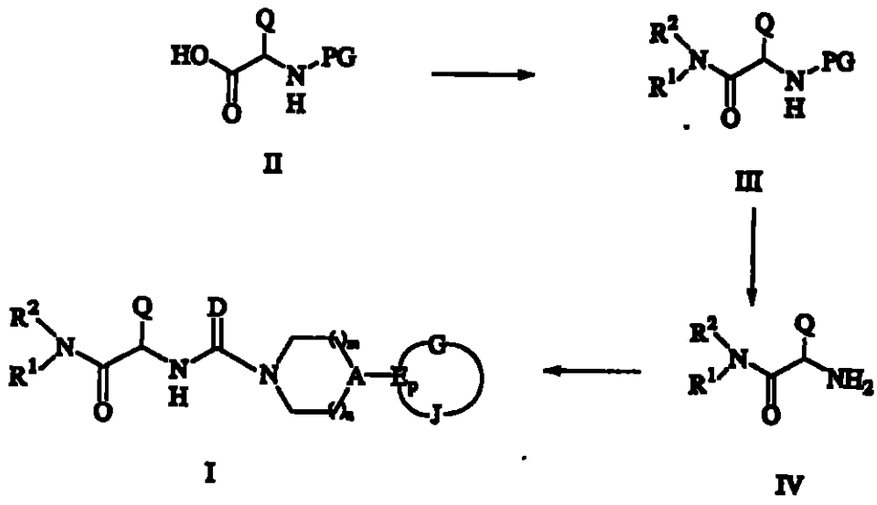
Mientras que la dosificación de 0.01 mg/kg a 30 mg/kg se contempla para los compuestos de la presente invención, la dosificación y régimen de dosificación y la planificación de los compuestos de la presente invención deben ajustarse cuidadosamente en cada caso, utilizando un juicio profesional bien pensado y considerando la edad, peso y condición del receptor, la ruta de administración y la naturaleza y grado de la condición de la enfermedad. De acuerdo con la buena práctica clínica, se prefiere administrar los presentes compuestos en un nivel de concentración el cual producirá efectos benéficos, efectivos sin causar ningún efecto colateral dañino o desfavorable.

## Síntesis

Los compuestos de la presente invención pueden sintetizarse de acuerdo con los esquemas de reacción generales proporcionados a continuación. Las variables proporcionadas en los esquemas de reacción posteriores se definen de acuerdo con la descripción de los compuestos de

la fórmula anterior a menos que se especifique de otra manera. Los compuestos de la presente invención pueden prepararse de acuerdo con el esquema de reacción 1 o el esquema de reacción 2. También puede ser posible utilizar variaciones de los esquemas de reacción para preparar los compuestos de las presentes invenciones, las variaciones conocidas para aquellas personas expertas ordinarias en el campo.

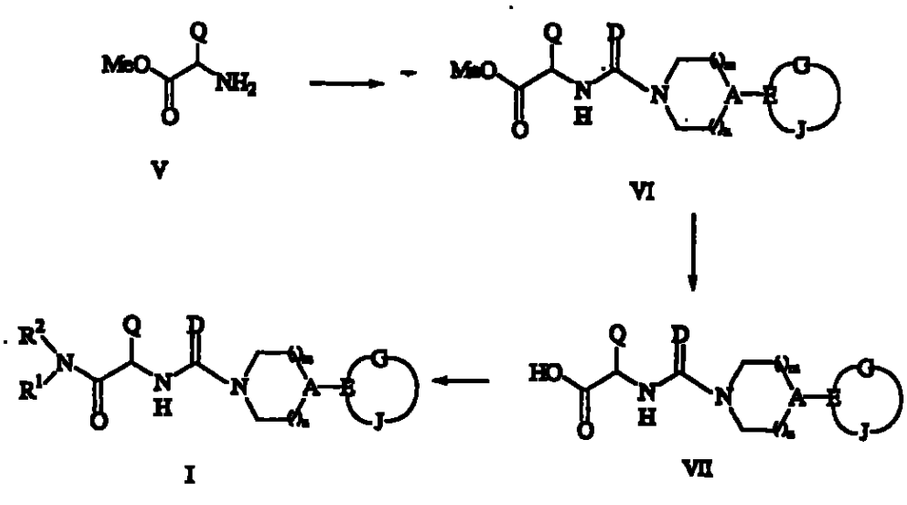
Esquema de Reacción 1. Síntesis de los Compuestos de la Fórmula I




La síntesis descrita en el esquema de reacción 1 comienza con un compuesto de la fórmula II, el cual es un aminoácido con una terminación amino protegida. Los grupos protectores amino comunes (PG) incluyen BOC, CBZ y FMOC y su adición y su remoción son bien conocidas en el campo. El

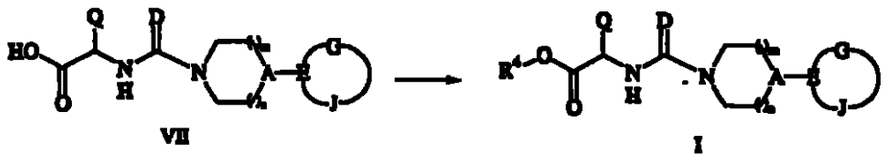
radical de ácido carboxílico de un compuesto de la fórmula II es acoplado con una amina de la fórmula $HNR^1R^2$ utilizando reactivos de acoplamiento peptídicos, estándar para formar una amida de la fórmula III. El grupo protector amino es removido para dar por resultado un compuesto de la fórmula IV. Este compuesto luego es acoplado con una amina de la fórmula V (véase posteriormente) en una reacción de urea mezclada o isóstero de urea, para generar un compuesto de la fórmula I. La formación de urea mezclada es llevada convenientemente utilizando fosgeno, carbonato de disuccinimidilo, carbonil-diimidazol u otros equivalentes. La formación de isósteros de urea, tal como cianoguanidinas y sulfonilguanidinas, es conocida en la literatura.

Esquema de Reacción 2. Síntesis de los Compuestos de la Fórmula I



La síntesis descrita por el esquema de reacción 2 comienza con un compuesto de la fórmula V, el cual es un aminoácido con una terminación de carboxilato protegida. La protección es generalmente un éster metílico, pero también se pueden utilizar otros grupos protectores tales como ésteres etílicos, t-butílicos y bencílicos. El compuesto de la fórmula V es acoplado con una amina de la fórmula VIII (véase posteriormente) en una reacción de urea mezclada o isóstero de urea, como antes, para generar un compuesto de la fórmula VI. El compuesto de la fórmula VI es convertido a un compuesto de ácido libre de la fórmula VII, el cual luego es acoplado con una amina de la fórmula $HNR^1R^2$ para generar un compuesto de la fórmula I.

Esquema de Reacción 3. Síntesis de los Compuestos de la Fórmula I



VII I

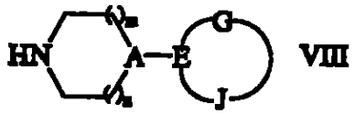
La síntesis descrita por el esquema de reacción 3 comienza con un compuesto de la fórmula VII del esquema de reacción 2. El compuesto de la fórmula V es acoplado con un alcohol, $R^4$-OH. Estas reacciones para la formación de ésteres son bien conocidas en el campo y se pueden llevar

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a cabo, por ejemplo, con reactivos de acoplamiento de carbodiimida, tales como N,N-diciclohexilcarbodiimida. Además, es frecuentemente ventajoso, especialmente para los ésteres de alcoholes secundarios y terciarios, incluir aditivos que aceleren las acilaciones, tal como 4-dimetilaminopiridina.

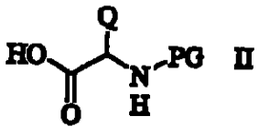
Preparación de aminas de $HNR^1R^2$ y la Fórmula VIII

Las aminas de la fórmula VIII y $HNR^1R^2$ son comercialmente disponibles, son elaboradas por medio de métodos bibliográficos o descritos en este texto.

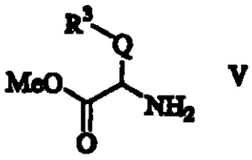


VIII

Preparación de aminoácidos de la Fórmula II y la Fórmula V



II

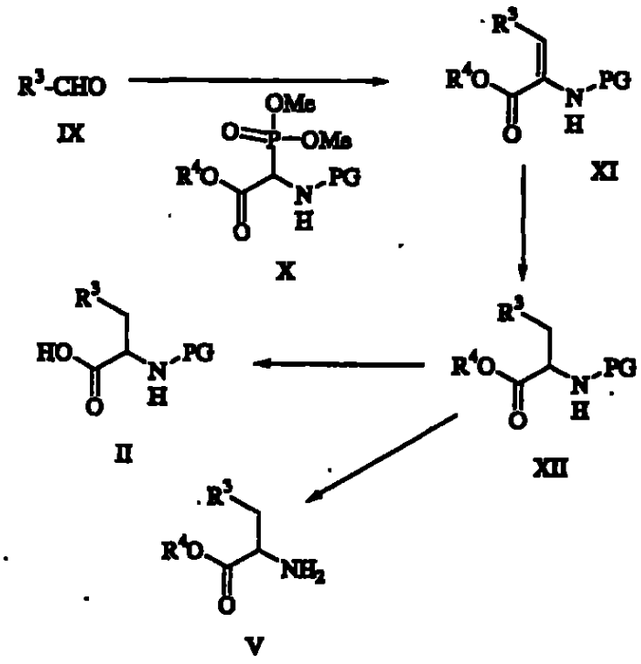


V

Los aminoácidos de la fórmula II y la fórmula V pueden ser comercialmente disponibles o se pueden elaborar como se describe en el esquema de reacción 4.

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Esquema de Reacción 4. Síntesis de los Compuestos de la Fórmula II y Fórmula V

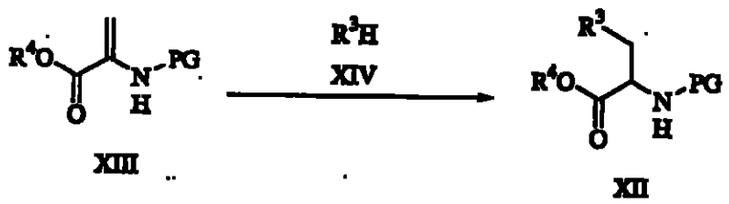



La síntesis descrita en el esquema de reacción IV comienza con un aldehído de la fórmula IX, el cual se hace reaccionar con un fosfonato de glicina de la fórmula X en una reacción de acoplamiento Wadsworth-Emmons. El compuesto de la fórmula X es desprotonado con una base, tal como diazabicicloundeceno y tetrametilguanidina u otras bases orgánicas o inorgánicas bien conocidas en el campo. El enlace doble del compuesto de la fórmula XI resultante se reduce para proporcionar los compuestos de la fórmula XII. La reducción se puede llevar a cabo para proporcionar ya sea un racemato o mediante el uso de un

catalizador estereoselectivo para proporcionar cualquier enantiómero de la fórmula XII. Estas reducciones pueden resultar de la hidrogenación de transferencia de donadores de hidrógeno tal como ácido fórmico o ciclohexadieno o la hidrogenación utilizando hidrógeno gaseoso, ambas en presencia de un catalizador adecuado. Los compuestos de la fórmula II se preparan mediante la hidrólisis de ácidos o bases del éster. Los compuestos de la fórmula V se preparan mediante la remoción del grupo protector (PG) utilizando métodos bien conocidos en el campo.

Otros derivados de aminoácidos de la fórmula XII pueden prepararse como se muestra en esquema de reacción 5.

Esquema de Reacción 5. Síntesis de la Fórmula XII

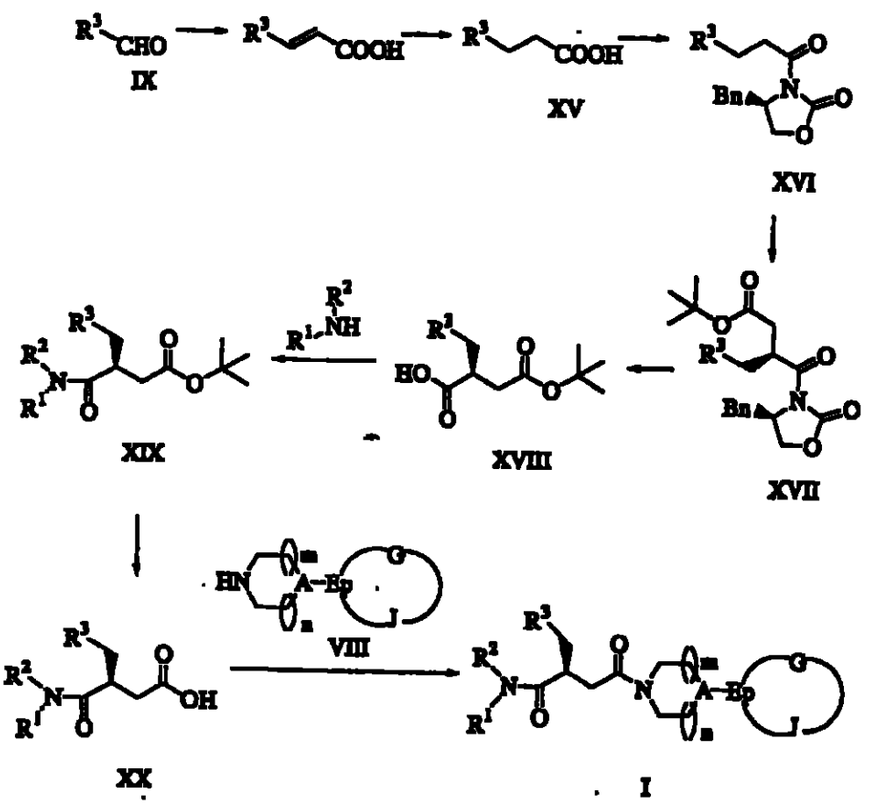



XIII XII

Donde, para propósitos del esquema de reacción 5, los compuestos de la fórmula XIV son compuestos nucleofílicos, tales 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 acuerdo con el esquema de reacción 6 o el esquema de reacción 7. También puede ser posible utilizar variaciones de los esquemas de reacción para preparar los compuestos de las presentes invenciones, las variaciones conocidas para aquellas personas de experiencia ordinaria en el campo

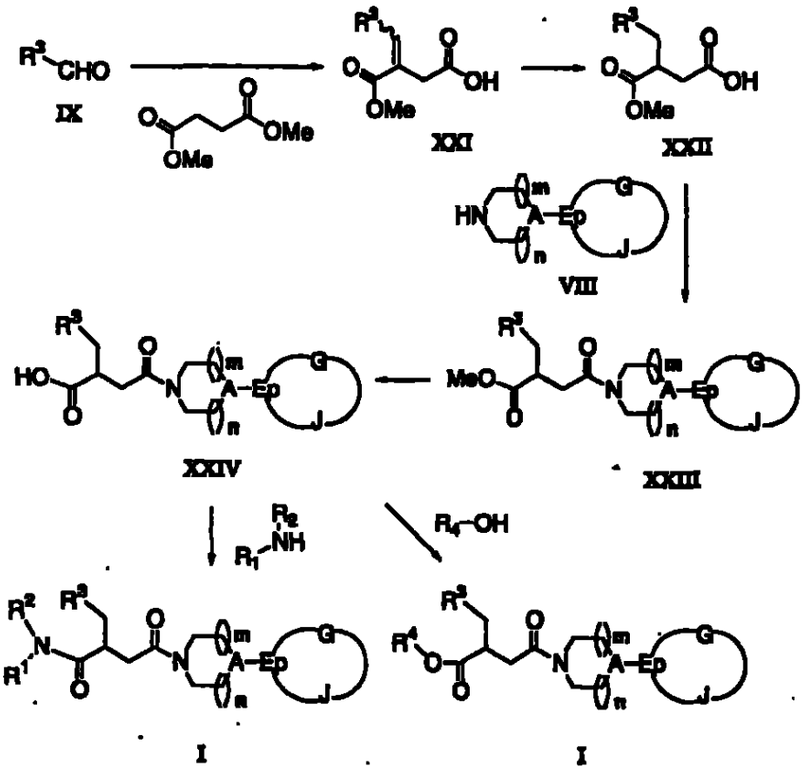
Esquema de Reacción 6. Síntesis de los Compuestos de la Fórmula I



La síntesis descrita en el esquema de reacción 6 comienza con aldehídos comercialmente disponibles o sintetizados. La homologación de dos átomos de carbono y la reducción de doble enlace son bien conocidos en la bibliografía y conducen a los compuestos de la fórmula XV. Algunos compuestos de la fórmula XV también son comercialmente disponibles y otros pueden prepararse por medio de otros métodos bien conocidos en el campo. La preparación de compuestos de la fórmula XVI y XVII es conocida en la bibliografía como substratos y productos de la síntesis asimétrica, quiral de Evans. La hidrólisis conduce 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 los compuestos de la fórmula XIX utilizando protocolos de acoplamiento de amida bien conocidos. La hidrólisis del éster *terc*-butílico conduce a los compuestos de la fórmula XX, los cuales pueden ser acoplados adicionalmente con los compuestos de la fórmula VIII para proporcionar los compuestos de la fórmula I.

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Esquema de Reacción 7. Síntesis de los Compuestos de la Fórmula I

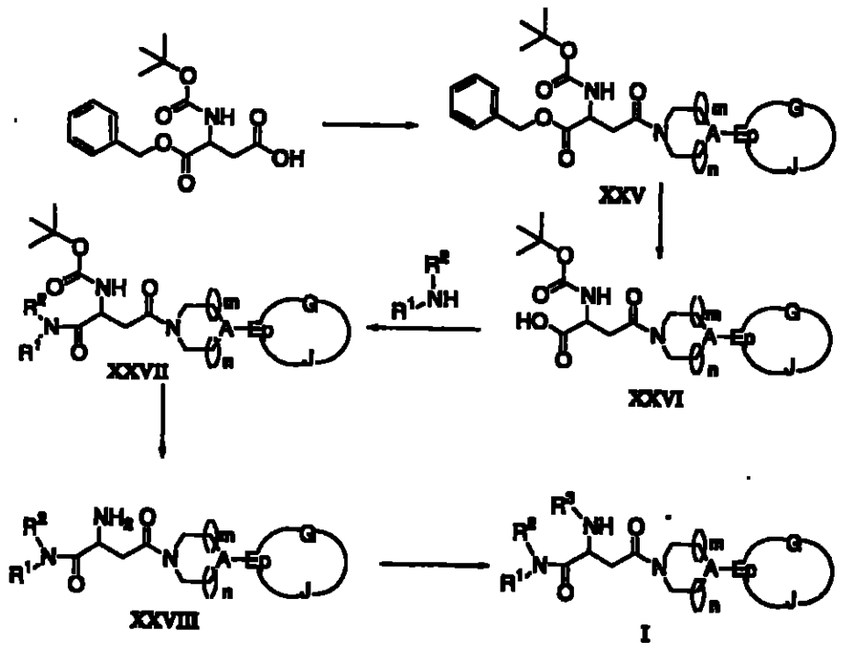



El esquema de reacción 7 también inicia con aldehídos comercialmente disponibles o sintetizados. Estos se hacen reaccionar con succinato de dimetilo en presencia de bases para proporcionar los compuestos de la fórmula XXI. El enlace doble del compuesto de la fórmula XXI es reducido para proporcionar los compuestos de la fórmula XXII. La reducción se puede llevar a cabo para proporcionar ya sea un racemato o mediante el uso de un catalizador esteroselectivo para proporcionar cualquier enantiómero de la fórmula XXII. Estas reducciones pueden resultar de la hidrogenación de transferencia de donadores de

hidrógeno, tales como ácido fórmico o ciclohexadieno, o la hidrogenación utilizando hidrógeno gaseoso, ambas en presencia de un catalizador adecuado. Un acoplamiento de amida con aminas de la fórmula VIII conduce a los compuestos de la fórmula XXIII utilizando protocolos de síntesis de amida bien conocidos. La hidrólisis de éster metílico conduce a los compuestos de la fórmula XXIV, los cuales son acoplados adicionalmente con varias aminas o alcoholes para proporcionar las amidas de la fórmula I y los ésteres de la fórmula I, respectivamente.

Los compuestos de fórmula I también se pueden preparar de acuerdo con el esquema de reacción 8.

Esquema de Reacción 8. Síntesis de los Compuestos de la Fórmula I

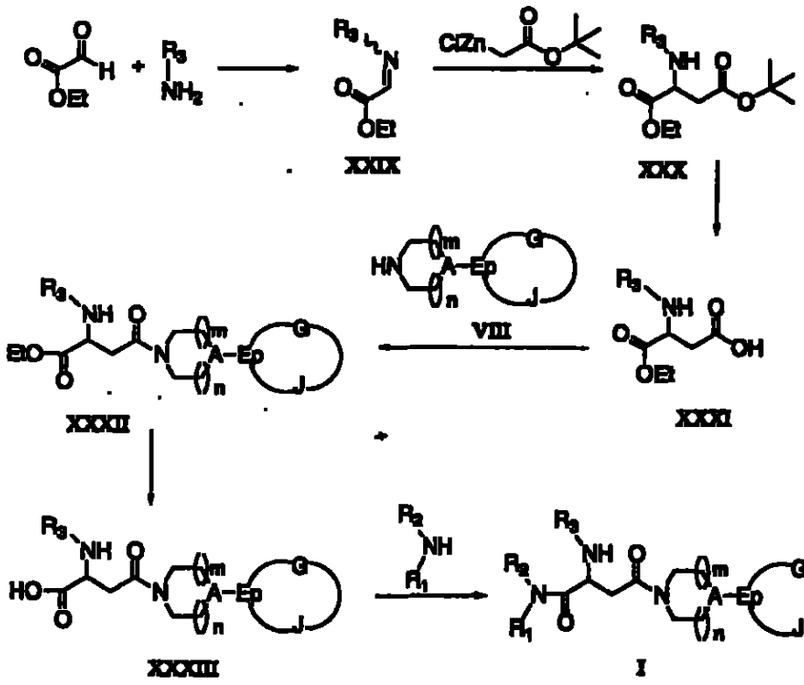


La síntesis descrita en el esquema de reacción 8 comienza con un éster bencílico del ácido N-*terc*-butiloxicarbonil-L-aspártico comercialmente disponible. De manera diferente, los derivados de ácido aspártico protegidos también pueden utilizarse por conveniencia sintética. El grupo beta-carboxilo es acoplado con aminas de la fórmula VIII utilizando protocolos de acoplamiento peptídicos estándar. El grupo protector alfa-carboxilo del compuesto de la fórmula XXV es removido por medio de la hidrogenólisis para proporcionar los compuestos de la fórmula XXVI. Estos son acoplados adicionalmente con aminas de la fórmula $HNR^1R^2$ para proporcionar los compuestos de la fórmula XXVII. El grupo protector amino es removido mediante el tratamiento con ácidos fuertes, tales como ácido trifluoroacético o cloruro de hidrógeno en solventes orgánicos. Los compuestos resultantes de la fórmula XXVIII luego se hacen reaccionar con una variedad de reactivos electrofílicos para generar los compuestos de la fórmula I. Por ejemplo, éstos pueden ser acoplados con compuestos halo-aromáticos utilizando métodos conocidos que involucran el calentamiento a diversas temperaturas o mediante la catálisis con metales de transición, tales como paladio o cobre, ya sea en cantidades estoquiométricas o como catalizadores. Estos también pueden reaccionar con varios aldehídos o cetonas bajo condiciones de alquilación reductiva, bien descritas en el campo. Estos

también pueden reaccionar con isocianatos, cloruros de acilo o cloruros de carbamoilo para generar derivados de urea, amida o carbamato, respectivamente. Se entiende que la secuencia de las modificaciones descritas anteriormente pueden cambiarse dependiendo de la selección de los grupos protectores y el orden de su remoción

Los compuestos de la fórmula I también se pueden preparar de acuerdo con el esquema de reacción 9.

Esquema de Reacción 9. Síntesis de los Compuestos de la Fórmula I




La síntesis descrita en el esquema de reacción 9 comienza con una imina de la fórmula XXIX, preparada mediante

la condensación de glioxalato de etilo y aminas de la fórmula $R^3$-$NH_2$. Estas se hacen reaccionar con cloruro de 2-*terc*-butoxi-2-oxoetilzinc para proporcionar los compuestos de la fórmula XXX. El tratamiento con ácidos fuertes remueve el grupo protector de éster *terc*-butílico para proporcionar ácidos libres de la fórmula XXXI, los cuales son acoplados a aminas de la fórmula VIII para producir los compuestos de la fórmula XXXII. El éster etílico es hidrolizado con una sal de hidróxido de metal o base acuosa para proporcionar ácidos alfa libres de la fórmula XXXIII. A su vez, estos son acoplados con aminas de la fórmula $HNR^1R^2$ para proporcionar los compuestos de la fórmula I.

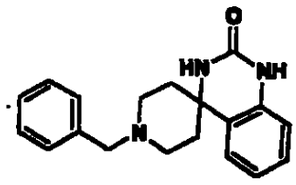
Productos Intermediarios de ureidoamida y Ejemplos

General. Los espectros de RMN $^1H$ y $^{13}C$ se desarrollaron en un instrumento Bruker de 500 o 300 MHz y los cambios 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, los análisis de CL/EM se llevaron a cabo en un instrumento Shimadzu utilizando una columna YMC C18 (3 x 50 mm) empleando un gradiente lineal de 2 minutos de 0% a 100% del solvente B en A en una corrida de 3 minutos. Para CL/EM y para el sistema de CLAR preparativa Shimadzu, el Solvente A fue: 10% de metanol/90% de agua/0.1% de ácido

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trifluoroacético, y el solvente B fue 90% de metanol/10% de agua/0.1% de ácido trifluoroacético con un detector de luz UV ajustado a 220 nm.

1-Bencil-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'(1'H)-quinazolina



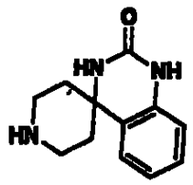

El ácido polifosfórico (113 g) se calentó a 100-110°C y se agitó mientras que se adicionaba 1-bencil-piperidin-4-ona (9.27 ml, 50 mmol). Inmediatamente después, se adicionó fenil-urea (9.55 g, 70.mmol) en porciones suficientemente pequeñas para evitar la formación excesiva de espuma. La mezcla se calentó a 150-160°C durante toda la noche. Luego se adicionó lentamente agua (200 mL) a la mezcla que se había dejado enfriar a 100-110°C (a temperaturas inferiores la mezcla se vuelve demasiado viscosa para agitarse). La solución resultante se neutralizó con NaOH 10N a aproximadamente pH 8, y luego se extrajo con cloroformo. La fase orgánica se secó sobre sulfato de magnesio y luego se concentró para proporcionar el producto crudo, el cual se purificó mediante la cromatografía en columna con evaporación instantánea sobre gel de sílice (acetato de etilo/hexanos 6:4) para proporcionar el producto deseado (9.0 g, 58%).

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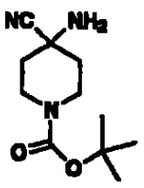
Espectro de Masas: 308.25 $(MH)^+$.

2',3'-Dihidro-2'-oxoespiro-[piperidin-4,4'(1'H)-quinazolina



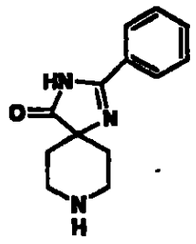
A una solución de 1-bencil-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'(1'H)-quinazolina (1.00 g) en metanol desgasificado (50 ml) y ácido clorhídrico 6N (2.0 ml) se adicionó carbón vegetal con paladio al 10% (150 mg). La mezcla se agitó en un aparato Parr bajo una atmósfera de hidrógeno a 4.213 $kg/cm^2$ (60 psi) durante toda la noche. La CL/EM mostró una reacción incompleta. Se adicionó más carbón vegetal con paladio al 10% (200 mg), y la mezcla se agitó durante 2 días más. En ese punto, todo el material de inicio se consumió. La mezcla se filtró y el producto filtrado se concentró para proporcionar 531 mg del compuesto deseado (64%). Espectro de Masas: 218.12 $(MH)^+$.

Ester *terc*-butílico del ácido 4-amino-4-ciano-piperidin-1-carboxílico



A una solución bien agitada de éster terc-butílico del ácido 4-oxo-piperidin-1-carboxílico (9.0 g, 45.3 mmol) en metanol se adicionó cloruro de amonio (2.66 g, 49.8 mmol) a temperatura ambiente y se agitó durante 1 hora. Se adicionó cianuro de sodio (2.44 g, 49.8 mmol) y la agitación continuó durante 16 horas adicionales. La mezcla de reacción se enfrió rápidamente con carbonato ácido de sodio acuoso al 5% (50 mL), se diluyó con agua y el metanol se removió mediante la evaporación giratoria. La cianoamina se extrajo con cloruro de metileno (3x 100 mL), se secó sobre sulfato de sodio y los solventes se evaporaron para proporcionar el compuesto deseado como un aceite en un rendimiento del 91%. RMN-$^1$H (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). Espectro de Masas: 226 $(MH)^+$.

Clorhidrato de 2-fenil-1,3,8-triaza-espiro[4.5]dec-1-en-4-ona




A una solución de éster *terc*-butílico del ácido 4-amino-4-ciano-piperidin-1-carboxílico (1.0 g, 4.44 mmol) en cloruro de metileno (30 mL) se adicionó trietilamina (1.24

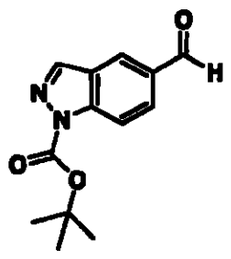
mL, 8.88 mol), seguido por cloruro de benzoilo (936 mg, 6.66 mmol). Después de 30 minutos, se adicionó la 4-(dimetilamino)piridina (40 mg, 0.33 mmol) y la agitación continuó durante 12 horas adicionales. La mezcla de reacción luego se enfrió rápidamente con hidróxido de sodio 1M (10 mL), se diluyó con 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 *terc*-butílico del ácido 4-benzoilamino-4-ciano-piperidin-1-carboxílico, se obtuvo en un rendimiento del 90% a través de la cristalización utilizando acetato de etilo al 30% en hexano como un solvente.

A una solución de éster *terc*-butílico del ácido 4-benzoilamino-4-ciano-piperidin-1-carboxílico (1.3 g, 4 mmol) en etanol (10 mL) se adicionó hidróxido de sodio 6M (1.5 mL) seguido por peróxido de hidrógeno al 30%. La mezcla de reacción luego se calentó a reflujo durante 3 horas. 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 *terc*-butílico del ácido 4-oxo-2-fenil-1,3,8-triaza-espiro[4.5]dec-1-en-8-carboxílico, se obtuvo en un rendimiento del 80% a través de la cristalización de acetato de etilo al 30% en

hexano. El éster *terc*-butílico luego se disolvió en cloruro de metileno (5 mL) y se adicionó una solución saturada de cloruro de hidrógeno en dioxano (25 mL). Después de 2 horas, el solvente se removió para proporçionar el clorhidrato de 2-fenil-1,3,8-triaza-espiro[4.5]dec-1-en-4-ona como un polvo de color blanco en un rendimiento del 95%. RMN-$^1$H (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, 1H), 2.47-2.44 (m, 4 H). Espectro de Masas: 230 $(MH)^+$.

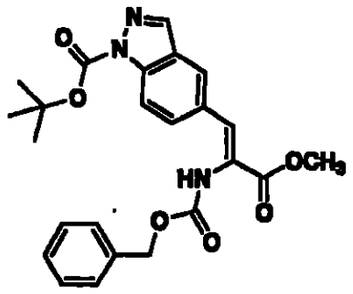
Ester *terc*-butílico del ácido 5-formil-indazol-1-carboxílico



Una solución en cloruro de metileno (2 mL) de di-*terc*-butildicarbonato (388 mg, 1.78 mmol) se adicionó gota a gota a temperatura ambiente a una solución de 1*H*-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 de color amarillo brillante, resultante se agitó a temperatura ambiente durante 16 horas. Los solventes se removieron *in vacuo* y el residuo

se sujetó a la cromatografía con evaporación instantánea con gel de sílice (25 g) y acetato de etilo/hexanos (1:1) que contenía trietilamina al 1% como eluyente para proporcionar el compuesto del título como un líquido de color amarillo pardusco castaño (414 mg, 90%). RMN-$^1$H ($CDCl_3$, 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). RMN-$^{13}$C ($CDCl_3$, 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.

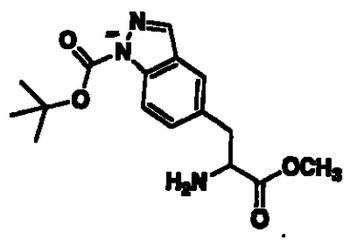
Ester *terc*-butílico del ácido 5-(2-benciloxicarbonilamino-2-metoxicarbonil-vinil)-indazol-1-carboxílico




Una solución de éster trimetílico de *N*-(benciloxicarbonil)-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 minutos. A esto se adicionó lentamente una solución de éster *terc*-butílico del ácido 5-formil-indazol-1-carboxílico (3.72 g, 15.1 mmol) en tetrahidrofurano (25 mL) por medio de una jeringa durante

10 minutos. La mezcla de reacción se agitó a -78°C durante 4 horas y luego se dejó calentar a temperatura ambiente durante toda la noche. El solvente se evaporó y el residuo resultante se sujetó a la cromatografía en columna con evaporación instantánea sobre gel de sílice (acetato de etilo/hexano 1:2) para proporcionar el compuesto del título como una espuma de color blanco (5.77 g, 85%). RMN-$^1$H ($CDCl_3$, 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 (s amplio, 5H), 6.43 (s amplio, 1H), 5.09 (s, 2H), 3.84 (s, 3H), 1.72 (s, 9H). Espectro de Masas: 452 $(NH)^+$.

Ester *terc*-butílico del ácido (±)-5-(2-amino-2-metoxicarbonil-etil)-indazol-1-carboxílico

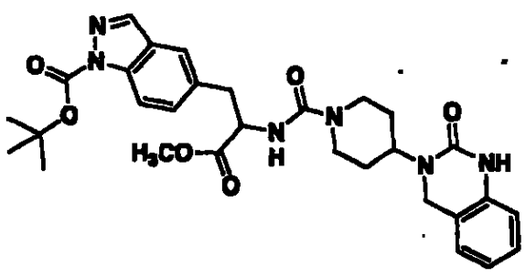


Una mezcla de éster *terc*-butílico del ácido 5-(2-benciloxicarbonilamino-2-metoxicarbonil-vinil)-indazol-1-carboxílico (524 mg, 1.16 mmol) y paladio al 10% sobre carbono (60 mg) en metanol (20 mL) se agitó durante 4.5 horas bajo una presión de hidrógeno gaseoso de 3.511 kg/cm$^2$ (50 psi) utilizando un hidrogenador 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 producto filtrado de metanol se evaporó para proporcionar el compuesto del título (351 mg, 95%). RMN-$^1$H ($CDCl_3$, 500 MHz) δ 8.12-8.10 (m, 2H), 7.55 (s amplio, 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 Masas: 320 (MH)+.

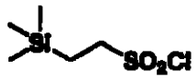
Ester *terc*-butílico del ácido (±)-5-(2-metoxicarbonil-2-{[4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carbonil]-amino}-etil)-indazol-1-carboxílico



Una solución de éster *terc*-butílico del ácido 5-(2-amino-2-metoxicarbonil-etil)-indazol-1-carboxílico (307 mg, 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 minutos a temperatura ambiente. Se adicionó la 3-piperidin-4-il-3,4-dihidro-1*H*-

quinazolin-2-ona (238 mg, 1.03 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. El solvente se evaporó y el residuo se sujetó a la cromatografía con evaporación instantánea utilizando cloruro de metileno/metanol/trietilamina (93:5:2) como eluyente, para proporcionar el producto (259 mg, 47%). RMN-$^1$H ($CDCl_3$, 300 MHz) δ 8.13-8.10 (m, 2H), 7.48 (s amplio, 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). Espectro de Masas: 577 $(MH)^+$.

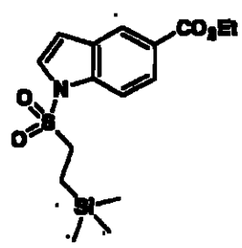
Cloruro de 2-trimetilsilanil-etanosulfonilo




El cloruro de sulfurilo (43 ml, 539 mmol) se adicionó en 3 minutos 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 tres cuellos, secado a la flama. Después de la agitación a 0°C durante 5 minutos, el baño de agua helada se removió y se adicionó 2-trimetilsililetanosulfonato de sodio (50 g, 245 mmol) en

porciones durante 10 minutos. La suspensión de color blanco, resultante se agitó a temperatura ambiente durante 16 horas, luego se filtró a través de una almohadilla de celite. El producto filtrado se concentró a aproximadamente 50 mL, se adicionaron acetato de etilo/hexanos (1:3, 1000 mL) y celite (40 g). La mezcla se agitó a temperatura ambiente durante 15 minutos 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-humedecida con gel de sílice (300 mL) utilizando acetato de etilo/hexanos 1:3 como el eluyente. Los solventes se removieron y el compuesto del título se obtuvo como un líquido de color canela claro (41.9 g, 85%). Si no se utiliza inmediatamente, el producto final se debe almacenar bajo nitrógeno en un congelador o refrigerador para minimizar la descomposición RMN-$^1$H ($CDCl_3$, 500 MHz) δ 3.61-3.57 (m, 2H), 1.32-1.27 (m, 2H), 0.10 (s, 9H).

Ester etílico del ácido 1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-carboxílico

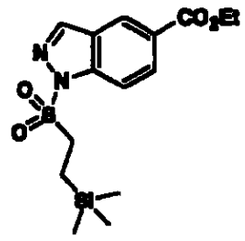



Una solución de éster etílico del ácido 1*H*-indol-5-

carboxílico (10.31 g, 58.8 mmol) en dimetilformamida (50 mL) se adicionó 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 minutos, luego se adicionó lentamente a 0°C una solución de cloruro de 2-trimetilsilaniletanosulfonilo (17.7 g, 88.2 mmol) en dimetilformamida (100 mL) a la mezcla anterior. Después de 2 horas, se adicionó cloruro de amonio acuoso, saturado (200 mL) 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 sujetó a la cromatografía con evaporación instantánea sobre gel de sílice utilizando cloruro de metileno/hexanos 1:1.5 como eluyente para proporcionar el compuesto del título como un sólido de color blanco (15.8 g, 79%). RMN-$^{1}$H ($CDCl_3$, 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). RMN-$^{13}$C ($CDCl_3$, 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 Masas 354.12 $(MH)^+$.

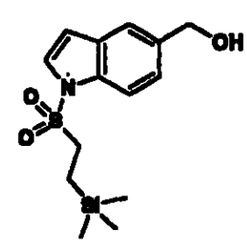
Preparado de manera similar:

Ester etílico del ácido 1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-carboxílico



RMN-$^{1}$H ($CDCl_3$, 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). RMN-$^{13}$C ($CDCl_3$, 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 Masas 355.13 $(MH)^{+}$.

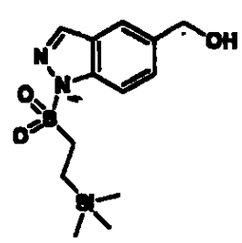
[1-(2-Trimetilsilanil-etanosulfonil)-1*H*-indol-5-il]-metanol



Una solución de hidruro de diisobutilaluminio (82.9 mL, 1M en tolueno, 82.9 mmol) se adicionó lentamente a 0°C a la solución del éster etílico del ácido 1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-carboxílico (8.81 g, 25.9 mmol) en

tolueno (200 mL). Después de que se agitó a 0°C durante 45 minutos, la reacción se enfrió rápidamente mediante la adición de metanol (26 mL), decahidrato de sulfato de sodio pulverizado (194 g) y celite (26 mL). La mezcla se calentó a temperatura ambiente en 1 hora y se filtró a través de una almohadilla de celite. Los solventes se removieron *in vacuo* para proporcionar el compuesto del título como un líquido muy viscoso, el cual se solidificó con el enfriamiento. Un sólido de color blanco (8.08 g, rendimiento del 100%). RMN-$^1$H ($CDCl_3$, 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 Masas 312.14 $(MH)^+$.

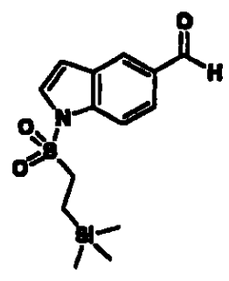
[1-(2-Trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-metanol




Una solución de éster etílico del ácido 1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-carboxílico (secado de manera azeotrópica con tolueno (2x), 5.77 g, 16.9 mmol) en tetrahidrofurano (50 mL) se adicionó a 0°C a una

mezcla de borohidruro de litio (3.68 g, 169 mmol) en tetrahidrofurano (100 mL). La mezcla se calentó a temperatura ambiente y se agitó durante 14 horas. Se enfrió a 0°C y se adicionó borohidruro de litio (3.5 g). La mezcla se calentó a temperatura ambiente y se agitó durante 14 horas. Se enfrió nuevamente a 0°C y se adicionó lentamente cloruro de amonio acuoso, saturado (25 mL). La suspensión de color blanco, resultante se filtró a través de una almohadilla de celite, los solventes se removieron y el residuo se sujetó a la cromatografía con evaporación instantánea utilizando acetato de etilo/hexanos (1:1.5) con trietilamina al 1% para proporcionar el compuesto del título como un sólido de color blanco (3.8 g, 72%). RMN-$^1$H ($CD_3OD$, 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); RMN-$^{13}$C ($CD_3OD$, 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 Masas 313.12 $(MH)^+$.

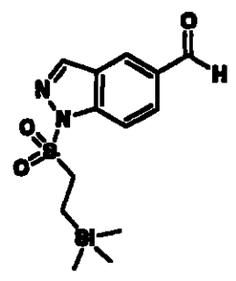
1-(2-Trimetilsilanil-etanosulfonil)-1*H*-indol-5-carbaldehído



Una solución de [1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-il]-metanol (2.1 g, 6.74 mmol) en cloruro de metileno (30 mL) se adicionó a 0°C a una mezcla de dióxido de manganeso activado (22 g, secado de manera azeotrópica con tolueno (2x)) y cloruro de metileno (70 mL) en un matraz de fondo redondo de 500 mL. La mezcla de reacción se agitó a 0°C durante 30 minutos 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 de color blanco (1.8 g, 80%) RMN-$^1$H ($CDCl_3$, 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). RMN-$^{13}$C ($CDCl_3$, 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 Masas 310.12 $(MH)^+$.

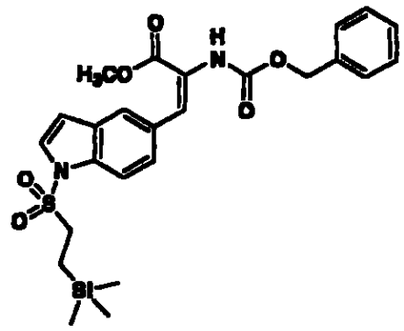
Preparado de manera similar:

1-(2-Trimetilsilaniletanosulfonil)-1*H*-indazol-5-carbaldehído




Espectro de Masas 311.10 $(MH)^+$.

Ester metílico del ácido 2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etanosulfonil)-1H-indol-5-il]-acrílico.

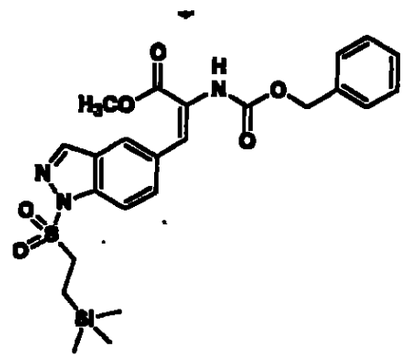


La 1,1,3,3-tetrametilguanidina (0.68 mL, 5.43 mmol) se adicionó a temperatura ambiente a una solución de éster trimetílico de la N-(benciloxicarbonil)-α-fofonoglicina (1.88 g, 5.69 mmol) en tetrahidrofurano (40 mL). La mezcla se agitó a temperatura ambiente durante 15 minutos y se enfrió a -78°C y se adicionó lentamente una solución de 1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-carbaldehído (1.6 g, 5.17 mmol) en tetrahidrofurano (15 mL). La mezcla de reacción se agitó a -78°C durante 2 horas y luego se calentó a temperatura ambiente en 3 horas. Los solventes se removieron *in vacuo* y el residuo se sujetó a la cromatografía con evaporación instantánea sobre gel de sílice utilizando cloruro de metileno/hexanos (1:1.5) con trietilamina al 1% como eluyente para proporcionar el compuesto del título como una mezcla de Z/E 92:8 (determinado mediante la integración de $CO_2CH_3$, para el isómero Z a 3.79 ppm, y el isómero E a 3.65 ppm). Para el isómero Z: RMN-$^1$H ($CD_3CN$, 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). Espectro de Masas 515.20 $(MH)^+$.

Preparado de manera similar:

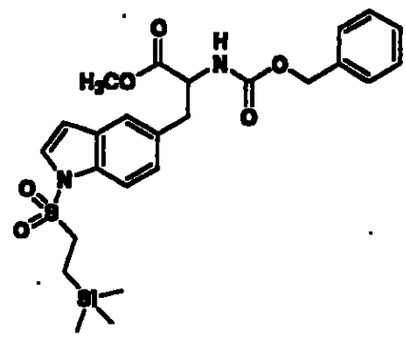
Ester metílico del ácido 2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-acrílico



La cromatografía con evaporación instantánea sobre gel de sílice utilizando cloruro de metileno que contenía trietilamina al 1% como eluyente proporcionó el compuesto del título como una mezcla de Z/E 95:5 (determinado mediante la integración de $-CH=C(CO_2Me)(NHCBz)$, 3.72g, 92%). Para el isómero Z: RMN-$^1$H ($CD_3CN$, 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).

Espectro de Masas 516.18 $(MH)^+$.

Ester metílico del ácido (±)-2-amino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-il]-propiónico

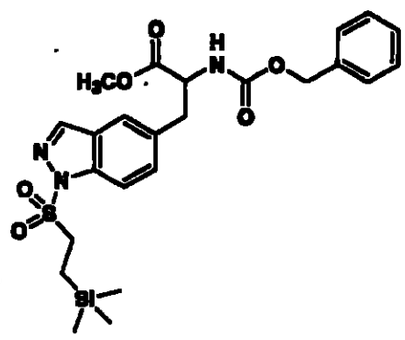


A un matraz de fondo redondo de 500 mL secado a la flama se adicionó éster metílico del ácido 2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-il]-acrílico (2.24 horas, 4.36 mmol), metanol (100 mL) y paladio al 10% sobre carbón vegetal (0.52g). La mezcla se desgasificó y se purgó con hidrógeno cinco veces. Se agitó a temperatura ambiente durante 1 hora y se filtró a través de una almohadilla de celite. Los solventes se removieron y el residuo se sujetó a la cromatografía con evaporación instantánea utilizando acetato de etilo/hexanos (1:1 y 2:1) que contenía trietilamina al 1% para proporcionar el compuesto del título como un líquido viscoso, incoloro (1.27 g, 76%), el cual se solidificó con el enfriamiento. RMN-$^1$H ($CD_3CN$, 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, H), 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). RMN-$^{13}$C ($CDCl_3$, 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 Masas 383.16 $(MH)^+$.

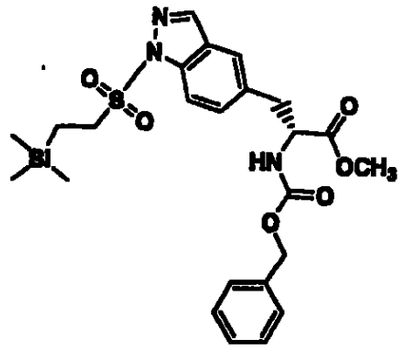
Preparado de manera similar:

Ester metílico del ácido (±)-2-amino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico



RMN-$^1$H ($CD_3CN$, 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). RMN-$^{13}$C ($CDCl_3$, 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 Masas 384.15 $(MH)^+$.

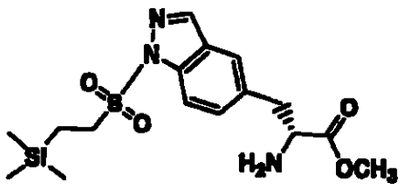
Ester metílico del ácido (*R*)-2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico



En una bolsa de manipulación con guantes que se sujetó a 3 ciclos de vacío/purga con nitrógeno, un matraz de reacción AIRFREE$^{MR}$ (Schlenk) equipado con una barra de agitación se cargó con trifluorometilsulfonato de (-)-1,2-bis((2R,5R)-2,5-dietilfosfolano)bencen(ciclooctadieno)rodio (I) (123 mg, 0.17 mmol, 5% en mol), sellado con un septo de caucho y se removió de la bolsa de manipulación con guantes. El éster metílico del ácido 2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-acrílico (1.75 g, 3.40 mmol) se pesó en un segundo matraz de reacción AIRFREE$^{MR}$ (Schlenk) equipado con una barra de agitación y sellado con un septo de caucho. Después de 3 ciclos de vacío/purga con nitrógeno, se disolvió en una mezcla de metanol anhidro (75 mL) y cloruro de metileno anhidro (15 mL). Ambos solventes se desoxigenaron antes de la adición mediante el burbujeo

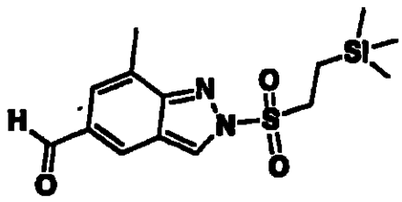
con nitrógeno durante al menos 1 hora. Una vez en solución, la mezcla se sujetó nuevamente a 3 ciclos de vacío/purga con nitrógeno. La solución de ácido deshidroamino se introdujo en el matraz de reacción AIRFREE$^{MR}$ (Schlenk) que contenía el catalizador por medio de una cánula. La mezcla de reacción de sujetó a 5 ciclos de vacío/purga con nitrógeno antes de abrir el matraz a 1 atmósfera de hidrógeno (balón). Después de 16 horas, la mezcla de reacción se purgó con 3 ciclos de vacío/purga con nitrógeno. El solvente se evaporó y el residuo se sujetó a la cromatografía en columna (gradiente de acetato de etilo/hexanos 1:4 a acetato de etilo/hexanos 1:2) para proporcionar 1.5 g (85%) del compuesto del título como un sólido de color blanco con 98.4% ee de terminado mediante el análisis de la CLAR utilizando una columna Chirocel OD con hexano al 80%/etanol al 20% como eluyente (tiempos de retención 13.9 minutos para el compuesto del título y 11.2 minutos para el enantiómero *S*). RMN-$^1$H ($CDCl_3$, 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 Masas: 518 $(MH)^+$.

Ester metílico del ácido (*R*)-2-amino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico



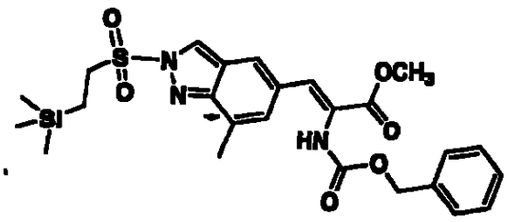
Una mezcla de éster metílico del ácido (*R*)-2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il)-propiónico (1.24 g, 2.40 mmol) y paladio al 10% sobre carbono (124 mg) en metanol (50 mL) se agitó durante 2 horas bajo una presión de hidrógeno de 3.511 kg/cm$^2$ (50 psi) utilizando un hidrogenador Parr. La mezcla de reacción se purgó con 3 ciclos de vacío/purga con 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 producto filtrado de metanol se evaporó para proporcionar 879 mg (96%) del compuesto del título como una goma pegajosa. RMN-$^1$H ($CDCl_3$, 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 Masas: 384 $(MH)^+$.

7-Metil-2-(2-trimetilsilanil-etanosulfonil)-2*H*-indazol-5-carbaldehído



A una suspensión de 7-metilindazol-5-aldehído (3.0 g, 18.7 mmol) en cloruro de metileno (150 mL) se adicionó trietilamina (7.83 mL, 56.2 mL, 3 equivalentes) seguido por la adición gota a gota de cloruro de 2-trimetilsilanil-etanosulfonilo puro (5.60 g, 28.1 mmol, 1.5 equivalentes). La mezcla se volvió homogénea gradualmente y se dejó agitar a temperatura ambiente durante 16 horas. La solución se concentró a una cantidad mínima de cloruro de metileno y luego se sujetó a la cromatografía en columna con evaporación instantánea sobre gel de sílice (acetato de etilo/hexanos 1:4) para proporcionar 4.7 g (77%) del producto como un sólido de color amarillo pálido. RMN-$^1$H ($CDCl_3$, 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).

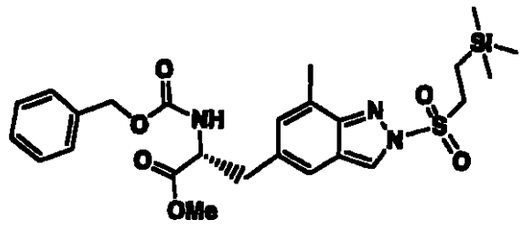
Ester metílico del ácido 2-benciloxicarbonilamino-3-[7-metil-2-(2-trimetilsilanil-etanosulfonil)-2*H*-indazol-5-il]-acrílico



A una solución de éster trimetílico de N-(benciloxicarbonil)-α-fosfonoglicina (4.93 g, 14.9 mmol, 1.1 equivalentes) en tetrahidrofurano anhidro (75 mL) se adicionó tetrametilguanidina (1.78 mL, 1.05 equiv). La mezcla se agitó a temperatura ambiente bajo nitrógeno durante 5 minutos y luego se enfrió a -78°C. Después de la agitación durante 15 minutos a -78°C se adicionó una solución de 7-metil-2-(2-trimetilsilanil-etanosulfonil)-2*H*-indazol-5-carbaldehído en tetrahidrofurano (25 mL). La mezcla de reacción se dejó calentar lentamente a temperatura ambiente durante toda la noche. Aunque la reacción fue incompleta, 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 con evaporación instantánea (acetato de etilo/hexanos 1:4) proporcionó 2.66 g (37%) del producto como una espuma de vidrio, de color blanco. RMN-$^1$H ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.62 (s, 1H),

7.38-7.25 (m, 7H), 6.48 (s amplio, 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 Masas: 530 $(MH)^+$.

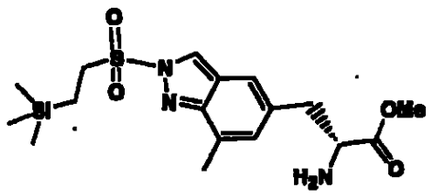
Ester metílico del ácido (*R*)-2-benciloxicarbonilamino-3-[7-metil-2-(2-trimetilsilanil-etanosulfonil)-2*H*-indazol-5-il]-propiónico




En una bolsa de manipulación con guantes que se sujetó a 3 ciclos de vacío/purga con nitrógeno, un matraz de reacción AIRFREE$^{MR}$ (Schlenk) equipado con una barra de agitación se cargó con trifluorometilsulfonato de (-)-1,2-bis((2R,5R)-2,5-dietilfosfolano)bencen(ciclooctadieno)rodio (I) (259 mg, 0.36 mmol, 9% en mol), se selló con un septo de caucho y se removió de la bolsa de manipulación con guantes. El éster metílico del ácido 2-benciloxicarbonilamino-3-[7-metil-2-(2-trimetilsilanil-etanosulfonil)-2*H*-indazol-5-il]-acrílico (2.03 g, 3.83 mmol) se pesó en un segundo matraz de reacción AIRFREE$^{MR}$ (Schlenk) equipado con una barra de agitación y sellado con un septo de caucho. Después de 3 ciclos de vacío/purga con nitrógeno, se disolvió en metanol anhidro (80 mL,

desoxigenado antes de la adición mediante el burbujeo con nitrógeno durante al menos 1 hora). Una vez en solución, se sujetó nuevamente a 3 ciclos de vacío/purga con nitrógeno. La solución de ácido deshidroamino se transfirió por medio de una cánula al matraz de reacción AIRFRE$^{MR}$ (Schlenk) que contenía el catalizador. La mezcla de reacción de purgó con 5 ciclos de vacío/purga de hidrógeno antes de abrir el matraz a un balón de hidrógeno (1 atm). Después de 2.5 horas, la mezcla de reacción se purgó con 3 ciclos de vacío/purga con nitrógeno. El solvente se evaporó y el residuo se sujetó a la cromatografía en columna (gradiente de acetato de etilo/hexanos 1:4 a acetato de etilo/hexanos 1:2) para proporcionar 1.4 g (68%; ee = 99.2%) del compuesto del título como un sólido de color blanco. RMN-$^1$H ($CDCl_3$, 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). RMN-$^{13}$C ($CDCl_3$, 125 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 Masas: 532 $(MH)^+$.

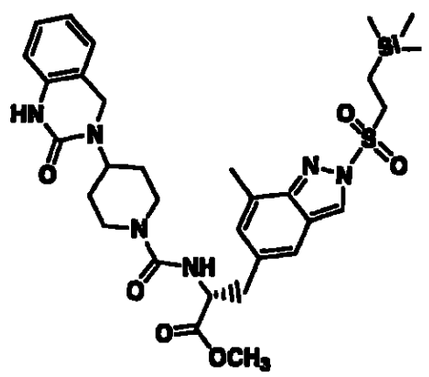
Ester metílico del ácido (*R*)-2-amino-3-[7-metil-2-(2-trimetilsilanil-etanosulfonil)-2*H*-indazol-5-il]-propiónico



El éster metílico del ácido 2-benciloxicarbonilamino-3-[7-metil-2-(trimetilsilanil-etanosulfonil)-2*H*-indazol-5-il]-propiónico (1.35 g, 2.54 mmol) y paladio al 10% sobre carbono (135 mg) en metanol (40 mL) se agitaron durante 3.0 horas bajo una presión de hidrógeno de 3.862 kg/cm$^2$ (55 psi) utilizando un aparato Parr. La mezcla de reacción se purgó con 3 ciclos de vacío/purga con 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 producto filtrado de metanol se evaporó para proporcionar el compuesto del título (1.01 g, rendimiento cuantitativo) como una goma pegajosa. RMN-$^1$H ($CDCl_3$, 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). RMN-$^{13}$C ($CDCl_3$, 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 Masas: 398 $(MH)^+$.

Ester metílico del ácido (*R*)-3-[7-metil-2-(2-trimetilsilanil-etanosulfonil)-2*H*-indazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carbonil]-camino}-propiónico

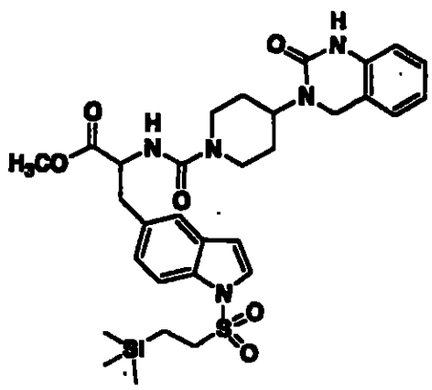


Una mezcla de éster metílico del ácido 2-amino-3-[7-metil-2-(2-trimetilsilanil-etanosulfonil)-2H-indazol-5-il]-propiónico (500 mg, 1.26 mmol), N,N-diisopropiletilamina (0.66 mL, 3.77 mmol) y disuccinimidilcarbonato (322 mg, 1.26 mmol) se agitaron conjuntamente con cloruro de metileno (20 mL) durante 30 minutos a temperatura ambiente. Luego, se adicionó 3-piperidin-4-il-3,4-dihidro-1*H*-quinazolin-2-ona (444 mg, 1.35 mmol) y la mezcla de reacción se dejó agitar durante toda la noche a temperatura ambiente. El solvente se evaporó y el residuo se sujetó a la cromatografía en columna con evaporación instantánea (acetona/acetato de etilo 1:4) para proporcionar 490 mg (rendimiento del 60%) del compuesto del título como un sólido de color blanco. RMN-$^1$H ($CDCl_3$, 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 Masas: 655 $(MH)^+$.

Preparado de manera similar:

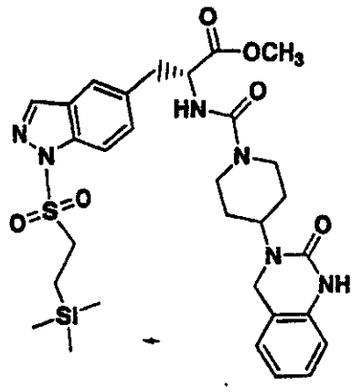
Ester metílico del ácido (±)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-il]-propiónico



RMN-$^1$H ($CD_3OD$, 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 Masas: 640.40 $(MH)^+$.

Ester metílico del ácido (*R*)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico

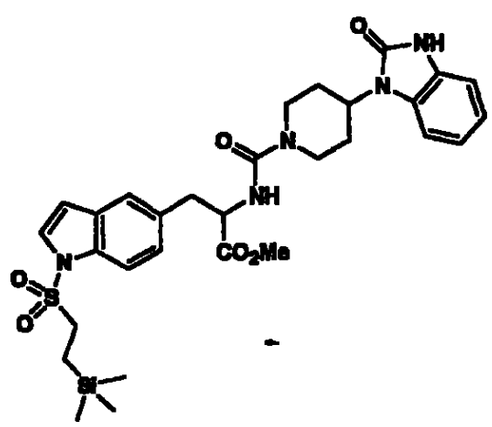


Una solución de éster metílico del ácido (*R*)-2-amino-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico (764 mg, 1.99 mmol), *N*,*N*-diisopropiletilamina (1.10 mL, 5.97 mmol) y disuccinimidilcarbonato (509 mg, 1.99 mmol) en cloruro de metileno (20 mL) se agitó durante 40 minutos a temperatura ambiente. Luego, se adicionó la 3-piperidin-4-il-3,4-dihidro-1*H*-quinazolin-2-ona (70% pura, 703 mg, 2.13 mmol) y la mezcla de reacción se dejó agitar durante toda la noche a temperatura ambiente. El solvente se evaporó *in vacuo* y el residuo se sujetó a la cromatografía en columna con evaporación instantánea (acetona/acetato de etilo 1:4)

para proporcionar 1.15 g (90%) del compuesto del título. RMN-$^1$H ($CDCl_3$, 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), 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 Masas: 641 $(MH)^+$.

Preparado de manera similar:

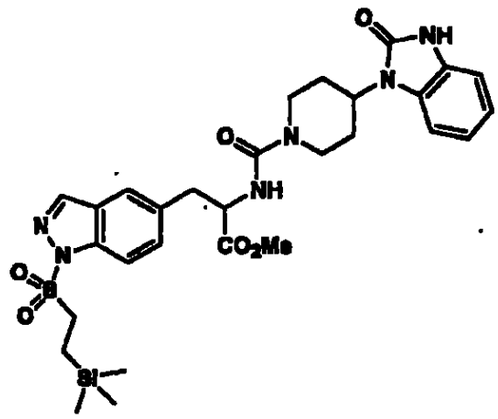
Ester metílico del ácido (±)-2-{[4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-il]-propiónico




RMN-$^1$H ($CD_3CN$, 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 (s amplio, 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 (s amplio, 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 Masas 626.26 $(MH)^+$.

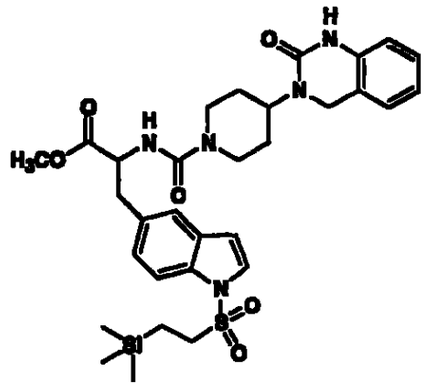
Ester metílico del ácido (±)-2-{[4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico




RMN-$^1$H ($CD_3CN$, 500 MHz) δ 9.61 (s amplio, 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), 5.90 (d, J = 7.9 Hz, 1H), 4.67-4.62 (m, 1H), 4.42-4.36 (m, 1H), 4.13-4.07 (s amplio, 1H), 3.68 (s, 3H), 3.45-

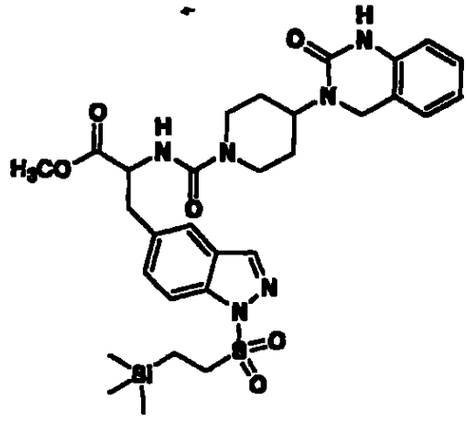
3.42 (m, 2H), 3.30 (dd, J = 14.0, 5.8 Hz, 1H), 3.20 (dd, J = 13.7, 8.8 Hz, 1H), 2.89-2.84 (m, 2H), 2.52 (s amplio, 1H), 2.33-2.23 (m, 2H), 1.72-1.69 (m, 2H), 0.80-0.76 (m, 2H), -0.07 (s, 9H). Espectro de Masas 627.25 $(MH)^+$.

Ester metílico del ácido (±)-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



RMN-$^1$H ($CD_3OD$, 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 Masas 640.40 $(MH)^+$.

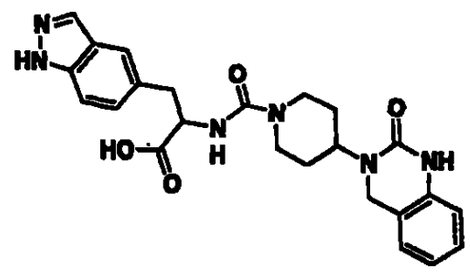
Ester metílico del ácido (±)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-il]-propiónico



RMN-$^1$H ($CD_3OD$, 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 (s amplio, 1H), 4.08 (s amplio, 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); RMN-$^{13}$C ($CD_3OD$, 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 Masas: 641.40 $(MH)^+$.

Ejemplo 1

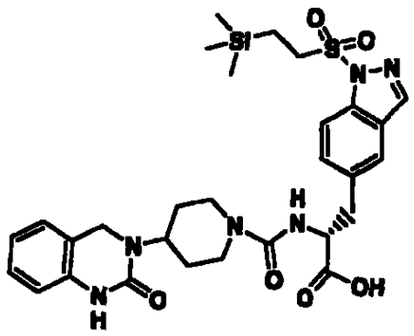
Acido (±)-3-(1*H*-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Una solución de éster *terc*-butílico del ácido 5-(2-metoxicarbonil-2-{[4-(2-oxo-1,4-dihidro-2*H*-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. Se adicionó una solución de monohidrato de hidróxido de litio (49 mg, 2.04 mmol) en agua (5 mL). La mezcla de reacción se agitó a 0°C durante 6 horas y luego se colocó en un congelador durante 16 horas 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 aproximadamente 1 con ácido clorhídrico 1N. El producto precipitado sólido, de color blanco, resultante se colectó por filtración. El sólido se secó bajo vacío para proporcionar el compuesto del título (108 mg, 80%). RMN-$^1$H (DMSO-$d_6$, 300 MHz) δ 12.94 (amplio, 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 Masas: 463 $(MH)^+$.

