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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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ENTRADA EN FASE NACIONAL

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54. TITULO

COMPUESTOS ARTIFICIALES COMO ANTAGONISTAS DEL RECEPTOR CGRP

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71. SOLICITANTE

BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO

PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. APODERADO

JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C.

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 Tra. 11 PATENTE I/II
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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)

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COMPANY

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Nacionalidad o Domicilio: Estados Unidos

Lugar de Constitución: Estados Unidos

Teléfono: Fax

E-mail

IDENTIFICACION

C.C. ☐NIT ☐C.E. ☐Otro ☐

Cual _____

Número _____

3

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Número 80 410.337 TP 57492

4

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Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)

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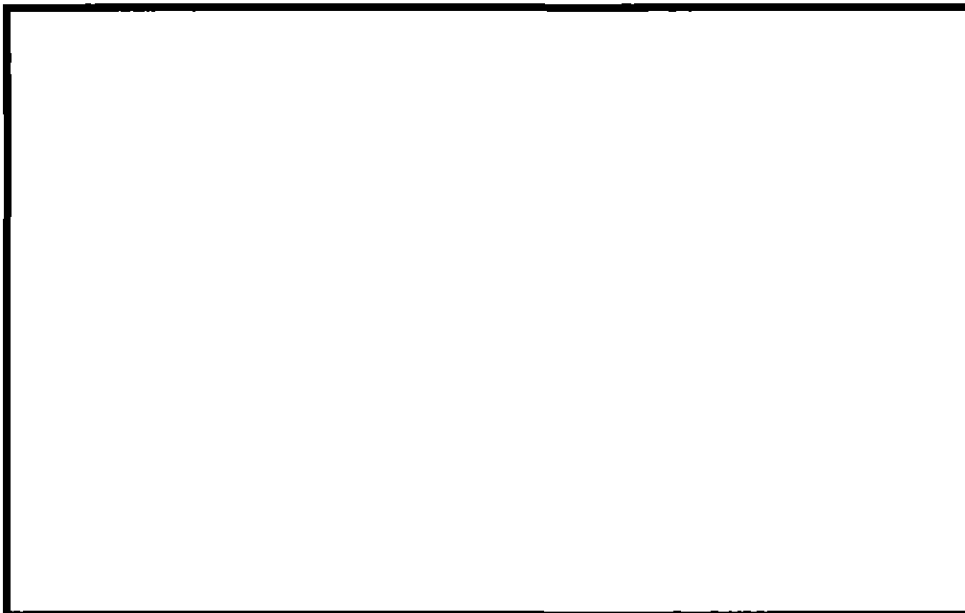
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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

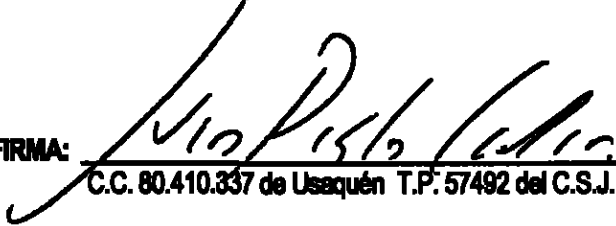
2020-F06 (01-11-15)

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$482.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaración Publicada bajo la Regla PCT 4.17.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las Comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
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12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTOFIRMA: 

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

As. 103.753

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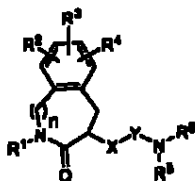
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

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

(54) Title: CONSTRAINED COMPOUNDS AS CGRP-RECEPTOR ANTAGONISTS



(I)

(57) Abstract: The invention encompasses constrained bicyclic and tricyclic CGRP-receptor antagonists, methods for identifying them, pharmaceutical compositions comprising them, and methods for their use in therapy for treatment of migraine and other headaches, neurogenic vasodilation, neurogenic inflammation, thermal injury, circulatory shock, flushing associated with menopause, airway inflammatory diseases, such as asthma and chronic obstructive pulmonary diseases (COPD), and other conditions the treatment of which can be effected by the antagonism of CGRP-receptors.

WO 2006/052378 A1

CONSTRAINED COMPOUNDS AS CGRP-RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 This application claims the benefit of U.S. provisional application serial numbers 60/624,655 filed November 3, 2004 and 60/678,099 filed May 5, 2005.

BACKGROUND OF THE INVENTION

- 10 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 (α CGRP and β CGRP) 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),
- 15 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
- 20 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, CGRP₁ and CGRP₂, 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 CGRP₂ receptors (Juaneda, C. et al. *TIPS* 2000, 21, 432-438). However,
- 25 there is lack of molecular evidence for the CGRP₂ receptor (Brain, S. D. et al, *TIPS* 2002, 23, 51-53). The CGRP₁ 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).
- 30 RAMP1 is required for transport of CRLR to the plasma membrane and for ligand binding to the CGRP-receptor (McLatchie, L. M. et al, *Nature* 1998, 393, 333-339). RCP is required for signal transduction (Evans B. N. et al., *J Biol Chem.* 2000, 275,

31438-43). There are known species-specific differences in binding of small molecule antagonists to the CGRP-receptor with typically greater affinity seen for antagonism of the human receptor than for other species (Brain, S. D. et al, *TIPS* 2002, 23, 51-53). The amino acid sequence of RAMP1 determines the species selectivity, in particular, the amino acid residue Trp74 is responsible for the phenotype of the human receptor (Mallee et al. *J Biol Chem* 2002, 277, 14294-8).

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

A number of non-peptidic, small molecule CGRP-receptor antagonists have been recently reported. WO 04/091514, WO 04/092166 and WO 04/092168 disclose cyclic compounds containing an amide bond in the ring as CGRP antagonists. 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.

5 WO 00/18764, WO 98/11128 and WO 00/55154 and equivalents disclose *inter alia* benzimidazoliny piperidines as antagonists to CGRP-receptor. Unrelated to CGRP, a series of somatostatin antagonists have been disclosed in WO 99/52875 and WO 01/25228 and equivalents. *See also* U.S. 6,344,449, U.S. 6,313,097, U.S. 6,521,609, U.S. 6,552,043, US 20030181462, US20030191068 and WO 03/076432 and related

10 applications. Thus, novel CGRP-receptor antagonists effective for the treatment of neurogenic inflammation, migraine and other disorders would be greatly advantageous.

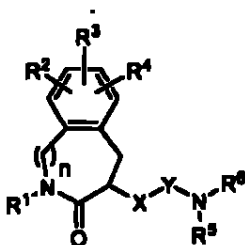
DESCRIPTION OF THE INVENTION

15

The invention encompasses compounds of Formula I and II which are CGRP antagonists. The invention also encompasses compositions incorporating these compounds and methods of using these compounds in therapeutic treatment.

20

One aspect of the invention is a compound of Formula I



I

wherein:

25

R¹ is C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkenyl, C₁₋₆(C₃₋₇cycloalkyl)alkyl, C₁₋₆haloalkyl, C₁₋₆(C₁₋₆alkoxy)alkyl, C₁₋₆(Ar¹)alkyl, C₁₋₆(NR⁷R⁸)alkyl, N-(R⁹)-pyrrolidinyl or N-(R⁹)-piperidinyl;

R^2 is hydrogen, halo, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, benzyloxy, or NR^7R^8 ;

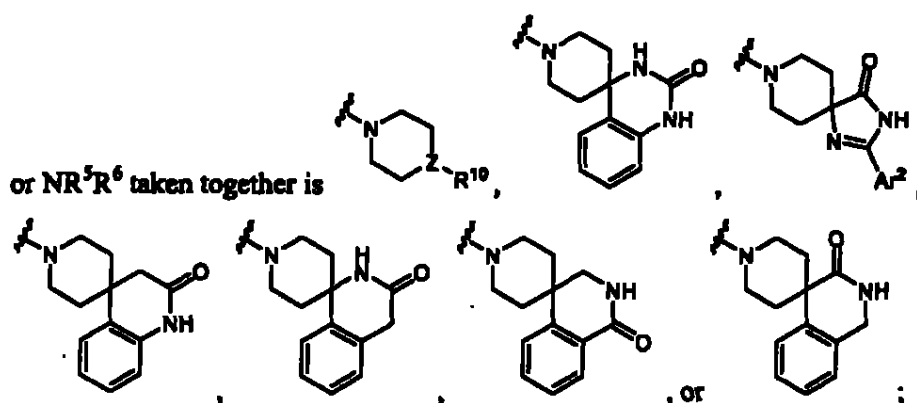
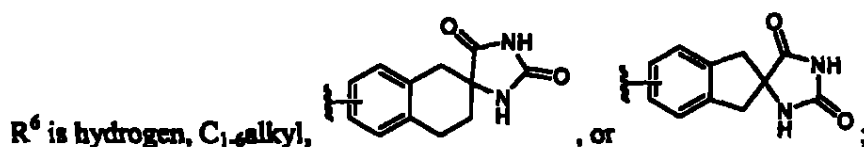
R^3 is hydrogen, hydroxy, halo, C_{1-6} alkyl, or C_{2-6} alkenyl;

5 or R^2 and R^3 taken together are $CHNHR^5$;

R^4 is hydrogen, halo or C_{1-6} alkyl, or C_{2-6} alkenyl,;

R^5 is hydrogen or C_{1-6} alkyl;

10



15

R^7 is hydrogen or C_{1-6} alkyl;

R^8 is hydrogen or C_{1-6} alkyl; or

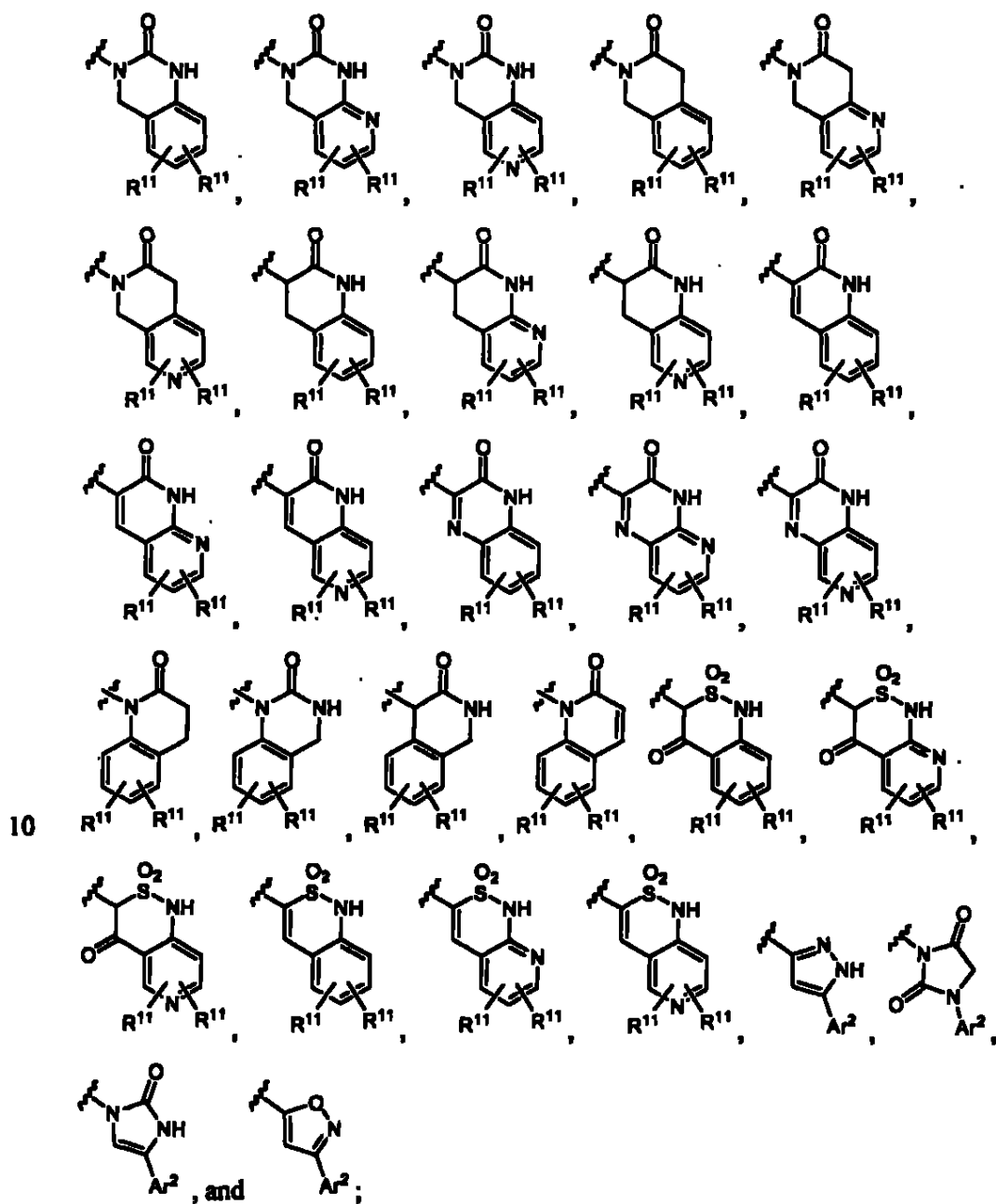
20 NR^7R^8 taken together is selected from the group consisting of pyrrolidinyl, piperidinyl, N-(R^9)-piperazinyl, morpholinyl, and thiomorpholinyl;

R^9 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, or C_{1-6} alkoxycarbonyl;

R^{10} is phenyl, naphthyl, pyridinyl, pyridinyl N-oxide, quinolinyl, quinolinyl N-oxide, isoquinolinyl, or isoquinolinyl N-oxide, and is substituted with 0-2 substituents selected from the group consisting of halo, C_1 -alkyl, C_1 -haloalkyl, C_1 -alkoxy, hydroxy, and phenyl;

5

or R^{10} is selected from the group consisting of



R^{11} is hydrogen, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

Ar^1 is phenyl, naphthyl, pyridinyl, or imidazolyl, and is substituted with 0-2 substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

5

Ar^2 is phenyl, naphthyl, or pyridinyl, and is substituted with 0-2 substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

$X-Y$ is aminocarbonyl, oxycarbonyl, methylenecarbonyl, ethylene, or amino(cyano)iminomethyl;

10

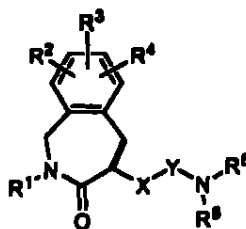
Z is N or CH; and

n is 0 or 1;

15

or a pharmaceutically acceptable salt or solvate thereof.

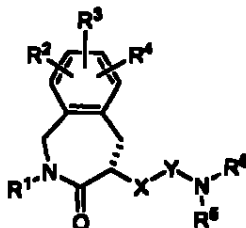
Another aspect of the invention is a compound of Formula Ia.



Ia

20

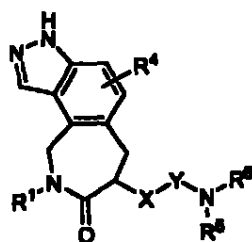
Another aspect of the invention is a compound of Formula Ib.



Ib

25

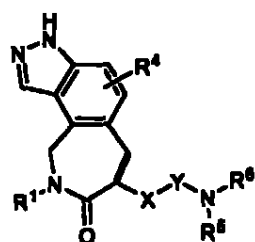
Another aspect of the invention is a compound of Formula II.



II

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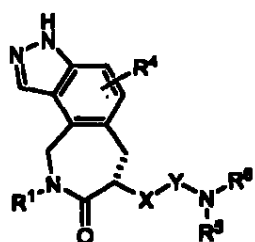
Another aspect of the invention is a compound of Formula IIa.



IIa

10

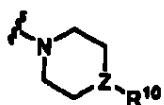
Another aspect of the invention is a compound of Formula IIb.



IIb

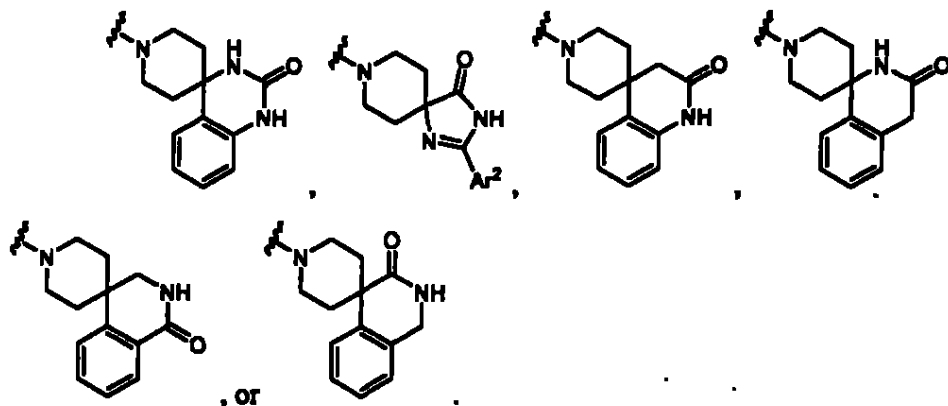
Another aspect of the invention is a compound of Formula I or II where R⁴ is
15 chloro, fluoro, or methyl.

Another aspect of the invention is a compound of Formula I or II where
NR⁵R⁶ taken together is

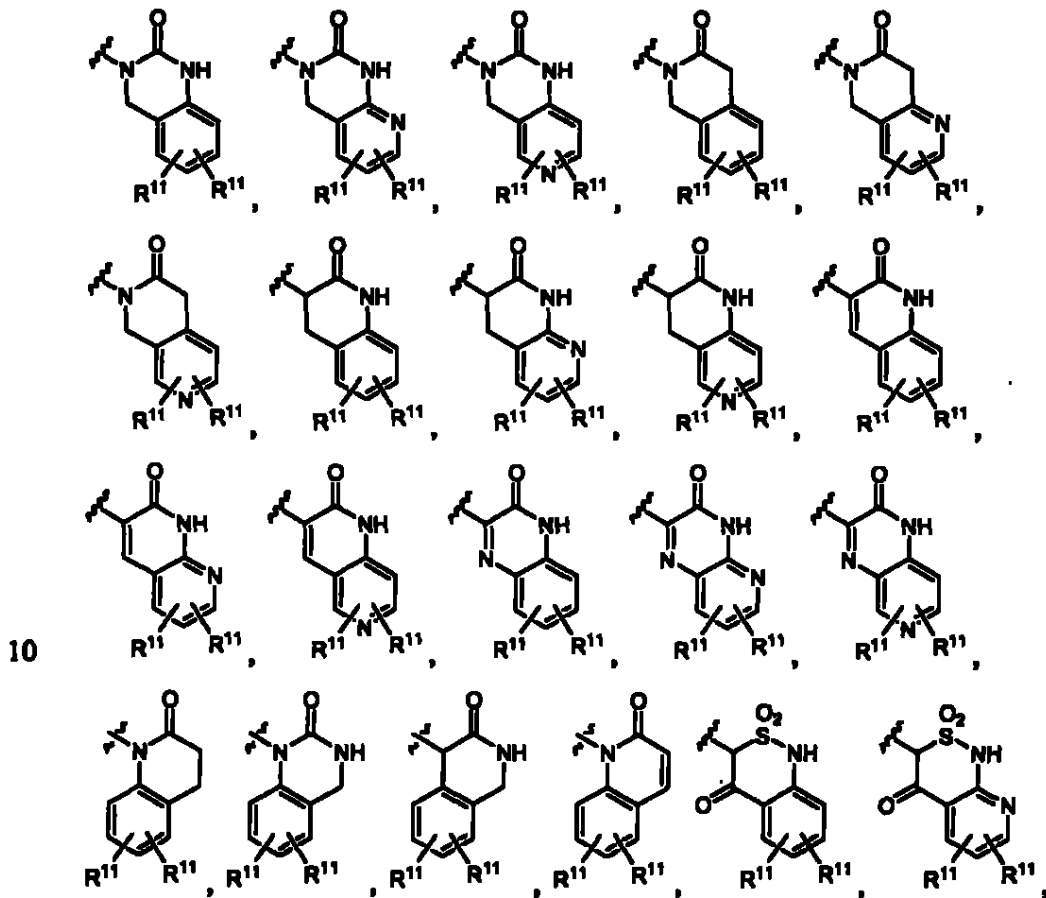


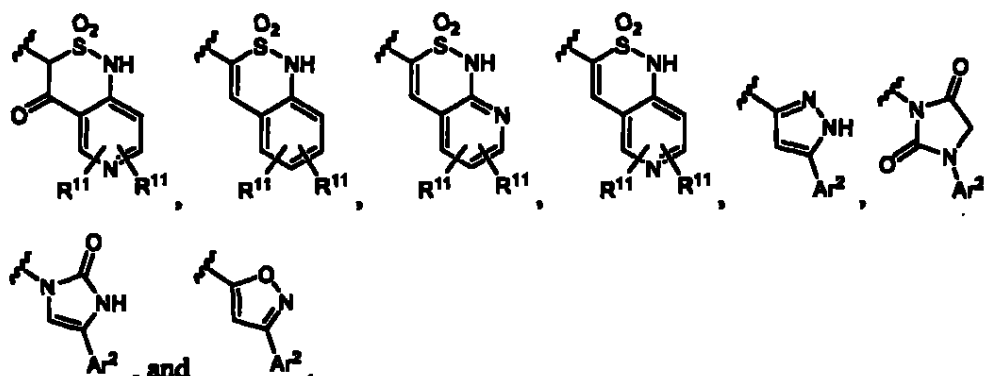
12

Another aspect of the invention is a compound of Formula I or II where NR^5R^6 taken together is



Another aspect of the invention is a compound of Formula I or II where R^{10} is selected from the group consisting of





Another aspect of the invention is a compound of Formula I or II where R¹¹ is
 5 hydrogen, chloro, fluoro, or methyl.

Another aspect of the invention is a compound of Formula I or II where Z is
 CH.

10 Another aspect of the invention is a compound of Formula I where n is 1.

Another aspect of the invention is that any scope of variables R¹, R², R³, R⁴,
 R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, Ar¹, Ar², X-Y, Z, and n can be used with any scope of the
 remaining variables

15

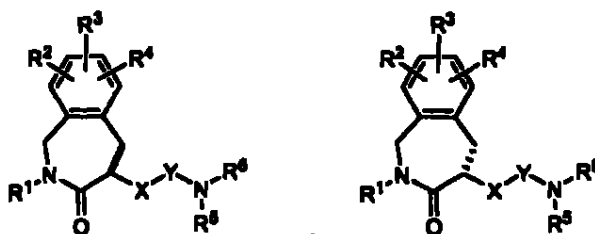
"Alkyl," "hydroxyalkyl," "alkoxy" and related terms with an alkyl moiety
 include straight and branched isomers. "Alkenyl" means a straight or branched alkyl
 group with at least one double bond. A term such as C₁₋₆(R)alkyl means a straight or
 branched alkyl group of one to six carbons substituted with the substituent R. A term
 20 such as N-(R)-pyrrolidinyll indicates that the nitrogen is substituted with the
 substituent R. "Haloalkyl" and "haloalkoxy" include all halogenated isomers from
 monohalo substituted alkyl to perhalo substituted alkyl. "Aryl" includes carbocyclic
 and heterocyclic aromatic ring systems. "Amino" includes includes primary,
 secondary, and tertiary moieties. "Carbonyl" means CO. "Oxy" means -O-.
 25 "Aminocarbonyl" means -N(R)C(=O)-. "Oxycarbonyl" means -OC(=O)-.
 "Methylenecarbonyl" means -CH₂C(=O)-. "Amino(cyano)iminomethyl" means
 -NHC(=NCN)-.

H 14

The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucuronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

The invention also includes all solvated forms of the compounds, particularly hydrates. Solvates do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. Solvates may form in stoichiometric amounts or may form from adventitious solvent or a combination of both. One type of solvate is hydrate, and some hydrated forms include monohydrate, hemihydrate, and dihydrate.

Some compounds of the invention may exist in stereoisomeric forms, one example of which is shown below. The invention includes all stereoisomeric and tautomeric forms of the compounds.



Synthetic Methods

The compounds described in the present invention can be synthesized according to Schemes 1-4 as well as other procedures known in the art. Starting

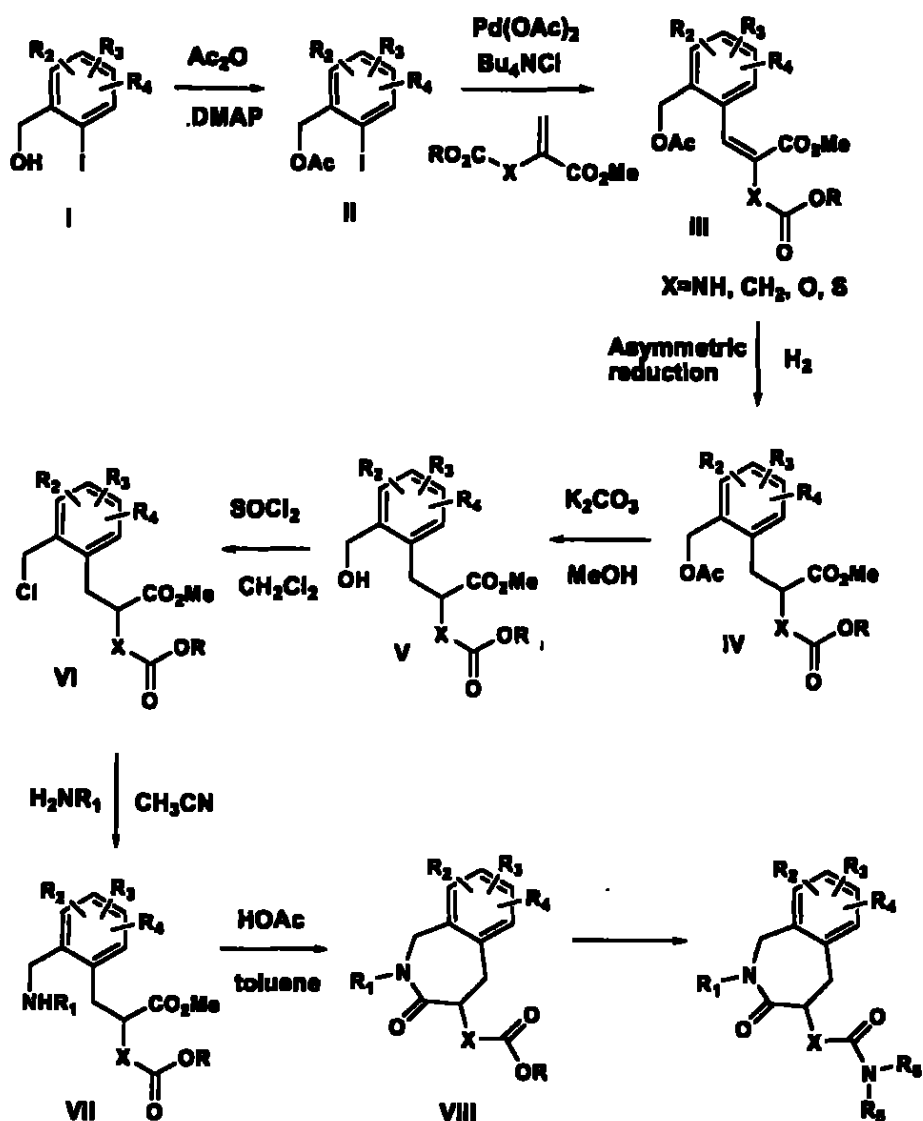
materials are commercially available or synthesized by common synthetic procedures. Variations of the compounds and the procedures to make them which are not illustrated are within the skill of the art.

5 Scheme 1 describes how to make certain compounds of the invention. Regiospecific introduction of iodine on a appropriately substituted aromatic ring can be accomplished using iodine monochloride. Aryl iodides (II) are good coupling partners in palladium-mediated Heck reactions. The Heck products (III) can be reduced with hydrogen mediated by number of asymmetric catalysts to produce
10 enantiomerically pure materials (IV). Subsequent hydrolysis of acetate functionality with methanolic potassium carbonate followed by treatment of alcohol (V) with thionyl chloride can produce benzylic chlorides (VI). Treatment of benzylic chlorides with various amines in acetonitrile can deliver requisite amines (VII).

15 The amines (VII) can be converted into desired azepinones (VIII) in refluxing toluene mediated by catalytic acetic acid. The azepinone intermediates VIII (X= NH, CH₂, O) can in turn be elaborated into final products. Hydrogenolysis of VIII (X=NH) under 10% Pd on carbon produces amine intermediate IX (Scheme II). The amine functionality can be transformed to the desired urea functionality (X) with the
20 assistance of phosgene or N,N'-disuccinimyl dicarbonate and various amines (Scheme 2). Alternatively, the succinic ester VIII (X=CH₂) can be converted to carboxylic acid (XI) with lithium hydroxide, followed by reaction with an appropriate amine under TBTU coupling conditions to give desired amides (XII) (Scheme 3).

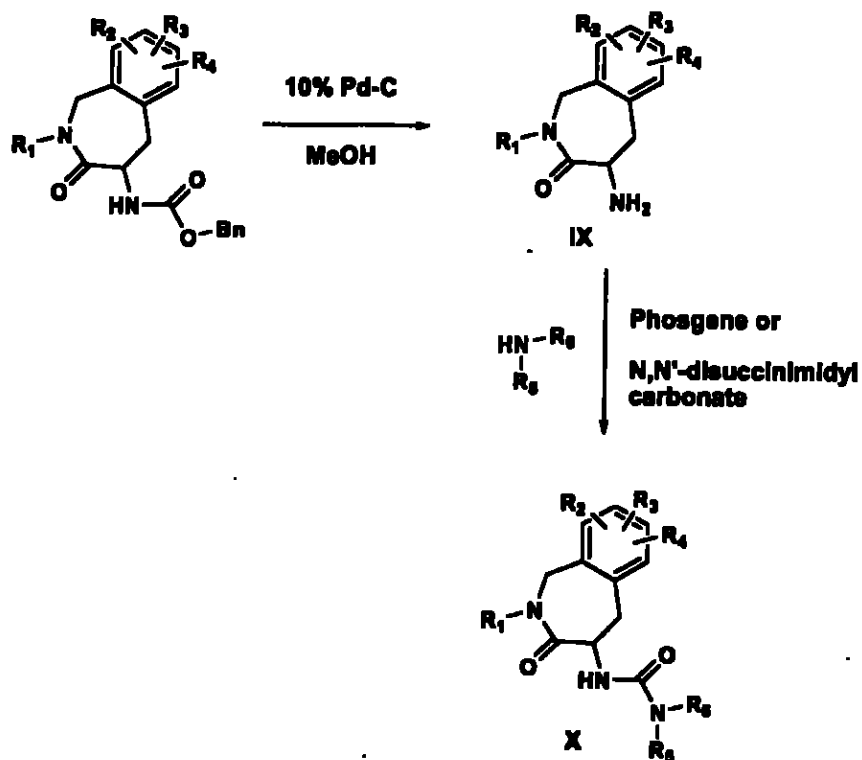
14 16

Scheme 1.



20 17'

Scheme 2.



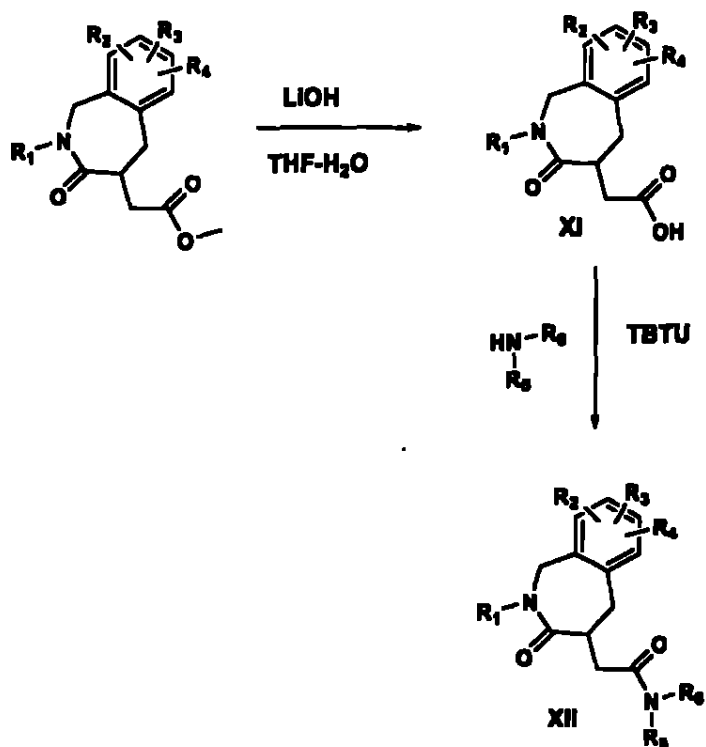
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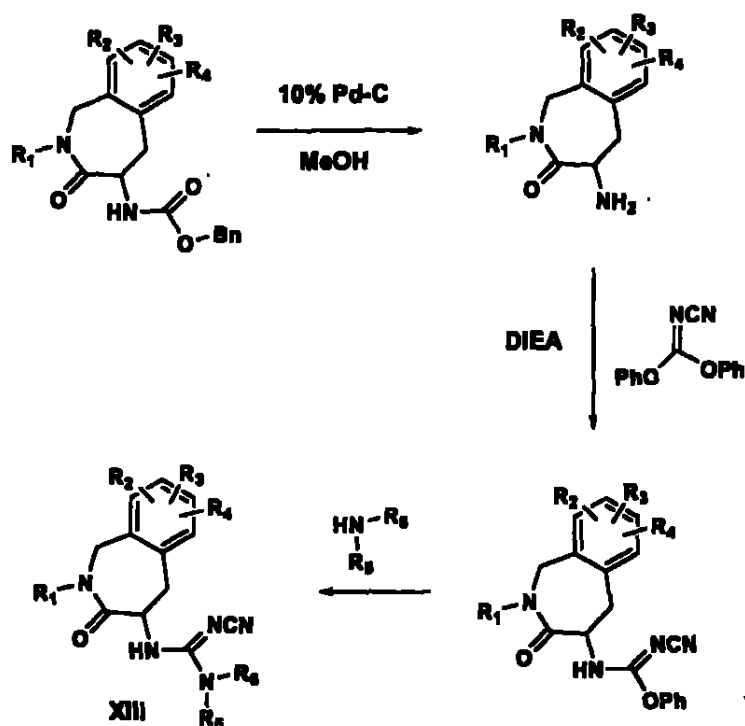
27 18

Scheme 3.



In a manner similar to urea formation, cyanoguanidine XIII can be prepared
 5 using diphenyl N-cyanocarboimide and various substituted amines (Scheme 4).

Scheme 4.



Biological methods

- 5 **CGRP Binding Assay. Tissue Culture.** SK-N-MC cells were grown at 37 °C in 5% CO₂ 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 Na₂HPO₄, 1.1 mM KH₂PO₄, pH 7.4), and incubated for 5-10 min. at 4 °C in
- 10 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.
- 15 The SK-N-MC homogenate was then aliquoted and stored at -80 °C until needed.

27 20

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 MgCl₂, 0.005% Triton X-100) and transferred (volume 50 µl) into 96 well assay plates. [¹²⁵I]-CGRP (Amersham Biosciences) was diluted to 60 pM in assay buffer and a volume of 50 µl was added to each well. SK-N-MC pellets were thawed, diluted in assay buffer with fresh 0.1% mammalian protease inhibitor cocktail (Sigma), and homogenized again. SK-N-MC homogenate (5 µg/well) was added in a volume of 100 µl. The assay plates were then incubated at room temperature for 2 h. Assays were stopped by addition of excess cold wash buffer (20 mM Tris-Cl pH 7.5, 0.1% BSA) immediately followed by filtration over glass fiber filters (Whatman GF/B) previously soaked in 0. 5% PEI. Non-specific binding was defined with 1 µM beta-CGRP. Protein bound radioactivity was determined using a gamma or scintillation counter. The IC₅₀ was defined as the concentration of a compound of invention required to displace 50% of radioligand binding.

Cyclic AMP Functional Antagonism Assay. Antagonism of the compounds of invention was determined by measuring the formation of cyclic AMP (adenosine 3'5'-cyclic monophosphate) in SK-N-MC cells that endogenously express the human CGRP receptor. CGRP receptor complex is coupled with Gs protein and CGRP binding to this complex leads to the cyclic AMP production via Gs - dependent activation of an adenylate cyclase (Juaneda C et al., TiPS, 2000; 21:432-438; incorporated by reference herein). Consequently, CGRP receptor antagonists inhibit CGRP - induced cyclic AMP formation in SK-N-MC cells (Doods H et al., Br J Pharmacol, 2000; 129(3):420-423) ; incorporated by reference herein). For cyclic AMP measurements SK-N-MC cells were incubated with 0.3 nM CGRP alone or in the presence of various concentrations of the compounds of invention for 30 min at room temperature. Compounds of invention were pre-incubated with SK-N-MC cells for 15 min before the addition of CGRP to allow receptor occupancy (Edvinsson et al., Eur J Pharmacol, 2001, 415:39-44; incorporated by reference herein). Cyclic AMP was extracted using the lysis reagent and its concentration was determined by radioimmunoassay using RPA559 cAMP SPA Direct Screening Assay Kit

(Amersham Pharmacia Biotech). IC₅₀ values were calculated using Excel fit. The tested compounds of invention were determined to be antagonists as they exhibited a dose – dependent inhibition of the CGRP – induced cyclic AMP production.

- 5 In the Table 4, results are denoted as follows: A 0.1-10 nM; B = 10-100 nM; C = 100-1000 nM; D > 1000 nM.

Table 4. CGRP Binding and cAMP Functional Data

Example	CGRP binding ¹ IC ₅₀ (nM)	cAMP Function ² IC ₅₀ (nM)
1	B	B
2	C	*
3	C	*
4	C	*
5	C	*
6	B	B
7	B	*
8	D	*
9	C	*
10	B	B
11	B	B
12	A	A
13	B	*
14	C	*
15	B	*
16	A	A
17	B	*
18	C	*
19	B	A
20	A	A
21	A	A
22	A	A
23	B	*
24	B	B
25	C	*
26	A	A
27	C	*
28	B	B
29	C	*
30	B	B
31	D	*
32	C	*
33	D	*

25 22

Example	CGRP binding ¹ IC ₅₀ (nM)	cAMP Function ² IC ₅₀ (nM)
34	C	*
35	B	*
36	B	B
37	A	B
38	C	*
39	B	B
40	A	A
41	A	A
42	B	B
43	A	A
44	A	A
45	A	A
46	A	A
47	B	B
48	B	*
49	A	A
50	A	A
51	A	*
52	A	A
53	A	A
54	A	A
55	C	*
56	C	*
57	C	*
58	C	*
59	C	*
60	D	*
61	D	*
62	B	*
63	C	*
64	D	*
65	D	*
66	B	*
67	B	*
68	C	*
69	B	*
70	C	*
71	C	*
72	D	*
73	D	*
74	D	*
75	A	*
76	B	*
77	B	*

76 23

Example	CGRP binding ¹ IC ₅₀ (nM)	cAMP Function ² IC ₅₀ (nM)
78	A	*
79	A	*
80	B	B
81	B	*
82	A	*
83	C	*
84	C	*
85	B	B
86	A	*
87	B	*
88	A	*
89	A	*
90	A	*
91	A	*
92	B	*
93	C	*
94	A	*
95	B	*
96	A	*
97	A	*
98	B	*
99	A	*
100	A	*
101	B	*
102	A	*
103	B	*
104	B	*
105	B	*
106	B	*
107	C	*
108	B	*
109	C	*
110	B	*
111	A	*
112	B	*
113	A	*
114	B	*
115	B	*
116	A	*
117	C	*
118	B	*
119	D	*
120	A	*

7# 24

Pharmaceutical Compositions and Methods of Treatment

The compounds of Formula I inhibit the CGRP receptor. As such, they are useful for treating disorders associated with aberrant CGRP levels or where
5 modulating CGRP levels may have therapeutic benefit.

Accordingly, another aspect of the invention is a pharmaceutical composition comprising a compound of Formula I with a pharmaceutically acceptable adjuvant, carrier, or diluent.

10

Compounds are generally given as pharmaceutical compositions comprised of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier and may contain conventional excipients. A therapeutically effective amount is the amount needed to
15 provide a meaningful patient benefit as determined by practitioners in that art. Pharmaceutically acceptable carriers are those conventionally known carriers having acceptable safety profiles. Compositions encompass all common solid and liquid forms including capsules, tablets, lozenges, and powders as well as liquid suspensions, syrups, elixers, and solutions. Solid compositions may be formed in
20 timed or sustained released formulations. Compositions are made using common formulation techniques and conventional excipients (such as binding and wetting agents) and vehicles (such as water and alcohols).

Solid compositions are normally formulated in dosage units providing from
25 about 1 to about 1000 mg of the active ingredient per dose. Some examples of solid dosage units are 0.1 mg, 1 mg, 10 mg, 100 mg, 500 mg, and 1000 mg. Liquid compositions are generally in a unit dosage range of 1-100 mg/mL. Some examples of liquid dosage units are 0.1 mg/mL, 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL, and 100 mg/mL.

30

The invention encompasses all conventional modes of administration including oral, parenteral, intranasal, sublingual, and transdermal methods. Typically, the daily dose will be 0.01-100 mg/kg body weight daily. Generally, more

28 5

compound is required orally and less parenterally. The specific dosing regime, however, should be determined by a physician using sound medical judgement.

Inhibitors at the receptor level to CGRP are postulated to be useful in
5 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;
10 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 P. J. 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
15 elevated basal CGRP levels compared to controls (Ashina M. et al., *Pain* 2000, 86(1-2), 133-8). Intravenous CGRP infusion produces lasting headache in migraineurs (Lassen L.H. et al. *Cephalalgia*. 2002, 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
20 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).

25 Another aspect of the invention is a method of treating migraine or headache.

"Migraine," "headache," and related terms are as understood by medical practitioners. Migraine encompasses all classes of migraine including common, classic, cluster, fulgurating, hemiplegic, ophthalmoplegic, and ophthalmic.
30

"Therapeutically effective" means there is a meaningful patient benefit as understood by medical practitioners.

“Patient” means a person who may benefit from treatment as determined by medical practitioners.

Another aspect of the invention relates to a method of treating inflammation (particularly neurogenic inflammation), 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.

Another aspect of the invention relates to methods 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. Department of Neuroscience, University of

- Minnesota, Minneapolis, Minnesota 55455, and Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, Kansas 66160 (e) Attenuation of antigen-induced airway hyperresponsiveness in CGRP-deficient mice. Aoki-Nagase, Tomoko; Nagase, Takahide; Oh-Hashi, Yoshio; Shindo, Takayuki; Kurihara, Yukiko; Yamaguchi, Yasuhiro; Yamamoto, Hiroshi; Tomita, Tetsuji; Ohga, Eijiro; Nagai, Ryozi; 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.

- Another aspect of this invention relates to a method of treatment using combinations of Formula I compounds 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.

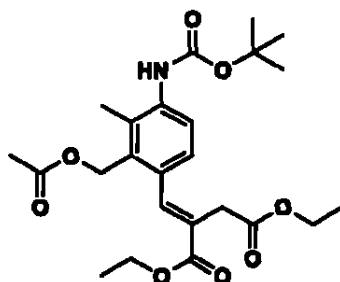
DESCRIPTION OF SPECIFIC EMBODIMENTS

- Proton magnetic resonance (¹H NMR) spectra were recorded on a Bruker AC 300 or AC 500. All spectra were determined in the solvents indicated and chemical shifts are reported in δ units downfield from the internal standard tetramethylsilane (TMS) and interproton coupling constants are reported in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Low resolution mass spectra (MS) and the apparent

3/18

molecular (MH⁺) or (M-H)⁺ was determined on a Micromass platform. The elemental analysis are reported as percent by weight. The products were purified by Prep HPLC using the column YMC S5 ODS (30 x 100 mm) at a flow rate of 40.0 mL/min and gradient time of 8.0 min. starting from solvent composition of 40% MeOH-60% H₂O-0.1% TFA and ending with solvent composition 95% MeOH-5% H₂O-0.1% TFA. The products were analyzed by a HPLC instrument using an XTERA column (3.0 x 50 mm S7) starting from solvent A (10% MeOH – 90% water – 0.1% trifluoroacetic acid (TFA)) and reaching solvent B (10% water – 90% methanol – 0.1% TFA) over a gradient time of 2 min. The flow rate is 5 mL/min. and retention time (R_f) of product was measured at 220 nm wavelength.

Intermediate 1



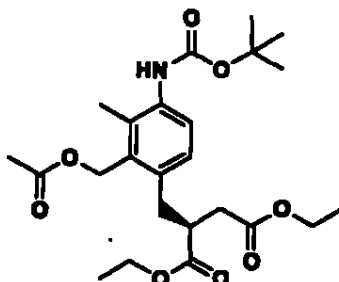
15 2-(Acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzylidene)-succinic acid diethyl ester. Nitrogen gas was bubbled through a solution of acetic acid 3-tert-butoxycarbonylamino-6-iodo-2-methyl-benzyl ester (3.85 g, 9.5 mmol), itaconic acid diethyl ester (2.2 mL, 12 mmol), tetrabutylammonium chloride (3.4 g, 12 mmol), and triethylamine (4.0 mL, 29 mmol) in *N,N*-dimethylformamide (25 mL) for 5 minutes. Palladium (II) acetate (0.32 g, 1.4 mmol) was added. Mixture was heated at 100 °C for 45 minutes. Mixture was cooled to room temperature then diluted with diethyl ether (100 ml). Mixture was washed successively with water (3 X 50 mL), and brine (25 mL). Organic was dried (MgSO₄), filtered and concentrated *in vacuo*. Silica gel purification yielded the desired product in 99% yield as an amber oil. ¹H NMR (300 MHz, CDCl₃): δ= 8.0 (s, 1H), 7.78 (d, *J*=8.4, 1H), 7.08 (d, *J*=8.4, 1H), 6.32 (s, 1H), 5.11 (s, 2H), 4.27 (q, *J*=7.3, 2H), 4.11 (q, *J*= 7.1, 2H), 3.30 (s, 2H),

20

25

2.24 (s, 3H), 2.04 (s, 3H), 1.55 (s, 3H), 1.51 (s, 9H), 1.32 (t, $J=7.1$, 3H), 1.23 (t, $J=7.3$, 3H). MS m/e (M-H)⁺ = 462.0.

Intermediate 2

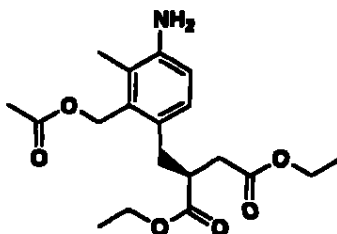


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2-(S)-(Acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzyl)-succinic acid diethyl ester. 2-(S)-(Acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzylidene)-succinic acid diethyl ester (4.4 g, 9.5 mmol) and (-)-1,2-bis((2R,5R)-diethylphospholano)benzene(cyclooctadiene)rhodium (I) trifluoromethane sulfonate (100 mg) was dissolved in ethanol (80 mL). Mixture was placed on a Parr hydrogenation apparatus. Reaction vessel was charged with 60 psi of hydrogen gas. Reaction mixture was allowed to shake at room temperature for 18 hours. Reaction mixture was concentrated *in vacuo*. Residue was passed through a plug of silica gel eluting 80% ethyl acetate-hexanes (250 mL). Filtrate was concentrated *in vacuo* to afford the desired product in 97% yield as an amber oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.62 (d, $J=8.1$, 1H), 7.01 (d, $J=8.4$, 1H), 6.20 (s, 1H), 5.20 (m, 2H), 4.09 (m, 4H), 3.14 (m, 1H), 2.69 (m, 2H), 2.38 (dd, $J_1=16.8$, $J_2=4.8$, 1H), 2.23 (s, 3H), 2.07 (s, 3H), 1.56 (s, 3H), 1.50 (s, 9H), 1.22 (m, 6H). MS m/e (M-H)⁺ = 464.0.

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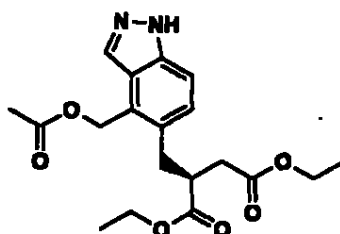
Intermediate 3



2-(S)-(2-Acetoxyethyl-4-amino-3-methyl-benzyl)-succinic acid diethyl ester.

Trifluoroacetic acid (10 mL) was added to a solution of 2-(S)-(acetoxyethyl-4-*tert*-butoxycarbonylamino-3-methyl-benzyl)-succinic acid diethyl ester (4.6 g, 9.9 mmol) in dichloromethane (40 mL). Reaction mixture was stirred at room temperature for 1.5 hours. Mixture was concentrated *in vacuo*. Residue was dissolved in dichloromethane (75 mL) and washed successively with saturated aqueous sodium bicarbonate (2 X 50 mL) and brine (30 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield the desired product in 99% yield as an amber oil. ¹H NMR (300 MHz, CDCl₃): δ= 6.85 (d, *J*= 8.1, 1H), 6.67 (d, *J*= 8.4, 1H), 5.18 (m, 2H), 4.09 (m, 4H), 3.09 (dd, *J*₁= 6.2, *J*₂= 13.9, 1H), 2.96 (m, 1H), 2.66 (m, 2H), 2.37 (dd, *J*₁= 4.6, *J*₂= 16.7, 1H), 2.15 (s, 3H), 2.06 (s, 3H), 1.20 (m, 6H). MS *m/e* (M-C₂H₄O₂+H)⁺= 306.2.

Intermediate 4

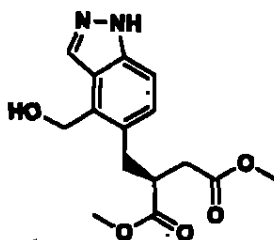


2-(S)-(4-Acetoxyethyl-1H-indazol-5-ylmethyl)-succinic acid diethyl ester.

Isoamyl nitrite (1.6 mL, 12 mmol) was added dropwise to a cooled (water ice bath) solution of 2-(S)-(2-acetoxyethyl-4-amino-3-methyl-benzyl)-succinic acid diethyl ester in carbontetrachloride (80 mL) and acetic acid (4 mL). Mixture was stirred at 0 °C for 2 hours. Mixture was warmed and stirred at ambient temperature for 14 hours. Mixture was concentrated *in vacuo*. Residue was dissolved in dichloromethane (75mL) then washed successively with saturated aqueous sodium bicarbonate (2 X 50 mL), and brine (30 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography (ethyl acetate - hexanes) afforded the product in 55% yield as an amber oil. ¹H NMR (300 MHz, CDCl₃): δ= 8.19 (s, 1H), 7.44 (d, *J*= 8.8, 1H), 7.24 (d, *J*= 8.8, 1H), 5.49 (s, 2H), 4.06 (m, 4H), 3.25 (m,

1H), 3.11 (m, 1H), 2.97 (m, 1H), 2.72 (dd, $J_1 = 8.8$, $J_2 = 16.5$, 1H) 2.43 (dd, $J_1 = 5.1$, $J_2 = 16.5$), 2.09 (s, 3H), 1.19 (m, 6H). MS m/e (M+H)⁺ = 377.1.

Intermediate 5



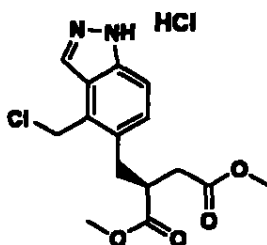
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2-(S)-(4-Hydroxymethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester.

Potassium carbonate (1.6 g, 11.6 mmol) was added to a solution of 2-(S)-(4-acetoxymethyl-1H-indazol-5-ylmethyl)-succinic acid diethyl ester (2.0 g, 5.5 mmol) in methanol (60 mL). Mixture was stirred at room temperature for 1.5 hours. Reaction was quenched with the addition of 1N hydrochloric acid (30 mL). Methanol was removed from the mixture *in vacuo*. Remaining aqueous was basified with sodium bicarbonate. Mixture was extracted with ethyl acetate (2 X 40 mL). Combined organic layers were washed successively with water (30 mL) and brine (30 mL). Organic was dried (magnesium sulfate), filtered then concentrated *in vacuo*. Desired product was obtained in 92% yield as an amber oil. ¹H NMR (300 MHz, CDCl₃): δ = 8.21 (s, 1H), 7.34 (d, $J = 9.2$, 1H), 7.17 (d, $J = 8.8$, 1H), 5.02 (dd, $J_1 = 12.4$, $J_2 = 17.9$, 1H) 3.63 (s, 6H), 3.23 (m, 1H), 2.98 (m, 1H), 2.77 (dd, $J_1 = 7.7$, $J_2 = 16.8$, 1H), 2.53 (dd, $J_1 = 6.4$, $J_2 = 16.7$, 1H). MS m/e (M+H)⁺ = 307.0.

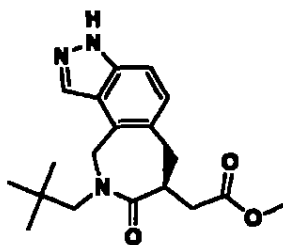
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Intermediate 6



2-(S)-(4-Chloromethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester hydrochloride. Thionyl chloride (5.0 mL) was added to a solution of 2-(S)-(4-hydroxymethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester (1.53 g, 5.0 mmol) in dichloromethane (30 mL). Reaction mixture was stirred at ambient temperature for 2 hours. Mixture was concentrated *in vacuo*. Residue was triturated in toluene (30 mL), then concentrated *in vacuo*. Residue was treated with dichloromethane (30 mL) then concentrated *in vacuo*. Desired product was obtained in 96% yield as an orange solid. ¹H NMR (300 MHz, CDCl₃): δ= 8.22 (s, 1H), 7.49 (d, *J*= 8.8, 1H), 7.15 (d, *J*= 8.8, 1H), 5.12 (s, 2H), 3.56 (s, 3H), 3.52 (s, 3H), 3.05 (m, 3H), 2.69 (dd, *J*₁= 8.1, *J*₂= 16.5), 2.54 (m, 1H). MS *m/e* (M+H)⁺= 325.2.

Intermediate 7



15 [9-(2,2-Dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Neopentylamine (2.0 mL, 17 mmol) was added to a mixture of potassium carbonate (1.2 g, 8.7 mmol) and 2-(S)-(4-chloromethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester hydrochloride (1.56 g, 4.3 mmol) in acetonitrile (30 mL). Reaction mixture was heated at reflux until starting material was deemed to be consumed by HPLC (1.5 hours). Mixture was cooled to room temperature then filtered. Filtrate was concentrated *in vacuo*. Residue was dissolved in a mixture of toluene (40 mL) and acetic acid (2 mL). Reaction mixture was heated at reflux until judged complete by HPLC (44 hours). Mixture was concentrated *in vacuo*. Residue was dissolved in ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate (2 X 25 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography (ethyl acetate-hexanes) yielded the desired product in 90% yield as a yellow foam. ¹H NMR (300 MHz, CDCl₃): δ= 8.01 (s, 1H), 7.35 (d, *J*= 8.4, 1H), 7.13

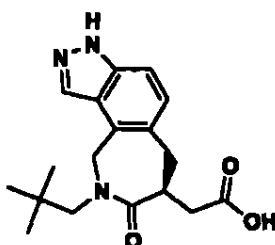
~~28~~

33

(d, $J=8.4$, 1H), 5.41 (d, $J=16.8$, 1H), 4.50 (d, $J=16.8$, 1H), 3.90 (m, 1H), 3.70 (s, 3H), 3.62 (m, 1H), 3.50 (d, $J=13.9$, 1H), 3.18 (d, $J=13.5$, 1H), 3.05 (m, 2H), 2.43 (dd, $J_1=16.7$, $J_2=5.3$, 1H), 0.83 (s, 9H). MS m/e (M-H) $^+=342.0$.

5

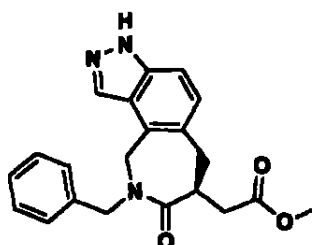
Intermediate 8



[9-(2,2-Dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Lithium hydroxide monohydrate (335 mg, 8.0 mmol) was added to a solution of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester (1.32 g, 3.8 mmol) in methanol (15 mL), tetrahydrofuran (15 mL) and water (15 mL). Reaction mixture was heated at 50 °C for 1 hour. The organic solvents were removed from the mixture *in vacuo*. Remaining aqueous was diluted with water (25 mL). Mixture was neutralized with 1 N hydrochloric acid (8.0 mL). Mixture was extracted with ethyl acetate (2 X 30 mL). Combined organic layers were washed with brine (20 mL) then dried (magnesium sulfate), filtered and concentrated *in vacuo*. Desired product was obtained in 88% yield as a light yellow solid. ^1H NMR (300 MHz, CDCl_3): δ = 7.98 (s, 1H), 7.36 (d, $J=8.8$, 1H), 7.10 (d, $J=8.8$, 1H), 5.38 (d, $J=16.8$, 1H), 4.48 (d, $J=16.8$, 1H), 3.85 (m, 1H), 3.49 (d, $J=13.5$, 1H), 3.18 (d, $J=13.9$, 1H), 3.08 (s, 2H), 2.92 (dd, $J_1=8.2$, $J_2=16.3$, 1H), 2.55 (dd, $J_1=16.5$, $J_2=4.8$, 1H) 0.81 (s, 9H). MS m/e (M-H) $^+=328.0$.

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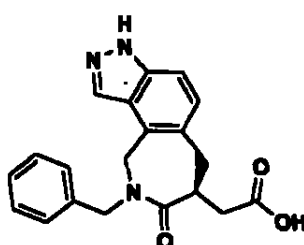
Intermediate 9



5 *(9-Benzyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl)-acetic acid methyl ester.* Benzylamine (250 μ L, 2.3 mmol) and 2-(S)-(4-Chloromethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester hydrochloride were converted following a procedure analogous to the preparation of [9-(2,2-Dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Silica gel chromatography (ethyl acetate – hexanes)
 10 afforded the desired product in 62% yield as an amber oil. ^1H NMR (300 MHz, CDCl_3): δ = 7.77 (s, 1H), 7.28 (m, 6H), 7.09 (d, J = 8.4, 1H), 5.18 (d, J = 16.8, 1H), 4.99 (d, J = 15.0, 1H), 4.43 (d, J = 5.9, 1H), 4.39 (d, J = 1.8, 1H), 4.34 (d, J = 4.0, 1H), 3.74 (s, 3H), 3.13 (m, 2H), 2.51 (dd, J_1 = 5.5, J_2 = 16.8, 1H). MS m/e ($M+H$) $^+$ = 364.0.

15

Intermediate 10

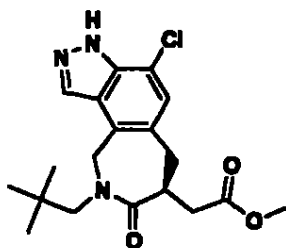


20 *(9-Benzyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl)-acetic acid.* Lithium hydroxide (32 mg, 0.76 mmol) and (9-benzyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl)-acetic acid methyl ester were reacted in a manner analogous to the preparation of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-

acetic acid. Desired product was obtained as a yellow oil in 99% yield. ¹H NMR (300 MHz, DMSO, D₆): δ= 7.72 (s, 1H), 7.28 (m, 4H), 7.16 (m, 2H), 7.06 (d, J= 8.8, 1H), 5.15 (d, J= 16.8, 1H), 4.95 (d, J= 15.0, 1H), 4.37 (m, 4H), 3.09 (m, 2H), 2.59 (dd, J1= 5.1, J2= 16.5, 1H). MS m/e (M+H)⁺= 350.0.

5

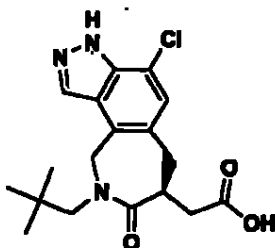
Intermediate 11



- 10 *[4-Chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester.* Potassium carbonate (190 mg, 1.4 mmol) was added to a solution of 2-(S)-(4-acetoxymethyl-7-chloro-1H-indazol-5-ylmethyl)-succinic acid diethyl ester (240 mg, 0.58 mmol) in methanol (10 mL) and ethanol (5 mL). Mixture was stirred at room temperature for 1.5 hours. Reaction was quenched with the addition of 1 N hydrochloric acid (10 mL). Organic
- 15 solvents were removed from the mixture *in vacuo*. Remaining aqueous was basified with sodium bicarbonate. Mixture was extracted 2X ethyl acetate (15 mL). Combined organic layers were dried (magnesium sulfate), filtered and concentrated. Residue was dissolved in dichloromethane (6 mL). Thionyl chloride (2 mL) was added to the mixture. Reaction was stirred at room temperature for 1.5 hours.
- 20 Mixture was concentrated *in vacuo*. Residue was treated with dichloromethane (25 mL) then concentrated *in vacuo*. Residue was suspended in acetonitrile (5 mL). Potassium carbonate (200 mg, 1.4 mmol) was added to the mixture followed by neopentylamine (150 μL, 1.3 mmol). Reaction mixture was heated at reflux for 1 hour. Mixture was cooled to room temperature then filtered through a 0.45 μm PTFE
- 25 membrane. Filtrate was concentrated. Residue was dissolved in a mixture of toluene (5 mL) and acetic acid (250 μL). Reaction mixture was heated at 100°C for 15 hours then warmed to reflux for 7 hours. Mixture was cooled to room temperature then diluted with ethyl acetate (15 mL). Mixture was washed successively 2X saturated

aqueous sodium bicarbonate (20 mL), water (15 mL) and brine (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography (ethyl acetate-hexanes) afforded the desired product in 48% yield as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ= 8.02 (s, 1H), 7.13 (s, 1H), 5.37 (m, 1H), 4.42 (d, *J*= 17.2, 1H), 3.88 (m, 1H), 3.70 (s, 3H), 3.53 (d, *J*= 13.9, 1H), 3.12 (d, *J*= 13.9, 1H), 3.03 (m, 3H), 2.44 (dd, *J*₁= 5.9, *J*₂= 16.9, 1H), 0.81 (s, 9H). MS *m/e* (M+H)⁺= 378.1.

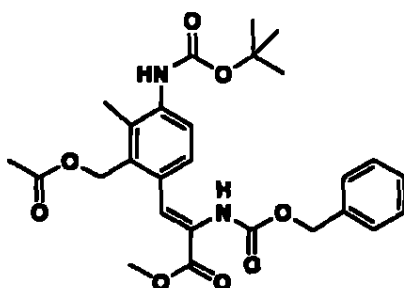
Intermediate 12



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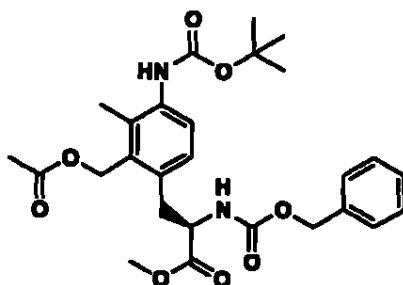
[4-Chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Lithium hydroxide monohydrate (30 mg, 0.71 mmol) was added to a solution of [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester (100 mg, 0.26 mmol) in methanol (2 mL), tetrahydrofuran (2 mL) and water (2 mL). Reaction mixture was stirred at ambient temperature for two hours followed by heating at 50 °C for 40 minutes. Organic solvents were removed from the mixture *in vacuo*. Remaining aqueous was neutralized with 1N hydrochloric acid (750 µL). Mixture was extracted 2X ethyl acetate (10 mL). Combined organic layers were washed with brine (10 mL) then dried (magnesium sulfate), filtered and concentrated *in vacuo*. Desired product was obtained in 93% yield as an orange solid. ¹H NMR (300 MHz, CDCl₃): δ= 7.98 (s, 1H), 7.09 (s, 1H), 5.35 (d, *J*= 17.2, 1H), 4.41 (d, *J*= 17.2, 1H), 3.82 (m, 1H), 3.48 (d, *J*= 13.9, 1H), 3.12 (d, *J*= 13.9, 1H), 3.02 (m, 2H), 2.92 (dd, *J*₁= 8.4, *J*₂= 16.8, 1H), 2.45 (dd, *J*₁= 5.1, *J*₂= 16.8, 1H), 0.78 (s, 9H). MS *m/e* (M-H)⁻= 362.0.

Intermediate 13



- 3-(2-Acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-phenyl)-2-benzyloxycarbonylamino-acrylic acid methyl ester. Palladium (II) acetate (105 mg, 0.43 mmol) was added to a mixture of acetic acid 3-tert-butoxycarbonylamino-6-iodo-2-methyl-benzyl ester (2.89 g, 7.1 mmol), Z-dehydroalanine methyl ester (2.20 g, 9.4 mmol), tetrabutylammonium chloride hydrate (2.70 g, 9.7 mmol), and sodium bicarbonate (1.80 g, 21.4 mmol) in THF (100 mL). Reaction was heated at reflux for 3.75 hours. Mixture was cooled to room temperature then filtered through a plug of silica gel eluting 70% ethyl acetate-hexanes (500 mL). Filtrate was concentrated *in vacuo*. Silica gel chromatography afforded the title compound as a yellow solid in 69% yield. ¹H NMR (300 MHz, CDCl₃): δ= 7.79 (d, *J*= 8.4, 1H), 7.42 (s, 1H), 7.27 (m, 6H), 6.30 (s, 1H), 5.11 (s, 2H), 5.02 (s, 2H), 3.81 (s, 3H), 2.21 (s, 3H), 2.02 (s, 3H), 1.51 (s, 9H). MS *m/e* (M-H)⁺= 511.0.

Intermediate 14



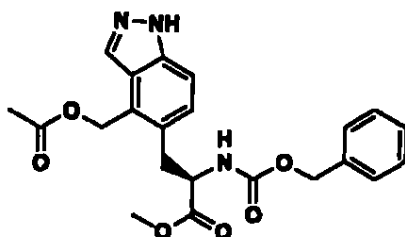
- 3-(2-Acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-phenyl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester. A solution of 3-(2-acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-phenyl)-2-

benzyloxycarbonylamino-acrylic acid methyl ester (2.51 g, 4.9 mmol) in methanol (50 mL) and ethyl acetate (15 mL) was reacted in a manner similar to the preparation of 2-(S)-(acetoxymethyl-4-*tert*-butoxycarbonylamino-3-methyl-benzyl)-succinic acid diethyl ester. Title compound was obtained as an off-white solid in 97% yield. ¹H

- 5 NMR (300 MHz, CDCl₃): δ= 7.66 (d, *J*= 7.9, 1H), 7.31 (m, 5H), 6.99 (d, *J*= 8.5, 1H), 6.21 (s, 1H), 5.31 (d, *J*= 7.6, 1H), 5.17 (d, *J*= 3.7, 2H), 5.04 (d, *J*= 5.80, 2H), 4.56 (m, 1H), 3.71 (s, 3H), 3.23 (dd, *J*₁= 5.80, *J*₂= 14.7, 1H), 3.07 (dd, *J*₁= 7.8, *J*₂= 14.2, 1H), 2.21 (s, 3H), 2.00 (s, 3H), 1.50 (s, 9H). MS *m/e* (M-H)⁺= 513.0.

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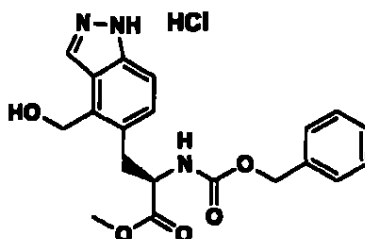
Intermediate 15



- 3-(4-Acetoxymethyl-1H-indazol-5-yl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester. Trifluoroacetic acid (2.5 mL) was added to a solution of
- 15 3-(2-acetoxymethyl-4-*tert*-butoxycarbonylamino-3-methyl-phenyl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester (770 mg, 1.5 mmol) in dichloromethane (10 mL). Reaction mixture was stirred at room temperature for 1.5 hours. Mixture was concentrated *in vacuo*. Residue was treated with chloroform (40 mL) then concentrated *in vacuo*. Residue was dissolved in 5% acetic acid in
- 20 chloroform (10 mL). Isoamyl nitrite (240 μL, 1.8 mmol) was added to the mixture. Reaction mixture was stirred at ambient temperature for 20 minutes. Potassium acetate (690 mg, 7.0 mmol) was added to the mixture. Reaction mixture was stirred at ambient temperature for 45 minutes. Mixture was washed successively with water (10 mL), and 2X saturated aqueous sodium bicarbonate (15 mL). Organic was dried
- 25 (magnesium sulfate), filtered and concentrated. Crude product was obtained in 81% yield as an amber oil and was used without further purification. ¹H NMR (300 MHz, CDCl₃): δ= 8.17 (s, 1H), 7.41 (d, *J*= 8.4, 1H), 7.25 (m, 6H), 5.54 (d, *J*= 8.1, 1H), 5.44

(s, 2H), 5.03 (s, 2H), 4.67 (m, 1H), 3.78 (s, 3H), 3.37 (dd, $J_1 = 5.9$, $J_2 = 14.3$, 1H), 3.22 (dd, $J_1 = 8.1$, $J_2 = 14.3$, 1H), 1.98 (s, 3H). MS m/e (M+H)⁺ = 426.0.

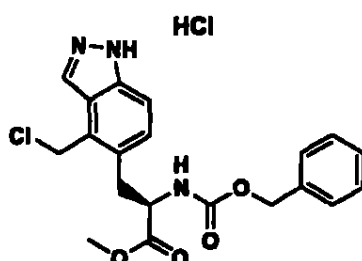
Intermediate 16



2-(R)-Benzyloxycarbonylamino-3-(4-tert-butoxycarbonylamino-2-hydroxymethyl-3-methyl-phenyl)-propionic acid methyl ester hydrochloride.

- Potassium carbonate (1.65 g, 12 mmol) was added to a solution of 3-(4-acetoxymethyl-1H-indazol-5-yl)-2-benzyloxycarbonylamino-propionic acid methyl ester (2.30 g, 5.4 mmol) in methanol (70 mL). Reaction mixture was stirred at room temperature for 2 hours. Reaction was quenched with 1N hydrochloric acid (50 mL). Methanol was removed from the mixture *in vacuo*. Remaining aqueous was basified with sodium bicarbonate. Aqueous was extracted with ethyl acetate (2 X 50 mL).
- Combined extracts were washed with water (30 mL) and brine (20 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Residue was dissolved in 1:1 ethyl acetate:hexanes (50 mL). 1N hydrochloric acid in 1,4 dioxane (1.4 mL), was added to the mixture dropwise causing a precipitate to form. Mixture was stirred at room temperature for 1 hour. Solids were filtered, washed with 1:1 ethyl acetate:hexanes, then dried *in vacuo*. Product was obtained in 61% yield as a tan solid. ¹H NMR (300 MHz, DMSO-D₆): δ = 8.67 (s, 1H), 7.49 (s, 2H), 7.22 (m, 5H), 4.99 (m, 4H), 4.50 (m, 1H), 3.73 (s, 3H), 3.41 (m, 1H), 3.13 (dd, $J_1 = 9.9$, $J_2 = 13.9$, 1H). MS m/e (M+H)⁺ = 384.0.