Acido (*R*)-2-{[4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-il]-propiónico

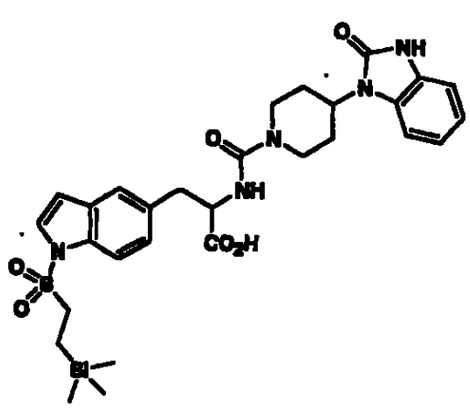


Una solución de éster metílico del ácido (*R*)-2-{[4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico (775 mg, 1.21 mmol) en tetrahidrofurano (9 mL) y metanol (3 mL) se enfrió a 0°C. Se adicionó una solución de monohidrato de hidróxido de litio (115 mg, 4.84 mmol) en agua (3 mL). La mezcla de reacción se agitó a 0°C durante 2 horas y luego se colocó en un congelador a -15°C durante 16 horas. Mientras que se enfriaba la mezcla de reacción con un baño de hielo, el pH se incrementó a aproximadamente 7 mediante la adición de ácido clorhídrico 1N (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 orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se evaporaron para proporcionar 684 mg (90%) del compuesto del título como un sólido de color blanco. RMN-$^1$H (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 Masas: 627 $(MH)^+$.

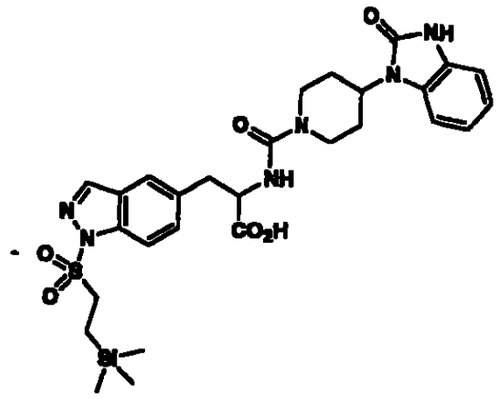
Preparado de manera similar:

Acido (±)-2-{[4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-il]-propiónico



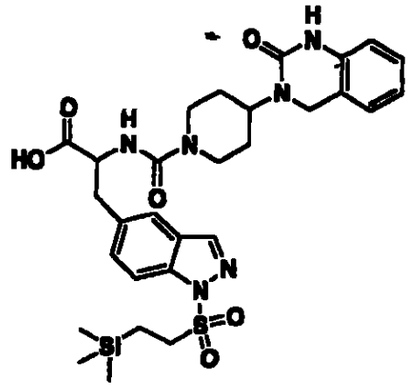

Espectro de Masas 612.25 $(MH)^+$.

Acido (±)-2-{[4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico



Espectro de Masas 613.26 $(MH)^+$.

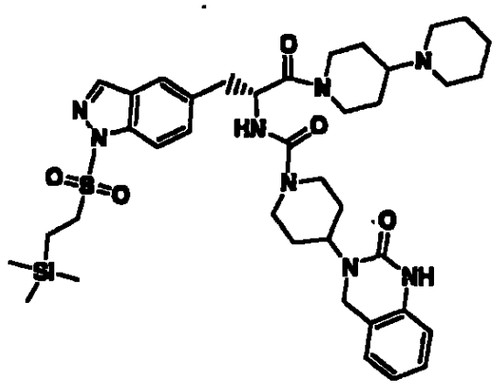
Acido (±)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-il]-propiónico



RMN-$^1$H ($CD_3CN$, 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 (s amplio, 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). Espectro de Masas: 627.30 $(MH)^+$.

{2-[1,4']Bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-ilmetil]-etil}-amida del ácido (*R*)-4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carboxílico

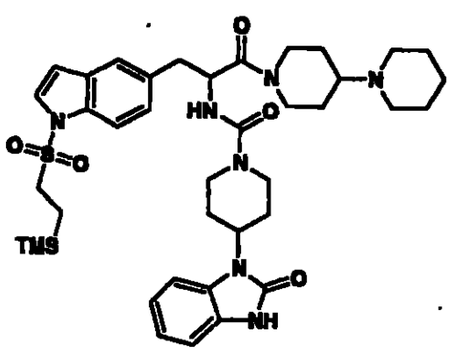


A una solución de ácido (*R*)-2-{[4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-il]-propiónico (554 mg, 0.88 mmol) y *N,N*-diisopropiletilamina (0.62 mL, 3.54 mmol) en cloruro de metileno (20 mL) se adicionó una solución de 4-piperidinopiperidina (164 mg, 0.97 mmol) y PyBOP® (460 mg, 0.88 mmol) en cloruro de metileno (15 mL). La mezcla de reacción se

agitó durante 16 horas a temperatura ambiente. Luego se concentró a aproximadamente 2 mL y se sujetó a la cromatografía en columna con evaporación instantánea utilizando cloruro de metileno/metanol/trietilamina (94:5:1) como eluyente para proporcionar 599 mg (87%) del compuesto del título como un sólido de color blanco. RMN-$^1$H ($CD_3CN$, 500 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 = 8.1Hz, 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 Masas: 778 $(MH)^+$.

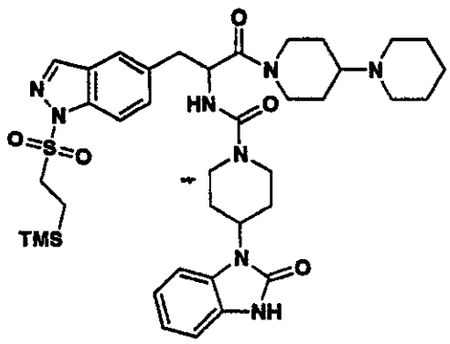
Preparado de manera similar:

{2-[1,4']Bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



RMN-$^1$H ($CD_3CN$, 500 MHz) δ 9.42 (s amplio, 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). CL/EM: $t_R$ = 2.47 minutos, 762.37 $(MH)^+$.

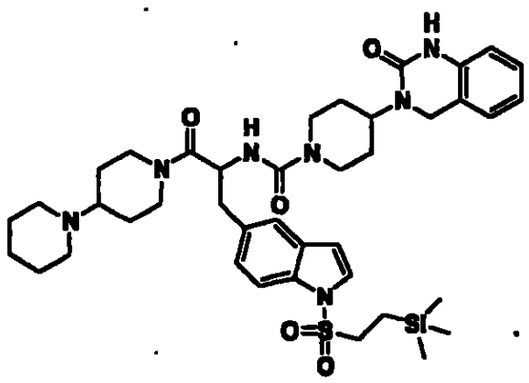
{2-[1,4']Bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico




RMN-$^1$H ($CD_3CN$, 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 (s amplio, 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 minutos, 763.35 $(MH)^+$.

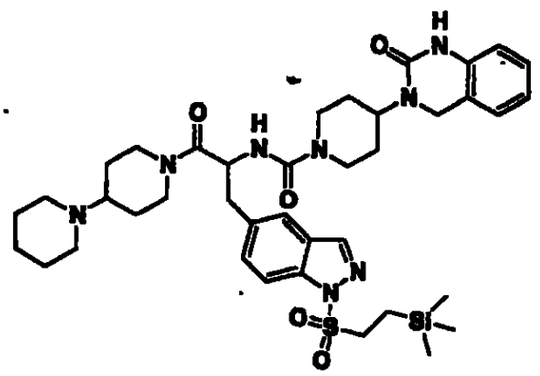
{2-[1,4']Bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



RMN-$^1$H ($CD_3CN$, 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). Espectro de Masas: 776.44 $(MH)^+$.

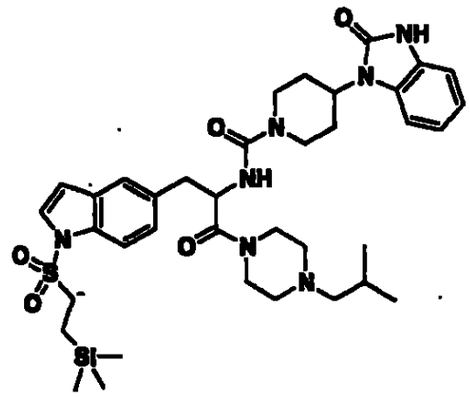
{2-[1,4']Bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Purificado mediante la cromatografía en gel de sílice utilizando cloruro de metileno:metanol/trietilamina (90:10:0.5) como eluyente. RMN-$^1$H ($CD_3CN$, 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 = 7.4Hz, 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). Espectro de Masas: 777.40 $(MH)^+$.

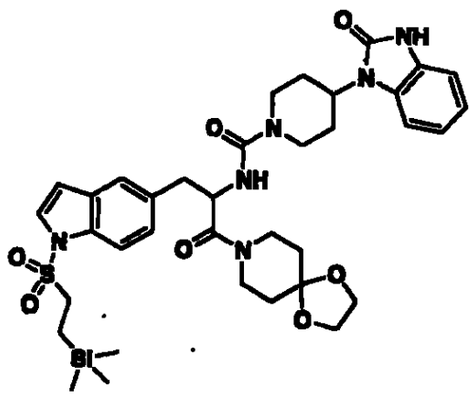
{2-(4-Isobutil-piperazin-1-il)-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



RMN-$^1$H ($CD_3CN$, 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 Masas: 736.40 $(MH)^+$.

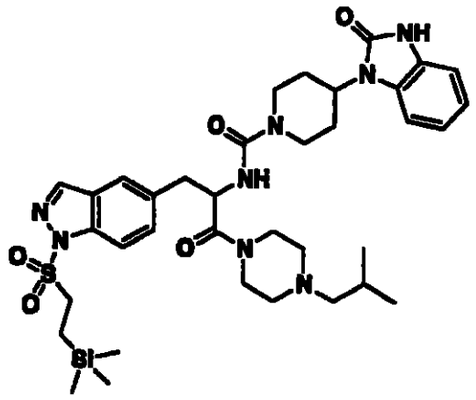
{2-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



RMN-$^1$H ($CD_3CN$, 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 Masas: 737.37 $(MH)^+$.

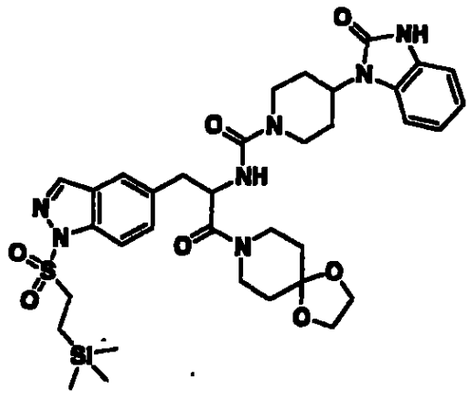
{2-(4-Isobutil-piperazin-1-il)-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



RMN-$^1$H ($CD_3CN$, 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). Espectro de Masas: 737.40 $(MH)^+$.

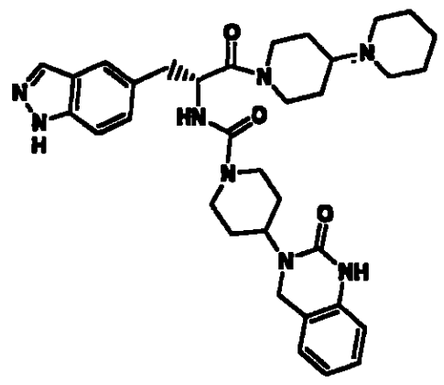
{2-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



RMN-$^1$H ($CD_3CN$, 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). Espectro de Masas: 738.32 $(MH)^+$.

Ejemplo 2

[2-[1,4']Bipiperidinil-1'-il-1-(1*H*-indazol-5-ilmetil)-2-oxo-etil]-amida () del ácido (*R*)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



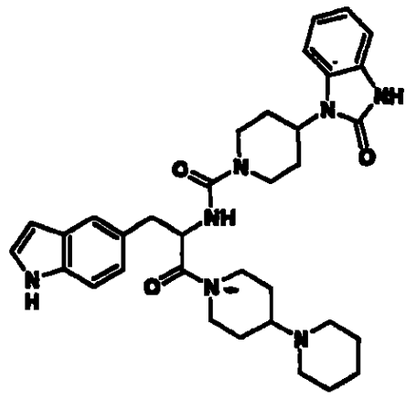
Una solución de {2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (*R*)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (568 mg, 0.73 mmol) fluoruro de cesio (1.11 g, 7.31 mmol) se calentó a 80°C en acetonitrilo (50 mL) durante 4.5 horas. La mezcla de reacción se concentró y el residuo se sujetó a la cromatografía en columna con evaporación instantánea (cloruro de metileno/metanol/trietilamina, 94:5:1) para proporcionar 280 mg (rendimiento del 63%) del compuesto del título como un sólido de color blanco con 98.2% ee determinado mediante el análisis de la CLAR utilizando una columna Chirocel OD con 20% de B (A = etanol, B = dietilamina al 0.05% en hexanos) como eluyente (Tiempos de retención: 9.51 minutos para el compuesto del título y 15.9 minutos para el enantiómero *S*).

RMN-$^1$H ($CD_3OD$, 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 a -0.24 (m, 0.75H). Espectro de Masas: 613 $(MH)^+$.

Preparado de manera similar:

Ejemplo 3

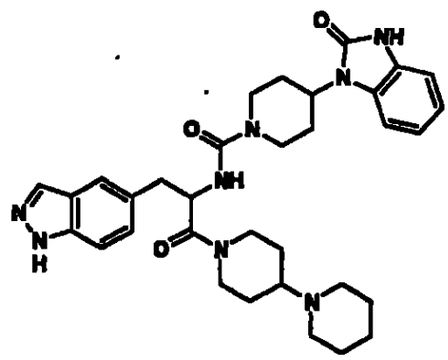
[2-[1,4']Bipiperidinil-1'-il-1-(1*H*-indol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



RMN-$^1$H (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 (s amplio, 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 (s amplio, 1H), 4.38-4.32 (m, 1H), 4.21-4.16 (m, 1H), 3.98 (s amplio, 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 minutos, 598.42 $(MH)^+$.

Ejemplo 4

[2-[1,4']Bipiperidinil-1'-il-1-(1*H*-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico

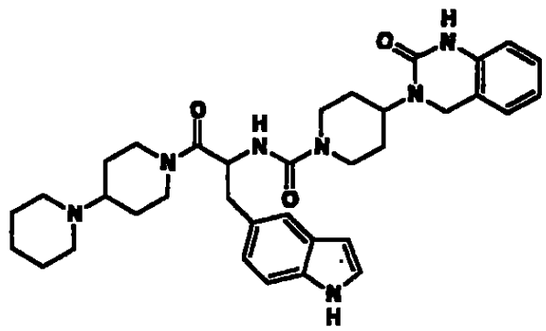


RMN-$^1$H (DMSO-$d_6$, 500 MHz) δ 10.70 (s, 1H), 8.22 (d, J = 8.2 Hz, 0.6H), 8.11 (s, 0.4H), 8.00 (s, 0.6H), 7.89 (d, J = 9.1

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 (s amplio, 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 minutos, 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

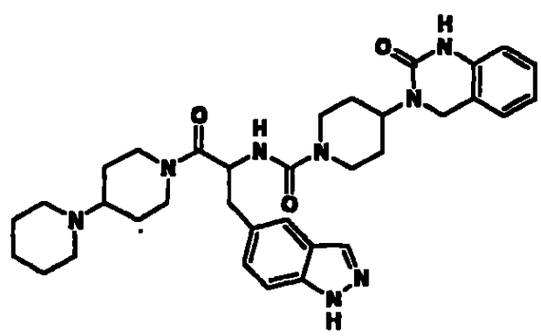


Una mezcla de (2-[1,4']bipiperidinil-1'il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indol-5-ilmetil]-etil)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (52 mg, 0.067 mmol), fluoruro de cesio (51 mg, 0.33 mmol) en acetonitrilo (5 mL) se calentó a 80°C durante 4 horas. Los solventes se removieron *in vacuo* y

el residuo se sujetó a la cromatografía sobre gel de sílice utilizando cloruro de metileno/metanol/trietilamina (93:5:2) como eluyente para proporcionar el compuesto del título como un sólido de color blanco (rendimiento del 70%). RMN-$^1$H ($CD_3CN$, 500 MHz) δ 9.30 (s, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 7.39 (d, J = 8.2 Hz, 0.6 H), 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, 1.6 H), 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 minutos, 612.44 $(MH)^+$.

Ejemplo 6

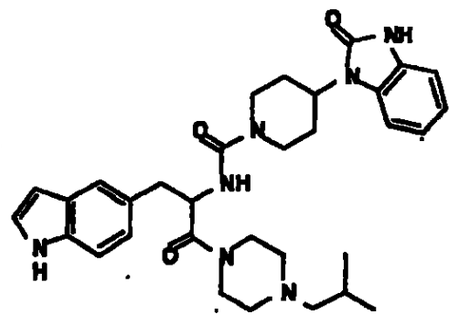
[2-[1,4']Bipiperidinil-1'-il-1-(1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Purificado mediante la cromatografía en gel de sílice utilizando cloruro de metileno:metanol:trietilamina (93:5:2) como eluyente para proporcionar el compuesto del título como un sólido de color blanco (rendimiento del 90%). RMN-$^1$H ($CD_3OD$, 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 (s amplio, 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 minutos, 613.44 $(MH)^+$. El enantiómero (R), cuya síntesis discreta se describe anteriormente (ejemplo 1), se obtuvo mediante la separación quiral del racemato al emplear las siguientes condiciones: columna preparativa Chiracel OD, 50 x 500 mm, 20 um; A = EtOH, B = dietilamina al 0.05%/hexano; 20% de B @ 65 ml/minuto durante 45 minutos; tiempos de retención: 20.5 minutos para el enantiómero R y 32.8 minutos para el enantiómero S.

Ejemplo 7

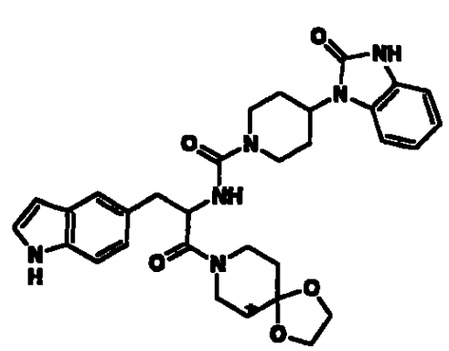
[1-(1H-indol-5-ilmetil)-2-(4-isobutil-piperazin-1-il)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



CL/EM: $t_R$ = 2.05 minutos, 572.31 $(MH)^+$.

Ejemplo 8

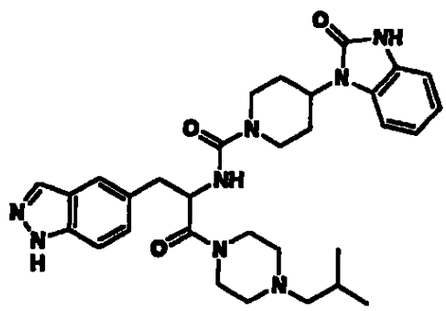
[2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-1-(1H-indol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



CL/EM: $t_R$ = 2.35 minutos, 573.26 $(MH)^+$.

Ejemplo 9

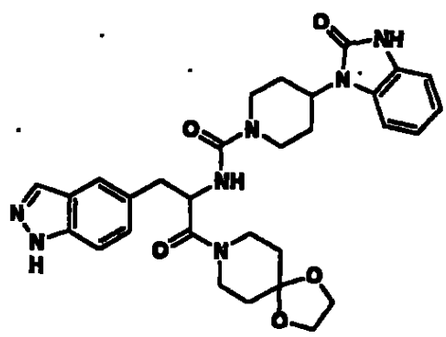
[1-(1H-indazol-5-ilmetil)-2-(4-isobutil-piperazin-1-il)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



CL/EM: $t_R$ = 1.86 minutos, 573.28 $(MH)^+$.

Ejemplo 10

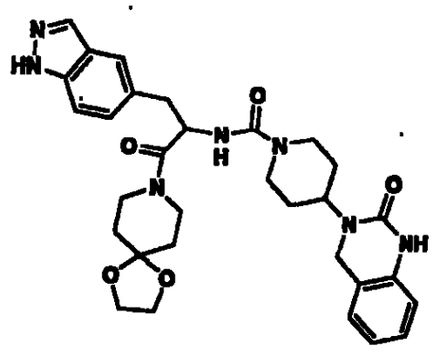
[2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-1-(1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



CL/EM: $t_R$ = 2.18 minutos, 574.23 $(MH)^+$.

Ejemplo 11

[2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-1-(1*H*-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carboxílico

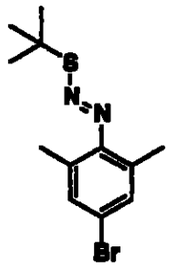


A una solución del ácido 3-(1*H*-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (95 mg, 0.21 mmol) y *N,N*-diisopropiletilamina (0.14 mL, 0.82 mmol) en dimetilformamida (5 mL) se adicionó una solución de 1,4-dioxa-8-azaespiro[4,5]decano (32 mg, 0.23 mmol) y PyBOP™ (107 mg, 0.21 mmol) en cloruro de metileno (5 mL). La mezcla de reacción se agitó durante 16 horas a temperatura ambiente. Todo el solvente se removió utilizando alto vacío. El residuo se sujetó a la cromatografía en columna con evaporación instantánea utilizando cloruro de metileno/metanol/trietilamina (93:5:2) para proporcionar el compuesto del título como un sólido de color blanco (67 mg, rendimiento del 56%). RMN-$^1$H ($CDCl_3$, 500 MHz) δ 10.52 (s,

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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 (t amplio, 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 Masas: 588 $(MH)^+$.

Sulfuro de 4-bromo-2,6-dimetilfenildiazo-t-butilo

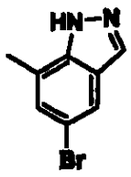



La 4-bromo-2,6-dimetilanilina (20.00 g, 100 mmol) se molió para formar un polvo con un mortero y mano de mortero y luego se suspendió en ácido clorhídrico al 24% (41 mL). La mezcla agitada se enfrió a -20°C y se trató gota a gota con nitrito de sodio (7.24 g, 1.05 equivalentes) en agua (16 mL) durante 40 minutos mientras que la temperatura se mantenía debajo de -5°C. Después de 30 minutos adicionales de -5°C a -20°C, la mezcla se amortiguó a aproximadamente pH 5

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con acetato de sodio sólido. Esta mezcla (mantenida a aproximadamente -10°C) se adicionó en porciones a una solución agitada de t-butil-tiol (11.3 mL, 1 equivalente) en etanol (100 mL) a 0°C durante aproximadamente 10 minutos. Después de la adición, la mezcla se agitó a 0°C durante 30 minutos y luego se adicionó hielo triturado (aproximadamente 150 mL). La mezcla se almacenó en un refrigerador durante toda la noche. El sólido de color café claro, resultante se colectó por filtración, se lavó con agua y se secó bajo alto vacío durante varias horas (26.90 g, 89%). El compuesto pareció ser estable como un sólido pero se sometió a una descomposición significante cuando se intentó la recristalización de etanol. RMN-$^1$H ($CDCl_3$, 500 MHz) δ 1.58 (9H, s), 1.99 (6H, s), 7.21 (2H, s). Espectro de Masas: 303.05 $(MH)^+$.

5-Bromo-7-metilindazol

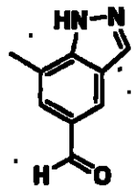



En un matraz de fondo redondo secado a la flama, se combinaron el sulfuro de 4-bromo-2,6-dimetilfenildiazo-t-butilo (12.50 g, 41.5 mmol) y el t-butóxido de potasio (46.56 g, 10 equivalentes). Se adicionó una barra de agitación y la

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mezcla se colocó bajo nitrógeno. A esto se adicionó DMSO seco (120 ml). La mezcla se agitó vigorosamente durante toda la noche a temperatura ambiente. La mezcla de reacción luego se vertió cuidadosamente en una mezcla de hielo triturado (400 mL) y ácido clorhídrico al 10% (200 mL). La suspensión resultante se dejó reposar a 4°C durante toda la noche y el sólido se colectó por filtración y se lavó con agua. El sólido crudo se disolvió en cloruro de metileno/metanol 5:1 y la solución se secó sobre sulfato de magnesio y se evaporó para proporcionar el producto como un sólido blanquecino (7.60 g, 87%). RMN-$^1$H ($CDCl_3/CD_3OD$, 500 MHz) δ 2.51 (3H, s), 7.22 (1H, s), 7.69 (1H, s), 7.94 (1H, s). Espectro de Masas: 211.03 $(MH)^+$.

7-Metilindazol-5-carboxaldehído



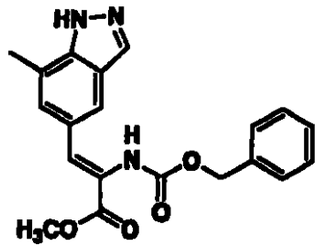

El 5-bromo-7-metilindazol (6.10 g, 28.9 mmol) e hidruro de sodio (60% en aceite mineral, 1.27 g, 1.1 equivalentes) se pesaron en un matraz de fondo redondo secado a la flama que contenía una barra de agitación magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, se adicionó tetrahidrofurano seco (30 mL). La

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mezcla se agitó a temperatura ambiente durante 15 minutos, tiempo durante el cual se volvió homogénea. La mezcla agitada se enfrió a -70°C y la solución de *sec*-butil-litio en ciclohexano (1.4M, 45 mL, 2.2 equivalentes) se adicionó durante varios minutos. Después de 1 hora a -70°C, se adicionó dimetilformamida (10 mL) durante varios minutos. La mezcla se dejó calentar a temperatura ambiente y se agitó durante toda la noche. Luego se enfrió a 0°C y se trató cuidadosamente con ácido clorhídrico 1N (60 mL). Después de algunos minutos, se adicionó bicarbonato de sodio sólido para basificar la mezcla a pH 9-10. Las capas se separaron y la fase acuosa se lavó dos veces con acetato de etilo. Las fases orgánicas, combinadas se extrajeron con sulfato ácido de sodio 0.8M (3 x 125 mL). Las fases acuosas, combinadas se lavaron con acetato de etilo (100 mL) y luego el pH se ajustó a aproximadamente 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 secaron (sulfato de magnesio) y se evaporaron para proporcionar el producto como un sólido de color canela claro (3.01 g, 65%). RMN-$^1$H ($CDCl_3$, 500 MHz) δ 2.63 (3H, s), 7.73 (1H, s), 8.12 (1H, s), 8.25 (1H, s), 10.03 (1H, s). Espectro de Masas: 161.06 $(MH)^+$.

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Ester metílico del ácido 2-benciloxicarbonilamino-3-(7-metil-1H-indazol-5-il)-acrílico

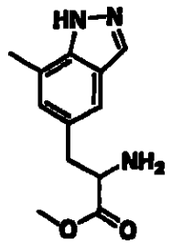



Una solución agitada de éster trimetílico de N-benciloxicarbonil-α-fosfonoglicina (5.51 g, 1.2 equivalentes) en tetrahidrofurano (30 mL) a temperatura ambiente se trató con tetrametilguanidina (1.91 mL, 1.1 equiv). Después de 10 minutos, se adicionó 7-metilindazol-5-carboxaldehído (2.22 g, 13.86 mmol) en tetrahidrofurano (20 mL). La desaparición del material de inicio se monitoreó mediante la CCD y la 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 ácido fosfórico al 2% y salmuera, se secó (sulfato de magnesio) y se evaporó. El residuo se purificó mediante la cromatografía con evaporación instantánea sobre gel de sílice, eluyendo con acetato de etilo/hexano 1) 1:1 y 2) 2:1 para proporcionar el producto como una espuma incolora (4.93 g, 97%). RMN-$^1$H ($CDCl_3$, 500 MHz) δ 2.43 (3H, s), 3.80 (3H, s), 5.12 (2H, s), 6.66 (1H, s), 7.28 (5H, s amplio), 7.33 (1H, s), 7.47 (1H, s), 7.74 (1H, s), 7.96 (1H, s).

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Espectro de Masas: 366.16 $(MH)^+$.

Ester metílico del ácido (±)-2-amino-3-(7-metil-1H-indazol-5-il)-propiónico

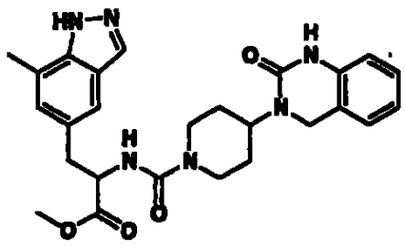



Una solución de éster metílico del ácido 2-benciloxicarbonilamino-3-(7-metil-1H-indazol-5-il)-acrílico (4.93 g, 13.49 mmol) en metanol (125 mL) se desgasificó al burbujear nitrógeno a través de ésta durante 30 minutos y luego se adicionó cuidadosamente paladio al 10% sobre carbón vegetal (0.6 g). La mezcla se hidrogenó a una presión de 2.809 $kg/cm^2$ (40 psi) en un aparato agitador Parr durante toda la noche. El catalizador se removió por filtración a través de una almohadilla de celite y el producto filtrado se concentró *in vacuo* para proporcionar el producto como una espuma incolora (3.62 g, cuantitativo). RMN-$^1H$ ($CD_3OD$, 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 Masas: 234.11 $(MH)^+$.

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Ejemplo 12

Ester metílico 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



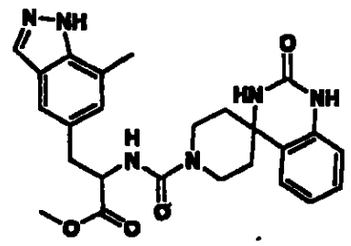
Una solución agitada de éster metílico del ácido (±)-2-amino-3-(7-metil-1H-indazol-5-il)-propiónico (162.9 mg, 0.698 mmol) en cloruro de metileno (3 mL) a temperatura ambiente se trató con diimidazol de carbonilo (113.2 mg, 1 equivalente). Después de 1.5 horas a temperatura ambiente se adicionó la 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (161.5 mg, 1 equivalente). La mezcla se agitó a temperatura ambiente durante toda la noche. Un producto precipitado de color blanco que se había formado se mostró que era el producto deseado. El solvente se evaporó y el residuo se trituró con cloruro de metileno. El producto se colectó por filtración, se lavó con cloruro de metileno y se secó in vacuo para proporcionar un sólido de color blanco (241.5 mg, 71%). Algo del producto permaneció en los licores madre. RMN-$^1$H

(DMF-$d_7$, 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). Espectro de Masas: 491.13 $(MH)^+$.

Preparado de manera similar:

Ejemplo 13

Ester metílico del ácido 3-(7-metil-1H-indazol-5-il)-2-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinazolin)carbonilamino]-propiónico.

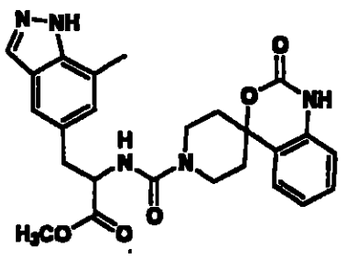


RMN-$^1$H (DMSO-$d_6$) δ 1.59 (4H, m), 2.46 (3H, s), 3.00-3.08 (4H, m), 3.6 (3H, S), 3.78-3.81 (2H, m), 4.30-4.32 (1H, m), 6.78-6.88 (4H, m), 7.03 (1H, s), 7.10 (1H, m), 7.13 (1H, s), 7.41 (1H, s), 7.96 (1H, s), 9.12 (1H, s). Espectro de Masas: 477.11 $(MH)^+$.

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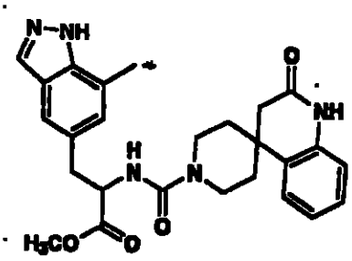
Ejemplo 14

Ester metílico 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



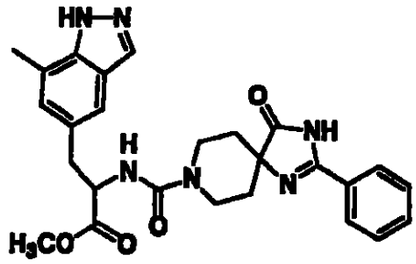
Espectro de Masas: 478.15 $(MH)^+$.

Ester metílico del ácido 3-(7-metil-1H-indazol-5-il)-2{3',4'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinolincarbonilamino}-propiónico



RMN-$^1$H (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 Masas: 476.17 $(MH)^+$.

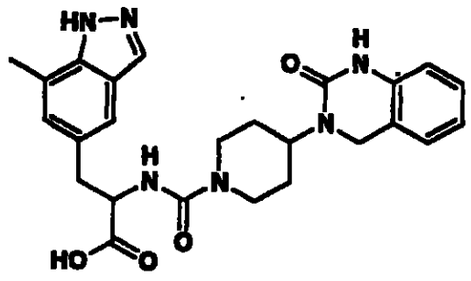
Ester metílico del ácido 3-(7-metil-1H-indazol-5-il)-2-[2'-fenil-1',3',8'-triaza-espiro(4',5')deo-1-en-8-carbonilamino]-propiónico



RMN-$^1$H (DMSO-$d_6$) δ 1.50 (2H, m), 1.68 (2H, m), 2.46 (3H, s se sobrepuso 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 Masas: 489.15 $(MH)^+$.

Ejemplo 15

Acido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

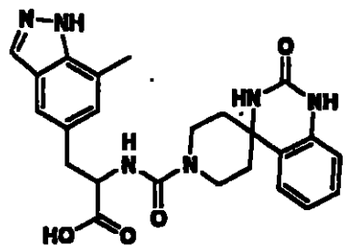


Una suspensión de éster metílico del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (240.0 mg, 0.489 mmol) en tetrahidrofurano/metanol 1:1 (20 mL) a temperatura ambiente se trató con una solución de hidróxido de litio (140.5 mg, 7 equivalentes) en agua (10 mL). Dentro de 1 minuto, la mezcla se volvió homogénea y se dejó reposar a 4°C durante toda la noche. Los solventes se evaporaron a aproximadamente 30°C y el pH se ajustó a aproximadamente 1 con ácido clorhídrico 1N. La suspensión resultante de color blanco se almacenó a 4°C durante varias horas y el producto se colectó por filtración, se lavó con una pequeña cantidad de agua y se secó in vacuo (169.0 mg, 73%). Se adicionó cloruro de sodio sólido al producto filtrado, para dar por resultado la precipitación de más producto (5.2 mg, rendimiento total del 75%). RMN-$^1$H ($CD_3OD$, 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 Masas: 477.13 $(MH)^+$.

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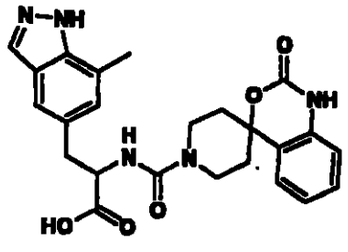
Preparado de manera similar:

Acido 3-(7-metil-1H-indazol-5-il)-2-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinazolincarbonilamino]-propiónico



RMN-$^1$H (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 Masas: 463.09 $(MH)^+$.

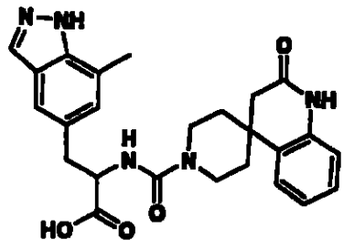
Ester metílico del ácido 3-(7-metil-1H-indazol-5-il)-2-(1,2-dihidro-2-oxoespiro-4H-3,1-dihidro-benzoxazin-4'4-piperidin-carbonilamino)-propiónico



RMN-$^1$H (DMSO-$d_6$) δ 1.63-1.98 (4H, m), 2.46 (3H, s, 7-Me se sobrepuso 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),

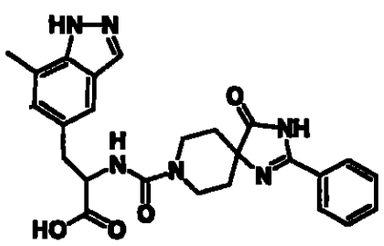
7.24 (1H, m), 7.41 (1H, s), 7.96 (1H, s), 10.22 (1H, s) 12.42 (1H, amplio) 13.02 (1H, m). Espectro de Masas: 464.07 $(MH)^+$.

Acido 3-(7-metil-1H-indazol-5-il)-2{3',4'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinolin-carbonilamino}-propiónico



$RMN-^1H$ ($DMSO-d_6$) 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 Masas: 462 $(MH)^+$.

Acido 3-(7-metil-1H-indazol-5-il)-2-[2'-fenil-1',3',8'-triaza-espiro(4',5')deo-1-en-8-carbonilamino]-propiónico

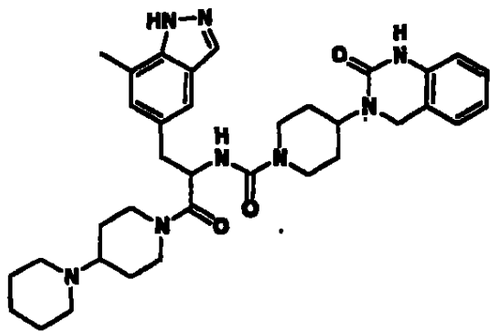


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RMN-$^1$H (DMSO-$d_6$) δ 1.36 (2H, m), 1.63 (2H, m), 2.46 (3H, s se sobrepuso con DMSO), 2.98-3.03 (2H, m), 3.09-3.11 (2H, m), 3.86 (2H, m), 4.21 (1H, m), 6.69 (1H, m), 7.04 (1H, s), 7.40 (1H, s), 7.52-7.58 (3H, m), 7.99 (3H, m), 11.55 (1H, m), 13.00 (1H, m). Espectro de Masas: 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-carbonil]-amino}-propiónico (65.7 mg, 0.138 mmol) en dimetilformamida/cloruro de metileno 2:1 (1.5 mL) a 0°C se trató con 4-(1-piperidil)-piperidina (46.5 mg, 2 equivalentes), diisopropiletilamina (0.048 mL, 2 equivalentes) y PyBOP$^{MR}$ (75.5 mg, 1.05 equivalentes). El baño de hielo se dejó fundir y la mezcla se agitó a

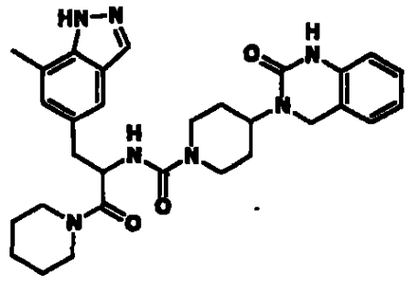
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temperatura ambiente durante toda la noche. Los solventes se removieron bajo alto vacío y el residuo se purificó mediante la cromatografía con evaporación instantánea sobre gel de sílice, eluyendo con cloruro de metileno/metanol 18:1 que contenía trietilamina al 1% para proporcionar el producto como un sólido de color amarillo pálido (80.4 mg, 93%). RMN-$^1$H ($CD_3OD$, 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, varios m), 6.81 (1H, d), 6.96 (1H, t), 7.16 (3H, m), 7.49 (1H, s), 8.03 (1H, s). Espectro de Masas: 627.29 $(MH)^+$.

Preparado de manera similar:

Ejemplo 17

[1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

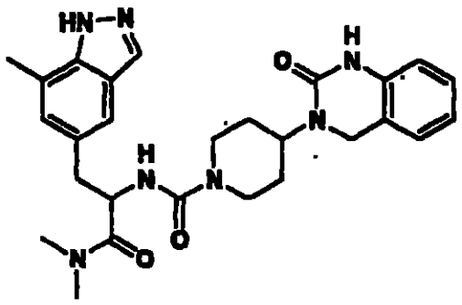



RMN-$^1$H ($CD_3OD$, 500 MHz) δ 0.87 (1H, m), 1.33 (1H, m), 1.47

(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 Masas: 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

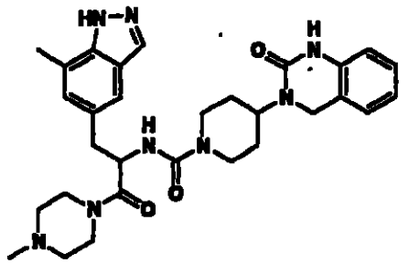


RMN-$^1$H ($CD_3OD$, 500 MHz) δ 1.12 (2H, d), 1.64 (2H, m), 2.57 (3H, s), 2.74 (1H, m), 2.87 (3H, s), 2.89 (3H, s), 2.86 (2H, m), 3.07 (2H, m), 3.20 (1H, m), 4.17 (1H, m), 4.25 (1H, Abq), 4.43 (1H, m), 4.97 (1H, M), 6.79 (1H, d), 6.95 (1H, t), 7.0-7.4 (3H, m), 7.48 (1H, d), 8.01 (1H, s). Espectro de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

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Ejemplo 19

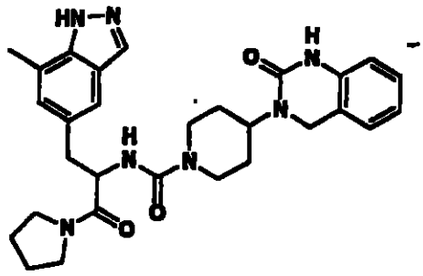
[1-(7-metil-1H-indazol-5-ilmetil)-2-(4-metil-piperazin-1-il)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



RMN-$^1$H ($CD_3OD$, 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 Masas: 559.23 $(MH)^+$.

Ejemplo 20

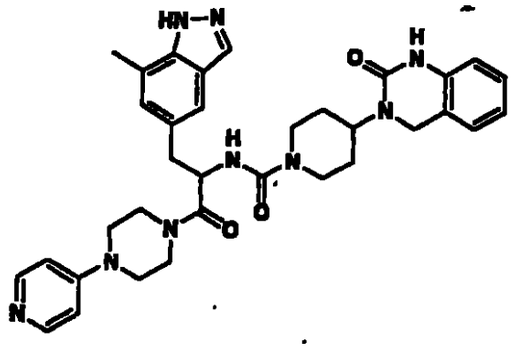
[1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-2-pirrolidin-1-il-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



RMN-$^1$H ($CD_3OD$, 500 MHz) δ 1.40-1.90 (5H, m), 2.02 (3H, s amplio), 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 Masas: 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



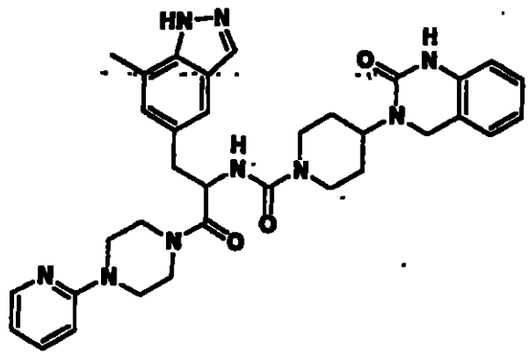
RMN-$^1$H ($CD_3OD$, 500 MHz) δ 1.38 (1H, t), 1.68 (2H, m), 1.81 (1H, m), 2.30 (1H, m), 2.53 (3H, s), 2.95 (4H, m), 3.13 (2H, d), 3.22 (1H, m), 3.35-3.65 (4H, m), 3.79 (1H, m), 4.18 (2H, d), 4.31 (2H, s), 4.42 (1H, m), 4.99 (1H, t), 6.64 (2H, d), 6.80 (1H, d), 6.89 (1H, m), 6.96 (1H, t), 7.14 (3H, m),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

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de Masas: 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

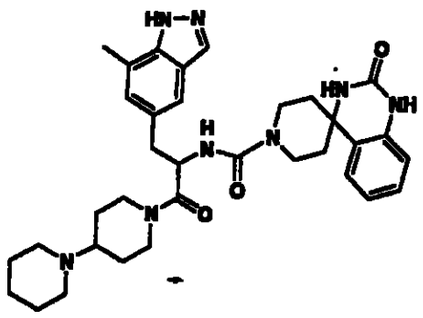


RMN-$^1$H ($CD_3OD$, 500 MHz) δ 1.27 (1H, m), 1.38 (1H, m), 1.67 (2H, m), 1.84 (1H, m), 2.54 (3H, s), 2.65 (1H, m), 2.88 (2H, m), 3.15 (4H, m), 3.35 (1H, m), 3.58 (3H, m), 3.77 (1H, m), 4.18 (2H, d), 4.30 (2H, s), 4.42 (1H, m), 5.01 (1H, t), 6.62 (1H, d), 6.70 (1H, t), 6.80 (1H, d), 6.95 (1H, t), 7.10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

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Ejemplo 23

(±)-1-(7-Metil-1H-imidazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolin]-1-carboxamida

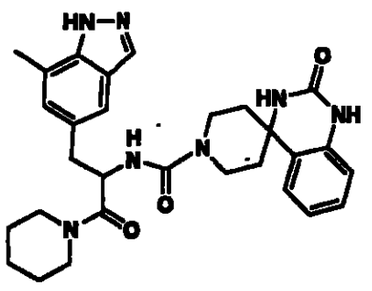


RMN-$^1$H (DMSO-$d_6$, 500 MHz) δ 1.2-1.73 (14H, m), 2.46 (3H, s), 2.75-3.24 (12H, m), 3.87 (2H, m), 4.45 (1H, m), 4.78-4.85 (1H, m), 6.80 (1H, m), 6.86 (1H, m), 7.05 (1H, m), 7.12 (1H, m), 7.21 (1H, m), 7.27 (2H, m), 7.98 (1H, m), 9.23 (1H, m).

Espectro de Masas: 613.25 $(MH)^+$.

Ejemplo 24

(±)-1-(7-Metil-1H-imidazol-5-ilmetil)-2-(1-piperidinil)-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolin]-1-carboxamida

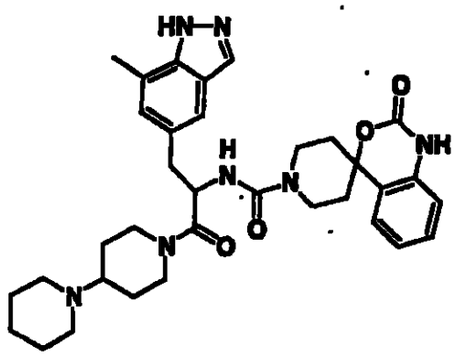


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RMN-$^1$H ($CD_3OD$, 500 MHz) δ 0.87 (1H, m), 1.28-1.47 (5H, m), 1.74-1.85 (4H, m), 2.53 (3H, s), 3.02-3.38 (8H, m), 3.92 (2H, m), 5.02 (1H, m), 6.82 (1H, d), 6.99 (1H, d), 7.04-7.09 (2H, m), 7.17 (1H, m), 7.32 (2H, s), 7.45 (1H, s), 7.96 (1H, s). Espectro de Masas: 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

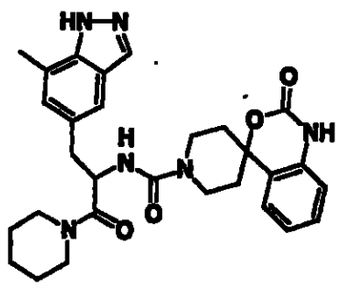



RMN-$^1$H (DMSO-$d_6$, 500 MHz) δ 1.88 (14H, m), 2.64 (3H, s), 2.78 (12H, m), 4.0 (2H, m), 4.4 (1H, m), 4.85 (1H, m), 6.80-6.88 (2H, m), 7.03 (2H, m), 7.11 (1H, m), 7.23 (1H, m), 7.36 (2H, m), 7.97 (1H, m). Espectro de Masas: 614.73 (MH)+.

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Ejemplo 26

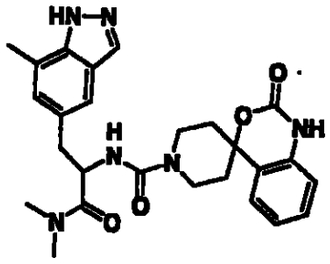
(±)-1-(7-Metil-1H-imidazol-5-ilmetil)-2-(1-piperidinil)-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin]-1-carboxamida



RMN-$^1$H (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 Masas: 531.23 $(MH)^+$.

Ejemplo 27

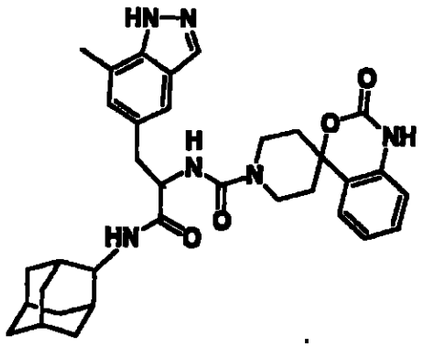
(±)-[1-Dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]-1',2'-dihidro-2'-oxoespiro[4H-3',1-benzoxazin-4,4'-piperidin]-1-carboxamida



RMN-$^1$H (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 Masas: 491.14 $(MH)^+$.

Ejemplo 28

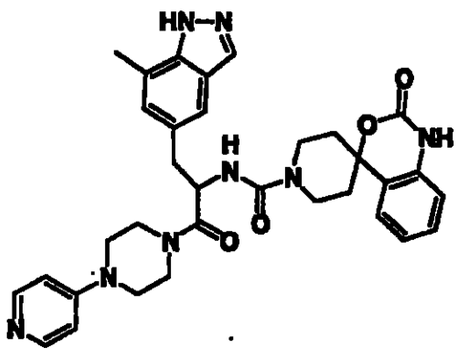
(±)-[1-(2-Adamantil-carbamoil-2-(7-metil-1H-indazol-5-il)-etil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin]-1-carboxamida




RMN-$^1$H ($CD_3OD$, 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 Masas: 597.27 $(MH)^+$.

Ejemplo 29

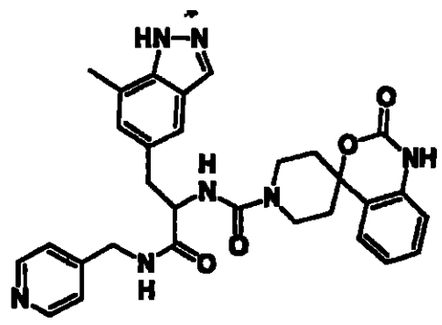
[1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido (±)-1',2'-dihidro-2'-oxoespiro[4H-3',1-benzoxazin-4,4'-piperidin-1-carboxílico



CL/EM: $t_R$ = 1.56 minutos, 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

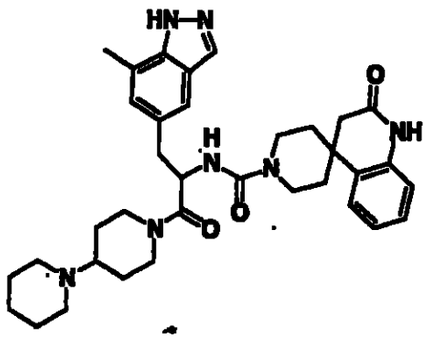


CL/EM: $t_R$ = 1.49 minutos, 553.12 $(MH)^+$.

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Ejemplo 31

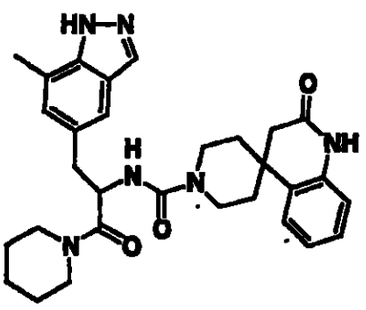
(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]3',4'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinolin]-1-carboxamida



RMN-$^1$H (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 Masas: 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

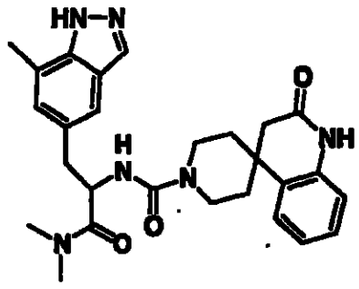


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RMN-$^1$H (DMSO-$d_6$, 500 MHz) δ 1.10-1.68 (10H, m), 2.46 (3H, s), 2.50-2.60 (2H, m), 2.82-2.97 (4H, m), 3.39 (2H, m), 3.85 (2H, m), 4.80 (1H, m), 6.68 (1H, m), 6.87 (1H, d), 6.94 (1H, m), 7.03 (1H, s), 7.06 (1H, m), 7.15 (1H, m), 7.37 (1H, s), 7.40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

Ejemplo 33

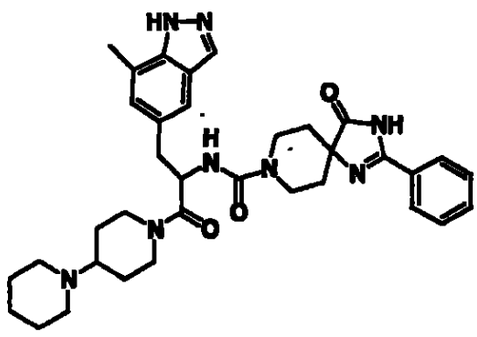
(±)-[1-Dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]1-3',4'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinolin]-1-carboxamida




RMN-$^1$H (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 Masas: 489.2 $(MH)^+$.

Ejemplo 34

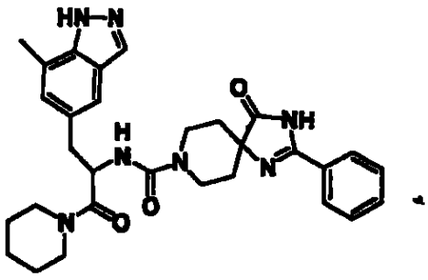
{1-(7-Metil-1H-indazol-5-ilmetil)-2-[1,4]bipiperidinil-1'-il-2-oxo-etil}-amida del ácido (±)-4-oxo-2-fenil-1,3,8-triaza-espiro[1,4]dec-1-en-8-carboxílico



RMN-$^1$H (DMSO-$d_6$, 500 MHz) δ 1.34-2.00 (14H, m), 2.48 (3H, s sobrepuesto con DMSO), 2.70-3.30 (12H, m), 3.90 (2H, m), 4.40 (1H, 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 Masas: 625.29 (MH)+.

Ejemplo 35

{1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piperidinilil]-2-oxo-etil}-amida del ácido (±)-4-oxo-2-fenil-1,3,8-triaza-espiro[4,5]dec-1-en-8-carboxílico



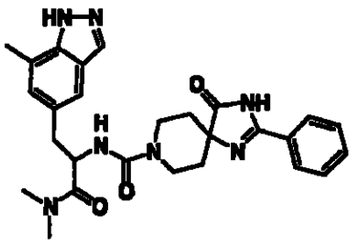
RMN-$^1$H (DMSO-$d_6$, 500 MHz) δ 1.10-1.62 (6H, m), 1.73 (4H, m),

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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 Masas: 543.26 $(MH)^+$.

Ejemplo 36

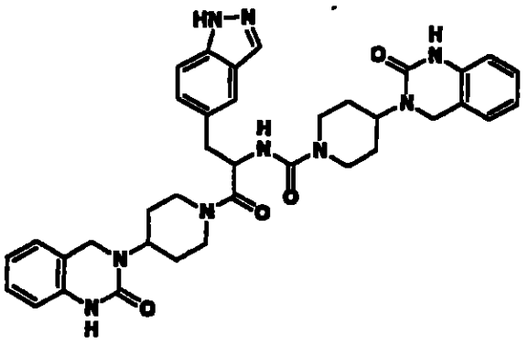
[1-dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]amida del ácido (±)-4-oxo-2-fenil-1,3,8-triaza-espiro[4,5]dec-1-en-8-carboxílico



RMN-$^1$H (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 Masas: 502.21 $(MH)^+$.

Ejemplo 37

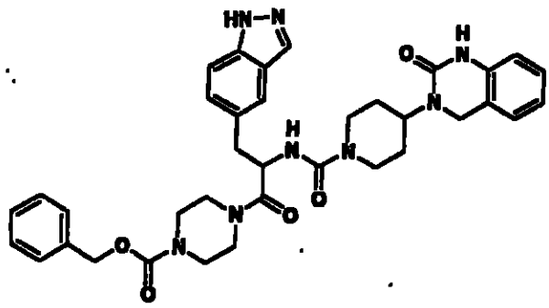
(1-(1H-indazol-5-ilmetil)-2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



CL/EM: $t_R$ = 1.51 minutos, 674 $(MH)^-$.

Ejemplo 38

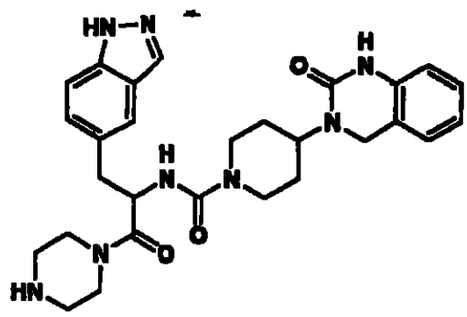
Ester bencílico del ácido 4-(3-(1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propionil)-piperazin-1-carboxílico



CL/EM: $t_R$ = 1.74 minutos, 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

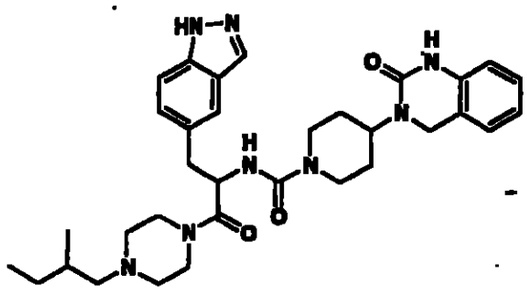


A una solución desgasificada de éster bencílico

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 adicionó carbón vegetal con paladio al 10% (50 mg). La mezcla se agitó en un aparato Parr bajo una atmósfera de hidrógeno a 3.511 kg/cm$^2$ (50 psi) durante 3 horas. La mezcla se filtró a través de celite. El producto filtrado se concentró bajo presión reducida para proporcionar el producto deseado en un rendimiento del 91%. CL/EM: $t_R$ = 1.22 minutos, 531 $(MH)^+$.

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

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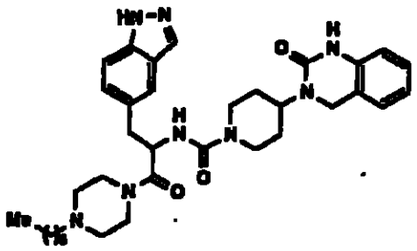
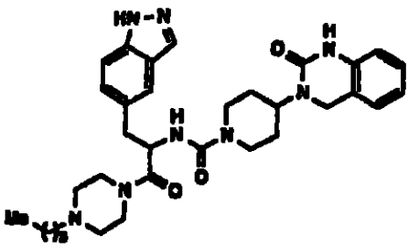
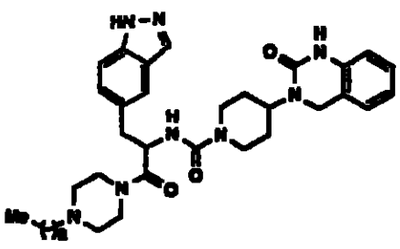
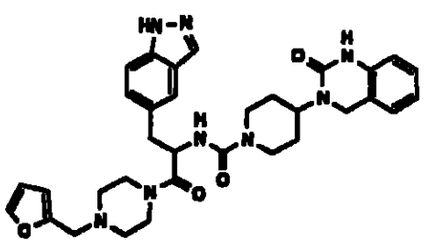
trató con 2-metil-butiraldehído (0.03 ml, 0.376 mmol). Después de 1 hora a temperatura ambiente, se adicionó triacetoxiborohidruro de sodio (80 mg, 0.316 mmol). La mezcla se dejó agitar durante toda la noche. La solución se filtró a través de un cartucho SCX. El cartucho se eluyó primero con metanol y luego con una solución 1M de amoníaco en metanol. El solvente se removió *in vacuo* para proporcionar el producto deseado en un rendimiento del 50%. CL/EM: $t_R$ = 1.31 minutos, 601 $(MH)^+$.

Procedimiento Experimental General para la Preparación de los Ejemplos 40b-40k.

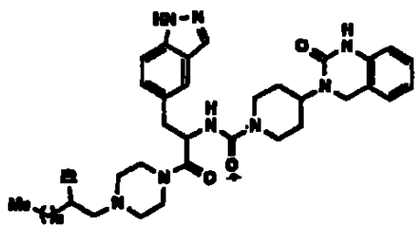
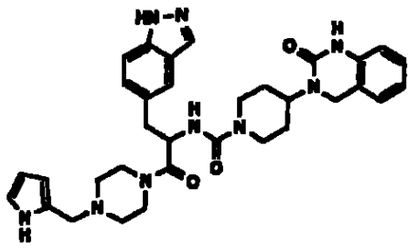
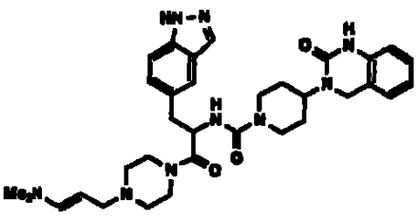
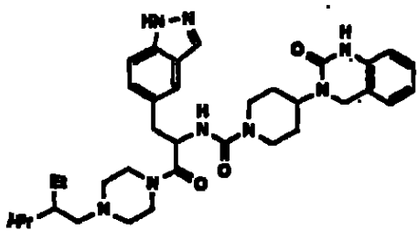
El aldehído apropiado (0.04 mmol) se adicionó a una solución del ejemplo 39, piperazina (0.02 mmol) en MeOH (2.0 mL) y la solución resultante se agitó a temperatura ambiente durante 1 hora. Luego se adicionó triacetoxiborohidruro de sodio (0.2 mmol) y la solución se dejó agitar durante toda la noche a temperatura ambiente. La solución luego se filtró a través de un cartucho SC y el cartucho se lavó con MeOH y una solución de amoníaco/MeOH. La solución de amoníaco/MeOH se concentró *in vacuo* y los productos crudos se purificaron mediante la CLAR preparativa para proporcionar los productos listados en la tabla 1.

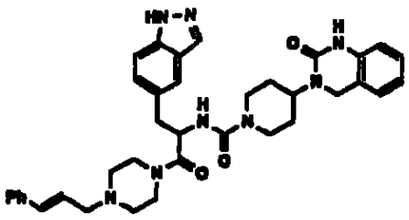
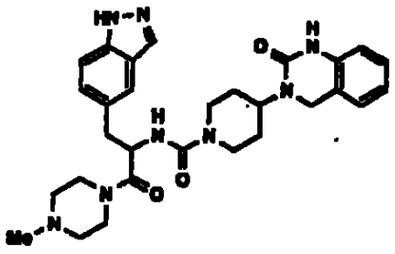
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**Tabla 1, Ejemplos 40b-40k**

| Ejemplo No. | Estructura | CLAR Tiempo de retención | Espec. de Masas $(MH)^+$ |
|---|---|---|---|
| 40b |  | 2.62 | 629 |
| 40c |  | 1.41 | 587 |
| 40d |  | 1.27 | 573 |
| 40e |  | 1.74 | 611 |

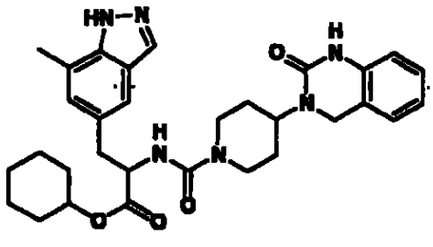
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| Ejemplo No. | Estructura | CLAR Tiempo de retención | Espec. de Masas $(MH)^+$ |
|---|---|---|---|
| 40f |  | 1.89 | 643 |
| 40g |  | 1.48 | 610 |
| 40h |  | 2.19 | 614 |
| 40i |  | 2.36 | 629 |

| Ejemplo No. | Estructura | CLAR Tiempo de retención | Espec. de Masas $(MH)^+$ |
|---|---|---|---|
| 40j |  | 1.66 | 647 |
| 40k |  | 2.16 | 545 |

Ejemplo 41a

Ester ciclohexílico 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

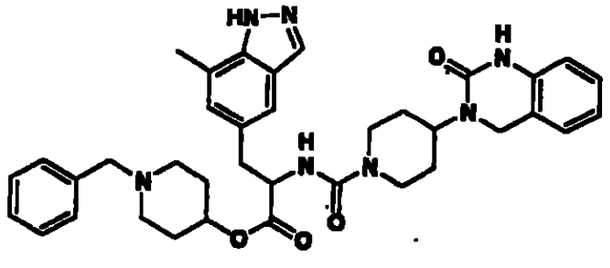


A una solución agitada de ácido (±)-2-amino-3-(7-metil-1H-indazol-5-il)-propínico (20 mg, 0.042 mmoles), 4-(dimetilamino)piridina (2.5 mg, 0.02 mmoles) y clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (33 mg, 0.17 mmoles) en cloruro de metileno (2 mL) y dimetilformamida (1 mL), se adicionó ciclohexanol (13.3 µL, 0.126 mmoles). La mezcla de reacción se agitó a 50-55°C durante 4 horas. El solvente se removió bajo presión reducida, el residuo se purificó mediante la CCD preparativa sobre gel de sílice (cloroformo/metanol 9:1) para proporcionar el producto deseado como un sólido de color blanco (9.4 mg, 40%). RMN-$^1$H (CD$_3$OD, 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 Masas: 559.22 $(MH)^+$.

Preparado de manera similar:

Ejemplo 41b

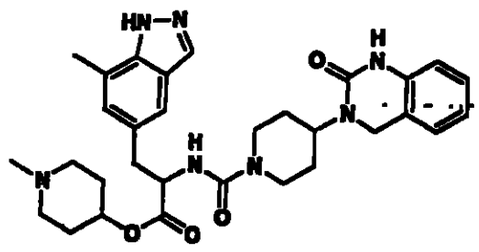
Ester 1-bencil-piperidin-4-ílico del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: $t_R$ = 1.76 minutos, 650.30 $(MH)^+$.

Ejemplo 41c

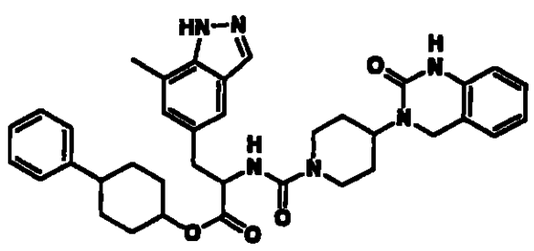
Ester 1-metil-piperidin-4-ílico del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: $t_R$ = 1.59 minutos, 574.27 $(MH)^+$.

Ejemplo 41d

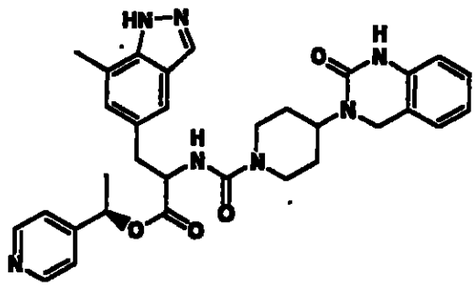
Ester 4-fenil-ciclohexílico del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: $t_R$ = 2.69 minutos, 635.29 $(MH)^+$.

Ejemplo 41e

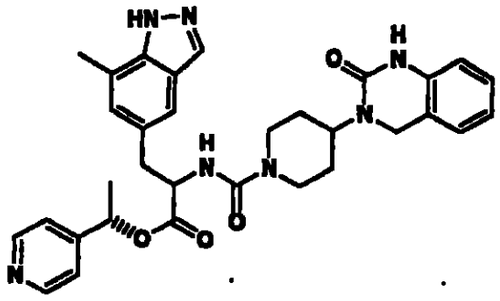
Ester (R)-1-piridin-4-il-etílico del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: $t_R$ = 1.66 minutos, 582.22 $(MH)^+$.

Ejemplo 41f

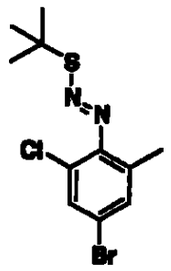
Ester (S)-1-piridin-4-il-etílico del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: $t_R$ = 1.65 minutos, 582.23 $(MH)^+$.