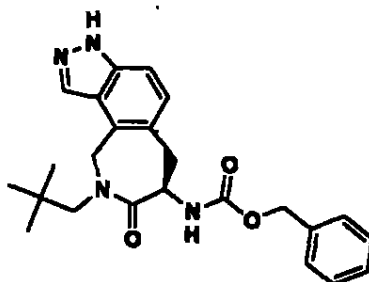
Intermediate 17



- 2-(R)-Benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-
 5 propionic acid methyl ester hydrochloride. 2-(R)-Benzyloxycarbonylamino-3-(4-
 tert-butoxycarbonylamino-2-hydroxymethyl-3-methyl-phenyl)-propionic acid methyl
 ester hydrochloride was reacted in a manner analogous to the preparation of 2-(S)-(4-
 chloromethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester hydrochloride.
 Title compound was obtained as an orange solid in 99% yield. ¹H NMR (300 MHz,
 10 CD₃OD): δ= 8.43 (s, 1H), 7.50 (d, *J*= 8.8, 1H), 7.38 (d, *J*= 8.4, 1H), 7.24 (m, 5H),
 5.06 (d, *J*= 11.0, 1H), 4.98 (d, *J*= 4.8, 2H), 4.56 (dd, *J*₁= 5.7, *J*₂= 9.3, 1H), 3.71 (s,
 3H), 3.42 (dd, *J*₁= 5.5, *J*₂= 14.3, 1H), 3.17 (dd, *J*₁= 9.3, *J*₂= 14.1, 1H). MS *m/e*
 (M+H)⁺= 402.0.

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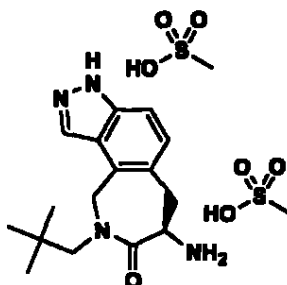
Intermediate 18



- [9-(2,2-Dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-
 cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. Neopentylamine (600 μL, 4.5
 20 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-
 propionic acid methyl ester hydrochloride were reacted in a manner analogous to the
 preparation of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-

(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Silica gel chromatography afforded the title compound as a lightly colored oil in 88% yield. . ¹H NMR (300 MHz, CDCl₃): δ= 7.97 (d, *J*= 2.9, 1H), 7.38 (d, *J*= 4.0, 3H), 7.31 (m, 3H), 7.06 (dd, *J*₁= 3.7, *J*₂= 8.8, 6.32 (d, *J*= 6.3, 1H), 5.24 (m, 2H), 5.15 (s, 2H), 4.42 (dd, *J*₁= 5.5, *J*₂= 17.2, 1H), 3.56 (d, *J*= 13.9, 1H), 3.45 (d, *J*= 16.5, 1H), 3.07 (m, 2H), 0.82 (s, 9H). (M+H)⁺= 421.0.

Intermediate 19

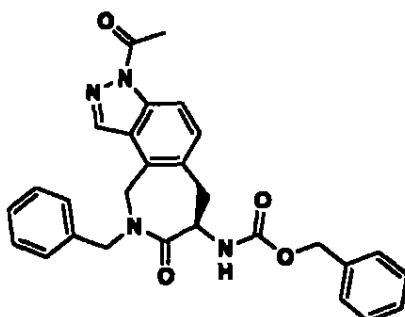


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7-(R)-Amino-9-(2,2-dimethyl-propyl)-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one bismethanesulfonate. Methanesulfonic acid (1 mL) was added to a solution of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester (145 mg, 0.34 mmol) and anisole (100 μL, 0.92 mmol) in dichloromethane (4 mL). Reaction mixture was stirred at room temperature for 2.5 hours. Mixture was diluted with diethyl ether (25 mL). Mixture was allowed to stand at room temperature for 30 minutes. Solvents were decanted off. Remaining residue was washed with diethyl ether (25 mL) then dried *in vacuo*. Crude product was obtained as an orange oil in quantitative yield, and was used without further purification. . ¹H NMR (300 MHz, CD₃OD): δ= 8.50 (s, 1H), 7.56 (d, *J*= 8.8, 1H), 7.39 (s, *J*= 8.8, 1H), 5.42 (d, *J*= 17.9, 1H), 5.10 (dd, *J*₁= 4.4, *J*₂= 12.4, 1H), 4.75 (d, *J*= 17.6, 1H), 3.84 (d, *J*= 13.5, 1H), 3.42 (m, 3H), 3.10 (d, *J*= 13.9, 1H), 2.71 (s, 6H), 0.82 (s, 9H). (M+H)⁺=287.1.

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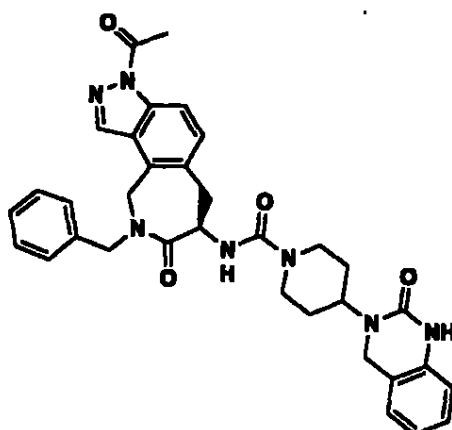
Intermediate 20



(3-Acetyl-9-benzyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza(R)-

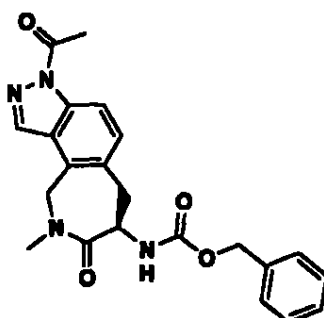
5 *cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester*. Benzylamine (53 μ L, 0.49 mmol) was added to a mixture of 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (125 mg, 0.31 mmol) and potassium carbonate (50 mg, 0.36 mmol) in acetonitrile (5 mL). Reaction was heated at reflux for 1 hour. Mixture was cooled to room temperature then filtered. Filtrate was
10 concentrated. Residue was dissolved in a mixture of toluene (5 mL) and acetic acid (50 μ L). Mixture was heated at reflux for 2 hours. Mixture was cooled to room temperature. Acetic anhydride (500 μ L) was added to the mixture. Reaction was stirred at room temperature for 2 hours. Mixture was diluted with ethyl acetate (20 mL). Mixture was washed successively with water (15 mL), 1N hydrochloric acid (2
15 X 10 mL), and brine (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Silica gel chromatography (ethyl acetate – hexanes) yielded the title compound in 43% yield as an amber oil. ^1H NMR (300 MHz, CDCl_3): δ = 8.33 (s, 1H), 7.47 (d, J = 8.8, 1H), 7.33 (m, 5H), 7.17 (m, 5H), 7.02 (d, J = 9.2, 1H), 6.28 (d, J = 6.6, 1H), 5.34 (m, 1H), 5.16 (s, 2H), 5.00 (m, 1H), 4.84 (m, 1H), 5.43 (t, J = 14.5, 1H), 4.43 (d, J = 5.9, 1H), 4.32 (d, J = 16.8, 1H), 4.11 (m, 1H), 2.02 (s, 3H). MS m/e ($\text{M}+\text{H}$) $^+$ = 483.2.

Intermediate 21



- 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (3-acetyl-9-benzyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-amide. A catalytic amount of 10% palladium on carbon was added to a mixture of acetic acid (200 μ L) and (3-acetyl-9-benzyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester (65 mg, 0.13 mmol) in methanol (10 mL). Reaction vessel was charged with 50 psi of hydrogen gas and placed on a Parr hydrogenation apparatus. Reaction mixture was shaken at room temperature for 2 hours. Mixture was filtered. Filtrate was concentrated. Residue was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate (5 mL). 20% phosgene in toluene (170 μ L, 0.32 mmol) was added to the mixture with vigorous stirring. 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)piperidinium acetate (110 mg, 0.38 mmol) was added to the mixture. Reaction mixture was stirred vigorously for 45 minutes. Layers were separated. Organic was washed with brine (10 mL) then dried (magnesium sulfate) and concentrated *in vacuo*. Preparatory reverse phase HPLC (acetonitrile – water, 0.2% trifluoroacetic acid) followed by removal of the acetonitrile *in vacuo* yielded an aqueous solution containing the title compound. Extracted from the aqueous solution with dichloromethane (20 mL). Combined extracts were washed with brine (20 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Desired product was obtained as a white solid in 23% yield. MS m/e ($M+H$)⁺ = 606.4. r_f = 2.09 min.

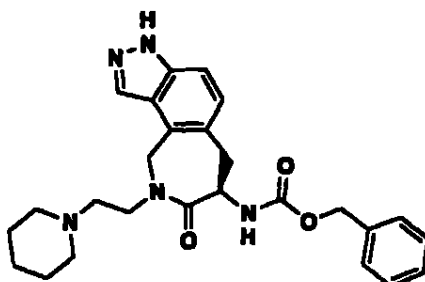
Intermediate 22



- (3-Acetyl-9-methyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-
5 cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester. Methylamine solution in methanol (2M, 2 mL, 4 mmol) was added to a mixture of potassium carbonate (130 mg, 0.94 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (165 mg, 0.41 mmol) in acetonitrile (5 mL). Mixture was heated at 40 °C for 1 hour. Mixture was cooled to room temperature.
- 10 Mixture was filtered. Filtrate was concentrated. Residue was treated with a mixture of toluene (5 mL) and acetic acid (200 µL). Mixture was heated at reflux for 45 minutes. Mixture was cooled to room temperature then acetic anhydride was added (2 mL). Reaction was stirred at room temperature for 16 hours. Mixture was diluted with ethyl acetate (10 mL) then washed successively with water (10 mL), saturated
- 15 aqueous sodium bicarbonate (2 X 15 mL) and brine (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Silica gel chromatography (ethyl acetate – hexanes) yielded the desired product as a yellow solid in 18% yield. ¹H NMR (300 MHz, CDCl₃): δ= 8.70 (s, 1H), 7.51 (d, J= 9.2, 1H), 7.34 (m, 5H), 7.05 (d, J= 9.2, 1 H), 6.19 (m, 1H), 5.23 (s, 2H), 5.13 (s, 2H), 4.18 (d, J= 17.2, 1H), 3.46
- 20 (d, J= 17.2, 1H), 3.11 (s, 3H), 2.95 (m, 1H), 2.89 (s, 3H). MS m/e (M+H)⁺= 407.2.

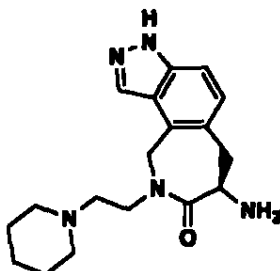
41

Intermediate 23



5 *[8-Oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester.* 1-(2-Aminoethyl)piperidine (150 μ L, 1.1 mmol) was added to a mixture of potassium carbonate (150 mg, 1.1 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester hydrochloride (220 mg, 0.50 mmol) in acetonitrile (5 mL). Reaction was heated at reflux for 1 hour. Mixture was cooled to room
10 temperature then concentrated. Residue was dissolved in a mixture of dichloromethane (10 mL) and acetic acid (200 μ L). Mixture was heated at 40 $^{\circ}$ C for 32 hours and heated at reflux for 8 hours. Mixture was cooled to room temperature then washed successively with saturated aqueous sodium bicarbonate (2 X 10 mL), water (10 mL) and brine (10 mL). Organic was dried (magnesium sulfate), filtered
15 and concentrated. Crude product was obtained as a maroon solid in 86% yield. Material was carried forward without further purification. MS m/e (M+H) $^{+}$ = 462.4. HPLC r_f = 1.19 min.

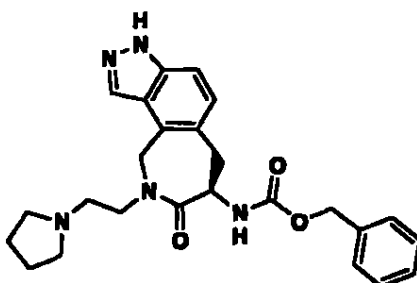
Intermediate 24



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7-(R)-Amino-9-(2-piperidin-1-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Methanesulfonic acid (1 mL) was added to a mixture of anisole (100 μ L, 0.92 mmol) and [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester (200 mg, 0.43 mmol) in dichloromethane (4 mL). Reaction was stirred at ambient temperature for 1 hour. Mixture was diluted with diethyl ether (30 mL). Mixture was allowed to stand at room temperature for 15 minutes. Solvents were decanted off. Remaining residue was dissolved in water (5 mL). Mixture was washed with diethyl ether (2 X 10 mL). Aqueous was basified with 1N sodium hydroxide (2 mL). Mixture was extracted with ethyl acetate (2 X 15 mL). Combined extracts were washed with brine (5 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Title compound was obtained as an amber oil in 42% yield. Material was carried forward without further purification. ^1H NMR (300 MHz, CDCl_3): δ = 8.06 (s, 1H), 7.35 (d, J = 8.4, 1H), 7.11 (d, J = 8.4, 1H), 5.16 (d, J = 16.8, 1H), 4.57 (d, J = 16.8, 1H), 4.40 (dd, J_1 = 12.8, J_2 = 4.4, 1H), 3.77 (m, 1H), 3.54 (m, 1H), 3.29 (m, 1H), 3.03 (m, 1H), 2.36 (m, 6H), 2.14 (m, 2H), 1.38 (m, 4H). MS m/e ($M+H$) $^+$ = 328.3.

Intermediate 25



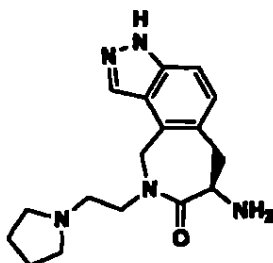
20

[8-Oxo-9-(2-pyrrolidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. 1-(2-Aminoethyl)pyrrolidine (90 μ L, 0.71 mmol) was added to a mixture of 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (100 mg, 0.23 mmol) and potassium carbonate (120 mg, 0.87 mmol) in acetonitrile (5 mL). Reaction was heated at reflux until HPLC suggested the starting material had been consumed (2

25

hours). Mixture was cooled to room temperature then filtered. Acetic acid (200 μ L) was added to the filtrate. Reaction was heated at reflux until judged complete by HPLC (1 hour). Mixture was diluted with ethyl acetate (20 mL) then washed successively with saturated aqueous sodium bicarbonate (15 mL), water (10 mL) and
5 brine (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Crude product was obtained in 69% yield as a yellow oil. Material was carried forward without further purification. ^1H NMR (300 MHz, CDCl_3): δ = 8.04 (s, 1), 7.38 (m, 5H), 7.28 (d, J = 8.4, 1H), 7.02 (d, J = 8.8, 1H), 6.25 (d, J = 6.2, 1H), 5.25 (m, 1H), 5.15 (s, 2H), 4.56 (d, J = 16.8, 1H), 3.70 (m, 2H), 3.47 (dd, J_1 = 3.5, J_2 = 16.7,
10 1H), 3.01 (m, 1H), 2.62 (m, 2H), 2.48 (m, 3H), 1.74 (m, 4H). MS m/e ($M+H$) $^+$ = 448.4.

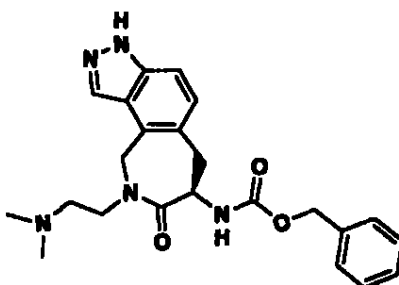
Intermediate 26



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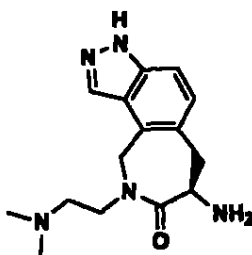
7-(R)-Amino-9-(2-pyrrolidin-1-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one. Title compound was obtained from [8-oxo-9-(2-pyrrolidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester following a procedure analogous to the preparation of
20 7-(R)-amino-9-(2-piperidin-1-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one. Material was obtained as an amber oil in 52% yield and used without further purification. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 8.06 (s, 1H), 7.33 (d, J = 8.8, 1H), 7.10 (d, J = 8.8, 1H), 5.16 (d, J = 16.8, 1H), 5.48 (d, J = 16.8, 1H), 4.40 (dd, J_1 = 13.0, J_2 = 4.2, 1H), 3.67 (m, 2H), 3.29 (dd, J_1 = 3.11, J_2 = 17.0,
25 1H), 3.01 (dd, J_1 = 16.8, J_2 = 12.8, 1H), 2.58 (m, 2H), 1.87 (m, 4H), 1.67 (m, 4H). MS m/e ($M+H$) $^+$ = 422.4.

Intermediate 27



- 5 *[9-(2-Dimethylamino-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester*. *N,N*-Ethylenediamine (70 μ L, 0.66 mmol) and 2-(*R*)-benzyloxycarbonylamino-3-(4-chloromethyl-1*H*-indazol-5-yl)-propionic acid methyl ester (100 mg, 0.23 mmol) were converted to the title compound following a procedure analogous to the preparation of [8-oxo-9-(2-pyrrolidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(*R*)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. Crude product was obtained as an amber oil in 52% yield. Material was carried forward without further purification. ^1H NMR (300 MHz, CDCl_3): δ = 7.99 (s, 1H), 7.36 (m, 6H), 6.27 (d, J = 6.2, 1H), 5.25 (m, 1H), 5.16 (s, 2H), 5.13 (m, 1H), 5.06 (d, J = 18.7, 1H), 4.52 (d, J = 17.2, 1H), 3.61 (t, J = 6.8, 2H), 3.45 (dd, J_1 = 2.4, J_2 = 16.7, 1H), 3.01 (m, 1H), 2.38 (m, 2H), 2.11 (s, 6H). MS
- 15 m/e ($M+H$) $^+$ = 422.4.

Intermediate 28

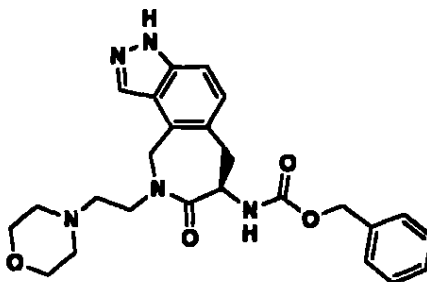


- 20 *7-(R)-Amino-9-(2-dimethylamino-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one*. [9-(2-Dimethylamino-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(*R*)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester (65

mg, 0.15 mmol) was converted to the desired product in a manner analogous to the preparation of 7-(R)-amino-9-(2-pyrrolidin-1-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Crude material was obtained as a yellow oil in 25% yield. Material was carried forward without further purification. ¹H NMR (300 MHz, CDCl₃): δ= 8.07 (s, 1H), 7.35 (d, J= 8.4, 1H), 7.12 (d, J= 8.4, 1H), 5.15 (d, J= 16.8, 1H), 4.58 (d, J= 16.8, 1H), 4.42 (dd, J1= 4.8, J2= 12.8, 1H), 3.62 (m, 2H), 3.30 (m, 1H), 3.01 (dd, J1= 13.0, J2= 16.7, 1H), 2.37 (m, 2H), 2.15 (s, 6H). MS m/e (M+H)⁺= 288.3.

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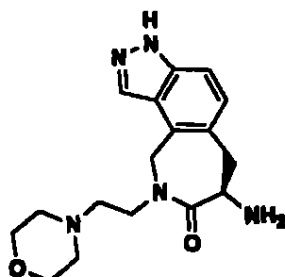
Intermediate 29



[9-(2-Morpholin-4-yl-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. 4-(2-Aminoethyl)morpholine (90 μL, 0.69 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (100 mg, 0.23 mmol) were converted into the title compound following a procedure analogous to the preparation of [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. Crude material was obtained as an amber oil in 92% yield. Product was carried forward without further purification. MS m/e (M+H)⁺= 464.4. HPLC rf = 1.15 min.

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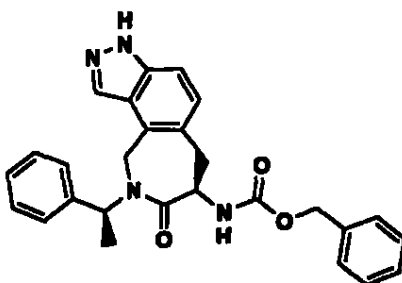
Intermediate 30



7-(R)-Amino-9-(2-morpholin-4-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-
 5 cyclohepta[e]inden-8-one. [9-(2-Morpholin-4-yl-ethyl)-8-oxo-3,6,7,8,9,10-
 hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester (95
 mg, 0.20 mmol) was converted into the title compound following a procedure
 analogous to the preparation of 7-(R)-amino-9-(2-piperidin-1-yl-ethyl)-6,7,9,10-
 tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Crude product was obtained as
 10 an amber oil in 62% yield. Material was carried forward without further purification.
¹H NMR (300 MHz, CDCl₃): δ= 8.06 (s, 1H), 7.34 (d, *J*= 8.4, 1H), 7.15 (d, *J*= 8.8,
 1H), 5.22 (d, *J*= 16.8, 1H), 4.51 (d, *J*= 17.2, 2H), 4.44 (m, 1H), 4.02 (m, 1H), 3.40 (t,
J= 4.8, 4H), 3.31 (m, 3H), 3.07 (m, 1H), 2.32 (m, 4H), 1.95 (m, 2H). MS *m/e*
 (M+H)⁺= 330.3.

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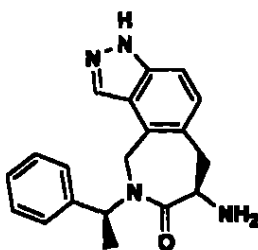
Intermediate 31



[8-Oxo-9-(1-(S)-phenyl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-
 20 cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. (S)-(-)-α-Methylbenzylamine
 (85 μL, 0.67 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-

indazol-5-yl)-propionic acid methyl ester (100 mg, 0.23 mmol) were converted into the desired product following a procedure analogous to the preparation of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Crude product was obtained as a dark oil in
5 quantitative yield. Material was carried forward without further purification. MS m/e (M+H)⁺ = 455.3. HPLC rf = 1.68 min.

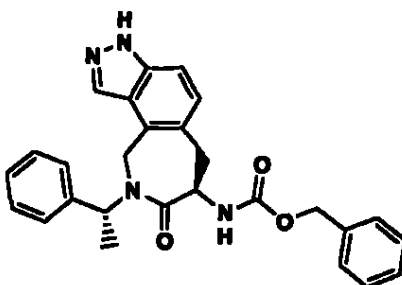
Intermediate 32



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7-Amino-9-(1-(S)-phenyl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-8-one. [8-Oxo-9-(1-(S)-phenyl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester (105 mg, 0.23 mmol) was reacted in a manner analogous to the preparation of 7-(R)-amino-9-(2-piperidin-1-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one.
15 Crude product was obtained as a dark oil in 82% yield. Material was carried forward without further purification. MS m/e (M-H)⁺ = 319.3. HPLC rf = 1.49 min.

Intermediate 33

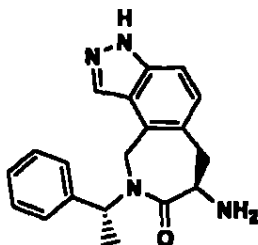


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[8-Oxo-9-(1-(R)-phenyl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. (R)-(+)- α -Methylbenzylamine (85 μ L, 0.67 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (100 mg, 0.23 mmol) were converted into
5 the title compound in a manner similar to the preparation of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Crude material was obtained as a dark foam in quantitative yield. Material was carried forward without further purification. MS m/e (M-H)⁺ = 453.4. HPLC r_f = 1.98 min.

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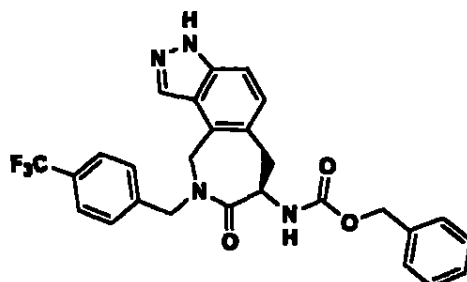
Intermediate 34



7-Amino-9-(1-(R)-phenyl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-8-one. [8-Oxo-9-(1-(R)-phenyl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester (105 mg, 0.23 mmol) was reacted in a manner analogous to the preparation of 7-(R)-amino-9-(2-piperidin-1-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Crude product was obtained as a maroon solid in 78% yield. Material was carried
20 forward without further purification. ¹H NMR (300 MHz, CDCl₃): δ = 7.88 (s, 1H), 7.40 (m, 6H), 7.14 (d, J = 8.8, 1H), 6.85 (m, 1H), 6.09 (m, 1H), 4.67 (d, J = 16.8, 1H), 4.47 (dd, J_1 = 4.6, J_2 = 12.6, 1H), 4.25 (d, J = 17.2, 1H), 1.48 (d, J = 7.0, 3H). MS m/e (M-H)⁺ = 319.3.

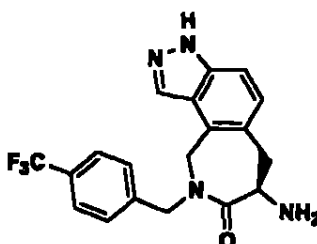
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Intermediate 35



[8-Oxo-9-(4-trifluoromethyl-benzyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. 4-Trifluoromethylbenzylamine (72 μ L, 0.51 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (100 mg, 0.23 mmol) were converted into the title compound in a manner similar to the preparation of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Crude material was obtained as a dark brown solid in quantitative yield. Material was carried forward without further purification. MS m/e ($M+H$)⁺ = 509.4. HPLC r_f = 1.67 min.

Intermediate 36



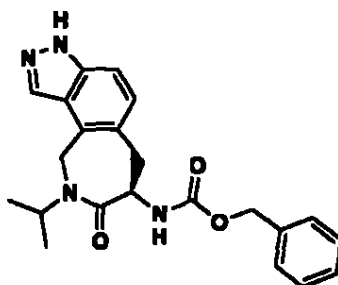
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7-Amino-9-(4-trifluoromethyl-benzyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-8-one bis-methanesulfonate. [8-Oxo-9-(4-trifluoromethyl-benzyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester was converted into the title compound in a manner analogous to the preparation of 7-(R)-amino-9-(2,2-dimethyl-propyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one bismethanesulfonate. Crude material was obtained

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as a dark foam in quantitative yield. Material was carried forward without further purification. MS m/e $(M+H)^+ = 375.2$. HPLC $r_f = 1.00$ min.

Intermediate 37

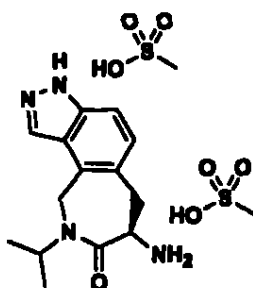


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(9-Isopropyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester. Isopropylamine (300 μ L, 3.5 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester were converted into the title compound following a procedure analogous to the preparation of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Crude product was obtained as a dark oil in quantitative yield. Material was carried forward without further purification. ^1H NMR (500 MHz, CDCl_3): $\delta = 8.09$ (s, 1H), 7.39 (m, 3H), 7.23 (m, 2H), 7.17 (m, 1H), 6.32 (d, $J = 5.8$, 1H), 5.25 (m, 1H), 5.15 (m, 2H), 4.90 (m, 1H), 4.82 (d, $J = 17.4$, 1H), 4.51 (m, 1H), 3.51 (m, 1H), 3.05 (t, $J = 13.6$, 1H), 1.56 (s, 6H). MS m/e $(M+H)^+ = 393.4$.

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Intermediate 38

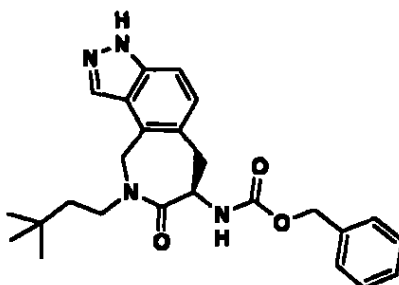


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7-(R)-Amino-9-isopropyl-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one bismethanesulfonate. (9-Isopropyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester (90 mg, 0.23 mmol) was converted into the title compound following a procedure analogous to the synthesis of 7-(R)-amino-9-(2,2-dimethyl-propyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one bismethanesulfonate. Crude product was obtained as a dark oil in quantitative yield. Crude material was carried forward without further purification. MS m/e ($M+H$)⁺ = 259.2. HPLC r_f = 0.60 min.

10

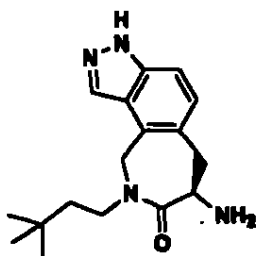
Intermediate 39



[9-(3,3-Dimethyl-butyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. 3,3-Dimethylbutylamine (100 μ L, 0.74 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester were converted into the title compound following a procedure analogous to the preparation of [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. Crude material was obtained as a dark oil in quantitative yield. Material was carried forward without further purification. ¹H NMR (300 MHz, CDCl₃): δ = 8.03 (m, 1H), 4.38 (m, 4H), 7.31 (m, 2H), 7.06 (d, J = 8.4, 1H), 6.26 (d, J = 6.2, 1H), 5.23 (m, 1H), 5.14 (s, 2H), 5.08 (m, 1H), 4.35 (dd, J_1 = 8.8, J_2 = 17.2, 1H), 3.50 (m, 2H), 1.33 (dd, J_1 = 6.2, J_2 = 11.0, 2H), 0.91 (m, 2H), 0.85 (s, 9H). MS m/e ($M+H$)⁺ = 435.1.

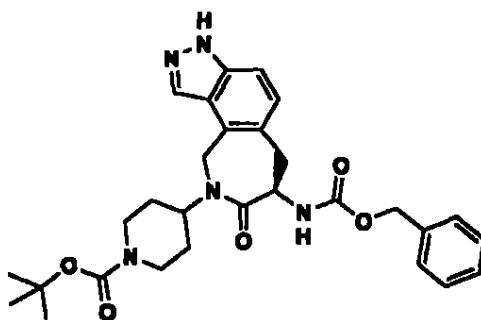
25

Intermediate 40



- 7-(R)-Amino-9-(3,3-dimethyl-butyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-
 5 cyclohepta[e]inden-8-one bismethanesulfonate. [9-(3,3-Dimethyl-butyl)-8-oxo-
 3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid
 benzyl ester (100 mg, 0.23 mmol) was converted into the title compound following a
 procedure analogous to the preparation of 7-(R)-amino-9-(2,2-dimethyl-propyl)-
 6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one bismethanesulfonate.
 10 Crude material was obtained as a dark oil in quantitative yield. Material was carried
 forward without further purification. MS m/e ($M+H$)⁺ = 301.2. HPLC r_f = 1.11 min.

Intermediate 41

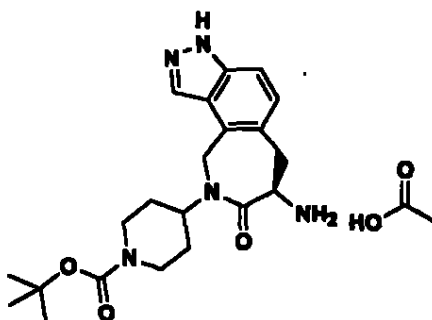


15

- 4-(7-(R)-Benzyloxycarbonylamino-8-oxo-6,7,8,10-tetrahydro-3H-2,3,9-triaza-
 cyclohepta[e]inden-9-yl)-piperidine-1-carboxylic acid tert-butyl ester. 4-Amino-1-
 N-Boc-piperidine (110 mg, 0.55 mmol) and 2-(R)-benzyloxycarbonylamino-3-(4-
 chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (150 mg, 0.34 mmol) was
 20 converted into the title compound in a manner analogous to the preparation of [9-
 (2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-

cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Crude product was obtained as a dark foam in quantitative yield. Material was carried forward without further purification. ¹H NMR (300 MHz, CDCl₃): δ= 8.05 (m, 1H), 7.35 (m, 6H), 7.15 (m, 1H), 6.27 (m, 1H), 5.28 (m, 1H), 5.15 (s, 2H), 4.87 (d, J= 16.5, 1H), 4.63 (m, 1H), 4.47 (m, 1H), 4.24 (m, 1H), 3.99 (m, 1H), 3.49 (m, 1H), 3.04 (m, 1H), 2.83 (m, 2H), 2.63 (m, 1H), 1.90 (m, 1H), 1.74 (m, 2H), 1.58 (s, 9H). MS m/e (M-H)⁺= 532.1.

Intermediate 42

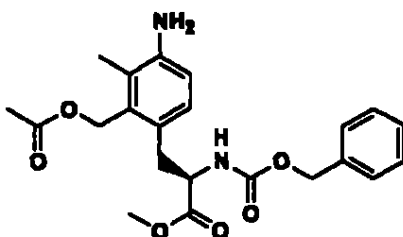


10

4-(7-(R)-Amino-8-oxo-6,7,8,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-9-yl)-piperidine-1-carboxylic acid tert-butyl ester acetate. A catalytic amount of 10% palladium on carbon was added to a solution of 4-(7-(R)-Benzyloxycarbonylamino-8-oxo-6,7,8,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (200 mg, 0.37 mmol) and acetic acid (100 μL, 1.7 mmol) in methanol (10 mL). Reaction vessel was placed on a Parr apparatus and charged with 30 psi of hydrogen gas. Mixture was allowed to shake at room temperature for 3 hours. Mixture was filtered. Filtrate was concentrated *in vacuo*. Crude compound was obtained as a dark oil in quantitative yield. Material was carried forward without further purification. ¹H NMR (300 MHz, CDCl₃): δ= 8.06 (s, 1H), 7.36 (d, J= 8.8, 1H), 7.12 (d, J= 8.8, 1H), 4.92 (d, J= 17.6, 1H), 4.67 (m, 1H), 4.49 (d, J= 17.2, 1H), 4.26 (m, 1H), 3.98 (m, 2H), 3.05 (m, 1H), 2.83 (m, 2H), 2.64 (m, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.45 (d, J= 2.9, 9H), 1.25 (m, 2H). MS m/e (M-C₄H₉+H)⁺= 344.2.

25

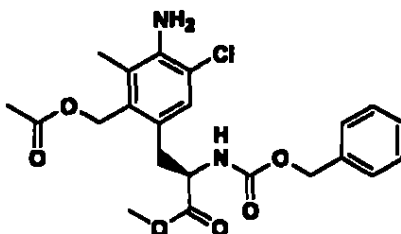
Intermediate 43

**3-(2-Acetoxymethyl-4-amino-3-methyl-phenyl)-2-(R)-**

- 5 **benzyloxycarbonylamino-propionic acid methyl ester.** 3-(2-Acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-phenyl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester was converted into 3-(2-Acetoxymethyl-4-amino-3-methyl-phenyl)-2-benzyloxycarbonylamino-(R)-propionic acid methyl ester following an analogous procedure to the synthesis of 2-(2-Acetoxymethyl-4-amino-3-methyl-benzyl)-(S)-
- 10 succinic acid diethyl ester. Desired product was obtained as a yellow oil in 95% yield. ¹H NMR (300 MHz, CDCl₃): δ= 7.31 (m, 5H); 6.81 (d, *J*= 8.1, 1H); 6.65 (d, *J*= 8.4, 1H); 5.35 (d, *J*= 8.1, 1H); 5.15 (s, 2H); 5.04 (s, 2H); 4.53 (m, 1H); 3.71 (s, 3H); 3.16 (m, 1H); 3.01 (m, 1H); 2.12 (s, 3H); 1.99 (s, 3H). MS *m/e* (M+H)⁺= 415.2.

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Intermediate 44

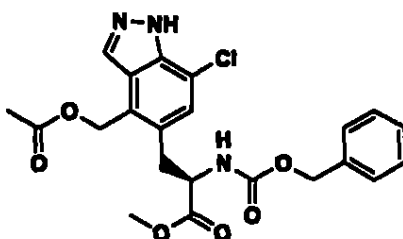
**3-(2-Acetoxymethyl-4-amino-5-chloro-3-methyl-phenyl)-2-(R)-**

- benzyloxycarbonylamino-propionic acid methyl ester. Desired product was obtained
- 20 from 3-(2-Acetoxymethyl-4-amino-3-methyl-phenyl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester in a manner analogous to the preparation of 2-(2-Acetoxymethyl-4-amino-5-chloro-3-methyl-benzyl)-(S)-succinic acid diethyl ester. Silica gel chromatography (ethyl acetate - hexanes) afforded the

product as an yellow oil in 40% yield. ¹H NMR (300 MHz, CDCl₃): δ= 7.31 (m, 5H); 6.96 (s, 1H); 5.36 (d, *J*=8.4, 1H); 5.12 (s, 2H); 5.05 (s, 2H), 4.53 (m, 1H); 3.72 (s, 3H); 3.15 (m, 1H), 2.99 (m, 1H); 2.15 (s, 3H); 1.99 (s, 3H). MS *m/e* (M-C₂H₄O₂+H)⁺= 398.3.

5

Intermediate 45

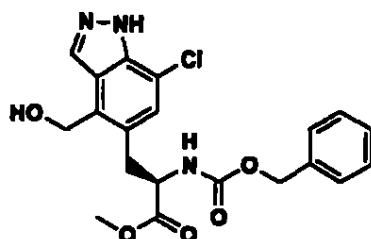


3-(4-Acetoxymethyl-7-chloro-1H-indazol-5-yl)-2-(R)-

- 10 *benzyloxycarbonylamino-propionic acid methyl ester*. Trifluoroacetic acid (70 μL, 0.91 mmol) was added to a solution of 3-(2-acetoxymethyl-4-amino-5-chloro-3-methyl-phenyl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester (345 mg, 0.77 mmol) in 5% acetic acid in chloroform (5.2 mL). Isoamyl nitrite (120 μL, 0.89 mmol) was added to the mixture drop-wise. Reaction mixture was stirred at room
- 15 temperature for 40 minutes. Potassium acetate (300 mg, 3.1 mmol) was added to the mixture. Reaction mixture was stirred at room temperature for 45 minutes. Mixture was diluted with dichloromethane (10 mL) then washed successively with water (2 X 10 mL), and saturated aqueous sodium bicarbonate (2 X 10 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Crude product was obtained
- 20 as an orange solid in 83 % yield. Material was carried forward without further purification. ¹H NMR (300 MHz, CDCl₃): δ= 8.20 (s, 1H); 7.29 (m, 5H); 7.21 (s, 1H); 5.53 (d, *J*=7.7, 1H); 5.40 (s, 2H); 5.04 (s, 2H); 4.67 (m, 1H); 3.74 (s, 3H); 3.34 (m, 1H); 3.21 (m, 1H); 2.02 (s, 3H). MS *m/e* (M+H)⁺= 460.1.

25

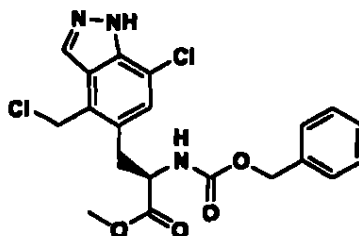
Intermediate 46



2-(R)-Benzyloxycarbonylamino-3-(7-chloro-4-hydroxymethyl-1H-indazol-5-yl)-propionic acid methyl ester. 3-(4-Acetoxymethyl-7-chloro-1H-indazol-5-yl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester (290 mg, 0.63 mmol) was converted into the desired product in a manner analogous to the preparation of 2-(R)-benzyloxycarbonylamino-3-(4-tert-butoxycarbonylamino-2-hydroxymethyl-3-methyl-phenyl)-propionic acid methyl ester. Crude product was obtained as an orange solid in 95% yield. Material was carried forward without further purification. ¹H NMR (300 MHz, CDCl₃): δ= 8.15 (s, 1H); 7.27 (m, 5H); 7.14 (s, 1H); 6.10 (m, 1H); 5.01 (d, J=4.8, 2H); 4.95 (s, 2H); 4.75 (m, 1H); 3.79 (s, 3H); 3.34 (m, 1H); 3.09 (m, 1H). MS m/e (M+H)⁺= 418.0.

15

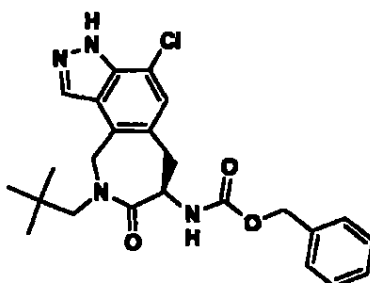
Intermediate 47



2-(R)-Benzyloxycarbonylamino-3-(7-chloro-4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester. Thionyl chloride (2 mL) was added to a solution of 2-(R)-benzyloxycarbonylamino-3-(7-chloro-4-hydroxymethyl-1H-indazol-5-yl)-propionic acid methyl ester (245 mg, 0.59 mmol) in dichloromethane (3 mL). Mixture was stirred at room temperature for 1.5 hours. Mixture was concentrated. Residue was dissolved in dichloromethane (15 mL) then washed with saturated

aqueous sodium bicarbonate (2 X 10 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Title compound was obtained as an orange solid in 86% yield. Material was carried forward without further purification. ¹H NMR (300 MHz, CDCl₃): δ= 8.19 (s, 1H), 7.32 (m, 5H), 7.16 (s, 1H), 5.49 (d, J= 7.3, 2H), 5.07 (d, J= 4.4, 2H), 4.85 (s, 2H), 4.68 (d, J= 7.0, 1H), 3.72 (s, 3H), 3.27 (m, 2H). MS m/e (M+H)⁺= 436.1.

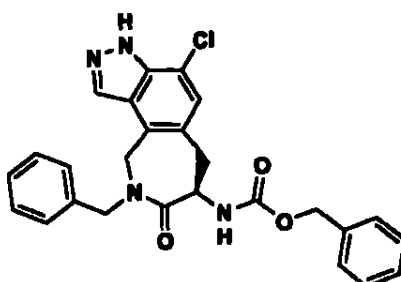
Intermediate 48



10
[4-Chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester. Neopentylamine (200 μL, 1.7 mmol) was added to a mixture of 2-(R)-benzyloxycarbonylamino-3-(7-chloro-4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (180 mg, 0.41 mmol) and potassium carbonate (160 mg, 1.2 mmol) in acetonitrile (5 mL). Reaction was heated at reflux for 1 hour. Mixture was cooled to room temperature then filtered through a 0.45 μm PTFE syringeless filter system. Filtrate was concentrated. Residue was dissolved in a mixture of toluene (5 mL) and acetic acid (200 μL). Mixture was heated at 110 °C overnight. Mixture was diluted with ethyl acetate (15 mL) then washed successively with water (15 mL), saturated aqueous sodium bicarbonate (2 X 15 mL) and brine (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Silica gel chromatography afforded the title compound in 52% yield as a yellow solid. ¹H NMR (300 MHz, CDCl₃): δ= 7.89 (d, J= 10.6, 1H), 7.38 (m, 5H), 6.96 (d, J= 10.3, 1H), 6.35 (d, J= 5.9, 1H), 5.25 (m, 1H), 5.19 m, 2H), 4.28 (m, 1H), 3.66 (m, 1H), 3.40 (m, 1H), 2.96 (dd, J1= 13.9, J2= 5.5, 2H), 0.76 (d, J= 2.6, 9H). MS m/e (M+H)⁺= 455.2.

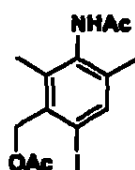
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Intermediate 49



- 5 *(9-Benzyl-4-chloro-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester.* Title compound was obtained from benzylamine (100 μ L, 0.92 mmol) and 2-(R)-Benzyloxycarbonylamino-3-(7-chloro-4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester (210 mg, 0.48 mmol) following a procedure analogous to the preparation of [4-Chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-
- 10 7-yl]-carbamic acid benzyl ester. Silica gel chromatography (ethyl acetate – hexanes) afforded the desired product as a yellow solid in 52% yield. ^1H NMR (300 MHz, CDCl_3): δ = 7.64 (s, 1H), 7.38 (m, 5H), 7.19 (m, 3H), 7.12 (m, 2H), 7.00 (s, 1H), 6.36 (d, J = 6.2 1H), 5.28 (m, 1H), 5.21 (s, 2H), 5.19 (m, 1H), 4.88 (m, 1H), 4.75 (d, J = 16.8, 1H), 4.34 (d, J = 14.6, 1H), 3.49 (m, 1H), 3.03 (m, 1H). MS m/e
- 15 $(\text{M}+\text{H})^+ = 475.0$.

Intermediate 50



- 20 *Acetic acid 3-acetylamino-6-iodo-2,4-dimethyl-benzyl ester.* To a well stirred solution of (3-amino-2,4-dimethyl-phenyl)-methanol (1.5 g) in methanol (70 mL) and solid sodium hydrogen carbonate (4.0 eq) was added a 1.0 M solution of iodine monochloride dropwise over a period of 5 min at 0 $^{\circ}\text{C}$. The cooling bath was removed after the addition of iodine monochloride. The reaction mixture was

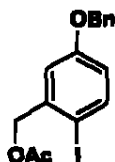
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brought to room temperature and stirring continued for another 1 h. The reaction mixture was concentrated to remove most of methanol, diluted with dichloromethane (50 mL) and washed with 10% solution of sodium thiosulfate and dried (Na₂SO₄). The desired compound was purified by trituration with dichloromethane and hexane to give in 1.9 g of iodide. The iodide was then treated with dichloromethane (100 mL) followed by acetic anhydride (4 eq) and catalytic amount of dimethylaminopyridine and stirred for a period of 12 h at room temperature. The reaction mixture was then washed with aqueous sodium hydrogen carbonate, 1.0 M hydrochloric acid and dried (Na₂SO₄). The desired compound was trituated with dichloromethane and hexane to give acetic acid 3-acetylamino-6-iodo-2,4-dimethylbenzyl ester in 95% yield. ¹H NMR (300 MHz, CDCl₃): in δ 7.68 (s, 1 H), 6.68 (s, 1 H), 2.28 (s, 3 H), 2.25 (s, 3 H), 2.18 (s, 3 H), 2.07 (s, 3 H); MS (ESI) 384 (M+Na); R_f = 1.12.

15

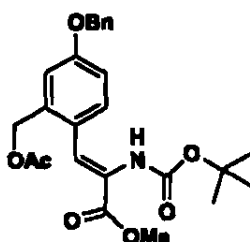
Intermediate 51



Acetic acid 5-benzyloxy-2-iodo-benzyl ester. To a well stirred solution of 3-benzyloxybenzyl alcohol (5.5 g, 25.7 mmol) in methanol (100 mL) and sodium hydrogencarbonate (8.4 g, 100 mmol) was added a 1.0 M solution of iodine monochloride in dichloromethane (30 mL) at 0 °C. The reaction mixture was brought to room temperature and stirring continued for additional 1h. The reaction mixture was concentrated and then diluted with dichloromethane (150 mL), washed with 10% aqueous sodium thiosulfate and dried (Na₂SO₄). The desired compound was purified by flash chromatography (silica) using 20% ethyl acetate in hexane to give 5-benzyloxy-2-iodobenzyl alcohol (6.2 g, 71% yield). The alcohol (4.2 g, 12.4 mmol) was dissolved in dichloromethane (100 mL) added acetic anhydride (2.52 g, 24.7 mmol) and catalytic amount of 4-dimethylaminopyridine. The reaction mixture was then stirred for 12 h, washed with aqueous sodium hydrogencarbonate and then

dried (Na_2SO_4) to give acetic acid 5-benzyloxy-2-iodo-benzyl ester in quantitative yield. MS (ESI) 405 ($\text{M}+\text{Na}$); $R_f = 2.27$.

Intermediate 52

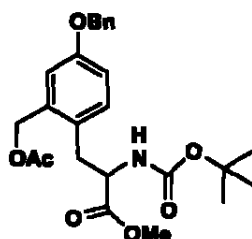


5

3-(2-Acetoxymethyl-4-benzyloxy-phenyl)-2-tert-butoxycarbonylamino-acrylic acid methyl ester. In a manner similar to 2-(acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzylidene)-succinic acid diethyl ester, 3-(2-acetoxymethyl-4-benzyloxy-phenyl)-2-tert-butoxycarbonylamino-acrylic acid methyl ester was prepared by reacting acetic acid 5-benzyloxy-2-iodo-benzyl ester with 2-tert-butoxycarbonylamino-acrylic acid methyl ester in 74% yield. MS (ESI) 456 ($\text{M}+\text{H}$); $R_f = 1.87$.

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Intermediate 53

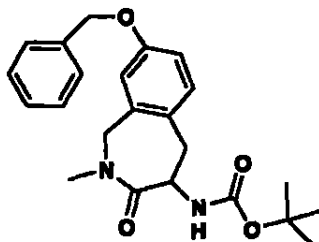


20

3-(2-Acetoxymethyl-4-benzyloxy-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester. To a solution of 3-(2-acetoxymethyl-4-benzyloxy-phenyl)-2-tert-butoxycarbonylamino-acrylic acid methyl ester (1.9 g, 4.2 mmol) in anhydrous methanol under nitrogen atmosphere was added 1,2-bis((2R,5R)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium (I) trifluoromethanesulfonate (50 mg) and stirred on a Parr shaker at 50 psi of hydrogen atmosphere for 18 h. The

solvent was evaporated and the desired product was crystallized from ethyl acetate-hexane in 90% yield. MS (ESI) 458 (M+H); R_f = 1.81.

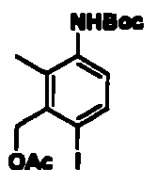
Intermediate 54



5

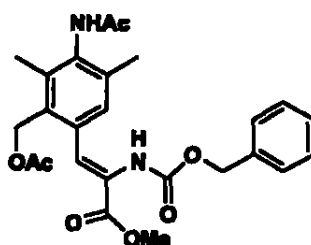
(8-Benzyloxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-carbamic acid tert-butyl ester. To a solution of 3-(2-acetoxymethyl-4-benzyloxy-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester (1.85 g, 4.0 mmol) in methanol (40 mL) was added potassium carbonate (560 mg, 4.0 mmol) at room temperature and stirred for 1 h. The reaction mixture was diluted with dichloromethane (150 mL), washed with 1.0 M aqueous hydrogen chloride and dried (Na_2SO_4) to give the pure 3-(4-benzyloxy-2-hydroxymethyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester in almost quantitative yield. To the alcohol (800 mg, 1.93 mmol) in dichloromethane (50 mL) was added methanesulfonyl chloride (0.18 mL, 2.3 mmol) followed by triethylamine (0.38 mL, 2.70 mmol) at 0 °C and then brought to room temperature. After 1 h, the reaction mixture was washed with aqueous sodium hydrogencarbonate, dried (Na_2SO_4). The solvent was removed, dissolved the crude product in anhydrous THF (20 mL) followed by addition of 2.0 M solution of methylamine in THF (10 mL) in a sealed tube. The sealed tube was heated at 80 °C for a period of 12 h and then removed the solvent. The crude product was purified by flash chromatography using 30% ethyl acetate in hexane to give (8-benzyloxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-carbamic acid tert-butyl ester in 39% overall yield. ^1H NMR (500 MHz, CDCl_3): in δ 7.40 – 7.31 (m, 5 H), 7.01 – 7.00 (m, 1 H), 6.83 – 6.82 (m, 1 H), 6.66 (s, 1 H), 5.91 – 5.90 (m, 1 H), 5.13 – 5.01 (m, 4 H), 3.50 – 3.46 (m, 1 H), 3.03 (s, 3 H), 2.85 – 2.78 (m, 1 H), 1.45 (s, 9 H).

Intermediate 55



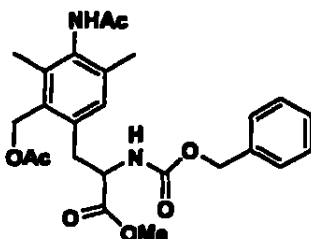
Acetic acid 3-tert-butoxycarbonylamino-6-iodo-2-methyl-benzyl ester. To a well stirred solution of 3-amino-2-methylbenzyl alcohol (10 g, 72.9 mmol) in methanol (250 mL) was added a 1.0 M solution of iodine monochloride in dichloromethane (76.6 mL) dropwise over a period of 5 min at 0 °C. The reaction mixture was then brought to room temperature and stirring continued for additional 2 h. The reaction mixture was then concentrated, diluted with dichloromethane (250 mL), washed with 10% aqueous sodium thiosulphate and dried (Na₂SO₄). The solvent was evaporated and the crude product was dissolved in THF (200 mL). Di-tert-butyl dicarbonate (15.9 g, 72.9 mmol) was added and the reaction mixture was refluxed for 48 h. The reaction mixture was then diluted with ether (400 mL) washed with 1 M HCl (2 x 100mL) followed by brine and dried (Na₂SO₄). The solvent was removed and the desired product was crystallized from 20% ethyl acetate in hexane to give (3-hydroxymethyl-4-iodo-2-methyl-phenyl)-carbamate acid tert-butyl ester (12.5 g). The filtrate was then concentrated and the desired product was purified by flash chromatography (silica) using 30% ethyl acetate to give additional 2.5 g of (3-hydroxymethyl-4-iodo-2-methyl-phenyl)-carbamate acid tert-butyl ester. To a stirred solution of 3-hydroxymethyl-4-iodo-2-methyl-phenyl)-carbamate acid tert-butyl ester (14.5 g, 40 mmol) in dichloromethane (150 mL) was added acetic anhydride (7.5 mL, 80 mmol) and catalytic amount of 4-dimethylaminopyridine and stirred for 12 h at room temperature. The reaction mixture was then quenched with aqueous sodium hydrogencarbonate, brine and dried (Na₂SO₄). The solvent was removed and the crude product was purified by crystallization from dichloromethane and hexane to give acetic acid 3-tert-butoxycarbonylamino-6-iodo-2-methyl-benzyl ester (15.5 g, 94%). ¹H NMR (500 MHz, CDCl₃): in δ 7.71 (d, J = 8.5 Hz, 1 H), 7.25 (d, J = 8.5 Hz, 1 H), 5.30 (s, 2 H), 2.28 (s, 3 H), 2.08 (s, 3 H), 1.50 (s, 9 H); MS (ESI) 428 (M+Na); R_f = 1.59.

Intermediate 56



- 3-(2-Acetoxymethyl-4-acetylamino-3,5-dimethyl-phenyl)-2-
 5 benzyloxycarbonylamino-acrylic acid methyl ester. In a manner similar to 2-(acetoxymethyl-4-*tert*-butoxycarbonylamino-3-methyl-benzylidene)-succinic acid diethyl ester, 3-(2-acetoxymethyl-4-acetylamino-3,5-dimethyl-phenyl)-2-benzyloxycarbonylamino-acrylic acid methyl ester was prepared by reacting acetic acid 3-acetylamino-6-iodo-2,4-dimethyl-benzyl ester with 2-
 10 benzyloxycarbonylamino-acrylic acid methyl ester in 74% yield. MS (ESI) 491 (M+H); R_f = 1.87.

Intermediate 57

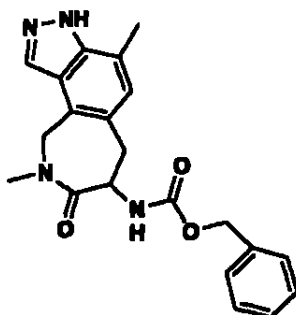


15

- 3-(2-Acetoxymethyl-4-acetylamino-3,5-dimethyl-phenyl)-2-
 benzyloxycarbonylamino-propionic acid methyl ester. In a manner similar to 3-(2-acetoxymethyl-4-benzyloxy-phenyl)-2-*tert*-butoxycarbonylamino-acrylic acid methyl ester, 3-(2-acetoxymethyl-4-acetylamino-3,5-dimethyl-phenyl)-2-
 20 benzyloxycarbonylamino-propionic acid methyl ester was prepared from 3-(2-acetoxymethyl-4-acetylamino-3,5-dimethyl-phenyl)-2-benzyloxycarbonylamino-acrylic acid methyl ester (1.5 g) using 1,2-bis((2R,5R)-2,5-

diethylphospholano)benzene(cyclooctadiene)rhodium (I) trifluoromethanesulfonate (25 mg) in 98% yield. MS (ESI) 491 (M+H); R_f = 1.87.

Intermediate 58

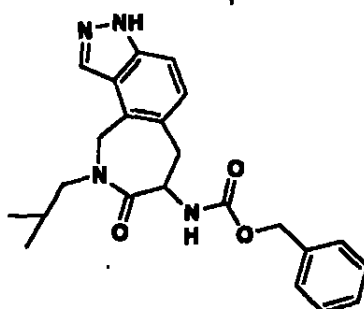


5

- (8-Acetylamino-2,7,9-trimethyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-carbamic acid benzyl ester. In a manner similar to 2-(R)-benzyloxycarbonylamino-3-(4-tert-butoxycarbonylamino-2-hydroxymethyl-3-methyl-phenyl)-propionic acid methyl ester hydrochloride, the title compound was prepared by hydrolyzing 3-(2-acetoxymethyl-4-acetylamino-3,5-dimethyl-phenyl)-2-benzyloxycarbonylamino-propionic acid methyl ester (1.84 g, 3.78 mmol) with potassium carbonate (525 mg, 3.8 mmol) in MeOH (40 mL). The alcohol was dissolved in dichloromethane (100 mL) and then treated with methanesulfonyl chloride (0.35 mL, 4.5 mmol) and triethylamine (0.68 mL, 4.9 mmol). The reaction mixture was stirred for 12 h, washed with aqueous sodium hydrogencarbonate, 1.0 M aqueous hydrogen chloride and dried (Na_2SO_4). The solvent was removed to give pure 3-(4-acetylamino-2-chloromethyl-3,5-dimethyl-phenyl)-2-benzyloxycarbonylamino-propionic acid methyl ester in almost quantitative yield.
- The chloride (480 mg, 1.08 mmol) was treated with 1.0 M methylamine solution in THF in a sealed tube for 3h at 90 °C. The solvent was removed and the crude product was dissolved in toluene and acetic acid (0.5 mL) and refluxed for 2 h to give (8-acetylamino-2,7,9-trimethyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-carbamic acid benzyl ester in 68% yield. To the acetate in chloroform (20 mL) was added acetic acid (0.5 mL) followed by isoamyl nitrite (1.0 mL) and 18-crown-6 (50 mg). The reaction mixture was refluxed for 12 h and removed the solvent. The crude

product was purified by flash chromatography using ethyl acetate as eluent to give (4,9-dimethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester as a major product in 37% overall yield. ¹H NMR (500 MHz, CDCl₃): in δ 7.96 (s, 1 H), 7.35 – 7.24 (m, 5 H), 6.7 (s, 1 H), 6.43 – 6.41 (m, 1 H), 5.25 – 5.05 (m, 3 H), 4.18 – 4.10 (m, 2 H), 3.07 – 3.05 (m, 2 H), 3.00 (s, 3 H), 2.40 (s, 3 H).

Intermediate 59



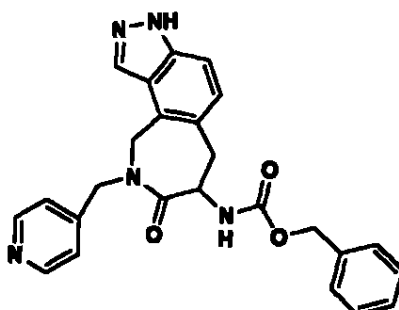
10

(9-Isobutyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester. In a manner similar to [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester, the title compound was prepared by treating 2-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester, hydrochloride with isobutylamine followed by treatment with acetic acid in refluxing toluene to give (9-Isobutyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester in 91% yield. MS (ESI) 407 (M+H)⁺; R_f = 1.58.

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25

Intermediate 60

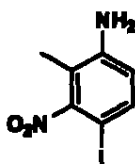


- 5 (8-Oxo-9-pyridin-4-ylmethyl-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester. In a manner similar to [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester, the title compound was prepared by treating 2-benzyloxycarbonylamino-3-(4-chloromethyl-1H-indazol-5-yl)-propionic acid methyl ester, hydrochloride with 4-(aminomethyl)pyridine followed by treatment with acetic acid in refluxing toluene to give (8-oxo-9-pyridin-4-ylmethyl-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester in 65% yield.

MS (ESI) 442 (M+H) ; R_f = 1.10.

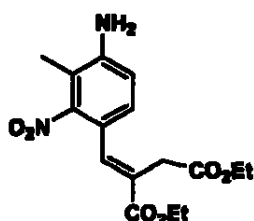
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Intermediate 61



- 4-Iodo-2-methyl-3-nitrobenzenamine. To a well stirred solution of 2-methyl-3-nitroaniline (10 g, 66 mmol) in methanol (150 mL) was added sodium hydrogencarbonate (264 mmol) followed by 1.0 M solution of iodine monochloride (72 mmol) at room temperature. After stirring for 1 h, the solvent was removed, diluted with ether, washed with 10% aqueous sodium thiosulfate solution. The solvent was removed and the crude iodide was in the next step.

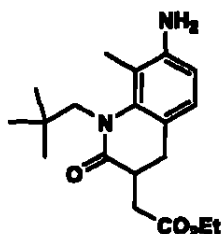
Intermediate 62



5 *(E)*-Diethyl 2-(4-amino-3-methyl-2-nitrobenzylidene)succinate. To a solution
 of 4-iodo-2-methyl-3-nitrobenzenamine (59 mmol) in dimethylformamide (100 mL)
 was added diethyl itaconate (13.2 g, 71 mmol), tetrabutylammonium chloride (16.4 g,
 59 mmol), triethylamine (236 mmol) and palladium acetate (675 mg, 3 mmol) under
 nitrogen. The reaction mixture was heated to 80 °C for 2 h. The crude reaction
 mixture was then filtered, diluted with ether (250 mL), washed with water (2 X 300
 10 mL). The crude product was purified by flash chromatography using 20% ethyl
 acetate in hexane to give 8.5 g of the title compound. ¹H NMR (500 MHz, CDCl₃): in
 δ 7.58 (s, 1 H), 7.10 (d, J = 8.5 Hz, 1 H), 6.73 (d, J = 8.5 Hz, 1 H), 4.24 – 4.15 (m, 4
 H), 3.40 (s, 2 H), 2.06 (s, 3 H), 1.30 – 1.23 (m, 6 H).

15

Intermediate 63



20 *Ethyl 2-(7-amino-8-methyl-1-neopentyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetate*. To a solution of *(E)*-diethyl 2-(4-amino-3-methyl-2-nitrobenzylidene)succinate (4.5 g, 13.4 mmol) in THF (100 mL) was added (Boc)₂O (16 mmol) followed by catalytic amount of dimethylaminopyridine (10 mg). The reaction mixture was heated in a sealed tube for 3 h at 100 °C. The reaction mixture was cooled, removed solvent, diluted with ether and then washed with aqueous

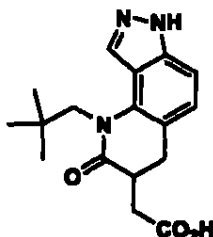
72

sodium hydrogencarbonate (50 mL). The crude product was found to contain both mono- and di-Boc protected compounds. The crude product was dissolved in methanol (200 mL) and was added water (150 ml) followed by ammonium chloride (14.3 g, 268 mmol) and iron powder (8.9 g, 160 mmol). The reaction mixture was heated at 50 °C for 1 h, cooled and then filtered over a pad of celite. The solvent was removed, extracted with ethyl acetate and then washed with brine and dried (Na₂SO₄). The crude product was purified by flash chromatography using 30% ethyl acetate in hexane as eluent to give the amine. The amine (4.1 g, 10 mmol) was dissolved in dichloroethane (100 mL) followed by addition of acetic acid (10 mL), trimethylacetaldehyde (11 mmol) and magnesium sulfate (5.0 g). The reaction mixture was stirred for 2 h and then filtered. To the filtered reaction mixture was added sodium triacetoxyborohydride (2.33 g, 11 mmol) and stirring continued for additional 2 h. The reaction mixture was diluted with hexane (150 mL), washed with water (2 X 100 mL), aqueous NaHCO₃ solution and dried (Na₂SO₄). The solvent was removed and the crude product was dissolved in methanol (100 mL) followed by addition of acetic acid (5 mL) and hydrogenated in a parr bottle at a pressure of 50 psi hydrogen. The catalyst was removed by filtration and the solvent was removed. The crude product was dissolved in toluene (100 mL) followed by addition of tosic acid (100 mg) and sodium cyanide (50 mg). The reaction mixture was refluxed for 12 h and the crude product was purified by flash chromatography using 50% ethyl acetate in hexane to give ethyl 2-(7-amino-8-methyl-1-neopentyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetate.

MS (ESI) 333 (M+H); R_f = 1.29.

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Intermediate 64



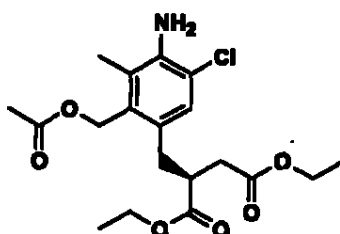
73

~~73~~

2-(1-Neopentyl-2-oxo-2,3,4,7-tetrahydro-1H-pyrazolo[3,4-h]quinolin-3-yl)acetic acid. To a solution of ethyl 2-(7-amino-8-methyl-1-neopentyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetate (170 mg, 0.51 mmol) in carbon tetrachloride (4.5 mL) was added acetic acid (0.5 mL) followed by isoamyl nitrite (0.04 mL) and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with dichloromethane (40 mL), washed with aqueous NaHCO₃ and dried. The solvent was removed and the crude product was dissolved in THF (15 mL) followed by addition of lithium hydroxide (43 mg, 1 mmol) and water (5 mL). After stirring for 12 h, the solvent was removed, acidified with 6 M HCl and extracted with ethyl acetate to give 2-(1-neopentyl-2-oxo-2,3,4,7-tetrahydro-1H-pyrazolo[3,4-h]quinolin-3-yl)acetic acid.

MS (ESI) 316 (M+H); R_f = 1.31.

Intermediate 65

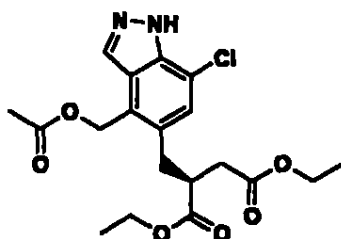


15

2-(S)-(2-Acetoxyethyl-4-amino-3-chloro-3-methyl-benzyl)-succinic acid diethyl ester. 2-(S)-(2-Acetoxyethyl-4-amino-3-methyl-benzyl)-succinic acid diethyl ester (3.0 g, 8.2 mmol) was dissolved in acetonitrile (40 mL). Mixture was warmed to 60 °C. N-Chlorosuccinimide (1.29 g, 9.7 mmol) was added to the warm solution. Reaction mixture was heated at reflux for 10 minutes. Mixture was cooled to room temperature then diluted with ethyl acetate (20 mL). Mixture was washed successively with saturated aqueous sodium bicarbonate (40 mL), and brine (20 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography (ethyl acetate-hexanes) afforded the desired product in 59% yield as an amber oil. ¹H NMR (300 MHz, CDCl₃): δ = 6.98 (s, 1H), 5.15 (d, J = 3.3, 2H), 4.09 (m, 4H), 2.99 (m, 2H), 2.69 (m, 2H), 2.39 (dd, J₁ = 4.8, J₂ = 16.5, 1H), 2.17 (s, 3H), 2.06 (s, 3H), 1.20 (m, 6H). MS m/e (M-C₂H₄O₂+H)⁺ = 340.0.

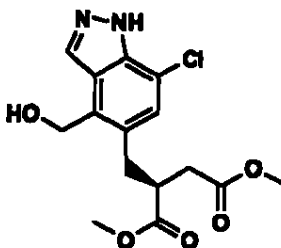
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Intermediate 66



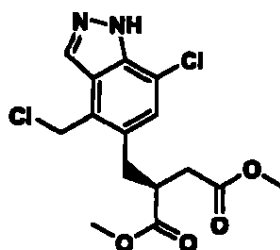
- 5 *2-(S)-(4-Acetoxymethyl-7-chloro-1H-indazol-5-ylmethyl)-succinic acid diethyl ester*. Isoamyl nitrite (700 μ L, 5.2 mmol), was added dropwise to an ice cold solution of 2-(S)-(2-Acetoxymethyl-4-amino-5-chloro-3-methyl-benzyl)-succinic acid diethyl ester (1.91 g, 4.8 mmol) in 5% acetic acid in toluene (81.2 mL). Mixture stirred at 0 $^{\circ}$ C for 45 minutes. Potassium acetate (1.50 g, 15.3 mmol) was added to
- 10 the mixture. Reaction was stirred at room temperature for 14 hours. Mixture was quenched with water. Mixture was extracted with ethyl acetate (30 mL). Mixture was washed 2X saturated aqueous sodium bicarbonate. Organic was dried (magnesium sulfate) filtered and concentrated. Silica gel chromatography (ethyl acetate-hexanes) afforded the desired product in 80% yield as an amber oil. ^{1} H NMR (300 MHz, CDCl_3): δ = 8.23 (s, 1H), 7.26 (s, 1H), 5.45 (s, 2H), 4.09 (q, J = 7.0, 4H), 3.20 (dd, J_1 = 7.32, J_2 = 13.2, 1H), 3.10 (m, 1H), 2.97 (dd, J_1 = 7.0, J_2 = 13.3, 1H), 2.73 (dd, J_1 = 8.4, J_2 = 16.8, 1H), 2.44 (dd, J_1 = 5.5, J_2 = 16.8, 1H), 2.08 (s, 3H), 1.18 (m, 6H). MS m/e ($M+H$) $^+$ = 411.0.

Intermediate 67



(S)-Dimethyl 2-((7-chloro-4-(hydroxymethyl)-1H-indazol-5-yl)methyl)succinate. 2-(*S*)-(2-Acetoxymethyl-4-amino-5-chloro-3-methyl-benzyl)succinic acid diethyl ester (2.21 g, 5.4 mmol) was converted to the title compound in a manner analogous to the preparation of 2-(*S*)-(4-Hydroxymethyl-1H-indazol-5-ylmethyl)succinic acid dimethyl ester. Material was obtained as amber solid in 99% yield. MS m/e $(M+H)^+ = 241.2$.