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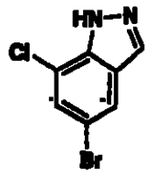
Sulfuro de 4-bromo-2-cloro-6-metilfenildiazo-t-butilo



La 4-bromo-2-cloro-6-metilanilina (4.0 g, 18.3 mmol) se suspendió en ácido clorhídrico al 24% (5 mL). La mezcla agitada se enfrió a -20°C y se trató gota a gota con nitrito de sodio (1.32 g, 1.05 equivalentes) en agua (2 mL), durante 10 minutos mientras que la temperatura se mantuvo debajo de -5°C. Después de 30 minutos adicionales de -5°C a -20°C, la mezcla se amortiguó a aproximadamente pH 5 con acetato de sodio sólido. Esta mezcla (mantenida a aproximadamente -10°C) se adicionó en porciones a una solución agitada de t-butil-tiol (2.06 mL, 1 equivalente) en etanol (18.5 mL) a 0°C durante aproximadamente 10 minutos. Después de la adición, la mezcla se agitó a 0°C durante 30 minutos y luego se adicionó hielo triturado (aproximadamente 50 mL). La mezcla se almacenó en el refrigerador durante toda la noche. El sólido resultante de color café claro se colectó por filtración, se lavó con agua y se secó bajo alto vacío durante varias horas (4.60 g, 78%). Espectro de Masas: 323.03 $(MH)^+$.

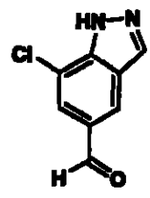
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5-Bromo-7-cloroindazol



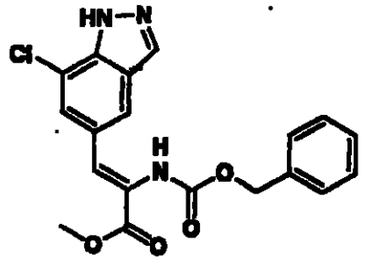
En un matraz de fondo redondo secado a la flama, se combinaron el sulfuro de 4-bromo-2,-cloro-6-metilfenildiazo-t-butilo (4.60 g, 14.4 mmol) y el t-butóxido de potasio (16.1 g, 10 equivalentes). Se adicionó una barra de agitación y la mezcla se colocó bajo nitrógeno. A esto se adicionó DMSO seco (50 mL). La mezcla se agitó vigorosamente durante 10 minutos a temperatura ambiente. La mezcla de reacción luego se vertió cuidadosamente en una mezcla de hielo triturado (150 mL) y ácido clorhídrico al 10% (74 mL). La suspensión resultante se dejó reposar a 4°C durante toda la noche y el sólido se colectó por filtración y se lavó con agua. El sólido se colectó y se secó in vacuo para proporcionar 2.86 g (86%) como un sólido de color beige. RMN-$^1$H ($CDCl_3$, 500 MHz) δ 7.52 (d, J = 1.5, 1H), 7.82 (d, J = 1.5, 1H), 8.08 (s, 1H). Espectro de Masas: 230.90 $(MH)^+$.

7-Cloroindazol-5-carboxaldehído



El 5-bromo-7-cloroindazol (2.0 g, 8.7 mmol) y el hidruro de sodio (221 mg, 1.1 equivalentes) se pesaron en un matraz de fondo redondo secado a la flama que contenía una barra de agitación magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, se adicionó tetrahidrofurano seco (30 mL). La mezcla se agitó a temperatura ambiente durante 15 minutos, tiempo durante el cual se volvió homogénea. La mezcla agitada se enfrió a -78°C y se adicionó una solución de *terc*-butil-litio en pentano (1.7 M, 10.5 mL, 2.0 equivalentes) durante varios minutos. Después de 30 minutos a -78°C, la reacción se calentó gradualmente a -50°C, mantenida durante 15 minutos y se enfrió nuevamente a -78°C. Se adicionó lentamente dimetilformamida (2.8 mL) y la mezcla se dejó calentar a -50°C. La solución se transfirió rápidamente a un embudo separatorio que contenía éter dietílico y agua. La capa acuosa se hizo ácida mediante la adición de sulfato ácido de potasio 1 M y se neutralizó mediante la adición de bicarbonato de sodio. La capa acuosa se extrajo con éter dietílico (3x), la cual se lavó con agua, luego con salmuera, se secó sobre sulfato de magnesio y se concentró para proporcionar 1.7 g (100%) del material casi puro. Se obtuvo una muestra analíticamente pura mediante la recristalización de metanol caliente. RMN-$^1$H ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H), 8.20 (s, 1H), 8.30 (s, 1H), 10.02 (s, 1H). Espectro de Masas: 181.09 $(MH)^+$.

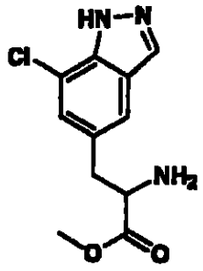
Ester metílico del ácido 2-benciloxicarbonilamino-3-(7-cloro-1H-indazol-5-il)-acrílico



Una suspensión agitada de *terc*-butóxido de potasio (375 mg, 1.2 equivalentes) en cloruro de metileno (20 mL) se enfrió a -20°C y se trató con una solución de éster trimetílico de N-benciloxicarbonil-α-fosfonoglicina (1.11 g, 1.2 equivalentes) en cloruro de metileno (5 mL). Después de 10 minutos, se adicionó 7-cloroindazol-5-carboxaldehído (0.50 g, 2.79 mmol) en cloruro de metileno (5 mL). La reacción se dejó calentar gradualmente a temperatura ambiente y se agitó durante 3 días. La reacción se vertió a un embudo separatorio que contenía agua y éter dietílico. La capa acuosa se extrajo con éter dietílico (3x) la cual se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró. La cromatografía en columna proporcionó 0.40 g (37%) del producto junto con 0.20 g (40%) de material de inicio. RMN-$^1$H ($CDCl_3$, 500 MHz) δ 3.64 (s, 3H), 5.11 (s, 2H), 6.44 (amplio, 1H), 7.30 (amplio, 5H), 7.43 (s, 1H), 7.62 (s, 1H), 7.80 (s, 1H), 8.07 (s, 1H). Espectro de Masas: 386.16 $(MH)^+$.

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Ester metílico del ácido (±)-2-amino-3-(7-cloro-1H-indazol-5-il)-propiónico

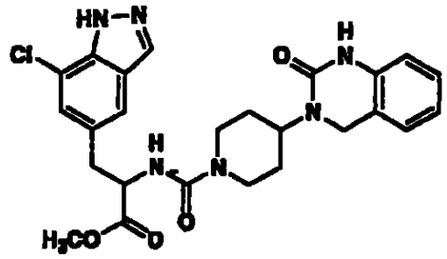



Una solución de éster metílico del ácido 2-benciloxicabonilamino-3-(7-cloro-1H-indazol-5-il)-acrílico (300 mg, 0.78 mmol) en metanol (10 mL) se trató con ácido trifluoroacético (0.2 mL), se inundó con nitrógeno y se trató con paladio al 10% sobre carbón vegetal (30 mg). El matraz se inundó con hidrógeno y se dejó agitar bajo una atmósfera de hidrógeno. Después de 4 días, se había consumido todo el material de inicio. La reacción se inundó con nitrógeno, se filtró a través de celite y se concentró. La cromatografía en columna proporcionó 78 mg (40%). RMN-$^1$H ($CDCl_3$, 500 MHz) δ 1:31 (amplio, 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 Masas: 254.06 $(MH)^+$.

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Ejemplo 42

Ester metílico 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



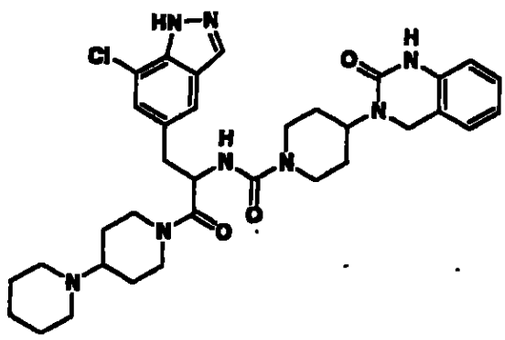
Una solución agitada de éster metílico del ácido (±)-2-amino-3-(7-cloro-1H-indazol-5-il)-propiónico (78 mg, 0.31 mmol) en tetrahidrofurano (2 mL) a 0°C se trató con carbonil-diimidazol (50 mg, 1 equivalente). La reacción se agitó durante 5 minutos, se calentó a temperatura ambiente, se agitó 10 minutos y se trató con 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (78 mg, 1.1 equivalentes). La mezcla se agitó a temperatura ambiente durante toda la noche. El solvente se evaporó y el residuo se purificó mediante la cromatografía en columna para proporcionar 148 mg (94%) como un polvo de color blanco. RMN-$^1$H (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),

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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 Masas: 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

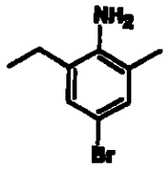


Una suspensión de éster metílico del ácido (±)-3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (15 mg, 0.029 mmol) in tetrahidrofurano/metanol 1:1 (1 mL) a temperatura ambiente se trató con una solución de hidróxido de litio (3.0 mg, 2.5 equivalentes) en agua (0.25 mL) y la solución resultante se agitó durante 1.5 horas. La solución se enfrió a 0°C, se trató con sulfato ácido de potasio 1 M, acuoso (60 µL, 2.0 equivalentes) y se concentró para proporcionar el ácido crudo, el cual se utilizó

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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 (10.1 mg, 2 equivalentes), diisopropiletilamina (10 µL, 2 equivalentes), y PyBOP$^{MR}$ (16.5 mg, 1.1 equivalentes). La solución se agitó 30 minutos y se concentró. El producto se purificó mediante la cromatografía en columna para proporcionar 14.7 mg (77%, 2 pasos). RMN-$^1$H ($CDCl_3$, 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 (s amplio, 1H), 7.91 (s, 0.4H), 7.95 (s, 0.6H), 11.25 (d amplio, J = 50.7, 1H). Espectro de Masas: 647.37 $(MH)^+$.

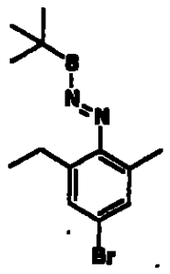
4-bromo-2-etil-6-metil-fenilamina




La 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 adicionó gota a gota bromuro (5.1 mL, 1 equivalente). Hubo una formación rápida de un producto precipitado de color blanco. El producto precipitado se filtró y se lavó con éter dietílico. El producto precipitado se suspendió en agua y se neutralizó con carbonato de potasio acuoso. Se formó un aceite, el cual se extrajo con éter dietílico. El producto etéreo se secó sobre carbonato de potasio, se filtró y se concentró para proporcionar 7.0 g (33%) como un aceite de color morado, el cual se utilizó sin purificación. Espectro de Masas: 214.01 $(MH)^+$.

Sulfuro de 4-bromo-2-etil-6-metilfenildiazo-t-butilo

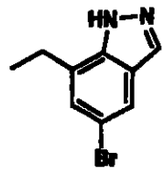


La 4-bromo-2-etil-6-metilanilina (7.0 g, 33 mmol) se suspendió en ácido clorhídrico 7.8 M (30 mL). La mezcla agitada se enfrió a -20°C y se trató gota agota con nitrito de sodio (2.27 g, 1.05 equivalentes) en agua (5 mL), durante 10 minutos mientras que la temperatura se mantuvo abajo de -5°C. Después de 30 minutos adicionales de -5°C a -20°C, la mezcla se amortiguó a aproximadamente pH 5 con acetato de

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sodio sólido. Esta mezcla (mantenida a aproximadamente -10°C) se adicionó en porciones a una solución agitada de t-butil-tiol (3.7 mL, 1 equivalente) en etanol (50 mL) a 0°C durante aproximadamente 10 minutos. Después de la adición, la mezcla se agitó a 0°C durante 30 minutos y luego se adicionó hielo triturado (aproximadamente 50 mL). La mezcla se almacenó en el refrigerador durante 2 horas. El sólido resultante de color café claro se colectó por filtración, se lavó con agua y se secó bajo alto vacío durante varias horas (9.47 g, 92%). Espectro de Masas: 315.05 $(MH)^+$.

5-Bromo-7-etil-1H-indazol

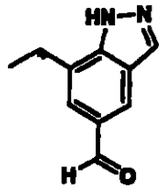



A una solución agitada de t-butóxido de potasio (33.6 g, 10 equivalentes) en DMSO (200 mL) se adicionó una solución de sulfuro de 4-bromo-2-etil-6-metilfenildiazo-t-butilo (9.4 g, 30 mmol) en DMSO (100 mL) por medio de una cánula. La mezcla se agitó vigorosamente durante 1 hora. La mezcla de reacción luego se vertió cuidadosamente en una mezcla de hielo triturado (500 mL), ácido clorhídrico concentrado (25 mL), y agua (100 mL). El producto precipitado resultante se filtró, se lavó con agua y se disolvió en

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metanol y se concentró para proporcionar 5.7 g (85%) como un sólido de color canela. RMN-$^1$H ($CDCl_3$, 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 Masas: 225.00 $(MH)^+$.

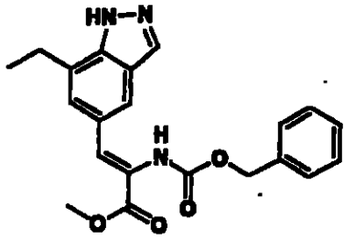
7-Etil-1H-indazol-5-carbaldehído




El 5-bromo-7-etil-1H-indazol (2.0 g, 8.9 mmol) y el hidruro de sodio (226 mg, 1.1 equivalentes) se pesaron en un matraz de fondo redondo secado a la flama que contenía una barra de agitación magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, se adicionó tetrahidrofurano seco (60 mL). La mezcla se agitó a temperatura ambiente durante 15 minutos. La mezcla se enfrió a -78°C y se adicionó una solución de *terc*-butil-litio en pentano (1.7 M, 10.5 mL, 2.0 equivalentes) durante varios minutos. Después de 15 minutos a -78°C, la reacción se calentó gradualmente a -50°C y se enfrió nuevamente a -78°C. Se adicionó lentamente dimetilformamida (2.8 mL) y la mezcla se dejó calentar a -50°C. La solución se transfirió rápidamente a una solución agitada de agua 300 mL y sulfato ácido de potasio 1 M (25

mL). La suspensión resultante se extrajo con éter dietílico, se lavó con agua, luego con salmuera, se secó sobre sulfato de magnesio y se concentró. La cromatografía en columna proporcionó 160 mg (10%) como un sólido de color blanco. RMN-$^1$H ($CD_3OD$, 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 Masas: 175.08 $(MH)^+$.

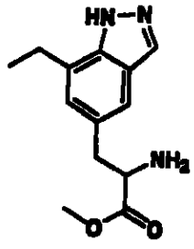
Ester metílico del ácido 2-benciloxicarbonilamino-3-(7-etil-1H-indazol-5-il)-acrílico




A una solución agitada de éster trimetílico de N-benciloxicarbonil-α-fosfonoglicina (0.61 g, 2.0 equivalentes) y 7-etil-1H-indazol-5-carbaldehído (160 mg, 0.92 mmol) en tetrahidrofurano (5 mL) a 0°C se adicionó tetrametilguanidina (0.22 mL, 1.9 equivalentes). La reacción se dejó calentar lentamente a temperatura ambiente durante toda la noche. La reacción se concentró, se disolvió en éter dietílico, se lavó con agua, luego con salmuera, se secó (sulfato de magnesio) y se concentró. El residuo se purificó mediante la cromatografía en columna para proporcionar 333 mg (95%) como

un aceite. RMN-$^1$H ($CDCl_3$, 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 (amplio, 1H), 7.29 (amplio, 5H), 7.43 (s, 1H), 7.50 (s, 1H), 7.78 (s, 1H), 8.04 (s, 1H). Espectro de Masas: 380.17 $(MH)^+$.

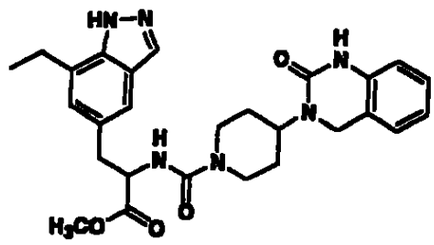
Ester metílico del ácido (±)-2-amino-3-(7-etil-1H-indazol-5-il)-propiónico




A una solución de éster metílico del ácido 2-benciloxicarbonilamino-3-(7-etil-1H-indazol-5-il)-acrílico (330 mg, 0.78 mmol) en metanol (5 mL) bajo nitrógeno se adicionó paladio sobre carbón vegetal (10%, 33 mg). El matraz se inundó con hidrógeno y se dejó agitar bajo una atmósfera de hidrógeno durante toda la noche. La reacción se inundó con nitrógeno, se filtró a través de celite y se concentró para proporcionar 210 mg (98%), el cual se utilizó sin purificación adicional. RMN-$^1$H ($CDCl_3$, 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). Espectro de Masas: 248.15 $(MH)^+$.

Ejemplo 44

Ester metílico 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

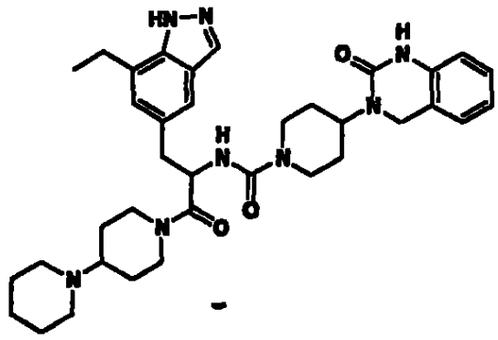


Una solución agitada de éster metílico del ácido (±)-2-amino-3-(7-etil-1H-indazol-5-il)-propiónico (100 mg, 0.41 mmol) en tetrahidrofurano (2 mL) a 0°C se trató con carbonil-diimidazol (66 mg, 1 equivalente). La reacción se agitó durante 5 minutos, se calentó a temperatura ambiente, se agitó durante 15 minutos y luego se trató con 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (103 mg, 1.1 equivalentes). La mezcla se agitó a temperatura ambiente durante toda la noche. El solvente se evaporó y el residuo se purificó mediante la cromatografía en columna para proporcionar 188 mg (92%) como un sólido de color blanco, RMN-$^1$H ($CDCl_3$, 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 Masas: 505.29 $(MH)^+$.

Ejemplo 45

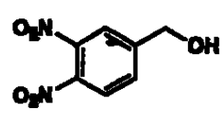
[2-[1,4']piperidinil-1'-1-(7-etil-1H-imidazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



A una solución de éster metílico 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 adicionó una solución de monohidrato de hidróxido de litio (3.0 mg, 2.5 equivalentes) en agua (0.1 mL) y la solución resultante se agitó durante 6 horas. La solución se enfrió a 0°C, se trató con sulfato ácido de potasio 1 M (60 µL, 2.0 equivalentes), y se concentró para proporcionar el ácido crudo, el cual se utilizó 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 equivalentes), diisopropiletilamina (12 µL, 2.3 equivalentes) y PyBOP^MR (19 mg, 1.2 equivalentes). La solución se agitó durante 15 minutos a 0°C, se calentó a temperatura ambiente, se agitó 1.5 horas y se concentró. El producto se purificó mediante la cromatografía en columna para proporcionar 14.5 mg (76%, 2 pasos). RMN-$^1$H ($CDCl_3$, 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). Espectro de Masas: 641.50 $(MH)^+$.

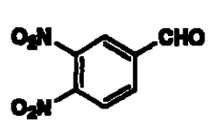
(3,4-Dinitro-fenil)-metanol




El complejo de $BH_3$-tetrahidrofurano (1M en tetrahidrofurano, 800 mL, 800 mmol) se adicionó a -20°C durante 45 minutos 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 hora y luego se calentó a temperatura ambiente y se agitó durante toda la noche. Se enfrió rápidamente mediante la adición de 32 mL de ácido acético/agua 1:1. Los solventes se removieron *in vacuo* y el residuo se vertió en 1000 mL de bicarbonato de sodio saturado, helado con agitación vigorosa durante 15 minutos. La mezcla se extraje con acetato de etilo (3 x 500 mL). Las capas orgánicas, combinadas se lavaron con bicarbonato de sodio saturado, salmuera y se secaron sobre sulfato de sodio. Después de la filtración, los solventes se removieron para proporcionar el compuesto del título como un sólido de color amarillo claro (100%). RMN-$^1$H ($CDCl_3$, 500 MHz) $\delta$ 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).

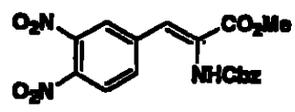
3,4-Dinitro-benzaldehído




Una solución de (3,4-dinitro-fenil)-metanol (95.3 g, 481 mmol) en cloruro de metileno (500 mL) se adicionó de repente 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 horas y luego se adicionó

éter (1500 mL). El sobrenadante se decantó a partir de la goma negra resultante y el residuo insoluble se lavó completamente con cloruro de metileno (3 X 250 mL). La solución orgánica, combinada se filtró a través de una almohadilla de florisil para proporcionar una solución clara de color amarillo brillante, claro. Los solventes se removieron *in vacuo* y el residuo se purificó mediante la cromatografía en gel de sílice utilizando cloruro de metileno como eluyente para proporcionar el compuesto del título como un sólido de color amarillo (71%). RMN-1H ($CDCl_3$, 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). RMN-$^{13}$C ($CD_3OD$, 125 MHz) δ 187.7, 139.2, 134.2, 126.2, 125.7.

Ester metílico del ácido 2-benciloxicarbonilamino-3-(3,4-dinitro-fenil)-acrílico

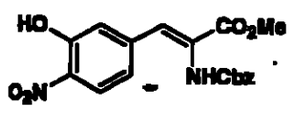



La 1,1,3,3-tetrametilguanidina (41.2 mL, 329 mmol) se adicionó a temperatura ambiente a una solución de éster trimetílico de N-(benciloxicarbonil)-alfa-fosfonoglicina (114.1 g, 344 mmol) en tetrahidrofurano (800 mL). La mezcla se agitó a temperatura ambiente durante 15 minutos y se enfrió a -78°C. Se adicionó 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 2 horas y luego se dejó calentar a temperatura ambiente durante toda la noche. Los solventes se removieron *in vacuo* y el residuo de color amarillo se disolvió en 4.5 L de acetato de etilo. La solución se lavó con 1.5 litros de ácido sulfúrico 1N, dos veces con agua, salmuera y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron *in vacuo* y el residuo se cristalizó a partir de acetato de etilo (20 g de producto crudo/100 mL de acetato de etilo). Los cristales de color amarillo se colectaron y se purificaron mediante la cromatografía en gel de sílice utilizando cloruro de metileno como eluyente. El compuesto del título se obtuvo como cristales de color amarillo (77%). RMN-$^1$H ($CDCl_3$, 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 (s amplio, 2H), 7.23 (s, 1H), 6.95 (s amplio, 1H), 5.07 (s, 2H), 3.90 (s, 3H).

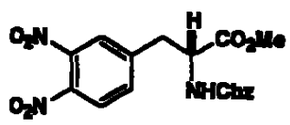
Preparado de manera similar:

Ester metílico del ácido 2-benciloxicarbonilamino-3-(3-hidroxi-4-nitro-fenil)-acrílico



RMN-$^1$H ($CDCl_3$, 500 MHz) δ 7.93 (d, J = 9.0 Hz, 1H), 7.32 (s amplio, 1H), 7.28 (s amplio, 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 (s amplio, 1H), 5.06 (s, 2H), 3.86 (s, 3H).

Ester metílico del ácido (R)-2-benciloxicarbonilamino-3-(3,4-dinitro-fenil)-propiónico

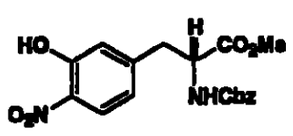



Un matraz Shlenck de 500 mL secado en un horno se colocó en una bolsa de manipulación con guantes llenada con nitrógeno. Después de que la bolsa de manipulación con guantes se evacuó y se llenó con nitrógeno (3x), el matraz se selló y se tomó de la bolsa de manipulación con guantes y se pesó. Se colocó nuevamente en la bolsa de manipulación con guantes y se evacuó y se llenó con nitrógeno (3x), luego se cargó con trifluorometanosulfonato de (-)-1,2-bis((2R,5R)-2,5-dietilfosfolano)bencen-(ciclooctadien)rodio (I). El matraz se selló y se tomó de la bolsa de manipulación con guantes y se pesó (784 mg, 1.08 mmol). Se adicionó éster metílico del ácido 2-benciloxicabonilamino-3-(3,4-dinitro-fenil)-acetílico (8.71 g, 21.7 mmol) a otros 500 mL del matraz Schlenck y se evacuó y se llenó con nitrógeno (3x). Se adicionó cloruro de metileno (350 mL, desgasificado con

nitrógeno durante 2 horas) y la solución resultante se transfirió al matraz catalítico por medio de una cánula. El matraz se purgó y se llenó con hidrógeno (4x) y la mezcla se agitó a temperatura ambiente durante 4 horas. Los solventes se removieron *in vacuo* y el residuo se purificó mediante la cromatografía en gel de sílice utilizando acetato de etilo/hexanos (1:1) como eluyente para proporcionar el compuesto del título como un sólido gomoso de color canela claro (rendimiento del 99% y 99.2% ee determinado mediante el análisis de la CLAR utilizando las siguientes condiciones: columna Chiralpak AD (4.6 x 250 mm, 10 um; A = etanol, B = hexano; 40% de B @ 1.0 mL/minuto durante 14 minutos; tiempos de retención: 10.9 minutos para el enantiómero R y 6.9 minutos para el enantiómero S). RMN-$^1$H ($CDCl_3$, 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).

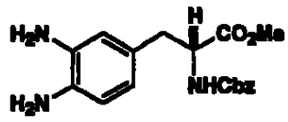
Preparado de manera similar:

Ester metílico del ácido (R)-2-benciloxicarbonilamino-3-(3-hidroxi-4-nitrofenil)-propiónico



RMN-$^1$H ($CDCl_3$, 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 = 12.5Hz, 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).

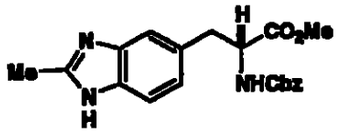
Ester metílico del ácido (R)-2-benciloxicarbonilamino-3-(3,4-diamino-fenil)-propiónico




El formiato de amonio sólido (2.27 g, 36 mmol) se adicionó en pequeñas porciones a 0°C a una suspensión de metanol (50 mL, desgasificado con nitrógeno durante 2 horas) de éster metílico 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 mmol). La mezcla resultante se agitó a temperatura ambiente durante toda la noche. Los solventes se removieron *in vacuo* y luego se adicionaron tolueno (30 mL, desgasificado) y acetato de etilo (30 mL, desgasificado), seguido por ácido acético (3 mL). La mezcla se diluyó adicionalmente hasta que se disolvieron todos los sólido orgánicos, luego se lavó con agua, salmuera y se secaron sobre sulfato de sodio. Después de la filtración, los solventes se removieron *in vacuo* para proporcionar el

compuesto del título que contenía 1 equivalente de ácido acético como un sólido gomoso, rojizo (85%). Espectro de Masas: 344.18 $(MH)^+$.

Ester metílico del ácido (R)-2-benciloxicarbonilamino-3-(2-metil-1H-benzoimidazol-5-il)-propiónico

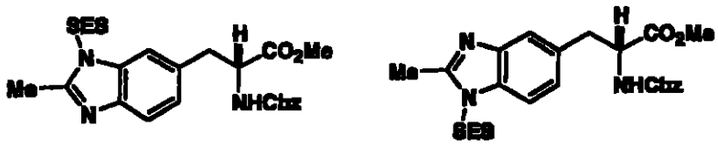



Una solución de éster metílico del ácido (R)-2-benciloxicarbonilamino-3-(3,4-diamino-fenil)-propiónico-ácido acético (640 mg) en ácido acético (8 mL) se calentó a 130°C durante 4 horas. La mezcla luego se vertió en agua y se enfrió a 0°C. El pH se ajustó a 8 mediante la adición gradual de bicarbonato 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 secaron sobre sulfato de sodio. Después de la filtración, los solventes se removieron para proporcionar el compuesto del título como un sólido espumoso, pardusco (95%). RMN-$^1$H ($CDCl_3$, 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 Masas: 368.19 $(MH)^+$.

Ester metílico del ácido (R)-2-benciloxicarbonilamino-3-[2-metil-3-(2-trimetilsilanil-etanosulfonil)-3H-benzoimidazol-5-il]-propiónico

y

Ester metílico del ácido (R)-2-benciloxicarbonilamino-3-[2-metil-1-(2-trimetilsilanil-etanosulfonil)-1H-benzoimidazol-5-il]-propiónico

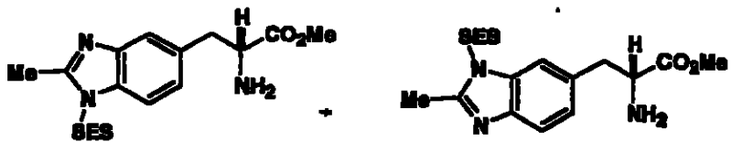


A una suspensión de éster metílico del ácido (R)-2-benciloxicarbonilamino-3-(2-metil-1H-benzoimidazol-5-il)-propiónico (533 mg, 1.96 mmol) y carbonato de sodio en acetonitrilo (20 mL) se adicionó cloruro de 2-trimetilsilanil-etanosulfonilo puro, de repente. La mezcla se agitó a temperatura ambiente durante toda la noche. Los solventes se removieron y el residuo se purificó mediante la cromatografía en gel de sílice utilizando 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 N3, 66%). RMN-$^1$H ($CDCl_3$, 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). Espectro de Masas: 532.26 $(MH)^+$.

Ester metílico del ácido (R)-2-amino-3-[2-metil-1-(2-trimetilsilanil-etanosulfonil)-1H-benzoimidazol-5-il]-propiónico y

Ester metílico del ácido (R)-2-amino-3-[2-metil-3-(2-trimetilsilanil-etanosulfonil)-3H-benzoimidazol-5-il]-propiónico

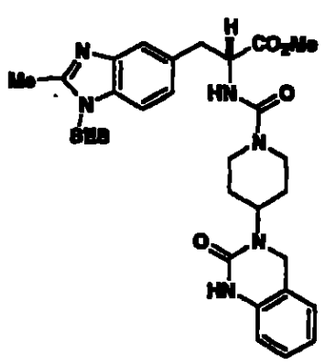


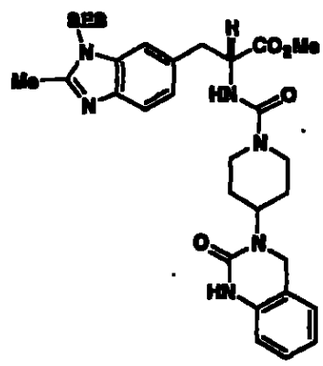
Una suspensión de metanol (50 mL) de éster metílico del ácido (R)-2-benciloxicarbonilamino-3-[2-metil-3-(2-trimetilsilanil-etanosulfonil)-3H-benzoimidazol-5-il]-propiónico y éster metílico del ácido (R)-2-benciloxicarbonilamino-3-[2-metil-1-(2-trimetilsilanil- etanosulfonil)-1H-benzoimidazol-5-il]-propiónico (mezcla 1:1, 600 mg), y paladio al 10% sobre carbón vegetal (180 mg) se agitó en un aparato Parr durante toda la noche bajo una presión de hidrógeno de 2.809 $kg/cm^2$ (40 psi) a temperatura ambiente. Después de reemplazar la atmósfera de hidrógeno por 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 de color canela (80%). RMN-$^1H$ ($CD_3OD$, 500 MHz) $\delta$ 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 = 9.0Hz, 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); RMN-$^{13}$C ($CD_3OD$, 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 Masas: 398.20 $(MH)^+$.

Ester metílico del ácido (R)-3-[2-metil-1-(2-trimetilsilanil-etanosulfonil)-1H-benzoimidazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico y

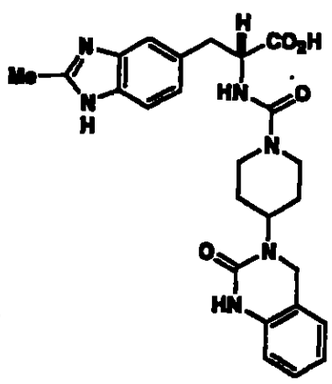
éster metílico del ácido (R)-3-[2-metil-3-(2-trimetilsilanil-etanosulfonil)-3H-benzoimidazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico





Preparados como se describe anteriormente para el éster metílico del 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. Purificado mediante la cromatografía en gel de sílice utilizando acetato de etilo con trietilamina al 1% como eluyente para proporcionar el compuesto del título como un sólido blanquecino (87%). RMN-$^{1}$H ($CD_3OD$, 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). RMN-$^{13}$C ($CD_3OD$, 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 Masas: 655.36 $(MH)^+$.

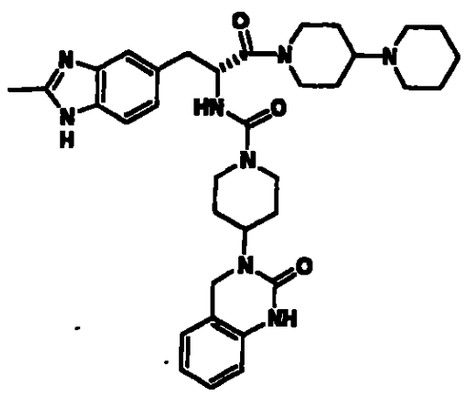
Acido (R)-3-(2-metil-1H-benzoimidazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



La mezcla 1:1 de éster metílico del ácido (R)-3-[2-metil-1-(2-trimetilsilanil-etanosulfonil)-1H-benzoimidazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico y éster metílico del ácido (R)-3-[2-metil-3-(2-trimetilsilanil-etanosulfonil)-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 el 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. Se utilizaron las condiciones de hidrólisis (hidróxido de litio/metanol-tetrahidrofurano-agua (1:1:1) a -15°C durante toda la noche. El compuesto del título se obtuvo como un sólido de color blanco (25%). Espectro de Masas: 477.24 $(MH)^+$.

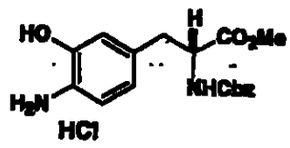
Ejemplo 46

[2-[1,4']Bipiperidinil-1'-il-1-(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 anteriormente para la {2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. Purificado mediante la cromatografía en gel de sílice utilizando cloruro de metileno:metanol:trietilamina (93:5:2) como eluyente para proporcionar un sólido de color blanco. Esto se disolvió en acetato de etilo (60 mL) y se lavó dos veces con bicarbonato de sodio saturado/salmuera 1:1 y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron para proporcionar el compuesto del título como un sólido de color blanco (rendimiento del 11%). CL/EM: $t_R$ 1.59 minutos, 627.34 $(MH)^+$.

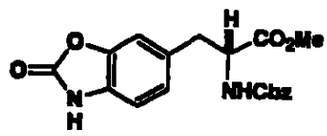
Clorhidrato de éster metílico del ácido (R)-3-(4-amino-3-hidroxi-fenil)-2-benciloxicarbonilamino-propiónico



El hierro en polvo (3.7 g, 66.4 mmol) y el cloruro de amonio (5.9 g, 111 mmol) se adicionaron a 0°C a una solución de éster metílico del ácido (R)-2-benciloxicarbonilamino-3-(3-hidroxi-4-nitro-fenil)-propiónico (2.07 g, 5.53 mmol) en metanol/agua 1:1 desgasificado (400 mL). La mezcla resultante se agitó a temperatura ambiente durante 48 horas. Se adicionó ácido trifluoroacético (7 mL) y la mezcla se remolineó hasta que fue una solución clara de color rojo intenso que contenía una suspensión de polvo de hierro sin reaccionar. La mezcla se filtró y el producto 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 adicionó 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 de color canela (80%). RMN-$^1$H ($CD_3OD$, 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 (s

amplio, 2H), 3.11 (dd, J = 14.0, 5.0 Hz, 1H), 2.90 (dd, J = 13.5, 9.0 Hz, 1H). RMN-$^{13}$C ($CD_3OD$, 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 Masas: 345.20 $(MH)^+$.

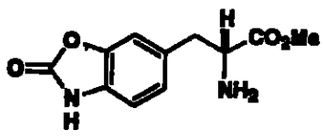
Ester metílico del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico




Una solución de cloruro de metileno (15 mL) de carbonil-diimidazol (498 mg, 3.07 mmol) se adicionó a 0°C a una solución de éster metílico 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 horas. Los solventes se removieron *in vacuo* y el residuo se purificó mediante la cromatografía en gel de sílice utilizando acetato de etilo/hexanos como eluyente para proporcionar el compuesto del título como un sólido de color blanco (51%). RMN-$^1$H ($CDCl_3$, 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). RMN-$^{13}$C ($CDCl_3$, 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 Masas: 371.18 $(MH)^+$.

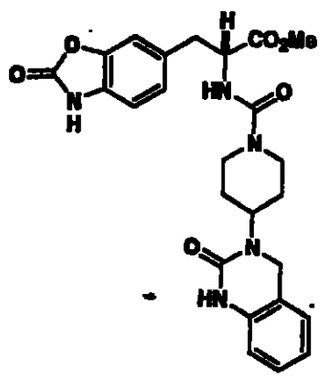
Ester metílico del ácido (R)-2-amino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico



Una solución de éster metílico del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico (310 mg) en ácido fórmico al 4.4% en metanol (20 ml, preparado recientemente en metanol desgasificado) se adicionó por medio de una cánula a una suspensión de paladio al 10% sobre carbón vegetal en ácido fórmico al 4.4% en metanol (20 ml, preparado recientemente en metanol desgasificado). La mezcla resultante se agitó a temperatura ambiente durante 4 horas. Después de la filtración a través de una almohadilla de celite, los solventes se removieron *in vacuo* para proporcionar un sólido de color canela. El sólido se disolvió en una mezcla de acetato de etilo (50 mL) tolueno (10 mL) y etanol (40 ml) y se adicionó bicarbonato de sodio sólido (3.1 g). La mezcla se agitó a temperatura ambiente

durante 2 horas y se filtró. Los solventes se removieron *in vacuo* para proporcionar el compuesto del título RMN-$^1$H ($CD_3OD$, 500 MHz) δ 8.41 (s amplio, 2H), 7.17 (s, 1H), 7.09 (s amplio, 2H), 4.32 (s, 1H), 3.83 (s, 3H), 3.33 (s, 1H), 3.30 (s, 1H), 3.22 (s, 1H). Espectro de Masas: 237.20 $(MH)^+$.

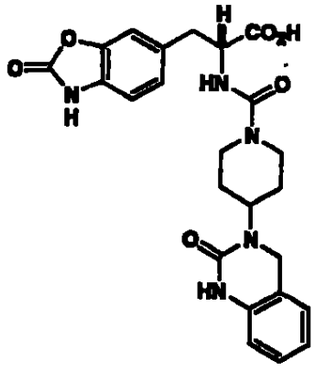
Ester metílico del ácido (R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describe anteriormente para el éster metílico del 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. Purificado mediante la cromatografía en gel de sílice utilizando cloruro de metileno:metanol:trietilamina (93:5:2) como eluyente para proporcionar el compuesto del título como un sólido de color blanco (33%). RMN-$^1$H ($CD_3OD$, 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 (s amplio, 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). RMN-$^{13}$C ($CD_3OD$, 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 Masas: 494.30 $(MH)^+$.

Acido (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

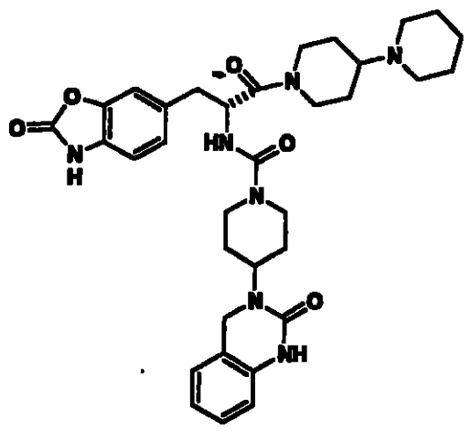


Preparado como se describe anteriormente para el ácido (R)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-il]-propiónico. Se utilizaron las condiciones de hidrólisis (hidróxido de litio/metanol-

tetrahidrofurano-agua (1:1:1) a -15°C durante toda la noche. El compuesto del título se obtuvo como un sólido de color blanco (95%). Espectro de Masas: 480.30 $(MH)^+$.

Ejemplo 47

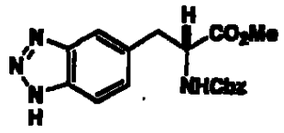
[2-[1,4']Bipiperidinil-1'-il-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Preparada como se describe anteriormente para la {2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-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 mediante la cromatografía en gel de sílice utilizando cloruro de metileno:metanol:trietilamina (93:5:2) como eluyente para proporcionar un sólido de color blanco. Esto se disolvió en acetato de etilo (60 ml) y se lavó dos veces con bicarbonato

de sodio saturado/salmuera 1:1 y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron para proporcionar el compuesto del título como un sólido de color blanco (70%). RMN-$^1$H ($CD_3OD$, 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 minutos, 630.31 $(MH)^+$.

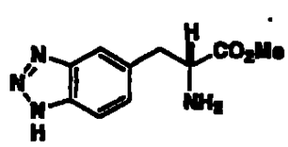
Ester metílico del ácido (R)-3-(1H-benzotriazol-5-il)-2-benciloxicarbonilamino-propiónico




A una solución de monoacetato de éster metílico del ácido (*R*)-2-benciloxicarbonilamino-3-(3,4-diamino-fenil)-propiónico (2.68 g, 6.65 mmol) en ácido acético (30 mL) y agua (40 mL), a temperatura ambiente se adicionó gota a gota una solución de nitrito de sodio (0.46 g, 6.65 mmol) en agua (8 mL), durante varios minutos. La mezcla resultante se agitó a temperatura ambiente durante 20 minutos, luego se enfrió a 0°C, se adicionó hidróxido de amonio concentrado para ajustar el pH a 11. La mezcla se extrajo dos veces con acetato de

etilo 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 mediante la cromatografía en gel de sílice utilizando acetato de etilo/hexanos (6:4) como eluyente para proporcionar el compuesto del título como un sólido de color canela (rendimiento del 94%). RMN-$^1$H ($CD_3OD$, 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). RMN-$^{13}$C ($CD_3OD$, 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 Masas 355.18 $(MH)^+$.

Ester metílico del ácido (R)-2-amino-3-(1H-benzotriazol-5-il)-propiónico

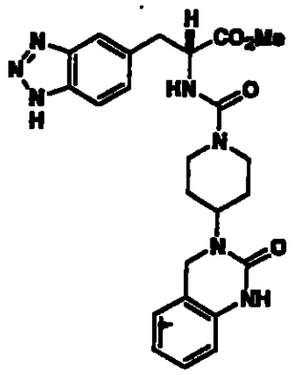



Preparado como se describe anteriormente para el éster metílico del ácido (R)-2-amino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico. RMN-$^1$H ($CD_3OD$, 500 MHz) δ 8.38 (s amplio, 2H), 7.89 (d, J = 7.5 Hz, 1H), 7.81 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 4.44 (s, 1H), 3.81 (s, 3H), 3.48-3.45

(m, 1H), 3.40-3.37 (m, 1H), 3.33 (s amplio, 1H). RMN-$^{13}$C ($CD_3OD$, 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 Masas 221.15 $(MH)^+$.

Ejemplo 48

Ester metílico del ácido (R)-3-(1H-benzotriazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

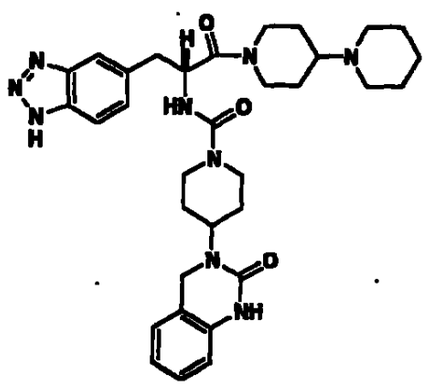


Preparado como se describe anteriormente para el éster metílico del ácido (*R*)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-il]-propiónico excepto que se utilizó carbonil-diimidazol en lugar del carbonato de *N,N*-disuccinimidilo (DSC). RMN-$^1$H ($CD_3OD$, 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 Masas 478.30 $(MH)^+$.

Ejemplo 49

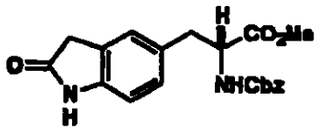
[1-(1H-Benzotriazol-5-ilmetil)-2-[1,4']bipiperidinil-1'-il-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Preparada como se describe anteriormente para {2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (*R*)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. Purificada mediante la cromatografía en gel de sílice utilizando cloruro de metileno/metanol/trietilamina (93:5:2) como eluyente. RMN-$^1$H ($CD_3OD$, 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 minutos, 614.28 $(MH)^+$.

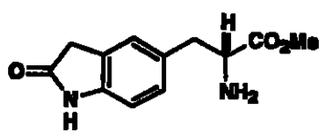
Ester metílico del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-1H-indol-5-il)-propiónico




El $PyHBr_3$ (1.28 g, 4.02 mmol) se adicionó en pequeñas porciones durante 30 minutos a una solución de éster metílico del ácido (R)-2-benciloxicarbonilamino-3-(1H-indol-5-il)-propiónico (0.47 g, 1.34 mmol) en t-butanol (10 mL) mientras que la temperatura de reacción se mantenía entre 25-30°C. La mezcla resultante se agitó a temperatura ambiente durante 3.5 horas. El solvente se removió *in vacuo* y el residuo se extrajo con acetato de etilo (2x). Las fases orgánicas, cembinadas 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 se adicionó polvo de zinc (0.88 g, 13.4 mmol). La mezcla se agitó a temperatura ambiente durante toda la noche. Después, el ácido acético se removió *in vacuo*, el residuo se purificó mediante la cromatografía con evaporación instantánea en gel de sílice utilizando acetato de etilo/hexanos [(1:3) primero y luego (3:2)] como eluyente para proporcionar el compuesto del título como un sólido de color blanco (41% para los 2 pasos). RMN-$^1$H ($CDCl_3$, 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). RMN-$^{13}$C ($CDCl_3$, 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 Masas 369.20 $(MH)^+$.

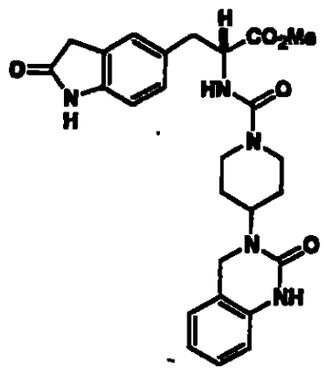
Ester metílico del ácido (R)-2-amino-3-(2-oxo-2,3-dihidro-1H-indol-5-il)-propiónico




Preparado como se describe anteriormente para el éster metílico del ácido (R)-2-amino-3-(2-oxo-2,3-dihidro-

benzooxazol-6-il)-propiónico. RMN-$^1$H ($CD_3OD$, 500 MHz) δ 8.48 (s amplio, 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). RMN-$^{13}$C ($CD_3OD$, 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 Masas 235.30 $(MH)^+$.

Ester metílico 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

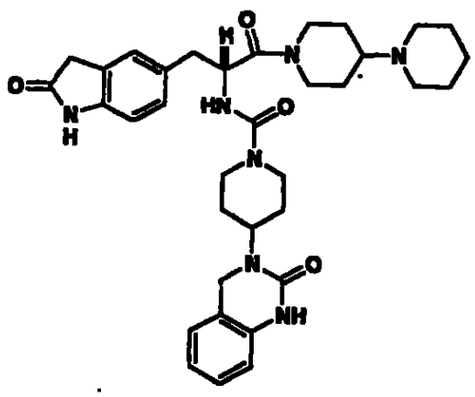


Una solución de fósgeno en tolueno (2M, 0.158 mL, 0.30 mmol) se adicionó a una mezcla agitada vigorosamente de éster metílico del ácido (*R*)-2-amino-3-(2-oxo-2,3-dihidro-1*H*-indol-5-il)-propiónico (70 mg, 0.25 mmol) en cloruro de metileno (15 mL) y bicarbonato de sodio saturado (7.5 mL). Después de que se agitó la mezcla a temperatura ambiente durante 30 minutos, se adicionó 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (58 mg, 0.25 mmol). La mezcla resultante

se agitó a temperatura ambiente durante 1.5 horas, se diluyó con acetato de etilo y se lavó con ácido clorhídrico 0.25 N que había sido saturado con cloruro de sodio sólido. Las capas 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 de color canela. CL/EM: $t_R$ = 2.01 minutos, 492.10 $(MH)^+$.

Ejemplo 50

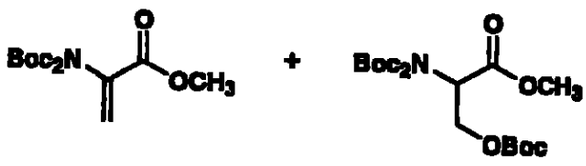
[2-[1,4']Bipiperidinil-1'-il-2-oxo-1-(2-oxo-2,3-dihidro-1H-indol-5-ilmetil)-etil]amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Preparada como se describe anteriormente para la {2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etanosulfonil)-1*H*-indazol-5-ilmetil]-etil}-amida del ácido (*R*)-4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carboxílico. Purificada mediante la cromatografía con evaporación instantánea en gel de sílice utilizando cloruro

de metileno/metanol/trietilamina (93:5:2) como eluyente. RMN-$^1$H ($CD_3OD$, 500 MHz) δ 7.20-7.09 (m, 4H), 6.97 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 7.9 Hz, 0.65H), 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 minutos, 628.40 $(MH)^+$.

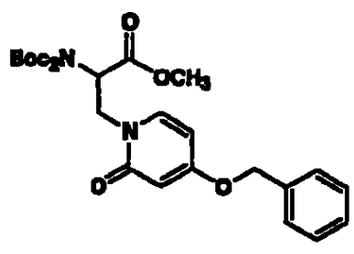
Ester metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-acrílico




A una solución de éster metílico del ácido 2-*terc*-butoxicarbonilamino-3-hidroxi-propiónico (10.0 g, 39 mmol) y di-*terc*-butil-dicarbonato (21.8 g, 2.6 equivalentes) en acetonitrilo (40 mL) se adicionó 4-metilaminopiridina (0.48 g, 0.1 equivalentes) a temperatura ambiente. La solución se agitó durante toda la noche y se concentró. El residuo se disolvió en éter dietílico, se lavó secuencialmente con

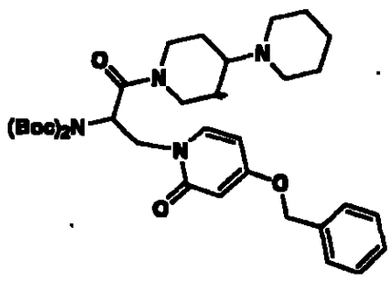
sulfato ácidõ de potasio 1 M (2x), bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de magnesio y se concentró para proporcionar 15.6 g (cuantitativo) como un aceite. La inspección de la RMN $^1H$ mostró una mezcla del compuesto del título y éster metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-3-*terc*-butoxicarboniloxi-propiónico. Como se descubrió después que ambos reaccionan con las aminas secundarias para proporcionar los mismos productos, la mezcla se utilizó sin separación. Ester metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-acrílico. RMN-$^1H$ ($CDCl_3$) δ 1.45 (s, 18H), 3.78 (s, 3H), 5.63 (s, 1H), 6.33 (s, 1H). Espectro de Masas: 324.14 $(M+Na)^+$. Ester metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-3-butoxicarboniloxi-propiónico: RMN-$^1H$ ($CDCl_3$, 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 Masas: 442.21 $(M+Na)^+$.

Ester metílico del ácido (±)-3-(4-benciloxi-2-oxo-2H-piridin-1-il)-2-(di-*terc*-butoxicarbonilamino)-propiónico



A una solución de éster metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-acrílico (900 mg, 3.0 mmol) y 4-benciloxi-1H-piridin-2-ona (630 mg, 1.03 equivalentes) en acetonitrilo (2.5 mL) se adicionó carbonato de cesio (100 mg, 0.10 equivalentes). La suspensión resultante se calentó a 80°C por medio de microondas durante 2 horas. 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 proporcionar 1.47 g (97%), las cuales se utilizaron sin purificación adicional. Espectro de Masas: 503.56 $(MH)^+$.

(±)-4-Benciloxi-1-[3-[1,4']bipiperidinil-1'-il-2-(di-*terc*-butoxicarbonilamino)-3-oxo-propil]-1H-piridin-2-ona

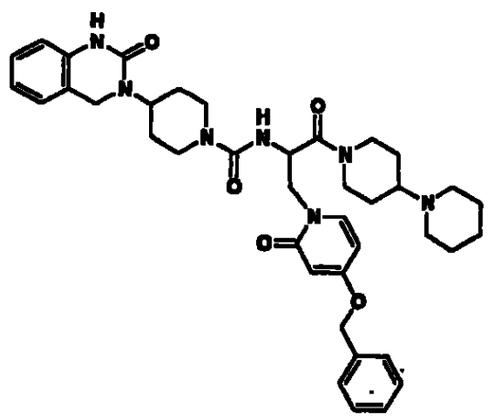



A una solución agitada de éster metílico del ácido 3-(4-benciloxi-2-oxo-2H-piridin-1-il)-2-(di-*terc*-butoxicarbonilamino)-propiónico (1.47 g, 2.9 mmol) en metanol (17 mL) se adicionó una solución de monohidrato de hidróxido de litio (0.50 g, 4 equivalentes) en agua (2.85 mL). La

mezcla de reacción se agitó durante 3 horas a temperatura ambiente, se enfrió a 0°C, se trató con ácido clorhídrico concentrado (0.99 mL) y se concentró para proporcionar el ácido crudo, la mitad del cual se tomó en el siguiente paso. El ácido crudo se disolvió en cloruro de metileno (6 mL), se enfrió a 0°C y se trató secuencialmente con 4-piperidil-piperidina (0.25 g, 1 equivalente), trietilamina (0.31 mL, 2.5 equivalentes) y cloruro bis-2-oxo-3-oxazolidinil)fosfínico (0.38 g, 1 equivalente). La reacción se dejó calentar a temperatura ambiente y se agitó durante toda la noche. La reacción se concentró y se purificó mediante la CLAR preparativa para proporcionar 489 mg (52%, 2 pasos). Espectro de Masas: 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-2H-quinazolin-3-il)-piperidin-1-carboxílico

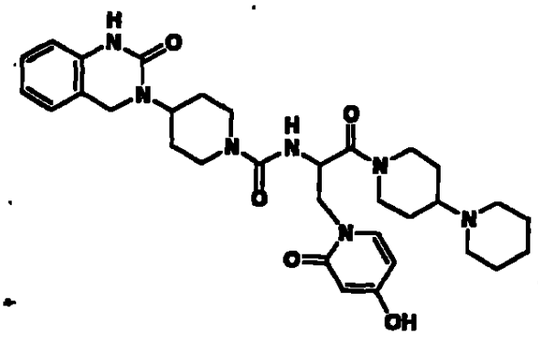


A una solución agitada de 4-benciloxi-1-[3-[1,4']bipiperidinil-1'-il-2-(di-terc-butoxicarbonilamino)-3-oxo-propil]-1H-piridin-2-ona en cloruro de metileno (3 mL) se adicionó ácido trifluoroacético (1 mL) a 0°C. Después de 2 horas, la reacción se concentró para proporcionar la amina cruda (151 mg, 97%) como su sal de ácido trifluoroacético [Espectro de Masas: 439.61 $(MH)^+$], la cual se dividió en dos porciones, utilizando la mitad en el siguiente procedimiento. A una solución de la amina cruda (75 mg, 0.11 mmol) y diisopropiletilamina (80 µL, 4 equivalentes) en cloruro de metileno (3 mL) a 0°C se adicionó carbonil-diimidazol (29 mg, 1.6 equiv, en 2 porciones). Después de la agitación durante 10 minutos, la solución se trató con ácido 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-acético (40 mg, 1.15 equivalentes). La reacción se calentó a temperatura ambiente y se agitó durante toda la noche. La reacción se concentró y se purificó mediante la CCD preparativa para proporcionar 40.8 mg (53%). RMN-$^1$H ($CD_3OD$, 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 (d amplio, 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). Espectro de Masas: 696.85 $(MH)^+$.

Ejemplo 52

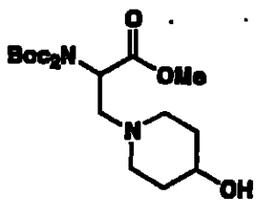
[2-[1,4']Bipiperidinil-1'-il-1-(4-hidroxi-2-oxo-2H-piridin-1-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



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 paladio al 10% sobre carbón vegetal (5 mg) en metanol (1 mL) se colocó bajo una atmósfera de hidrógeno. Después de 1 hora a temperatura ambiente, la reacción se inundó con nitrógeno, se filtró a través de celite y se concentró para proporcionar el producto. RMN-$^1$H ($CD_3OD$, 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),

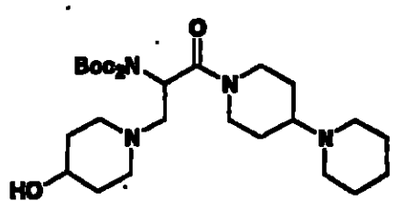
4.34 (amplio, 2H), 4.36-4.59 (m, 2H), 4.63 (d amplio, J = 12.8, 1H), 5.20 (m, 1H), 5.75 (dd, J = 7.3, 2.1, 1H), 5.97 (dd, J = 8.9, 7.6, 1H), 6.78 (d, J = 7.6, 1H), 6.93 (dd, J = 7.6, 7.3, 1H), 7.08-7.18 (m, 2H), 7.33 (dd, J = 18.3, 11.0, 1H). Espectro de Masas: 606.32 $(MH)^+$.

Ester metílico del ácido (±)-2-(di-*terc*-butoxicarbonilamino)-3-(4-hidroxi-piperidin-1-il)-propiónico



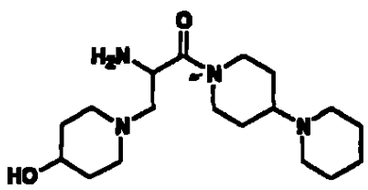

A una solución de éster metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-acrílico (1.0 g, 3.0 mmol) en acetonitrilo (10 mL) se adicionó piperidin-4-ol (0.33 g, 1.1 equivalentes). Una corriente suave de nitrógeno se colocó sobre la reacción mientras que se agitaba durante toda la noche. El aceite crudo que resultó se disolvió en acetato de etilo, se lavó con agua, luego con salmuera, se secó sobre sulfato de magnesio y se concentró para proporcionar 1.38 g (cuantitativo) como un aceite el cual se utilizó sin purificación. Espectro de Masas: 403.42 $(MH)^+$.

(±)-1-[1,4']Bipiperidinil-1'-il-2-(di-*terc*-butoxicarbonil-amino)-3-(4-hidroxi-piperidin-1-il)-propan-1-ona



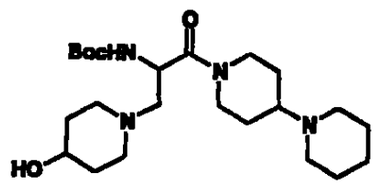

A una solución de éster metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-3-(4-hidroxi-piperidin-1-il)-propiónico (1.0 g, 2.5 mmol) en metanol (6 mL) se adicionó una solución de monohidrato de hidróxido de litio (400 mg, 3.9 equivalentes) en agua (1 mL). La reacción se agitó 6 horas, se enfrió a 0°C, se neutralizó con ácido clorhídrico concentrado y se concentró. El ácido crudo se utilizó sin purificación adicional. El ácido crudo se suspendió en cloruro de metileno (25 mL), se trató con algunas gotas de metanol para ayudar en la disolución del ácido y se enfrió a 0°C. La suspensión resultante se trató secuencialmente con 4-piperidil-piperidina (0.53 g, 1.25 equivalentes), trietilamina (0.70 mL, 2 equivalentes) y cloruro bis-2-oxo-3-oxazolidinil)fosfínico (0.80 g, 1.25 equivalentes). La reacción se dejó calentar a temperatura ambiente durante toda la noche. La reacción se concentró y luego se purificó mediante la CLAR preparativa para proporcionar 310 mg (23%, 2 pasos). Espectro de Masas: 539.49 $(MH)^+$.

(±)-2-Amino-1-[1,4']bipiperidinil-1'-il-3-(4-hidroxi-piperidin-1-il)-propan-1-ona



A una solución de 1-[1,4']bipiperidinil-1'-il-2-(di-*terc*-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 adicionó ácido trifluoroacético (2.0 mL). El baño de hielo se removió y la reacción se agitó durante 30 minutos. La reacción se concentró para proporcionar el producto como su sal de ácido trifluoroacético (400 mg, cuantitativo), el cual se utilizó sin purificación. Espectro de Masas: 339.46 $(MH)^+$.

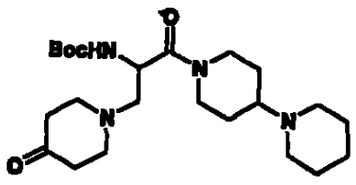
Ester *terc*-butílico del ácido (±)-[2-[1,4']bipiperidinil-1'-il-1-(4-hidroxi-piperidin-1-ilmetil)-2-oxo-etil]-carbámico



A una solución de 2-amino-1-[1,4']bipiperidinil-1'-il-3-(4-hidroxi-piperidin-1-il)-propan-1-ona (sal de ácido trifluoroacético, 300 mg, 0.58 mmol) y diisopropiletilamina

(0.30 mL, 4 equivalentes) en tetrahidrofurano (5 mL) se adicionó di-*terc*-butil-dicarbonato (128 mg, 1 equivalente). La solución resultante se agitó a temperatura ambiente durante 1 hora y se concentró. El residuo se disolvió en acetato de etilo, se lavó con agua, luego con salmuera, se secó sobre sulfato de magnesio y se concentró para proporcionar 248 mg (98%) lo cual se utilizó sin purificación. Espectro de Masas: 439.65 $(MH)^+$.

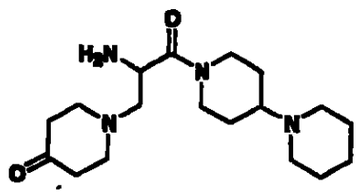
Ester *terc*-butílico del ácido (±)-[2-[1,4']bipiperidinil-1'-il-2-oxo-1-(4-oxo-piperidin-1-ilmetil)-etil]-carbámico




A una solución de 1-[1,4']bipiperidinil-1'-il-2-(di-*terc*-butoxicarbonilamino)-3-(4-hidroxi-piperidin-1-il)-propan-1-ona (200 mg, 0.37 mmol) en cloruro de metileno (4 mL) se adicionó peryodinano Dess-Martin (316 mg, 2 equivalentes) en dos porciones. Después de 1 hora, la reacción se enfrió rápidamente mediante 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 proporcionar 187 mg (94%), lo cual se

utilizó sin purificación. Espectro de Masas: 437.63 $(MH)^+$.

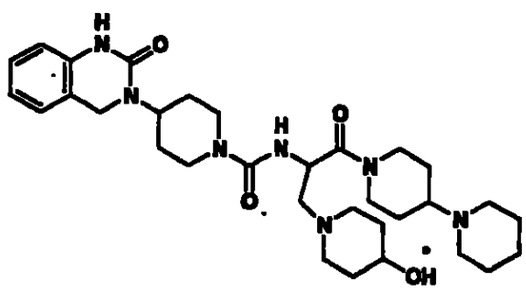
(±)-1-(2-Amino-3-[1,4']bipiperidinil-1'-il-3-oxo-propil)-piperidin-4-ona



A una solución de éster *terc*-butílico del ácido [2-[1,4']bipiperidinil-1'-il-2-oxo-1-(4-oxo-piperidin-1-ilmetil)-etil]-carbámico (100 mg, 0.23 mmol) en cloruro de metileno (5 mL) a 0°C se adicionó ácido trifluoroacético. El baño de hielo se removió, la agitación continuó durante 1 hora y la reacción se concentró para proporcionar 150 mg (96%) como su sal de ácido trifluoroacético, la cual se utilizó sin purificación. Espectro de Masas: 337.64 $(MH)^+$.

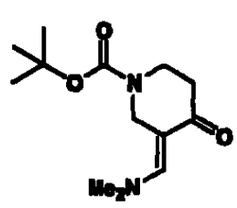
Ejemplo 53

[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 (3 sal de ácido trifluoroacético, 200 mg, 0.39 mmol) en cloruro de metileno (5 mL) a 0°C se adicionó diisopropiletilamina (0.27 mL, 3.9 equivalentes) y carbonil-diimidazol (63 mg, 1 equivalente). Después de la agitación durante 15 minutos, la solución se trató con 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (sal de ácido acético, 142 mg, 1.25 equivalentes). La solución se calentó a temperatura ambiente y se agitó durante toda la noche. La reacción se concentró y se purificó mediante la CCD preparativa para proporcionar 130 mg (56%) como un aceite. CL/EM: $t_R$ = 1.17 minutos, 596.44 $(MH)^+$.

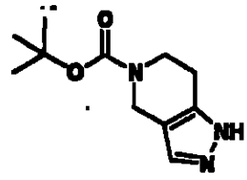
Ester *terc*-butílico del ácido 3-dimetilaminometilen-4-oxo-piperidin-1-carboxílico



El éster *terc*-butílico del ácido 4-oxo-piperidin-1-carboxílico (10 g, 50 mmol) se disolvió en dimetil-formamida-dimetilacetal (50 mL) y se calentó a reflujo durante 1.25 horas. La solución se enfrió, se concentró y se purificó

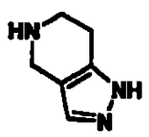
mediante la cromatografía con evaporación instantánea para proporcionar 2.55 g (19%). Espectro de Masas: 255.16 $(MH)^+$.

Ester *terc*-butílico del ácido 1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-carboxílico



A una solución de éster *terc*-butílico del ácido 3-dimetilaminometilen-4-oxo-piperidin-1-carboxílico (2.55 g, 10 mmol) en metanol (50 mL) se adicionó hidrato de hidracina (0.61 mL, 1.25 equivalentes). La solución se calentó a reflujo, inmediatamente se dejó enfriar a temperatura ambiente y se concentró para proporcionar 1.4 g (63%), lo cual se utilizó sin purificación. Espectro de Masas: 224.11 $(MH)^+$.

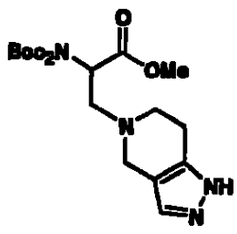
4,5,6,7-Tetrahidro-1H-pirazolo[4,3-c]piridina



El éster *terc*-butílico del ácido 1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-carboxílico (0.70 g, 3.1 mmol) se disolvió en ácido trifluoroacético (10 mL) a 0°C, se

agitó durante 1 hora se concentró. El residuo se disolvió en etanol y se trató con ácido clorhídrico concentrado (1 mL). La sal de bis-clorhidrato se precipitó como un sólido de color blanco el cual se filtró para proporcionar 510 mg (83%). La base libre se preparó como fue necesario al disolver la sal en agua, al cargarla en una columna SCX, al inundarla con metanol y luego al eluirla con amoníaco 2 M en metanol.

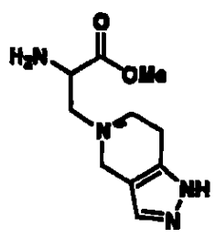
Ester metílico del ácido (±)-2-(di-*terc*-butoxicarbonilamino)-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico




A una solución de 4,5,6,7-tetrahidro-1H-pirazolo[4,3-c]piridina (160 mg) en 2.5 mL de metanol se adicionó éster metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-acrílico (400 mg). La reacción se concentró a aproximadamente 1.5 mL mediante la aplicación de una corriente suave de nitrógeno. La solución se agitó a temperatura ambiente durante toda 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 suficientemente puro para utilizarse sin purificación. RMN-$^1$H ($CDCl_3$, 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 Masas: 425.23 $(MH)^+$.

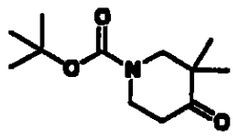
Ester metílico del ácido (±)-2-amino-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico




A una solución de éster metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (0.55 g, 1 equivalente) en cloruro de metileno (5 mL, 0°C) se adicionó ácido trifluoroacético (1.5 mL). El baño de hielo se removió y la agitación continuó durante 2 horas. La solución se concentró, se disolvió nuevamente en metanol y se pasó sobre una columna de resina de intercambio catiónico, fuerte. Después de la inundación con metanol, el producto se removió de la columna al eluir con amoníaco 2M en metanol para proporcionar el producto como su base libre (275 mg, 95%). RMN-$^1$H ($CDCl_3$, 500 MHz) δ 2.71

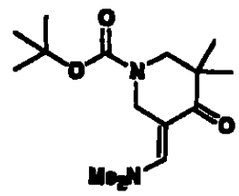
(dd, J = 12.8, 8.6, 1H), 2.74-2.91 (m, 6H), 3.48 (s, 2H), 3.54 (d, J = 13.4, 1H), 3.62 (d, J = 13.4, 1H), 3.69 (dd, J = 8.2, 4.9, 1H), 3.73 (s, 3H), 7.27 (s, 1H). Espectro de Masas: 225.16 $(MH)^+$.

Ester *terc*-butílico del ácido 3,3-dimetil-4-oxo-piperidin-1-carboxílico



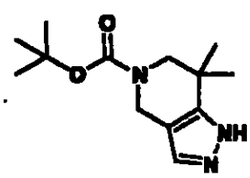
A una solución de éster *terc*-butílico del ácido 4-oxo-piperidin-1-carboxílico (16 g, 80 mmol) en tetrahidrofurano (400 mL) a 0°C se adicionó hidruro de sodio (4.1 g, 2.1 equivalentes) en 4 porciones. A esto se adicionó gota a gota yodometano (12.5 mL, 2.5 equivalentes). La reacción se dejó calentar gradualmente a temperatura ambiente y se agitó durante toda la noche. La reacción se concentró, se disolvió en éter dietílico, se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró. El producto se cristalizó de pentano caliente (2X) para proporcionar 5.9 g (32%). RMN-$^1$H ($CDCl_3$, 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 Masas: 250.12 $(M+Na)^+$.

Ester *terc*-butílico del ácido 5-dimetilaminometilen-3,3-dimetil-4-oxo-piperidin-1-carboxílico



El éster *terc*-butílico 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 horas. La mezcla de reacción luego se calentó a 130°C durante 1 hora por medio de microondas y se concentró para proporcionar 6.43 g (cuantitativo) como un aceite, el cual se utilizó sin purificación. RMN-$^1$H ($CDCl_3$, 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 (s amplio, 1H).

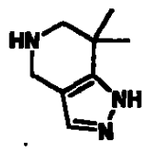
Ester *terc*-butílico del ácido 7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-carboxílico



A una solución de éster *terc*-butílico del ácido 5-dimetilaminometilen-3,3-dimetil-4-oxo-piperidin-1-carboxílico (6.35 g, 22 mmol) en metanol (15 mL) se adicionó hidrato de

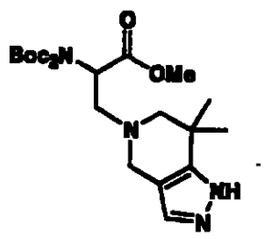
hidrazina (1.2 mL, 1.1 equivalentes). La solución se agitó a temperatura ambiente durante toda la noche y se concentró para proporcionar 5.3 g (94%) el cual se utilizó sin purificación. Espectro de Masas: 252.19 $(MH)^+$.

7,7-Dimetil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-c]piridina



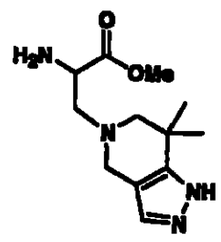

A una solución de éster *terc*-butílico del ácido 7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-carboxílico (5.3 g, 21 mmol) en cloruro de metileno (10 mL) a 0°C se adicionó ácido trifluoroacético (5 mL). La reacción se dejó calentar a temperatura ambiente, se agitó 15 minutos y se trató con ácido trifluoroacético adicional (5 mL). Después de 1 hora, la reacción se concentró, se disolvió en etanol (10 mL), se enfrió a 0°C, se trató con ácido clorhídrico concentrado (3 mL) y se concentró. El sólido resultante se trituró con etanol y se filtró para proporcionar 3.02 g (64%) como su sal de bis-clorhidrato. La base libre se preparó como fue necesario al disolver la sal en agua, al cargarla en una columna SCX, al inundarla con metanol y luego al eluirla con amoníaco 2M en metanol. RMN-$^1$H ($D_2O$, 500 MHz) δ 1.49 (s, 6H), 3.46 (s, 2H), 4.39 (s, 2H), 7.86 (s, 1H). Espectro de Masas: 152.14 $(MH)^+$.

Ester metílico del ácido (±)-2-(di-*terc*-butoxicarbonilamino)-3-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico



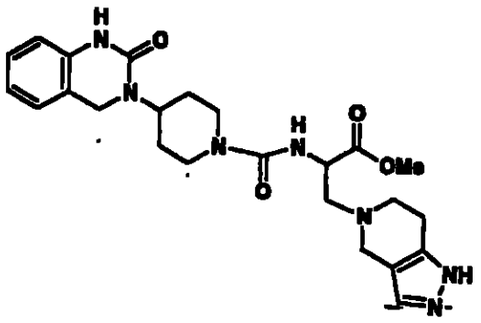

A una solución de 7,7-dimetil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-c]piridina (160 mg) en metanol (3 mL) se adicionó éster metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-acrílico (331 mg). Se aplicó una corriente suave de nitrógeno y la reacción se agitó durante toda la noche. En la mañana, el volumen se redujo en gran medida. Los últimos indicios de solvente se removieron bajo alto vacío para proporcionar 490 mg (cuantitativo), lo cual se utilizó sin purificación. RMN-$^1$H ($CD_3OD$, 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 Masas: 453.30 $(MH)^+$.

Ester metílico 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 éter metílico del ácido 2-(di-*terc*-butoxicarbonilamino)-3-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (0.49 g, 1 equivalente) en cloruro de metileno (5 mL, 0°C). se adicionó ácido trifluoroacético (1.5 mL). El baño de hielo se removió y la agitación continuó durante 2 horas. La solución se concentró, se disolvió nuevamente en metanol y se cargó en una columna de resina de intercambio catiónico, fuerte. Después de la inundación con metanol, el producto se removió de la columna al eluir con amoníaco 2M en metanol para proporcionar el producto como su base libre (250 mg, 94%). RMN-$^1$H ($CDCl_3$, 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 Masas: 253.16 $(MH)^+$.

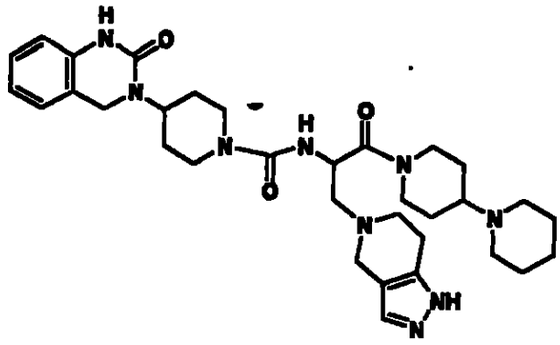
Ester metílico del ácido (±)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico



A una solución de éster metílico del ácido 2-amino-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (260 mg, 1 equivalente) en cloruro de metileno (2 mL, 0°C) de adicionó carbonil-diimidazol (188 mg, 1 equivalente). Después de 15 minutos, se adicionó 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (295 mg, 1.1 equivalentes) en una porción. El baño de hielo se removió y la agitación continuó durante toda la noche. La reacción se concentró y se purificó mediante la cromatografía en columna para proporcionar 118 mg (21%). RMN-$^1$H ($CDCl_3$, 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 (s amplio, 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 Masas: 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

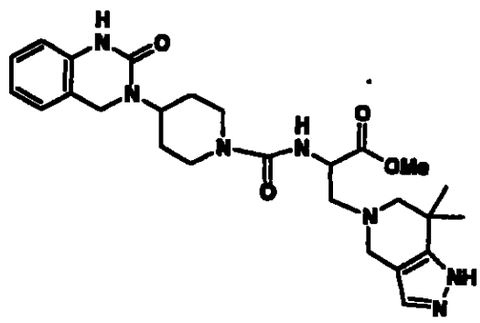


A una solución de éster metílico del ácido 2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (16 mg, 1 equivalente) en metanol (0.6 mL) se adicionó monohidrato de hidróxido de litio (3 mg, 2.2 equivalentes) en agua (0.1 mL) y se agitó durante 4 horas a temperatura ambiente. La solución se enfrió a 0°C, se trató con sulfato ácido de potasio acuoso 1M (60 µl, 1.8 equivalentes) y se concentró para proporcionar el ácido crudo el cual se utilizó 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 (11 mg, 2 equivalentes), diisopropiletilamina (12 µL, 2 equivalentes) y PyBOP® (19 mg, 1.1 equivalentes). La

solución se agitó 30 minutos y se concentró. El producto se purificó mediante la cromatografía en columna para proporcionar 17.6 mg (85%, 2 pasos). RMN-$^1$H ($CDCl_3$, 500 MHz) δ 1.30-1.60 (m, 9H), 1.62-1.78 (m, 5H), 1.81 (d amplio, 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 (s amplio, 1H). Espectro de Masas: 618.34 $(MH)^+$.

Ejemplo 55

Ester metílico 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

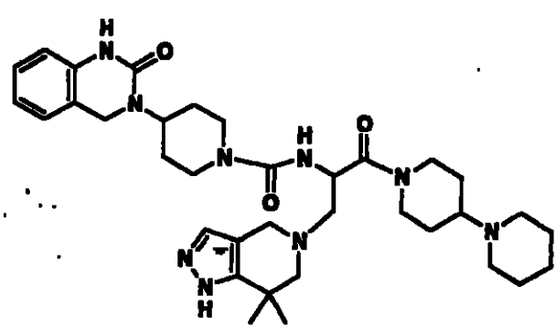



A una solución de éster metílico del ácido 2-amino-3-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (250 mg, 1 equivalente) en tetrahidrofurano (4 mL,

0°C) se adicionó carbonil-diimidazol (162 mg, 1 equivalentes). Después de 5 minutos, el baño de hielo se removió y la reacción se agitó a temperatura ambiente durante 30 min. A esto se adicionó 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (250 mg, 1.1 equivalentes) en una porción y la reacción se agitó durante toda la noche. La reacción se concentró y se purificó mediante la cromatografía en columna para proporcionar 228 mg (45%). RMN-$^1$H ($CD_3OD$, 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). Espectro de Masas: 510.27 (MH)+.

Ejemplo 56

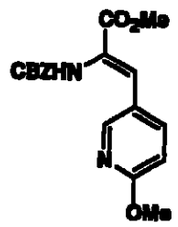
[2-[1,4']Bipiperidinil-1'-il-1-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



A una solución de éster metílico 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 equivalente) en metanol (0.6 mL) se adicionó monohidrato de hidróxido de litio (4 mg, 2.2 equivalentes) en agua (0.1 mL) y se agitó durante 4 horas a temperatura ambiente. La solución se enfrió a 0°C, se trató con sulfato ácido de potasio acuoso 1M (75 µL, 1.8 equivalentes) y se concentró para proporcionar el ácido crudo, el cual se utilizó 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 equivalentes), diisopropiletilamina (14 µL, 2 equivalentes) y PyBOP$^{MR}$ (22 mg, 1.1 equivalentes). La solución se agitó 1.5 horas y se concentró. El producto se purificó mediante la cromatografía en columna para proporcionar 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 proporcionó 18.3 mg (72%, 2 pasos). RMN-$^1$H ($CD_3OD$, 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 (d amplio, J = 12.8, 1H). Espectro de Masas: 646.43 $(MH)^+$.

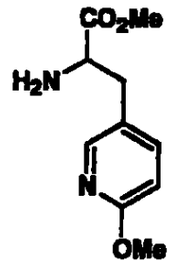
Éster metílico del ácido 2-benciloxicarbonilamino-3-(6-metoxi-piridin-3-il)-acrílico




A una suspensión de *terc*-butóxido de potasio (1.23 g, 1.5 equivalentes) en cloruro de metileno (70 mL, -20°C) se adicionó una solución de éster trimetílico de N-benciloxicarbonil-α-fosfonoglicina (3.63 g, 1.5 equivalentes) en cloruro de metileno (15 mL). La solución resultante se agitó 5 minutos y se trató con 6-metoxi-piridin-3-carbaldehído (1.0 g, 7.3 mmol) en cloruro de metileno (15 mL). Después de la agitación durante 1.5 horas, la reacción se calentó a 0°C se agitó 1 hora. La reacción se vertió rápidamente en un embudo separatorio que contenía acetato de etilo y agua. Se adicionó salmuera para ayudar en la

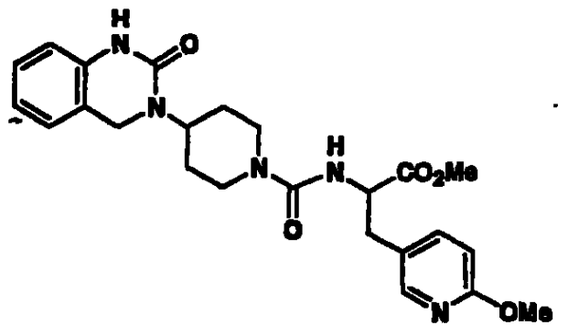
separación de las capas. La capa acuosa se extrajo con acetato de etilo (3x), la cual se lavó a su vez con salmuera, se secó sobre sulfato de magnesio y se concentró para proporcionar 2.63 g (cuantitativo) lo cual se utilizó sin purificación. Espectro de Masas: 343.08 $(MH)^+$.

Ester metílico del ácido (±)-2-amino-3-(6-metoxi-piridin-3-il)-propiónico




Un matraz que contenía éster metílico del ácido 2-benciloxicarbonilamino-3-(6-metoxi-piridin-3-il)-acrílico (620 mg), paladio sobre carbón vegetal (10%, 100 mg), acetato de etilo (10 mL) y metanol (20 mL) se inundó con nitrógeno, luego con hidrógeno, antes de añadir finalmente un balón de hidrógeno. La reacción se dejó agitar durante toda la noche. El matraz se inundó con nitrógeno, se filtró a través de celite y se concentró para proporcionar 390 mg (cuantitativo) lo cual se utilizó sin purificación. Espectro de Masas: 211.11 $(MH)^+$.

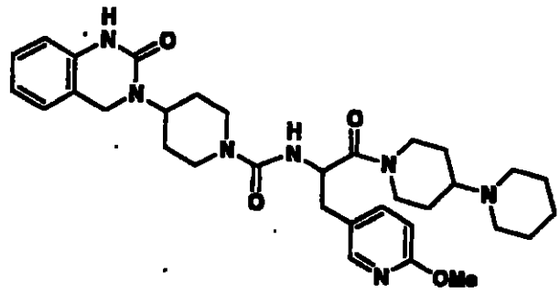
Ester metílico del ácido (±)-3-(6-metoxi-piridin-3-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



A una solución de éster metílico 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 adicionó carbonato de *N,N'*-disuccinimidilo (158 mg). Después de 30 minutos, se adicionó 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (120 mg) en cloruro de metileno (1 mL) por medio de una cánula. La reacción se calentó a temperatura ambiente y se agitó durante toda la noche. La reacción se concentró y se purificó mediante la CLAR preparativa para proporcionar 160 mg (55%). Espectro de Masas: 468.19 $(MH)^+$.

Ejemplo 57

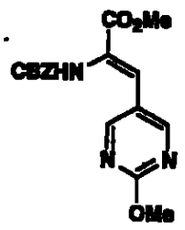
[2-[1,4']Bipiperidinil-1'-il-1-(6-metoxi-piridin-3-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



A una solución de éster metílico 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 adicionó una solución de monohidrato de hidróxido de litio (29 mg) en agua (1 mL). La reacción se agitó a temperatura ambiente durante 4 horas y se enfrió 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 toda la noche, se concentró y se purificó mediante la CLAR preparativa para proporcionar 94 mg (45%). CL/EM: $t_R$ = 1.86 minutos, 604.51 $(MH)^+$.

424

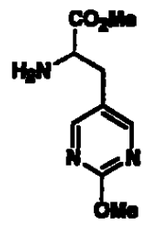
Ester metílico del ácido 2-benciloxicarbonilamino-3-(2-metoxi-pirimidin-5-il)-acrílico




A una suspensión de t-butóxido de potasio (1.23 g) en cloruro de metileno (70 mL, -30°C) se adicionó una solución de éster trimetílico de N-benciloxicarbonil-α-fosfonoglicina (3.63 g) en cloruro de metileno (15 mL). La solución resultante se agitó 5 minutos y se trató con 2-metoxi-pirimidin-5-carbaldehído (1.0 g) en cloruro de metileno (15 mL). Después de la agitación durante 1.5 horas, la reacción se calentó a 0°C y se agitó 1 hora. La reacción se vertió rápidamente en un embudo separatorio que contenía acetato de etilo y agua. Se adicionó salmuera para ayudar en la separación de las capas. La capa acuosa se extrajo con acetato de etilo (3X), la cual se lavó a su vez con salmuera, se secó sobre sulfato de magnesio y se concentró. El producto crudo se recristalizó de metanol caliente para proporcionar 1.4 g de material puro. Espectro de Masas: 344.10 $(MH)^+$.

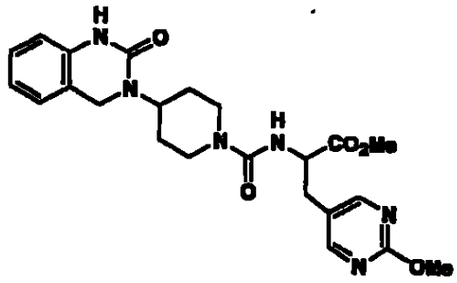
925

Ester metílico del ácido (±)-2-amino-3-(2-metoxi-pirimidin-5-il)-propiónico



Un matraz que contenía éster de amino (700 mg), paladio sobre carbón vegetal (10%, 100 mg) y metanol (20 mL) se inundó con nitrógeno, luego con hidrógeno, antes de añadir finalmente un balón de hidrógeno. La reacción se dejó agitar durante toda la noche. El matraz se inundó con nitrógeno, se filtró a través de celite y se concentró para proporcionar 379 mg (88%), lo cual se utilizó sin purificación. Espectro de Masas: 212.08 $(MH)^+$.

Ester metílico del ácido (±)-3-(2-metoxi-pirimidin-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



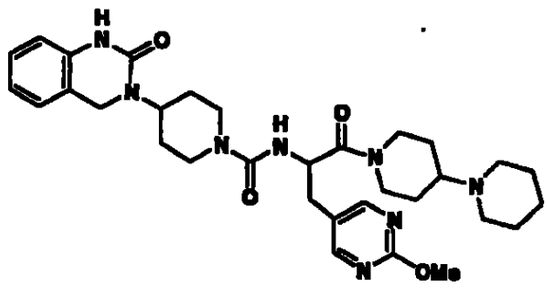
A una solución de éster metílico del ácido 2-amino-

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3-(2-metoxi-pirimidin-5-il)-propiónico (125 mg) y diisopropiletilamina (0.3 mL) en cloruro de metileno (2 mL, 0°C) se adicionó carbonato de *N,N'*-disuccinimidilo (155 mg). Después de 30 minutos, se adicionó 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (120 mg) en cloruro de metileno (2 mL) por medio de una cánula. La reacción se calentó a temperatura ambiente y se agitó durante toda la noche. La reacción se concentró y se purificó mediante la CLAR preparativa para proporcionar 99 mg (36%). Espectro de Masas: 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

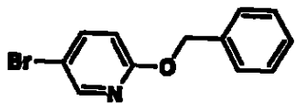



A una solución de éster metílico del ácido 3-(2-metoxi-pirimidin-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (99 mg) en metanol (6 mL) se adicionó una solución de monohidrato

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de hidróxido de litio (18 mg) en agua (1 mL). La reacción se agitó a temperatura ambiente durante 4 horas y se enfrió a 0°C. La reacción se trató con ácido clorhídrico 1H (0.4 mL), se 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 de bis-2-oxo-3-oxazolidinil)fosfínico (71 mg). La reacción se agitó durante toda la noche, se concentró y se purificó mediante la CLAR preparativa para proporcionar 103 mg (45%). CL/EM: $t_R$ = 1.23 minutos, 605.54 $(MH)^+$.

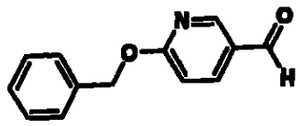
2-Benciloxi-5-bromo-piridina




Una suspensión de 2,5-dibromopiridina (2.0 g, 8.4 mmol), dibenzo-18-corona-6 (0.14 g, .05 equivalentes), alcohol bencílico (1.1 mL, 1.3 equivalentes) e hidróxido de potasio (1.1 g, 2.4 equivalentes) en tolueno (30 mL) se calentaron a reflujo durante 3 horas en un aparato equipado con una trampa Dean-Stark. La suspensión se enfrió, se concentró, se suspendió en agua y se extrajo con cloruro de metileno. Las fases orgánicas, combinadas se lavaron con agua, luego con salmuera, se secaron sobre sulfato de magnesio y se concentraron para proporcionar 1.9 g (85%), lo cual se utilizó

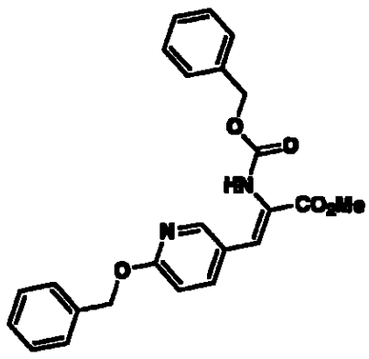
sin purificación. Espectro de Masas: 264.25 $(MH)^+$.

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 adicionó n-butil-litio (2.5 M en hexano, 2.61 mL, 1.05 equivalentes). Después de 1 hora a -78°C, se adicionó dimetilformamida (0.97 mL, 2 equivalentes), y la mezcla se agitó durante 30 minutos. La reacción se vertió rápidamente en una solución agitada de bicarbonato de sodio acuoso al 5% (50 mL) y se extrajo con éter dietílico (3X). La capa etérea se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró para proporcionar 1.16 g (cuantitativo) lo cual se utilizó sin purificación. Espectro de Masas: 186.34 $(MH)^+$.

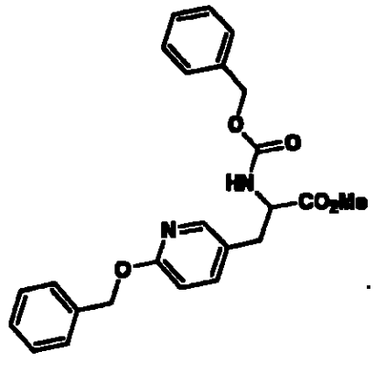
Ester metílico del ácido 2-benciloxicarbonilamino-3-(6-benciloxi-piridin-3-il)-acrílico



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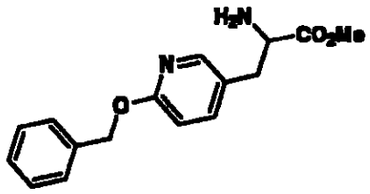
A una suspensión agitada de *terc*-butóxido de potasio (0.440 g, 1.7 equivalentes) en cloruro de metileno (25 mL) a -20°C se adicionó éster trimetílico de N-benciloxicarbonil-α-fosfonoglicina (1.3 g, 1.7 equivalentes) en cloruro de metileno (5 mL). La solución resultante se agitó durante 5 minutos y se trató con 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 hora, se dejó calentar gradualmente a 0°C, y se vertió en un embudo separatorio que contenía agua y éter dietílico. La reacción se extrajo con éter dietílico (2x), se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró para proporcionar 0.98 g (cuantitativo) como un aceite, el cual se utilizó sin purificación. Espectro de Masas: 419.32 $(MH)^+$.

Ester metílico del ácido (±)-2-benciloxicarbonilamino-3-(6-benciloxi-piridin-3-il)-propiónico



Un matraz se cargó con éster metílico del ácido 2-benciloxicarbonilamino-3-(6-benciloxi-piridin-3-il)-acrílico (0.50 g, 1.2 mmol), catalizador de Wilkinson (200 mg, 0.2 equivalentes), metanol (5 mL) y tolueno (3 mL). El matraz se inundó con nitrógeno, luego con hidrógeno, se calentó a 35°C y se dejó agitar bajo una atmósfera de hidrógeno durante 4 días. La reacción se inundó con nitrógeno, se diluyó con metanol, se filtró y se concentró para proporcionar el producto crudo, el cual se purificó mediante la cromatografía en columna para proporcionar 145 mg (29%).

Ester metílico del ácido (±)-2-amino-3-(6-benciloxi-piridin-3-il)-propiónico

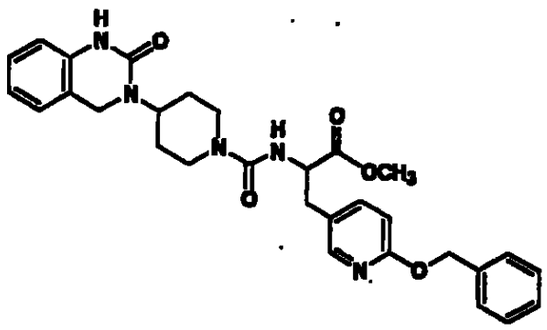



A una solución agitada de éster metílico del ácido 2-benciloxicarbonilamino-3-(6-benciloxi-piridin-3-il)-propiónico (130 mg, 0.31 mmol) en cloruro de metileno (5 mL, 0°C) se adicionó yoduro de trimetilsililo (44 µL, 1.0 equivalente). El baño de hielo se removió y la agitación continuó durante 1 hora. La reacción se vertió en bicarbonato de sodio saturado, se extrajo con acetato de etilo (3x), se lavó con salmuera, se secó sobre sulfato de magnesio y se

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concentró para proporcionar 81 mg (91%), lo cual se utilizó sin purificación. Espectro de Masas: 287.37 $(MH)^+$.

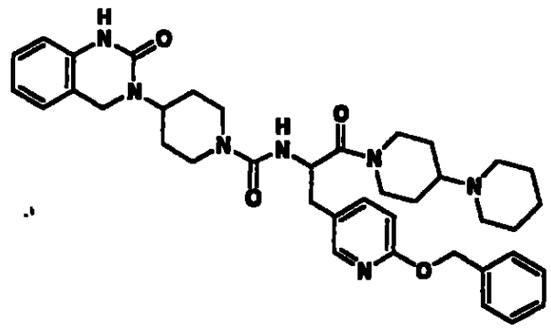
Ester metílico del ácido (±)-3-(6-benciloxi-piridin-3-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



A una solución agitada de éster metílico 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 adicionó carbonil-diimidazol (34 mg, 1.0 equivalente). Después de 15 minutos, se adicionó una solución de 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (58 mg, 1.2 equivalentes) en cloruro de metileno (0.5 mL) por medio de una cánula. El baño de hielo se removió y la agitación continuó durante toda la noche. La reacción se concentró y se purificó mediante la cromatografía para proporcionar 59 mg (52%). Espectro de Masas: 544.49 $(MH)^+$.

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

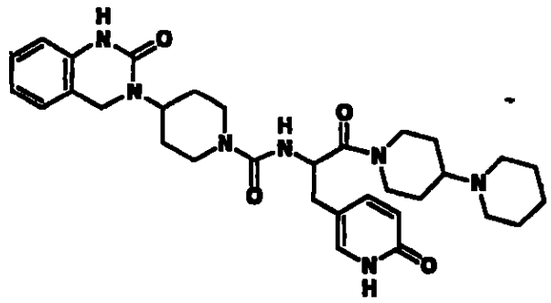


A una solución agitada del éster metílico del ácido 3-(6-benciloxi-piridin-3-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (59 mg, 0.11 mmol) en metanol (3 mL) se adicionó una solución de monohidrato de hidróxido de litio (9.1 mg, 2 equivalentes) en agua (0.5 mL). La reacción se agitó 2 horas a temperatura ambiente, se enfrió a 0°C, se enfrió rápidamente por la adición de ácido clorhídrico 1 N (0.15 mL) y se concentró. El producto crudo se utilizó sin purificación. El ácido crudo se disolvió en cloruro de metileno (2 mL, 0°C) y se trató secuencialmente con 4-piperidino-piperidina (34 mg, 1.8 equivalentes), trietilamina (35 µL, 2.3 equivalentes) y cloruro bis-2-oxo-3-oxazolidinil)-fosfínico (34 mg, 1.2 equivalentes). El baño de hielo se removió y la reacción se

dejó agitar durante toda la noche. La reacción se concentró y se purificó mediante la CCD preparativa para proporcionar 30.3 mg (41%). CL/EM: $t_R$ = 1.49 minutos, 680.29 $(MH)^+$.

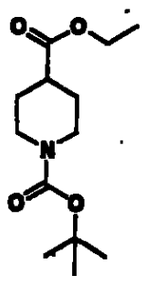
Ejemplo 60

[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 la [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 sobre carbón vegetal (10%, 4 mg) y metanol (1 mL). El matraz se inundó con nitrógeno, luego hidrógeno y se dejó agitar bajo una atmósfera de hidrógeno durante toda la noche. El matraz se inundó con nitrógeno y la reacción se filtró a través de celite para proporcionar 22.1 mg (94%). CL/EM: $t_R$ = 0.93 minutos, 590.32 $(MH)^+$.

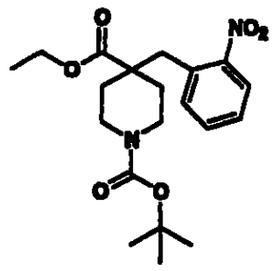
Ester 4-etílico del éster 1-*terc*-butílico del ácido piperidin-1,4-dicarboxílico



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 adicionó lentamente una solución de di-*terc*-butildicarbonato (7.2 g, 0.033 mol) en diclorometano (25 mL). La mezcla de reacción se agitó a temperatura ambiente durante toda 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 se concentró *in vacuo* para proporcionar el producto deseado (8.23 g, 100%) como un aceite incoloro. RMN $^1$H ($C_6D_6$, 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 Masas: 280.44 $(M+Na)^+$.

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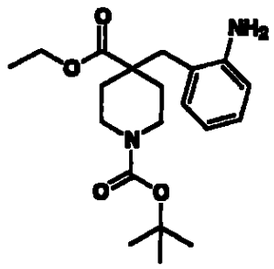
Ester 4-etílico del éster 1-*terc*-butílico del ácido 4-(2-nitro-bencil)-piperidin-1,4-dicarboxílico



A una solución del éster 4-etílico del éster 1-*terc*-butílico del ácido piperidin-1,4-dicarboxílico (8.23 g, 0.032 mol) en tetrahidrofurano (85 mL) se adicionó lentamente una solución de bis(trimetilsilil)amida de sodio (44 mL, 0.044 mol). Después de que la mezcla resultante se había agitado -78°C durante 1 hora, se adicionó una solución de bromuro de 2-nitrobencilo (8.21 g, 0.038 mol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante toda la noche. Luego se concentró 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 de la mezcla de reacción compleja por medio de la cromatografía en columna sobre gel de sílice (eluyente-hexanos-acetato de etilo 4:1) para proporcionar el producto deseado (1.61 g, 13%) como un aceite de color café. Espectro de Masas: 415.38 $(M+Na)^+$.

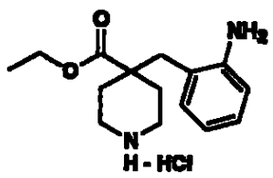
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Ester 4-etílico del éster 1-*terc*-butílico del ácido 4-(2-amino-bencil)-piperidin-1,4-dicarboxílico



Una mezcla del éster 4-etílico del éster 1-*terc*-butílico del ácido 4-(2-nitro-bencil)-piperidin-1,4-dicarboxílico (1.61 g, 4.102 mmol) y paladio al 10% sobre carbón vegetal (0.10 g) en etanol (190 mL) se hidrógeno a 3.511 $kg/cm^2$ (50 psi) durante toda la noche. La mezcla resultante se filtró a través de un tapón de celite y el producto filtrado se concentró bajo vacío para proporcionar el producto deseado (1.29 g, 99%) como un aceite incoloro. Espectro de Masas: 363.45 $(MH)^+$.

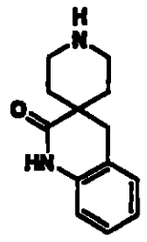
Clorhidrato de éster etílico del ácido 4-(2-amino-bencil)-piperidin-4-carboxílico



A una solución del éster 4-etílico del éster 1-*terc*-butílico del ácido 4-(2-amino-bencil)-piperidin-1,4-

dicarboxílico (1.29 g, 4.102 mmol) en diclorometano (15 mL) se adicionó una solución 4.0 M de cloruro de hidrógeno en dioxano (5 mL). La solución resultante se agitó a temperatura ambiente durante toda la noche. La concentración de la solución bajo vacío proporcionó el compuesto del título (1.23 g, 100%) como un sólido blanco, el cual se utilizó en el siguiente paso sin purificación. Espectro de Masas: 263.40 $(MH)^+$.

3,4-Benzo-2,9-diazaespiro[5.5]undecan-1-ona

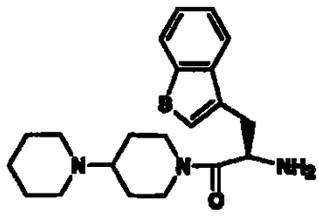



Una solución del clorhidrato de éster etílico del ácido 4-(2-amino-bencil)-piperidin-4-carboxílico (1.23 g, 4.102 mmol) se disolvió en metanol y la solución resultante se agitó a temperatura ambiente durante toda la noche. La solución se diluyó por la mitad con agua y se pasó a través de un tapón corto de la forma de hidróxido de la resina de intercambio iónico AG$^{MR}$ 1-X2 (maya 100-200), eluyendo con metanol acuoso al 50%. La evaporación de las fracciones colectadas proporcionó el producto deseado (0.89 g, 100%) como un sólido de color blanco. RMN-$^1$H ($CD_3OD$, 500 MHz) δ

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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 Masas: 217.46 $(MH)^+$.

Diclorhidrato de (R)-2-amino-3-benzo[b]tiofen-3-il-1-[1,4']bipiperidinil-1'il-propan-1-ona

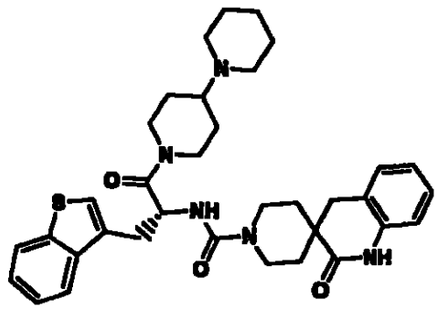



A una solución bien agitada del ácido 3-benzo[b]tiofen-3-il-(2R)-2-*terc*-butoxicarbonilamino-propiónico (1.0 g, 3.1 mmol) en cloruro de metileno (30 mL) a temperatura ambiente se adicionó 4-piperidinopiperidina (573 mg, 3.4 mmol), trietilamina (1.3 mL, 9.3 mmol) seguido por 3-(dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona (1.02 g, 3.4 mmol). Después de 3 horas, 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 mediante la cromatografía con evaporación instantánea utilizando metanol al 5% en cloruro de metileno para proporcionar el éster *terc*-butílico del ácido (1R)-1-benzo[b]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-carbámico en un rendimiento del 82%. El éster *terc*-

butílico 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 adicionó a una solución saturada de cloruro de hidrógeno en dioxano (20 mL) y se agitó durante 2 horas. Los solventes se removieron para proporcionar el diclorhidrato de (2R)-2-amino-3-benzo[b]tiofen-3-il-1-[1,4']bipiperidinil-1'-il-propan-1-ona en un rendimiento del 98%. RMN-$^1$H (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, 9H), 1.92-1.44 (m, 12H). Espectro de Masas: 372 $(MH)^+$.

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-en-9-carboxílico

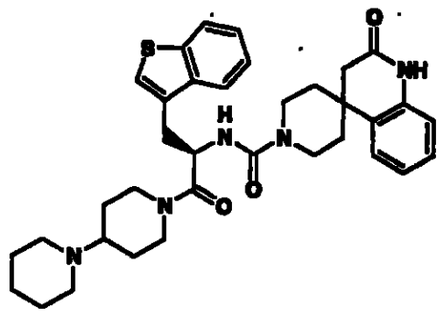



A una solución de la 2-amino-3-benzo[*b*]tiofen-3-il-1-[1,4']bipiperidinil-1'-il-propan-1-ona (50.0 mg, 0.135 mmol) en 1,2-dicloroetano (1.5 mL) se adicionó carbonato de

*N,N'*-disuccinimidilo (34.6 mg, 0.135 mmol) y diisopropiletilamina (0.09 mL, 0.500 mmol). La solución resultante se agitó durante 1 hora, punto en el cual se adicionó la 3,4-benzo-2,9-diazaespiro[5.5]undeca-1-ona (30.4 mg, 0.140 mmol). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche y se concentró. La purificación se logró por medio de la CLAR preparativa de fase inversa para proporcionar el producto deseado (75.5 mg, 77%) como un aceite de color café. RMN-$^1$H ($CD_3OD$, 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). Espectro de Masas: 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)-quinolin]-1-carboxamida

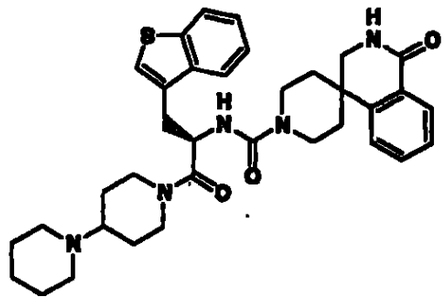


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Preparada como se describe para la (1-benzo[*b*]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-amida del ácido (R)-1-oxo-3,4-benzo-2,9-diaza-espiro[5.5]undec-3-en-9-carboxílico a partir de 3'4'-dihidro-2-oxoespiro-[piperidin-4,4'(1H)-quinolina (M. S. Chambers y colaboradores, J. Med. Chem., 1992, 35, 2033-2039; WO-94/13696). RMN-$^1$H ($CDCl_3$, 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, s amplio), 9.17 (1H, s amplio). Espectro de Masas: 614.36 $(MH)^+$.

Ejemplo 63

N-[(1R)-1-(Benzo[b]tien-3-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-2',3'-dihidro-1-oxoespiro-[piperidin-4,4'(1H)-quinolin]-1-carboxamida

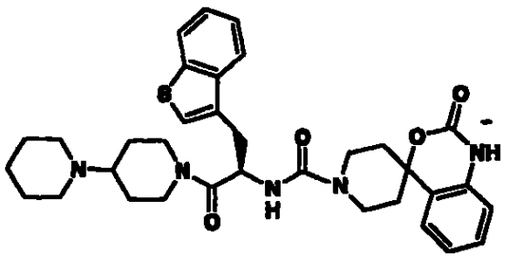


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Preparada como se describe para la (1-benzo[*b*]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-amida del ácido (R)-1-oxo-3,4-benzo-2,9-diaza-espiro[5.5]undec-3-en-9-carboxílico a partir de 2',3'-dihidro-1-oxoespiro-[piperidin-4,4'(1H)-isoquinolina (M. S. Chambers y colaboradores, J. Med. Chem., 1992, 35, 2033-2039; WO-94/13696). RMN-$^1$H ($CDCl_3$, 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, s amplio), 7.38 (5H, m), 7.51 (1H, m), 7.77 (1H, m), 7.85 (1H, m), 8.11 (1H, d). Espectro de Masas: 614.42 $(MH)^+$.

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-benzoxazin-4,4'-piperidin]-1'-carboxamida



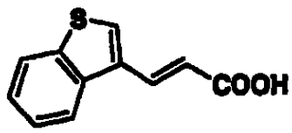
Preparada como se describe para (1-benzo[*b*]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-amida del

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ácido (R)-1-oxo-3,4-benzo-2,9-diaza-espiro[5.5]undec-3-en-9-carboxílico a partir de la 1,2-dihidro-2-oxoespiro-[4H-3,1-benzoxazin-4,4'-piperidina (preparada como se describe en Takai y colaboradores, Chem. Pharm. Bull. 1985, 33, 1129-1139) para proporcionar el compuesto del título (76%). Espectro de Masas: 616 $(MH)^+$. $R_f$= 1.42.

Productos Intermedios de Succinato y Ejemplos

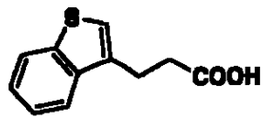
Acido 3-benzo[b]tiofen-3-il-acrílico




Una suspensión del 1-benzotiofen-3-carbaldehído (4.9 g, 0.03 mol), ácido malónico (6.6 g, 0.06 mol) y piperidina (1 mL) en 100 mL de piridina anhidra se calentó a 110°C durante toda 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 se adicionó ácido clorhídrico 1 N para ajustar el pH de esta solución a aproximadamente 3. La suspensión se filtró y el sólido de color amarillo se colectó, se lavó con agua (3 x 50 mL) y se concentró *in vacuo* para proporcionar el producto indicado con una pureza del 95% (5.65 g, 91%).

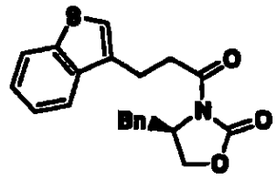
444

Acido 3-benzo[b]tiofen-3-il-propiónico




Una suspensión del ácido 3-benzo[b]tiofen-3-il-acrílico: (5.6 g, 0.027 mol) y Pd al 10%/C (600 mg) en metanol/acetato de etilo 1:1 (50 mL) se hidrógeno en un aparato Parr a 3.511 kg/cm$^2$ (50 psi) durante toda la noche. La mezcla se filtró y se concentró para proporcionar el producto crudo sin purificación adicional (aproximadamente 100% de conversión). Espectro de Masas: 205 $(MH)^-$.

3-(3-Benzo[b]tiofen-3-il-propionil)-4(R)-bencil-oxazolidin-2-ona

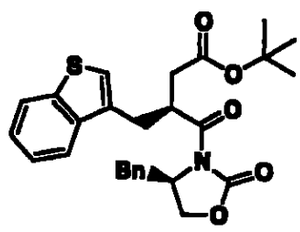



A una solución del ácido 3-benzo[b]tiofen-3-il-propiónico (2.1 g, 0.010 mol), trietilamina (4.12 g, 0.040 mol) en tetrahidrofurano anhidro (100 mL) a 0°C se adicionó cloruro de pivaloilo (1.38 mL, 0.011 mol). Después de la agitación durante 1.5 horas a 0°C, se adicionó cloruro de litio (0.475 g, 0.011 mol) y (R)-4-bencil-2-oxazolidinona (1.988 g, 0.011 mol). La mezcla de reacción se dejó calentar

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a temperatura ambiente y se agitó durante toda la noche. Luego, la mezcla se lavó con agua (3 x 150 mL). La capa orgánica se separó, se secó y se evaporó para proporcionar el producto crudo. El producto del título se obtuvo como un aceite de color café (90%) mediante la cromatografía con evaporación instantánea sobre gel de sílice eluyendo con cloruro de metileno al 100%. Este compuesto se utilizó inmediatamente en el siguiente procedimiento.

Ester *terc*-butílico del ácido 3(S)-benzo[b]tiofen-3-ilmetil-4-(4-bencil-2-oxo-oxazolidin-3-il)-4-oxo-butírico

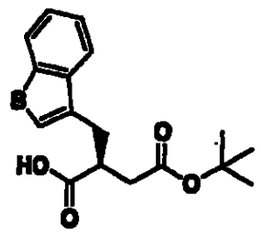



A una solución de la 3-(3-benzo[b]tiofen-3-il-propionil)-4-bencil-oxazolidin-2-ona (3.35 g, 9.18 mmol) en 100 mL de tetrahidrofurano anhidro a -78°C se adicionó diisopropilamida de litio en tetrahidrofurano (6.1 mL, 11.01 mmol) y la mezcla de reacción se agitó durante 30 minutos. Después de la adición de bromoacetato de t-butilo (1.62 mL, 11.01 mmol) a -78°C, la mezcla se agitó durante toda la noche mientras se dejaba calentar a temperatura ambiente. El solvente se evaporó y el residuo se diluyó con acetato de

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etilo. La capa orgánica se lavó con agua (3 x 100 mL), se secó, se filtró y se concentró para proporcionar el producto crudo. El producto del título se obtuvo por medio de la filtración a través de una almohadilla de sílice, eluyendo con cloruro de metileno (49%).

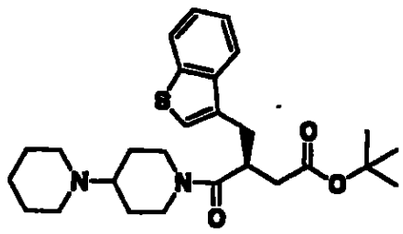
Ester 4-*terc*-butílico del ácido 2(S)-benzo[b]tiofen-3-ilmetil-succínico



A una solución agitada del éster *terc*-butílico 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 adicionó peróxido de hidrógeno acuoso al 30% (1 mL) seguido por hidróxido de litio (0.2155 g, 8.98 mmol). La mezcla de reacción se agitó durante toda la noche. El tetrahidrofurano se removió *in vacuo* y la solución resultante se acidificó con ácido cítrico al 10% y se extrajo con acetato de etilo (3 x 50 mL). La capa orgánica se lavó con una solución de bisulfito de sodio, se secó y se concentró para proporcionar el producto del título.

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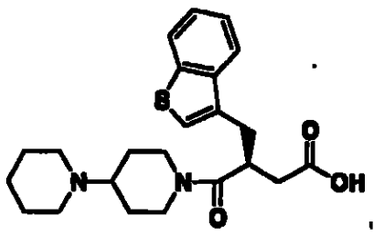
Ester *terc*-butílico del ácido 3-(S)-benzo[b]tiofen-3-ilmetil-4-[1,4']bipiperidinil-1'-il-4-oxo-butírico



Una solución del éster 4-*terc*-butílico 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 100 mL de cloruro de metileno se trató con 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 1.8953 g, 6.34 mmol). La mezcla se agitó durante toda 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 proporcionar el producto crudo. Este se purificó adicionalmente por medio de la cromatografía con evaporación instantánea sobre gel de sílice, eluyendo con amoníaco 2 M al 0-10% en metanol/cloruro de metileno, para proporcionar el producto deseado. Este producto se llevó sin purificación adicional.

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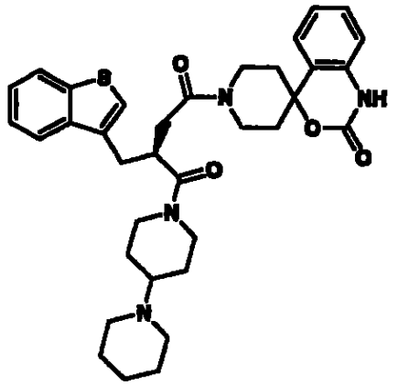
Acido 3(S)-benzo[b]tiofen-3-ilmetil-4-[1,4']bipiperidinil-1'-il-4-oxo-butírico



Una solución del éster *terc*-butílico del ácido 3-benzo[b]tiofen-3-ilmetil-4-[1,4']bipiperidinil-1'-il-4-oxo-butírico en 15 mL de cloruro de metileno se trató con ácido trifluoroacético (3 mL) y la mezcla de reacción se agitó durante toda la noche a temperatura ambiente. El solvente se evaporó para proporcionar la sal de trifluoroacetato correspondiente del producto del título (99%).

Ejemplo 65

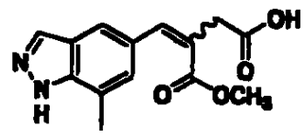
1-[1,4']Bipiperidinil-1'-il-2-(3(S)-benzo[b]tiofen-3-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3'-1-benzoxazin-4,4'-piperidinil]-butan-1,4-diona



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Una solución del 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-benzoxazin-4'4-piperidina (15.7 mg, 0.072 mmol) y trietilamina (7.3 mg, 0.072 mmol) en 5 mL de cloruro de metileno a temperatura ambiente se trató con 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 21.5 mg, 0.072 mmol). La solución se agitó durante toda la noche y luego se lavó con agua (3 X 5 mL). La capa orgánica se secó, se concentró y el producto crudo se purificó por medio de la cromatografía con evaporación instantánea sobre gel de sílice, eluyendo con amoníaco 2 M al 0-10% en metanol/cloruro de metileno, para proporcionar el producto deseado en un rendimiento del 60%. CL/EM: $t_R$= 1.34 minutos, 615.45 $(MH)^+$.

Ester 1-metílico del ácido 2-(7-metil-1H-indazol-5-ilmetilen)-succínico

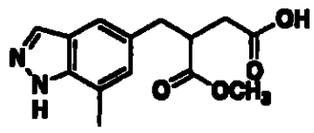



A una mezcla del aldehído de 7-metil-indazol (0.2619 g, 1.64 mmol) y éster dibásico de DBE-4 (succinato de dimetilo) (0.32 mL, 2.45 mmol) en t-butanol (20 mL) se adicionó t-butóxido de potasio (0.4036 g, 3.60 mmol). La mezcla de reacción se calentó a 50°C durante 2 horas bajo

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nitrógeno. Después de 16 horas adicionales a temperatura ambiente, el 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 acidificó con ácido clorhídrico 1 N a pH 3 ~ 4 y se extrajo con acetato de etilo (3 x 50 mL). La solución combinada de acetato de etilo se secó y se concentró *in vacuo* para proporcionar el producto crudo como un sólido de color amarillo (99%, isómero cis/trans aproximadamente 40:60). La mezcla cruda se llevó al siguiente paso sin purificación adicional. Espectro de Masas: 275 $(MH)^+$.

Ester 1-metílico del ácido (+)-2-(7-metil-1H-indazol-5-ilmetil)-succínico

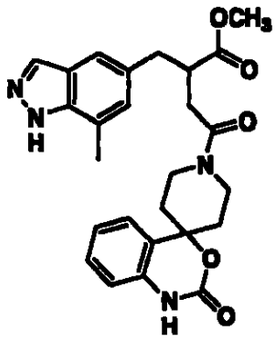



Una suspensión del éster 1-metílico del ácido 2-(7-metil-1H-indazol-5-ilmetilen)-succínico (0.4440 g, 1.62 mmol) y Pd al 10%/C (0.04 g) en acetato de etilo (15 mL) y metanol (5 mL) se hidrogenó en un aparato Parr durante toda la noche a 3.511 $kg/cm^2$ (50 psi). La mezcla de reacción se filtró a través de una almohadilla de celite y el producto filtrado se evaporó para proporcionar el producto deseado como un sólido de color amarillo (100%). Espectro de Masas: 277 $(MH)^+$.

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Ejemplo 66

Ester metílico del ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3'-1-benzoxazin-4,4'-piperidinil]-butírico



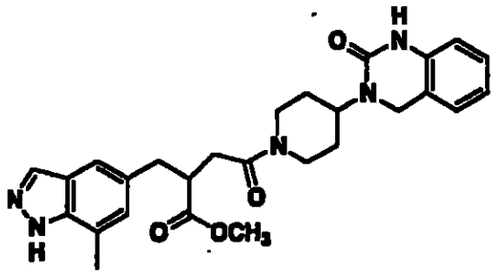
Una solución del éster 1-metílico del ácido 2-(7-metil-1H-indazol-5-ilmetil)-succínico (0.2253 g, 0.82 mmol), 1,2-dihidro-2-oxoespiro-4H-3,1-dihidro-benzoxazin-4'4-piperidina (0.1938 g, 0.89 mmol) y trietilamina (0.099 g, 0.98 mmol) en cloruro de metileno (15 mL) se trató con 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 0.2685 g, 0.90 mmol). La mezcla se agitó durante toda 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 medio de la cromatografía con evaporación instantánea sobre gel de sílice, eluyendo con amoníaco 2 M al 0-10% en metanol/cloruro de metileno, para proporcionar el producto deseado (53%). CL/EM: $t_R$= 1.40 minutos, 477.28 $(MH)^+$.

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Preparado de manera similar:

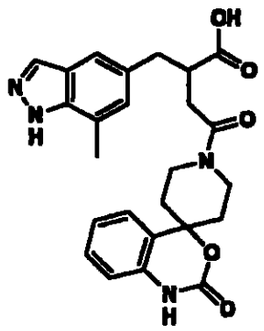
Ejemplo 67

Ester metílico 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



RMN-$^1$H (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 Masas: 490.32 $(MH)^+$.

Acido (±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1'2'-dihidro-2'-oxoespiro-[4H-3'-1-benzoxazin-4,4'-piperidinil]-butírico

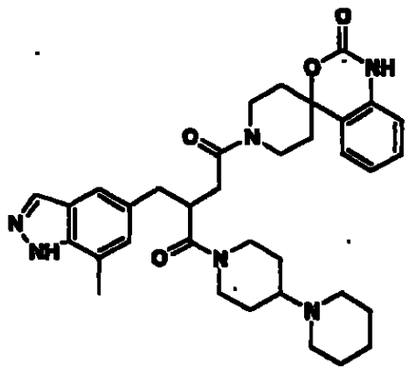


453

Una solución de éster metílico del ácido 2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3'-1-benzoxazin-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 toda la noche a temperatura ambiente. La mezcla de reacción se acidificó con ácido clorhídrico 1 N a aproximadamente pH 1 y se concentró para remover el tetrahidrofurano *in vacuo* para proporcionar un producto precitado, sólido, de color blanco el cual se colectó por medio de la filtración. El sólido se lavó dos veces con cantidades pequeñas de agua y se secó *in vacuo* durante toda la noche (100%). Espectro de Masas: 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-benzoxazin-4,4'-piperidinil]-butan-1,4-diona



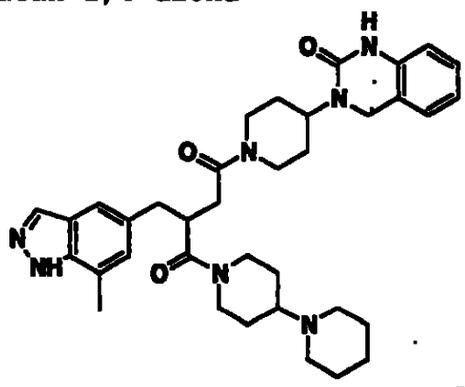
454

Una solución del ácido 2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-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 toda 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 mediante de la CDD preparativa sobre gel de sílice (10%, hidróxido de amonio 2 M/metanol en cloruro de metileno) para proporcionar el producto deseado (36%). CL/EM: $t_R$= 1.18 minutos, 613.47 $(MH)^+$.

Preparado de manera similar:

Ejemplo 69

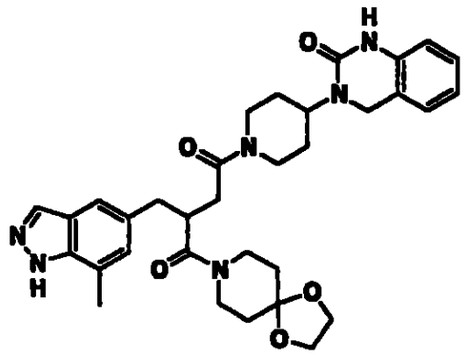
(±)-1-[1,4']Bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona



RMN-$^1$H (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). Espectro de Masas: 626.34 $(MH)^+$.

Ejemplo 70

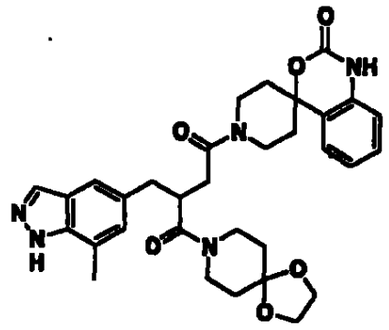
(±)-1-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-(7-metil-1H-indazol-5-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona



RMN-$^1$H (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 Masas: 601.38 $(MH)^+$.

Ejemplo 71

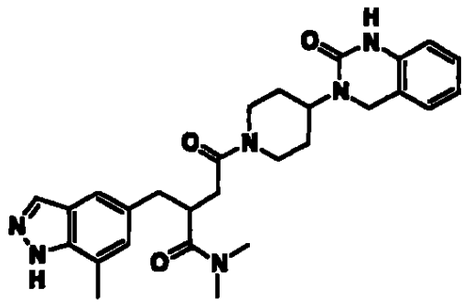
(±)-1-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidinil]-butan-1,4-diona



RMN-$^1$H (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 Masas: 588.36 $(MH)^+$.

Ejemplo 72

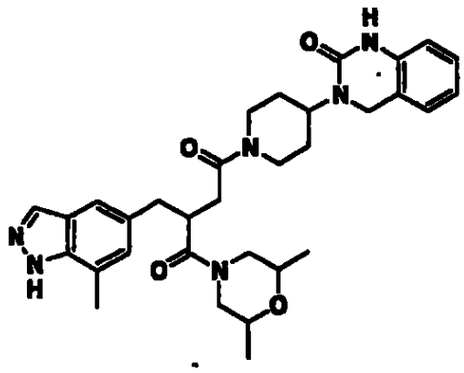
(±)-*N*,*N*-Dimetil-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiramida



CL/EM: $t_R$=1.36 minutos, 525.35 $(M+Na)^+$.

Ejemplo 73

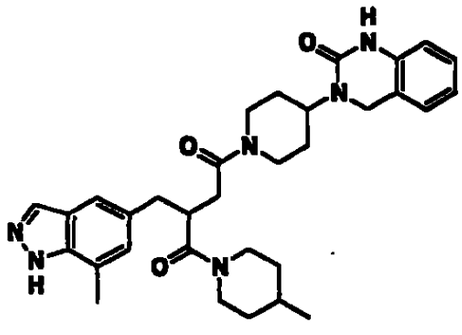
(±)-1-(2,6-Dimetil-morfolin-4-il)-2-(7-metil-1H-indazol-5-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona



CL/EM: $t_R$= 1.41 minutos, 573.39 $(MH)^+$.

Ejemplo 74

(±)-2-(7-Metil-1H-indazol-5-ilmetil)-1-(4-metil-piperidin-1-il)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona

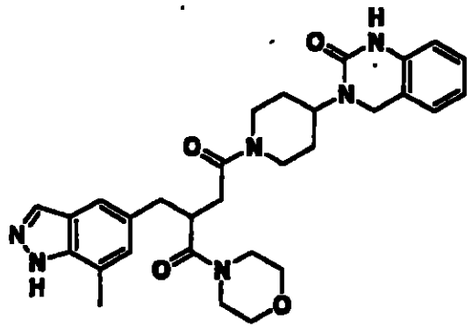


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RMN-$^1$H (400 MHz, $CDCl_3$) δ 8.06 (1H, b), 7.60-6.73 (7H, m), 4.71 (1H, m), 4.54 (2H, m), 4.26 (2H, m), 4.05-3.89 (2H, m), 3.65 (1H, m), 3.09-2.81 (4H, m), 2.61 (3H, s), 2.41 (2H, m), 1.76-0.51 (15H, m). Espectro de Masas: 557.38 $(MH)^+$.

Ejemplo 75

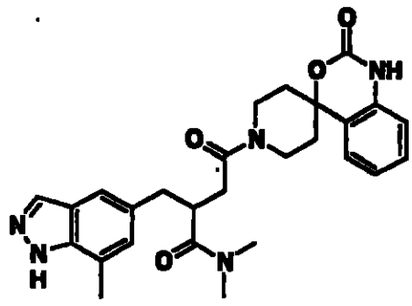
(±)-2-(7-Metil-1H-indazol-5-ilmetil)-1-morfolin-4-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona



CL/EM: $t_R$= 1.32 minutos, 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-benzoxazin-4,4'-piperidinil]-butiramida

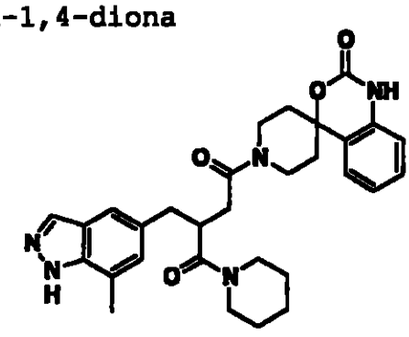


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CL/EM: $t_R$= 1.27 minutos, 512.30 $(M+Na)^+$.

Ejemplo 77

(±)-2-(7-Metil-1H-indazol-5-ilmetil)-1-(piperidin-1-il)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidinil]-butan-1,4-diona

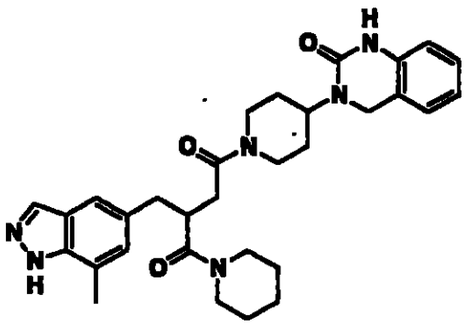


RMN-$^1$H (400 MHz, $CDCl_3$) δ 9.26-9.01 (1H, m), 8.09 (1H, s), 7.42-6.89 (7H, m), 4.56 (1H, m), 3.84 (1H, m), 3.65 (3H, m), 3.30 (2H, m), 3.05 (3H, m), 2.81 (1H, M), 2.60 (3H, s), 2.39 (1H, m), 2.09 (2H, m), 1.85 (1H, m), 1.43-0.79 (9H, m).

Espectro de Masas: 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-butan-1,4-diona

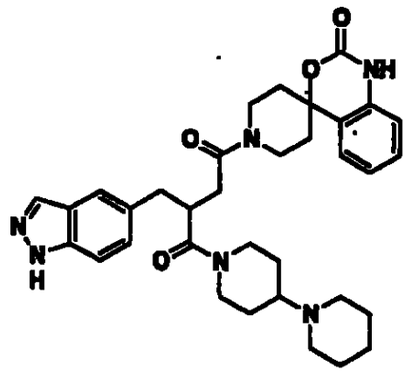


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RMN-$^1$H (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.82 (1H, m), 7.37 (1H, m), 7.14 (1H, m), 7.04-6.90 (3H, m), 6.73 (1H, d, J = 8.0 Hz), 4.69 (1H, m), 4.56 (1H, m), 4.24 (2H, d, J = 7.2 Hz), 4.02 (1H, m), 3.65 (2H, m), 3.33 (3H, m), 3.07 (3H, m), 2.78 (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 Masas: 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-benzoxazin-4,4'-piperidinil]-butan-1,4-diona

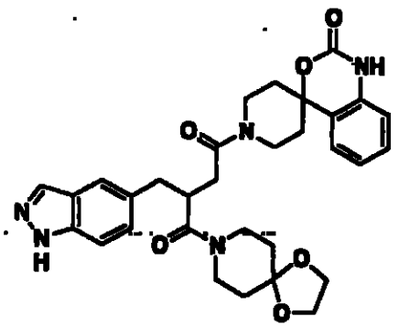


RMN-$^1$H (400 MHz, $CDCl_3$) δ 8.86 (1H, m), 7.98 (1H, s), 7.54-6.85 (7H, m), 4.73-4.48 (3H, m), 3.96-.80 (3H, m), 3.73-3.58 (3H, m), 3.17-2.78 (5H, m), 2.55-2.24 (5H, m), 2.02-1.79 (6H, m), 1.70-0.79 (7H, m). Espectro de Masas: 599.31 $(M+Na)^+$.

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Ejemplo 80

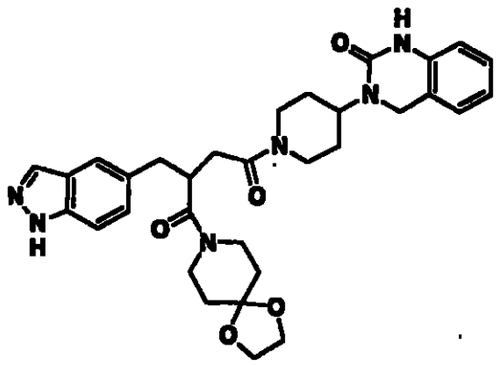
(±)-1-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-(1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidinil]-butan-1,4-diona



CL/EM: $t_R$= 1.25 minutos, 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]-butan-1,4-diona

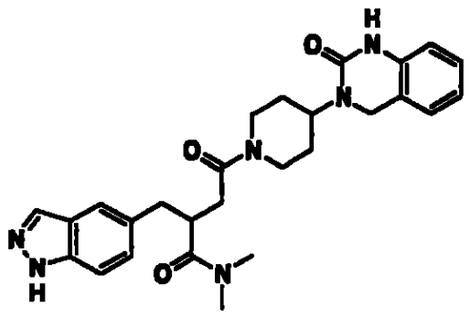


CL/EM: $t_R$= 1.34 minutos, 587.38 $(MH)^+$.

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Ejemplo 82

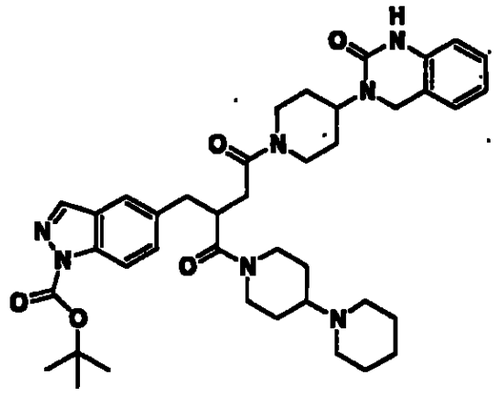
(±)-2-(1H-Indazol-5-ilmetil)-N,N-dimetil-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiramida



CL/EM: $t_R$= 1.28 minutos, 489.33 $(MH)^+$.

Ejemplo 83

Ester *terc*-butílico 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

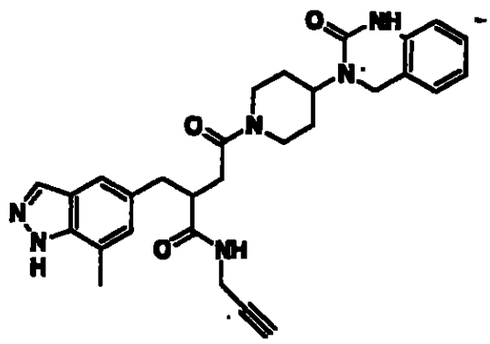


CL/EM: $t_R$= 1.47 minutos, 742.55 $(M+Na)^+$.

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Ejemplo 84

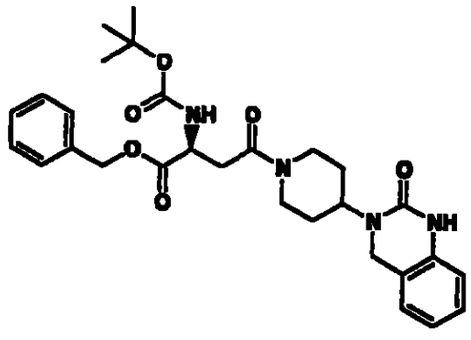
(±)-2-(7-Metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-N-prop-2-inil-butiramida



CL/EM: $t_R$= 1.33 minutos, 535.32 $(M+Na)^+$.