Intermediate 68

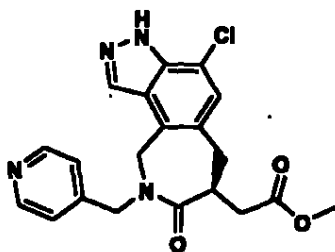


10

(S)-Dimethyl 2-((7-chloro-4-(chloromethyl)-1H-indazol-5-yl)methyl)succinate. (*S*)-Dimethyl 2-((7-chloro-4-(hydroxymethyl)-1H-indazol-5-yl)methyl)succinate (2.0 g, 5.9 mmol) was dissolved in dichloromethane (35 mL). Thionyl chloride (5.0 mL) was added to the mixture. Reaction stirred at room temperature for 1.5 hours. Mixture was concentrated. Residue was dissolved in ethyl acetate. Mixture was washed twice with aqueous sodium bicarbonate and once with brine. Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as amber solid in 89% yield. MS m/e $(M+H)^+ = 359.1$.

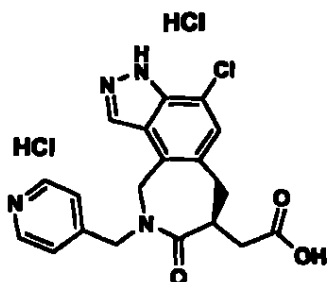
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Intermediate 69



(S)-Methyl 2-(4-chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl)acetate. *(S)*-Dimethyl 2-((7-chloro-4-(chloromethyl)-1H-indazol-5-yl)methyl)succinate (120 mg, 0.33 mmol) was dissolved in DMF (1.0 mL). 4-Aminomethylpyridine (100 μ L, 1.0 mmol) was added to the mixture. Reaction stirred at room temperature for 24 hours. Mixture was diluted with ethyl acetate. Mixture was washed twice with water and once with brine. Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was dissolved in toluene (4 mL). Acetic acid (1 mL) was added to the mixture. Reaction was heated at reflux for 3.5 hours. Mixture was cooled to room temperature then diluted with ethyl acetate. Material was washed once with water and twice with aqueous sodium bicarbonate. Aqueous was made basic with sodium bicarbonate. Back extracted from the aqueous twice with ethyl acetate. Combined organics were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was purified with silica gel chromatography eluting dichloromethane and 2N ammonia in methanol. Title compound was obtained as yellow solid in 48% yield. MS m/e ($M+H$)⁺ = 399.2.

Intermediate 70

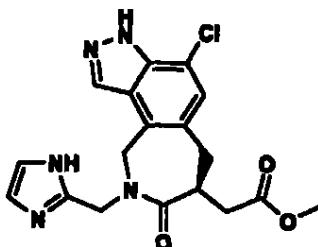


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(S)-2-(4-Chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl)acetic acid dihydrochloride. *(S)*-Methyl 2-(4-chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl)acetate (21 mg, 0.05 mmol) was dissolved in 1N hydrochloric acid (1.0 mL). Reaction was heated at 50 $^{\circ}$ C for 5 hours. Another 1 mL of 1N hydrochloric acid was added to the mixture. Reaction was heated at 50 $^{\circ}$ C for 17 hours. Mixture was concentrated *in vacuo*. Residue was treated with acetonitrile and then the material

was concentrated. Title compound was obtained as dark yellow solid in 83% yield.
MS m/e (M+H)⁺ = 385.2.

Intermediate 71

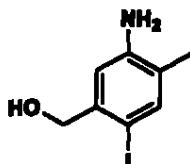


5

(S)-Methyl 2-(9-((1H-imidazol-2-yl)methyl)-4-chloro-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)acetate. (S)-Dimethyl 2-((7-chloro-4-(chloromethyl)-1H-indazol-5-yl)methyl)succinate (250 mg, 0.63 mmol) and (1H-imidazol-2-yl)methanamine dihydrochloride (170 mg, 1.0 mmol) were combined and
10 suspended in acetonitrile (10 mL). Triethylamine (800 μ L, 5.7 mmol) was added to the mixture. Reaction was warmed to reflux for 3 hours. Acetic acid (1.5 mL) was added to the mixture. Reaction was heated at reflux for 20 hours. Mixture was cooled to room temperature then diluted with dichloromethane. Mixture was
15 extracted twice with water. Aqueous layer was concentrated *in vacuo*. Residue was purified by preparatory HPLC. Water was lyophilized off. Remaining residue was passed through a column of Dowex 1x4-200 ion exchange resin eluting methanol. Title compound was recovered as amber residue in 24% yield. MS m/e (M+H)⁺ = 388.1.

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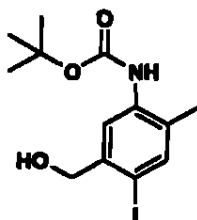
Intermediate 72



5 *5-Amino-2-iodo-4-methylbenzyl alcohol*. To an ice cooled solution of 3-amino-4-methylbenzyl alcohol (10.0 g, 72.9 mmol) in methanol (200 mL) 1M iodine monochloride in dichloromethane (80.0 mL, 80.0 mmol) was added dropwise over 30 minutes. Ice bath was removed. Reaction was stirred at ambient temperature for 40 minutes. Mixture was concentrated *in vacuo*. Residue was treated with dichloromethane (250 mL). Solids were filtered off and washed with dichloromethane. Solids were partitioned between ethyl acetate and 1N aqueous sodium hydroxide. Layers were partitioned. Organic layer was washed with 1N aqueous sodium hydroxide. The combined aqueous layers were back extracted two times with ethyl acetate. Combined organic layers were washed with brine. Combined extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Desired product was obtained as tan solid in 81% yield. MS m/e ($M+H$)⁺ = 264.

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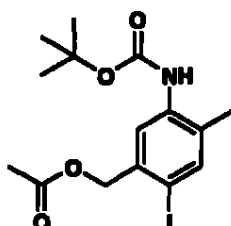
Intermediate 73



20 *tert-Butyl 5-(hydroxymethyl)-4-iodo-2-methylphenylcarbamate*. 5-Amino-2-iodo-4-methylbenzyl alcohol (4.60 g, 17.5 mmol) was dissolved in tetrahydrofuran (80 mL). Di-*tert*-butyl dicarbonate (5.30 g, 24.3 mmol) was added to the mixture. Reaction was heated at 60°C for 20 hours. Mixture was concentrated. Residue was purified by silica gel chromatography eluting ethyl acetate-hexanes. Title compound was obtained as off-white solid. MS m/e ($M-C_4H_9O+H$)⁺ = 290.

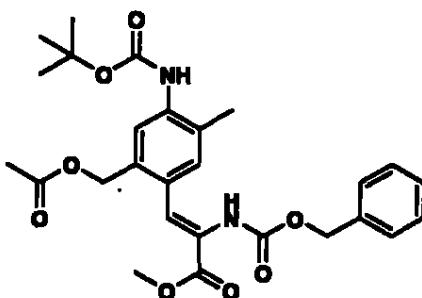
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Intermediate 74



- 5 *5-(tert-Butoxycarbonyl)-2-iodo-4-methylbenzyl acetate*. *tert*-Butyl 5-(hydroxymethyl)-4-iodo-2-methylphenylcarbamate (4.32 g, 11.9 mmol) was dissolved in dichloromethane (60 mL). Acetic anhydride (2.6 mL, 27.6 mmol) was added to the mixture followed by potassium acetate (2.0 g, 20.4 mmol). Reaction was stirred at room temperature over 15 hours. Mixture was warmed to 50 °C and held for 1 hour. Mixture was cooled to room temperature then diluted with
- 10 dichloromethane. Mixture was washed twice with water, and once with saturated aqueous sodium bicarbonate. Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was treated with 10% ethyl acetate-hexanes (100 mL). Material was concentrated *in vacuo*. Desired compound was obtained as white solid in 98% yield. ¹H NMR (300 MHz, CD₃OD): δ= 7.64 (s, 1H), 7.54 (s, 1H),
- 15 4.51 (s, 2H), 2.19 (s, 3H), 1.51 (s, 9H).

Intermediate 75

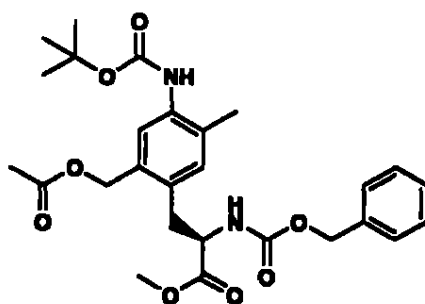


- 20 *3-(2-Acetoxymethyl-4-tert-butoxycarbonylamino-5-methyl-phenyl)-2-benzyloxycarbonylamino-acrylic acid methyl ester*. Title compound was prepared in a manner analogous to the preparation of 3-(2-Acetoxymethyl-4-tert-

butoxycarbonylamino-3-methyl-phenyl)-2-benzyloxycarbonylamino-acrylic acid methyl ester. Material was obtained as a white solid in 65% yield. MS m/e (M+H)⁺ = 513.

5

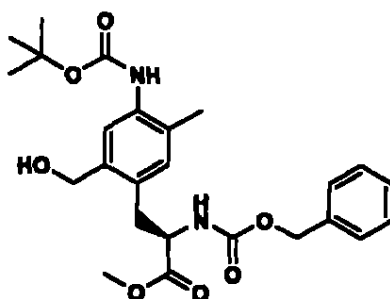
Intermediate 76



10

3-(2-Acetoxymethyl-4-tert-butoxycarbonylamino-5-methyl-phenyl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester. Title compound was prepared in a manner analogous to the preparation of 2-(S)-(acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzyl)-succinic acid diethyl ester. Material was obtained as clear colorless oil in 99% yield. MS m/e (M-H)⁻ = 513.

Intermediate 77

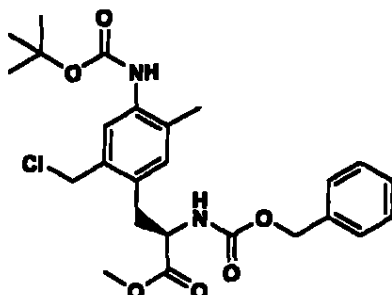


15

3-(2-Hydroxymethyl-4-tert-butoxycarbonylamino-5-methyl-phenyl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester. Title compound was obtained in a manner analogous to the preparation of 2-(R)-Benzyloxycarbonylamino-3-(4-tert-butoxycarbonylamino-2-hydroxymethyl-3-methyl-phenyl)-propionic acid methyl ester. Material was obtained as white solid in 94% yield.

20

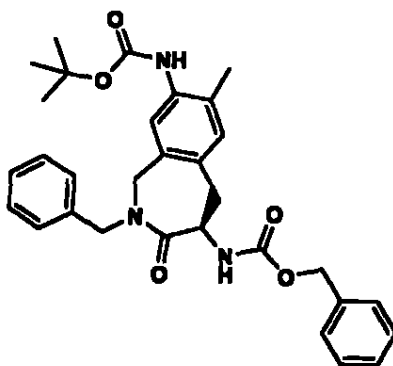
Intermediate 78



3-(2-Chloromethyl-4-tert-butoxycarbonylamino-5-methyl-phenyl)-2-(R)-
5 benzyloxycarbonylamino-propionic acid methyl ester. 3-(2-Hydroxymethyl-4-tert-butoxycarbonylamino-5-methyl-phenyl)-2-(R)-benzyloxycarbonylamino-propionic acid methyl ester (510 mg, 1.1 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (250 μ L, 1.8 mmol) was added to the mixture followed by methanesulfonyl chloride (100 μ L, 1.3 mmol). Mixture was stirred at room
10 temperature for 1.5 hours. Mixture was diluted with dichloromethane then washed once with water, twice with 1N hydrochloric acid, and once with brine. Organics were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as white solid in 91% yield. MS m/e (M+H)⁺= 491.

15

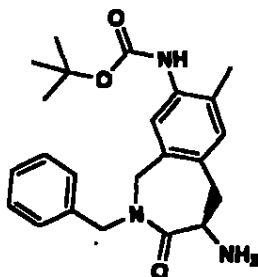
Intermediate 79



(R)-Benzyl 8-tert-butoxycarbonylamido-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-ylcarbamate. 3-(2-Chloromethyl-4-tert-butoxycarbonylamino-5-methyl-phenyl)-2-(*R*)-benzyloxycarbonylamino-propionic acid methyl ester (335 mg, 0.72 mmol) was dissolved in acetonitrile (10 mL).

- 5 Potassium carbonate (220 mg, 1.6 mmol) was added to the mixture followed by benzylamine (150 μ L, 1.4 mmol). Reaction was heated to reflux for 4.5 hours. Mixture was cooled to room temperature. Mixture was filtered over celite. Filtrate was concentrated. Residue was dissolved in toluene (15 mL). Acetic acid (100 μ L) was added to the mixture. Reaction was heated at reflux for 3 hours. Mixture was
- 10 cooled to room temperature. Mixture was concentrated. Residue was purified by silica gel chromatography eluting ethyl acetate-hexanes. Title compound was obtained as clear colorless oil in 81% yield. MS m/e ($M+H$)⁺ = 530.

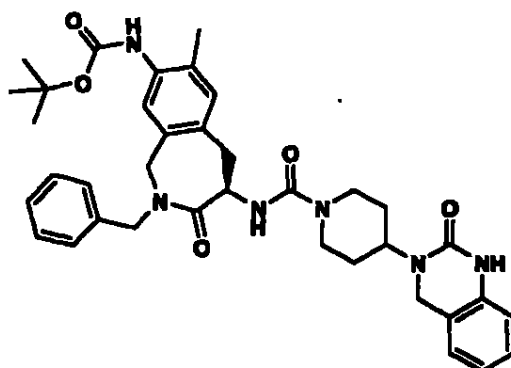
Intermediate 80



15

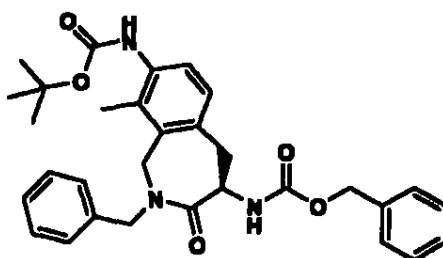
- (R)*-tert-Butyl 4-amino-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylcarbamate. (*R*)-Benzyl 8-tert-butoxycarbonylamido-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-ylcarbamate (305 mg, 0.58
- 20 mmol) was dissolved in methanol. A catalytic amount of 10% palladium on carbon was added to the mixture. Reaction was placed on a Parr apparatus under 50 psi of hydrogen gas. Reaction shook at room temperature for 1 hour. Reaction was removed from the apparatus. Catalyst was filtered off. Filtrate was concentrated *in vacuo*. Title compound was obtained as clear colorless oil in 97% yield. MS m/e
- 25 ($M+H$)⁺ = 396.

Intermediate 81



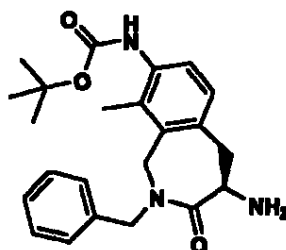
(R)-tert-Butyl 2-benzyl-7-methyl-3-oxo-4-(4-(2-oxo-1,2-dihydroquinazolin-
5 3(4H)-yl)piperidine-1-carboxamido)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-
ylcarbamate. *(R)*-tert-Butyl 4-amino-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-
1H-benzo[c]azepin-8-ylcarbamate (155 mg, 0.39 mmol) was dissolved in
dichloromethane (10 mL). Aqueous sodium bicarbonate (10 mL) was added to the
mixture. A solution of 20% phosgene in toluene (230 μ L, 0.43 mmol) was added to
10 the mixture with vigorous stirring. Reaction stirred at room temperature for 20
minutes. 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidine acetate (140 mg, 0.48
mmol) was added to the mixture. Reaction stirred at room temperature for 1 hour.
Reaction layers were partitioned. Organic layer was washed successively with 1N
hydrochloric acid and brine. Organic was dried (magnesium sulfate), filtered and
15 concentrated *in vacuo*. Title compound was obtained as off-white solid in 94% yield.
MS m/e ($M+H$)⁺ = 653.

Intermediate 82



(R)-Benzyl 8-*tert*-butoxycarbonylamido-2-benzyl-9-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-ylcarbamate. 3-(2-Chloromethyl-4-*tert*-butoxycarbonylamino-3-methyl-phenyl)-2-(*R*)-benzyloxycarbonylamino-propionic acid methyl ester was reacted in a manner analogous to the preparation of (*R*)-benzyl 8-*tert*-butoxycarbonylamido-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-ylcarbamate. Title compound was obtained as white solid in 78% yield. MS *m/e* (*M*+*H*)⁺ = 530.

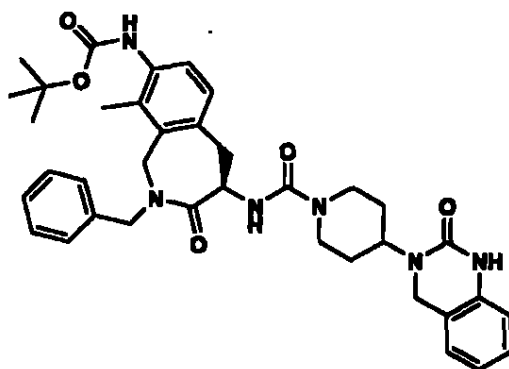
Intermediate 83



10

(R)-*tert*-Butyl 4-amino-2-benzyl-9-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ylcarbamate. (*R*)-Benzyl 8-*tert*-butoxycarbonylamido-2-benzyl-9-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-ylcarbamate was reacted in a manner analogous to the preparation of (*R*)-*tert*-butyl 4-amino-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ylcarbamate. Title compound was obtained as clear colorless oil in 99% yield. MS *m/e* (*M*+*H*)⁺ = 340.

Intermediate 84

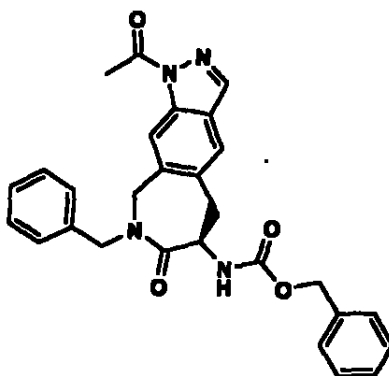


20

(R)-tert-Butyl 2-benzyl-9-methyl-3-oxo-4-(4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidine-1-carboxamido)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylcarbamate. *(R)*-tert-Butyl 4-amino-2-benzyl-9-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylcarbamate was reacted in a manner analogous to the preparation of *(R)*-tert-butyl 2-benzyl-7-methyl-3-oxo-4-(4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidine-1-carboxamido)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylcarbamate. Title compound was obtained as off-white solid in 94% yield.

10

Intermediate 85

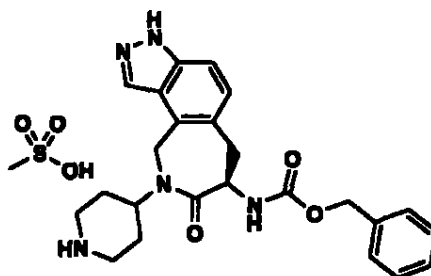


(R)-Benzyl 1-acetyl-8-benzyl-7-oxo-1,5,6,7,8,9-hexahydroazepino[4,3-f]indazol-6-ylcarbamate. 3-(2-Chloromethyl-4-tert-butoxycarbonylamino-5-methylphenyl)-2-(*(R)*-benzyloxycarbonylamino-propionic acid methyl ester (160 mg, 0.33 mmol) was dissolved in dichloromethane (3 mL). Trifluoroacetic acid (1 mL) was added to the mixture. Reaction was stirred at room temperature for 45 minutes. Mixture was concentrated to a yellow oil. Residue was dissolved in chloroform (3 mL). Acetic acid (100 μ L) was added to the mixture followed by isoamyl nitrite (50 μ L, 0.37 mmol) then potassium acetate (65 mg, 0.66 mmol). Reaction was heated at reflux for 30 minutes. Mixture was cooled to room temperature then diluted with dichloromethane. Mixture was washed once with water, and twice with aqueous sodium bicarbonate. Organics were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was dissolved in acetonitrile (3 mL). Benzylamine (100 μ L, 0.92 mmol) was added to the mixture followed by potassium carbonate (50

mg, 0.36 mmol). Reaction was heated at reflux for 1 hour. Mixture was cooled to room temperature. Solids were filtered. Filtrate was concentrated *in vacuo*. Residue was treated with toluene (3 mL) and acetic acid (100 μ L). Reaction was heated at reflux for 1 hour. Mixture was cooled to room temperature. Acetic anhydride (1 mL) was added to the mixture. Reaction was stirred at room temperature for 1 hour. Mixture was concentrated. Residue was purified by silica gel chromatography eluting ethyl acetate-hexanes. Title compound was obtained as amber oil in 27% yield. MS m/e $(M+H)^+ = 483$.

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Intermediate 86

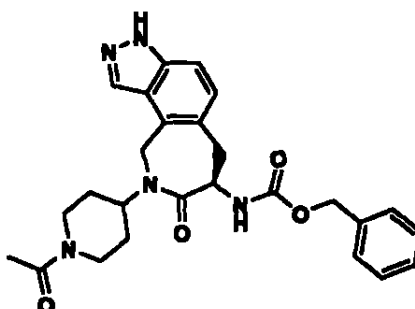


(*R*)-benzyl 8-oxo-9-(piperidin-4-yl)-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-ylcarbamate methanesulfonate. 4-(7-(*R*)-Benzyloxycarbonylamino-8-oxo-6,7,8,10-tetrahydro-3*H*-2,3,9-triaza-cyclohepta[*e*]inden-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (100 mg, 0.19 mmol) was dissolved in dichloromethane (2 mL). Anisole (100 μ L, 0.92 mmol) was added to the mixture followed by methanesulfonic acid (200 μ L). Reaction stirred at room temperature for 30 minutes. Mixture was diluted with diethyl ether, and the mixture stirred at room temperature for 30 minutes. Solvents were decanted off. Residue was dried *in vacuo*. Title compound was obtained as dark oil in quantitative yield. MS m/e $(M+H)^+ = 434$.

25

83

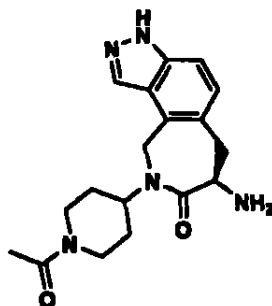
Intermediate 87



(R)-benzyl 9-(1-acetylpiperidin-4-yl)-8-oxo-3,6,7,8,9,10-
5 hexahydroazepino[3,4-e]indazol-7-ylcarbamate. (R)-benzyl 8-oxo-9-(piperidin-4-yl)-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-ylcarbamate methanesulfonate (100 mg, 0.19 mmol) was dissolved in a mixture of dichloromethane (4 mL) and triethylamine (500 μ L, 3.6 mmol). Acetic anhydride (500 μ L, 5.3 mmol) was added to the mixture. Reaction stirred at room temperature overnight. Reaction mixture
10 was washed successively 1x water, 2x 1N hydrochloric acid, 2x 1N sodium hydroxide, and 1x brine. Organic was dried (magnesium sulfate), and filtered. Filtrate was concentrated *in vacuo*. Residue was treated with methanol (3 mL). Potassium carbonate (40 mg, 0.29 mmol) was added to the mixture. Reaction stirred at room temperature for 2 hours. Reaction was quenched with 1N hydrochloric acid
15 (6 mL). Methanol was removed from the mixture *in vacuo*. Remaining aqueous mixture was made basic with sodium bicarbonate. Mixture was extracted with ethyl acetate. Organic layer was dried (magnesium sulfate), filtered and concentrated. Title compound was obtained as yellow solid in 43% yield. MS *m/e* (M+H)⁺ = 476.

20

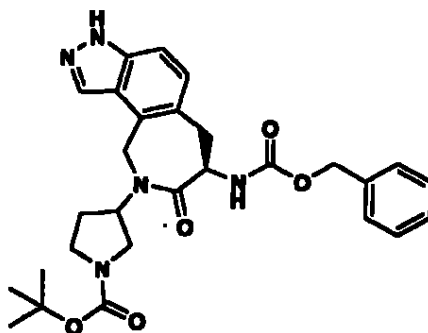
Intermediate 88



(R)-9-(1-acetylpiperidin-4-yl)-7-amino-6,7,9,10-tetrahydroazepino[3,4-
e]indazol-8(3*H*)-one methanesulfonate. (*R*)-benzyl 9-(1-acetylpiperidin-4-yl)-8-oxo-
3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-ylcarbamate (38 mg, 0.08 mmol) was
dissolved in dichloromethane (1 mL). Anisole (30 μ L, 0.27 mmol) was added to the
5 mixture followed by methanesulfonic acid (250 μ L). Reaction stirred at room
temperature for 2 hours. Mixture was diluted with diethyl ether. Mixture sat at room
temperature for 30 minutes. Solvents were decanted off. Remaining residue was
dried *in vacuo*. Title compound was obtained as dark oil in quantitative yield. MS
m/e ($M+H$)⁺=342.

10

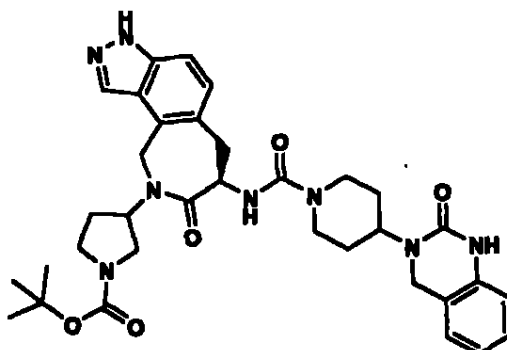
Intermediate 89



tert-butyl 3-((*R*)-7-(benzyloxycarbonyl)-8-oxo-7,8-dihydroazepino[3,4-
e]indazol-9(3*H*,6*H*,10*H*)-yl)pyrrolidine-1-carboxylate. 2-(*R*)-
15 Benzyloxycarbonylamino-3-(4-chloromethyl-1*H*-indazol-5-yl)-propionic acid methyl
ester hydrochloride (150 mg, 0.31 mmol) and *R,S*-3-amino-1-*N*-Boc-pyrrolidine (90
 μ L, 0.48 mmol) were reacted in a manner analogous to the preparation of [9-(2,2-
dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(*S*)-cyclohepta[*e*]inden-
20 7-yl]-acetic acid methyl ester. Title compound was obtained without purification as
dark foam in 96% yield. MS m/e ($M+H$)⁺=342.

25

Intermediate 90

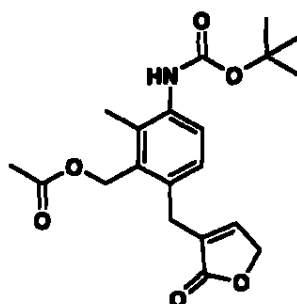


tert-butyl 3-((R)-8-oxo-7-(4-(2-oxo-1,2-dihydroquinazolin-3(4H)-
5 *yl)piperidine-1-carboxamido)-7,8-dihydroazepino[3,4-e]indazol-9(3H,6H,10H)-*
yl)pyrrolidine-1-carboxylate. *tert-butyl 3-((R)-7-(benzyloxycarbonyl)-8-oxo-7,8-*
dihydroazepino[3,4-e]indazol-9(3H,6H,10H)-yl)pyrrolidine-1-carboxylate was
dissolved in methanol (10 mL). Acetic acid (300 μ L) was added to the mixture
followed by 10% palladium on carbon. Reaction vessel was placed on a Parr
10 apparatus and charged with 30 psi of hydrogen gas. Reaction shook at ambient
temperature for 2 hours. Reaction mixture was filtered. Filtrate was concentrated *in*
vacuo. Residue was dissolved in dichloromethane (2 mL). Triethylamine (500 μ L,
3.6 mmol) was added to the mixture followed by *N,N'*-disuccinimidyl carbonate (90
mg, 0.35 mmol). Reaction stirred at room temperature for 30 minutes. 3-(piperidin-
15 4-yl)-3,4-dihydroquinazolin-2(1H)-one acetate (80 mg, 0.27 mmol) was added to the
mixture. Reaction stirred at room temperature for 1 hour. Mixture was diluted with
dichloromethane. Mixture was washed with water. Organic layer was concentrated.
C18 preparative HPLC purification afforded the title compound as yellow solid in
24% yield. MS *m/e* ($M-C_5H_9O_2+H$)⁺=543.

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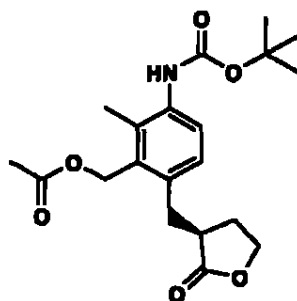
Intermediate 91



3-(*tert*-butoxycarbonyl)-2-methyl-6-((2-oxo-2,5-dihydrofuran-3-yl)methyl)benzyl acetate. Acetic acid 3-*tert*-butoxycarbonylamino-6-iodo-2-methylbenzyl ester (575 mg, 1.4 mmol) was dissolved in *N,N*-dimethylformamide (2.5 mL). α -Methylene- γ -butyrolactone (190 μ L, 2.2 mmol) was added to the mixture followed by potassium acetate (420 mg, 4.3 mmol), and then palladium(II) acetate (16 mg, 0.07 mmol). Reaction mixture was heated at 80°C for 26 hours. Mixture was cooled to room temperature and partitioned between ethyl acetate and aqueous sodium bicarbonate. Layers were separated. Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound as off-white solid in 54% yield. MS *m/e* (M-H)⁺ = 374.

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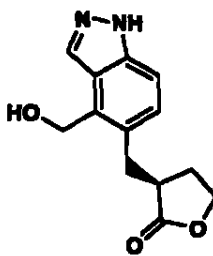
Intermediate 92



(*S*)-3-(*tert*-butoxycarbonyl)-2-methyl-6-((2-oxo-tetrahydrofuran-3-yl)methyl)benzyl acetate. 3-(*tert*-butoxycarbonyl)-2-methyl-6-((2-oxo-2,5-dihydrofuran-3-yl)methyl)benzyl acetate (280 mg, 0.75 mmol) was dissolved in a mixture of ethyl acetate (10 mL) and methanol (10 mL). A catalytic amount of (-)-

1,2-bis((2R,5R)-diethylphospholano)benzene(cyclooctadiene)rhodium (I) tetrafluoroborate was added to the mixture. Reaction vessel was placed on a Parr apparatus and charged with 50 psi of hydrogen gas. Reaction shook at room temperature for 16 hours. A fresh portion of (-)-1,2-bis((2R,5R)-diethylphospholano)benzene(cyclooctadiene)rhodium (I) tetrafluoroborate was added to the mixture. Reaction vessel was charged with 50 psi of hydrogen gas. Reaction shook at room temperature for 24 hours. Reaction mixture was concentrated *in vacuo*. Residue was passed through a plug of silica gel eluting 80% ethyl acetate-hexanes. Filtrate was concentrated *in vacuo*. Title compound was obtained as clear colorless oil in 69% yield. MS *m/e* (M-H)⁺ = 376.

Intermediate 93

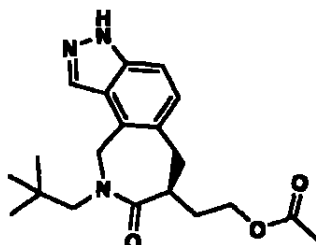


(S)-3-((4-(hydroxymethyl)-1H-indazol-5-yl)methyl)-dihydrofuran-2(3H)-one. (S)-3-(tert-butoxycarbonyl)-2-methyl-6-((2-oxo-tetrahydrofuran-3-yl)methyl)benzyl acetate (190 mg, 0.50 mmol) was dissolved in dichloromethane (4 mL). Trifluoroacetic acid (1 mL) was added to the mixture. Reaction stirred at room temperature for 30 minutes. Mixture was diluted with dichloromethane and then concentrated *in vacuo*. Residue was dissolved in chloroform (5 mL). Acetic acid (250 μ L) was added to the mixture followed by isoamyl nitrite (80 μ L, 0.60 mmol). Reaction stirred at room temperature for 20 minutes. Potassium acetate (400 mg, 4.1 mmol) was added to the mixture. Reaction stirred at room temperature for 1 hour. Mixture was diluted with dichloromethane. Mixture was washed successively 1x water, 2x aqueous sodium bicarbonate. Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was dissolved in methanol (5 mL). Potassium carbonate (120 mg, 0.87 mmol) was added to the mixture. Reaction stirred at room temperature for 1 hour. Reaction was quenched with 1N hydrochloric

acid. Methanol was removed from the mixture *in vacuo*. Remaining aqueous was extracted 2x diethyl ether, made basic with sodium bicarbonate, and then extracted again 2x diethyl ether. Combined extracts were dried (magnesium sulfate), filtered, and concentrated *in vacuo*. Title compound was obtained as amber oil in 73% yield.

5 MS m/e ($M+H$)⁺=247.

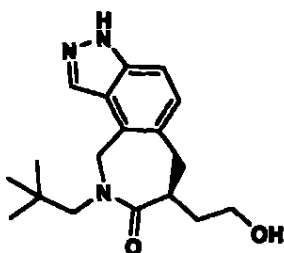
Intermediate 94



- 10 (S)-2-(9-neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)ethyl acetate. (S)-3-((4-(hydroxymethyl)-1H-indazol-5-yl)methyl)-dihydrofuran-2(3H)-one (70 mg, 0.28 mmol), was dissolved in dichloromethane (1.5 mL). Thionyl chloride (500 μ L) was added to the mixture. Reaction stirred at room temperature for 45 minutes. Mixture was concentrated. Residue was treated with dichloromethane
- 15 and re-concentrated. Residue was dissolved in acetonitrile (3 mL). Potassium carbonate (150 mg, 1.1 mmol) was added to the mixture followed by neopentylamine (100 μ L, 0.85 mmol). Mixture was heated at reflux for 45 minutes. Mixture was cooled to room temperature and filtered. Filtrate was concentrated *in vacuo*. Residue was dissolved in toluene (5 mL). Acetic acid (200 μ L) was added to the mixture.
- 20 Reaction was heated at reflux for 5.5 hours. Mixture was concentrated *in vacuo*. Preparatory HPLC purification gave the title compound as yellow solid in 19% yield. MS m/e ($M-H$)⁻= 356.

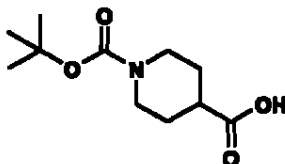
89

Intermediate 95



5 *(S)*-7-(2-hydroxyethyl)-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-
e]indazol-8(3H)-one. *(S)*-2-(9-neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-
e]indazol-7-yl)ethyl acetate (18 mg, 0.05 mmol) was dissolved in methanol (1 mL).
Potassium carbonate (20 mg, 0.14 mmol) was added to the mixture. Reaction stirred
at room temperature for 1 hour. Amberlite IRC-50 ion exchange resin was added to
the mixture. Reaction stirred at room temperature for 15 minutes. Mixture was
10 filtered. Filtrate was concentrated *in vacuo*. The title compound was obtained as
yellow residue in 94% yield. MS *m/e* (*M*+H)⁺=316.