Productos Intermedios de Aspartato y Ejemplos

Ester bencílico del ácido (L)-2-*terc*-butoxicarbonilamino-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico

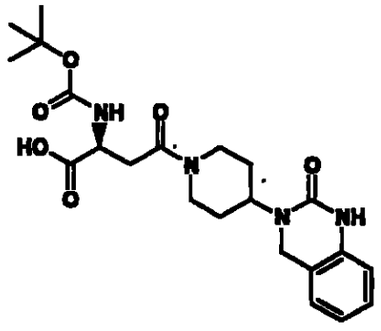


A una solución agitada del éster alfa-bencílico del

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ácido N-*terc*-butiloxicarbonil-*L*-aspártico (1.4 g, 4.33 mmol) y la 3,4-dihidro-3-(4-piperidinil-2(1H)-quinazolinona (1.26 g, 4.33 mmol) en cloruro de metileno (12 mL) se adicionó la 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 1.425 g, 4.76 mmol) en una porción seguido por la adición gota a gota de trietilamina (0.724 mL, 5.20 mmol). La suspensión resultante se volvió gradualmente homogénea con agitación y se agitó a temperatura ambiente durante toda la noche (15 horas). 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 proporcionar una espuma de color amarillo claro. El producto crudo se purificó por medio de la cromatografía en columna con evaporación instantánea (metanol al 10% en cloruro de metileno) para proporcionar un aceite incoloro. Espectro de Masas: 559 $(M+Na)^+$.

Acido (L)-2-*terc*-Butoxicarbonilamino-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico

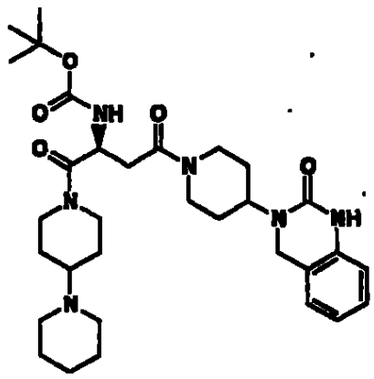


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A una solución del éster bencílico del ácido 2-*terc*-butoxicarbonilamino-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico (1.48 g, 2.76 mmol) en acetato de etilo/metanol (16 mL, 1:1) en una botella Parr se adicionó carbón vegetal con paladio al 10% (150 mg) en una porción. La hidrogenación se llevó a cabo con un aparato Parr a 3.651 kg/cm$^2$ (52 psi) durante 1 hora. La CDD (metanol al 10% en cloruro de metileno) indicó una conversión cuantitativa. La mezcla se filtró y se concentró *in vacuo* para proporcionar un sólido incoloro, vítreo (1.14 g, 93%).

Ejemplo 85

Ester *terc*-butílico 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

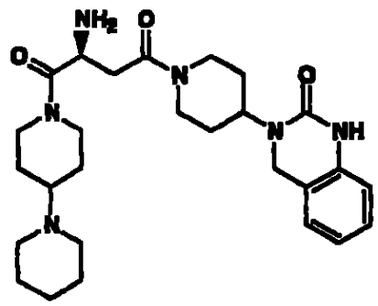


A una solución agitada del ácido 2-*terc*-butoxicarbonilamino-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-

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 adicionó la 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 840 mg, 2.81 mmol) en una porción seguido por la adición gota a gota de trietilamina (0.427 mL, 3.06 mmol). La mezcla resultante se agitó a temperatura ambiente durante toda la noche (15 horas). La mezcla se diluyó con cloruro de metileno y se lavó con una 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 proporcionar una espuma de color amarillo claro. El producto crudo se purificó por medio de la cromatografía en columna con evaporación instantánea (10% (amoníaco 1 M en metanol) en cloruro de metileno) para proporcionar una espuma incolora (1.08 g, 71%). RMN-$^1$H (400 MHz, $CDCl_3$) δ 8.86-8.55 (1H, amplio), 7.05 (1H, amplio), 6.93 (1H, amplio), 6.82 (1H, amplio), 6.72 (1H, d, J = 7.6 Hz), 6.10-5.68 (1H, amplio), 5.20 (1H, m), 54.70-4.40 (2H, amplio), 4.20 (2H, amplio), 4.01-3.82 (2H, amplio), 3.10-2.88 (3H, amplio), 2.99 (3H, amplio), 2.53 (6H, amplio), 1.90-1.10 (23H, m). Espectro de Masas: 597 $(MH)^+$.

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(L)-2-Amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona

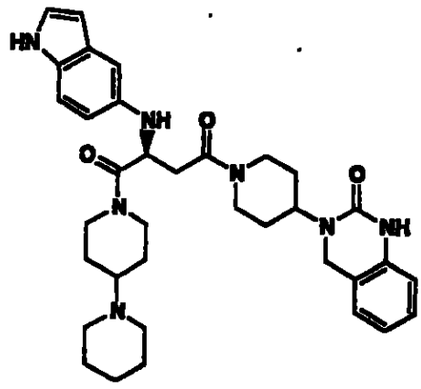


A una solución agitada del éster *terc*-butílico del ácido {1-([1,4']bipiperidinil-1'-carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil}-carbámico (1.05 g, 1.76 mmol) en cloruro de metileno (12 mL) se adicionó ácido trifluroacético (2 mL). La mezcla se agitó a temperatura ambiente hasta que se completó la conversión (monitoreada por medio de CL-EM, aproximadamente 15 horas). La mezcla luego se diluyó con agua y se adicionó lentamente hidróxido de sodio (1.5 g) 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 proporcionar una espuma de color amarillo claro (860 mg, 98%). Espectro de Masas: 497 $(MH)^+$.

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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]-butan-1,4-diona



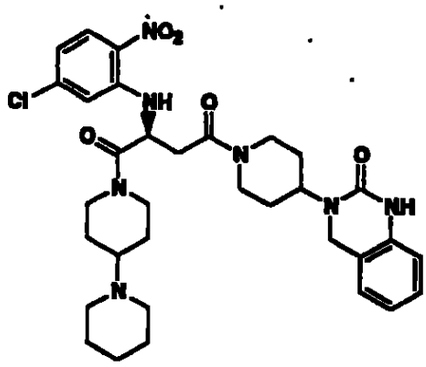
A una solución de la 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona (52 mg, 0.105 mmol) y N-*terc*-BOC-5-bromo-indol (preparado como se describe en *Tetrahedron* 2000, páginas 8473-8482) (31 mg, 0.105 mmol) en tetrahidrofurano (1 mL) en un frasquito cilíndrico de 5 mL se adicionó el 2-diciclohexilfosfino-2'-(*N*,*N*-dimetilamino)-bifenilo (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 frasquito se selló con una tapa recubierta con teflón$^{MR}$. La mezcla de reacción de color anaranjado intenso se calentó a 80°C con agitación. La reacción continuó a 80°C durante toda la noche. La conversión alcanzó aproximadamente 50% después de 17 horas. El solvente se removió *in vacuo* y el residuo se

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disolvió en cloruro de metileno y se filtró. El producto deseado se purificó mediante la CDD preparativa (metanol al 10% en cloruro de metileno) para proporcionar el producto protegido por *terc*-butiloxicarbonilo (11 mg, 15%). Espectro de Masas: 712 $(MH)^+$. Este producto intermedio (11 mg) se disolvió en 3 mL de cloruro de metileno y se trató con ácido trifluoroacético (1.5 mL). La solución incolora se tornó de color canela y se agitó a temperatura ambiente durante 1.5 horas. La mezcla se concentró *in vacuo* y se secó bajo alto vacío para proporcionar un polvo de color canela (15 mg, 100%). Espectro de Masas: 612 $(MH)^+$.

Ejemplo 87

(L)-1-[1,4']Bipiperidinil-1'-il-2-(5-cloro-2-nitro-fenilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona

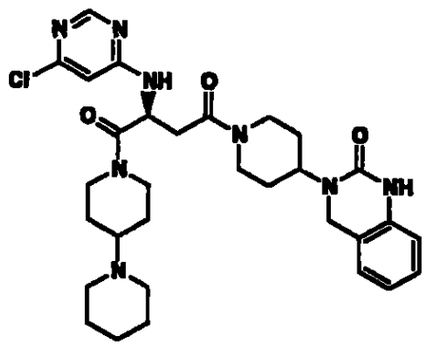



A una solución agitada de la 2-amino-1-

[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-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 adicionó una solución saturada de bicarbonato de sodio (4 gotas). La mezcla se agitó a temperatura ambiente durante 70 horas para una conversión de aproximadamente 60%. El producto se purificó mediante la CLAR preparativa para proporcionar un sólido de color amarillo (17.7 mg, 40%). Espectro de Masas: 652 $(MH)^+$.

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]-butan-1,4-diona



Una mezcla de la 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

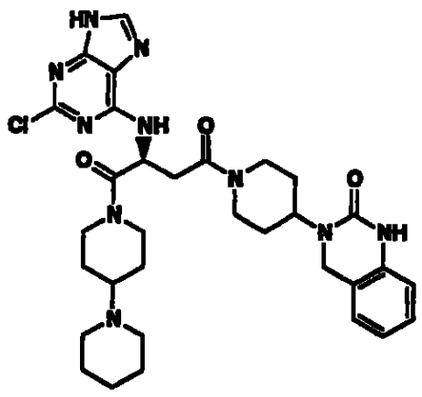
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il]-butan-1,4-diona (22.3 mg, 0.045 mmol) y 4,6-dicloropirimidina (16 mg; 0.095 mmol) en 2-propanol (0.5 mL) en un frasquito utilizable en condiciones de microondas se calentó a 130°C bajo irradiación de microondas durante 40 minutos. La CL/EM indicó 90% de conversión. El solvente se removió *in vacuo* y el residuo se dividió entre cloruro de metileno y una 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 medio de la cromatografía en columna con evaporación instantánea (10% (amoníaco 1 N en metanol) en cloruro de metileno) para proporcionar un sólido de color blanco (23 mg, 84%). RMN-$^1$H (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, amplio), 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). Espectro de Masas: 609 $(MH)^+$.

Preparada de manera similar:

Ejemplo 89

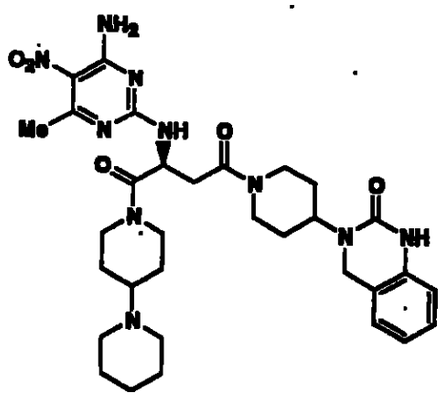
(L)-1-[1,4']Bipiperidinil-1'-il-2-(2-cloro-9H-purin-6-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona



CL/EM: $t_R$ = 1.10 minutos, 649 $(MH)^+$.

Ejemplo 90

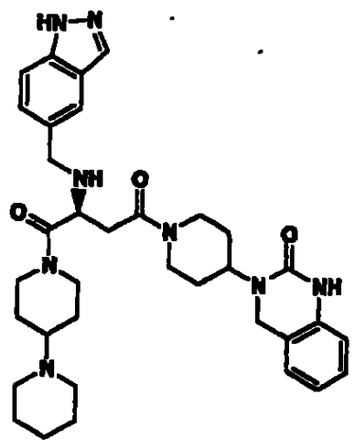
(L)-2-(4-Amino-6-metil-5-nitro-pirimidin-2-ilamino)-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona



CL/EM: $t_R$ = 1.12 minutos, 649 $(MH)^+$.

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]-butan-1,4-diona

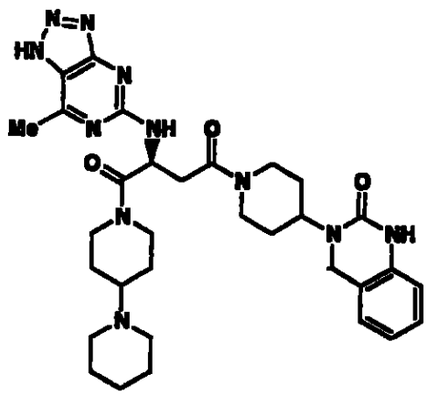


A una solución de la 2-(4-amino-6-metil-5-nitro-pirimidin-2-ilamino)-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona en metanol/acetato de etilo 2:1 (6 mL) en una botella Parr se adicionó carbón vegetal con paladio al 10% (60 mg). La mezcla se agitó bajo una atmósfera de hidrógeno a 3.862 kg/cm$^2$ (55 psi) durante 20 horas. La mezcla se filtró a través de celite y el producto filtrado se concentró *in vacuo* para proporcionar un sólido incoloro (41.2 mg, 49.2% para los dos pasos). CL/EM: $t_R$ = 0.86 minutos, 619 $(MH)^+$.

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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]-butan-1,4-diona



A una solución agitada de la 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]-butan-1,4-diona (10.6 mg, 0.0125 mmol) en ácido acético (1.5 mL) se adicionó nitrito de sodio (24 mg) seguido por algunas gotas de agua. La solución resultante de color amarillo claro se agitó a temperatura ambiente durante 6 horas. La mezcla de reacción se diluyó con agua y metanol y se purificó por medio de la CLAR preparativa para proporcionar un aceite/sólido incoloro (3.0 mg, 28%). CL/EM: $t_R$ = 1.07 minutos, 630 $(MH)^+$.

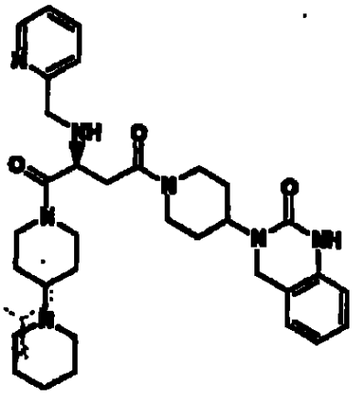
475

Procedimiento general para la síntesis de los ejemplos 93-95:

Una mezcla de la 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona (0.014 mmol), uno de una serie de aldehídos (0.07 mmol, 5 equivalentes) y sulfato de magnesio anhidro, sólido (0.031 mmol, 2.2 equivalentes) en 1,2-dicloroetano (3.0 mL) se trató con una cantidad catalítica de ácido acético y se agitó durante toda la noche. Luego se adicionó cianoborohidruro de sodio (0.07 mmol, 5 eq) en una porción y la suspensión se agitó nuevamente durante toda la noche. La purificación se llevó a cabo ya sea por medio de la filtración a través de un cartucho SCX o por medio de la 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]-butan-1,4-diona

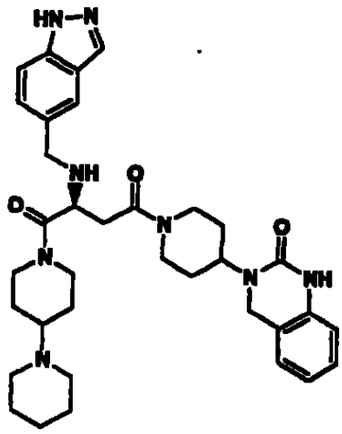


476

CL/EM: $t_R$ = 0.87 minutos, 588 $(MH)^+$.

Ejemplo 94

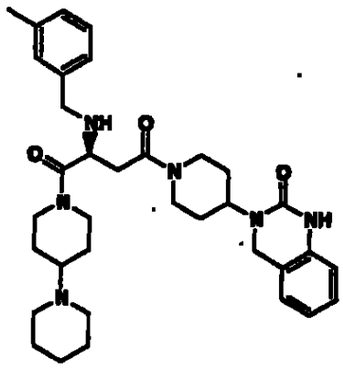
(L)-1-[1,4']Bipiperidinil-1'-il-2-((5'-indazolil)-metil-amino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona



CL/EM: $t_R$ = 0.92 minutos, 626 $(MH)^+$.

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]-butan-1,4-diona

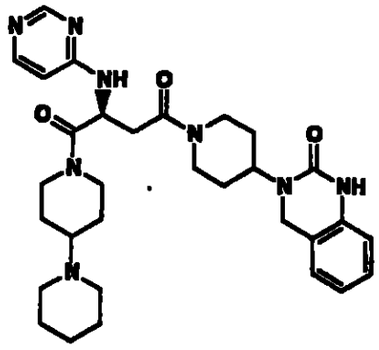


477

CL/EM: $t_R$ = 1.08 minutos, 600 $(MH)^+$.

Ejemplo 96

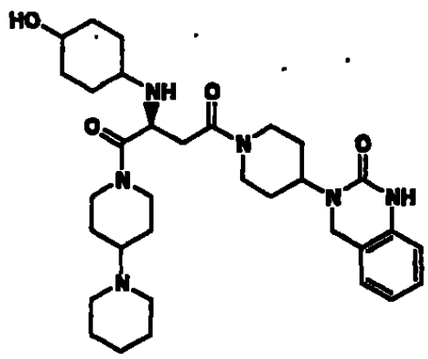
(L)-1-[1,4']Bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-2-(pirimidin-1-ilamino)-butan-1,4-diona



A una solución de la 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]-butan-1,4-diona (21 mg) disuelta en 4 mL de acetato de etilo/metanol (1:1) en una botella Parr se adicionó carbón vegetal con paladio al 10% (10 mg). La hidrogenación se llevó a cabo en un aparato Parr a 3.862 $kg/cm^2$ (55 psi) durante toda la noche. La mezcla desgasificada luego se filtró y se concentró *in vacuo*. El residuo se purificó mediante la CLAR preparativa para proporcionar un sólido de color amarillo (12.4 mg, 45%). Espectro de Masas: 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]-butan-1,4-diona




A una mezcla agitada de la 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-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 adicionó cloruro de zinc en exceso seguido por cianoborohidruro de sodio (5 equivalentes). La suspensión se agitó a temperatura ambiente durante 6 días. El metanol se removió *in vacuo* y el residuo se dividió entre cloruro de metileno e hidróxido de sodio 1 N. La capa acuosa se extrajo con cloruro de metileno (3x). La solución combinada de cloruro de metileno se pasó a través de un cartucho de celite y se concentró *in vacuo*. El residuo se

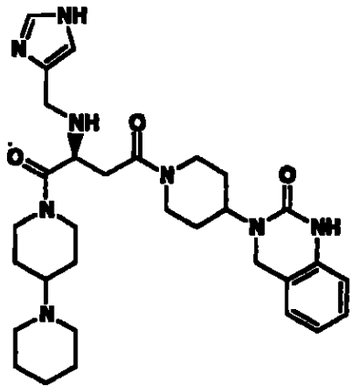
479

purificó por medio de la CDD preparativa (10% (amoníaco 1 N en metanol) en cloruro de metileno) para proporcionar el producto deseado como un sólido de color blanco (15.3 mg, 27%).

Espectro de Masas: 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]-butan-1,4-diona



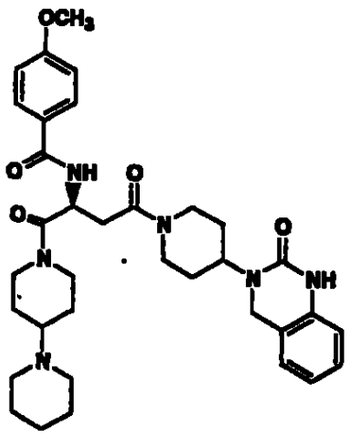
A una solución agitada de la 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona (20.6 mg, 0.0415 mmol) y 4-imidazolcarboxialdehído (4 mg, 0.0415 mmol) en cloruro de metileno (1.0 mL) se adicionó cianoborohidruro de sodio (8.8 mg, 0.0415 mmol) en una porción. La suspensión se agitó a temperatura ambiente durante 2 días y luego se dividió entre cloruro de metileno e hidróxido de sodio 1 N.

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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 medio de la CDD preparativa (10% (amoníaco 1 N en metanol) en cloruro de metileno) para proporcionar el producto deseado como un aceite incoloro que se solidificó con el reposo (6.1 mg, 26%). RMN-$^1$H (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 Masas: 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



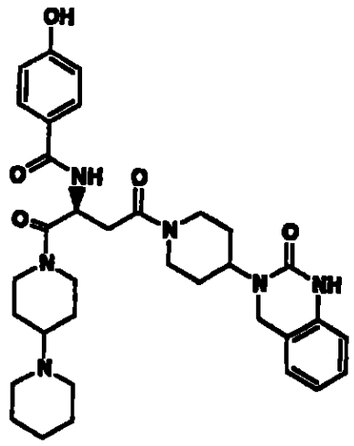
A una mezcla agitada de la 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona (91.5 mg, 0.184 mmol) y cloruro de *p*-anisoilo (34.6 mg, 0.203 mmol) en cloruro de metileno se adicionaron dos gotas de trietilamina (35 µL). La solución de color amarillo claro se agitó a temperatura ambiente durante 2.5 horas para lograr la conversión completa. La mezcla de reacción se lavó con hidróxido de sodio (1 N) y la capa acuosa luego se extrajo con cloruro de metileno. Las capas orgánicas, combinadas se pasaron a través de un cartucho de celite y se concentraron *in vacuo* para proporcionar un sólido vítreo. El producto crudo se purificó por medio de la cromatografía en columna con evaporación instantánea (10% (amoníaco 1 N en metanol) en cloruro de metileno) para proporcionar un sólido vítreo (92.8 mg, 80%). RMN-$^1$H (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, amplio), 4.75-4.40 (3H, m), 4.40-4.05 (3H, m), 4.05-3.82 (1H, amplio), 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 Masas: 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-

482

hidroxi-benzamida

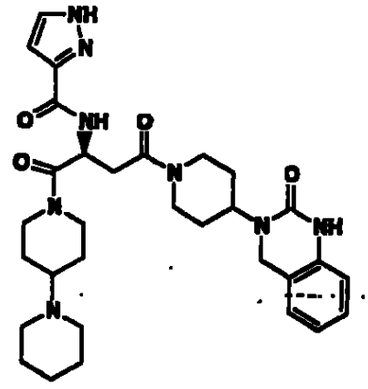


Una solución agitada de la *N*-{1-([1,4']bipiperidinil-1'-carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil}-4-metoxi-benzamida en cloruro de metileno (69 mg) se trató con tribromuro de boro (1 M en cloruro de metileno, 0.6 mL), gota a gota a temperatura ambiente. La suspensión resultante se agitó a temperatura ambiente durante 7 horas y luego la reacción se enfrió rápidamente con trietilamina en exceso seguido por metanol. Los solventes se removieron *in vacuo* y el residuo se disolvió en metanol y se purificó por medio de la CLAR preparativa. CL/EM: $t_R$ = 1.03 minutos, 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

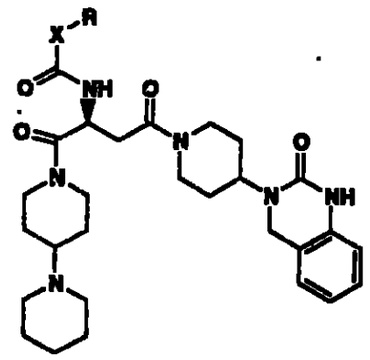
ácido (L)-1H-pirazol-3-carboxílico



A una solución agitada del ácido pirazol-3-carboxílico (4 mg, 0.036 mmol) y la 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona (13 mg, 0.026 mmol) en cloruro de metileno (1 mL) se adicionó la 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 toda la noche (15 horas). La mezcla luego se dividió 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). La CL-EM indicó que el producto permaneció en la capa acuosa. El producto se purificó por medio de la CLAR preparativa para proporcionar un aceite de color amarillo (17.2 mg, 94%). Espectro de Masas: 591 $(MH)^+$.

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Procedimiento general para la síntesis de los ejemplos 102-134:

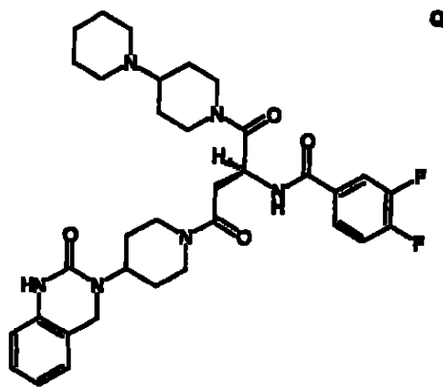
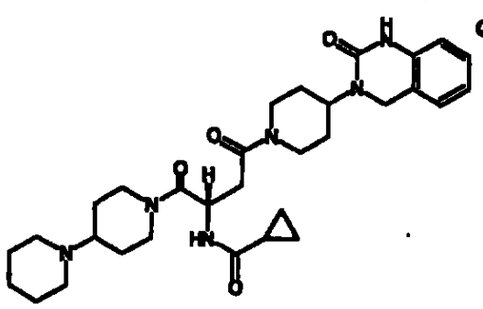
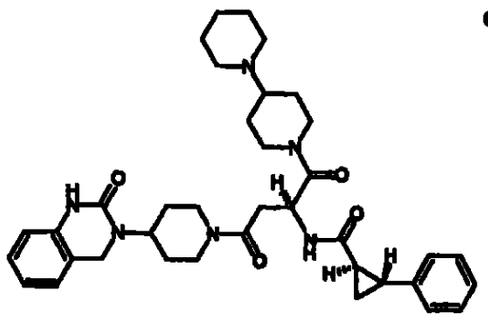


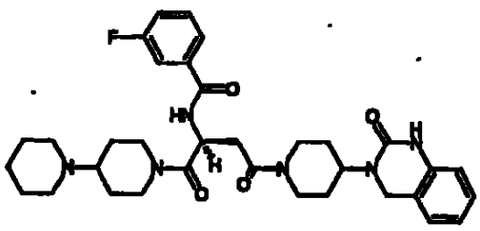
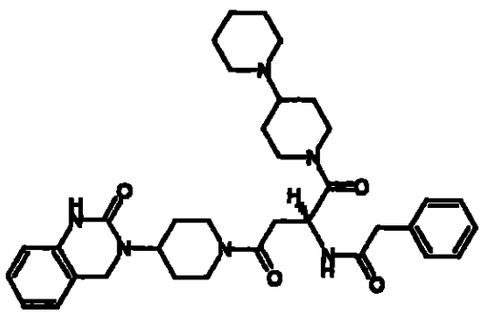
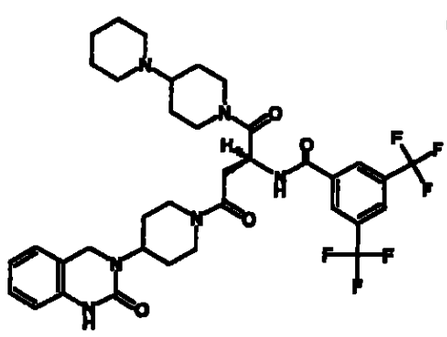
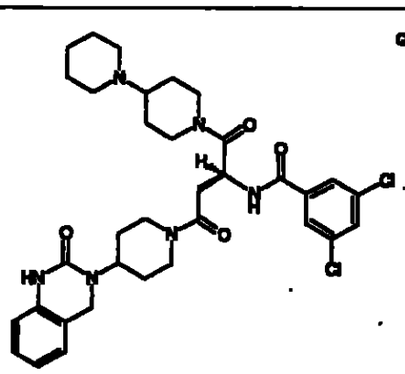
X=C, O

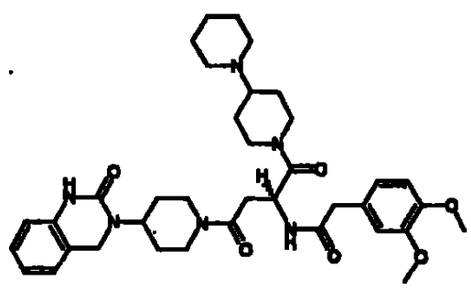
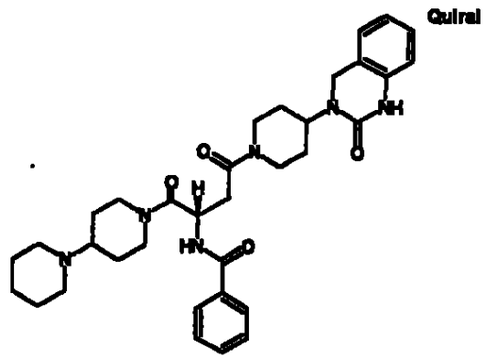
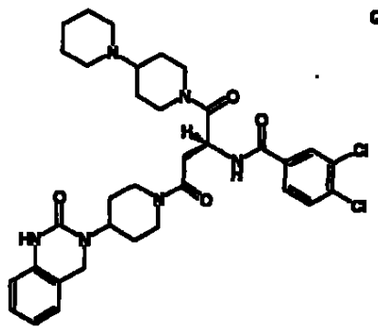
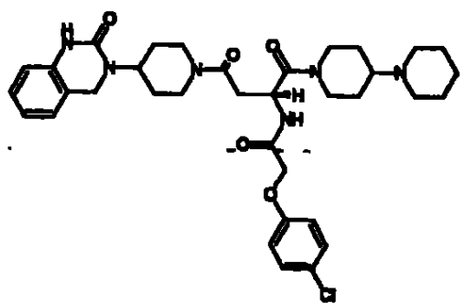
La amina de inicio, 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona, se dispersó en un mini-reactor de 96 pocillos de aproximadamente 10 mg cada uno) en 1 mL de dicloroetano. Los cloruros de acilo individuales (aproximadamente 2 equivalentes) se adicionaron seguidos por una base de piperidina en fase sólido unida a resina (4 equivalentes). El bloque se agitó durante toda la noche. Se adicionaron aproximadamente 4 equivalentes de esta resina de tris-amina a cada pocillo y el mini-reactor se agitó durante otras 5 horas. Las mezclas de reacción se filtraron y se purificaron mediante ya sea la CLAR preparativa o la filtración a través de un cartucho SCX o ambos. Los tiempos de retención de CLAR y los datos espectrales de masas para cada ejemplo se listan en la tabla 2.

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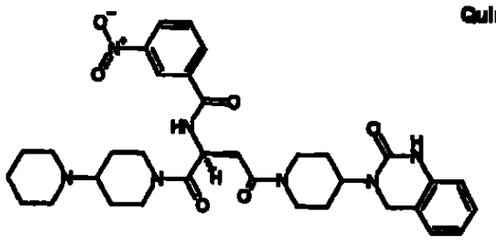
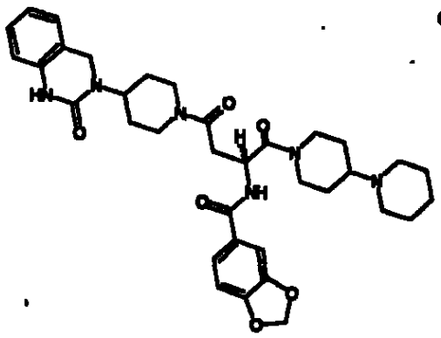
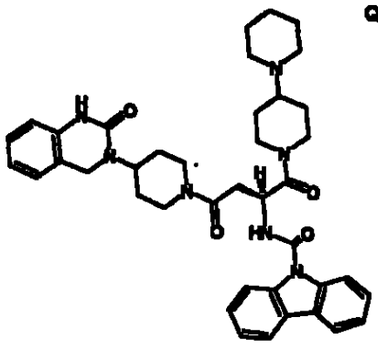
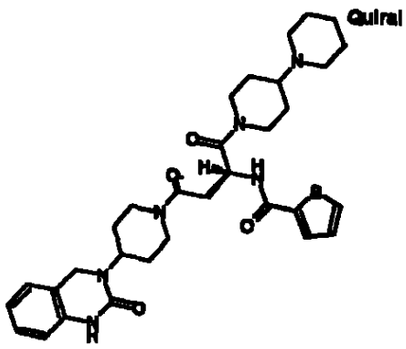
Tabla 2. Amidas y Carbamatos

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 102 |  | 1.84 | 637.38 |
| 103 |  | 1.39 | 565.45 |
| 104 |  | 1.89 | 641.46 |

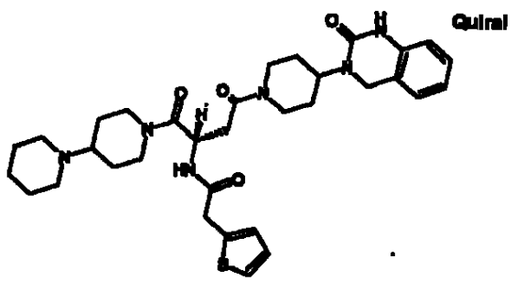
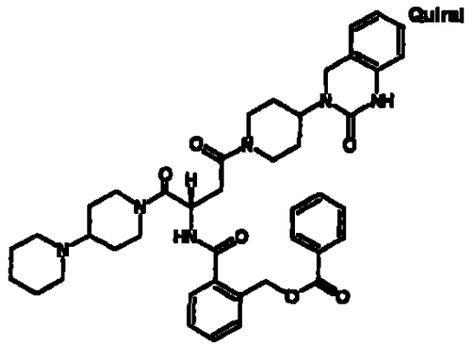
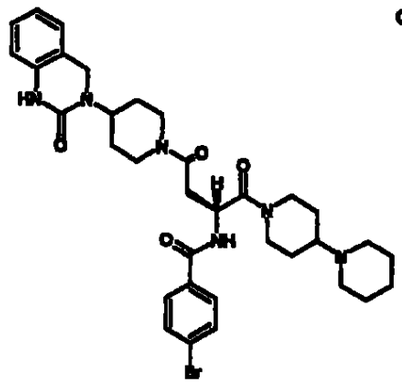
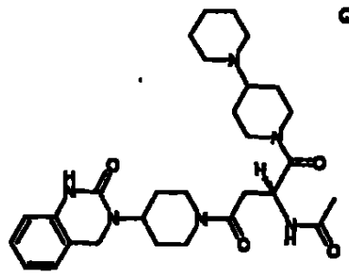
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 105 |  Quiral | 1.73 | 619.42 |
| 106 |  Quiral | 1.62 | 615.41 |
| 107 |  Quiral | 2.25 | 737.37 |
| 108 |  Quiral | 2.12 | 669.3 |

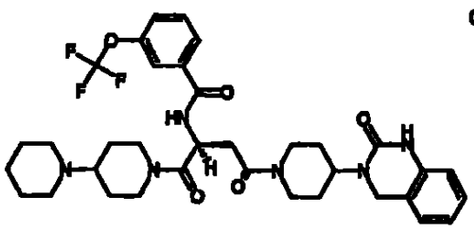
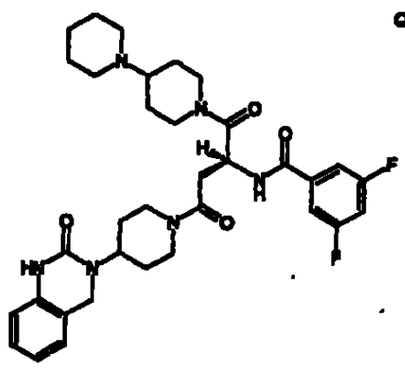
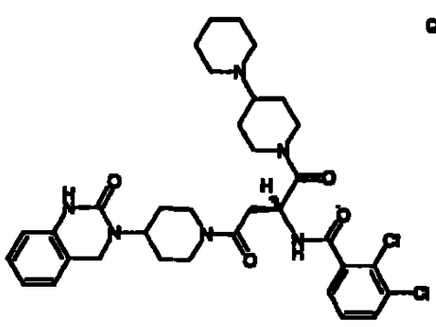
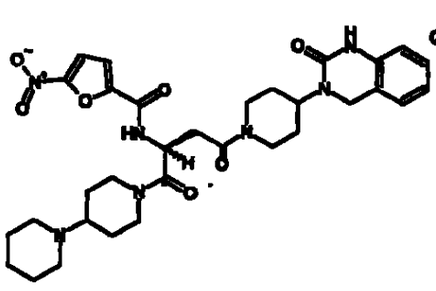
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 109 |  | 1.59 | 675.46 |
| 110 |  | 1.62 | 601.43 |
| 111 |  | 2.09 | 669.33 |
| 112 |  | 1.91 | 665.36 |

488

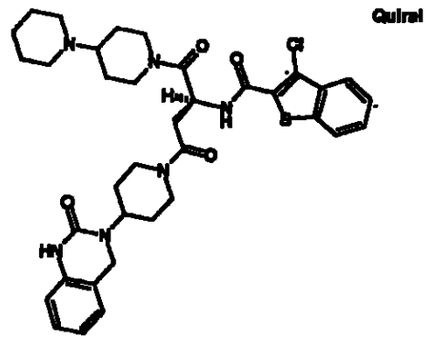
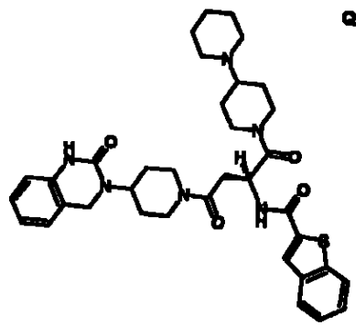
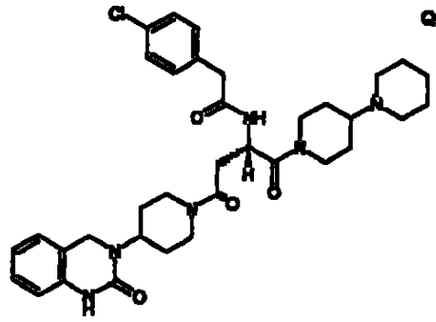
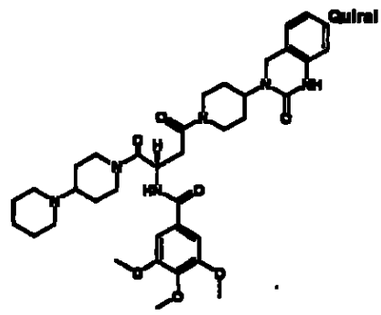
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 113 |  | 1.68 | 646.37 |
| 114 |  | 1.66 | 645.4 |
| 115 |  | 2.14 | 690.45 |
| 116 |  | 1.59 | 607.39 |

489

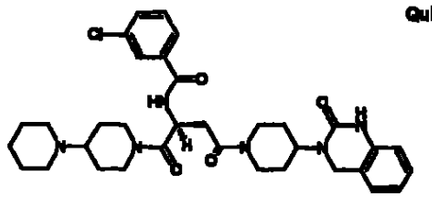
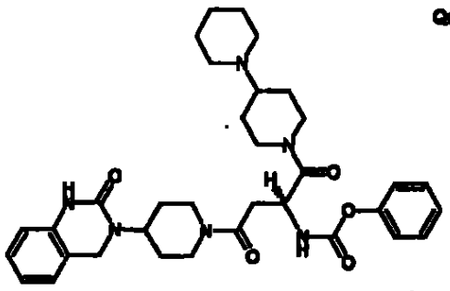
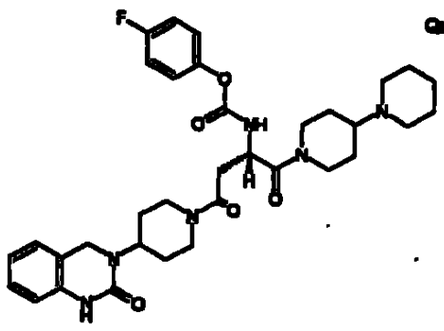
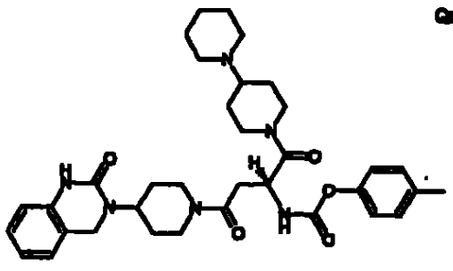
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 117 |  | 1.59 | 621.4 |
| 118 |  | 2.01 | 735.43 |
| 119 |  | 1.92 | 679.32 |
| 120 |  | 1.22 | 537.4 |

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 121 |  | 2.03 | 685.4 |
| 122 |  | 1.79 | 637.38 |
| 123 |  | 1.84 | 669.3 |
| 124 |  | 1.53 | 636.35 |

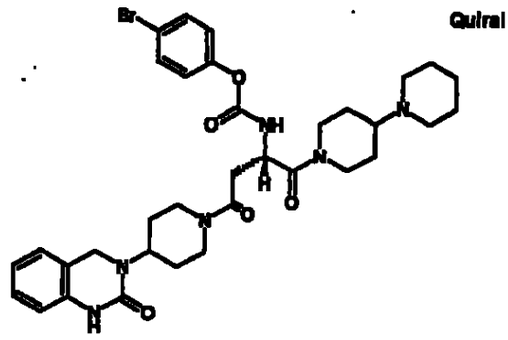
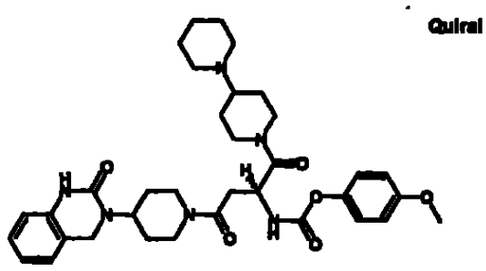
491

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 125 |  | 2.04 | 691.35 |
| 126 |  | 1.89 | 657.35 |
| 127 |  | 1.86 | 649.39 |
| 128 |  | 1.67 | 691.42 |

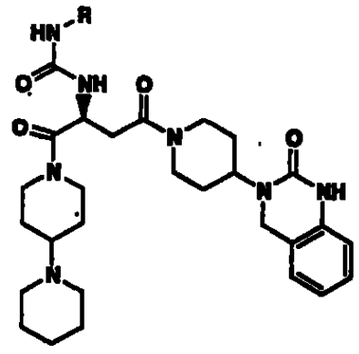
492

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 129 |  | 1.84 | 635.38 |
| 130 |  | 1.69 | 617.42 |
| 131 |  | 1.74 | 635.38 |
| 132 |  | 1.84 | 631.44 |

493

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 133 |  | 1.94 | 695.28 |
| 134 |  | 1.7 | 647.41 |

Procedimiento general para la síntesis de los ejemplos 135-200

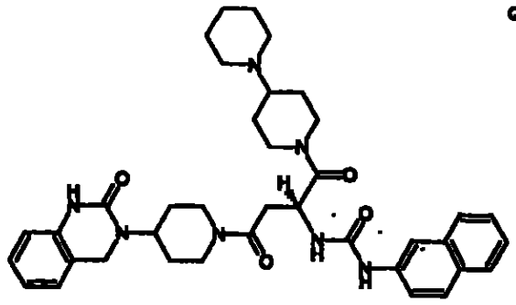


La amina de inicio, 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona, se dispersó en un mini-reactor de 96

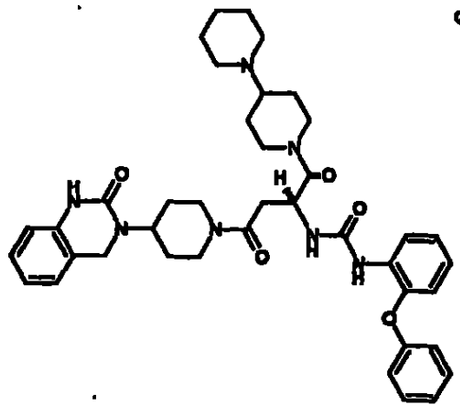
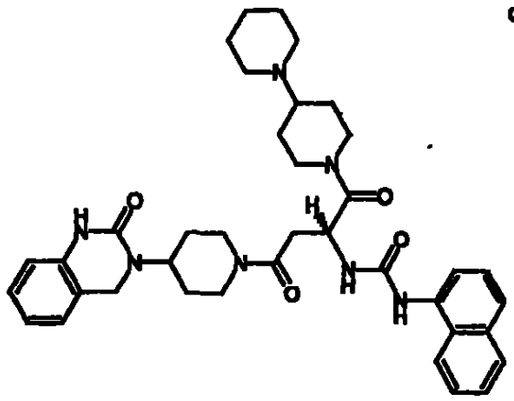
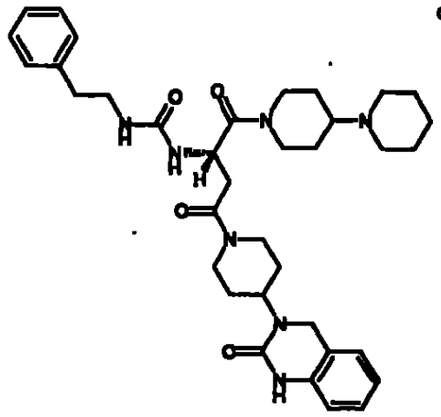
494

pocillos (de aproximadamente 10 mg en cada pocillo) en dicloroetano (1 mL). Se adicionaron isocianatos individuales (aproximadamente 2 equivalentes) a pocillos individuales. El bloque se agitó durante 2 días. Se adicionaron aproximadamente 4 equivalentes de la resina de tris-amina ca ada pocillo y el mino-reactor se agitó durante otros dos días. Las mezclas de reacción se filtraron y el producto individual se purificó ya sea mediante la CLAR preparativa o la filtración a través de un cartucho SCX o ambos. Los tiempos de retención de CLAR y los datos espectrales de masas para cada ejemplo se listan en la tabla 3.

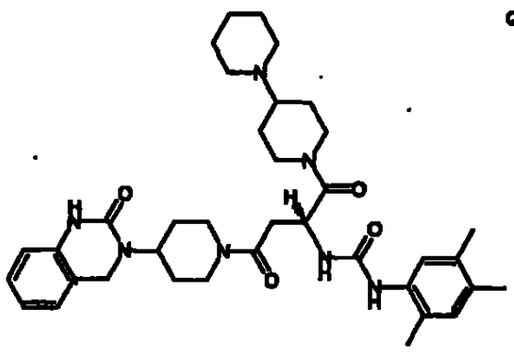
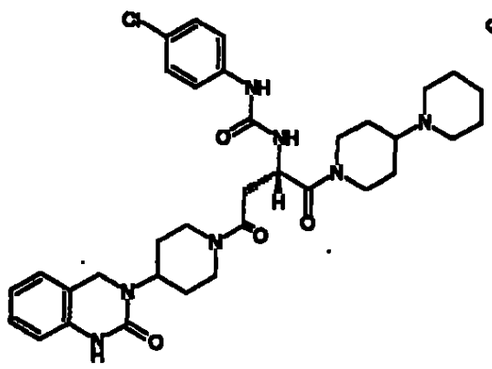
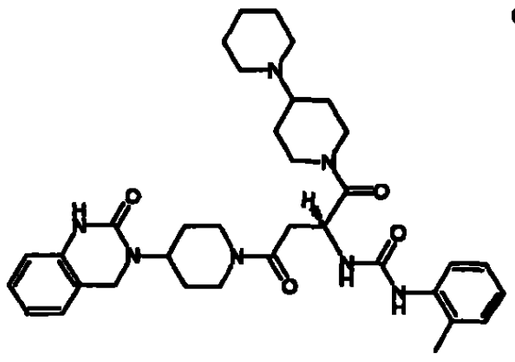
Tabla 3. Ureas

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 135 |  | 1.43 | 665.84 |

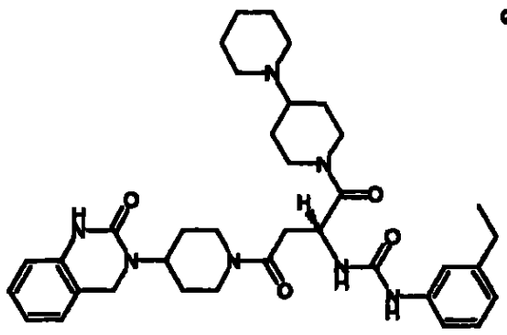
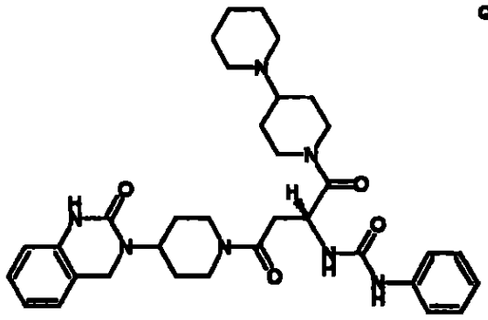
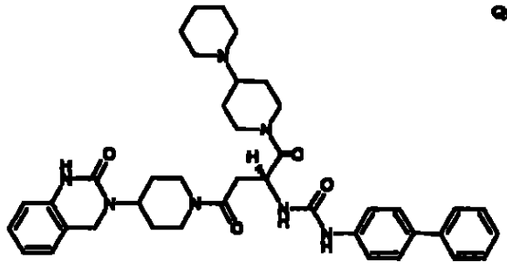
495

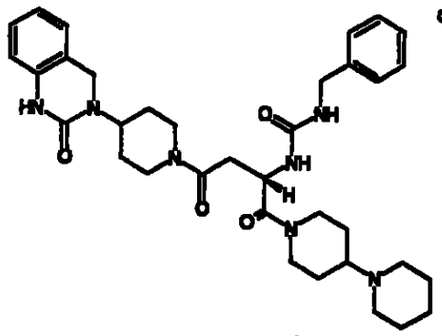
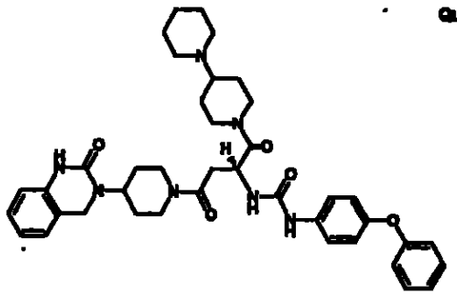
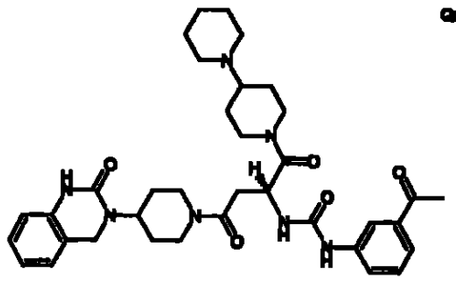
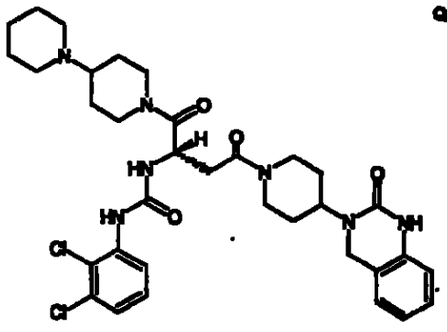
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 136 |  | 1.56 | 707.88 |
| 137 |  | 1.39 | 665.84 |
| 138 |  | 1.3 | 643.83 |

496

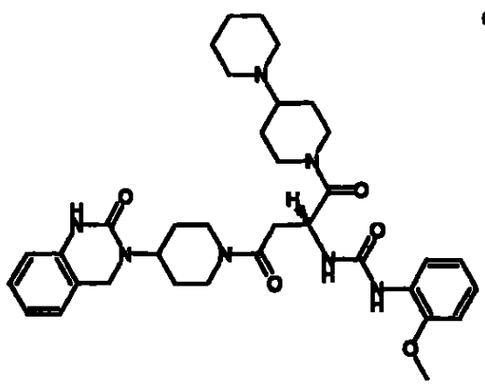
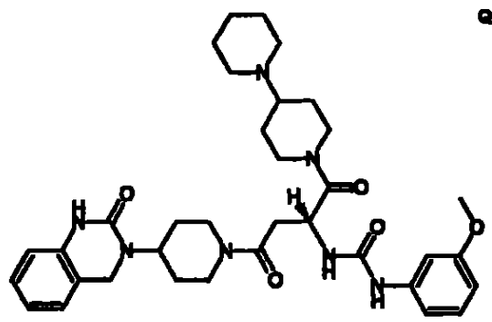
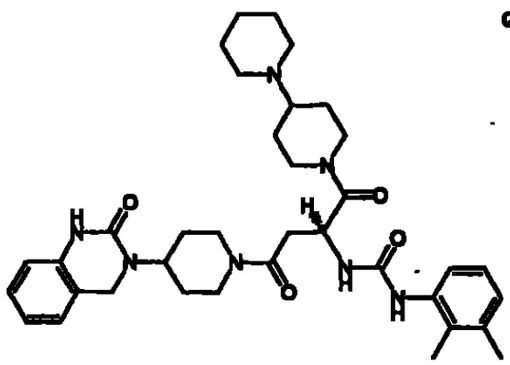
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 139 |  | 1.44 | 657.86 |
| 140 |  | 1.42 | 650.22 |
| 141 |  | 1.26 | 629.81 |

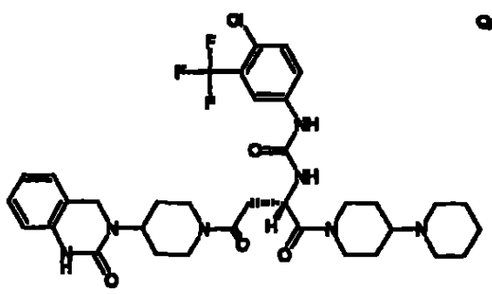
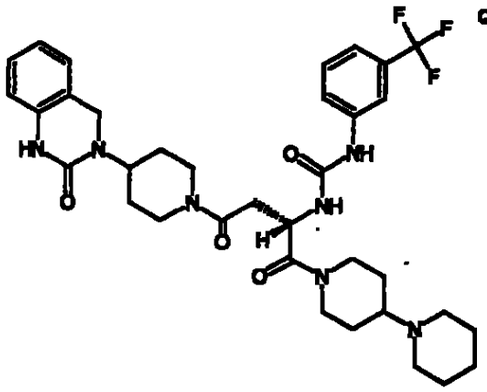
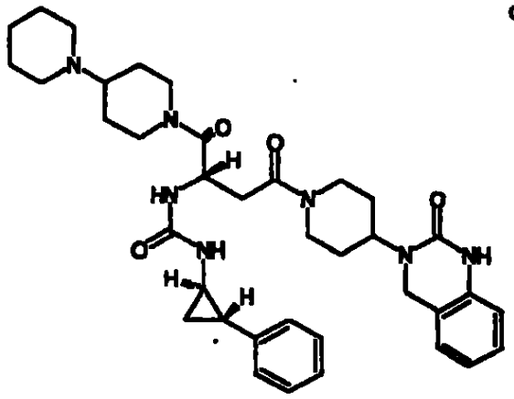
497

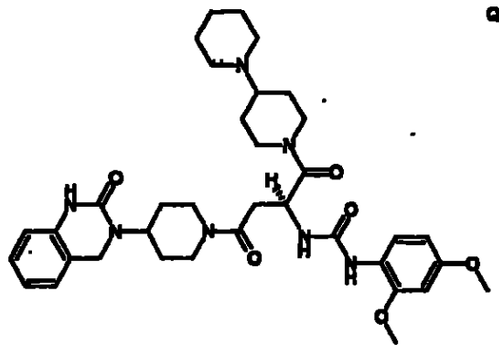
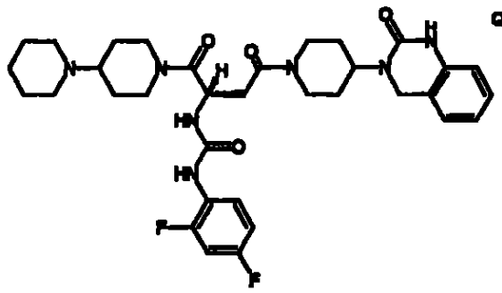
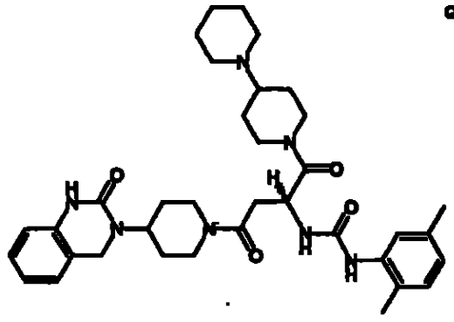
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 142 |  | 1.41 | 643.83 |
| 143 |  | 1.24 | 615.78 |
| 144 |  | 1.53 | 691.88 |

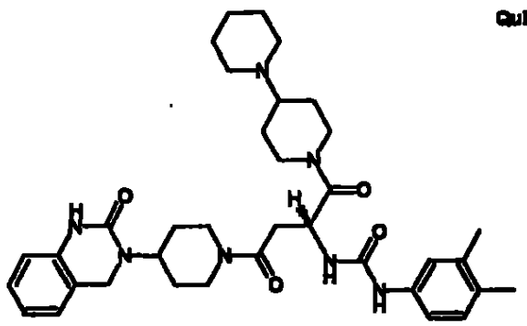
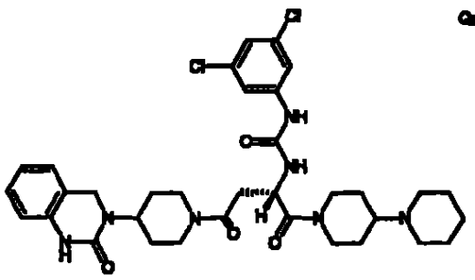
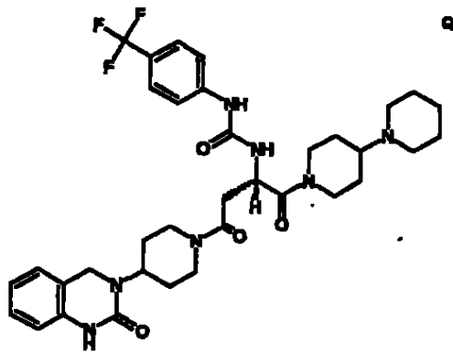
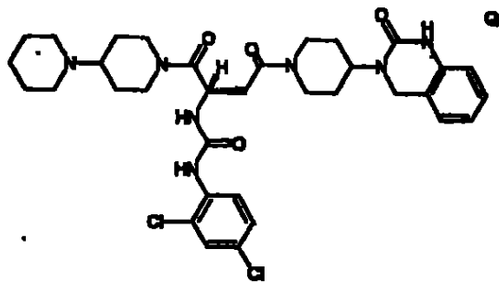
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 145 |  | 1.21 | 629.81 |
| 146 |  | 1.52 | 707.88 |
| 147 |  | 1.19 | 657.82 |
| 148 |  | 1.44 | 684.67 |

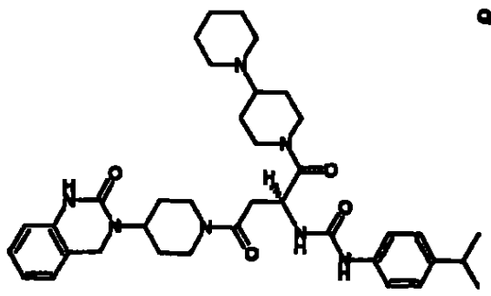
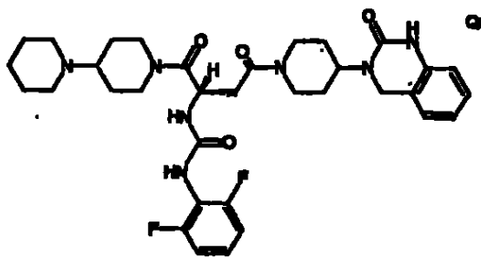
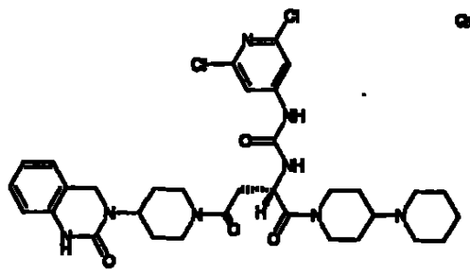
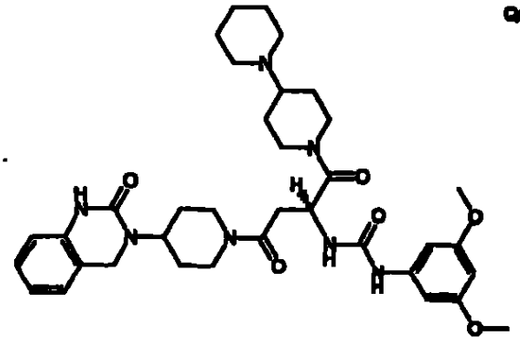
499

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 149 |  Quiral | 1.3 | 645.81 |
| 150 |  Quiral | 1.24 | 645.81 |
| 151 |  Quiral | 1.33 | 643.83 |

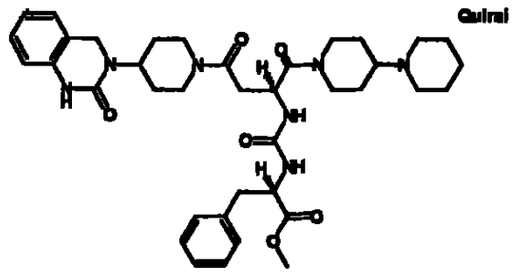
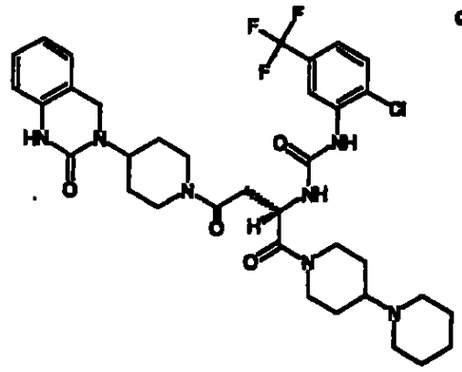
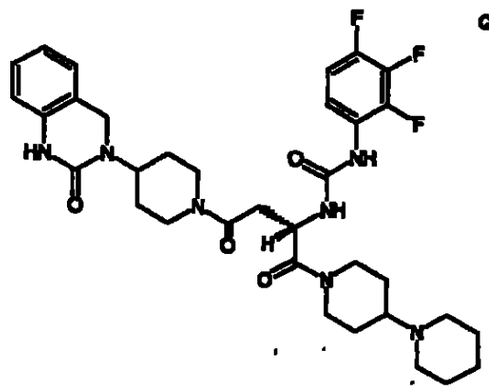
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 152 |  | 1.56 | 718.22 |
| 153 |  | 1.55 | 683.78 |
| 154 |  | 1.37 | 655.84 |

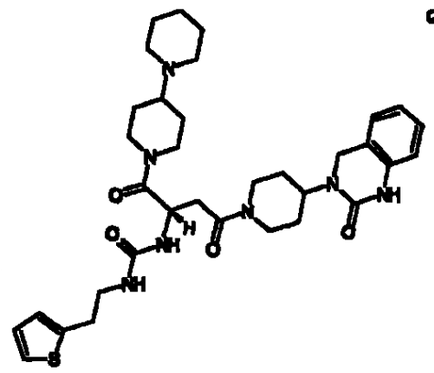
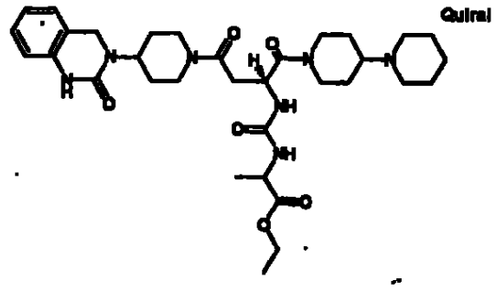
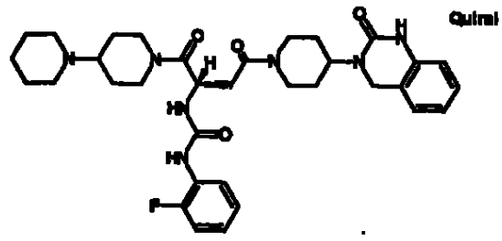
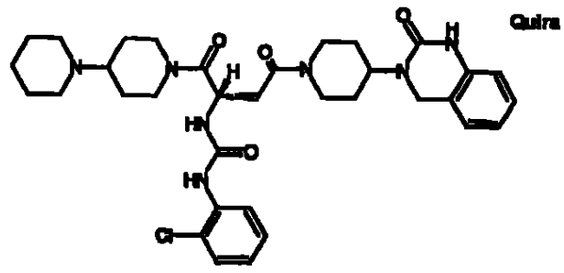
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 155 |  | 1.27 | 675.83 |
| 156 |  | 1.26 | 651.76 |
| 157 |  | 1.39 | 643.83 |

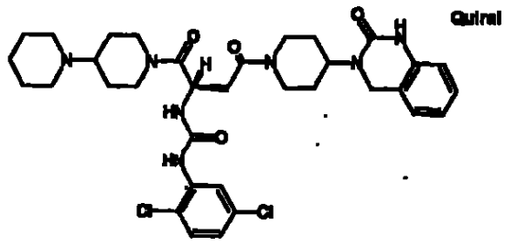
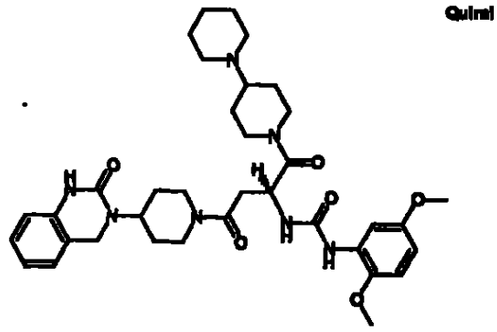
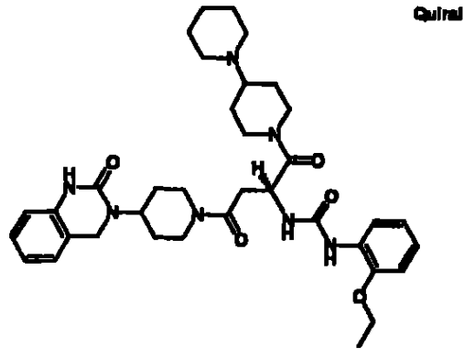
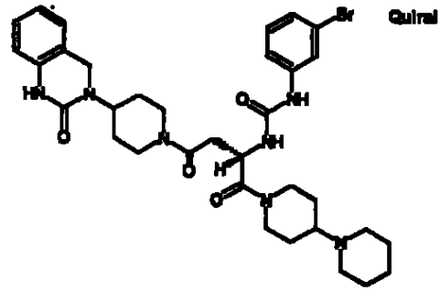
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 158 |  | 1.43 | 643.83 |
| 159 |  | 1.57 | 684.67 |
| 160 |  | 1.46 | 683.78 |
| 161 |  | 1.48 | 684.67 |

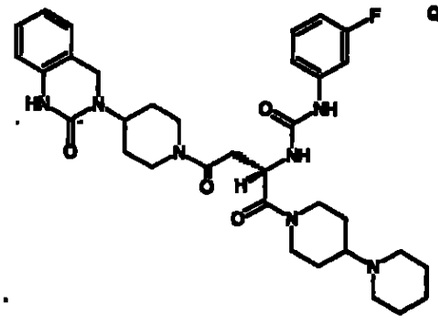
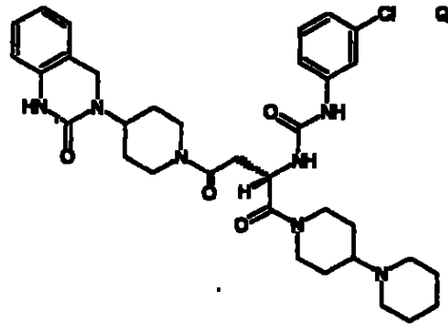
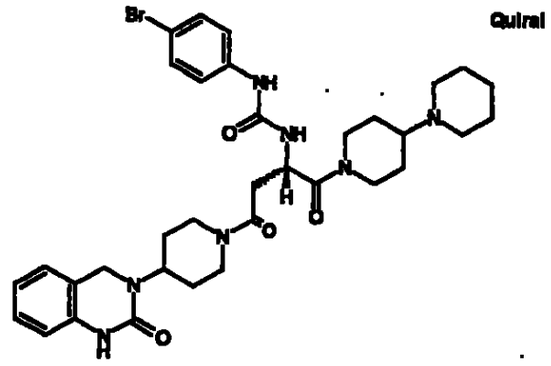
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 162 |  | 1.5 | 657.86 |
| 163 |  | 1.14 | 651.76 |
| 164 |  | 1.34 | 685.66 |
| 165 |  | 1.26 | 675.83 |

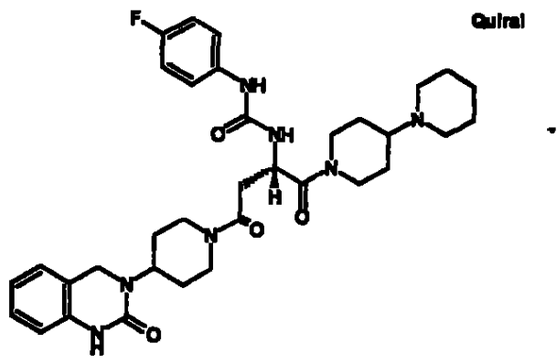
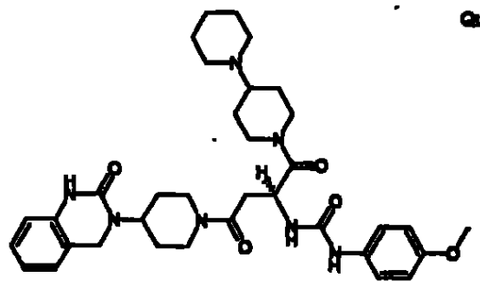
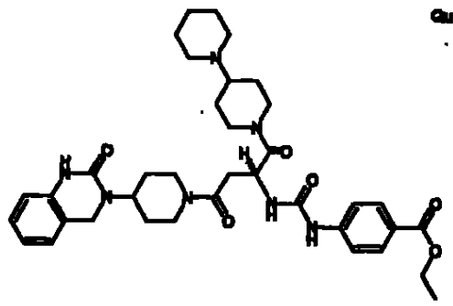
504

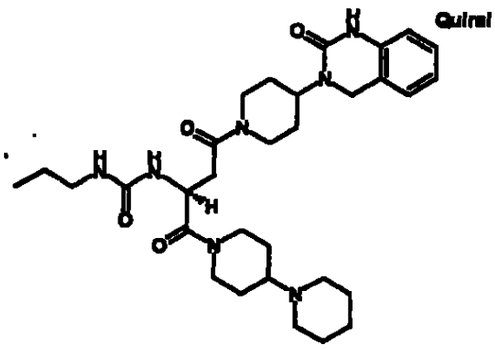
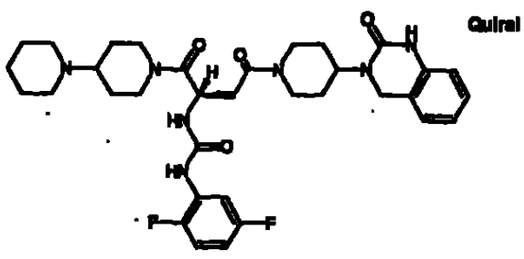
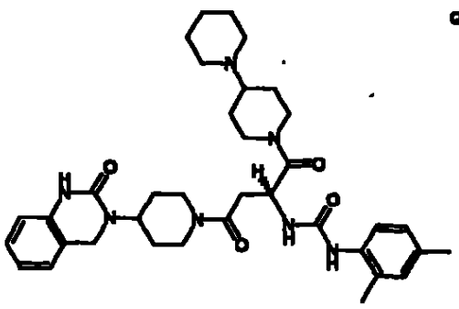
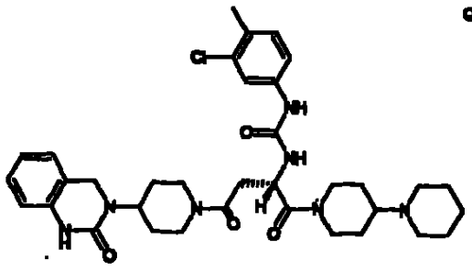
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 166 |  | 1.28 | 701.87 |
| 167 |  | 1.52 | 718.22 |
| 168 |  | 1.35 | 669.75 |

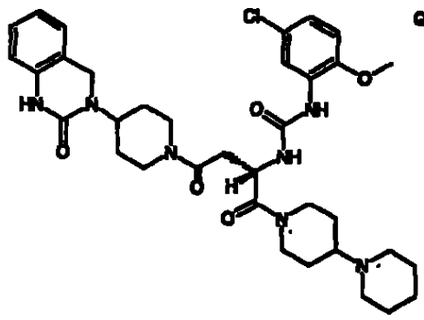
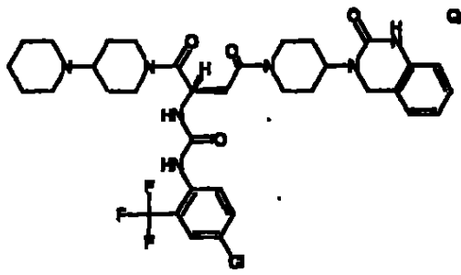
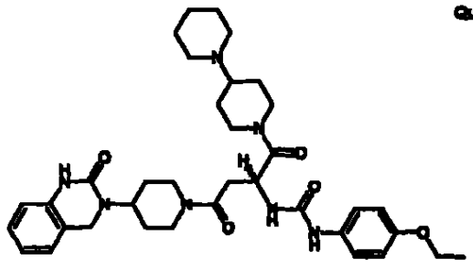
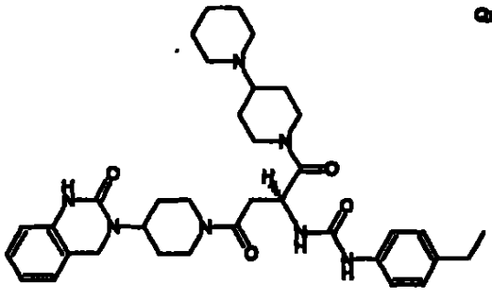
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 169 |  | 1.24 | 649.86 |
| 170 |  | 1.11 | 639.8 |
| 171 |  | 1.31 | 633.77 |
| 172 |  | 1.34 | 650.22 |

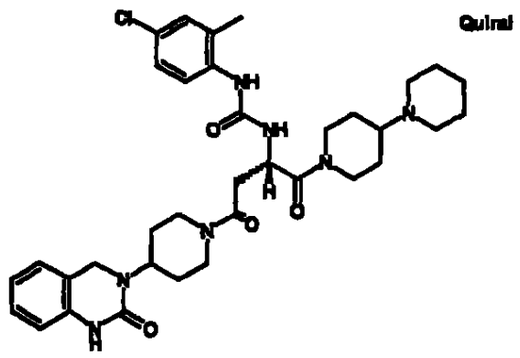
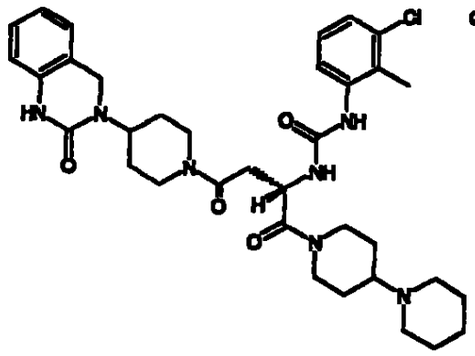
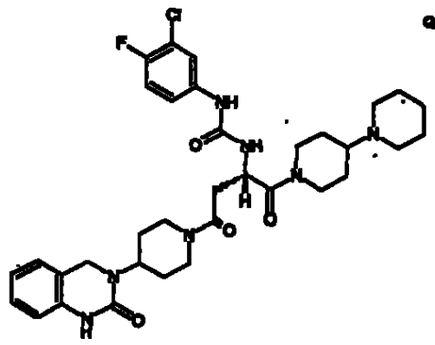
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 173 |  | 1.47 | 684.67 |
| 174 |  | 1.27 | 675.83 |
| 175 |  | 1.34 | 659.83 |
| 176 |  | 1.41 | 694.68 |

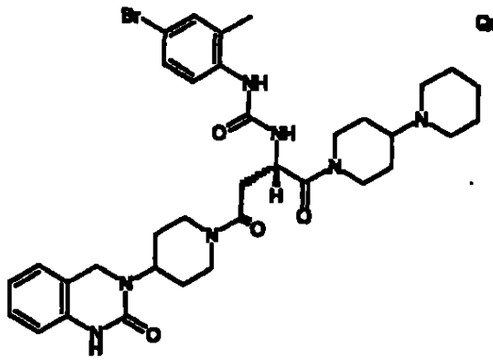
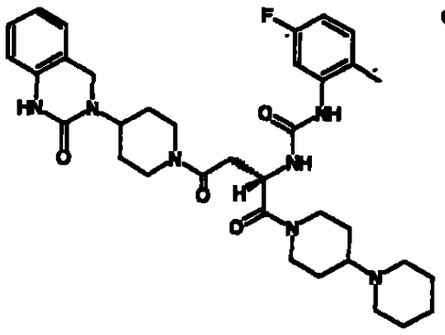
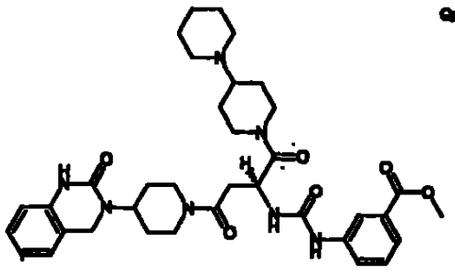
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 177 |  | 1.28 | 633.77 |
| 178 |  | 1.39 | 650.22 |
| 179 |  | 1.42 | 694.68 |

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 180 |  | 1.26 | 633.77 |
| 181 |  | 1.19 | 645.81 |
| 182 |  | 1.34 | 687.84 |

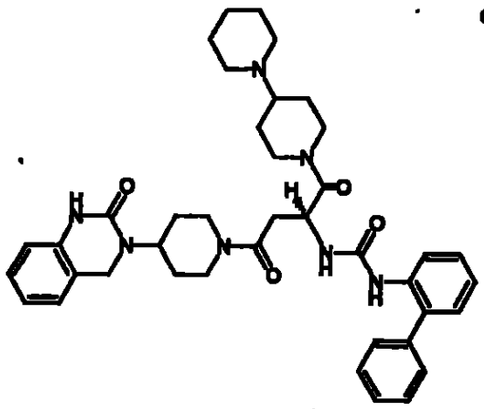
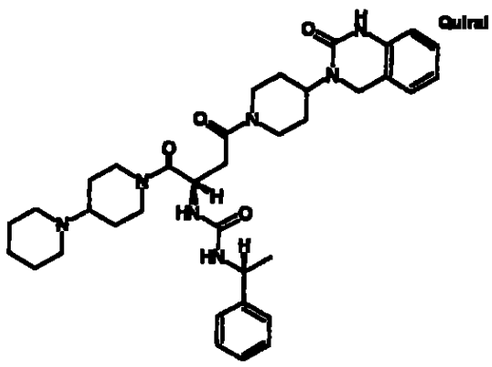
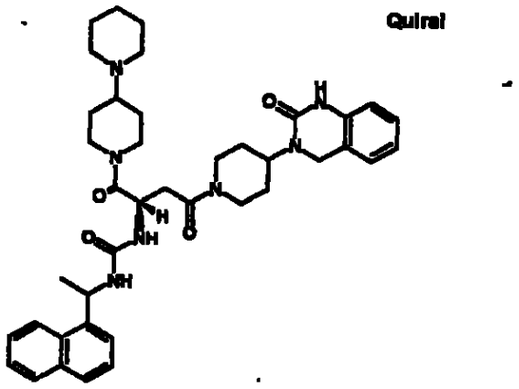
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 183 |  | 1.08 | 581.76 |
| 184 |  | 1.31 | 651.76 |
| 185 |  | 1.39 | 643.83 |
| 186 |  | 1.33 | 664.25 |

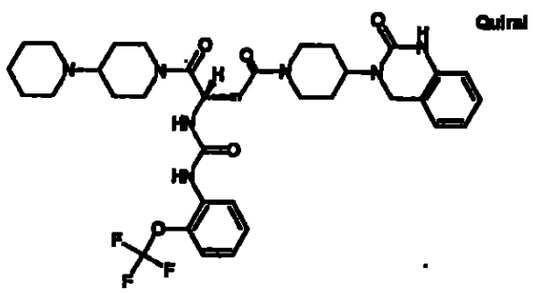
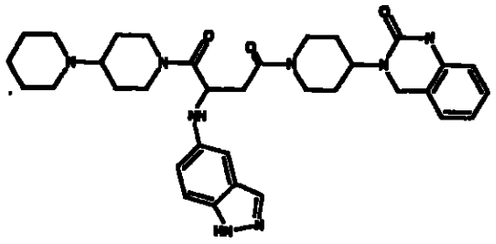
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 187 |  | 1.41 | 680.25 |
| 188 |  | 1.48 | 718.22 |
| 189 |  | 1.28 | 659.83 |
| 190 |  | 1.41 | 643.83 |

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 191 |  | 1.41 | 664.25 |
| 192 |  | 1.41 | 664.25 |
| 193 |  | 1.41 | 668.21 |

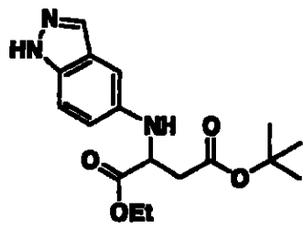
| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 194 |  | 1.45 | 708.71 |
| 195 |  | 1.39 | 647.8 |
| 196 |  | 1.27 | 673.82 |

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| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 197 |  | 1.45 | 691.88 |
| 198 |  | 1.26 | 643.83 |
| 199 |  | 1.45 | 693.89 |

| Ejemplo | Estructura | CLAR $t_R$ (min) | EM (M+) |
|---|---|---|---|
| 200 |  | 1.4 | 699.78 |
| 201 |  | 0.917 | 613.54 |

Éster 1-etílico del éster 4-*terc*-butílico 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 adicionó una

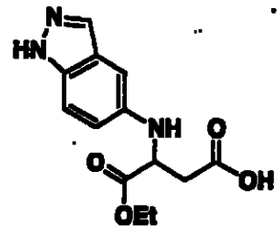
515

solución de glioxalato de etilo (aproximadamente 50% en tolueno, 1.7 mL, 1.1 equivalentes) en una porción seguido por sulfato de magnesio (4.6 g). La mezcla se agitó a temperatura ambiente durante toda la noche (23 horas) y luego se filtró y se concentró *in vacuo*. El producto intermedio de imina cruda, resultante (1.3 g, 6 mmol) se secó mediante la destilación azeotrópica con benceno anhidro y se secó adicionalmente bajo alto vacío. El residuo luego se disolvió en tetrahidrofurano (20 mL) y se enfrió a 0°C. Luego se adicionó lentamente una solución de cloruro de 2-*terc*-butoxi-2-oxoetilzinc (0.5 M en éter, 24 mL, 2 equivalentes). Después de la agitación a °C durante 1 hora, la mezcla se almacenó a 4°C durante toda la noche. La mezcla luego se diluyó con acetato de etilo y se enfrió rápidamente con una solución semisaturada de cloruro de amonio junto 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 una solución saturada de bicarbonato de sodio. La capa orgánica se secó sobre sulfato de sodio y se concentró in vacuo. El producto crudo se purificó mediante la cromatografía en columna con evaporación instantánea sobre gel de silice, eluyendo con metanol al 10% en cloruro de metileno, para proporciona el producto deseado (1.3 g,

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65%) como un aceite de color canela. RMN-$^1$H (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 Masas: 356.24 $(M+Na)^+$, 278.23 $(M-^tBu)^+$, $t_R$ = 1.287 minutos.

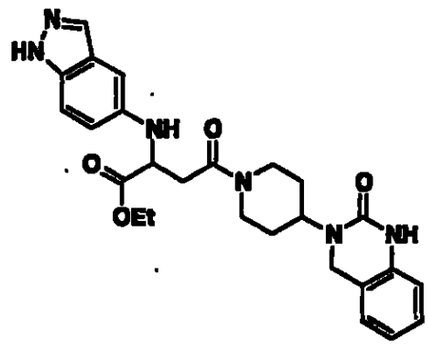
Éster etílico del ácido 2-(1H-indazol-5-ilamino)-succínico




Una solución agitada del éster 1-etílico del éster 4-terc-butílico 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 toda la noche. La mezcla de reacción luego se diluyó con acetato de etilo y se lavó con una solución saturada de cloruro de amonio, agua y salmuera. La capa orgánica se secó y se concentró para proporcionar un aceite de color verde oscuro: CL/EM: $t_R$ = 0.643 minutos, 278.19 $(MH)^+$.

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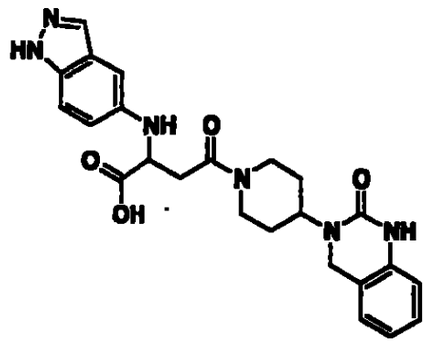
Éster 1-etílico del ácido 2-(1H-indazol-5-ilamino)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico



A una solución agitada del éster 1-etílico del ácido 2-(1H-indazol-5-ilamino)-succínico (84 mg, 0.215 mmol) en cloruro de metileno (1 mL) se adicionó la amina (99 mg, 0.429 mmol, 2 equivalentes) seguida por DEPBT (128 mg, 0.43 mmol, 2 equivalentes) y trietilamina (70 µL, 0.47 mmol, 2.2 equivalentes). La mezcla se agitó durante toda la noche y luego se diluyó con acetato de etilo y se lavó con una solución semisaturada de cloruro de amonio, agua y salmuera. La capa orgánica se secó y se concentró a un aceite de color canela. El producto crudo se purificó mediante la cromatografía en columna con evaporación instantánea sobre gel de sílice, eluyendo con metanol al 10% en cloruro de metileno, para proporcionar el producto deseado (36.2 mg, 34.5% para los dos pasos) como un aceite de color rojizo. RMN-$^1$H (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 minutos, 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

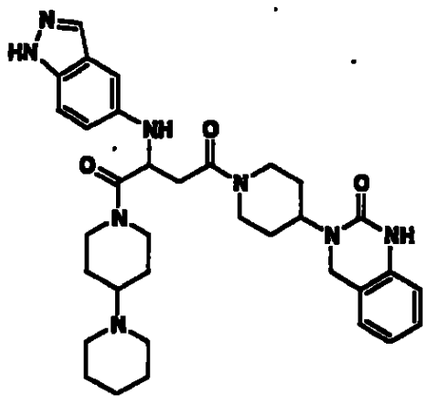


A una solución del éster etílico (34 mg, 0.069 mmol) en tetrahidrofurano (0.3 mL) se adicionó hidróxido de litio en agua (1 M, 280 µL, 4 equivalentes) y la mezcla se agitó a temperatura ambiente durante 17 horas. La solución se secó bajo una corriente de nitrógeno. Al residuo se adicionaron 0.2 mL de tetrahidrofurano y 0.2 mL de benceno anhidro y la suspensión se secó con soplado nuevamente con una corriente de nitrógeno. CL/EM: $t_R$ = 0.900 minutos, 463.30 $(MH)^+$.

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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

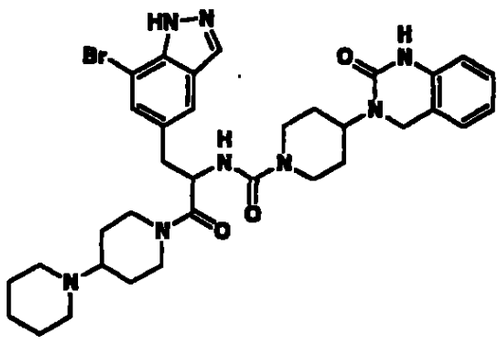


A una solución del éster etílico del ácido 2-(1H-indazol-5-ilamino)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico (0.069 mmol) en dimetilformamida (0.5 mL) en un frasquito cilíndrico, tapado se adicionó piperidinilpiperidina (14.3 mg, 0.076 mmol, 1.1 equivalentes), DEPBT (22.8 mg, 1.1 equivalentes) y trietilamina (8 gotas, aproximadamente 160 µL). La mezcla se agitó a temperatura ambiente durante toda la noche. El producto final se purificó mediante la CLAR preparativa para proporcionar el producto deseado (15 mg, 26% para los dos pasos) como un sólido de color canela. CL/EM: $t_R$ = 0.917 minutos, 613.54 $(MH)^+$.

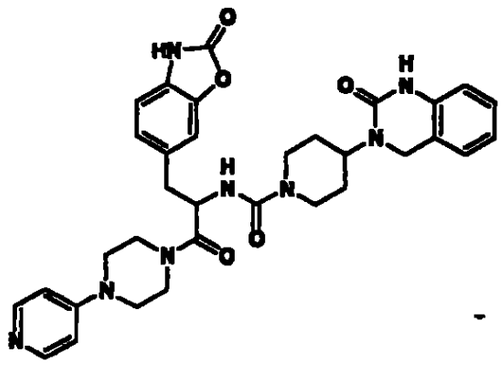
Entre otros compuestos contemplados dentro de la presente invención y que se pueden elaborar de acuerdo con la

descripción proporcionada en este texto o aquellos métodos conocidos para aquellas personas expertas en el campo incluyen los siguientes ejemplos proféticos:

[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

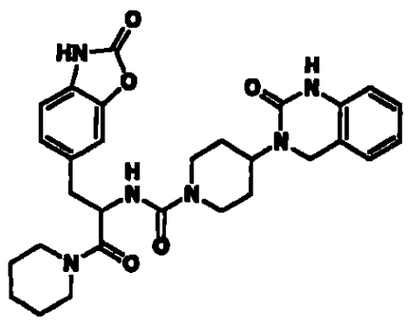


[2-Oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

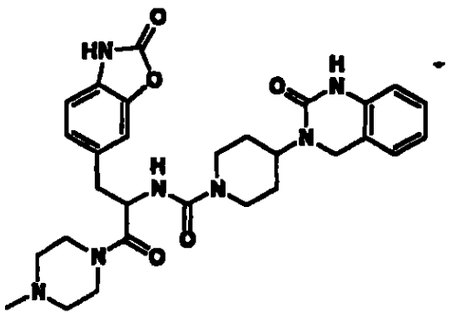


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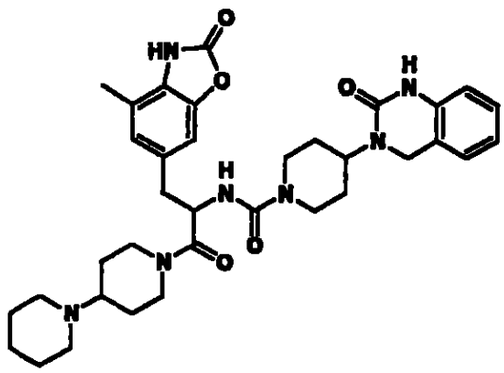
[2-Oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



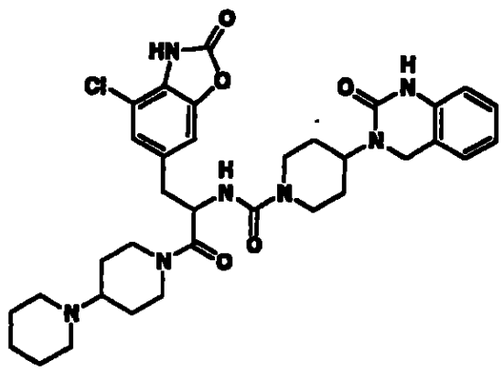
[2-(4-Metil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



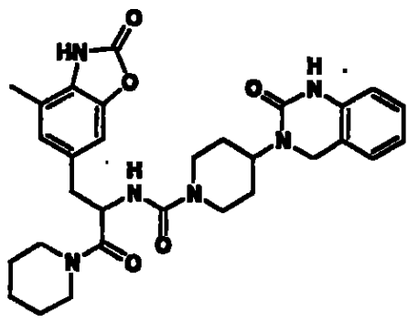
[2-[1,4']Bipiperidinil-1'-il-1-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



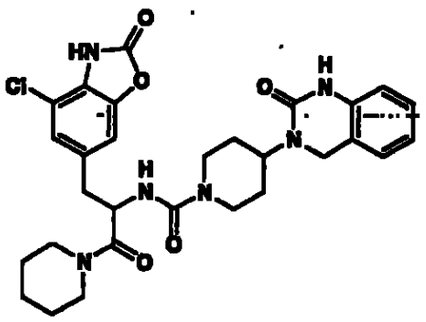
[2-[1,4']Bipiperidinil-1'-il-1-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



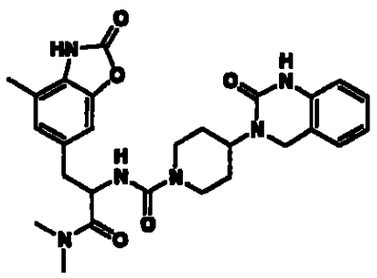
[1-(4-Metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



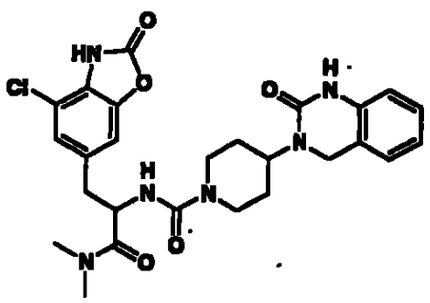
[1-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



[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

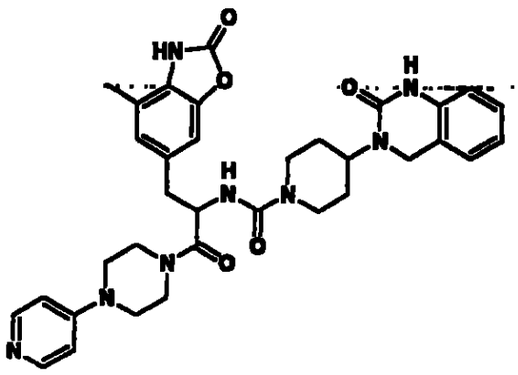


[2-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-1-dimetilcarbamoil-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

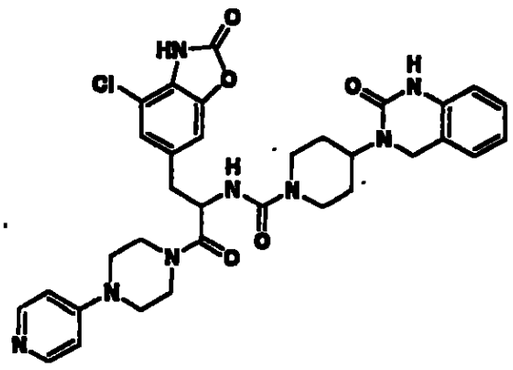


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[1-(4-Metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

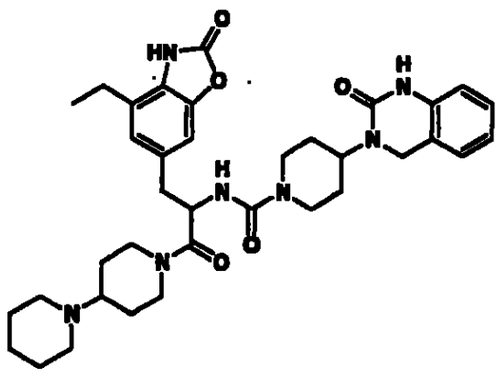


[1-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

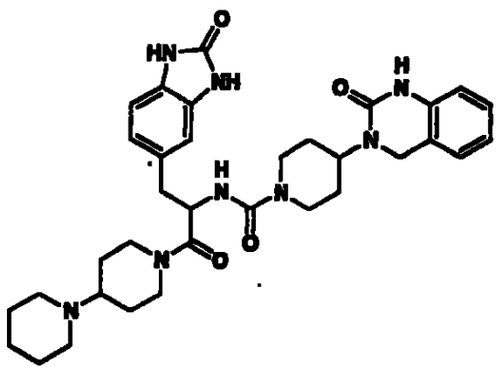


[2-[1,4']Bipiperidinil-1'-il-1-(4-etil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

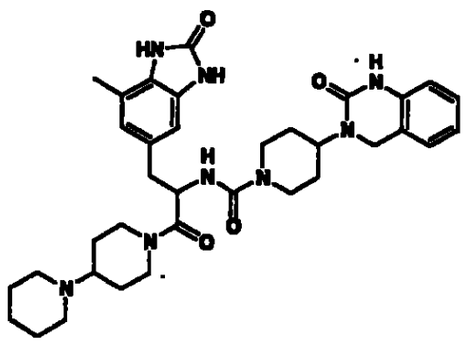
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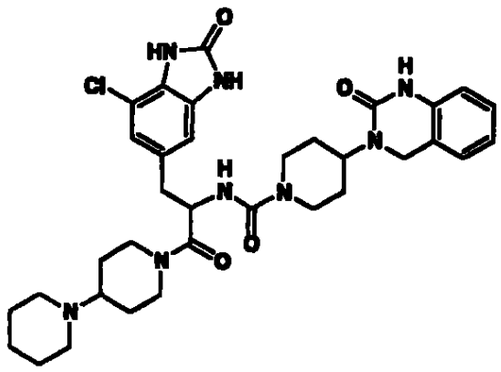
[2-[1,4']Bipiperidinil-1'-il-2-oxo-1-(2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



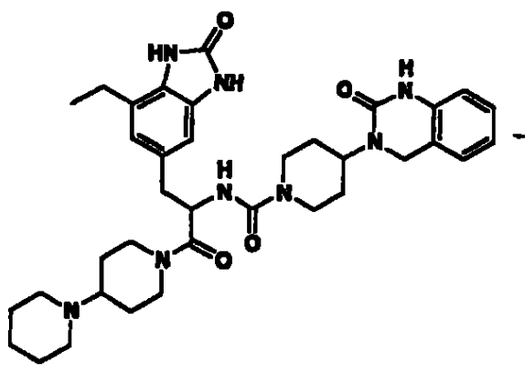
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[2-[1,4']Bipiperidinil-1'-il-1-(7-cloro-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

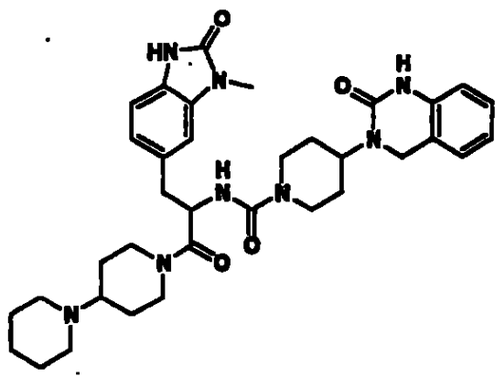


[2-[1,4']Bipiperidinil-1'-il-1-(7-etil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

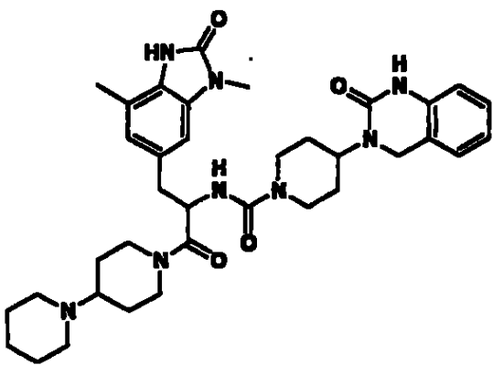


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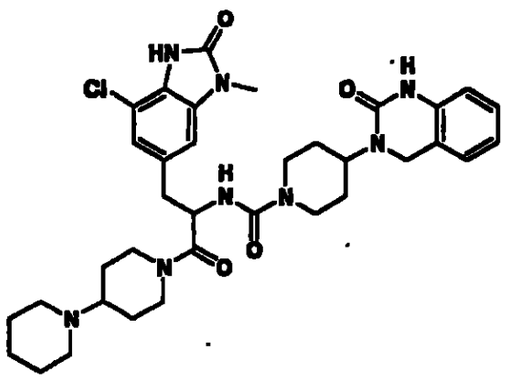
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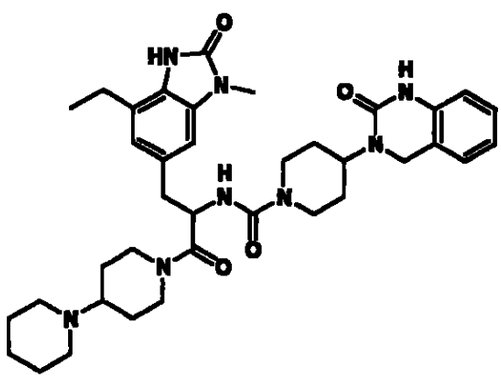
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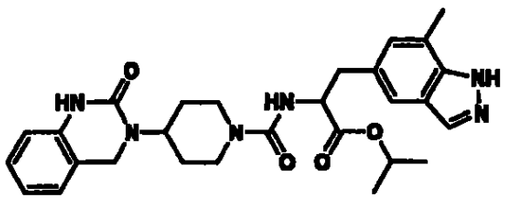
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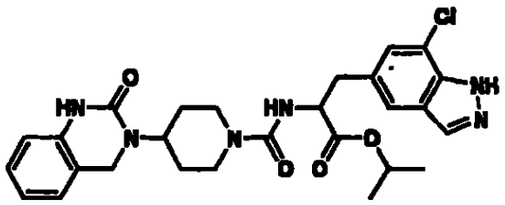
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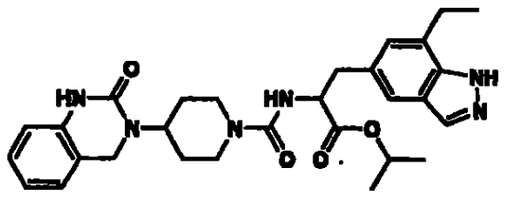
Éster isopropílico del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



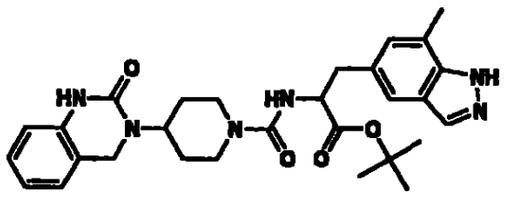
Éster isopropílico del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



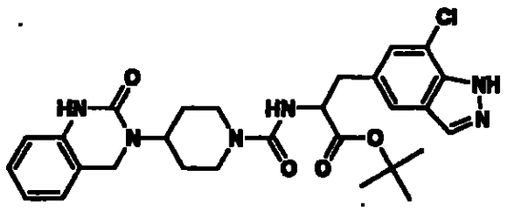
Éster isopropílico del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



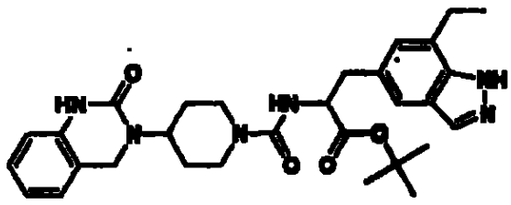
Éster terc-butílico del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-imino}-propiónico



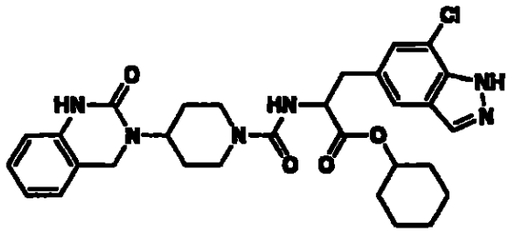
Éster terc-butílico del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Éster terc-butílico 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

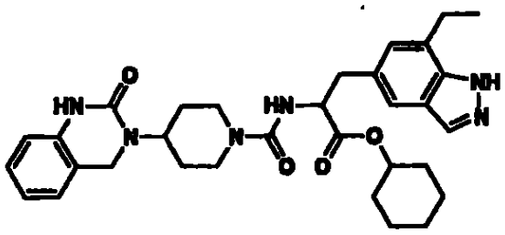


Éster ciclohexílico del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

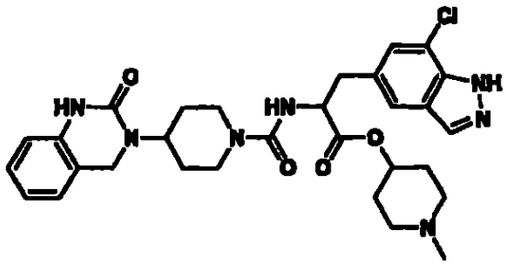


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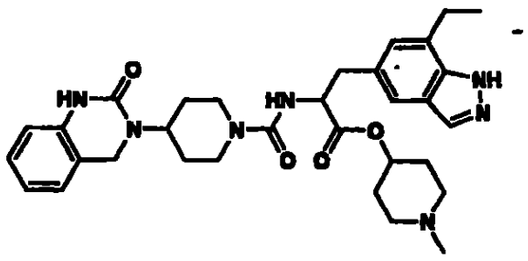
531



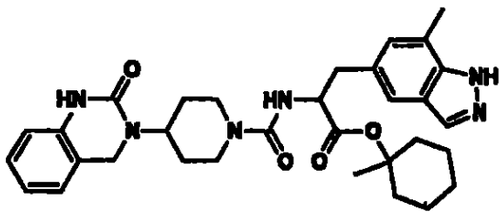
Éster 1-metil-piperidin-4-ílico del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



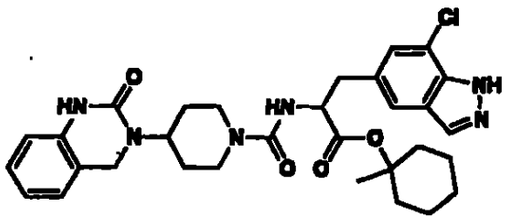
Éster 1-metil-piperidin-4-ílico del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



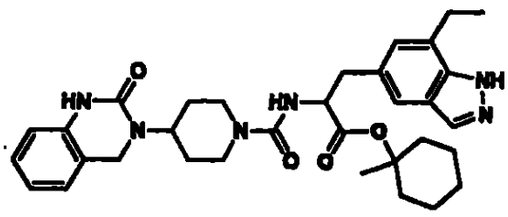
Éster 1-metil-ciclohexílico del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



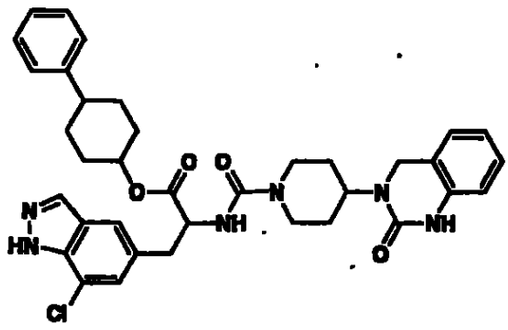
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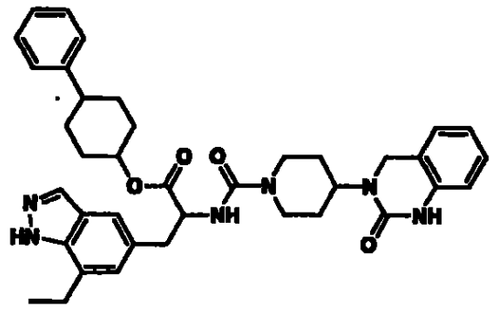
Éster 1-metil-ciclohexílico del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Éster 4-fenil-ciclohexílico 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 4-fenil-ciclohexílico 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 Unión de CGRP

*Cultivo de Tejido.* Las células SK-N-MC se desarrollaron a 37°C en $CO_2$ al 5% como una monocapa en un medio que consistía de MEM con sales de Earle y L-glutamina (Gibco) complementado con suero bovino fetal al 10% (Gibco).

*Pelotillas de Células.* Las células se enjuagaron dos veces con solución salina amortiguada con fosfato (NaCl 155 mM, $Na_2HPO_4$ 3.3 mM, $KH_2PO_4$ 1.1 mM, pH 7.4) y se incubaron

durante 5-10 minutos a 4°C en amortiguador de lisis hipotónico que consistía de Tris 10 mM (pH 7.4) y EDTA 5 mM. Las células se transfirieron de las placas a tubos de polipropileno (16 x 100 mm) y se homogenizaron utilizando un dispositivo polytron. Los homogenados se centrifugaron a 32,000 x g durante 30 minutos. Las pelotillas se resuspendieron en amortiguador de lisis hipotónico, frío con un cóctel inhibidor de proteasa de mamífero al 0.1% (Sigma) y se sometieron a ensayo para la concentración de proteína. El homogenado de SK-N-MC luego se prorrateó y se almacenó a -80°C hasta que fue necesario.

*Ensayo de Unión de Radioligandos*. Los compuestos de la invención se solubilizaron y se llevaron a través de diluciones en serie utilizando DMSO al 100%. Las alícuotas de las diluciones en serie de los compuestos se diluyeron adicionalmente 25 veces en el amortiguador de ensayo (Tris-Cl 50 mM pH 7.5, $MgCl_2$ 5 mM, Triton X-100 0.005%) y se transfirieron (volumen de 50 µl) dentro de placas de ensayo de 96 pocillos. El [$^{125}$I]-CGRP (Amersham Biosciences) se diluyó a 60 pM en amortiguador de ensayo y se adicionó un volumen de 50 µl a cada pocillo. Las pelotillas de SK-N-MC se descongelaron, se diluyeron en amortiguador de ensayo con un cóctel inhibidor de proteasa de mamífero al 0.1% reciente (Sigma) y se homogenizaron nuevamente. El homogenado de SK-N-

MC (5 µg/pocillo) se adicionó en un volumen de 100 µl. Las placas de ensayo luego se incubaron a temperatura ambiente durante dos horas. Los ensayos se detuvieron por la adición de un amortiguador de lavado, frío en exceso (Tris-Cl 20 mM pH 7.5, BSA al 0.1%) seguido inmediatamente por la filtración a través de filtros de fibra de vidrio (Whatman GF/B) remojados previamente en PEI al 0.5%. La unión no especificada se definió con beta-CGRP 1 µM. La radioactividad unida a la proteína se determinó utilizando un contador gamma o de centelleo. El valor $IC_{50}$ se definió como la concentración de un compuesto de la invención requerida para desplazar 50% de la unión de radioligando.

En la tabla posterior, los resultados se indican como se sigue: A $\leq$ 10 nM; 10 nM $\leq$ B $\leq$ 100 nM; 100 nM < C $\leq$ 1000 nM; D > 1000 nM.

Tabla 4. Datos de Unión de CGRP, Función de cAMP y Arteria Cerebral Humana Ex Vivo

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 1 | C | * | * |
| 2 | A | A | A |

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| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 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 | * |

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 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 | * |
| 37 | A | B | * |
| 38 | B | B | * |
| 39 | C | C | * |
| 40a | A | A | * |
| 40b | B | * | * |
| 40c | D | * | * |
| 40d | C | * | * |
| 40e | D | * | * |
| 40f | D | * | * |
| 40g | D | * | * |

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| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 40h | D | * | * |
| 40i | B | * | * |
| 40j | D | * | * |
| 40k | D | * | * |
| 41a | B | * | * |
| 41b | A | * | * |
| 41c | A | * | * |
| 41d | B | * | * |
| 41e | A | * | * |
| 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 | * | * |

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 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 |
| 71 | A | A | A |
| 72 | A | A | A |
| 73 | B | B | * |
| 74 | A | A | A |
| 75 | A | B | * |

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 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 | * | * |

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 98 | D | * | * |
| 99 | D | D | * |
| 100 | C | * | * |
| 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 | * | * |

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 120 | C | * | * |
| 121 | C | * | * |
| 122 | C | * | * |
| 123 | B | * | * |
| 124 | C | * | * |
| 125 | C | * | * |
| 126 | C | * | * |
| 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 | * | * |

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 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 | * | * |
| 161 | B | * | * |
| 162 | C | * | * |
| 163 | C | * | * |

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 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 | * | * |

| Ejemplo # | Unión de CGRP[1] $IC_{50}$ (nM) | Función de cAMP[2] $IC_{50}$ (nM) | Arteria Cerebral[3] $EC_{50}$ (nM) |
|---|---|---|---|
| 186 | C | * | * |
| 187 | C | * | * |
| 188 | C | * | * |
| 189 | C | * | * |
| 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 de AMP Cíclico

*Antagonismo Funcional*. El antagonismo de los compuestos de la invención se determinó al medir la formación de AMP cíclico (3'5'-monofosfato de adenosina cíclico) en células SK-N-MC que expresan de manera endógena el receptor de CGRP de

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humano. El complejo deL receptor de CGRP es acoplado con la proteína Gs y la unión de CGRP a este complejo conduce a la producción de AMP cíclico por medio de la activación dependiente de Gs de una adenilato-ciclasa (Juaneda C y colaboradores, TiPS, 2000; 21:432-438; incorporada en este texto a manera de referencia). Consecuentemente, los antagonistas de receptores de CGRP inhiben la formación de AMP cíclico inducida por CGRP en células SK-N-MC (Doods H y colaboradores, Br J Pharmacol, 2000; 129(3):420-423); incorporada en este texto a manera de referencia). Para las mediciones de AMP cíclico, las células SK-N-MC se incubaron con CGRP 0.3 nM solo o en presencia de varias concentraciones de los compuestos de la invención durante 30 minutos a temperatura ambiente. Los compuestos de la invención se incubaron previamente con las células SK-N-MC durante 15 minutos antes de la adición de CGRP para permitir la ocupación del receptor (Edvinsson y colaboradores, Eur J Pharmacol, 2001, 415:39-44; incorporada en este texto a manera de referencia). El AMP cíclico se extrajo utilizando el reactivo de lisis y su concentración de se determinó por medio de un radioinmunoensayo utilizando el Equipo de Ensayo de Examen Directo SPA de cAMP RPA559 (Amersham Pharmacia Biotech). Los valores $IC_{50}$ se calcularon utilizando un ajuste de Excel[MR]. Se determinó que los compuestos sometidos a prueba de la invención eran antagonistas ya que exhibieron

una inhibición dependiente de la dosis de la producción de AMP cíclico inducida por CGRP. Véase la tabla 3 para un resumen de los resultados.

*Análisis Schild.* El análisis Schild se puede utilizar para caracterizar la naturaleza del antagonismo de los compuestos de la invención. La respuesta a la dosis de la producción de cAMP estimulada por CGRP se generó ya sea con CGRP solo o en presencia de varias concentraciones de los compuestos de la invención. La dosis de antagonista se colocó en el diagrama como X contra relación de dosis (definida como valor $IC_{50}$ de agonista con la presencia de los compuestos dividido por el valor $IC_{50}$ del agonista solo) menos 1 como Y. La regresión lineal luego se realizó con tanto el eje X como Y transformados logaritmicamente. Una pendiente que no difiere significantemente de la unidad (1) indica un antagonismo competitivo. $K_b$ es la constante de disociación del antagonista.

Tabla 5. Análisis Schild

| Ejemplo # | $K_b$(nM) | pendiente |
|---|---|---|
| 2 | 0.16 | 0.94 |
| 3 | 55 | 0.96 |
| 5 | 3 | 0.92 |
| 6 | 0.36 | 0.93 |

| Ejemplo # | $K_b$(nM) | pendiente |
|---|---|---|
| 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 |

Véase la figura 1. Análisis Schild.

Ensayo de Arteria Cerebral de Humano Ex Vivo

*Razón Fundamental y Compendio*. Para la evidencia directa, proporcionada de la capacidad de los compuestos novedosos para invertir la dilatación inducida por CGRP en los vasos cerebrales de humano, se diseño un ensayo ex vivo. En resumen, los anillos de vasos aislados se montaron en un baño de tejido donde los vasos se contrajeron previamente con cloruro de potasio (KCl) y se dilataron completamente con hCGRP, luego esta relajación se invirtió por la adición cumulativa de antagonistas de receptores de CGRP (enseguida se encuentran los detalles completos).

*Muestras de Tejido*. Las muestras de autopsia de arterias de humano se obtuvieron de vendedores (ABS Inc. o NDRI). Todos los vasos se transportaron en amortiguador HEPES enfriado con hielo (composición en mM: NaCl 130, KCl 4, KH2PO4 1.2, MgSO4 1.2, CaCl2 1.8, Glucosa 6, NaHCO3 4, HEPES 10, EDTA 0.025). Con la recepción, los vasos se colocaron en un amortiguador frío de Kreb (composición en mM: NaCl 118.4, KCl 4.7, KH2PO4 1.2, MgSO4 1.2, CaCl2 1.8, Glucosa 10.1, NaHCO3 25) saturado con carbógeno (CO2 al 5% y oxígeno al 95%).

*Baños de Tejido Aislado*. Los vasos se limpiaron de tejido conectivo y se cortaron en segmentos cilíndricos de 4-5 mm de longitud. Los vasos luego se montaron en baños de tejido entre dos ganchos de acero inoxidable; uno de los cuales está fijo y el otro de los cuales está conectado a un transductor de desplazamiento de fuerza. La tensión a los vasos se registró continuamente utilizando un sistema de adquisición de datos (Powerlab, ADInstruments, Mountain View, CA) conectado al transductor. Los baños de tejido que contenían amortiguador de Krebs y los vasos montados se controlaron en cuanto a la temperatura (37°C) y pH (7.4) con ebullición continua de carbógeno. Los segmentos de arterias se dejaron equilibrar durante aproximadamente 30-45 minutos hasta que se alcanzó un aspecto de reposo estable. Antes del ensayo, los vasos se cebaron (acondicionaron) con KCl 100 mM y se lavaron

subsecuentemente. Los vasos se contrajeron previamente con KCl 10 mM y de dilataron completamente con HCGRP 1 nM. Las curvas de respuesta a la concentración para los antagonistas de receptores de CGRP se realizaron por medio de la adición. Acumulativa de fármacos en unidades casi logarítmicas en vasos completamente dilatados. En cada concentración los efectos los fármacos se expresaron como % inverso de relajación inducida por CGRP en cada vaso. El ensayo real y el análisis de datos se realizaron para cada vaso individual, ajustando los datos de respuesta a la concentración a una función logística de cuatro parámetros mediante el análisis de regresión no lineal, para estimar los valores $EC_{50}$. Un resumen de los resultados se proporciona en la tabla 3.

Método no Terminal para Valorar la Eficacia In Vivo de Antagonistas de Receptores de CGRP de Molécula Pequeña en Mamíferos

*Resumen*. El bloqueo de la dilatación de arterias cerebrales inducida por el péptido relacionado con el gen de calcitonina (CGRP) ha sido propuesto como un tratamiento para el dolor de cabeza por migraña, sin embargo, los antagonistas de receptores de CGRP de molécula pequeña novedosos han mostrados diferencias específicas para las especies con una actividad relativamente pobre en roedores. (Mallee y colaboradores, J Biol Chem 2002 277:14294) lo que requiere

nuevos modelos para la valoración de la eficacia *in vivo*. Los primates no humanos (por ejemplo, titis) son los únicos animales conocidos que tienen farmacología de receptores de CGRP similares a los humanos conferida por la presencia del residuo de aminoácido específico (Trp74) en su secuencia de RAMP1 que es responsable del fenotipo del receptor humano (Mallee y colaboradores, J Biol Chem 2002 277:14294). Puesto que los modelos de migraña actuales utilizan principalmente ratas (Escott y colaboradores, Brain Res 1995 669:93; Williamson y colaboradores, Cephalalgia 1997 17:525) o son procedimientos terminales, invasivos en primates (Doods y colaboradores, Br J Pharmacol 2000 129:420), un modelo de supervivencia, no invasivo, novedoso en primates no humanos para la valoración de la eficacia *in vivo* de los antagonistas de receptores de CGRP como en la presente invención es una contribución significante. Mientras que se sabe que la activación trigeminal incrementa el flujo sanguíneo tanto cerebral (Goadsby & Edvinsson, 1993) como facial (Doods y colaboradores, 2000), la demostración de una relación directa entre el flujo sanguíneo facial y la dilatación de arterias cerebrales conducida en los mismos animales no fue conocida. Por lo tanto, antes de iniciar los estudios en primates no humanos, una medición con la técnica Laser Doppler del flujo sanguíneo facial se validó directamente en la rata como un sustituto para la dilatación de arterias cerebrales en

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estudios terminales que midió tanto el diámetro de arterias cerebrales como los cambios en el flujo sanguíneo facial en los mismos animales (véase figura 2. Validación Directa del Flujo Sanguíneo Facial como Sustituto para la Dilatación de Arterias Cerebrales en Ratas). En ambas mediciones, se indujeron incrementos comparables por el CGRP i.v. y se bloquearon por el antagonista peptídico de hαCGRP(8-37). Después, el método de los cambios inducidos por CGRP i.v. en el flujo sanguíneo facial se validó 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 se completó un estudio de respuesta a la dosis que caracteriza la actividad de CGRP i.v. (véase la figura 3. Respuesta a la Dosis para hαCGRP en el Flujo Sanguíneo Facial con la técnica Laser Doppler en Primates no Humanos). Los antagonistas de receptores de CGRP peptídicos y de molécula pequeña se utilizaron para validar el modelo de primates no humanos. El tratamiento previo con antagonistas de molécula pequeña o hαCGRP(8-37) inhibió de manera dependiente de la dosis los incrementos estimulados por CGRP i.v. en el flujo sanguíneo facial de primates (véase la figura 4. Inhibición de Cambios Inducidos por CGRP en el Flujo Sanguíneo Facial de Primates no Humanos), sin alterar la presión sanguínea (véase la figura 5. Efecto del antagonista de CGRP sobre la Presión Sanguínea de Primates no

Humanos). El tratamiento posterior de antagonistas también invirtió los incrementos inducidos por CGRP en el flujo sanguíneo facial (no mostrado). Este modelo de supervivencia proporciona un nuevo procedimiento de recuperación no invasivo para evaluar los efectos profilácticos y abortivos de los antagonistas de receptores de CGRP en primates no humanos o en animales transgénicos con RAMP1 humanizada (Trp74) que tienen farmacología de receptores de CGRP similar, como un marcador sustituto para la actividad en el diámetro de vasos cerebrales.

*Animales*. Los titís comunes tanto machos como hembras, adultos (Callithrix jacchus) adquiridos de Harlan y que pesaban 350-550 g sirvieron como sujetos. Otros mamíferos que expresan de manera endógena la RAMP1 que tiene Trp 74 o mamíferos transgénicos con RAMP1 humanizada que tienen Trp 74 también se pueden emplear en el método descrito en este texto.

*Anestesia y Preparación Quirúrgica*. Los animales se anestesiaron mediante la inhalación de isoflurano en una cámara de inducción (inducción 4-5% rápida, mantenida con 1-2.5%; Solomon y colaboradores, 1999). La anestesia se mantuvo mediante el suministro constante de aire:oxígeno (50:50) e isoflurano por medio de una mascara facial o por medio de la

intubación y ventilación (con el monitoreo de gas sanguíneo). La temperatura corporal se mantiene a 38 ± 0.5°C mediante la colocación en una superficie de temperatura controlada automatizada con una sonda rectal. Se remueve un área pequeña de pelaje (aproximadamente 1.5 $cm^2$) de uno o ambos lados de la cara mediante la aplicación de una crema depilatoria y/o afeitada. Las áreas quirúrgicas se sujetan y se preparan con betadina. Una línea i.v. se coloca en cualquier vena accesible para la administración de los compuestos de prueba y el antagonista de receptores de CGRP y, si es necesario, el retiro de muestras sanguíneas (máximo 2.5 ml, 10%) para el monitoreo de gas sanguíneo y el análisis de contenido. Una solución de dextrosa al 5% se administra i.v. a fin de mantener los niveles de glucosa en la sangre. La profundidad de la anestesia se monitorea al medir la presión sanguínea y la frecuencia cardiaca utilizando un método de esfigmomanómetro no invasivo y un oxímetro de pulso, respectivamente. Se puede proporcionar guanetidina 5-10 mg/kg i.v., complementada con 5 mg/kg i.v. como sea necesario, para estabilizar el flujo pico en el flujo sanguíneo facial observado con los cambios inducidos por la estimulación repetida en el flujo sanguíneo (Escott y colaboradores, 1999; incorporada en este texto a manera de referencia). El flujo sanguíneo microvascular se monitorea al unir una sonda de flujo de la técnica Laser Doppler autoadhesiva a la piel

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facial.

*Administración de los Compuestos*. Los compuestos de prueba se pueden administrar i.v. (0.01-5 ml/kg), i.m. (0.01-0.5 ml/kg), s.c. (0.01-5 ml/kg) o p.o. (0.1-10 ml/kg) (Diehl y colaboradores, 2001; incorporada en este texto a manera de referencia). Los antagonistas de receptores de CGRP pueden administrarse i.v. (0.01-5 ml/kg), i.d. (10-100 µl/sitio) o s.c. (10-100 µl/sitio).

*Flujometría Laser Doppler*. Un incremento de control en el flujo sanguíneo facial es inducido 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 es administrado ya sea antes (tratamiento previo) o después (tratamiento posterior) de la administración repetida, subsecuente del agente vasodilatador para proporcionar la capacidad para valorar las acciones profilácticas o terapéuticas. La presión sanguínea es monitoreada continuamente para asegurar una profundidad adecuada de la anestesia y el agente anestésico se ajusta para mantener niveles estables que sean iguales a los valores del tratamiento previo. Durante la colección de los datos de flujometría Laser Doppler, se puede reducir el isoflurano a

0.25-0.75% ya que los estudios electrofisiológicos previos en titis descubrieron que los registros fueron sensibles a la concentración de isoflurano (Solomon, 1999; incorporada en este texto a manera de referencia). Para reducir el número de animales utilizados, el efecto del compuesto de prueba en los cambios inducidos por vasodilatores i.v. en el flujo sanguíneo se puede repetir hasta 6 veces en una sola sesión.

*Recuperación*. Los animales se regresaron a la jaula de transporte, la cual está colocada sobre una superficie de temperatura controlada para mantener calientes los animales hasta que despierten completamente y deambulen. Los animales se pueden someter a prueba nuevamente después de 7-14 días de descanso y se pueden someter a prueba de manera repetida en intervalos de 7-14 días dependiendo de la salud del animal.

*Véase*, Diehl KH, Hull R, Morton D, Pfister R, Rabemampianina Y, Smith D, Vidal JM, van de Vorstenbosch C. Una buena guía práctica para la administración de sustancias y la remoción de sangre, que incluye rutas y volúmenes. J Appl Toxicol. Enero-Febrero de 2001; 21(1):15-23; Doods H, Hallermayer G, Wu D, Entzeroth M, Rudolf K, Engel W, Eberlein W. Pharmacological profile of BIBN4096BS, el primer antagonista de receptores de CGRP de molécula pequeña, selectivo. Br J Pharmacol. Febrero de 2000; 129(3):420-3; Edvinsson L. Péptido relacionado con el gen de calcitonina

(CGRP) y la patofisiología del dolor de cabeza: implicaciones terapéuticas. CNS Drugs 2001; 15(10):745-53; Escott KJ, Beattie DT, Connor HE, Brain SD. La estimulación de ganglios, trigeminales incrementa el flujo sanguíneo de la piel facial en la rata: un papel principal del péptido relacionado con el gen de calcitonina. Brain Res. 9 de Enero de 1995; 669(1):93-9; Goadsby PJ, Edvinsson L. El sistema trigeminovascular y la migraña: estudios que caracterizan los cambios cerebrovasculares y neuropeptídicos observados en humanos y gatos. Ann Neurol. Enero de 1993; 33(1):48-56; Lassen 1H, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olsen J. El CGRP puede jugar un papel causante en la migraña. Cephalalgia, 2002, 22, 54-61; Mallee JJ, Salvatore CA, LeBourdelles B, Oliver KR, Longmore J, Koblan KS, Kane SA. La RAMP1 determina la selectividad de especies de los antagonistas de receptores de CGRP no peptídicos. J Biol Chem. 14 de Febrero de 2002 [epub ahead of print]; Solomon SG, White AJ, Martin PR. La sensibilidad de contraste temporal en el núcleo geniculado, lateral de un mono de Nuevo mundo, el titi Callithrix jacchus. J Physiol. 15 de Junio de 1999;517 (Pt 3): 907-17; todas incorporadas a manera de referencia en este texto.

*Desviaciones de Otros Modelos de Migraña*. Esta invención representa un modelo novedoso de migraña y es remarcadamente distinto de otros modelos de migraña. Algunas

de las características distintivas del método de la presente invención incluyen: (i) el único modelo de supervivencia de migraña en cualquier especie; (ii) el único modelo para demostrar los efectos abortivos (tratamiento posterior) de antagonistas de CGRP sobre incrementos inducidos, activos en el flujo sanguíneo; (iii) la única demostración de una relación directa entre el flujo sanguíneo facial y la dilatación de arterias intracraniales llevada a cabo en los mismos animales; (iv) el único modelo para utilizar técnicas quirúrgicas no invasivas y no requiere colocación de catéter, intubación o bloqueo neuromuscular; (v) el único modelo en primates para utilizar CGRP exógeno como el estímulo y demostrar el bloqueo de tratamiento previo por el antagonista de CGRP y la reversión posterior al tratamiento por el antagonista de CGRP; (vi) el único modelo de migraña para utilizar anestesia de isoflurano en animales que respiran espontáneamente. En los modelos descritos en Williamson y colaboradores, el Sumatriptan inhibe la vasodilatación neurogénica de vasos sanguíneos durales en estudios en microscopio vitales en ratas anestesiadas. Cephalalgia. Junio de 1997 Jun; 17(4):525-31; Williamson DJ, Hargreaves RJ, Hill RG, Shepheard SL. Los estudios en microscopio vitales sobre los efectos de agonistas neuroquímicos y el péptido relacionado con el gen de calcitonina sobre el diámetro de vasos durales en ratas anestesiadas. Cephalalgia.

Junio de 1997; 17(4):518-24; Escott KJ y colaboradores, la estimulación de ganglios trigenimales incrementa el flujo sanguíneo de la piel facial en ratas: un papel principal para el péptido relacionado con el gen de calcitonina. Brain Res. 9 de Enero de 1995; 669(1):93-9; Chu DQ y colaboradores, el antagonista de péptidos relacionados con el gen de calcitonina (CGRP) CGRP(8-37) bloquea la vasodilatación en la piel inflamada de rata: involucramiento de la adrenomedulina además de CGRP. Neurosci Lett. 14de Septiembre de 2001; 310(2-3):169-72; Escott KJ, Brain SD. Efecto de un antagonista de péptidos relacionados con el gen de calcitonina (CGRP8-37) sobre la vasodilatación de la piel o edema inducido por la estimulación del nervio safeno de rata. Br J Pharmacol. Octubre de 1993; 110(2):772-6; Hall JM, Siney L, Lippton H, Hyman A, Kang-Chang J, Brain SD. Interacción de adrenomedulina 13-52 de humano con receptores de péptidos relacionados con el gen de calcitonina en la microvasculatura de rata y hámster. Br J Pharmacol. Febrero de 1995; 114(3):592-7; Hall JM, Brain SD. Interacción de amilina con receptores de péptidos relacionados con el gen de calcitonina en la microvasculatura del saco de mejilla de hámster *in vivo*. Br J Pharmacol. Enero de 1999; 126(1): 280-4; y Doods H, Hallermayer G, Wu D, Entzeroth M, Rudolf K, Engel W, Eberlein W. Perfil farmacológico de BIBN4096BS, el primer antagonista de receptores de CGRP de molécula pequeña,

selectivo. Br J Pharmacol. Febrero de 2000; 129(3):420-1 fallan en poseer las características remarcables del método de la presente invención.

En la siguiente tabla, los resultados se indican como sigue: W $\leq$ 25%; 25% < X $\leq$ 50%; 50% < Y $\leq$ 75%; Z > 75%.

Tabla 6. Inhibición del Incremento Inducido por CGRP en el Flujo Sanguíneo Facial con la Técnica Laser Doppler en Primate no Humano (por ejemplo, Titi Común)

| | Primate no Humano (% de Inhibición) de incremento inducido por CGRP (10 μg/kg, iv) en el flujo sanguíneo facial con la técnica Laser Doppler | | | | |
|---|---|---|---|---|---|
| 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 $\leq$ 25%; 25% < X $\leq$ 50%; 50% < Y $\leq$ 75%; Z > 75%. | | | | |

Véase la figura 5. Efecto del Antagonista de CGRP

Sobre la Presión Sanguínea en Primates no Humanos.

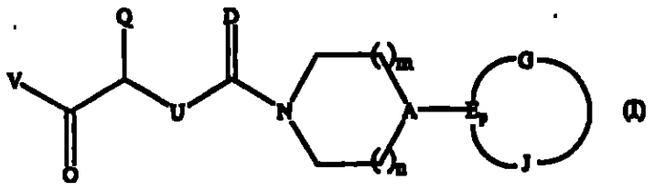
Se hace constar que con relación a esta fecha, el mejor método conocido por la solicitante para llevar a la práctica la citada invención, es el que resulta claro de la presente descripción de la invención.