Intermediate 96

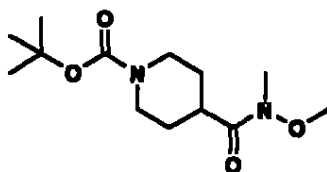


15

1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid. Isonipecotic acid (1.05
g, 8.1 mmol) was suspended in a mixture of tetrahydrofuran (20 mL) and 1N sodium
hydroxide (20 mL). Di-*tert*-butyl dicarbonate was added to the mixture. Reaction
stirred at room temperature for 2.5 hours. Mixture was made acidic with 1N
20 hydrochloric acid. Mixture was extracted 2x ethyl acetate. Combined organics were
washed with brine and then dried (magnesium sulfate), filtered and concentrated *in*
vacuo. Title compound was obtained as white solid in 94% yield. MS *m/e* (*M*-H)⁻=
228.0.

25

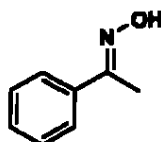
Intermediate 97



5 *tert*-Butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate. *tert*-Butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (640 mg, 2.8 mmol) and *o*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.0 g, 3.1 mmol) were combined and dissolved in *N,N*-dimethylformamide (12 mL). *N,N*-Diisopropylethylamine was added to the mixture. Reaction stirred at room temperature for 45 minutes. *N,O*-Dimethylhydroxylamine hydrochloride (450 mg, 10 4.6 mmol) was added to the mixture. Reaction stirred at room temperature for 1.5 hours. Mixture was diluted with diethyl ether and then washed 3x water, 1x 1N hydrochloric acid. Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as clear colorless oil in 70% yield. MS *m/e* ($M-C_4H_9+H$)⁺=217.1.

15

Intermediate 98

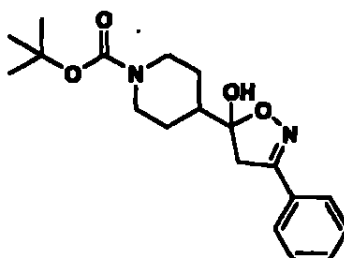


20 *Acetophenone oxime*. Acetophenone (5.0 mL, 43 mmol) was dissolved in methanol (50 mL). Hydroxylamine hydrochloride (6.1 g, 88 mmol) was added to the mixture followed by 10N sodium hydroxide (10 mL, 100 mmol). Reaction was stirred at room temperature for 20 minutes. 10N Sodium hydroxide (5 mL, 50 mmol) was added to the mixture. Reaction was heated at reflux for 1 hour. Mixture was cooled to room temperature and stirred for 4 hours. Reaction mixture was 25 concentrated *in vacuo*. Residue was treated with water. Mixture was extracted 2x diethyl ether. Combined extracts were washed 1x water, 1x brine. Organic layer was

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dried (magnesium sulfate), filtered and concentrated. Title compound was obtained as white solid in 76% yield. MS m/e (M+H)⁺=136.0.

Intermediate 99

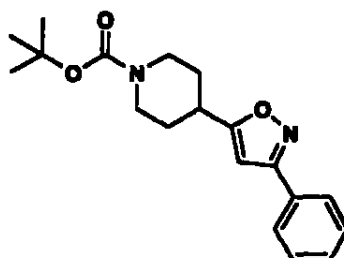


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tert-Butyl 4-(5-hydroxy-3-phenyl-4,5-dihydroisoxazol-5-yl)piperidine-1-carboxylate. Acetophenone oxime (180 mg, 1.3 mmol) was dissolved in tetrahydrofuran (15 mL). Mixture was cooled to 0°C. 2.0M Butyllithium in pentanes (1.35 mL, 2.7 mmol) was added to the mixture drop-wise. Reaction stirred at 0°C for 1 hour. A solution of *tert*-Butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (360 mg, 1.3 mmol) in tetrahydrofuran (5 mL) was added to the reaction mixture drop-wise. Reaction stirred at 0°C for 1 hour. Reaction was quenched with aqueous ammonium chloride. Mixture was extracted 2x ethyl acetate. Combined
10 extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound as clear colorless oil in 71% yield. MS m/e (M-H)⁻=345.1.

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Intermediate 100



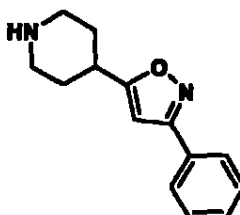
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U4 96

tert-Butyl 4-(3-phenylisoxazol-5-yl)piperidine-1-carboxylate. *tert*-Butyl 4-(5-hydroxy-3-phenyl-4,5-dihydroisoxazol-5-yl)piperidine-1-carboxylate (320 mg, 0.92 mmol) was dissolved in methanol (10 mL). A solution of sodium carbonate (200 mg, 1.9 mmol) in water (10 mL) was added to the mixture. Reaction was stirred at reflux
5 for 2 hours. Methanol was removed from the reaction mixture *in vacuo*. Remaining aqueous was extracted 2x ethyl acetate. Combined extracts were washed with brine. Organic layer was dried (magnesium sulfate), filtered, and concentrated. Title compound was obtained as off-white solid in 86% yield. $(M-C_4H_9+H)^+=273.1$.

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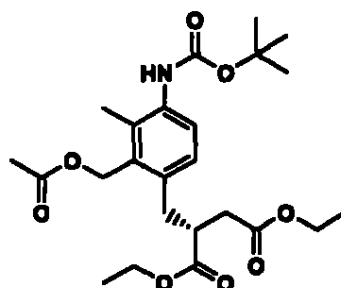
Intermediate 101



4-(3-Phenylisoxazol-5-yl)piperidine. *tert*-Butyl 4-(3-phenylisoxazol-5-yl)piperidine-1-carboxylate (225 mg, 0.78 mmol) was diluted in dichloromethane (3 mL). Trifluoroacetic acid (3 mL) was added to the mixture. Reaction stirred at room
15 temperature for 1 hour. Mixture was diluted with dichloromethane and then concentrated *in vacuo*. Residue was treated with aqueous sodium bicarbonate. Mixture was extracted 2x ethyl acetate. Combined extracts were washed 1x water, 1x brine. Organic layer was dried (magnesium sulfate), filtered and concentrated *in*
20 *vacuo*. Title compound was obtained as white solid in 76% yield. MS *m/e* $(M+H)^+=229.1$.

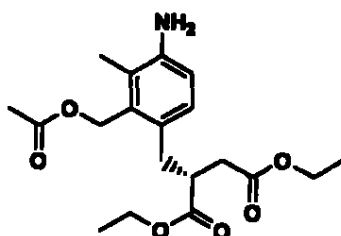
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Intermediate 102



2-(R)-(Acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzyl)-succinic acid diethyl ester. 2-(S)-(Acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzylidene)-succinic acid diethyl ester (700 mg, 1.5 mmol) was hydrogenated in a manner analogous to the preparation of 2-(S)-(acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzyl)-succinic acid diethyl ester using (+)-1,2-bis((2S,5S)-diethylphospholano)benzene(cyclooctadiene)rhodium(I) trifluoromethane sulfonate as the catalyst. Silica gel chromatography afforded the title compound as lightly colored oil in 75% yield. MS m/e (M-H)⁻=464.0.

Intermediate 103



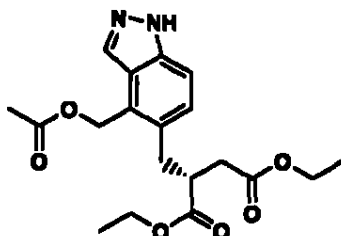
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2-(R)-(2-Acetoxymethyl-4-amino-3-methyl-benzyl)-succinic acid diethyl ester. Trifluoroacetic acid (2.5 mL) was added to a solution of 2-(R)-(acetoxymethyl-4-tert-butoxycarbonylamino-3-methyl-benzyl)-succinic acid diethyl ester (525 mg, 1.1 mmol) in dichloromethane (10 mL). Reaction mixture was stirred at room temperature for 1 hour. Mixture was concentrated *in vacuo*. Residue was treated with aqueous sodium bicarbonate and extracted with ethyl acetate (2x 20 mL). Combined organic layers were dried (magnesium sulfate), filtered and concentrated

257 98

in vacuo. The title compound was obtained as amber oil in 99% yield. MS m/e (M-C₂H₄O₂+H)⁺= 306.1.

Intermediate 104



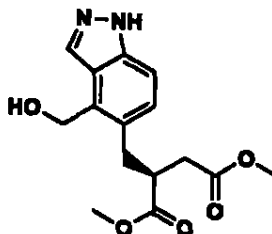
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2-(R)-(4-Acetoxyethyl-1H-indazol-5-ylmethyl)-succinic acid diethyl ester.

Isoamyl nitrite (170 μ L, 1.3 mmol) was added dropwise to a cooled (water ice bath) solution of 2-(R)-(2-acetoxyethyl-4-amino-3-methyl-benzyl)-succinic acid diethyl ester in 5% acetic acid – chloroform (5 mL). Mixture was stirred at 0 °C for 1.5 hours. Mixture was diluted with dichloromethane (20mL) and then washed with saturated aqueous sodium bicarbonate (2 X 20 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as amber oil in 99% yield. MS m/e (M+H)⁺= 377.1.

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Intermediate 105



2-(R)-(4-Hydroxymethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester.

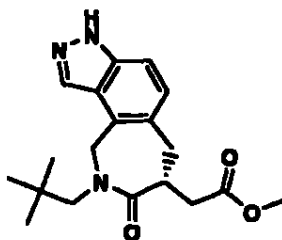
Potassium carbonate (380 mg, 2.7 mmol) was added to a solution of 2-(R)-(4-acetoxyethyl-1H-indazol-5-ylmethyl)-succinic acid diethyl ester (420 mg, 1.1 mmol) in methanol (10 mL). Mixture was stirred at room temperature for 2 hours. Reaction was quenched with 1N hydrochloric acid. Methanol was removed from the mixture *in vacuo*. Remaining aqueous made basic with sodium bicarbonate. Mixture

20

was extracted with ethyl acetate (2 X 20 mL). Combined organic layers were washed successively with water (20 mL) and brine (20 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as amber oil in 92% yield. MS m/e (M+H)⁺ = 307.1.

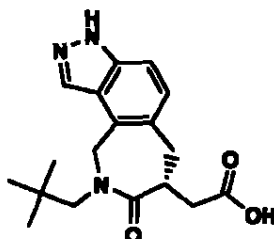
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Intermediate 106



- 10 [9-(2,2-Dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Thionyl chloride (2 mL) was added to a solution of 2-(R)-(4-hydroxymethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester (280 mg, 0.91 mmol) in dichloromethane (4 mL). Reaction was stirred at room temperature for 1 hour. Mixture was diluted with dichloromethane and then concentrated *in vacuo*. Residue was suspended in acetonitrile (5 mL).
- 15 Potassium carbonate (300 mg, 2.2 mmol) was added to the mixture followed by neopentylamine (250 μ L, 2.1 mmol). Reaction was heated at reflux for 30 minutes. Neopentylamine (150 μ L, 1.3 mmol) was added to the mixture. Reaction was heated at reflux for 20 minutes. Mixture was cooled to room temperature and filtered. Filtrate was concentrated *in vacuo*. Residue was dissolved in toluene (5 mL). Acetic acid (300 μ L) was added to the mixture. Reaction was heated at reflux for 16 hours.
- 20 Mixture was cooled to room temperature and diluted with ethyl acetate. Mixture was washed successively with aqueous sodium bicarbonate (2x), water, and brine. Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound as amber oil in 29% yield.
- 25 MS m/e (M-H)⁺ = 342.1.

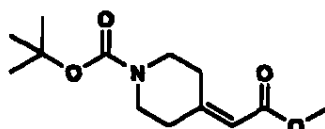
Intermediate 107



5 *[9-(2,2-Dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-acetic acid.* Lithium hydroxide monohydrate (31 mg, 0.74 mmol) was added to a solution of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester (90 mg, 0.26 mmol) in methanol (2.5 mL), tetrahydrofuran (2 mL) and water (2.5 mL). Reaction mixture was heated at 50 °C for 1.5 hours. The organic solvents were removed from the mixture *in vacuo*. Remaining aqueous was neutralized with 1 N hydrochloric acid (730 µL). Mixture was extracted with ethyl acetate (2 X 20 mL). Combined organic layers were washed with brine (20 mL) and then dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as amber solid in 88% yield. MS *m/e* (M-H)⁺ = 328.1.

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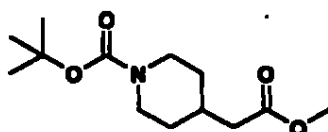
Intermediate 108



20 *tert-Butyl 4-(2-methoxy-2-oxoethylidene)piperidine-1-carboxylate.* 60% sodium hydride in mineral oil (7.92 g, 198.02 mmoles) was washed with hexanes then suspended in *N,N*-dimethylformamide (220.00 mL). The mixture was cooled to 0°C. Trimethyl phosphonoacetate (29.0 mL, 189.82 mmoles) was added drop-wise to the reaction. The mixture was held at 0°C with stirring on and held for 20 min. A solution of *N-tert*-butoxycarbonyl-4-piperidone (30.41 g, 152.62 mmoles) in 80 mL *N,N*-dimethylformamide was added to the mixture drop-wise. Reaction was stirred at 25 room temperature for 3 hours. Mixture was diluted with diethyl ether (650 mL).

Mixture was washed once with water. Aqueous layer was back extracted once with diethyl ether. Organic layers were combined. The mixture was washed 4 times with water and the aqueous phase was discarded. The mixture was washed with brine and the aqueous phase was discarded. The material was dried over MgSO₄, filtered, and concentrated to dryness. Title compound was obtained as white solid in 92% yield. ¹H NMR (300 MHz, CDCl₃): δ= 5.68 (s, 1H), 3.66 (s, 3H), 3.40-3.51 (m, 4H), 2.90 (t, J=5.49, 2H), 2.25 (t, J=5.49, 2H), 1.44 (s, 9H).

Intermediate 109

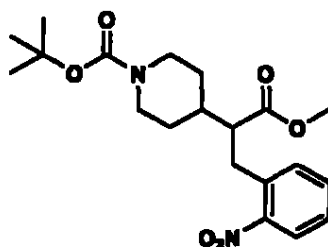


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tert-Butyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate. *tert*-Butyl 4-(2-methoxy-2-oxoethylidene)piperidine-1-carboxylate (35.71 g, 140 mmol) was dissolved in a mixture of ethyl acetate (110 mL) and methanol (110 mL). 50% wet 10% palladium on carbon (3.3 g) was added to the mixture. Reaction vessel was charged with 55 psi of hydrogen gas. Reaction shook on a Parr apparatus at room temperature for 16 hours. Reaction mixture was filtered to remove the catalyst. Filtrate was concentrated *in vacuo*. Title compound was obtained as clear colorless oil in 97% yield. ¹H NMR (300 MHz, CDCl₃): δ= 4.04 (d, J=10.25, 2H), 3.64 (s, 3H), 2.68 (t, J=12.44, 2H), 2.21 (d, J=6.95, 2H), 1.98-1.77 (m, 1H), 1.64 (d, J=13.54, 2H), 1.41 (s, 9H), 1.25-0.99 (m, 2H).

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Intermediate 110



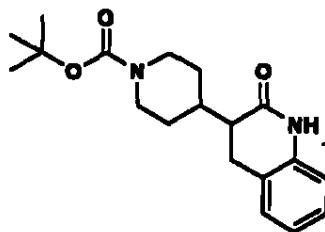
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tert-butyl 4-(1-methoxy-3-(2-nitrophenyl)-1-oxopropan-2-yl)piperidine-1-carboxylate. *tert*-Butyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate (240 mg, 0.93 mmol) was dissolved in tetrahydrofuran (7 mL). Mixture was cooled to -78°C. A 0.5 M solution of potassium bistrimethylsilylamide in toluene (2.2 mL, 1.1 mmol) was added to the mixture drop-wise. Reaction stirred at -78°C for 20 minutes. A solution of 2-nitrobenzylbromide (240 mg, 1.1 mmol) in tetrahydrofuran (2 mL) was added to the reaction mixture drop-wise. Reaction stirred at -78°C for 40 minutes. Dry ice bath was removed and the reaction mixture was allowed to warm to room temperature over 30 minutes. Reaction was quenched with aqueous ammonium chloride. Mixture was extracted with ethyl acetate (2x 20 mL). Combined extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound as yellow oil in 41% yield. MS *m/e* ($M-C_4H_9+H$)⁺ = 337.3.

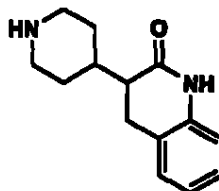
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Intermediate 111



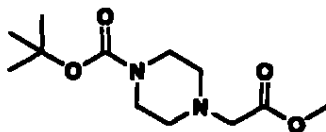
tert-Butyl 4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperidine-1-carboxylate. *tert*-butyl 4-(1-methoxy-3-(2-nitrophenyl)-1-oxopropan-2-yl)piperidine-1-carboxylate (660 mg, 1.7 mmol) was dissolved in a mixture of ethyl acetate (15 mL) and methanol (15 mL). Acetic acid (250 μ L, 4.4 mmol) was added to the mixture. A catalytic amount of 50% wet 10% palladium on carbon was added to the mixture. Reaction vessel was charged with 15 psi of hydrogen gas. Reaction shook on a Parr apparatus at room temperature for 2 hours. Reaction mixture was filtered to removed the catalyst. Filtrate was concentrated *in vacuo*. Silica gel chromatography gave the title compound as orange foam in 47% yield. MS *m/e* ($M-H$)⁻ = 329.1.

Intermediate 112



5 **3-(piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one.** Trifluoroacetic acid (3 mL) was added to a solution of *tert*-Butyl 4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperidine-1-carboxylate (260 mg, 0.79 mmol) in dichloromethane (3 mL). Reaction stirred at room temperature for 1 hour. Reaction mixture was concentrated *in vacuo*. Residue was dissolved in methanol. Dowex 1x4-200 ion exchange resin was added to the mixture to create a slurry. Mixture stirred at room temperature for
10 30 minutes. Resin was filtered off and washed with methanol. Filtrate was concentrated. Title compound was obtained as dark foam in quantitative yield. MS m/e (M+H)⁺ = 231.1.

Intermediate 113



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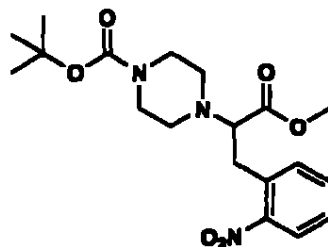
***tert*-Butyl 4-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate.** Potassium carbonate (3.4 g, 25 mmol) was added to a mixture of *N*-Boc-piperazine (3.0 g, 16 mmol) in acetonitrile (20 mL). Methyl bromoacetate (1.5 mL, 16 mmol) was added
20 to the mixture. Reaction stirred at room temperature for 1.5 hours. Mixture was filtered over celite. Filtrate was concentrated *in vacuo*. Residue was treated with diethyl ether (10 mL), filtered and concentrated *in vacuo*. Bulb to bulb distillation (165°C at 700 mtorr) gave the title compound as clear colorless oil in 60% yield. MS m/e (M+H)⁺ = 259.4.

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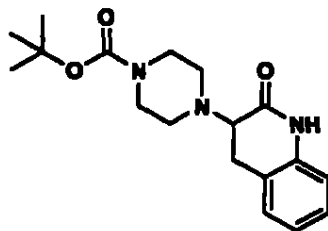
Intermediate 114



tert-Butyl 4-(1-methoxy-3-(2-nitrophenyl)-1-oxopropan-2-yl)piperazine-1-carboxylate. *tert*-Butyl 4-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate (1.0 g, 3.9 mmol) and 2-nitrobenzylbromide (1.0 g, 4.6 mmol) were reacted in a manner analogous to the preparation of *tert*-butyl 4-(1-methoxy-3-(2-nitrophenyl)-1-oxopropan-2-yl)piperidine-1-carboxylate. Title compound was obtained as amber oil in 51% yield. MS m/e ($M+H$)⁺ = 394.4.

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Intermediate 115

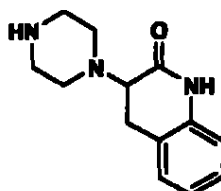


tert-Butyl 4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperazine-1-carboxylate. *tert*-Butyl 4-(1-methoxy-3-(2-nitrophenyl)-1-oxopropan-2-yl)piperazine-1-carboxylate (770 mg, 2.0 mmol) was reacted in a manner analogous to the preparation of *tert*-butyl 4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperidine-1-carboxylate. Title compound was obtained as amber oil in quantitative yield. MS m/e ($M+H$)⁺ = 332.3.

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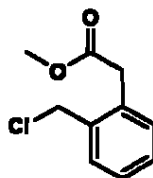
Intermediate 116



5 ***3-(Piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one. tert-Butyl 4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperazine-1-carboxylate*** (640 mg, 1.9 mmol) was reacted in a manner analogous to the preparation of 3-(piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one. Title compound was obtained as light brown solid in quantitative yield. MS m/e ($M+H$)⁺ = 232.4.

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Intermediate 117

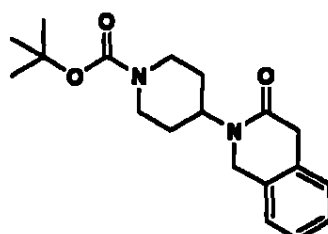


15 ***Methyl 2-(2-(chloromethyl)phenyl)acetate.*** Hydrogen chloride gas was bubbled through a solution of 3-isochromanone (1.2 g, 8.1 mmol) in methanol (30 mL) for 3 minutes. Reaction stirred at room temperature for 8 hours. Mixture was diluted with water (70 mL). Mixture was extracted with dichloromethane (2x40 mL). Combined organic layers were washed with brine (20 mL). Mixture was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as clear colorless oil in 90% yield. ¹H NMR (300 MHz, CDCl₃): δ = 7.40-7.26 (m, 4H), 4.67 (s, 2H), 3.80 (s, 2H), 3.69 (s, 3H).

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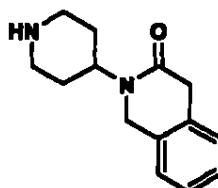
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Intermediate 118



- tert*-Butyl 4-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-1-carboxylate. Potassium carbonate (1.4 g, 10 mmol) was added to a solution of methyl 2-(2-(chloromethyl)phenyl)acetate (940 mg, 4.7 mmol) in acetonitrile (20 mL). 4-Amino-*N*-Boc-piperidine (1.13 g, 5.6 mmol) was added to the mixture. Reaction was heated at reflux for 1 hour. Mixture was cooled to room temperature and then filtered over celite. Filtrate was concentrated *in vacuo*. Residue was treated with toluene (29 mL). Acetic acid (1.5 mL) was added to the mixture. Reaction was heated at reflux for 2 hours. Mixture was concentrated *in vacuo*. Residue was treated with ethyl acetate (50 mL). Mixture was washed successively with aqueous sodium bicarbonate (2x30 mL), 1N hydrochloric acid (30 mL), and brine (20 mL). Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography gave the title compound as lightly colored oil in 40% yield. MS *m/e* (M+H)⁺ = 331.2.

Intermediate 119

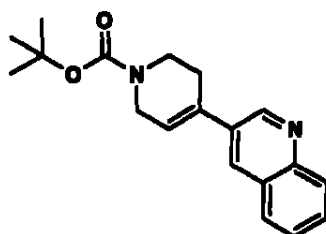


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- 2-(Piperidin-4-yl)-1,2-dihydroisoquinolin-3(4H)-one. *tert*-Butyl 4-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-1-carboxylate (730 mg, 2.2 mmol) was reacted in a manner analogous to the preparation of 3-(piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one. Title compound was obtained as yellow solid in 96% yield. MS *m/e* (M+H)⁺ = 231.4.

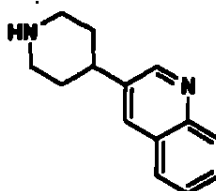
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Intermediate 120



- tert*-Butyl 4-(quinolin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate. 3-
- 5 Quinolineboronic acid (250 mg, 1.4 mmol) and *tert*-butyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (580 mg, 1.8 mmol) were combined and dissolved in a mixture of toluene (10 mL) and ethanol (1 mL). 2M aqueous sodium bicarbonate solution (1.5 mL, 3.0 mmol) was added to the mixture followed by lithium chloride (180 mg, 4.2 mmol). Nitrogen gas was bubbled
- 10 through the mixture for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (75 mg, 0.07 mmol) was added to the mixture. Reaction was heated at reflux for 3.5 hours. Mixture was cooled to room temperature and diluted with ethyl acetate (50 mL). Mixture was washed successively with water (2x30 mL) and brine (20 mL). Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*.
- 15 Silica gel chromatography afforded the desired product as lightly colored oil in 76% yield. MS *m/e* ($M-C_4H_9+H$)⁺ = 255.1.

Intermediate 121



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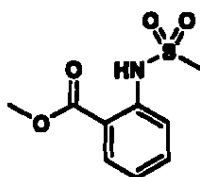
- 3-(Piperidin-4-yl)quinoline. A catalytic amount of 50% wet 10% palladium on carbon was added to a mixture of *tert*-butyl 4-(quinolin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (260 mg, 0.84 mmol) in methanol (10 mL). Reaction vessel was placed on a Parr apparatus and charged with 10 psi of hydrogen gas. Reaction shook
- 25 at room temperature for 4 hours. Mixture was filtered to removed catalyst. Filtrate

11A 108

was concentrated *in vacuo*. Residue was dissolved in dichloromethane (4 mL). Trifluoroacetic acid (1 mL) was added to the mixture. Reaction stirred at room temperature for 2 hours. Reaction mixture was concentrated *in vacuo*. Residue was dissolved in dichloromethane (20 mL). Mixture was washed with aqueous sodium bicarbonate (20 mL). Aqueous layer was back extracted with dichloromethane (30 mL). Organic layers were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as yellow oil in 45% yield. MS $m/e (M+H)^+ = 213.2$.

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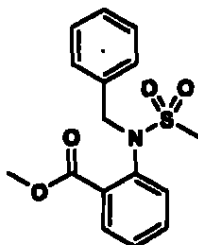
Intermediate 122



Methyl 2-(methanesulfonylamido)benzoate. Methanesulfonyl chloride (3.4 mL, 44 mmol) was added to a solution of methyl acanthranilate (5.0 mL, 39 mmol) in pyridine (10 mL, 124 mmol). Mixture stirred at room temperature for 16 hours. Reaction was quenched with 1N hydrochloric acid (150 mL). Mixture was extracted with ethyl acetate (2x200 mL). Organic layers were washed successively with 1N hydrochloric acid (2x100 mL) and brine (50 mL). Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was crystallized from 50 mL isopropyl alcohol. Solids were filtered, washed with isopropyl alcohol and dried *in vacuo*. Title compound was obtained as pink crystals in 75% yield. MS $m/e (M-H)^- = 228.0$.

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Intermediate 123

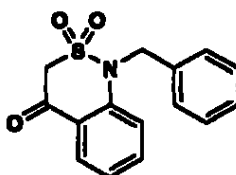


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112 ✓ 104

Methyl 2-(N-benzylmethan-2-ylsulfonamido)benzoate. 60% Sodium hydride in mineral oil (650 mg, 16.3 mmol) was washed with hexanes and then suspended in *N,N*-dimethylformamide (50 mL). Mixture was cooled to 0°C. A solution of methyl 2-(methylsulfonamido)benzoate (3.1 g, 13.5 mmol) in *N,N*-dimethylformamide (10 mL) was added to the mixture drop-wise with stirring. Reaction was held at 0°C with stirring for 15 minutes. Benzylbromide (1.9 mL, 15.9 mmol) was added to the mixture drop-wise. Reaction was stirred at room temperature for 16 hours. Reaction was quenched with 1N hydrochloric acid (50 mL). Mixture was extracted with diethyl ether (2x50 mL). Organic layers were combined and washed successively with water (2x50 mL) and brine (30 mL). Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound as clear colorless oil in 76% yield. MS *m/e* (M-CH₃O+H)⁺= 288.1.

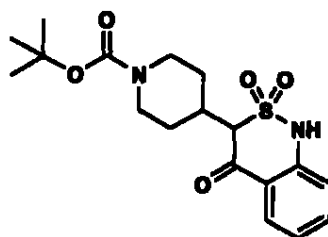
Intermediate 124



15

1-Benzyl-2,2-dioxo-2,3-dihydro-1H-2,1-benzothiazin-4-one. 60% Sodium hydride in mineral oil (500 mg, 12.5 mmol) was washed with hexanes and then suspended in *N,N*-dimethylformamide (15 mL). Mixture was cooled to 0°C. A solution of methyl 2-(N-benzylmethan-2-ylsulfonamido)benzoate (3.25g, 10.2 mmol) in *N,N*-dimethylformamide (20 mL) was added to the mixture drop-wise. Mixture was warmed to room temperature. Reaction stirred at room temperature for 3 hours. Reaction was quenched with 1N hydrochloric acid (40 mL). Mixture was extracted with diethyl ether (2x40 mL). Combined organic layers were washed with water (2x40mL). Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as light yellow solid in 85% yield. MS *m/e* (M-H)⁻= 286.1.

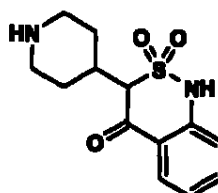
Intermediate 125



- 4-(2,2,4-Trioxo-1,2,3,4-tetrahydro-2,1-benzothiazin-3-yl)-piperidine-1-carboxylic acid tert-butyl ester. 1-Benzyl-2,2-dioxo-2,3-dihydro-1H-2,1-benzothiazin-4-one (1.51 g, 5.26 mmol) was dissolved in pyridine (50 mL). *N*-tert-Butoxycarbonyl-4-piperidinone (1.24 g, 6.33 mmol) was added to the mixture followed by piperidine (110 μ L, 1.11 mmol). Molecular sieves were added to the mixture. Reaction stirred at room temperature for 40 hours. Reaction mixture was filtered over celite. Filtrate was concentrated *in vacuo*. Residue was purified by silica gel chromatography. The major component was isolated and the fractions concentrated *in vacuo*. Residue was dissolved in methanol (50 mL). A catalytic amount of 50% wet 10% palladium on carbon was added to the mixture. Reaction vessel was placed on a Parr apparatus and charged with 55 psi of hydrogen gas.
- Reaction shook at room temperature for 2 hours. Reaction mixture was filtered over celite. Fresh catalyst was added to the filtrate. Reaction vessel was placed on a Parr apparatus and charged with 55 psi of hydrogen gas. Reaction shook at room temperature for 1 hour. Mixture was filtered over celite. A third batch of fresh catalyst was added to the mixture. Reaction vessel was placed on a Parr apparatus and charged with 55 psi of hydrogen gas. Reaction shook at room temperature for 7.5 hours. Catalyst was filtered off. Filtrate was concentrated *in vacuo*. Silica gel chromatography afforded the title compound as pale yellow solid in 24% yield. MS m/e (M-H)⁻ = 379.1.

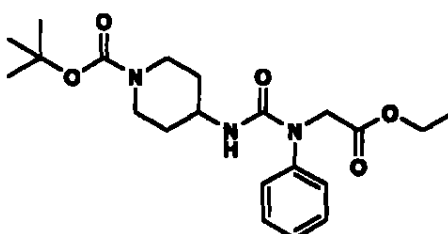
Intermediate 126

HCl



- 2,2-Dioxo-3-piperidin-4-yl-2,3-dihydro-1H-2,1-benzothiazin-4-one
5 hydrochloride. 4-(2,2,4-Trioxo-1,2,3,4-tetrahydro-2,1-benzothiazin-3-yl)-piperidine-
1-carboxylic acid *tert*-butyl ester (175 mg, 0.46 mmol) was dissolved in 4M
hydrogen chloride in 1,4-dioxane (3.0 mL, 12.0 mmol). Reaction stirred at room
temperature for 45 minutes. Reaction mixture was concentrated to dryness *in vacuo*.
Title compound was obtained as pink solid in quantitative yield. MS *m/e* (M+H)⁺=
10 281.1.

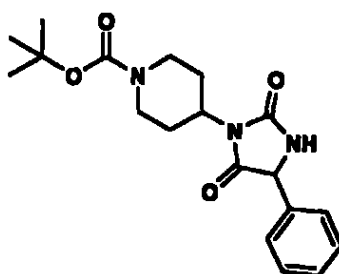
Intermediate 127



- 15 *tert*-Butyl 4-(3-(2-ethoxy-2-oxoethyl)-3-phenylureido)piperidine-1-
carboxylate. 4-Amino-1-*N*-Boc-piperidine (760 mg, 3.79 mmol) was dissolved in a
mixture of dichloromethane (40 mL) and aqueous sodium bicarbonate (30 mL). A
solution of 20% phosgene in toluene (10 mL, 18.9 mmol) was added to the mixture
with vigorous stirring. Reaction stirred vigorously at room temperature for 40
20 minutes. Reaction layers were partitioned. Organic layer was dried (magnesium
sulfate), filtered and concentrated *in vacuo*. Residue was dissolved in toluene (30
mL). *N*-Phenylglycine ethyl ester was added to the mixture. Reaction was heated at
reflux for 15 hours. Mixture was cooled to room temperature and diluted with ethyl
acetate (50 mL). Mixture was washed successively with 1N hydrochloric acid (3x50

mL) and brine (30 mL). Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound as pale yellow solid in 63% yield. ¹H NMR (300 MHz, CDCl₃): δ= 7.47-7.26 (m, 5H), 4.30 (s, 1H), 4.16 (q, *J*=7.32, 2H), 3.88 (d, *J*=12.81, 2H), 3.81-3.69 (m, 1H), 2.89-2.70 (m, 2H), 1.83 (dd, *J*₁=12.62, *J*₂=3.11, 2H), 1.38 (s, 9H), 1.23 (t, *J*=7.14, 3H), 1.19-1.03 (m, 2H).

Intermediate 128



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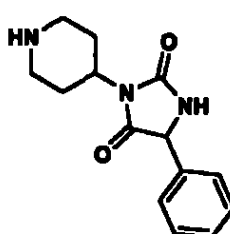
tert-Butyl 4-(2,5-dioxo-4-phenylimidazolidin-1-yl)piperidine-1-carboxylate.

Triethylamine (200 μL, 1.43 mmol) was added to a solution of *tert*-butyl 4-(3-(2-ethoxy-2-oxoethyl)-3-phenylureido)piperidine-1-carboxylate (90 mg, 0.22 mmol) in ethanol (1.8 mL). Reaction was held at 60°C with stirring for 3 hours. Reaction mixture was concentrated *in vacuo*. Residue was treated with dichloromethane (20 mL) and then concentrated *in vacuo*. Title compound was obtained as white solid in 81% yield. MS *m/e* (M-C₄H₈+H)⁺= 304.2.

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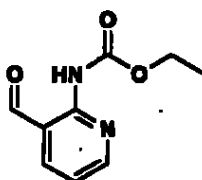
Intermediate 129

HCl



5 *5-Phenyl-3-(piperidin-4-yl)imidazolidine-2,4-dione hydrochloride. tert-Butyl 4-(3-(2-ethoxy-2-oxoethyl)-3-phenylureido)piperidine-1-carboxylate* (60 mg, 0.17 mmol) was dissolved in 4M hydrogen chloride solution in 1,4-dioxane (2.0 mL). Reaction stirred at room temperature for 30 minutes. Solids were filtered off and washed with diethyl ether and dried. Title compound was obtained as white solid in quantitative yield. MS m/e $(M+H)^+ = 260.2$.

Intermediate 130

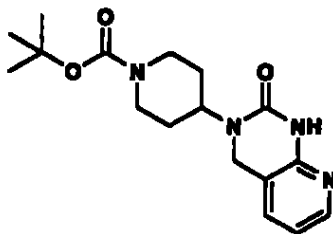


10

Ethyl 3-formylpyridin-2-ylcarbamate. Diethyl pyrocarbonate (570 μ L, 3.9 mmol) was added to a solution of 2-aminopyridine-3-carboxaldehyde (400 mg, 3.3 mmol) in benzene (20 mL). Mixture was warmed to 60°C and held for 4 hours. Diethyl pyrocarbonate (1 mL, 6.8 mmol) was added to the mixture. Reaction was warmed to 60°C and held for 1 hour. Mixture was cooled to room temperature. Diethyl pyrocarbonate (1 mL, 6.8 mmol) was added to the mixture. Reaction stirred at room temperature for 16 hours. Mixture was concentrated *in vacuo*. Silica gel chromatography afforded to title compound as white solid in 58% yield. MS m/e $(M+H)^+ = 195.1$.

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Intermediate 131

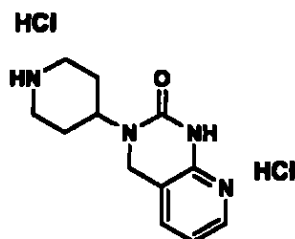


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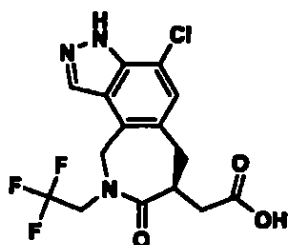
tert-Butyl 4-(2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-3(4*H*)-yl)piperidine-1-carboxylate. 4-Amino-1-*N*-Boc-piperidine (290 mg, 1.4 mmol) was added to a solution of ethyl 3-formylpyridin-2-ylcarbamate (240 mg, 1.2 mmol) in methanol (10 mL). Mixture was warmed to 60°C and held for 1.5 hours. Mixture was cooled to room temperature. Sodium borohydride (62 mg, 1.6 mmol) was added to the mixture. Reaction stirred at room temperature for 30 minutes. Toluene (20 mL) was added to the mixture followed by acetic acid (1.0 mL). Mixture was warmed to 110°C. Methanol was driven from the reaction mixture and collected in a Dean-Stark trap. Mixture was held at 110°C for 5 hours. Mixture was cooled to room temperature and held for 16 hours. Reaction was quenched with aqueous sodium bicarbonate. Mixture was extracted with ethyl acetate (2x30 mL). Combined organics were washed successively with water (30 mL) and brine (20 mL). Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound as white solid in 44% yield. MS *m/e* (M-H)⁺ = 311.2.

Intermediate 132



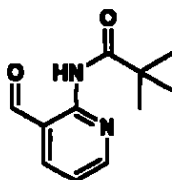
3-(Piperidin-4-yl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-one dihydrochloride. A suspension of *tert*-butyl 4-(2-oxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-3(4*H*)-yl)piperidine-1-carboxylate (220 mg, 0.66 mmol) in 4*N* hydrogen chloride in 1,4-dioxane (5.0 mL) was stirred at room temperature for 45 minutes. Mixture was concentrated *in vacuo*. Crystallization from ethanol and ethyl acetate afforded the title compound as white solid in 62% yield. (M+H)⁺ = 233.2.

Intermediate 133



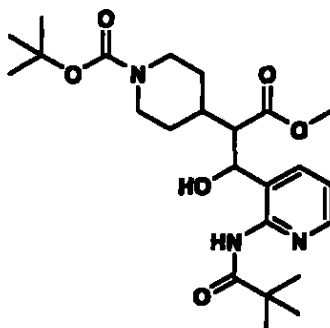
- 5 *[4-Chloro-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-*
(S)-cyclohepta[e]inden-7-yl]acetic acid. 2-(S)-(4-acetoxymethyl-7-chloro-1H-
indazol-5-ylmethyl)-succinic acid diethyl ester (530 mg, 1.48 mmol) and 2,2,2-
trifluoroethylamine (1 mL, 12.5 mmol) was reacted following reaction scheme and
procedures analogous to the preparation of [4-Chloro-9-(2,2-dimethyl-propyl)-8-oxo-
3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Title
10 compound was obtained as white solid in 20% yield. MS m/e (M-H)⁺ = 374.0.

Intermediate 134



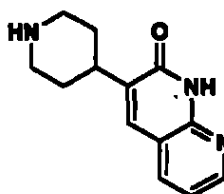
- 15 *N-(3-Formylpyridin-2-yl)pivalamide.* Triethylamine (7.6 mL, 54 mmol), was
added to a solution of 2-aminopyridine-3-carboxaldehyde (4.45 g, 36 mmol) in
dichloromethane (70 mL). Mixture was cooled to 0°C. A solution of pivaloyl
chloride (5.3 mL, 43 mmol) in dichloromethane (30 mL) was added to the mixture.
Reaction was warmed to room temperature. Mixture stirred at room temperature for
20 63 hours. Mixture was washed successively with water (2x50 mL) and brine (30
mL). Organic layer was dried (magnesium sulfate), filtered and concentrated *in*
vacuo. Silica gel chromatography afforded the title compound as off-white solid in
90% yield. (M+H)⁺ = 207.1.

Intermediate 135



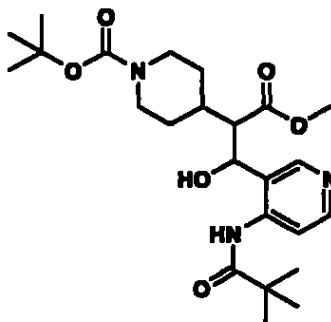
- tert*-Butyl 4-(1-hydroxy-3-methoxy-3-oxo-1-(2-pivalamidopyridin-3-yl)propan-2-yl)piperidine-1-carboxylate. A solution of diisopropylamine (6.0 mL, 43 mmol) in tetrahydrofuran (200 mL) was cooled to -78°C. A 2.5M solution of *n*-butyllithium in hexanes (17.0 mL, 43 mmol) was added to the mixture drop-wise. Mixture was held at -78°C with stirring for 20 minutes. A solution of *tert*-butyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate (9.3g, 36 mmol) in tetrahydrofuran (35 mL) was added to the mixture drop-wise. Mixture was held at -78°C for 1.5 hours. In a separate flask, 60% sodium hydride in mineral oil (1.57 g, 39 mmol) was washed in hexanes and then suspended in tetrahydrofuran (70 mL). Mixture was cooled to 0°C. A solution of *N*-(3-formylpyridin-2-yl)pivalamide (6.74 g, 33 mmol) in tetrahydrofuran (20 mL) was added to the mixture drop-wise. Reaction was held at 0°C with stirring for 2 hours. Mixture was warmed to room temperature and then added to the butyllithium containing solution drop-wise. Reaction mixture was held at -78°C with stirring for 2 hours. Mixture was allowed to slowly warm to room temperature. Mixture stirred at room temperature for 14 hours. Reaction was quenched with aqueous ammonium chloride. The mixture was extracted with ethyl acetate (2x100 mL). Organic extracts were combined, dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound as white foam in 93% yield. (M+H)⁺ = 464.2.

Intermediate 136

*3-(Piperidin-4-yl)-1,8-naphthyridin-2(1H)-one dihydrochloride.*

- 5 Concentrated hydrochloric acid (25 mL, 305 mmol) was added with stirring to a mixture of *tert*-butyl 4-(1-hydroxy-3-methoxy-3-oxo-1-(2-pivalamidopyridin-3-yl)propan-2-yl)piperidine-1-carboxylate (14.0 g, 30.2 mmol) and water (75 mL). Reaction was heated to reflux and held for 25 hours. Mixture was concentrated *in vacuo*. Residue was crystallized from ethanol. Title compound was obtained as
- 10 white solid in 33% yield. $(M+H)^+ = 230.2$.

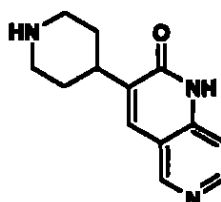
Intermediate 137



- 15 *tert*-Butyl 4-(1-hydroxy-3-methoxy-3-oxo-1-(4-pivalamidopyridin-3-yl)propan-2-yl)piperidine-1-carboxylate. *tert*-butyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate (1.33g, 5.2 mmol) and *N*-(3-formyl-4-pyridinyl)-2,2-dimethylpropanamide (1.0 g, 4.7 mmol) were reacted in a manner analogous to the preparation of *tert*-butyl 4-(1-hydroxy-3-methoxy-3-oxo-1-(2-pivalamidopyridin-
- 20 3-yl)propan-2-yl)piperidine-1-carboxylate. Title compound was obtained as white foam in 54% yield. $(M+H)^+ = 464.2$.

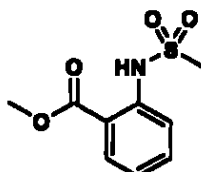
114

Intermediate 138



3-(piperidin-4-yl)-1,6-naphthyridin-2(1H)-one. Concentrated hydrochloric acid (8.0 mL, 97 mmol) was added with stirring to a mixture of *tert*-butyl 4-(1-hydroxy-3-methoxy-3-oxo-1-(4-pivalamidopyridin-3-yl)propan-2-yl)piperidine-1-carboxylate (1.2 g, 2.6 mmol) and water (24 mL). Reaction was heated to reflux and held for 14 hours. Mixture was concentrated *in vacuo*. Residue was treated with acetonitrile (70 mL) and then concentrated *in vacuo*. Residue was crystallized from ethanol. Title compound was obtained as white solid in 77% yield. (M+H)⁺ = 230.1.

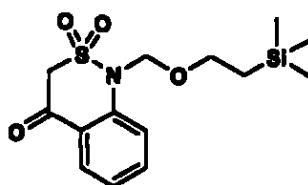
Intermediate 139



Methyl 2-(methanesulfonylamido)benzoate. Methyl anthranilate (11.73 g, 77.6 mmol) was dissolved in pyridine (25 mL, 309 mmol). Mixture was cooled to 0°C. Methanesulfonyl chloride (6.60 mL, 85.3 mmol) was added to the mixture drop-wise. Reaction mixture was warmed to room temperature and held with stirring overnight. Mixture was diluted with ethyl acetate. Material was washed twice with water and three times with 1N hydrochloric acid. Organic layer was dried (magnesium sulfate), filtered and then concentrated. Residue was triturated with 50% diethyl ether in hexanes. Solids were filtered off, washed with 50% diethyl ether-hexanes, washed with hexanes and then dried under high vacuum. Title compound was obtained as an off-white solid in 88% yield. MS m/e (M-H)⁻ = 227.9.

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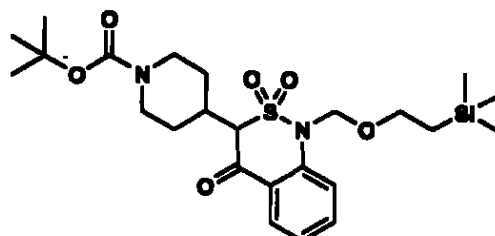
Intermediate 140



- 2,2-Dioxo-1-(2-trimethylsilanyl-ethoxymethyl)-2,3-dihydro-1H-2λ⁶-2,1-benzothiazin-4-one. In a dry round bottom flask under a blanket of nitrogen 60% sodium hydride in mineral oil (1.05 g, 26 mmol) was washed with hexanes and then suspended in *N,N*-dimethylformamide (50 mL). Mixture was cooled to 0°C. A solution of methyl 2-(methylsulfonamido)benzoate (5.0 g, 22 mmol) in 10 mL *N,N*-dimethylformamide was added to the mixture drop-wise. Reaction was held at 0°C with stirring for 25 minutes. 2-(Trimethylsilyl)ethoxymethyl chloride was added to the mixture drop-wise. Reaction stirred for 2 hours slowly warming to ambient temperature. Reaction was quenched with 1N hydrochloric acid. Material was extracted twice with ethyl acetate. Material was washed successively with water and brine. Organic phase was dried (magnesium sulfate), filtered and concentrated to dryness. Residue was dissolved in *N,N*-dimethylformamide (5 mL) and added drop-wise to a mixture of 60% sodium hydride in mineral oil (1.02 g, 26 mmol) that had been washed with hexanes, suspended in *N,N*-dimethylformamide (50 mL) and cooled to 0°C. Ice bath was removed and the mixture was allowed to warm to room temperature. Reaction was held at room temperature overnight with stirring. Reaction was quenched with 1N hydrochloric acid. Material was extracted twice with ethyl acetate. Organic phase was washed successively with water and brine. Organic phase was dried (magnesium sulfate), filtered and concentrated to dryness. Silica gel chromatography (ethyl acetate-hexanes) afforded the title compound as a white solid in 72% yield. MS *m/e* (M-H)⁺ = 326.0.

127 120

Intermediate 141

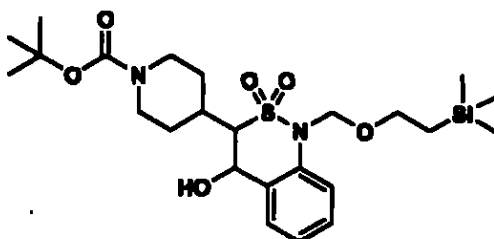


- 4-[2,2,4-Trioxo-1-(2-trimethylsilylanyl-ethoxymethyl)-1,2,3,4-tetrahydro-2 λ^6 -
 5 2,1-benzothiazin-3-yl]-piperidine-1-carboxylic acid tert-butyl ester. *N*-tert-
 Botoxycarbonyl-4-piperidinone (2.44 g, 12 mmol) was dissolved in 1,2-
 dichloroethane (20 mL). Piperidine (1.2 mL, 12 mmol) was added to the mixture.
 Reaction was heated to 50°C and held with stirring for 1.25 hours. Mixture was
 cooled to room temperature. A solution of 2,2-Dioxo-1-(2-trimethylsilylanyl-
 10 ethoxymethyl)-2,3-dihydro-1H-2 λ^6 -2,1-benzothiazin-4-one (2.0 g, 6.1 mmol) in
 pyridine (5.0 mL, 62 mmol) was added to the mixture. Reaction was held overnight
 at room temperature with stirring. Material was concentrated by roto-vap. Residue
 was dissolved in ethyl acetate. Material was washed successively with three portions
 of 1N hydrochloric acid and one portion of water. Organic phase was dried
 15 (magnesium sulfate), filtered and concentrated to dryness. Residue was purified by
 silica gel chromatography (ethyl acetate-hexanes). Major peak was isolated and the
 fractions were concentrated to dryness. Residue was dissolved in methanol (40 mL).
 A catalytic amount of 10% palladium on carbon was added to the solution. Reaction
 vessel was placed on a Parr apparatus and charged with 60 psi of hydrogen gas.
 20 Reaction shook at room temperature overnight. Mixture was filtered over celite.
 Fresh catalyst was added to the filtrate. Reaction vessel was placed on a Parr
 apparatus and charged with 60 psi of hydrogen gas. Reaction shook at room
 temperature for 7 hours. Mixture was filtered over celite and the filtrate was
 concentrated to dryness. Material was purified by silica gel chromatography (ethyl
 25 acetate-hexanes). Major peak was isolated and the fractions were concentrated to
 dryness. Residue was dissolved in methanol (40 mL). Fresh catalyst was added to
 the mixture. Reaction vessel was placed on a Parr apparatus and charged with 60 psi
 of hydrogen gas. Reaction shook at room temperature overnight. Mixture was

filtered over celite. Filtrate was concentrated to dryness. Silica gel chromatography (ethyl acetate-hexanes) afforded the title compound as yellow oil in 43% yield. MS m/e (M-H)⁺ = 509.1.

5

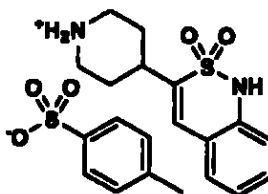
Intermediate 142



4-[4-Hydroxy-2,2-dioxo-1-(2-trimethylsilyl-ethoxymethyl)-1,2,3,4-tetrahydro-2λ⁶-2,1-benzothiazin-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

10 Title compound was obtained as yellow oil in 85% yield. Material was carried forward without purification.

Intermediate 143



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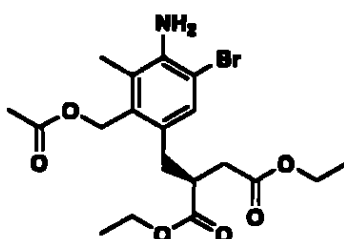
3-Piperidin-4-yl-1H-2,1-benzothiazine 2,2-dioxide para-toluenesulfonate.

4-[2,2,4-Trioxo-1-(2-trimethylsilyl-ethoxymethyl)-1,2,3,4-tetrahydro-2λ⁶-2,1-benzothiazin-3-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (865 mg, 1.7 mmol) was dissolved in methanol (25 mL). Mixture was cooled to 0°C. Sodium
 20 borohydride (100 mg, 2.6 mmol) was added to the mixture in three portions. Reaction stirred at 0°C for 3 hours. Mixture was concentrated by roto-vap. Residue was treated with 1N hydrochloric acid. Material was extracted twice with ethyl acetate. Organic phase was dried (magnesium sulfate), filtered and concentrated to dryness. Residue was dissolved in benzene (20 mL). *p*-Toluenesulfonic acid
 25 monohydrate (475 mg, 2.5 mmol) was added to the mixture. Reaction was heated to

124 122

reflux and held with stirring for 1 hour. Mixture was cooled to room temperature. Solids were filtered off. The sticky solid was treated with hot isopropyl alcohol (10 mL). Mixture was cooled to room temperature and allowed to stand overnight. Solids were filtered off, washed with isopropyl alcohol and then dried under high vacuum. Title compound was obtained as tan solid in 65% yield. MS m/e (M+H)⁺ = 265.2.

Intermediate 144

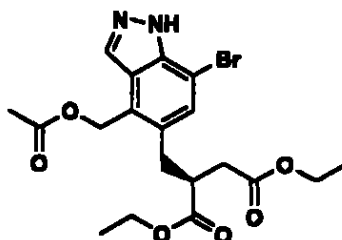


10

2-(S)-(2-Acetoxymethyl-4-amino-5-bromo-3-methyl-benzyl)-succinic acid diethyl ester. 2-(S)-(2-Acetoxymethyl-4-amino-3-methyl-benzyl)-succinic acid diethyl ester (7.6 g, 21 mmol) was dissolved in acetic acid (100 mL). Sodium acetate (4.2 g, 51 mmol) was added to the solution. Reaction vessel was placed in a cool water bath to control reaction exotherm. Bromine (1.1 mL, 22 mmol) was added to the mixture in one portion. Reaction stirred at ambient temperature for 10 minutes. Mixture was poured into 1N aqueous sodium thiosulfate solution (400 mL). Material was extracted twice with ethyl acetate. Organic phase was washed successively with water and brine. Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Silica gel chromatography (ethyl acetate-hexanes) afforded the desired product in 77% yield as an amber oil. MS m/e (M-H)⁻ = 440.0, 442.0.

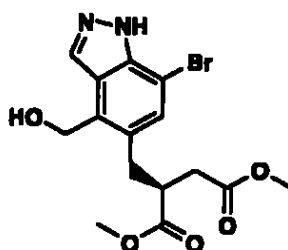
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Intermediate 145



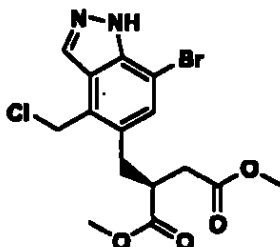
2-(S)-(4-Acetoxyethyl-7-bromo-1H-indazol-5-ylmethyl)-succinic acid diethyl ester. Isoamyl nitrite (2.3 mL, 17 mmol), was added drop-wise to an ice cold solution of 2-(S)-(2-Acetoxyethyl-4-amino-5-bromo-3-methyl-benzyl)-succinic acid diethyl ester (7.14 g, 16 mmol) in 5% acetic acid in toluene (280 mL). Mixture stirred at 0°C for 40 minutes. Potassium acetate (4.00 g, 41 mmol) was added to the mixture. Mixture was slowly warmed to room temperature. Reaction was stirred at room temperature for 14 hours. Mixture was washed twice with water and once with brine. Organic was dried (magnesium sulfate) filtered and concentrated. Silica gel chromatography (ethyl acetate-hexanes) afforded the desired product in 77% yield as an amber oil. MS m/e (M+H)⁺ = 455.0, 457.0.

Intermediate 146



(S)-dimethyl 2-((7-bromo-4-(hydroxymethyl)-1H-indazol-5-yl)methyl)succinate. 2-(S)-(2-Acetoxyethyl-4-amino-5-bromo-3-methyl-benzyl)-succinic acid diethyl ester (2.78 g, 6.1 mmol) was converted to the title compound in a manner analogous to the preparation of 2-(S)-(4-Hydroxymethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester. Material was obtained as amber solid in 96% yield. MS m/e (M-H)⁻ = 383.0, 385.0.

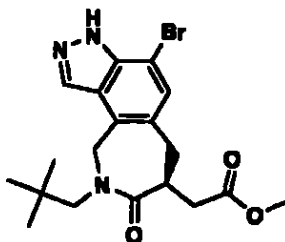
Intermediate 147



(S)-dimethyl 2-((7-bromo-4-(chloromethyl)-1H-indazol-5-yl)methyl)succinate.

(S)-dimethyl 2-((7-bromo-4-(hydroxymethyl)-1H-indazol-5-yl)methyl)succinate (2.25 g, 5.8 mmol) was dissolved in 2M thionyl chloride in dichloromethane (42 mL, 84 mmol). Reaction stirred at room temperature for 2.0 hours. Mixture was concentrated. Residue was treated with toluene and then concentrated by roto-vap. Residue was dissolved in ethyl acetate. Mixture was washed twice with aqueous sodium bicarbonate. Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as amber solid in 99% yield. MS *m/e* (M+H)⁺ = 404.9, 403.0, 406.9

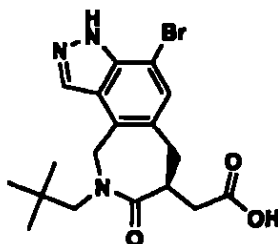
Intermediate 148



[4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-
15 *(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester.* (S)-dimethyl 2-((7-bromo-4-(chloromethyl)-1H-indazol-5-yl)methyl)succinate (860 mg, 2.1 mmol) was dissolved in acetonitrile (50 mL). Potassium carbonate (625 mg, 4.5 mmol) was added to the mixture followed by neopentylamine (800 μ L, 6.78 mmol). Mixture was heated to reflux and held with stirring for 1.5 hours. Mixture was cooled to room temperature.
20 Mixture was filtered over celite. Filtrate was concentrated by roto-vap. Residue was dissolved in a mixture of toluene (50 mL) and acetic acid (3 mL). Mixture was heated to reflux and held with stirring for 37 hours. Mixture concentrated by roto-vap. Silica gel chromatography (ethyl acetate-hexanes) afforded the title compound as tan solid in 75% yield. MS *m/e* (M-H)⁻ = 420.0, 422.0.

121

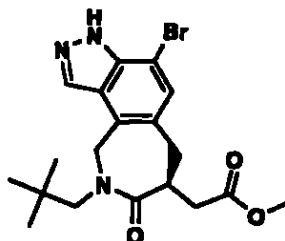
Intermediate 149



5 *[4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-*
(S)-cyclohepta[e]inden-7-yl]-acetic acid. [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-
 3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl
 ester (160 mg, 0.38 mmol) was dissolved in a mixture of tetrahydrofuran (5.0 mL)
 and methanol (5.0 mL). Water (5.0 mL) was added to the mixture followed by
 lithium hydroxide monohydrate (41 mg, 0.98 mmol). Mixture was heated to 50°C
 10 and held with stirring for 5 hours. Mixture was cooled to room temperature. Organic
 solvents were removed from the mixture *in vacuo*. Remaining aqueous was diluted
 with water and then made neutral with 1 mL of 1N hydrochloric acid. Material was
 extracted twice with ethyl acetate. Organic phase was dried (magnesium sulfate),
 filtered and concentrated to dryness. Title compound was obtained as tan solid in
 15 quantitative yield. ¹H NMR (300 MHz, CDCl₃) δ=0.77 (s, 9 H) 2.31 - 2.60 (m, 3 H)
 2.91 (dd, *J*=16.47, 8.42 Hz, 1 H) 2.98 - 3.05 (m, 1 H) 3.09 (d, *J*=13.54 Hz, 1 H) 3.47
 (d, *J*=13.91 Hz, 1 H) 3.71 - 3.89 (m, 1 H) 4.39 (d, *J*=17.20 Hz, 1 H) 5.30 (d, *J*=17.20
 Hz, 1 H) 7.25 (s, 1 H) 8.00 (s, 1 H).

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Intermediate 150



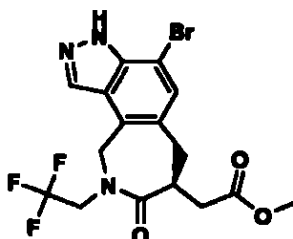
[4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-
(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. (S)-dimethyl 2-((7-bromo-4-

(chloromethyl)-1H-indazol-5-yl)methyl)succinate (860 mg, 2.1 mmol) was dissolved in acetonitrile (50 mL). Potassium carbonate (625 mg, 4.5 mmol) was added to the mixture followed by neopentylamine (800 μ L, 6.78 mmol). Mixture was heated to reflux and held with stirring for 1.5 hours. Mixture was cooled to room temperature.

5 Mixture was filtered over celite. Filtrate was concentrated by roto-vap. Residue was dissolved in a mixture of toluene (50 mL) and acetic acid (3 mL). Mixture was heated to reflux and held with stirring for 37 hours. Mixture concentrated by roto-vap. Silica gel chromatography (ethyl acetate-hexanes) afforded the title compound as tan solid in 75% yield. MS m/e (M-H)⁻ = 420.0, 422.0.

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Intermediate 151



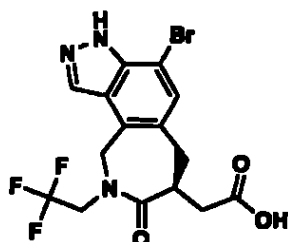
[4-Bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-

15 (S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester. 2-(S)-(4-chloromethyl-7-bromo-1H-indazol-5-ylmethyl)-succinic acid diethyl ester (325 mg, 0.81 mmol) was dissolved in acetonitrile (10 mL). Potassium carbonate (310 mg, 2.2 mmol) was added to the mixture with 2,2,2-trifluoroethylamine (1.2 mL, 15 mmol). Mixture was heated at 60°C and held with stirring for 15 hours. Mixture was cooled to room

20 temperature. Mixture was filtered over celite. Filtrate was concentrated by roto-vap. Residue was dissolved in a mixture of toluene (10 mL) and acetic acid (600 μ L). Mixture was heated to reflux and held with stirring for 22 hours. Mixture was concentrated by roto-vap. Residue was dissolved in ethyl acetate. Material was washed successively with water and aqueous sodium bicarbonate. Organic phase was

25 dried (magnesium sulfate), filtered and concentrated to dryness. Title compound was obtained as amber residue in 74% yield. MS m/e (M-H)⁻ = 431.9, 433.9.

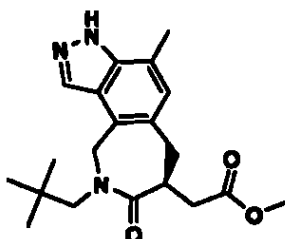
Intermediate 152



5 *[4-Bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid.* [4-Bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester (250 mg, 0.58 mmol) was reacted in a manner analogous to the preparation of [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Title compound was obtained as light yellow solid in quantitative yield. MS *m/e* (M-H)⁺ = 417.9, 419.9.

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Intermediate 153



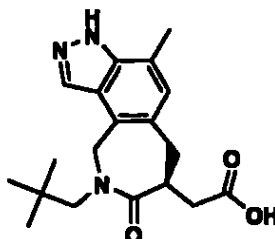
15 *[4-Methyl-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester.* [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester (110 mg, 0.26 mmol) was dissolved in *N,N*-dimethylformamide (1.0 mL). Nitrogen gas was bubbled through the mixture for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (6.0 mg, 0.01 mmol) was added to the mixture followed by tetramethyltin (100 μ L, 0.72 mmol). Reaction vessel was flushed with nitrogen gas and then sealed. Reaction was subjected to microwave heating at 175°C for 35 minutes. Mixture was diluted with ethyl acetate. Material was washed successively with water and brine. Silica gel chromatography (ethyl

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157 128

acetate-hexanes) afforded the title compound as white solid in 83% yield. MS m/e (M+H)⁺ = 358.2.

Intermediate 154



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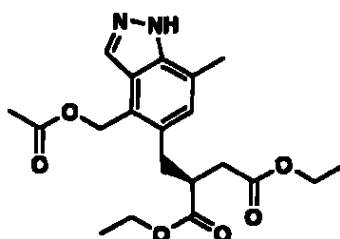
[4-Methyl-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. [4-Methyl-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid

10 methyl ester (70 mg, 196 μ mol) was dissolved in tetrahydrofuran (2.0 mL). Methanol (2.0 mL) was added to the mixture followed by water (2.0 mL) and then lithium hydroxide hydrate (20 mg, 477 μ mol). Reaction was warmed to 50°C and held with stirring for 1.5 hours. Mixture was cooled to room temperature. Organic solvents were removed from the mixture by roto-vap. Remaining aqueous was

15 diluted with water and then neutralized with 1N hydrochloric acid (500 μ L). Mixture was extracted twice with ethyl acetate. Organics were dried MgSO₄, filtered and then concentrated to dryness. Title compound was obtained as white solid in 95% yield. MS m/e (M-H)⁻ = 342.2.

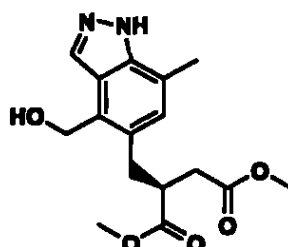
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Intermediate 155



2-(S)-(4-Acetoxymethyl-7-methyl-1H-indazol-5-ylmethyl)-succinic acid diethyl ester. 2-(S)-(4-Acetoxymethyl-7-bromo-1H-indazol-5-ylmethyl)-succinic acid diethyl ester (350 mg, 0.77 mmol) and tetramethyltin (150 μ L, 1.1 mmol) were reacted in a manner analogous to the preparation of [4-Methyl-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester. Title compound was obtained as pale yellow solid in 68% yield. MS m/e (M-H)⁺ = 389.1.

Intermediate 156

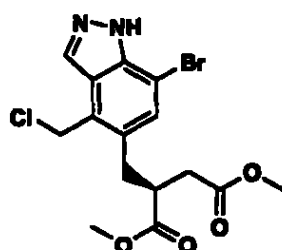


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(S)-dimethyl 2-((7-methyl-4-(hydroxymethyl)-1H-indazol-5-yl)methyl)succinate. 2-(S)-(2-Acetoxymethyl-4-amino-5-methyl-3-methyl-benzyl)-succinic acid diethyl ester (230 mg, 0.59 mmol) was converted to the title compound in a manner analogous to the preparation of 2-(S)-(4-Hydroxymethyl-1H-indazol-5-ylmethyl)-succinic acid dimethyl ester. Material was obtained as off-white solid in 98% yield. MS m/e (M-H)⁺ = 319.2.

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Intermediate 158



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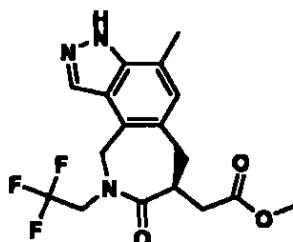
(S)-dimethyl 2-((7-methyl-4-(chloromethyl)-1H-indazol-5-yl)methyl)succinate. (S)-dimethyl 2-((7-methyl-4-(hydroxymethyl)-1H-indazol-5-yl)methyl)succinate (180 mg, 0.56 mmol) was dissolved in dichloromethane (4.0 mL). 2M Thionyl chloride in dichloromethane (4.0 mL, 8.0 mmol) was added to the mixture. Reaction stirred at room temperature for 2.5 hours. Mixture was concentrated. Residue was

132 130

treated with toluene and then concentrated by roto-vap. Residue was dissolved in dichloromethane and then concentrated to dryness. Title compound was obtained as amber solid in 99% yield. MS m/e (M+H)⁺ = 339.1.

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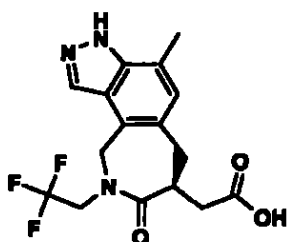
Intermediate 159



[4-Methyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester. 2-(S)-(4-chloromethyl-7-methyl-1H-indazol-5-ylmethyl)-succinic acid diethyl ester (190 mg, 0.56 mmol) and 2,2,2-trifluoroethylamine (45 μ L, 0.56 mmol) were reacted in a manner analogous to the preparation of [4-bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester. Title compound was obtained as amber residue in 76% yield. MS m/e (M+H)⁺ = 370.1.

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Intermediate 160



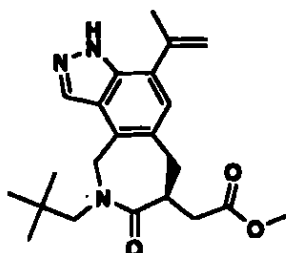
[4-Methyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid. [4-Methyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester (250 mg, 0.58 mmol) was reacted in a manner analogous to the preparation of [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-

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cyclohepta[e]inden-7-yl]-acetic acid. Title compound was obtained as white solid in 97% yield. MS m/e (M-H)⁺= 354.2.

Intermediate 161

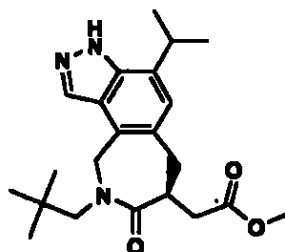


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[(S)-9-(2,2-Dimethyl-propyl)-4-isopropenyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl]-acetic acid methyl ester. [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid methyl ester (100 mg, 0.24 mmol) was dissolved in 2-propanol (1.0 mL). Nitrogen gas was bubbled through the mixture for 5 minutes. Triethylamine (60 μ L, 0.43 mmol) was added to the mixture followed by [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (19 mg, 0.02 mmol) and potassium 2-propenyltrifluoroborate (41 mg, 0.28 mmol). Reaction vessel was flushed with nitrogen gas and then sealed. Reaction was subjected to microwave heating at 150°C for 30 minutes. Silica gel chromatography (ethyl acetate-hexanes) afforded the title compound as amber solid in 73% yield. MS m/e (M+H)⁺= 384.4.

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Intermediate 162



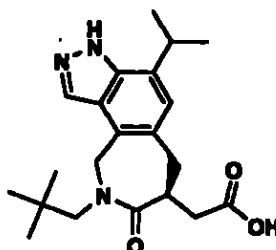
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[(S)-9-(2,2-Dimethyl-propyl)-4-isopropyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl]-acetic acid methyl ester. [(S)-9-(2,2-Dimethyl-

131 132

propyl)-4-isopropenyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl]-acetic acid methyl ester (100 mg, 0.26 mmol) was dissolved in a mixture of ethyl acetate (5.0 mL) and methanol (5.0 mL). A catalytic amount of 10% palladium on carbon was added to the mixture. Reaction vessel was placed on a Parr apparatus and charged with 50 psi of hydrogen gas. Reaction shook at room temperature for 1 hour. Mixture was filtered and the filtrate was concentrated to dryness. Title compound was obtained as brown residue in 90% yield. MS m/e (M+H)⁺= 386.3.