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**REIVINDICACIONES**

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes reivindicaciones:

1. Un compuesto de conformidad con la fórmula (I)



o una sal o solvato farmacéuticamente aceptable del mismo caracterizado porque

V es $-N(R^1)(R^2)$ u $OR^4$;

$R^4$ es H, alquilo de 1 a 6 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono o $(alquileno\text{-}C_1\text{-}C_4)_{0\text{-}1}R^{4'}$

$R^{4'}$ es cicloalquilo de 3 a 7 átomos de carbono, 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 sustituido opcionalmente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de halo, ciano, alquilo de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, hidroxi, amino, cicloalquilo de 3 a 7 átomos de carbono, alquilamino de 1 a 3 átomos de carbono, dialquilamino de 1 a 3 átomos de carbono, (alquil-$C_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo; y

$R^{4'}$ contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del 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 de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de

carbono, alquinilo de 2 a 6 átomos de carbono, -alquilen-$C_1$-$C_6$-amino(alquilo-$C_1$-$C_3$)$_2$, cicloalquilo de 3 a 7 átomos de carbono, 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 sustituidos cada uno opcional e independientemente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de halo, ciano, alquilo de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, hidroxi, amino, cicloalquilo de 3 a 7 átomos de carbono, alquilamino de 1 a 3 átomos

de carbono, dialquilamino 1 a 3 átomos de carbono, (alquilo-$G_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo;

$R^1$ y $R^2$ contienen opcional e independientemente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los heterociclos que comprenden $R^1$ y $R^2$;

en donde $L^1$ es interrumpido opcional e independientemente del átomo de nitrógeno al cual está unido por $L^2$, en donde $L^2$ es independientemente alquileno de 1 a 3 átomos de carbono o alquilideno de 1 a 3 átomos de carbono; o

$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es azetidinilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piperazinilo, piperidinilo, morfolino o tiomorfolino;

en donde X es sustituido opcionalmente por

Y, en donde Y es dioxolanilo, alquilo de 1 a 9 átomos de carbono, alquenilo de 2 a 9 átomos de carbono, alquinilo de 2 a 9 átomos de carbono, alquilamino de 1 a 4 átomos de carbono, dialquilamino de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, fenilo, azetidinilo, furanilo, tienilo, pirrolilo, pirrolinilo, pirrolidinilo, pirrolidinonilo, imidazolilo, imidazolinilo, imidazolidinilo, imidazolidinonilo, pirazolilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piridilo, pirimidinilo, dihidrobencimidazolonilo, piperazinilo, piperidinilo, morfolino, benzotiazolilo, bencisotiazolilo o tiomorfolino;

y en donde X e Y son interrumpidos opcionalmente por Z, en donde Z es -NHC(O)O-, -NHC(O)NH-, NC(O)$NH_2$, -NH-,

-alquileno- de 1 a 3 átomos de carbono, -alquileno- de 1 a 3 átomos de carbono, alquenilen-$C_1$-$C_3$-NHC(O)O-alquileno de 1 a 3 átomos de carbono; y

sustituidos opcional e independientemente por 1 o 2 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de alquilo de 1 a 4 átomos de carbono, amino, alquilamino de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_6$-amino (alquilo-$C_1$-$C_3$)$_2$, (alquil-$C_1$-$C_3$)$_{0-2}$ureido, fenilo y bencilo;

X e Y contienen opcional e independientemente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los heterociclos que comprenden X e Y;

con la condición que si X es sustituido por Y, y si X e Y no son interrumpidos por Z,

entonces

X e Y comparten opcionalmente un átomo de carbono y juntos forman un radical espirociclico;

Q es Q' o Q";

en donde

Q' es $(S^y)_sR^3$; y

Q" es $NH(S^y)_sR^3$, $NHC(O)(S^y)_sR^3$, $NHC(O)O(S^y)_sR^3$ o $NHC(O)NH(S^y)_sR^3$;

en donde $S^y$ es alquileno de 1 a 3 átomos de carbono o alquilideno de 1 a 3 átomos de carbono y s es 0 o 1;

U es $CH_2$ o NH;

con la condición que si Q es Q", entonces U es $CH_2$;

$R^3$ es $R^{3a}$ o $R^{3b}$

en donde

$R^{3a}$ es

(i) un heterociclo que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cinco de los mismos o

diferentes heteroátomos seleccionados del grupo que consiste de O, N y S y el heterociclo contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro de los anillos fusionados;

(ii) un heterociclo de 4 a 6 miembros que contiene de uno a tres de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S, que contiene opcionalmente de 1 a 2 carbonilos, en donde el átomo de carbono del carbonilo es un miembro del heterociclo de 4 a 6 miembros;

(iii) cicloalquilo de 3 a 7 átomos de carbono;

(iv) carbazolilo, fluorenilo, fenilo, -O-fenilo, -O-alquilen-$C_1$-$C_4$-fenilo o naftilo; o

(v) alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$, $-C(O)O-R^{3'}$ o

alquinilo de 2 a 7 átomos de carbono; y

en donde $R^{3a}$ es sustituido opcionalmente por 1 a 3 de los mismos o diferentes sustituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilenfenilo de 1 a 3 átomos de carbono, -alquilen-$C_1$-$C_3$-OC(O)-fenilo, ciano, amino, nitro, halo, alquilo de 1 a 6 átomos de carbono, mono-bi-tri-haloalquilo de 1 a 3 átomos de carbono, mono-bi-tri-haloalquiloxi de 1 a 3 átomos de carbono, (alquil-$C_1$-$C_3$)$_{1-2}$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 de 1 a 6 átomos de carbono;

con la condición que si $R^{3a}$ es -$C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ o -$C(O)O-R^{3'}$,

entonces $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ o $-C(O)O-R^{3'}$ no son sustituidos;

$R^{3b}$ 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, 1-(1,1-dimetiletoxicarbonilo)-1H-indol-3-ilo, 4-imidazolilo, 1-metil-4-imidazolilo, 2-tienilo, 3-tienilo, tiazolilo, 1H-indazol-3-ilo, 1-metil-1H-indazol-3-ilo, benzo[b]fur-3-ilo, benzo[b]tien-3-ilo, piridinilo, quinolinilo o isoquinolinilo; sustituido opcionalmente en el esqueleto de carbono por mono-, di- o trisustituido por átomos de flúor, cloro o bromo o por grupos alquilo de cadena recta o ramificada, grupos -cicloalquilo de 3 a 8 átomos de carbono, 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, dialquilaminocarbonilo, alcanoilo, ciano, tetrazolilo, fenilo, piridinilo, tiazolilo, furilo, trifluorometoxi, trifluorometiltio, trifluorometilsulfinilo o trifluorometilsulfonilo;

en donde los sustituyentes pueden ser los mismos o diferentes y los grupos benzoilo, benzoilamino y benzoilmetilamino mencionados anteriormente pueden ser sustituidos adicionalmente, a su vez, en el radical fenilo por un átomo de flúor, cloro o bromo o por un grupo alquilo, trifluorometilo, amino o acetilamino;

D es O, NCN o $NSO_2$-alquilo de 1 a 3 átomos de carbono;

A es C, N o CH;

m y n son independientemente 0, 1 o 2;

con la condición que

si m y n son 0, entonces A no es N;

si m es 2, entonces n no es 2; o

si n es 2, entonces m no es 2;

E es N, CH o C;

P es 0 o 1;

si p es 1, entonces G, J y E juntos forman $A^X$ o $A^Y$;

$A^X$ es un heterociclo fusionado que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene de uno a cuatro de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S; y

que contiene opcionalmente 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro del heterociclo fusionado;

$A^Y$ es un heterociclo de 4 a 6 miembros que contiene de uno a tres heteroátomos seleccionados del grupo que consiste

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de O, N y S; y

que contiene opcionalmente 1 a 2 carbonilos, en donde el átomo de carbono del carbonilo es un miembro del heterociclo de 4 a 6 miembros;

en donde $A^x$ y $A^y$ son sustituidos opcionalmente por alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, ciano, cicloalquilo de 3 a 7 átomos de carbono, fenilo, halofenilo, halo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, piridilo, pirimidinilo, piperidinilo, piperazinilo o morfolino; o

si p es 0, de tal manera que G y J sean unidos cada uno a A, entonces A es C, y G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema

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que contienen 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 que

$A^x$ no sea un heterociclo 1,3-diaza-fusionado; y

$A^y$ no sea un 1,3-diaza-heterociclo;

y con la condición adicional que

si Q es Q", entonces $R^3$ es $R^{3a}$; y

si Q es Q', entonces

$R^3$ es $R^{3b}$; o

$R^3$ es $R^{3a}$, p es 0 y G, J y A juntos forman GJA".

2. Un compuesto de conformidad con la reivindicación 1, caracterizado porque Q es Q' y $R^3$ es $R^{3b}$.

3. Un compuesto de conformidad con la reivindicación 1, caracterizado porque Q es Q', $R^3$ es $R^{3a}$ y p es 0 de tal manera que G, J y A juntos forman GJA".

4. Un compuesto de conformidad con la reivindicación 2 o 3, caracterizado porque Q es Q' y U es $CH_2$.

5. Un compuesto de conformidad con la

reivindicaciónes 2 o 3, caracterizado porque Q es Q' y U es NH.

6. Un compuesto de conformidad con la reivindicación 1, caracterizado porque Q es Q".

7. Un compuesto de conformidad con la reivindicación 6, caracterizado porque Q" es $NH(S^y)_sR^3$.

8. Un compuesto de conformidad con la reivindicación 6, caracterizado porque Q" es $NHC(O)(S^y)_sR^3$.

9. Un compuesto de conformidad con la reivindicación 6, caracterizado porque Q" es $NHC(O)O(S^y)_sR^3$.

10. Un compuesto de conformidad con la reivindicación 6, caracterizado porque Q" es $NHC(O)NH(S^y)_sR^3$.

11. Un compuesto de conformidad con la reivindicación 1, caracterizado porque V es $OR^4$.

12. Un compuesto de conformidad con la reivindicación 1, caracterizado porque V es $-N(R^1)(R^2)$.

13. Un compuesto de conformidad con la reivindicación 1, caracterizado porque $R^4$ es H, alquilo de 1 a 6 átomos de carbono o $(alquileno\text{-}C_1\text{-}C_4)_{0\text{-}1}R^{4'}$ y $R^{4'}$ es cicloalquilo de 3 a 7 átomos de carbono.

14. Un compuesto de conformidad con la reivindicación 1, caracterizado porque 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 consiste de H, alquilo de 1 a 6 átomos de carbono, $-alquilen\text{-}C_1\text{-}C_6\text{-}amino(alquil\text{-}C_1\text{-}C_3)_2$,

cicloalquilo de 3 a 7 átomos de carbono, 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 átomo de nitrógeno al cual están unidos ,forman X,

en donde X es azetidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piperazinilo, piperidinilo, morfolino o tiomorfolino;

en donde X es sustituido por Y, en donde Y es dioxolanilo, alquilo de 1 a 4 átomos de carbono, alcoxi de

1 a 4 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono, fenilo, azetidinilo, pirrolilo, pirrolinilo, pirrolidinilo, pirrolidinonilo, imidazolilo, imidazolinilo, imidazolidinilo, imidazolidinonilo, pirazolilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piridilo, pirimidinilo, dihidrobencimidazolonilo, piperazinilo, piperidinilo, morfolino, benzotiazolilo, bencisotiazolilo o tiomorfolino; y en donde X e Y comparten opcionalmente un átomo de carbono y juntos forman un radical espirocíclico.

14. Un compuesto de conformidad con la reivindicación 1, caracterizado porque 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 de 1 a 6 átomos de carbono, o

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$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo o morfolino;

en donde X es sustituido por Y, en donde Y es dïoxolanilo, alquilo de 1 a 4 átomos de carbono o piperidinilo;

y en donde X e Y comparten opcionalmente un átomo de carbono y juntos forman un radical espirocíclico.

15. Un compuesto de conformidad con la reivindicación 1, caracterizado porque V es $-N(R^1)(R^2)$ y en donde $R^1$ y $R^2$ son cada uno independientemente $L^1$, en donde $L^1$ se selecciona del grupo que consiste de H, alquilo de 1 a 6 átomos de carbono.

16. Un compuesto de conformidad con la reivindicación 1, caracterizado porque V es $-N(R^1)(R^2)$ y en donde

$R^1$ y $R^2$ junto, con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo ó morfolino;

en donde X es sustituido por Y, en donde Y es dioxolanilo, alquilo de 1 a 4 átomos de carbono o piperidinilo;

y en donde X e Y comparten

opcionalmente un átomo de carbono y juntos forman un radical espirocíclico.

16. Un compuesto de conformidad con la reivindicación 1, caracterizado porque V es $-N(R^1)(R^2)$ y en donde

$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo;

en donde X es sustituido por Y, en donde Y es piperidinilo.

17. Un compuesto de conformidad con la reivindicación 1, caracterizado porque V es $-N(R^1)(R^2)$ y en donde.

$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es morfolino;

en donde X es sustituido por Y, en donde Y es alquilo de 1 a 4 átomos de carbono.

18. Un compuesto de conformidad con la reivindicación 1, caracterizado porque V es $-N(R^1)(R^2)$ y en donde

$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo;

en donde X es sustituido por Y, en donde Y es alquilo de 1 a 4 átomos de carbono.

19. Un compuesto de conformidad con la reivindicación 1, caracterizado porque V es $-N(R^1)(R^2)$ y en donde

$R^1$ y $R^2$, junto con el átomo de nitrógeno al cual están unidos, forman X,

en donde X es piperidinilo;

en donde X es sustituido por Y, en donde Y es dioxolanilo,

y en donde X e Y comparten un átomo de carbono y juntos forman un radical espirocíclico.

20. Un compuesto de conformidad con la reivindicación 1, caracterizado porque $R^3$ es $R^{3a}$ y $R^{3a}$ es fenilo sustituido o no sustituido, hidroxifenilo, azetidinilo, naftilo, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, dihidroquinolinonilo, hidroquinolinonilo, quinolinilo, dihidroisoquinolinonilo, hidroisoquinolinonilo, isoquinolinilo, dihidroquinazolinonilo, hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, bencimidazolilo, indazolilo,

dihidrobencimidazolonilo, hidrobencimidazolonilo, bencimidazolinilo, dihidrobenztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzoxazolilo, benzotriazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo, benzotienilo, dihidrobenzofuranonilo, hidrobenzofuranonilo, benzofuranilo, benzdioxolanilo, 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.

21. Un compuesto de conformidad con la reivindicación 1, caracterizado porque $R^3$ es $R^{3b}$ y $R^{3b}$ es dihidrobencimidazolonilo sustituido o no sustituido, hidrobencimidazolonilo, bencimidazolinilo, dihidrobenztiazolonilo, 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; sustituido opcionalmente como se proporciona en la primera modalidad del primer aspecto.

22. Un compuesto de conformidad con la reivindicación 1, caracterizado porque D es O y m y n son cada uno 1.

23. Un compuesto de conformidad con la reivindicación 1, caracterizado porque p es 1; y G, J y E juntos forman $A^x$ o $A^y$.

24. Un compuesto de conformidad con la reivindicación 1, caracterizado porque p es 0, de tal manera que G y J son unidos cada uno a A, entonces A es C y G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA' o GJA".

25. Un compuesto de conformidad con la reivindicación 1, caracterizado porque p es 0, de tal manera que G y J son unidos cada uno a A, entonces A es C y G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA'.

26. Un compuesto de conformidad con la reivindicación 1, caracterizado porque p es 0, de tal manera que G y J son unidos cada uno a A, entonces A es C y G, J y A. forman juntos un sistema de anillos espirocíclicos con los

anillos del sistema que contienen A y en donde G, J y A juntos son GJA".

27. Un compuesto de conformidad con la reivindicación 1, caracterizado porque p es 0, de tal manera que G y J son unidos cada uno a A, entonces A es C y G, J y A forman juntos un sistema de anillos espirocíclicos con los anillos del sistema que contienen 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, dihidrobencimidazolonilo, dihidrobencimidazolilo, dihidro-benztiazolonilo, dihidrobenztiazolilo, dihidrobenzotiofenonilo, dihidrobenzofuranonilo, dihidroindolonilo, indolinilo, pirazolinilo, pirazolidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, piperidinilo, piperazinilo y morfolino; en donde el heterociclo es sustituido opcionalmente por alquilo de 1 a 4 átomos de carbono, alcoxi de 1 a 4 átomos de carbono, haloalquilo de 1 a 4 átomos de carbono, ciano, cicloalquilo de 3 a 7 átomos de carbono, fenilo, halofenilo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, piridilo,

pirimidinilo, piperidinilo, piperazinilo o morfolino.

28. Un compuesto seleccionado del grupo que consiste de ácido (±)-3-(1*H*-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

[2-[1,4']bipiperidinil-1'-il-1-(1*H*-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (*R*)-4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']bipiperidinil-1'-il-1-(1*H*-indol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico;

[2-[1,4']bipiperidinil-1'-il-1(1*H*-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico;

[2-[1,4']bipiperidinil-1'-il-1-(1*H*-indol-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-(1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[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;

[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;

[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;

[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-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico;

[2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-1-(1*H*-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2*H*-quinazolin-3-il)-piperidin-1-carboxílico;

éster metílico 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 metílico del ácido 3-(7-metil-1H-indazol-5-il)-2-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinazolin)carbonil amino]-propiónico;

éster metílico 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;

ácido (±)-3-(7-metil-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-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(7-etil-1H-indazol-5-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-(7-metil-1H-indazol-5-il)-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[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-(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;

[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-(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-(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;

(±)-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-(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-(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-dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin]-1-carboxamida;

(±)-[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;

[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;

{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;

(±)-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-(7-metil-1H-indazol-5-ilmetil)-2-[1-piperidinil]-2-oxoetil]3',4'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinolin]-1-carboxamida;

(±)-[1-dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]1-3',4'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinolin]-1-

carboxamida;

{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-en-8-carboxílico;

{1-(7-metil-1H-indazol-5-ilmetil)-2-[1-piperidinilil]-2-oxo-etil}-amida del ácido (±)-4-oxo-2-fenil-1,3,8-triaza-espiro[4,5]dec-1-en-8-carboxílico;

[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-en-8-carboxílico;

{1-(1H-indazol-5-ilmetil)-2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

éster bencílico 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;

[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;

{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;

éster ciclohexílico 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 metílico 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;

[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;

éster metílico 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;

[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;

[2-[1,4']bipiperidinil-1'-il-1-(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;

[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;

éster metílico del ácido (R)-3-(1H-benzotriazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

[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;

[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;

[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;

[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;

[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;

[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;

éster metílico 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;

[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;

[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;

[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;

[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;

[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;

(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-en-9-carboxílico;

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)-quinolin]-1-carboxamida;

N-[(1R)-1-(benzo[b]tien-3-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-2',3'-dihidro-1-oxoespiro-[piperidin-4,4'(1H)-isoquinolin]-1-carboxamida;

N-[(1R)-1-(benzo[b]tien-3-ilmetil)-2-[1,4'-bipiperidin]-1'-il-2-oxoetil]-1,2-dihidro-2-oxoespiro-[4H-3,1-benzoxazin-4,4'-piperidin]-1'-carboxamida;

1-[1,4']bipiperidinil-1'-il-2-(3(S)-benzo[b]tiofen-3-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3'-1-benzoxazin-

4,4'-piperidinil]-butan-1,4-diona;

éster metílico del ácido (±)-2-(7-metil-1H-indazol-5-ilmetil]-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3'-1-benzoxazin-4,4'-piperidinil]-butírico;

éster metílico 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-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidinil]-butan-1,4-diona;

(±)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]-butan-1,4-diona;

(±)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]-butan-1,4-diona;

(±)-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-benzoxazin-4,4'-piperidinil]-butan-1,4-diona;

(±)-*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;

(±)-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]-butan-1,4-diona;

(±)-2-(7-metil-1H-indazol-5-ilmetil)-1-(4-metil-piperidin-1-il)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona;

(±)-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]-butan-1,4-diona;

(±)-*N*,*N*-dimetil-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3'-1-benzoxazin-4,4'-piperidinil]-butiramida;

(±)-2-(7-metil-1H-indazol-5-ilmetil)-1-(piperidin-1-il)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidinil]-butan-1,4-diona;

(±)-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-butan-1,4-diona;

(±)-1-[1,4']bipiperidinil-1'-il-2-(1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidinil]-butan-1,4-diona;

(±)-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-benzoxazin-4,4'-piperidinil]-butan-1,4-diona;

(±)-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]-butan-1,4-diona;

(±)-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;

éster *terc*-butílico 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;

(±)-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;

éster *terc*-butílico 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;

(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]-butan-1,4-diona;

(L)-1-[1,4']bipiperidinil-1'-il-2-(5-cloro-2-nitro-fenilàmino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butan-1,4-diona;

(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]-butan-1,4-diona;

(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]-butan-1,4-diona;

(L)-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]-butan-1,4-diona;

(L)-1-[1,4']bipieridinil-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]-butan-1,4-diona;

(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]-butan-1,4-diona;

(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]-butan-1,4-diona;

(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]-butan-1,4-diona;

(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]-butan-1,4-diona;

(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)-butan-1,4-diona;

(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]-butan-1,4-diona;

(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]-butan-1,4-diona;

(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;

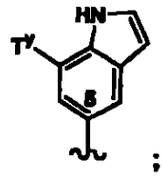
(L)-N-{1-([1,4']bipiperidinil-1'-carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil}-4-hidroxi-benzamida;

{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-carboxílico; y

(±)-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]-butan-1,4-diona;

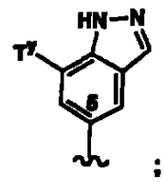
y sales y solfatos farmacéuticamente aceptables de los mismos.

29. Un compuesto de conformidad con la reivindicación 1, caracterizado porque $R^3$ es $R^{3b}$ y $R^{3b}$ es 1H-indol-5-ilo



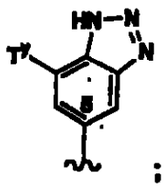

;

1H-indazol-5-ilo



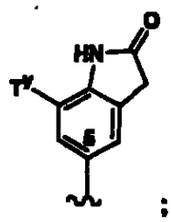

;

1H-benzotriazol-5-ilo



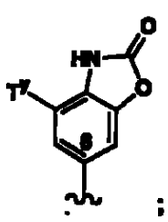
;

1,3-dihidro-indol-2-on-5-ilo



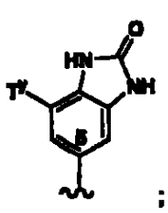
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3H-benzooxazol-2-on-6-ilo



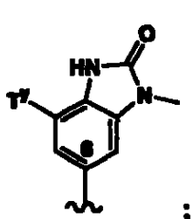
;

1,3-dihidro-benzoimidazol-2-on-5-ilo



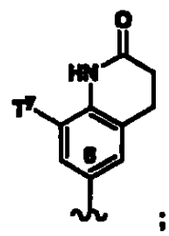
;

1-metil-1,3-dihidro-benzoimidazol-2-on-6-ilo



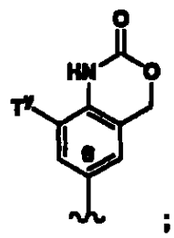
;

3,4-dihidro-1H-quinolin-2-on-6-ilo



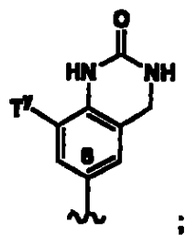
;

1,4-dihidro-benzo[d][1,3]oxazin-2-on-6-ilo



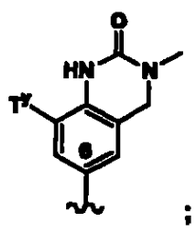
;

3,4-dihidro-1H-quinazolin-2-on-6-ilo



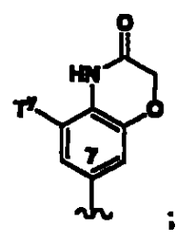
;

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 de 1 a 4 átomos de carbono, F, Cl, Br o nitrilo.

30. 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;

[2-[1,4']bipiperidinil-1'-il-1-(4-cloro-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-carbóxilico;

[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-benzooxazo-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-2-oxo-1-(2-oxo-2,3-dihidro-1H-benzoimidazol-5-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-(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 isopropílico 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 isopropílico 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 isopropílico 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 terc-butílico 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 terc-butílico 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 terc-butílico 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 ciclohexílico 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 ciclohexílico 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 1-metil-piperidin-4-ílico 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 1-metil-piperidin-4-ílico 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 1-metil-piperidin-4-ílico 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 1-metil-ciclohexílico 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 1-metil-ciclohexílico 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 1-metil-ciclohexílico 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 1-fenil-ciclohexílico 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 4-fenil-ciclohexílico 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 4-fenil-ciclohexílico 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 1-bencil-piperidin-4-ílico 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 1-piperidin-4-il-etílico 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; y

éster 1-piperidin-3-il-etílico 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

o sales o solvatos farmacéuticamente aceptables de los mismos.

31. Una composición farmacéutica, caracterizada porque comprende un compuesto de conformidad con la reivindicación 1.

32. Un método para tratar la migraña en un paciente en necesidad del mismo, caracterizado porque comprende la administración de una cantidad efectiva antimigraña de una composición que comprende un compuesto de conformidad con la reivindicación 1.

33. Un método no terminal, in vivo para identificar compuestos anti-migraña caracterizado porque comprende administrar un agonista de receptores de 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 capaz de invertir el incremento inducido por CGRP en el flujo sanguíneo, en donde el mamífero es un mamífero transgénico con RAMP1 humanizada que tiene Trp74 o un mamífero que expresa de manera endógena la RAMP1 que tiene Trp74.

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34. Un método no terminal, in vivo para identificar compuestos anti-migraña, caracterizado porque comprende administrar a un mamífero un compuesto de prueba antes del suministro de un agonista de receptores de CGRP en donde el agonista de receptores de CGRP es administrado en una cantidad capaz de inducir un incremento en el flujo sanguíneo y en donde el compuesto de prueba es administrado en una cantidad capaz de suprimir el incremento inducido por CGRP en el flujo sanguíneo, en donde el mamífero es un mamífero transgénico con RAMP1 humanizada que tiene Trp74 o un mamífero que expresa de manera endógena la RAMP1 que tiene Trp74.

35. Un método no terminal, *in vivo* para identificar compuestos anti-migraña, caracterizado porque comprende administrar a un mamífero un agonista de receptores de CGRP en una cantidad capaz de inducir un incremento en el diámetro de arterias periféricas, seguido por la administración de un compuesto de prueba en una cantidad capaz de invertir el incremento inducido por CGRP en el diámetro de arterias periféricas, en donde el mamífero es un mamífero transgénico con RAMP1 humanizada que tiene Trp74 o un mamífero que expresa de manera endógena la RAMP1 que tiene Trp74.

36. Un método no terminal, in vivo para identificar compuestos anti-migraña, caracterizado porque

comprende administrar a un mamífero un compuesto de prueba antes del suministro de un agonista de receptores de CGRP en donde el agonista de receptores de CGRP es administrado en una cantidad capaz de inducir un incremento en el diámetro de arterias periféricas y en donde el compuesto de prueba es administrado en una cantidad capaz de suprimir el incremento inducido por CGRP en el diámetro de arterias periféricas, en donde el mamífero es un mamífero transgénico con RAMP1 humanizada que tiene Trp74 o un mamífero que expresa de manera endógena la RAMP1 que tiene Trp74.

**Figura 1**

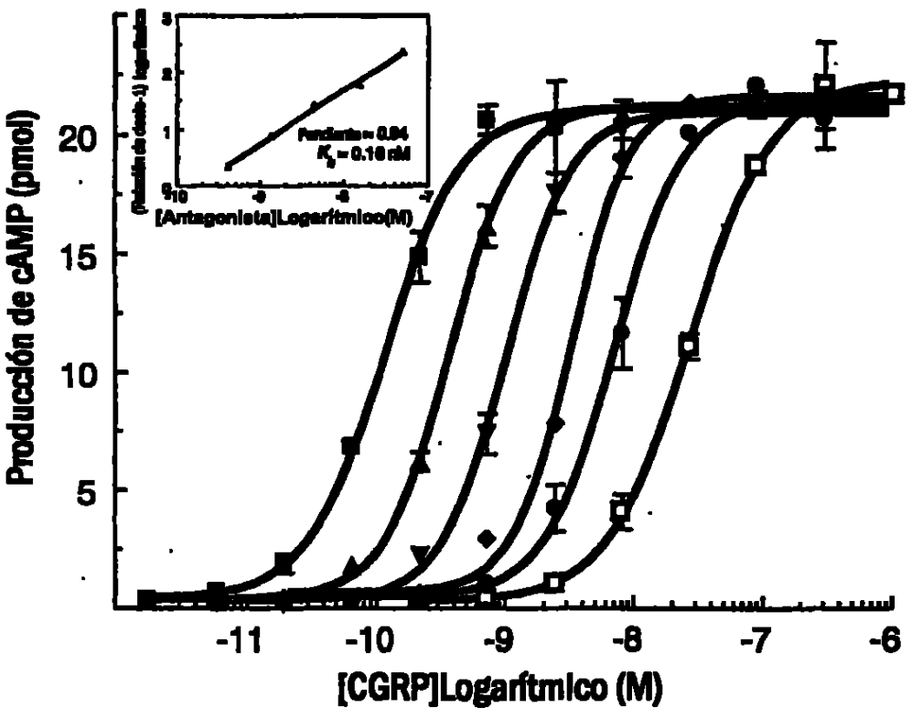
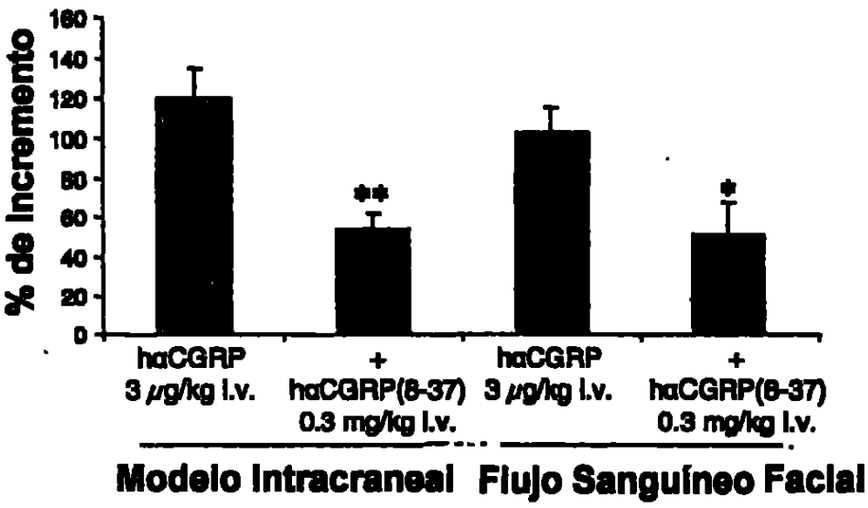

Producción de cAMP (pmol)
20
15
10
5
-11
-10
-9
-8
-7
-6
[CGRP]Logarítmico (M)
[Antagonista]Logarítmico(M)

**Figura 2**


% de 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 Intracraneal Flujo Sanguíneo Facial

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**Figura 3**


% 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**

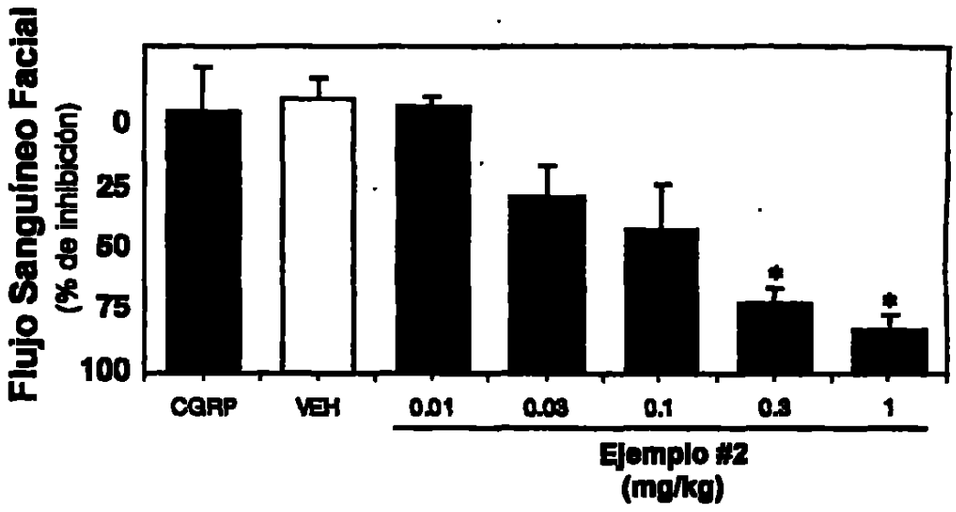
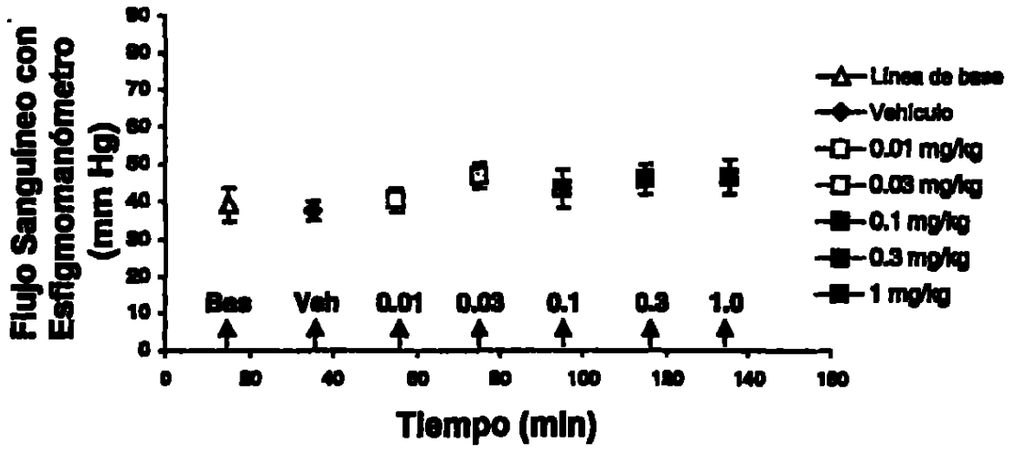

Flujo Sanguíneo Facial
(% de inhibición)
0
25
50
75
100
CGRP
VEH
0.01
0.03
0.1
0.3
1
Ejemplo #2
(mg/kg)

**Figura 5**


Flujo Sanguíneo con Esfigmomanómetro (mm Hg)
Tiempo (min)
Base
Veh
0.01
0.03
0.1
0.3
1.0
Línea de base
Vehículo
0.01 mg/kg
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg

CT2777-NO-PCT

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# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
SHAH R. MAKUJINA
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

# PCT

## NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

| Date of Mailing (day/month/year) | 10 FEB 2004 |
|---|---|
| Applicant's or agent's file reference | IMPORTANT NOTIFICATION |
| CT2777 | |

| International application No. | International filing date (day/month/year) | Priority date (day/month/year) |
|---|---|---|
| PCT/US03/16576 | 27 May 2003 (27.05.2003) | 05 June 2002 (05.06.2002) |

Applicant

BRISTOL-MYERS SQUIBB COMPANY

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

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

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

4. **REMINDER**

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

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

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

RECEIVED
PATENT LAW
FEB 12 2004

| Name and mailing address of the IPEA/US | Authorized officer |
|---|---|
| Mail Stop PCT, Attn: IPEA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450 | Telephone No. (703)308-1235 |
| Facsimile No. (703)305-3230 | |

Form PCT/IPEA/416 (July 1992)

Docketed Item NO SIPE
Due Date
Attorney Shah

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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| Applicant's or agent's file reference<br>CT2777 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/US03/16576 | International filing date *(day/month/year)*<br>27 May 2003 (27.05.2003) | Priority date *(day/month/year)*<br>05 June 2002 (05.06.2002) |
| International Patent Classification (IPC) or national classification and IPC<br>IPC(7): C07D 487/14, 487/22; A61K 31/517, 31/496, 31/4427; A61P 11/00, 11/06, 25/06 and US Cl.: 544/284, 286, 336; 546/186, 193, 195, 199; 514/259, 252.14, 336, 337 | | |
| Applicant<br>BRISTOL-MYERS SQUIBB COMPANY | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 20 November 2003 (20.11.2003) | 15 January 2004 (15.01.2004) |
| Name and mailing address of the IPEA/US<br>Mail Stop PCT, Attn: IPEA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703)305-3230 | Authorized officer:<br>Valerie Bell-Harrison<br>Telephone No. (703)308-1235 |

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/16576

615 52

## I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-275 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 276-307, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/16576

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. STATEMENT

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-36 | YES |
| | Claims | NONE | NO |
| Inventive Step (IS) | Claims | 1-36 | YES |
| | Claims | NONE | NO |
| Industrial Applicability (IA) | Claims | 1-36 | YES |
| | Claims | NONE | NO |

2. CITATIONS AND EXPLANATIONS

Claims 1-36 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the compound of formula I shown in claim1, composition and method of use embraced in the instant claims.

Claims 1-36 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry as therapeutic agents for treating various diseases including asthma.

# TRATADO DE COOPERACION EN MATERIA DE PATENTES

# PCT

## REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

**(Artículo 36 y Regla 70 del PCT)**

| Referencia de registro del solicitante o del apoderado: CT2777 | PARA UNA ACCION ADICIONAL | Véase la Notificación de Transmisión del Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/416) |
|---|---|---|
| No. de solicitud internacional: PCT/US03/16576 | Fecha de presentación internacional (día/mes/año): 27 de Mayo de 2003 (27.05.2003) | Fecha de prioridad (día/mes/año): 05 de Junio de 2002 (05.06.2002) |

Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC:
IPC(7): C07D 487/14, 487/22; A61K 31/517, 31/496, 31/4427; A61P 11/00, 11/06, 25/06 y US Cl.: 544/284, 286, 336; 546/186, 193, 195, 199; 514/259, 252.14, 336, 337

Solicitante:
BRISTOL-MYERS SQUIBB COMPANY

1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Examen Preliminar Internacional y se transmite al solicitante de acuerdo con el Artículo 36.

2. Este REPORTE consiste de un total de 3 hojas, incluyendo esta portada.

   ☐ Este reporte también está acompañado de ANEXOS, es decir, hojas de la descripción, las reivindicaciones y/o los dibujos, los cuales han sido enmendados y son la base de este reporte y/o las hojas que contienen las rectificaciones hechas antes de esta Autoridad. (Véase la Regla 70.16 y la Sección 607 de las Instrucciones Administrativas conforme al PCT).

   Estos anexos consisten de un total de 0 hojas.

3. Este reporte contiene las indicaciones que se relacionan con los siguientes puntos:

   I ☒ Base del reporte

   II ☐ Prioridad

   III ☐ No se establece reporte con respecto a la novedad, paso inventivo o aplicabilidad industrial;

   IV ☐ Carencia de unidad de la invención

   V ☒ Declaración razonada conforme al Artículo 35(2) con respecto a la novedad, paso inventivo o aplicabilidad industrial; citas y explicaciones que soportan tal declaración

   VI ☐ Ciertos documentos citados

   VII ☐ Ciertos defectos en la solicitud internacional

   VIII ☐ Ciertas observaciones en la solicitud internacional

| Fecha de presentación de la solicitud | Fecha de terminación de este reporte |
|---|---|
| 20 de Noviembre de 2003 (20.11.2003) | 15 de Enero de 2004 (15.01.2004) |


Nombre y dirección de correspondencia de la IPEA/US

Registro de Correos del PCT, Atn: IPEA/US
Comisionado de Patentes
P.O.Box 1450
Alejandria, Virginia 22313-1450
Fax: (703)305-3230

Funcionario autorizado:

Venkataraman Balasubramanian

Teléfono No. (703)308-1235

**REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL**

No. de Solicitud Internacional
PCT/US003/16576

**I. Bases del reporte**

1. Con respecto a los elementos de la solicitud internacional:*

☒ la solicitud internacional como se presentó originalmente.
☒ la descripción:
páginas 1-275, como se presentaron originalmente
páginas NINGUNA, presentadas con la solicitud
páginas NINGUNA, presentadas con la carta del _____.

☒ las reivindicaciones:
páginas 276-307, como se presentaron originalmente
páginas NINGUNA, como se enmendaron (conjuntamente con cualquier declaración) conforme al Artículo 19
páginas NINGUNA, presentadas con la solicitud
páginas NINGUNA, presentadas con la carta del _____.

☒ los dibujos:
páginas NINGUNA, como se presentaron originalmente
páginas NINGUNA, presentadas con la solicitud
páginas NINGUNA, presentadas con la carta del _____.

☐ la parte del listado de secuencias de la descripción:
páginas NINGUNA, como se presentaron originalmente
páginas NINGUNA, presentadas con la solicitud
páginas NINGUNA, presentadas con la carta del _____.

2. Con respecto al idioma, todos los elementos marcados anteriormente fueron disponibles o proporcionados a esta Autoridad en el idioma en el cual la solicitud internacional se presentó, a menos que se indique de otra manera conforme a este artículo. Estos elementos fueron disponibles o proporcionados a esta Autoridad en el siguiente idioma _____el cual es:

☐ el idioma de una traducción proporcionada para los propósitos de la búsqueda internacional (conforme a la Regla 23.1(b)).
☐ el idioma de publicación de la solicitud internacional (conforme a la Regla 48.3(b)).
☐ el idioma de la traducción proporcionada para los propósitos del examen preliminar internacional (conforme a las Reglas 55.2 y/o 55.3).

3. Con respecto a cualquier secuencia de nucleótidos y/o aminoácidos descrita en la solicitud internacional, el examen preliminar internacional se llevó a cabo en base del listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita.
☐ presentado junto con la solicitud internacional en forma leíble por computadora.
☐ proporcionado subsecuentemente a la Autoridad en forma escrita.
☐ proporcionado subsecuentemente a la Autoridad en forma leíble por computadora.
☐ Ha sido proporcionada la declaración que el listado de secuencias escrito, subsecuentemente proporcionado no va más allá de la descripción en la solicitud internacional como se presentó.
☐ Ha sido proporcionada la información registrada en forma leíble por computadora que es idéntica al listado de secuencias escrito.

4. ☒ Las enmiendas han dado por resultado la cancelación de:
☒ la descripción, páginas NINGUNA
☒ las reivindicaciones, Nos. NINGUNA
☒ los dibujos, hojas/fig NINGUNA

5. ☐ Este reporte ha sido redactado como si (alguna de) las enmiendas no han sido hechas, puesto que éstas han sido consideradas que van más allá de la descripción como se presentó, como se indicó en el Cuadro Suplemental (Regla 70.2(c)).**

** Las hojas de reemplazo las cuales han sido proporcionadas a la Oficina de recepción en respuesta a una invitación conforme al Artículo 14 son referidas en este reporte como "presentadas originalmente" y no se anexan a este reporte puesto que éstas no contienen las enmiendas (Reglas 70.16 y 17.17).*

*** Cualquier hoja de reemplazo que contenga estas enmiendas debe ser referida conforme al artículo 1 y anexada a este reporte.*

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**REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL**

No. de Solicitud Internacional
PCT/US03/16576

**V. Declaración razonada conforme al Artículo 66.2(a)(ii) con respecto a la novedad, paso inventivo o aplicabilidad industrial; citaciones y explicaciones que soportan esta declaración.**

1. DECLARACION

| | | |
|---|---|---|
| **Novedad (N)** | **Reivindicaciones** 1-36 | **SI** |
| | **Reivindicaciones** NINGUNA | **NO** |
| **Paso Inventivo (IS)** | **Reivindicaciones** 1-36 | **SI** |
| | **Reivindicaciones** NINGUNA | **NO** |
| **Aplicabilidad Industrial (AI)** | **Reivindicaciones** 1-36 | **SI** |
| | **Reivindicaciones** NINGUNA | **NO** |

2. CITAS Y EXPLICACIONES

Las reivindicaciones 1-36 cumplen con los criterios expuestos en el Artículo 33(2)-(3) del PCT, debido a que la técnica anterior no enseña o sugiere claramente el compuesto de la fórmula I mostrado en la reivindicación 1, la composición y el método de uso incluidos en las presentes reivindicaciones.

Las reivindicaciones 1-36 cumplen con los criterios expuestos en el Artículo 33(4) del PCT y, de esta manera, tienen aplicabilidad industrial ya que el tema reclamado puede elaborarse o utilizarse en la industria como agentes terapéuticos para el tratamiento de diversas enfermedades, que incluyen el asma.

RECEIVED
BMS PATENT LAW
OCT 30 2003

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

Docketed Item DOS-US 12/28/03
Due Date PCT
Attorney Shah M.

To:
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

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

(PCT Rule 44.1)

| | |
|---|---|
| Applicant's or agent's file reference CT2111 | Date of Mailing (day/month/year) 28 OCT 2003 |
| International application No. PCT/US03/16576 | FOR FURTHER ACTION See paragraphs 1 and 4 below |
| Applicant BRISTOL-MYERS SQUIBB COMPANY | International filing date (day/month/year) 27 May 2003 (27.05.2003) |

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.

10 2003

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<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703)305-3230 | Authorized officer<br>Valerie Bell-Harris for<br>Telephone No. (703)308-1235 |

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

STATUS OF U.S. CASES FOR CT2777 SERIES

| Attorney | Dkt. No. | Country | Filing number | Type | Index | Event |
|---|---|---|---|---|---|---|
| MAKUJINA | CT2777 | US | 10/445523 | NP | | Filing |

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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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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference CT2777 | 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/US03/16576 | International filing date (*day/month/year*) 27 May 2003 (27.05.2003) | (Earliest) Priority Date (*day/month/year*) 05 June 2002 (05.06.2002) |
| 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/US03/16576 |

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07D 487/14, 487/22; A61K 31/517, 31/496, 31/4427; A61P 11/00, 11/06, 25/06
US CL : 544/284, 286, 336; 546/186, 193, 195, 199; 514/259, 252.14, 336, 337

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/284, 286, 336; 546/186, 193, 195, 199; 514/259, 252.14, 336, 337

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 6552,043 B1 (PATCHETT et al) 22 April 2003 (22.04.2003), see entire document especially formula I on column 1. | 1-36 |

☐ 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 |
|---|---|
| 09 September 2003 (09.09.2003) | 28 OCT 2003 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703)305-3230 | Authorized officer<br>Valerie Sud-Harris for<br>Telephone No. (703)308-1235 |

Form PCT/ISA/210 (second sheet) (July 1998)

# 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 | véase Notificación de la Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como también, donde sea aplicable, el inciso 5 posterior | |
|---|---|---|---|
| CT2777 | | | |
| No. de Solicitud Internacional | Fecha de presentación internacional (día/mes/año): | | Fecha de prioridad (la más reciente) (día/mes/año): |
| PCT/US 03/16576 | 27 de Mayo de 2003 (27.05.2003) | | 5 de Junio de 2002 (05.06.2002) |
| Solicitante: | | | |
| BRISTOL-MYERS SQUIBB COMPANY | | | |

Este reporte de Búsqueda Internacional ha sido preparado por esta Autoridad de la Búsqueda Internacional y se transmite al solicitante de acuerdo con el Artículo 18. Una copia está siendo transmitida a la Oficina Internacional

Este Reporte de Búsqueda Internacional consiste de un total de 2 hojas.

[X] También está acompañado por 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 llevó a cabo en base a la solicitud internacional en el idioma en el cual se presentó, a menos que se indique de otra manera conforme a este artículo

   [ ] la búsqueda internacional se llevó a cabo en base a una traducción de la solicitud internacional proporcionada a esta Autoridad (Regla 23.1(b)).

   b. Con respecto a cualquier secuencia de nucleótidos y/o aminoácidos descrita en la solicitud internacional, la búsqueda 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 leíble por computadora.

   [ ] proporcionado subsecuentemente a la Autoridad en forma escrita.

   [ ] proporcionado subsecuentemente a la Autoridad en forma leíble por computadora.

   [ ] ha sido proporcionada la declaración que el listado de secuencias escrito subsecuentemente proporcionado no va más allá de la descripción en la solicitud internacional como se presentó.

   [ ] ha sido proporcionada la declaración que la información registrada en forma leíble por computadora es idéntica al listado de secuencias escrito.

2. [ ] Se encontró que ciertas reivindicaciones no son investigables (Véase el Cuadro I).

3. [ ] La unidad de la invención es deficiente (Véase el Cuadro II).

4. Con respecto al título,

   [X] el texto se aprueba como lo presentó el solicitante.

   [ ] esta Autoridad ha establecido que el texto se lee como sigue:

5. Con respecto al resumen,

   [X] el texto se aprueba como lo presentó el solicitante

   [ ] esta autoridad ha establecido el texto es, 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, proporcionar 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 el solicitante le faltó sugerir una figura.

   [ ] porque la figura caracteriza mejor la invención.

# REPORTE DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US 03/16576

**A. CLASIFICACIÓN DEL TEMA**

IPC(7) : C07D 487/14, 487/22; A61K 31/517, 31/496, 31/4427; A61P 11/00, 11/06, 25/06
US CL : 544/284, 286, 336; 546/186, 193, 195, 199; 514/259, 252.14 336, 337

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a tanto la clasificación nacional como la IPC.

**B. CAMPOS BUSCADOS**

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):
U.S. : 544/284, 286, 336; 546/186, 193, 195, 199; 514/259, 252.14, 336, 337

Documentación buscada diferente a la documentación mínima, al grado que tales documentos están incluidos en los campos buscados:

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):
CAS ONLINE, EAST

**C. DOCUMENTOS CONSIDERADOS QUE SON RELEVANTES**

| Categoría* | Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes | Pertinente para la reivindicación No. |
|---|---|---|
| A | US 6552,043 B1 (PATCHETT y colaboradores) 22 de Abril de 2003 (22.04.2003), véase documento completo, especialmente la fórmula I en la columna 1. | 1-36 |

☐ Los documentos adicionales se listan en la continuación del cuadro C. ☐ Los miembros de la familia de patentes se listan en el anexo

*categorías especiales de los documentos citados:

"A" documento que define el estado general de la técnica, el cual no se considera que es de particular relevancia.

"E" primer documento publicado en o después de la fecha de presentación internacional.

"L" documento el cual puede arrojar dudas sobre la(s) reivindicación(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)

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

"P" documento publicado antes de la fecha de representación 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 no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.

"X" documento de relevancia particular; la invención reclamada no puede ser considerada nueva o no se puede considerar que involucra una paso inventivo cuando el documento se toma solo.

"Y" documento de particular relevancia; no se puede considerar que la invención reclamada involucra un paso inventivo cuando el documento es combinado con uno o más de tales documentos, tal combinación que es obvia para una persona experimentada en la técnica.

"&" documento miembro de la misma familia de patentes.

| Fecha de la terminación actual de la búsqueda internacional | Fecha de envío del reporte de búsqueda internacional |
|---|---|
| 09 de Septiembre de 2003 (09.09.2003) | 28 DE OCTUBRE DE 2003 |

| Nombre y dirección de correo de la ISA/US | Funcionario autorizado |
|---|---|
| Registro de Correos del PCT, Atn: ISA/US<br>Comisionado de Patentes<br>P.O.Box 1450<br>Alejandría, Virginia 22313-1450<br>No. de Facsimil (703) 305-3230 | Venkataraman Balasubramanian<br><br>Teléfono No. (703)308-1235 |

Forma PCT/ISA/210 (segunda hoja) (Julio de 1998)

*The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:*

IPEA/ US

# PCT

**CHAPTER II**

## DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

| For International Preliminary Examining Authority use only | |
|---|---|
| Identification of IPEA | Date of receipt of DEMAND |

| Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION | | Applicant's or agent's file reference: CT2777 |
|---|---|---|
| International application No.: PCT/US03/16576 | International filing date *(day/month/year)*: 27 May 2003 | (Earliest) Priority date *(day/month/year)*: 05 Jun 2002 |
| Title of invention: Calcitonin Gene Related Peptide Receptor Antagonists | | |

**Box No. II APPLICANT(S)**

| Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)* | Telephone No. / Facsimile No. / Teleprinter No. / Applicant's registration No. with the Office |
|---|---|
| BRISTOL-MYERS SQUIBB COMPANY<br>P. O. Box 4000<br>Route 206 and Provinceline Road<br>Princeton, NJ 08543-4000<br>United States of America | 609-252-4000<br>609-252-4526 |

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
CHATURVEDULA, Prasad V.
190 Lancaster Way
Cheshire, CT 06420
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
CHEN, Ling
193 McCormick Lane
Middletown, CT 06457
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| CN | US |

☒ Further applicants are indicated on a continuation sheet.

Sheet No. 2.

International application No.
PCT/US03/16576

**Continuation of Box No. II APPLICANT(S)**

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
CIVIELLO, Rita
90 Cow Hill Road
Killingworth, CT 06419
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
CONWAY, Charles Mark
825 Farmington Drive
Cheshire, CT 06410
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
DEGNAN, Andrew P.
123 York Street, Apt. 22-P
New Haven, CT 06511
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
DUBOWCHIK, Gene M.
65 Spring Street
Middlefield, CT 06455
United Staes of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

☒ Further applicants are indicated on another continuation sheet.

Sheet No. 3.

International application No.
PCT/US03/16576

**Continuation of Box No. II APPLICANT(S)**

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HAN, Xiaojun
65 Ridgecrest Drive
Cheshire, CT 06410
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| CN | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KARAGEORGE, George N.
34 Fox Run Road
Portland, CT 06480
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LUO, Guanglin
135 Devonshire Lane
Madison, CT 06443
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| CN | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MACOR, John E.
644 Mosse Hill Road
Guilford, CT 06437
United States of America

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

☒ Further applicants are indicated on another continuation sheet.

Sheet No. 4.

International application No.
PCT/US03/16576

Continuation of Box No. II APPLICANT(S)

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
POINDEXTER, Graham
15 Fox Hollow Road
Old Saybrook, CT 06475
United States of America

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*
VIG, Shikha
15 Park Place
Durham, CT 06422
United States of America

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/US03/16576

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MAKUJINA, Shah R.
BRISTOL-MYERS SQUIBB COMPANY
P. O. Box 4000
Princeton, NJ 08543-4000
United States of America

Telephone No.
203-677-7268

Facsimile No.
203-677-6900

Teleprinter No.

Agent's registration No. with the Office
41,174

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**

**Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

**Language for the purposes of international preliminary examination:** English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

International application No.
PCT/US03/16576

**Box No. VI CHECK LIST**

| The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination: | | | For International Preliminary Examining Authority use only: received | not received |
|---|---|---|---|---|
| 1. translation of international application | : | sheets | ☐ | ☐ |
| 2. amendments under Article 34 | : | sheets | ☐ | ☐ |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets | ☐ | ☐ |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets | ☐ | ☐ |
| 5. letter | : | sheets | ☐ | ☐ |
| 6. other *(specify)* | : | sheets | ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listings in computer readable form
7. ☐ tables in computer readable form related to sequence listings
8. ☐ other *(specify)*:

**Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

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

_____, Agent

Shah R. Makujina

Date: 11/20/05

**For International Preliminary Examining Authority use only**

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

**For International Bureau use only**

Demand received from IPEA on:

633

**CHAPTER II**

# PCT

## FEE CALCULATION SHEET

**Annex to the Demand**

| | |
|---|---|
| International application No. PCT/US03/16576 | For International Preliminary Examining Authority use only |
| Applicant's or agent's file reference CT2777 | Date stamp of the IPEA |

Applicant

BRISTOL-MYERS SQUIBB COMPANY, ET AL.

### CALCULATION OF PRESCRIBED FEES

| | | |
|---|---|---|
| 1. Preliminary examination fee ..... | 490.00 P | |
| 2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)* ..... | 172.00 H | |
| 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box ..... | 662.00 TOTAL | |

### MODE OF PAYMENT

- [X] authorization to charge deposit account with the IPEA (see below)
- [ ] cash
- [ ] cheque
- [ ] revenue stamps
- [ ] postal money order
- [ ] coupons
- [ ] bank draft
- [ ] other *(specify)*:

### AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

*(This mode of payment may not be available at all IPEAs)*

IPEA/ US

- [X] Authorization to charge the total fees indicated above.
- [X] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 19-3880

Date: 11/24/03

Name: Shah R. Makujina

Signature:



*See Notes to the fee calculation sheet*

CT2777 634

## PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 27.05.2003 02:55:20 PM

(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 01.04.2003) | | |
| 0-8 | Applicant's or agent's file reference | | CT2777 | | |
| 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<br>Basic fee<br>(first 30 sheets) | b1 | 476 | | |
| 12-4 | Remaining sheets | | 285 | | |
| 12-5 | Additional amount | (X) | 12 | | |
| 12-6 | Total additional amount | b2 | 3,420 | | |
| 12-7 | b1 + b2 = | B | 3,896 | | |
| 12-8 | Designation fees<br>Number of designations contained in international application | | 95 | | |
| 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 | ⇨ | 4,268 | |
| 12-14 | Fee for priority document<br>Number of priority documents requested | | 5 | | |
| 12-15 | Fee per document | (X) | 20 | | |
| 12-16 | Total priority document fee | P | ⇨ | 100 | |
| 12-17 | TOTAL FEES PAYABLE (T+S+I+P) | | ⇨ | 5,308 | |
| 12-19 | Mode of payment | | authorization to charge deposit account | | |
| 12-20 | Deposit account instructions<br>The receiving Office: | | United States Patent and Trademark Office (USPTO) (RO/US) | | |
| 12-20-1 | Authorization to charge the total fees indicated above. | | ✓ | | |

CT2777

## PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 27.05.2003 02:55:20 PM

| | | |
|---|---|---|
| 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 | 27 May 2003 (27.05.2003) |
| 12-23 | Name and signature | MAKUJINA, Shah |

## VALIDATION LOG AND REMARKS

| | | |
|---|---|---|
| 13-1-1 | Applicant remarks | Abstract contains chemical structure. |

| | | |
|---|---|---|
| 13-2-7 | Validation messages Contents | Green?<br>The international application contains no drawings. Please verify. |
| 13-2-9 | Validation messages Payment | Green?<br>Please ensure that you have a valid deposit account with the receiving Office selected. |
| 13-2-10 | Validation messages Annotate | Green?<br>All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication. |

636 X

CT2777

# PCT POWER OF ATTORNEY

| | | |
|---|---|---|
| 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 01.04.2003) |
| 1 | The undersigned applicant(s) | CHATURVEDULA, Prasad V.; CHEN, Ling; CIVIELLO, Rita; CONWAY, Charles Mark; DEGNAN, Andrew P.; DUBOWCHIK, Gene M.; HAN, Xiaojun; KARAGEORGE, George N.; LUO, Guanglin; MACOR, John E.; POINDEXTER, Graham; VIG, Shikha |
| 1-1-1 | hereby appoints (appoint) the following person | MAKUJINA, Shah; RYAN, Richard; BABAJKO, Suzanne; BAKAM, 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<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, NJ 08543-4000<br>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 | CT2777 |
| 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 | Prasad V. Chaturvedula |
| 2-2-1 | Name | CHATURVEDULA, Prasad V. |
| 2-3 | Signature of applicant | Ling Chen |
| 2-3-1 | Name | CHEN, Ling |

**PCT POWER OF ATTORNEY**

CT2/RD

| | | |
|---|---|---|
| 2-4 | Signature of applicant | |
| 2-4-1 | Name | CIVIELLO, Rita |
| 2-5 | Signature of applicant | |
| 2-5-1 | Name | CONWAY, Charles Mark |
| 2-6 | Signature of applicant | |
| 2-6-1 | Name | DEGNAN, Andrew P. |
| 2-7 | Signature of applicant | |
| 2-7-1 | Name | DUBOWCHIK, Gene M. |
| 2-8 | Signature of applicant | |
| 2-8-1 | Name | HAN, Xiaojun |
| 2-9 | Signature of applicant | |
| 2-9-1 | Name | KARAGEORGE, George N. |
| 2-10 | Signature of applicant | |
| 2-10-1 | Name | LUO, Guanglin |
| 2-11 | Signature of applicant | |
| 2-11-1 | Name | MACOR, John E. |
| 2-12 | Signature of applicant | |
| 2-12-1 | Name | POINDEXTER, Graham |
| 2-13 | Signature of applicant | |
| 2-13-1 | Name | VIG, Shikha |
| 3 | Date | 22 May 2003 |

## PCT POWER OF ATTORNEY

CT2777

| | | |
|---|---|---|
| 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 01.04.2003) |
| 1 | The undersigned applicant(s) | BRISTOL-MYERS SQUIBB COMPANY |
| 1-1-1 | hereby appoints (appoint) the following person | 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; MAKUJINA, Shah; VANATTEN, Mary, K.; VOLLES, Warren, K.; LAMERDIN, John; KORSEN, Elliott; EPPERSON, James<br>Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, NJ 08543-4000<br>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 | CT2777 |
| 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 | 14 May 2003 |

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639

# 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

PCT REQUEST

Original (for SUBMISSION) - printed on 27.05.2003 02:55:20 PM

| | | |
|---|---|---|
| 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 01.04.2003) |
| 0-5 | Petition<br>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 | CT2777 |
| 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<br>Route 206 and Provinceline Road<br>Princeton, NJ 08543-4000<br>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) | CHATURVEDULA, Prasad, V. |
| III-1-5 | Address: | 190 Lancaster Way<br>Cheshire, CT 06410<br>United States of America |
| III-1-6 | State of nationality | US |
| III-1-7 | State of residence | US |

PCT REQUEST



CTZ/77

| | | |
|---|---|---|
| III-2 | Applicant and/or Inventor | |
| III-2-1 | This person is: | applicant and inventor |
| III-2-2 | Applicant for | US only |
| III-2-4 | Name (LAST, First) | CHEN, Ling |
| III-2-5 | Address: | 193 McCormick Lane<br>Middletown, CT 06457<br>United States of America |
| III-2-6 | State of nationality | CN |
| III-2-7 | 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<br>Killingworth, CT 06419<br>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) | CONWAY, Charles, Mark |
| III-4-5 | Address: | 825 Farmington Drive<br>Cheshire, CT 06410<br>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) | DEGNAN, Andrew, P. |
| III-5-5 | Address: | 123 York Street, Apt. 22-P<br>New Haven, CT 06511<br>United States of America |
| III-5-6 | State of nationality | US |
| 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) | DUBOWCHIK, Gene, M. |
| III-6-5 | Address: | 65 Spring Street<br>Middlefield, CT 06455<br>United States of America |
| III-6-6 | State of nationality | US |
| III-6-7 | State of residence | US |

PCT REQUEST

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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) | HAN, Xiaojun |
| III-7-5 | Address: | 65 Ridgecrest Drive<br>Cheshire, CT 06410<br>United States of America |
| III-7-6 | State of nationality | CN |
| 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) | KARAGEORGE, George, N. |
| III-8-5 | Address: | 34 Fox Run Road<br>Portland, CT 06480<br>United States of America |
| III-8-6 | State of nationality | US |
| III-8-7 | State of residence | US |
| III-9 | Applicant and/or inventor | |
| III-9-1 | This person is: | applicant and inventor |
| III-9-2 | Applicant for | US only |
| III-9-4 | Name (LAST, First) | LUO, Guanglin |
| III-9-5 | Address: | 135 Devonshire Lane<br>Madison, CT 06443<br>United States of America |
| III-9-6 | State of nationality | CN |
| III-9-7 | State of residence | US |
| III-10 | Applicant and/or inventor | |
| III-10-1 | This person is: | applicant and inventor |
| III-10-2 | Applicant for | US only |
| III-10-4 | Name (LAST, First) | MACOR, John, E. |
| III-10-5 | Address: | 644 Mosse Hill Road<br>Guilford, CT 06437<br>United States of America |
| III-10-6 | State of nationality | US |
| III-10-7 | State of residence | US |
| III-11 | Applicant and/or inventor | |
| III-11-1 | This person is: | applicant and inventor |
| III-11-2 | Applicant for | US only |
| III-11-4 | Name (LAST, First) | POINDEXTER, Graham |
| III-11-5 | Address: | 15 Fox Hollow Road<br>Old Saybrook, CT 06475<br>United States of America |
| III-11-6 | State of nationality | US |
| III-11-7 | State of residence | US |

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|---|---|---|
| III-12 | Applicant and/or inventor | |
| III-12-1 | This person is: | applicant and inventor |
| III-12-2 | Applicant for | US only |
| III-12-4 | Name (LAST, First) | VIG, Shikha |
| III-12-5 | Address: | 15 Park Place<br>Durham, CT 06422<br>United States of America |
| III-12-6 | State of nationality | IN |
| III-12-7 | State of residence | US |
| IV-1 | Agent or common representative; or address for correspondence<br>The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: | agent |
| IV-1-1 | Name (LAST, First) | MAKUJIMA, Shah |
| IV-1-2 | Address: | Bristol-Myers Squibb Company<br>P.O. Box 4000<br>Princeton, NJ 08543-4000<br>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-1-5 | 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); BAKAM, 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, 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) |

PCT REQUEST

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| | | |
|---|---|---|
| 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: 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<br>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<br>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<br>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 |
| 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 BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW |
| V-5 | Precautionary Designation Statement<br>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-6 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-6 | Exclusion(s) from precautionary designations | NONE |
| VI-1 | Priority claim of earlier national application | |
| VI-1-1 | Filing date | 05 June 2002 (05.06.2002) |
| VI-1-2 | Number | 60/386,138 |
| VI-1-3 | Country | US |

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**PCT REQUEST**

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| | | | |
|---|---|---|---|
| VI-2 | Priority claim of earlier national application | | |
| VI-2-1 | Filing date | 13 June 2002 (13.06.2002) | |
| VI-2-2 | Number | 60/388,617 | |
| VI-2-3 | Country | US | |
| VI-3 | Priority claim of earlier national application | | |
| VI-3-1 | Filing date | 19 June 2002 (19.06.2002) | |
| VI-3-2 | Number | 60/389,870 | |
| VI-3-3 | Country | US | |
| VI-4 | Priority claim of earlier national application | | |
| VI-4-1 | Filing date | 01 July 2002 (01.07.2002) | |
| VI-4-2 | Number | 60/393,200 | |
| VI-4-3 | Country | US | |
| VI-5 | Priority claim of earlier national application | | |
| VI-5-1 | Filing date | 25 September 2002 (25.09.2002) | |
| VI-5-2 | Number | 60/413,534 | |
| VI-5-3 | Country | US | |
| VI-6 | Priority document request | | |
| | The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): | VI-1, VI-2, VI-3, VI-4, VI-5 | |
| 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) | 7 | - |
| IX-2 | Description | 275 | - |
| IX-3 | Claims | 32 | - |
| IX-4 | Abstract | 1 | EABST00.TXT |
| IX-5 | Drawings | 0 | - |
| IX-7 | TOTAL | 315 | |

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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) | MAKUJIMA, Shoji | |

**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<br>0-1 | Para uso únicamente de la Oficina Receptora<br>Solicitud Internacional No. | |
| 0-2 | Fecha de Presentación Internacional | |
| 0-3 | Nombre de la Oficina Receptora y "Solicitud Internacional PCT" | |
| | | |
| 0-4<br>0-4-1 | Forma – Solicitud PCT PCT/RO/101<br>Utilización preparada | PCT-EASY Versión 2.92 (actualizado 01.04.2003) |
| 0-5 | Solicitud<br>El signatario solicitó que la presente solicitud internacional se procese de acuerdo al Tratado de Cooperación en Patente | |
| 0-6 | Oficina Receptora (especificada por el solicitante) | Oficina Norteamericana de Patentes y Marcas (USPTO) (RO/US) |
| 0-7 | Referencia de archivo del agente o solicitante | CT2777 |
| I | Título de la invención | ANTAGONISTAS DE RECEPTORES DE PEPTIDOS RELACIONADOS CON EL GEN DE CALCITONINA |
| II<br>II-1<br>II-2<br>II-4<br>II-5<br><br><br><br>II-6<br>II-7<br>II-8<br>II-9 | Solicitante<br>Esta persona es:<br>Solicitante para<br>Nombre<br>Dirección:<br><br><br><br>Estado de nacionalidad<br>Estado de residencia<br>Número Telefónico<br>Número Facsímil | <br>únicamente solicitante<br>todos los Estados designados excepto US<br>BRISTOL-MYERS SQUIBB COMPANY<br>P.O. Box 4000<br>Route 206 and Provinceline Road<br>Princeton, NJ 08543-4000<br>Estados Unidos de América<br>US<br>US<br>609-252-4000<br>609-252-4526 |
| III-1<br>III-1-1<br>III-1-2<br>III-1-4<br>III-1-5<br><br><br><br>III-1-6<br>III-1-7 | Solicitante y/o Inventor<br>Esta persona es:<br>Solicitante para<br>Nombre (ULTIMO, Primero)<br>Dirección:<br><br><br><br>Estado de nacionalidad<br>Estado de residencia | <br>solicitante e inventor<br>únicamente US<br>CHATURVEDULA, Prasad, V.<br>190 Lancaster Way<br>Cheshire, CT 06410<br>Estados Unidos de América<br>US<br>US |

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| | | |
|---|---|---|
| III-2 | Solicitante y/o inventor | |
| III-2-1 | Esta persona es: | solicitante e inventor |
| III-2-2 | Solicitante para | únicamente US |
| III-2-4 | Nombre (ULTIMO, Primero) | CHEN, Ling |
| III-2-5 | Dirección: | 193 McCormick Lane<br>Middletown, CT 06457<br>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 | únicamente US |
| III-3-4 | Nombre (ULTIMO, Primero) | CIVIELLO, Rita |
| III-3-5 | Dirección: | 90 Cow Hill Road<br>Killingworth, CT 06419<br>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 | únicamente US |
| III-4-4 | Nombre (ULTIMO, Primero) | CONWAY, Charles, Mark |
| III-4-5 | Dirección: | 825 Farmington Drive<br>Cheshire, CT 06410<br>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 | únicamente US |
| III-5-4 | Nombre (ULTIMO, Primero) | DEGNAN, Andrew, P. |
| III-5-5 | Dirección: | 123 York Street, Apt. 22-P<br>New Haven, CT 06511<br>Estados Unidos de América |
| III-5-6 | Estado de nacionalidad | US |
| III-5-7 | Estado de residencia | US |

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| | | |
|---|---|---|
| III-6 | Solicitante y/o inventor | |
| III-6-1 | Esta persona es: | solicitante e inventor |
| III-6-2 | Solicitante para | únicamente US |
| III-6-4 | Nombre (ULTIMO, Primero) | DUBOWCHIK, Gene, M. |
| III-6-5 | Dirección: | 65 Spring Street<br>Middlefield, CT 06455<br>Estados Unidos de América |
| III-6-6 | Estado de nacionalidad | US |
| III-6-7 | Estado de residencia | US |
| OIII-7 | Solicitante y/o inventor | |
| III-7-1 | Esta persona es: | solicitante e inventor |
| III-7-2 | Solicitante para | únicamente US |
| III-7-4 | Nombre (ULTIMO, Primero) | HAN, Xiaojun |
| III-7-5 | Dirección: | 65 Ridgecrest Drive<br>Cheshire, CT 06410<br>Estados Unidos de América |
| III-7-6 | Estado de nacionalidad | CN |
| III-7-7 | Estado de residencia | US |
| III-8 | Solicitante y/o inventor | |
| III-8-1 | Esta persona es: | solicitante e inventor |
| III-8-2 | Solicitante para | únicamente US |
| III-8-4 | Nombre (ULTIMO, Primero) | KARAGEORGE, George, N. |
| III-8-5 | Dirección: | 34 Fox Run Road<br>Portland, CT 06480<br>Estados Unidos de América |
| III-8-6 | Estado de nacionalidad | US |
| III-8-7 | Estado de residencia | US |
| III-9 | Solicitante y/o inventor | |
| III-9-1 | Esta persona es: | solicitante e inventor |
| III-9-2 | Solicitante para | únicamente US |
| III-9-4 | Nombre (ULTIMO, Primero) | LUO, Guanglin |
| III-9-5 | Dirección: | 135 Devonshire Lane<br>Madison, CT 06443<br>Estados Unidos de América |
| III-9-6 | Estado de nacionalidad | CN |
| III-9-7 | Estado de residencia | US |

| | | |
|---|---|---|
| III-10 | Solicitante y/o inventor | |
| III-10-1 | Esta persona es: | solicitante e inventor |
| III-10-2 | Solicitante para | únicamente US |
| III-10-4 | Nombre (ULTIMO, Primero) | MACOR, Jonh, E. |
| III-10-5 | Dirección: | 644 Mosse Hill Road<br>Guilford, CT 06437<br>Estados Unidos de América |
| III-10-6 | Estado de nacionalidad | US |
| III-10-7 | Estado de residencia | US |
| III-11 | Solicitante y/o inventor | |
| III-11-1 | Esta persona es: | solicitante e inventor |
| III-11-2 | Solicitante para | únicamente US |
| III-11-4 | Nombre (ULTIMO, Primero) | POINDEXTER, Graham |
| III-11-5 | Dirección: | 15 Fox Hollow, Road<br>Old Saybrook, CT 06475<br>Estados Unidos de América |
| III-11-6 | Estado de nacionalidad | US |
| III-11-7 | Estado de residencia | US |
| III-12 | Solicitante y/o inventor | |
| III-12-1 | Esta persona es: | solicitante e inventor |
| III-12-2 | Solicitante para | únicamente US |
| III-12-4 | Nombre (ULTIMO, Primero) | VIG, Shikha |
| III-12-5 | Dirección: | 15 Park Place<br>Durham, CT 06422<br>Estados Unidos de América |
| III-12-6 | Estado de nacionalidad | IN |
| III-12-7 | Estado de residencia | US |
| IV-1 | Agente o representante común; o dirección para correspondencia<br>Por la presente la persona identificada en lo siguiente es / ha sido nombrada para actuar a nombre de el o los solicitantes ante las Autoridades Internacionales competentes como: | agente |
| IV-1-1 | Nombre (ULTIMO, Primero) | MAKUJINA, Shah |
| IV-1-2 | Dirección: | Bristol-Myers Squibb Company<br>P.O Box 4000<br>Princeton, NJ 08543-4000<br>Estados Unidos de América |
| IV-1-3 | Número Teléfono | 203-677-7268 |
| IV-1-4 | Número Facsimil | 203-677-6900 |
| IV-1-5 | correo electrónico | shah.makujina@bms.com |
| IV-1-6 | Registro de agente No. | 41,174 |

| | | |
|---|---|---|
| | | agente(s) adicional(es) con la misma dirección como el primer agente nombrado<br>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, Audrey (39,024); ALGIERI, Aldo (13,697); 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 | Estados Designados | |
| V-1 | Patente Regional<br>(otras clases de protección o tratamiento, si existen, son especificadas entre paréntesis después de la o las designaciones concernientes) | AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW y cualquier otro Estado que sea miembro del protocolo de Harare y miembro del PCT<br>EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro Estado que sea miembro del acuerdo Euroasiático sobre patentes y miembro del PCT<br>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 y cualquier otro Estado que sea miembro del acuerdo Europeo sobre patentes y miembro del PCT<br>OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro Estado que sea miembro del acuerdo OAPI sobre patentes y miembro del PCT |

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| | | |
|---|---|---|
| V-2 | Patente Nacional (otras clases de protección o tratamiento, si existen, son especificadas entre paréntesis después de la o las designaciones concernientes) | AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW |
| V-5 | Declaración de Designación Precautoria<br><br>En adición a las designaciones hechas bajo los puntos V-1, V-2 y V-3, el solicitante también hace todas las designaciones bajo la Regla 4.9(b) que deban ser permitidas bajo el PCT excepto cualesquiera designaciones del o los Estados indicados bajo el punto V-6 siguiente. El solicitante declara que aquellas designaciones adicionales son objeto para confirmación y que cualquier designación que no es confirmada después del término de 15 meses de la fecha de prioridad para ser relacionada como retiro por el solicitante en el término de ese tiempo límite. | |
| V-6 | Exclusión(es) de las designaciones precautorias | NINGUNA |
| VI-1 | Reclamo de prioridad de la solicitud nacional anterior. | |
| VI-1-1 | Fecha de presentación | 5 de Junio de 2002 (05.06.2002) |
| VI-1-2 | Número | 60/386,138 |
| VI-1-3 | País | US |
| VI-2 | Reclamo de prioridad de la solicitud nacional anterior. | |
| VI-2-1 | Fecha de presentación | 13 de Junio de 2002 (13.06.2002) |
| VI-2-2 | Número | 60/388,617 |
| VI-2-3 | País | US |
| VI-3 | Reclamo de prioridad de la solicitud nacional anterior. | |
| VI-3-1 | Fecha de presentación | 19 de Junio de 2002 (19.06.2002) |
| VI-3-2 | Número | 60/389,870 |
| VI-3-3 | País | US |
| VI-4 | Reclamo de prioridad de la solicitud nacional anterior. | |
| VI-4-1 | Fecha de presentación | 1 de Julio de 2002 (01.07.2002) |
| VI-4-2 | Número | 60/393,200 |
| VI-4-3 | País | US |

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| VI-5 | Reclamo de prioridad de la solicitud nacional anterior. | | |
| VI-5-1 | Fecha de presentación | 25 de Septiembre de 2002 (25.09.2002) | |
| VI-5-2 | Número | 60/413,534 | |
| VI-5-3 | País | US | |
| VI-2 | Solicitud de documento de prioridad Se solicita a la oficina receptora que prepare y transmita a la Oficina Internacional una copia certificada de la(s) primera(s) solicitud(es) identificada(s) anteriormente como cuadro(s): | VI-1, VI-2, VI-3, VI-4, VI-5 | |
| VII-1 | Autoridad de Búsqueda Internacional Seleccionada | Oficina Norteamericana de Patentes y Marcas (USPTO) (ISA/US) | |
| VIII | Aclaraciones | Número de aclaraciones | |
| VIII-1 | Acerca de la identidad del inventor | - | |
| VIII-2 | Acerca de la autorización del solicitante de solicitar y obtener una patente en el momento de la solicitud internacional | - | |
| VIII-3 | Acerca de la autorización del solicitante de reclamar la prioridad de una solicitud anterior, en el momento de la solicitud internacional | - | |
| VIII-4 | Aclaración de los inventores (solo para los Estados Unidos de América) | - | |
| VIII-5 | Aclaraciones con respecto a publicaciones no dañinas o a excepciones de daños a la novedad | - | |
| IX | Lista verificada | número de hojas | archivo(s) electrónicos anexos |
| IX-1 | Solicitud (incluyendo hojas de aclaraciones) | 7 | - |
| IX-2 | Descripción | 275 | - |
| IX-3 | Reivindicaciones | 32 | - |
| IX-4 | Resumen | 1 | EZABST00.TXT |
| IX-5 | Dibujos | 0 | - |
| IX-7 | TOTAL | 315 | |
| | Artículos anexos | Documento(s) anexos | Archivos(s) Electrónicos |
| IX-8 | Copia de la hoja de cálculo | ✓ | - |
| IX-9 | Copia del poder general del apoderado | ✓ | - |
| IX-17 | Disco flexible PCT-EASY | - | Disco flexible |
| IX-18 | Otro (especificar): | Certificación | - |
| IX-19 | Figura de los dibujos que debe ser unida al resumen | | |
| IX-20 | Idioma de presentación de la solicitud internacional | Inglés | |
| X-1 | Firma del solicitante, agente o representante común | | |
| X-1-1 | Nombre (LAST, First) | MAKUJINA, Shah | |
| **PARA USO ÚNICAMENTE DE LA OFICINA RECEPTORA** | | | |
| 10-1 | Fecha de recepción actual de la Solicitud Internacional propuesta | | |
| 10-2 | Dibujos: | | |

PETITORIO PCT

Original (para presentación) - Impreso el 27.05.2003 02:56:20 PM

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CT2777

| | | |
|---|---|---|
| 10-2-1<br><br>10-2-2 | Recibido<br><br>No recibido | |
| 10-3 | Fecha corregida de la recepción actual debido a los documentos o dibujos recibidos posteriormente pero a tiempo que complementan la solicitud internacional propuesta | |
| 10-4 | Fecha de recepción a tiempo de las correcciones requeridas conforme al Artículo 11(2) del PCT | |
| 10-5 | Autoridad de Búsqueda Internacional | ISA/US |
| 10-6 | Transmisión de copia de búsqueda retardada hasta que la cuota de búsqueda sea pagada | |
| **PARA USO ÚNICAMENTE DE LA OFICINA INTERNACIONAL** | | |
| 11-1 | Fecha de recepción de la copia de registro por la Oficina Internacional | |

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

**NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

To:

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

| | |
|---|---|
| Date of mailing (day/month/year)<br>29 July 2003 (29.07.03) | |
| Applicant's or agent's file reference<br>CT2777 | IMPORTANT NOTIFICATION |
| International application No.<br>PCT/US03/16576 | International filing date (day/month/year)<br>27 May 2003 (27.05.03) |
| International publication date (day/month/year)<br>Not yet published | Priority date (day/month/year)<br>05 June 2002 (05.06.02) |
| Applicant<br>BRISTOL-MYERS SQUIBB COMPANY et al | |

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| Priority date | Priority application No. | Country or regional Office or PCT receiving Office | Date of receipt of priority document |
|---|---|---|---|
| 05 June 2002 (05.06.02) | 60/386,138 | US | 30 June 2003 (30.06.03) |
| 13 June 2002 (13.06.02) | 60/388,617 | US | 07 July 2003 (07.07.03) |
| 19 June 2002 (19.06.02) | 60/389,870 | US | 07 July 2003 (07.07.03) |
| 01 July 2002 (01.07.02) | 60/393,200 | US | 01 July 2003 (01.07.03) |
| 25 Sept 2002 (25.09.02) | 60/413,534 | US | 30 June 2003 (30.06.03) |

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

Facsimile No. (41-22) 338.89.70

Authorized officer

Hélène CAMPIN (Fax 338 8970)

Telephone No. (41-22) 338 9716

WO 03/104236
PCT/US03/16576

CT2777-wo-PCT

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

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

(PCT Rule 47.1(c), first sentence)

RECEIVED
BMS PATENT LAW

To:

MAKUJINA, Shah
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AME

JAN 06 2004
Docketed Item
Due Date
Attorney Shah

| Date of mailing *(day/month/year)* | |
|---|---|
| 18 December 2003 (18.12.03) | |
| Applicant's or agent's file reference | IMPORTANT NOTICE |
| 2042.1 | |

JAN 13 2004

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US03/16576 | 27 May 2003 (27.05.03) | 05 June 2002 (05.06.02) |

Applicant

BRISTOL-MYERS SQUIBB COMPANY et al

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

   AU, AZ, BY, CH, CN, CO, DE, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

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

   AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

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

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 18 December 2003 (18.12.03) under No. WO 03/104236

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

   The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

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

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

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

   The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>Judith Zahra |
|---|---|
| Facsimile No.(41-22) 740.14.35 | Telephone No.(41-22) 338.91.11 |

Form PCT/IB/308 (April 2002)

US006552043B1

(12) **United States Patent**
**Patchett et al.**

(10) **Patent No.: US 6,552,043 B1**
(45) **Date of Patent: Apr. 22, 2003**

(54) **BENZIMIDAZOLINYL PIPERIDINES AS CGRP LIGANDS**

(75) Inventors: **Arthur A. Patchett, Westfield, NJ (US); Raymond George Hill, Royston (GB); Lilas Yang, Edison, NJ (US)**

(73) Assignees: **Merck Sharpe & Dohme Ltd., Hertfordshire (GB); Merck & Co, Inc., Rahway, NJ (US)**

( * ) Notice: **Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.**

(21) Appl. No.: **09/806,372**

(22) PCT Filed: **Sep. 22, 1999**

(86) PCT No.: **PCT/GB99/03154**

§ 371 (c)(1),
(2), (4) Date: **May 30, 2001**

(87) PCT Pub. No.: **WO00/18764**

PCT Pub. Date: **Apr. 6, 2000**

**Related U.S. Application Data**

(60) **Provisional application No. 60/102,492, filed on Sep. 30, 1998.**

(51) **Int. Cl.**[7] ..... **A61K 31/445; C07D 609/14**
(52) **U.S. Cl.** ..... **514/322; 514/321; 514/323; 546/199; 546/202; 546/205**
(58) **Field of Search** ..... **514/321, 322, 514/323; 546/199, 202, 205**

(56) **References Cited**

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| WO | WO 98/44921 | 10/1998 |
| WO | WO 98/44922 | 10/1998 |
| WO | WO 98/45285 | 10/1998 |

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* cited by examiner

*Primary Examiner*—Cecilia Chang
(74) *Attorney, Agent, or Firm*—Raynard Yuro; David L. Ross

(57) **ABSTRACT**

**The present invention relates to benzimidazolinylpiperidine derivatives useful as ligands for CGRP (Calcitonin Gene-Related Peptide) receptors, their use in therapy, pharmaceutical compositions comprising them and methods of treatment using them.**

**5 Claims, No Drawings**

# BENZIMIDAZOLINYL PIPERIDINES AS CGRP LIGANDS

This application is a US National Phase application under 35 U.S.C. §371 of PCT Application No. PCT/GB99/03154, filed on Sep. 22, 1999, which claims priority under 35 U.S.C. 119 to U.S. Provisional No. 60/102,492, filed on Sep. 30, 1998.

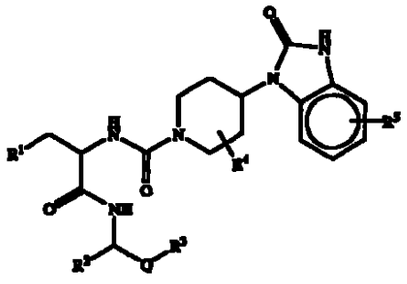
The present invention relates to benzimidazolinylpiperidine derivatives useful as ligands for CGRP (Calcitonin Gene-Related Peptide) receptors, processes for their preparation, their use in therapy, pharmaceutical compositions comprising them and methods of treatment using them.

CGRP is a naturally occurring 37-amino acid peptide that is generated by tissue-specific alternate processing of calcitonin messenger RNA and is widely distributed in the central and peripheral nervous system. CGRP is localised predominantly in sensory afferent and central neurons and exhibits several biological actions, including vasodilation. CGRP is expressed in α- and β-forms that vary by one and three amino acids in the rat and human, respectively.

CGRPα and CGRPβ display similar biological properties. When released from the cell, CGRP initiates its biological responses by binding to specific cell surface receptors that are predominantly coupled to the activation of adenylyl cyclase. CGRP receptors have been identified and pharmacologically evaluated in several tissues and cells, including those of brain, cardiovascular, endothelial, and smooth muscle origin.

Based on pharmacological properties, these receptors are divided into at least two subtypes, denoted $CGRP_1$ and $CGRP_2$. Human (h) CGRP-(8–37)α, a fragment of CGRP that lacks seven N-terminal amino acid residues, is a selective antagonist of $CGRP_1$-Rs, whereas the linear analogue of CGRP, diacetoamido methyl cystine CGRP ([Cys(ACM)2, 7]CGRP), is a selective agonist of $CGRP_2$-Rs.

We have now surprisingly found a class of compounds which are ligands, and preferably antagonists for CGRP receptors. In particular, they preferably bind selectively to human rather than rodent CGRP.



(I)

wherein:

$R^1$ is naphthyl or benzothienyl which is unsubstituted or substituted at up to three substitutable positions independently by $C_{1-6}$ alkyl, halogen, $C_{1-6}$ alkoxy, $CF_3$, $OCF_3$, $NO_2$, CN, methylenedioxy or ethylenedioxy;

$R^2$ is hydrogen, $C_{1-8}$ alkyl, $-(CH_2)_t$-aryl wherein aryl is selected from phenyl, biphenyl and naphthyl, $-(CH_2)_t$-heteroaryl wherein heteroaryl is selected from tetrazolyl, oxadiazolyl, thiadiazolyl, triazolyl and pyrazinyl, $-(CH_2)_qC(O)OR^6$, $-(CH_2)_qOR^6$, $-(CH_2)_qOC(O)R^6$, $-(CH_2)_qC(O)R^6$, $-(CH_2)_qC(O)(CH_2)_t$aryl, $-(CH_2)_qN(R^6)C(O)R^6$, $-(CH_2)_qC(O)N(R^6)_2$, $-(CH_2)_qN(R^6)SO_2R^6$, $-(CH_2)_qN(R_6)C(O)N(R^6)_2$, $-(CH_2)_qOC(O)N(R^6)_2$, $-(CH_2)_qN(R^6)C(O)OR^6$, $-(CH_2)_qN(R^6)SO_2N(R^6)_2$ and $-(CH_2)_qS(O)_mR^6$;

$R^3$ is $NH_2$;

$R^4$ is hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $OCF_3$ or $CF_3$;

$R^5$ is hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $OCF_3$ or $CF_3$;

$R^6$ is hydrogen, $C_{1-8}$ alkyl or $C_{3-7}$ cycloalkyl, and when two $R^6$ groups are present and both represent $C_{1-8}$ alkyl they may optionally together with the atom to which they are both attached form a $C_{3-8}$ ring;

Q is $-(CH_2)_t-C(R^7)(R^{7a})-(CH_2)_y-$ or $-(CH_2)_x-V-(CH_2)_y-$;

$R^7$ and $R^{7a}$ are independently chosen from hydrogen, $CF_3$, halogen, $C_{1-6}$ alkyl and $C_{1-6}$ alkoxy;

V is a $C_{3-8}$ non-aromatic cyclic or bicyclic ring or an aromatic ring which is benzene or naphthalene, said ring being unsubstituted or substituted at up to three substitutable positions independently by $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $OCF_3$, $CF_3$, CN, $NO_2$, methylenedioxy or ethylenedioxy;

m is 0, 1 or 2;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

x and y are independently 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

$R^1$ is preferably unsubstituted or substituted with one or two groups selected from methyl, methoxy, $CF_3$ or halogen. Most preferably $R^1$ is unsubstituted.

$R^2$ is preferably hydrogen, methyl or $(CH_2)_qC(O)OR^6$, for example $R^2$ is $^t$butyloxycarbonyl or hydrogen.

$R^4$ is preferably hydrogen, methyl, methoxy, halogen, $OCF_3$ or $CF_3$. In particular, $R^4$ is hydrogen.

$R^5$ is preferably hydrogen, methyl, methoxy, halogen $OCF_3$ or $CF_3$. In particular $R^5$ is hydrogen.

$R^6$ is preferably hydrogen, $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl. In particular $R^6$ may be hydrogen or $^t$butyl.

$R^7$ and $R^{7a}$ are preferably independently chosen from hydrogen, halogen, $CF_3$, methyl, methoxy and $OCF_3$. In particular both are hydrogen.

V is preferably an unsubstituted or substituted $C_{3-6}$ cycloalkyl or benzene. It is to be noted that the group $(CH_2)_y$ or, as the case may be $R^5$ is attached to any position of this ring, but the 3- and 4-positions are preferred. Most particularly V is cyclohexane or benzene.

m is preferably 0 or 2

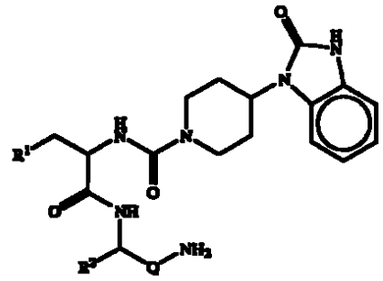
q is preferably 0, 1 or 2

t is preferably 0 or 1

x+y is preferably 0, 1, 2, 3 or 4, in particular 0 or 3.

Thus there is a preferred subclass of compounds of formula Ia:

(I)



wherein $R^1$ is unsubstituted naphthyl or benzothienyl;

$R^2$ is hydrogen or $C(O)OR^6$;

$R^6$ is $C_{1-4}$ alkyl;

Q is $-(CH_2)_x-C(R^7)(R^{7a})-(CH_2)_y-$ or $-(CH_2)_x-V-(CH_2)_y-$;

V is cycloalkyl or benzene;

x is 0, 1 or 2;

y is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical which may be straight, branched or cyclic. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl and t-butyl. "Alkoxy" groups are to be construed analogously.

The term "$C_{3-8}$ cyclic ring" includes groups such as cyclopentyl, cyclohexyl and methylcyclohexyl.

The term "halogen" is intended to include fluorine, chlorine, bromine and iodine.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following:

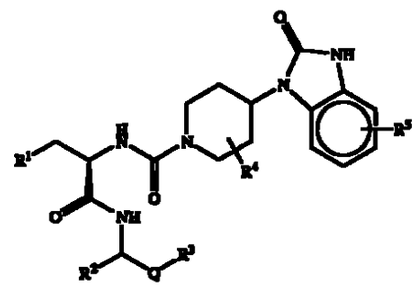
Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Camsylate, Carbonate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluconate, Glutamate, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, Tannate, Tartrate, Tosylate, and Valerate. A preferred salt is Hydrochloride.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention. Therefore, where a compound is chiral, the separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

Asymmetric centers may be present in the compounds of the instant invention depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixture and as pure or partially purified compounds are included within the ambit of this invention.

A prefered chiral configuration of the compounds of formula I is:

(I)



The ability of the compounds of the present invention to act as ligands for CGRP makes them useful as pharmacological agents for humans and animals, but particularly humans, for the treatment and prevention of disorders where CGRP may be involved. Such disorders include migraine, pain, cardiovascular disorders, inflammation, diabetes, Reynaud's syndrome, peripheral arterial insufficiency, subarachnoid and other cranial haemorrhages and as antitumour agents by controlling the flow of blood to tumours. Of these conditions, the treatment of migraine is particularly important.

The present invention therefore also provides a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Intravenous dosages or oral dosages of the compounds of the present invention, when used for the indicated effects, will range between about 0.001 to 5 mg/kg and 0.1 to 50 mg/kg, respectively. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, prefered compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and

are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The present invention also provides a compound of the present invention or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human or animal body by surgery, therapy or diagnosis.

There is also provided the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a condition with which CGRP is associated such as migraine, pain, cardiovascular disorders, inflammation, diabetes, Raynaud's syndrome, peripheral arterial insufficiency, subarachnoid and other cranial haemorrhages and tumours by controlling blood flow.

There is further disclosed a method of treating or protecting a subject suffering from or prone to a condition associated with CGRP by administering to that subject a therapeutically or prophylactically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof.

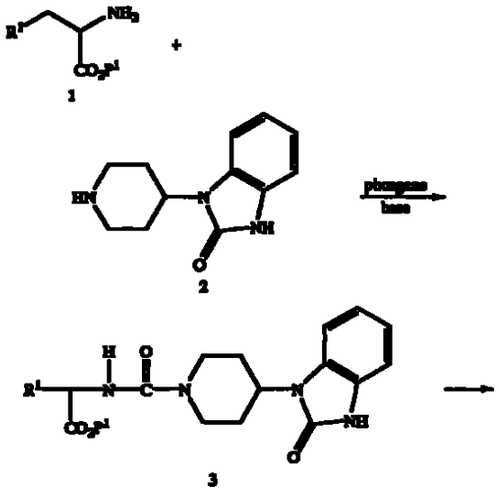
The preparation of compounds of Formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I are presented in the following reaction schemes.

The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The phrase "mixed urea formation" refers to conversion of two different amines to form their mixed urea by using phosgene or equivalents such as CDI, DSC, or p-nitrophenyl chloroformate. The reaction involves reacting one amine first with the phosgene or equivalents in the presence of a base such as NMM, TEA or DIEA in a inert solvent such as dichloromethane, THF and DMF or mixtures thereof, followed by addition of the second amine and a base such as NMM, TEA or DIEA. The uses of protective groups for amines and carboxylic acids to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present can be found in Greene, T. and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, N.Y. 1991. CBZ and BOC were used extensively and their removal conditions are known to those skilled in the art. For example, removal of CBZ groups can be achieved by a number of methods such as catalytic hydrogenation in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethyl sulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride, methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid, hydrochloric acid or hydrogen chloride gas.

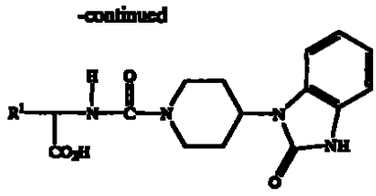
The protected amino acid derivatives required in the synthesis of compounds of Formula 1 are, in many cases, commercially available, where the protecting group ($P^1$) is, for example, methyl, allyl or benzyl groups. Other protected amino acid can be prepared by literature methods (Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press: Oxford, 1989). Many of the piperidines of Formula 2 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. Some of these methods are illustrated in the subsequent schemes. Purification procedures include crystallization, normal phase or reverse phase chromatography.

The compounds of the present invention can be prepared readily according to the following Schemes or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. The definition for $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^{7a}$ and Q is described above unless otherwise stated.

SCHEME 1



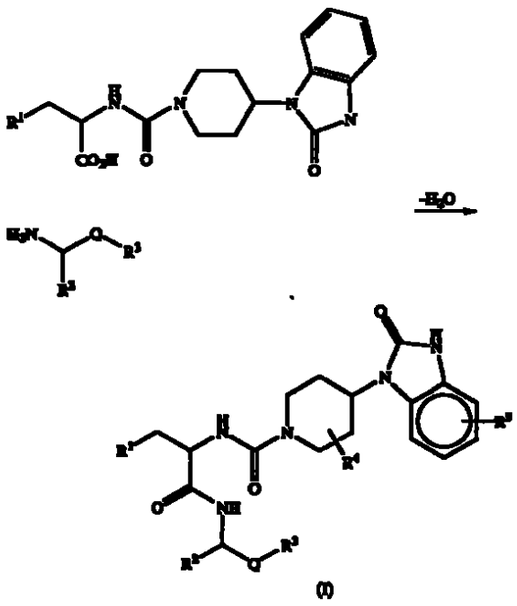
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4A

Intermediates of Formula 4A can be synthesized as described in Scheme 1. Mixed urea formation between the protected amino acid 1 and the piperidine of Formula 2, is conveniently carried out under usual urea formation reactions use phosgene or equivalents such as CDI, DSC, or p-nitrophenyl chloroformate. Removal of the $P^1$ protecting group can be achieved by saponification for most esters, or by catalytic hydrogenolysis when $P^1$ is benzyl, or by palladium (0) based homogeneous catalysis when $P^1$ is allyl. Intermediate 4A can be used as a common intermediate with variation of the rest of the molecule of Formula I as shown in Scheme 2.

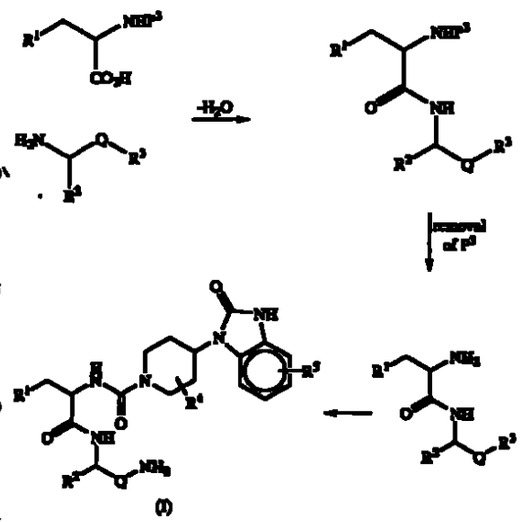
SCHEME 2



(I)

Intermediates of formula 4 (the first compound above) can be coupled to intermediates of formula 5 (the second compound above) under standard ester or peptide coupling reaction conditions. Primary amine $R^3$ may be protected by a group such as BOC, Cbz, etc. which is subsequently removed. Many of the selectively protected diamines or amino alcohols of Formula 5 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. Some of these methods are illustrated in subsequent schemes. The compound 4 is also generally protected with a protecting group as defined above.

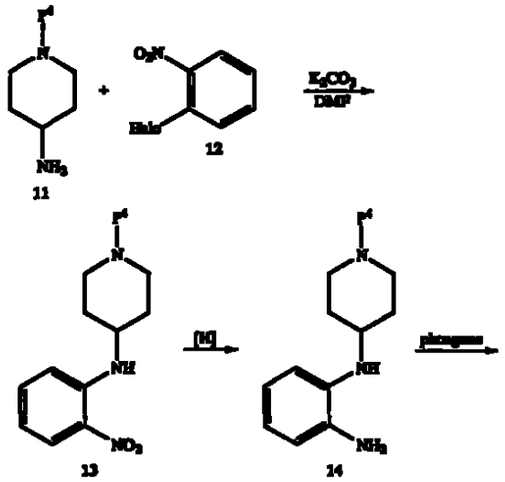
SCHEME 3



(I)

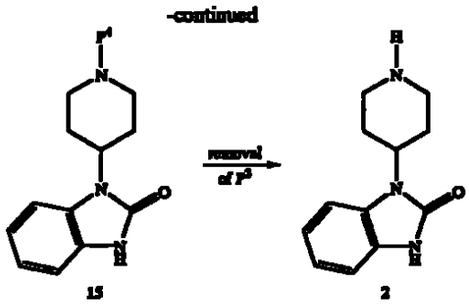
Alternatively, compounds of Formula I can be prepared starting from compound 5. The protected amino acid derivatives 8 (the first compound above) are in many cases commercially available, where P3 is, for example, BOC, Cbz, Fmoc, and the like. N-Protected amino acid 8 can be coupled to intermediates of formula 5, to afford compounds of Formula 9 (the first product above) under standard ester or peptide coupling reaction conditions. The protecting group in compound 8 is selected with the criteria that its removal can be achieved without removing $P^2$. When the $P^2$ protecting group is removed to afford compound 10 (the second product above), this compound can be further converted to compounds of formula I-A according to the procedures described in Scheme 1. Again $R^3$ is optionally protected.

SCHEME 4



11 12 13 14

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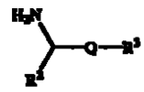



15 2

The piperidinylbenzimidazolinone 2 without substitution is commercially available; derivatives with substituents on the benzene ring are prepared by the methods shown in Scheme 4 as described in *J. Med. Chem.*, 30, 814–819 (1987) and U.S. Pat. No. 3,910,930, hereby incorporated by reference. $P^4$ is a protecting group such as benzyl, methyl, BOC, Cbz, ethyloxycarbonyl and the like. Thus, condensation of the commercially available 4-aminopiperidine 11, where $P^4$ is C(O)OEt, with a substituted o-halo nitrobenzene 12 gives the nitro compound 13. Reduction of the nitro group to an amine can be accomplished by catalytic hydrogenation with a catalyst such as Raney Ni, palladium on carbon or platinum on carbon in a protic solvent such as ethanol. Ring closure can be effected by phosgene or its equivalent such as DSC, CDI in the presence of a base. The protecting group $P^4$ can be removed by alkaline hydrolysis in the case of C(O)OEt or can be removed by the standard deprotection conditions as described in Greene, T. and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, N.Y. 1991.

In many cases, compounds of Formula 5 or its mono protected form within the scope of this invention are either commercially available or known in the art. Mono Boc protected amine can be prepared by reacting excess diamine with $Boc_2O$ in methanol, where Boc protected amino alcohols can be prepared by reacting the amino alcohol with $BOc_2O$.

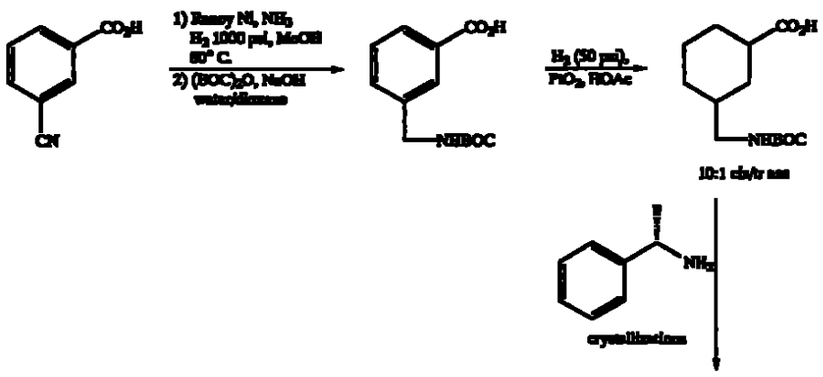
Other compounds in the above schemes are commercially available or can be made from commercially available compounds by standard methods.



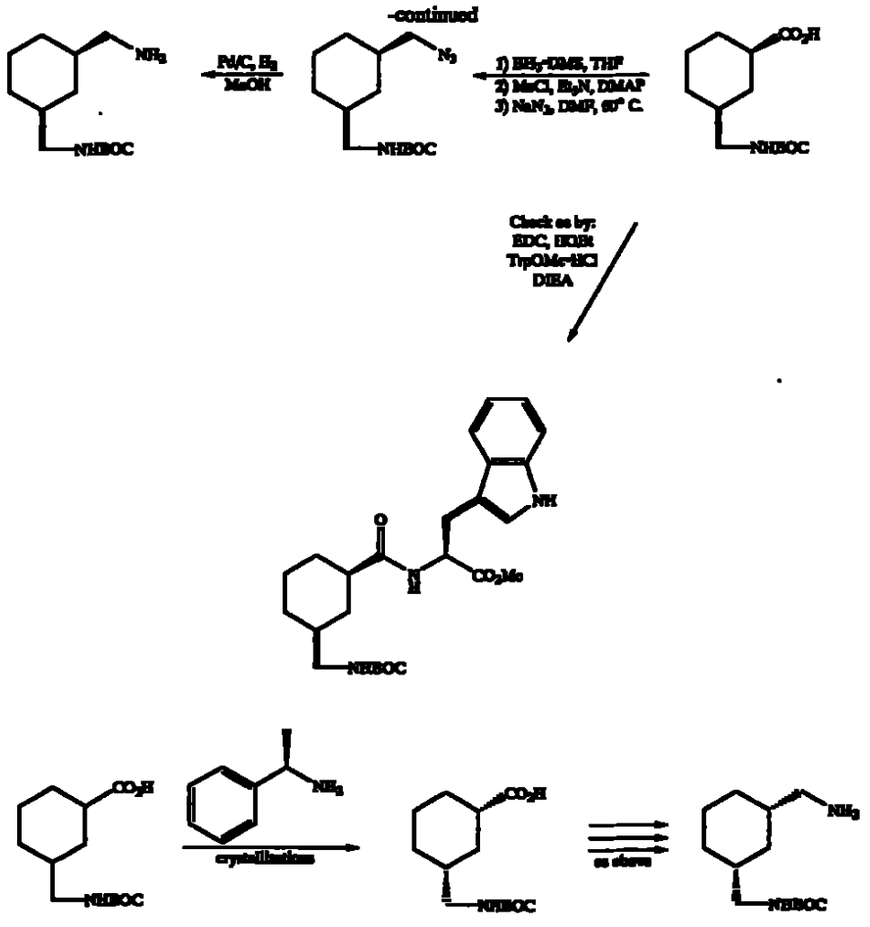
Compounds of Formula 5 can be amino acids, which in some cases are commercially available. Amino acids can be modified to give compounds as defined by the scope of the instant application. For example, with the two amino groups properly protected, the carboxylic acid can be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. The acid can also be converted amides with a variety of amines as defined. The acid can be reduced to alcohol, which can be converted to ether by alkylation or reduced with methods known to those skilled in the art.

Optically pure cis-3-aminomethyl-1-BOC-aminomethyl cyclohexane enantiomers are prepared (Scheme 5) starting from commercially available m-cyanobenzoic acid. Reduction of the nitrile with Raney $Ni/H_2$ is followed by protection of the resulting 1° amino group. Reduction of the aromatic ring is then accomplished using $PtO_2$ as catalyst to give predominantly the cis-cyclohexane carboxylic acid. A sequence of crystallizations using either (S) or (R)-a-methylbenzylamine to form the salt, generates the homochiral cis acids as shown below. Enantiomeric purity is evaluated by derivatization of the acids with Trp-OMe and integration of the methoxy methyl singlets in the $^1H$ NMR spectra. The absolute stereochemistries are determined by solving the x-ray structure for the pure salt obtained from crystallization with the S-enantiomer of a-methylbenzylamine and are as shown in Scheme 5 below. Borane reduction of the pure acids, followed by conversion of the resulting alcohols to their mesylates and displacement with azide anion furnishes the corresponding azidomethyl compounds. Reduction of the azide group (Pd/C, $H_2$) gives the desired amines, ready for incorporation into final target compounds.

SCHEME 5

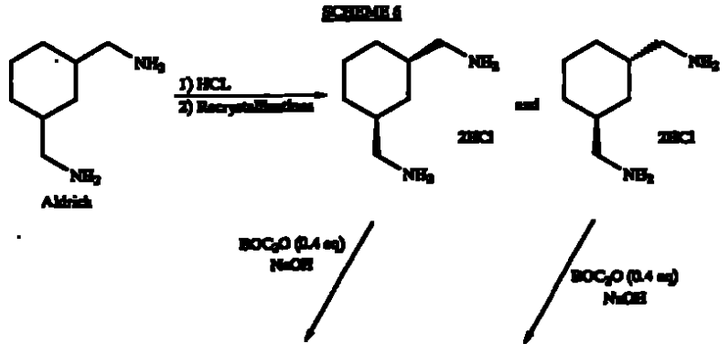


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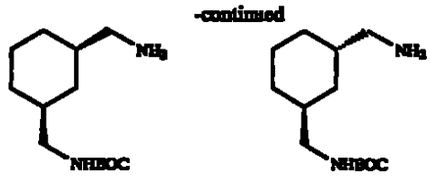



The racemic cis and trans-3-aminomethyl-1-BOC-aminomethyl cyclohexane isomers are also prepared (Scheme 6) and incorporated into target compounds. Commercially available bis-aminomethylcyclohexane (sold as a mixture of cis and trans isomers) is resolved into the pure cis and pure trans isomers by conversion to the dihydrochloride salts and crystallization from methanol/ethyl acetate. Mono-BOC protection is accomplished by slow addition of $BOC_2O$ to an excess of the diamines.

SCHEME 6



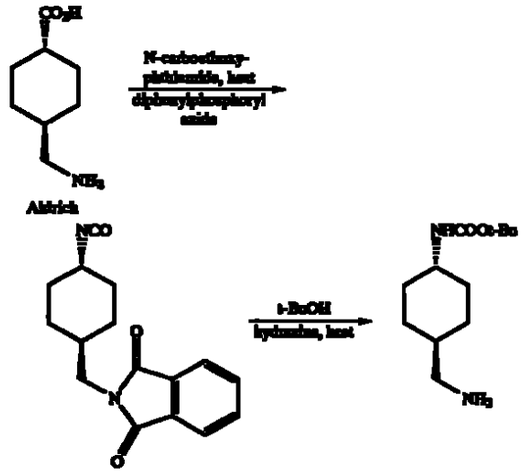
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racemic racemic

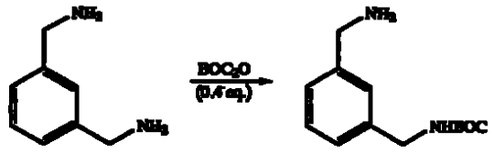
Trans-1-N-BOC-amino-4-aminomethylcyclohexanes are prepared from the commercially available amino acid shown below (Scheme 10). Protection of the amine as its phthalimide, followed by Curtius rearrangement gives the amino-protected isocyanate. Trapping of the isocyanate with t-butanol, is then followed by removal of the phthalimide protecting group using hydrazine to provide the target amine, which is incorporated into various analogs.

SCHEME 10



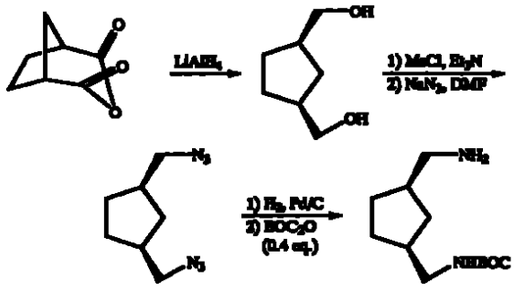

Mono-protected-1,3-bisaminomethylbenzene intermediates also lead to potent analogs. These are prepared (Scheme 11) starting from commercially available m-xylylenediamine. Slow addition of $BOC_2O$ to an excess of diamine furnishes the mono-protected amine, which is employed in the synthesis of target compounds.

SCHEME 11




Racemic cis-3-aminomethyl-1-BOC-aminomethylcyclopentane is prepared as shown in Scheme 12. Reduction of the commercially available anhydride give cis-hydroxymethylcyclopentane. Conversion to the bis-mesylate, followed by displacement with azide results in the corresponding bis-azide. Reduction of the azide groups and mono-protection (as described previously) provides the desired intermediate amine.

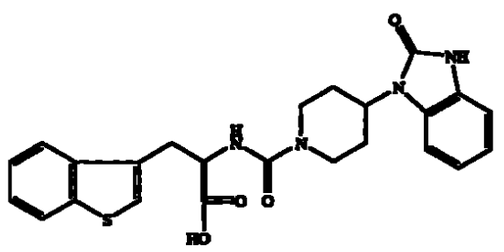
SCHEME 12




The compounds of the present invention have been tested in a cell assay for activity as ligands for the human CGRP receptor. The methodology for this is as described in Semark et al. Molecular Neuropharmacology (1992) 2, 311–317. Likewise their functional activity can be determined by methods in that paper. The specific Examples of the present invention all inhibited [$^{125}$I]hCGRP in SK-N-MC cell membranes with a Ki of less than 10 μM.

The preferred compounds of the invention are any or all of those specifically set forth in the Examples below. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

Intermediate 1

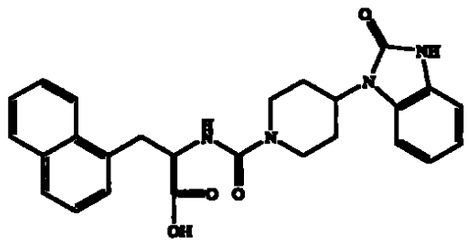



A suspension of D-β-(3-benzothienyl)alanine methyl ester (2.45 mmol), disuccinimidyl carbonate (0.626 g, 1.0 equiv.) and DIEA (0.426 mL, 4 equiv.) in dichloromethane (20 mL) was stirred at room temperature for 30 minutes, during which time the reaction becomes clear. 4-(2-Keto-1-benzimidazolinyl)piperidine (0.568 g) was added and the

mixture was permitted to stir overnight. The reaction mixture was diluted with dichloromethane, and washed in succession with 1N HCl, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude product was purified by silica flash column chromatography eluting with ethyl acetate to afford the methyl ester intermediate (1.09 g).

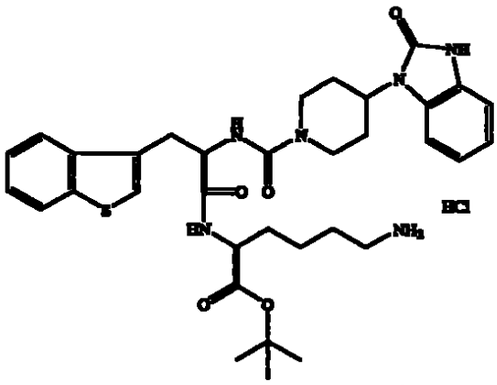
To a stirred solution of the methyl ester (1.09 g) from the previous step in THF/AMeOH/$H_2O$ (1:1:1) was added lithium hydroxide (384 mg) at 0° C. The reaction mixture was stirred for 4 h and was quenched by the addition of hydrochloric acid (2 equiv.). The mixture was then evaporated to remove the solvents, and partitioned between dilute hydrochloric acid and ethyl acetate. The organic extracts were washed with brine, dried over magnesium sulfate and evaporated to give the desired intermediate (1.1 g, crude).

Intermediate 2



Intermediate 2 was similarly prepared as Intermediate 1 using D-β-(1-naphthyl)-Alanine methyl ester and 4-(2-Keto-1-benzimidazolinyl)piperidine.

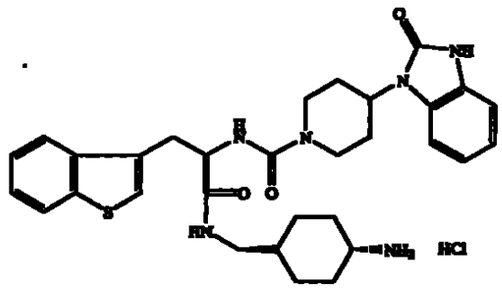
EXAMPLE 1



To a solution of Intermediate 1 (53 mg), HOBt (1 equiv.), and Lys(Cbz)OBu$^t$ (41 mg) in dichloromethane (2 mL) at 0° C., was added EDC (32 mg, 1.5 equiv.) and the resulting solution was stirred for 4 h. The reaction mixture was then diluted with dichloromethane and washed with dilute HCl, brine, saturated $NaHCO_3$ and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by silica eluting with 2% methanol in ethyl acetate to give the Cbz intermediate (79 mg).

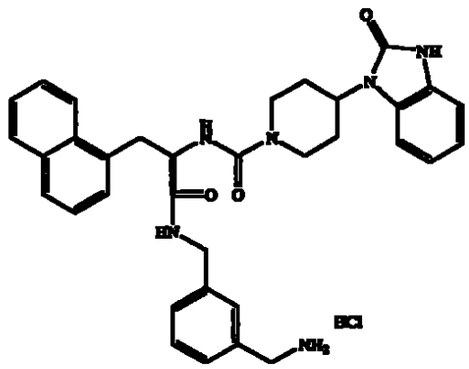
The intermediate prepared as described above (60 mg) was combined with 10% Pd/C (10 mg) and concentrated HCl (1 equiv.) in ethanol (5 mL). This mixture was stirred under a $H_2$ balloon for 1 day and during which time 3 batches 10% Pd/C (10 mg each) was added. The mixture filtered through celite. The filter cake was washed with an additional 10 mL of ethanol and the combined filtrates were concentrated to give the desired product as a hydrochloride salt (50 mg).

EXAMPLE 2



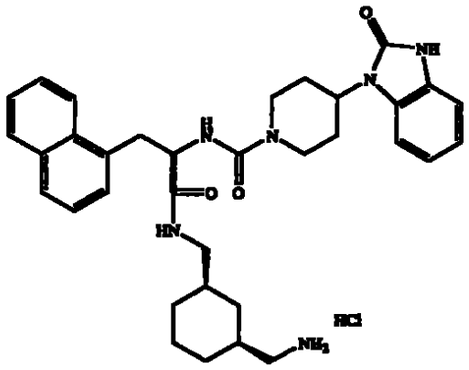
To a solution of Intermediate 1 (53 mg), HOBt (1 equiv.), and trans-4-aminomethyl-1-(cyclohexylmethyll-carbamic acid tert-butyl ester (58 mg) in dichloromethane (2 mL) at 0° C., was added EDC (32 mg, 1.5 equiv.) and the resulting solution was stirred for 4 h. The reaction mixture was then diluted with dichloromethane and washed with dilute HCl, brine, saturated $NaHCO_3$ and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by silica eluting with 5% methanol in ethyl acetate to give the Boc intermediate (58 mg). Treatment of the intermediate with 4 N HCl in dioxane (1 mL) in ethyl acetate (2 mL) gave the desired product (41 mg) after evaporation.

EXAMPLE 3



To a solution of Intermediate 2 (120 mg), HOBt (1 equiv.), and 3-aminomethylbenzyl-carbamic acid tert-butyl ester (62 mg) in dichloromethane (5 mL) at 0° C., was added EDC (60 mg, 1.5 equiv.) and the resulting solution was stirred for 2 days during which time the reaction mixture was warmed to ambient temperature. The reaction mixture was diluted with dichloromethane and washed with dilute HCl, brine, saturated $NaHCO_3$ and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by silica eluting with 7% methanol in ethyl acetate to give the Boc intermediate (110 mg). Treatment of the intermediate with 4 N HCl in dioxane (2 mL) in ethyl acetate (2 mL) gave the desired product (90 mg) after evaporation.

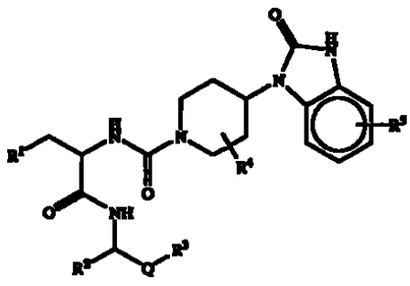
EXAMPLE 4



To a solution of Intermediate 2 (100 mg, 0.218 mmol), HOBt (31 mg, 1.05 equiv.), and [3(R)-aminomethyl-1(S)-cyclohexylmethyl]-carbamic acid tert-butyl ester (56 mg, 1.05 equiv.) in dichloromethane (8 mL) at 0° C., was added EDC (50 mg, 1.2 equiv.) and the resulting solution was stirred for 2 days. The reaction mixture was then diluted with dichloromethane and washed with dilute HCl, brine, saturated $NaHCO_3$ and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by silica eluting with 7% methanol in ethyl acetate to give the Boc intermediate (100 mg). Treatment of the intermediate with 4 N HCl in dioxane (1 mL) in ethyl acetate (2 mL) gave the desired product after evaporation.

What is claimed is:

1. A compound of formula I



(I)

wherein:

$R^1$ is naphthyl or benzothienyl which is unsubstituted or substituted at up to three substitutable positions independently by $C_{1-6}$ alkyl, halogen, $C_{1-6}$ alkoxy, $CF_3$, $OCF_3$, $NO_2$, CN, methylenedioxy or ethylenedioxy;

$R^2$ is hydrogen, $C_{1-6}$ alkyl, $-(CH_2)_t$-aryl wherein aryl is selected from phenyl, biphenyl and naphthyl, $-(CH_2)_t$-heteroaryl wherein heteroaryl is selected from tetrazolyl, oxadiazolyl, thiadiazolyl, triazolyl and pyrazinyl, $-(CH_2)_qC(O)OR^6$, $-(CH_2)_qOR^6$, $-(CH_2)_qOC(O)R^6$, $-(CH_2)_qC(O)R^6$, $-(CH_2)_qC(O)(CH_2)_t$aryl, $-(CH_2)_qN(R^6)C(O)R^6$, $-(CH_2)_qC(O)N(R^6)_2$, $-(CH_2)_qN(R^6)SO_2R^6$, $-(CH_2)_qN(R^6)C(O)N(R^6)_2$, $-(CH_2)_qOC(O)N(R^6)_2$, $-(CH_2)_qN(R^6)C(O)OR^6$, $-(CH_2)_qN(R^6)SO_2N(R^6)_2$ and $-(CH_2)_qS(O)_mR^6$;

$R^3$ is $NH_2$;

$R^4$ is hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $OCF_3$ or $CF_3$;

$R^5$ is hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $OCF_3$ or $CF_3$;

$R^6$ is hydrogen, $C_{1-6}$ alkyl or $C_{3-7}$ cycloalkyl, and when two $R^6$ groups are present and both represent $C_{1-6}$ alkyl they may optionally together with the atom to which they are both attached form a $C_{3-6}$ ring;

Q is $-(CH_2)_x-C(R^7)(R^{7a})-(CH_2)_y-$ or $-(CH_2)_x-V-(CH_2)_y-$;

$R^7$ and $R^{7a}$ are independently chosen from hydrogen, $CF_3$, halogen, $C_{1-6}$ alkyl and $C_{1-6}$ alkoxy;

V is a $C_{3-6}$ non-aromatic cyclic or bicyclic ring or an aromatic ring which is benzene or naphthalene, said ring being unsubstituted or substituted at up to three substitutable positions independently by $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $OCF_3$, $CF_3$, CN, $NO_2$, methylenedioxy or ethylenedioxy;

m is 0, 1 or 2;

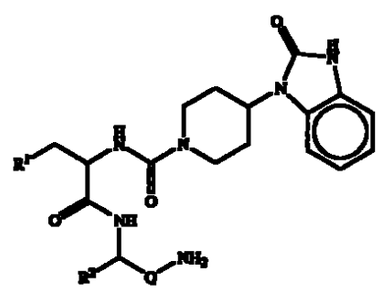
q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

x and y are independently 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula Ia:



(Ia)

wherein $R^1$ is unsubstituted naphthyl or benzothienyl;

$R^2$ is hydrogen or $C(O)OR^6$;

$R^6$ is $C_{1-4}$ alkyl;

Q is $-(CH_2)_x-C(R^7)(R^{7a})-(CH_2)_y-$ or $-(CH_2)_x-V-(CH_2)_y-$;

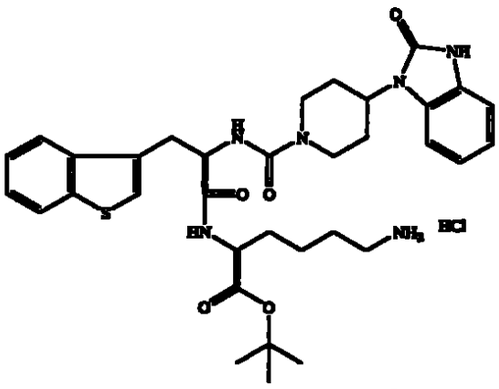
V is cycloalkyl or benzene;

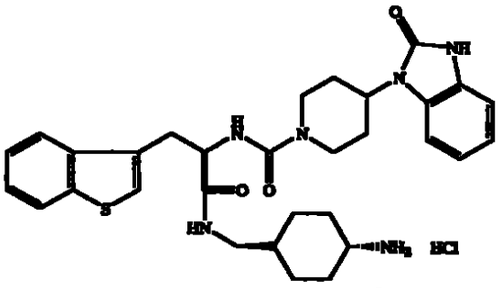
X is 0, 1 or 2;

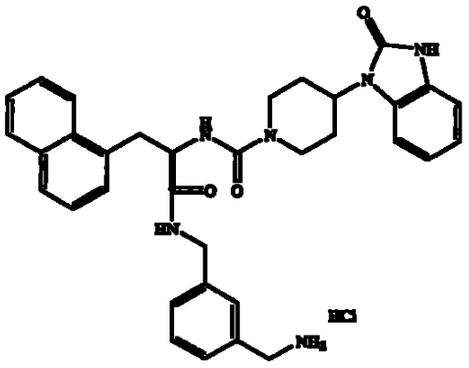
y is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

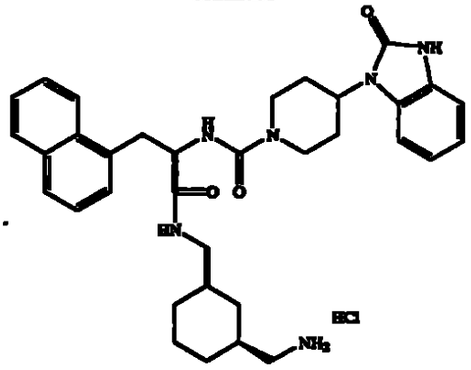
3. A compound which is:







-continued



in free base form or as a pharmaceutically acceptable salt.

4. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

5. A method of treating a disease or condition selected from the group consisting of:

(a) migraine,
(b) pain,
(c) cardiovascular disorder,
(d) inflammation,
(e) diabetes,
(f) Reynaud's syndrome,
(g) peripheral arterial insufficiency,
(h) cranial hemorrhage and
(i) tumor, comprising administering to said patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

* * * * *

# REPUBLICA DE COLOMBIA

## MINISTERIO DE RELACIONES EXTERIORES
## CONSULADO GENERAL DE COLOMBIA EN NUEVA YORK

79542 79694

**Fecha:** ABRIL 22 de 1999/09:12:25 **Comprobante de ingreso No.** 200283

**Solicitante:** BRISTOL MEYERS & SQUIBB

| CANTIDAD | CONCEPTO | VALOR |
|---|---|---|
| 1 | CERTIFICACION - POWER OF ATTORNEY | 57.00 |
| | | |
| | | |

**VALOR TOTAL RECIBIDO EN DOLARES**

**SON:** CINCUENTA Y SIETE DOLARES **US$** 57.00

DERECHOS CONSULARES 50

IMPUESTOS DE TIMBRE 7

CANCELADO

LUIS E. CARRERA A.
Firma Responsable
y Sello

**Original** : Usuario
**1a. Copia** : Consulado
**2a. Copia** : Cancilleria

**Forma AC - 20**

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que antecede con el original que se ha tenido a la vista.

22 NOV. 2000

NOTARIO CUARENTA

Si desea reclamar dirijase a Control Interno
Cra. 5a. No. 9-45 Of. 301 Santafé de Bogotá, Colombia

69

STATE OF NEW JERSEY, County of Mercer } ss.

I, CATHERINE DICOSTANZO, Clerk of the County of Mercer,

Do Hereby Certify that Diane C. Bertram Esq., whose name is subscribed to the acknowledgment, proof or affidavit of the annexed instrument, and thereon written, is and was at the time of taking the same, a Notary Public in and for said State, dwelling in said County, commissioned and sworn and duly authorized by the laws thereof to take the proofs and acknowledgments of deeds or other instruments of writing, and affidavits to be recorded in said State, and that I am well acquainted with the handwriting of said official, and verily believe that the signature is genuine.

Further Certify that impression of Seal of Notaries Public not required by law be filed in my office.

In Testimony Whereof, I have hereunto set my hand and affixed the seal of said County and Courts, at Trenton this 15th day of April A.D. nineteen hundred and Thirty nine.

Catherine DiCostanzo ..... Mercer County Clerk.

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que coincide con el original que se ha tenido a la vista.

22 NOV. 2004

NOTARIO CUARENTA

Agustín Castillo Zafra

Bogotá, D.C., Colombia

# Brigard & Castro

SANTA FE DE BOGOTA - COLOMBIA

620

## PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, de Santafé 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 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/o demás 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 creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

El 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: **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, 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 19

Firma

Nombre

Cargo

## POWER OF ATTORNEY

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciled in Princeton, New Jersey, USA

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, of Santafé de Bogotá, Colombia, my (our) true and lawfull 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 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; penal demands, actions of indemnities for 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.

La Suscrita Cónsul de esta Oficina no se responsabiliza por cualquier inconsistencia que ofrezca este documento con el original que se le tuvo a la vista.
22 NOV. 2004
NOTARIO CHARMAINE
Consulado de Colombia, Cónsul, Colombia

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 appoint **RAMIRO CASTRO DUQUE** and/or **HECTOR GOMEZ MEJIA**, 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 Princeton, New Jersey, USA

this 14th day of April 199 9

Signature BRISTOL-MYERS SQUIBB COMPANY

Name Stephen B. Davis

Title Associate Counsel Patents

## 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 es

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 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)

## NOTARIAL CERTIFICATE (CORPORATION)

On this 14th day of April of 1998
personally appeared before me
Stephen.B. Davis
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

Associate Counsel Patents

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 Delaware
under date of November 13, 1989

and that he (she) who grants the present power of attorney is its Representative.

Diane C. Bartram

Diane C. Bartram Public Notary (Seal)
Notary Public of New Jersey
My Commission Expires March 9, 2000

## 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)

## NOTARIAL CERTIFICATE NATURAL PERSON

On this 14th day of April of 1999
personally appeared before me

Stephen B. Davis

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.

Diane C. Bartram

Notary Public (Seal)

Diane C. Bartram
Notary Public of New Jersey
My Commission Expires March 9, 2000

LEGALIZACION ANTE CONSUL COLOMBIANO ES REQUERIDA.

LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED.

77689

671

***EL SUSCRITO CONSUL DE COLOMBIA***

***VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS***

**CERTIFICA**

Que el Señor (a), **CATHERINE Dicostanzo** Clerck del condado de Mercer estado de New Jersey, autenticó la firma de la notario(a) publico(a) sr (a). **DIANE C. BARTRAN** del estado de New Jersey, Estados Unidos de América y quien ejercia las funciones antes expresadas, y que la firma y sello que en el documento aparecen como suyos, son los que usa y acostumbra en sus actos oficiales;

Que la notario(a) antes citada autenticó la firma del señor **STEPHEN B. DAVIS-** quien actua en calidad de Asesor de Patentes de la Compañia **BRISTOL-MEYERS SQUIBB COMPANY** sociedad que existe y esta legalmente organizada bajo las leyes del estado de Delaware U.S.A

Que ha tenido a la vista los documentos probatorios de los hechos citados y constatados por el notario público y el County Clerck del estado de New Jersey, los cuales forman parte integral del presente documento.

Se expide la presente certificación en cumplimiento de los artículos 259 del Código de Procedimiento Civil y 480 del Código de Comercio y a solicitud del interesado el 20 de Abril de 1999.

**NO SE ASUME RESPONSABILIDAD POR EL CONTENIDO DEL DOCUMENTO ADJUNTO.**

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que coincide con el original que se ha tenido a la vista.

22 NOV. 2004

NOTARIO CUARENTA

Agustín Castillo Zafra

Bogotá, D.C., Colombia

**PAGADO IMPUESTO DE TIMBRE Y DERECHOS CONSULARES.**

**VALOR CINCUENTA Y SIETE DOLARES US$57.oo RECIBO No.** 200283

*Federico Mejía Mejía*

*Cónsul de Colombia*

MINISTERIO DE RELACIONES EXTERIORES

044498

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑO LAS FUNCIONES INDICA

NO SE ASUME RESPONSABILIDAD DEL TEXTO

99 APR 29 AM 9:43

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

En la Notaría Cuarenta del Círculo se cotejó la presente fotocopia que coincide con el original que se ha tenido a la vista.

22 NOV. 2004

NOTARIO CUARENTA
Agustín Castillo Zárate
Bogotá, D.C., Colombia

672

TRADUCCION OFICIAL No. 260/99 de las Legalizaciones que se encuentran a continuación de un Poder otorgado por BRISTOL-MYERS SQUIBB COMPANY, una sociedad domiciliada en Princenton, New Jersey, Estados Unidos de América al doctor RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, D.C., Colombia, del inglés al español, las cuales para su identificación se sellan con el Sello del Traductor al mismo tiempo que la presente.-

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

ANEXOS: El Poder arriba mencionado, Certificaciones Notariales, Certificación de las Firmas Notariales, Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

Diane C. Bartram (firmado)
Notario Público
HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

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Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que coincide con el original que se ha tenido a la vista.
22 NOV. 2000
NOTARIO CUARENTA
Agustín Castillo Zárate
Bogotá, D.C. Colombia

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Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

623

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Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

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Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

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Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

Es la Notaría Cuarenta de esta ciudad
extendió la presente fotocopia que coincide
el original que se ha tenido a la vista.
22 NOV. 2004 2
NOTARIO CUARENTA
Agustín Castillo Zapata
Bogotá, D.C., Colombia

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ESTADO DE NEW JERSEY
Condado de Mercer

Yo, CATHERINE DiCOSTANZO, Escribano del Condado de Mercer,

Por Medio del Presente Certifico que Diane C. Bartram, cuyo nombre está suscrito al reconocimiento, prueba o declaración jurada del instrumento anexo, y en éste escrito, es y era en el momento de tomar el mismo, un Notario Público en y para dicho Estado, residente en dicho Condado, comisionado y juramentado y debidamente autorizado por las leyes de éste para tomar las pruebas y recono-

674

cimientos de escrituras u otros instrumentos escritos, y declaraciones juradas para ser registrados en dicho Estado, y que estoy familiarizado con la caligrafía de dicho funcionario, y de veras creo que la firma es genuina.
Además Certifico que la impresión del Sello de Notarios Públicos no está requerida por la ley para ser presentada en mi oficina.

En Testimonio de lo Cual, he firmado el presente de mi puño y letra y fijado el sello de dichos Condado y Tribunales, en Tranton este día 15 de Abril del A.D. de mil novecientos noventa y nueve.

Catherine DiConstanzo (fdo.) Escribano del Condado de Mercer.

SELLO EN RELIEVE.

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EN ESPAÑOL: La Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América bajo el número 200283 de fecha 20 de Abril de 1999; Autenticación hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 044498 de fecha 29 de Abril de 1999.

(Pagado Impuesto de Timbre y Derechos Consulares por valor de $57.oo Dólares).

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ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS.

En la Notaría Cuarenta del círculo se autenticó la presente fotografía que coincide con el original que me fue mostrado a la vista.
22 NOV. 2004 · 2
NOTARIO CUARENTA
Agustín Castillo Zárate
Bogotá, D.C., Colombia

Resolución número 1876 del Ministerio de Justicia.

Fecha: Mayo 3 de 1999.

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.
99 MAY -4 AM 11:09

MINISTERIO DE RELACIONES EXTERIORES
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

REPÚBLICA DE COLOMBIA

GAVIRIA 6358

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

# REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

**Datos de la oficina de registro**

| Clase de oficina: | Registraduría | | Notaría | X | Consulado | | Corregimiento | | Insp. de Policía | | Código | 9795 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C NOTARIA 32.

**Datos del inscrito**

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

| Documento de identificación (Clase y número) | Sexo (en Letras) |
|---|---|
| C.C.No. 170322 DE BOGOTA ---------- | MASCULINO |

**Datos de la defunción**

Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

| Fecha de la defunción | | | | | | | | | | Hora | Número de certificado de defunción |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Año | 2004 | Mes | 10 | | Día | 30 | | | | 04:10 PM | A- 2094375. |

Presunción de muerte

| Juzgado que profiere la sentencia | Fecha de la sentencia | | | |
|---|---|---|---|---|
| | Año | Mes | Día | |

| Documento presentado | | | | Nombre y cargo del funcionario |
|---|---|---|---|---|
| Autorización judicial | | Certificado Médico | X | ANDRES DIAZ CAMPOS.- R.M. No. 79982662 |

**Datos del denunciante**

Apellidos y nombres completos

EDGAR DAVID REGINO II.

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| C.C.No. 15.030.154 DE LORICA/ CORDOBA | |

**Primer testigo**

Apellidos y nombres completos

---

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| --- | --- |

**Segundo testigo**

Apellidos y nombres completos

---

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| --- | --- |

| Fecha de inscripción | | | | | | | | | | Nombre y firma del funcionario que autoriza |
|---|---|---|---|---|---|---|---|---|---|---|
| Año | 2004 | Mes | 11 | | Día | 02 | | | | BLANCA LUCIA COLEGIO RESTREPO NOTARIA 32 E |

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

**CERTIFICO QUE:**

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número: ST6229 ..... que expido en la ciudad de Bogotá D.C., hoy: 05 NOV. 2004 .....

HELADIO LOPEZ G.
SECRETARIO DELEGADO