Intermediate 163

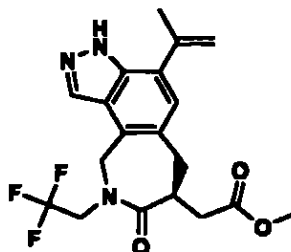


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[(S)-9-(2,2-Dimethyl-propyl)-4-isopropyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl]acetic acid. [(S)-9-(2,2-Dimethyl-propyl)-4-isopropyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl]-acetic acid methyl ester (90 mg, 0.23 mmol) was reacted in a manner analogous to the preparation of [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Title compound was obtained as white solid in 92% yield. MS m/e (M-H)⁻= 370.3.

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Intermediate 164

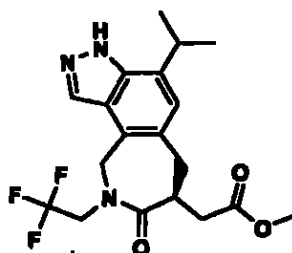


[4-Isopropenyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester. [4-Bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester (400 mg, 0.92 mmol) and potassium 2-

- 5 propenyltrifluoroborate (165 mg, 1.1 mmol) were reacted in a manner analogous to the preparation of [(S)-9-(2,2-Dimethyl-propyl)-4-isopropenyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl]-acetic acid methyl ester. Title compound was obtained as amber oil in 71% yield. MS m/e (M-H)⁻ = 394.1.

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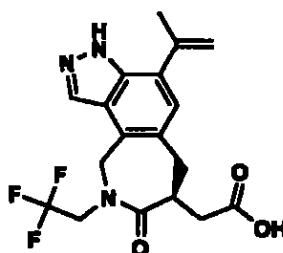
Intermediate 165



[4-Isopropyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester. [4-Isopropenyl-

- 15 3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester (150 mg, 0.38 mmol) was reacted in a manner analogous to the preparation of [(S)-9-(2,2-Dimethyl-propyl)-4-isopropyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl]-acetic acid methyl ester. Title compound was obtained as white solid in 73% yield. MS m/e (M+H)⁺ =
20 398.2.

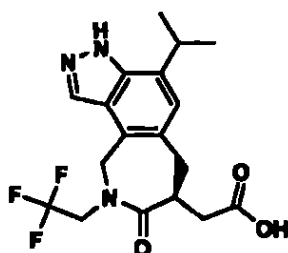
Intermediate 166



134 134

[4-Isopropenyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid. [4-Isopropenyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester (100 mg, 0.25 mmol) was reacted in a manner analogous to the preparation of [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Title compound was obtained as off-white solid in 98% yield. MS m/e (M-H)⁺ = 380.2.

Intermediate 167

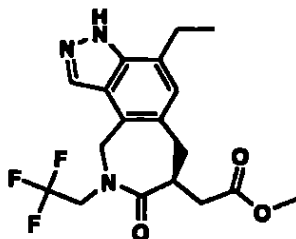


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[4-Isopropyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid. [4-Isopropyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester (105 mg, 0.26 mmol) was reacted in a manner analogous to the preparation of [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Title compound was obtained as white solid in 99% yield. MS m/e (M-H)⁺ = 382.2.

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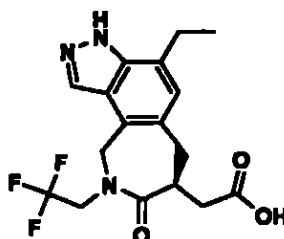
Intermediate 168



[4-Ethyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester. [4-Bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester (150 mg, 0.35 mmol) and tetraethyltin (200 μ L, 1.0 mmol) were reacted in a manner analogous to the preparation of [(S)-9-(2,2-Dimethyl-propyl)-4-methyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl]-acetic acid methyl ester. Title compound was obtained as clear colorless oil in 28% yield. MS m/e (M+H)⁺ = 384.2.

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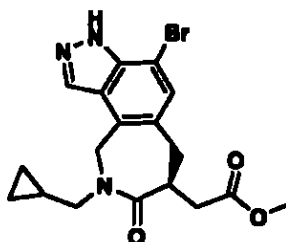
Intermediate 169



[4-Ethyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid. [4-Ethyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid methyl ester (105 mg, 0.26 mmol) was reacted in a manner analogous to the preparation of [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Title compound was obtained as white solid in 73% yield. MS m/e (M-H)⁻ = 368.3.

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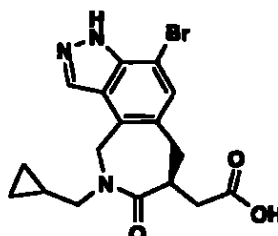
Intermediate 170



124 136

((S)-4-Bromo-9-cyclopropylmethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl)-acetic acid methyl ester. (S)-dimethyl 2-((7-bromo-4-(chloromethyl)-1H-indazol-5-yl)methyl)succinate (630 mg, 1.6 mmol) was dissolved in acetonitrile (5 mL). Potassium carbonate (560 mg, 4.1 mmol) was added to the mixture followed by (aminomethyl)cyclopropane (700 μ L, 8.1 mmol). Mixture was heated to reflux and held with stirring for 1.5 hours. Mixture was cooled to room temperature. Mixture was filtered. Filtrate was concentrated by roto-vap. Residue was dissolved in a mixture of toluene (10 mL) and acetic acid (1 mL). Mixture was heated to reflux and held with stirring for 18 hours. Mixture was concentrated by roto-vap. Silica gel chromatography (ethyl acetate-hexanes) afforded the title compound as tan solid in 64% yield. MS m/e (M+H)⁺ = 406.0, 408.0.

Intermediate 171

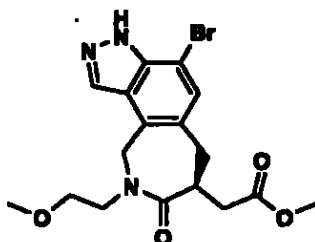


15

((S)-4-Bromo-9-cyclopropylmethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl)-acetic acid. ((S)-4-Bromo-9-cyclopropylmethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl)-acetic acid methyl ester (290 mg, 0.71 mmol) was reacted in a manner analogous to the preparation of [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid. Title compound was obtained as yellow solid in 96% yield. MS m/e (M-H)⁻ = 390.0, 392.0.

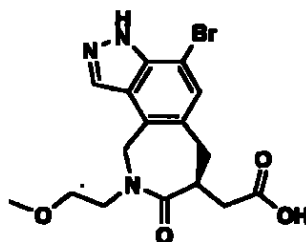
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Intermediate 172



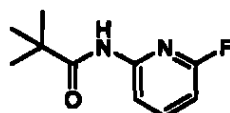
5 *[(S)-4-Bromo-9-(2-methoxy-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triazacyclohept[e]inden-7-yl]-acetic acid methyl ester.* (S)-dimethyl 2-((7-bromo-4-(chloromethyl)-1H-indazol-5-yl)methyl)succinate (400 mg, 0.99 mmol) and 2-methoxyethylamine were reacted in a manner analogous to the preparation of ((S)-4-Bromo-9-cyclopropylmethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triazacyclohept[e]inden-7-yl)-acetic acid methyl ester. Title compound was obtained as
10 tan solid in 66% yield. MS m/e (M-H)⁺ = 408.1, 410.0.

Intermediate 173



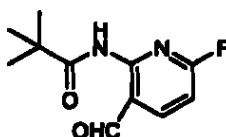
15 *[(S)-4-Bromo-9-(2-methoxy-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triazacyclohept[e]inden-7-yl]-acetic acid.* [(S)-4-Bromo-9-(2-methoxy-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triazacyclohept[e]inden-7-yl]-acetic acid methyl ester (265 mg, 0.65 mmol) was reacted in a manner analogous to the preparation of [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triazacyclohept[e]inden-7-yl]-acetic acid. Title compound was obtained as tan solid in
20 89% yield. MS m/e (M-H)⁺ = 394.1, 396.0.

Intermediate 174



- N*-(6-Fluoropyridin-2-yl)pivalamide. 6-fluoropyridin-2-amine (13.1 g, 117 mmol) was dissolved in anhydrous pyridine (100 mL), and cooled to 0 °C followed by fast dropwise addition of trimethylacetyl chloride (15.9 mL, 129 mmol) over 2 min. 5 min later, the resulting slurry was stirred over night at room temperature. Partial of the solvent was removed on rotary vacuum. The residue was partitioned between saturated ammonium chloride (200 mL) and EtOAc (200 mL). After separation, the organic layer was washed with brine (50 mL), dried over MgSO₄, concentrated on rotary vacuum, and purified on flash chromatography eluting with 25–75% EtOAc/Hexanes (1400 mL) to afford the expected product as a white solid (21.4 g, 93% yield); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.29 (s, 9 H), 6.63 (dd, *J*=8.06, 2.01 Hz, 1 H), 7.76 (q, *J*=8.14 Hz, 1 H), 7.85 (s, 1 H), 8.09 (dd, *J*=8.06, 1.76 Hz, 1 H); Mass spec. 197.15 (M⁺), Calc. for C₁₀H₁₃FN₂O 196.1

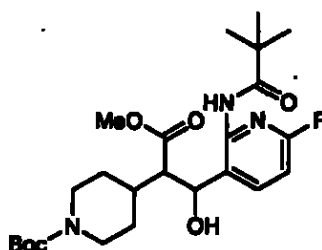
Intermediate 175



- N*-(6-Fluoro-3-formylpyridin-2-yl)pivalamide. *N*-(6-fluoropyridin-2-yl)pivalamide (1.67 g, 8.5 mmol) was dissolved in THF (15 mL) at room temperature, and the colorless solution was cooled to -78 °C, followed by dropwise addition of *t*-BuLi (10.3 mL, 1.7 M in heptane, 17.4 mmol) under nitrogen gas over 10 min. The resulting yellow solution was continued stirring at -78 °C for 3 hr, followed by dropwise addition of DMF (2.0 mL, 25.5 mmol) over 5 min. The light yellow solution was stirred for additional 30 min at -78 °C. Thus the mixture was quenched with saturated NH₄Cl (30 mL), partitioned between H₂O/EtOAc (100 mL/100 mL). After separation, the organic phase was washed with brine (30 mL), dried over

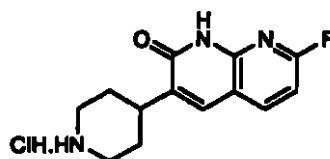
MgSO₄, concentrated on rotary vacuum, and purified on flash chromatography eluting with 25~50% EtOAc/hexanes (1400 mL) to afford an expected product, as a white solids(343mg, 18% yield), plus the recovered starting material(622mg); ¹H NMR (400 MHz, CDCl₃) δppm 1.23 - 1.30 (s, 9 H), 8.12 (s, 1 H), 8.18 - 8.27 (m, 2 H), 10.13 (s, 1 H); Mass spec. 225.13 (MH⁺), Calc. for C₁₁H₁₃FN₂O₂ 224.1

Intermediate 176



10 *tert-butyl 4-(1-(6-Fluoro-2-pivalamidopyridin-3-yl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate*. To diisopropylamine(0.47mL, 3.35 mmol) in anhydrous THF (10mL) was dropwise added n-BuLi(2.5 M in heptane, 1.4 mL, 3.48mmol) at -78 ° C under N₂ over 10 min. 15 min later, *tert-butyl 4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate*(861 mg, 3.35 mmol) in THF(10mL) was dropwise
15 added at -78 °C over 10 min. The resulting mixture was stirred for 45 min. At the same time, N-(6-fluoro-3-formylpyridin-2-yl)pivalamide(500mg, 2.23 mmol), was dissolved in anhydrous THF (10mL) in another oven dried round bottom flask, and dropwise added to NaH(60% in mineral oil, 93.7mg, 2.34 mmol) in THF(10 mL) at ° C. The resulting yellow suspension was stirred at 0 ° C under N₂ for 1 hr, which
20 then was transferred to the above anion solution at -78 ° C through a syringe over 10 min. The resulting suspension was continued stirring at -78 ° C for 1hr. Quenched with saturated NH₄Cl(50 mL), extracted with EtOAc (2x100mL). The combined organic layers were washed with brine(30 mL), dried on MgSO₄, concentrated on rotary vacuum and purified on flash chromatography column eluting with 20~75%
25 EtOAc/hexanes(1000mL), 75~100% EtOAc/hexanes (600mL) to afford the expected inseparable stereo isomer mixture, as a white product(536 mg, 50% yield), plus recovered starting material, N-(6-fluoro-3-formylpyridin-2-yl)pivalamide (140mg); Mass spec. 482.23 (MH⁺), Calc. for C₂₄H₃₆FN₃O₆ 481.26

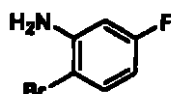
Intermediate 177



7-Fluoro-3-(piperidin-4-yl)-1,8-naphthyridin-2(1H)-one hydrochloride. The mixture of tert-butyl 4-(1-(6-fluoro-2-pivalamidopyridin-3-yl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate (238 mg, 0.494mmol), and concentrated HCl(1mL) in MeOH (1mL) and H₂O(1mL) was refluxed under N₂ over night. The solvents were removed on rotary vacuum, the residue, as a yellow solid, was triturated with cold EtOH (2x3mL), filtrated and dried under vacuum to afford an expected product, a yellow solid(139 mg, 99% yield); ¹H NMR (400 MHz, MeOD) δ ppm 1.27 (s, 1 H), 1.83 - 1.95 (m, 2 H), 2.13 (d, J =14.10 Hz, 2 H), 3.06 - 3.18 (m, 3 H), 3.49 (d, J =12.84 Hz, 2 H), 6.47 (d, J =8.81 Hz, 1 H), 7.69 (s, 1 H), 7.85 (d, J =9.06 Hz, 1 H); Mass spec. 248.13 (MH⁺), Calc. for C₁₃H₁₄FN₃O 247.11

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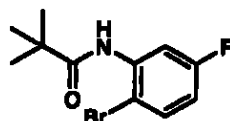
Intermediate 178



2-Bromo-5-fluorobenzeneamine. To a solution of 1-bromo-4-fluoro-2-nitrobenzene (5.0g, 22.7 mmol) in HOAc/EtOH (20mL/20mL) was added iron powder in one portion at room temperature. The mixture was bubbled with N₂ for 5min, and then refluxed for 2 hrs. Partial of the solvents were removed on rotary vacuum, then the residue was partitioned between aqueous NaOH (10N, 200mL) and Et₂O (200mL). After separation, the organic phase was washed with H₂O(50 mL), brine (50 mL), dried on MgSO₄, and concentrated on rotary vacuum to afford the expected product, as an light tan oil (quantitative yield), which was pure enough to be used in next step without further purification; ¹H NMR (400 MHz, CDCl₃) δ ppm

4.15 (s, 1 H), 6.34 (td, $J=8.44$, 2.77 Hz, 1 H), 6.46 (dd, $J=10.20$, 2.90 Hz, 1 H), 7.31 (dd, $J=8.81$, 5.79 Hz, 1 H); Mass spec. 189.94 (MH^+), Calc. for C_6H_5BrFN 188.96

Intermediate 179

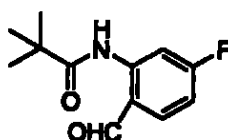


5

N-(2-Bromo-5-fluorophenyl)pivalamide. Trimethylacetyl chloride (4.2mL, 34.1mL) was fast dropwise added to a solution of 2-bromo-5-fluorobenzenamine (4.31g, 22.7mmol) in CH_2Cl_2 (50 mL) at room temperature, followed by the addition of DIEA (7.9 mL, 45.4mmol). The resulting mixture was stirred at room temperature for 2 hrs, and then partitioned between HCl (1N, 200mL) and EtOAc(250mL). After separation, the organic phase was washed with brine(50mL), dried on $MgSO_4$, concentrated on rotary vacuum, and purified on flash chromatography eluting with 20~40% EtOAc/hexanes (1200mL) to afford the expected product, as a colorless oil(6.07g, 98% yield); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.33 (s, 9 H), 6.69 (ddd, $J=8.81$, 7.55, 3.02 Hz, 1 H), 7.45 (dd, $J=8.81$, 5.79 Hz, 1 H), 8.04 (s, 1 H), 8.28 (dd, $J=11.08$, 3.02 Hz, 1 H); Mass spec. 274.04 (MH^+), Calc. for $C_{11}H_{13}BrFNO$ 273.02

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Intermediate 180



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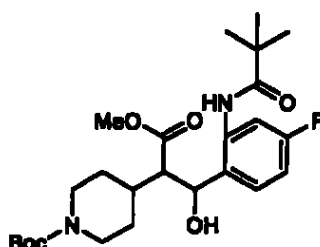
N-(5-Fluoro-2-formylphenyl)pivalamide. *N*-(2-bromo-5-fluorophenyl)pivalamide(2.4g, 8.75mmol) was dissolved in THF(30mL) at room temperature, and the colorless solution was cooled to $-78^\circ C$, followed by fast dropwise addition of *t*-BuLi (10.3mL, 1.7M in heptane, 17.4 mmol) under N_2 over 10min. The resulting yellow solution was continued stirring at $-78^\circ C$ for 1 hr, followed by dropwise addition of DMF(2.7 mL, 35.0 mmol) over 5 min. The light

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yellow solution was stirred for additional 30 min at -78 ° C. Thus the mixture was quenched with saturated NH₄Cl (30 mL), extracted with Et₂O (2x150mL). The combined organic phase was washed with brine(30 mL), dried over MgSO₄, concentrated on rotary vacuum, and purified on flash chromatography eluting with 25~50% EtOAc/hexanes (1400 mL) to afford an expected product , as a white solids(1.03g, 53% yield); ¹H NMR (400 MHz, CDCl₃) δppm 1.30 (s, 9 H), 6.80 - 6.86 (m, 1 H), 7.63 (dd, J=8.56, 6.04 Hz, 1 H), 8.53 (dd, J=12.21, 2.39 Hz, 1 H), 9.83 (s, 1 H), 11.54 (s, 1 H); Mass spec. 224.16(MH⁺), Calc. for C₁₂H₁₄FNO₂ 223.1.

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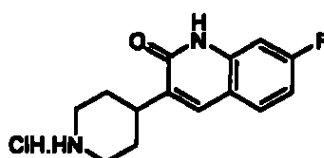
Intermediate 181



tert-butyl 4-(1-(4-Fluoro-2-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate. The procedure was the same as the synthesis of *t-butyl 4-(1-(6-fluoro-2-pivalamidopyridin-3-yl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl) piperidine-1-carboxylate*. The reaction gave an inseparable stereo isomer mixture, *tert-butyl 4-(1-(4-fluoro-2-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl) piperidine-1-carboxylate*. The crude compound was used directly in the next step without further purification. Mass spec. 481.25(MH⁺), Calc. for C₂₅H₃₇FN₂O₆ 480.26.

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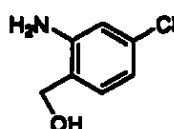
Intermediate 182



Vlf 143

7-Fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride. The procedure was the same as the synthesis of 7-fluoro-3-(piperidin-4-yl)-1,8-naphthyridin-2(1H)-one, and gave the expected product, 7-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride, as a white solid at the 41% yield after two steps; ¹H NMR (400 MHz, MeOD) δ ppm 1.84 - 1.96 (m, 2 H), 2.15 (d, $J=14.10$ Hz, 2 H), 3.07 - 3.16 (m, 3 H), 3.50 (d, $J=12.84$ Hz, 2 H), 6.98 - 7.05 (m, 2 H), 7.69 (dd, $J=8.56, 5.79$ Hz, 1 H), 7.78 (s, 1 H); Mass spec. 247.12(MH⁺), Calc. for C₁₄H₁₃FN₂O 246.12.

Intermediate 183

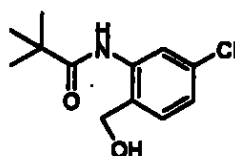


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(2-Amino-4-chlorophenyl)methanol. Methyl 2-amino-4-chlorobenzoate (1.5g, 8.08 mmol) in THF (15mL) was dropwise added to the suspension of LAH(429mg, 11.3 mmol) in THF (10mL) under N₂ at 0 ° C over 10 min. The resulting mixture was stirred at room temperature for 2 hrs, then the reaction was quenched at 0 ° C with saturated Na₂SO₄ (50 mL), extracted with Et₂O (2x70 mL). The combined organic solutions were washed with brine (30 mL), dried on MgSO₄, and concentrated on rotary vacuum to afford the expected product as a white solid (874 mg, 69% yield); ¹H NMR (400 MHz, MeOD) δ ppm 4.50 (s, 2 H), 6.58 (dd, $J=8.06, 2.01$ Hz, 1 H), 6.70 (d, $J=2.01$ Hz, 1 H), 7.01 (d, $J=8.06$ Hz, 1 H); Mass spec. 157.06 (MH⁺), Calc. for C₇H₆ClNO 157.03.

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Intermediate 184

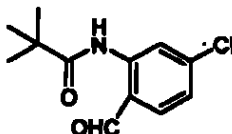


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N-(5-Chloro-2-(hydroxymethyl)phenyl)pivalamide. Trimethylacetyl chloride (0.72 mL, 5.82 mmol) was fast dropwise added to (2-amino-4-

chlorophenyl)methanol (874 mg, 5.55mmol) in CH₂Cl₂ (20mL) and THF(6mL) at 0 °C, and followed by the addition of DIEA (2.41 mL, 13.9 mmol). The resulting mixture was stirred for 30 min. Then the mixture was partitioned between saturated NaHCO₃ (50mL) and CH₂Cl₂ (100mL). After separation, the organic phase was washed with brine (30mL), dried on MgSO₄, and concentrated on rotary vacuum to afford the expected crude product (1.34, 100% yield), which was pure enough to be used in next step. Mass spec. 242.08 (MH⁺), Calc. for C₁₂H₁₆ClNO₂ 241.09.

Intermediate 185

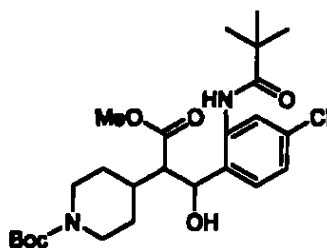


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N-(5-Chloro-2-formylphenyl)pivalamide. Pyridiniumchlorochromate (1.67g, 7.77mmol) was added to *N*-(5-chloro-2-(hydroxymethyl) phenyl) pivalamide (1.34g, 5.55mmol) in CH₂Cl₂ (100mL) at 0 °C. 5 min later, the reaction mixture was stirred at room temperature for 3 hrs. Then it was passed through a thin silica gel pad with CH₂Cl₂(100mL), concentrated on rotary vacuum and purified on flash chromatography eluting with 20~40% EtOAc/hexanes (800mL) to afford the expected product as a white solid(937mg, 70% yield). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.28 - 1.34 (s, 9 H), 7.15 (dd, *J*=8.31, 2.01 Hz, 1 H), 7.53 - 7.59 (m, 1 H), 8.87 (d, *J*=2.01 Hz, 1 H), 9.84 - 9.88 (m, 1 H), 11.42 (s, 1 H); Mass spec. 240.07 (MH⁺), Calc. for C₁₂H₁₄ClNO₂ 239.07.

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Intermediate 186

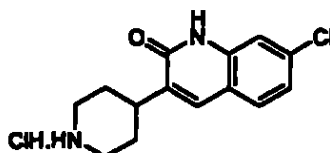


118 145

tert-butyl 4-(1-(4-Chloro-2-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate. The reaction procedure was the same as the synthesis of *tert-butyl 4-(1-(6-fluoro-2-pivalamidopyridin-3-yl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate*. The reaction afforded *tert-butyl 4-(1-(4-chloro-2-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate* stereoisomer mixture as a white solid (73%total yield) after purification on flash chromatography, which was directly used in next step. Mass spec. 497.19 (MH⁺), Calc. for C₂₅H₃₇ClN₂O₆ 496.23.

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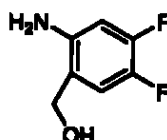
Intermediate 187



7-Chloro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride. The procedure was the same as the synthesis of *7-fluoro-3-(piperidin-4-yl)-1, 8-naphthyridin-2(1H)-one*. After reaction, partial of the solvent was removed on rotary vacuum, the expected product came out from the solution, filtration and washing with EtOH to gave a white solid (71% yield). ¹H NMR (400 MHz, MeOD) δppm 1.83 - 1.94 (m, 2 H), 2.14 (d, J=12.84 Hz, 2 H), 3.07 - 3.19 (m, 3 H), 3.48 (s, 1 H), 3.51 (d, J=3.02 Hz, 1 H), 7.18 - 7.23 (m, J=6.30, 4.34, 2.20, 2.01 Hz, 1 H), 7.30 - 7.35 (m, 1 H), 7.59 - 7.65 (m, 1 H), 7.74 - 7.78 (m, 1 H); Mass spec. 263.07 (MH⁺), Calc. for C₁₄H₁₅ClN₂O 262.09.

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Intermediate 188

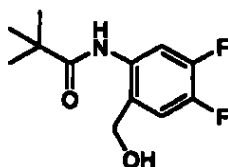


(2-Amino-4,5-difluorophenyl)methanol. 2-Amino-4,5-difluorobenzoic acid (5.37g, 31.0 mmol) in THF(50mL) was dropwise added to the suspension on LAH

(1.65g, 43.5 mmol) in THF (15 mL) at room temperature under N₂ over 10 min. The resulting suspension was stirred at room temperature for 1 hr. Then the mixture was cooled down to 0 °C, quenched with saturated Na₂SO₄ (100mL), and extracted with Et₂O (2x100mL), the combined organic layers were washed with brine (60 mL), dried over MgSO₄, and concentrated on rotary vacuum to afford the expected crude product as a brown solid, which was pure enough to be used in next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.07 (s, 1 H), 4.56 (s, 2 H), 6.46 (dd, J=11.71, 6.92 Hz, 1 H), 6.87 (dd, J=10.58, 8.56 Hz, 1 H); Mass spec. 160.04 (MH⁺), Calc. for C₇H₇F₂NO 159.05.

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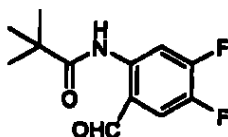
Intermediate 189



N-(4,5-Difluoro-2-(hydroxymethyl)phenyl)pivalamide. Trimethylacetyl chloride (4.01mL, 32.55mmol) was added to the solution of the crude (2-amino-4, 5-difluorophenyl) methanol in CH₂Cl₂/THF (50mL/10mL) at 0 °C, followed by the addition of DIEA (10.8mL, 62 mmol). The resulting mixture was stirred for 30 min, and then partitioned between saturated NaHCO₃ (100mL) and CH₂Cl₂ (150mL). After separation, the organic phase was washed with brine (40 mL), dried over MgSO₄, and concentrated on rotary vacuum to afford the expected product, which was pure enough to be used in next step without further purification; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.28 (s, 9 H), 4.62 (s, 2 H), 6.94 (dd, J=10.20, 8.44 Hz, 1 H), 8.08 (dd, J=12.72, 7.68 Hz, 1 H), 9.04 (s, 1 H); Mass spec. 244.11 (MH⁺), Calc. for C₁₂H₁₃F₂NO₂ 243.11.

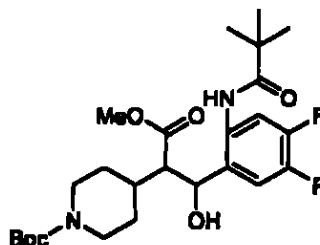
25

Intermediate 190



N-(4,5-Difluoro-2-formylphenyl)pivalamide. Pyridiniumchlorochromate (9.36g, 43.4 mmol) was added to the solution of the crude *N*-(4, 5-difluoro-2-(hydroxymethyl) phenyl) pivalamide in CH₂Cl₂ (150mL) at rt. The yellow solution turned into dark brown in 10 min, and the mixture was continued stirring for 3hr, and then passed through a thin silica gel pad with CH₂Cl₂ (2x50mL). The combined organic solution was concentrated on rotary vacuum, and purified on flash chromatography eluting with 20~60%EtOAc/hexanes(1300 mL) to afford the expected product as a brown solid(1.91g, 26% yield after three step); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.29 (s, 9 H), 7.42 - 7.48 (m, 1 H), 8.75 (dd, *J*=13.35, 7.30 Hz, 1 H), 9.77 - 9.80 (m, 1 H), 11.40 (s, 1 H); Mass spec. 242.08 (MH⁺), Calc. for C₁₂H₁₃F₂NO₂ 241.09

Intermediate 200

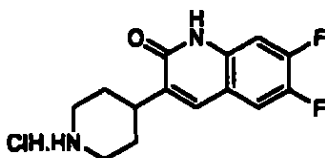


15

tert-butyl 4-(1-(4,5-Difluoro-2-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate. The reaction procedure was the same as the synthesis of *tert*-butyl 4-(1-(6-fluoro-2-pivalamidopyridin-3-yl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl) piperidine-1-carboxylate. The reaction afforded an inseparable *tert*-butyl 4-(1-(4, 5-difluoro-2-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl) piperidine-1-carboxylate stereo isomer mixture, as a white solid (70% total yield) after purification on flash chromatography, which was used in next step. Mass spec. 499.19 (MH⁺), Calc. for C₂₅H₃₆F₂N₂O₆ 498.25

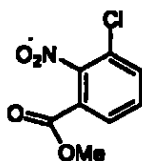
25

Intermediate 201



5 *6,7-Difluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride.* The procedure was the same as the synthesis of 7-fluoro-3-(piperidin-4-yl)-1, 8-naphthyridin-2(1H)-one. After reaction, partial of the solvent was removed on rotary vacuum, the expected product came out from the solution, filtration and washing with ethanol to gave a white solid (77% yield); ^1H NMR (400 MHz, MeOD) δ ppm 1.81 - 1.93 (m, 2 H), 2.13 (d, $J=2.01$ Hz, 2 H), 3.07 - 3.19 (m, 4 H), 3.50 (d, $J=14.35$ Hz, 2 H), 7.16 - 7.23 (m, 1 H), 7.55 - 7.62 (m, 1 H), 7.71 - 7.77 (m, 1 H); Mass spec. 265.07 (MH^+), Calc. for $\text{C}_{14}\text{H}_{14}\text{F}_2\text{N}_2\text{O}$ 264.11

Intermediate 202



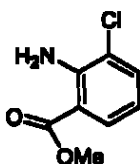
15

Methyl 3-chloro-2-nitrobenzoate. To 3-chloro-2-nitrobenzoic acid (3.15g, 15.6 mmol) in methanol/acetonitrile (20mL/20mL) was dropwise added TMSCHN_2 (2N in hexanes, 11.7 mL, and 23.4 mmol) at 0 °C under N_2 over 10 min until the yellow color persist. The mixture was continued stirring for 20 min, followed by dropwise addition of HOAc until the yellow color disappeared to kill excessive TMSCHN_2 . Partial of the solvent was removed on rotary vacuum, the product came out solution as a light yellow solid, which was filtered and washed with Et_2O (2x2mL) to afford the expected product as a white solid (2.5g, 74% yield); ^1H NMR (400 MHz, CDCl_3) δ ppm 3.91 (s, 3 H), 7.51 (t, $J=8.06$ Hz, 1 H), 7.70 (dd, $J=8.06$, 1.26 Hz, 1 H), 7.97 (dd, $J=7.81$, 1.26 Hz, 1 H); Mass spec. 216.02 (MH^+), Calc. for $\text{C}_8\text{H}_5\text{ClNO}_4$ 215.00.

25

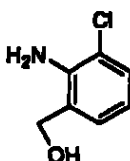
128 149

Intermediate 203



Methyl 2-amino-3-chlorobenzoate. Iron powder (1.94g, 34.8 mmol) was
5 added to the solution of methyl 3-chloro-2-nitrobenzoate (2.5g, 11.6mmol) in
EtOH/HOAc (100mL/100mL) at room temperature, and then the suspension was
refluxed under N₂ for 2 hrs. After cooling down to room temperature, partial of the
solvents was removed on rotary vacuum, the resulting residue was partitioned
between H₂O/EtOAc (200mL/300mL). The separated organic phase was washed
10 with aqueous NaOH (1N, 50mL), brine (50 mL), dried over MgSO₄, and
concentrated on rotary vacuum to afford the expected product as a tan oil (1.7g, 79%
yield) which became wax type solid standing on bench. The crude product was pure-
enough to be used in next step without further purification; ¹H NMR (400 MHz,
CDCl₃) δppm 3.86 (s, 3 H), 6.25 (s, 2 H), 6.57 (t, J=7.93 Hz, 1 H), 7.39 (dd, J=7.81,
15 1.51 Hz, 1 H), 7.79 (dd, J=8.06, 1.51 Hz, 1 H); Mass spec. 185.95 (MH⁺), Calc. for
C₈H₈ClNO₂ 185.02.

Intermediate 204



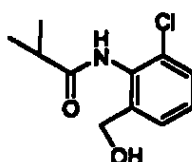
20

(2-Amino-3-chlorophenyl)methanol. A solution of methyl 2-amino-3-
chlorobenzoate(1.7g, 9.16 mmol) in THF (40 mL) was dropwise added to a
suspension of the LAH(521mg, 13.7 mmol) in THF(15mL) at room temperature over
10 min under N₂, and stirred for 2 hrs. The reaction was carefully quenched with
25 saturated Na₂SO₄ (10 mL) at 0 ° C, extracted with Et₂O (2x50mL). The combined
organic layers were washes with brine(30mL), dried on MgSO₄, and concentrated on

rotary vacuum to afford the expected product as a yellow solid(1.08g, 75%), which was pure enough to be used in the next step without further purification; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.65 (s, 1 H), 4.59 - 4.70 (m, 4 H), 6.60 - 6.65 (m, 1 H), 6.96 (dd, *J*=7.55, 1.26 Hz, 1 H), 7.19 - 7.25 (m, 1 H); Mass spec. 158.02 (MH⁺),

5 Calc. for C₇H₈ClNO₂ 157.03.

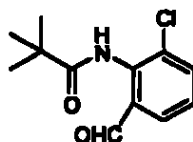
Intermediate 205



10 *N*-(2-Chloro-6-(hydroxymethyl)phenyl)pivalamide. To the crude (2-amino-3-chlorophenyl)methanol(1.08g, 6.88mmol) in CH₂Cl₂(15mL) was fast dropwise added trimethylacetyl chloride(.89mL, 7.23 mmol), followed by DIEA(2.4mL, 13.8 mmol) at 0 °C. 5 min later, the reaction mixture was stirred at room temperature for 1 hr. Normal aqueous work-up to afford the expected product as a white solid(1.58g, 95%
15 yield), which was pure enough to be used in next step; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.30 (s, 9 H), 3.35 (s, 2 H), 4.36 (d, *J*=6.29 Hz, 1 H), 7.06 - 7.22 (m, *J*=7.81, 7.81 Hz, 1 H), 7.29 - 7.33 (m, 2 H), 7.58 (s, 1 H); Mass spec. 242.08 (MH⁺), Calc. for C₁₂H₁₀ClNO₂ 241.09.

20

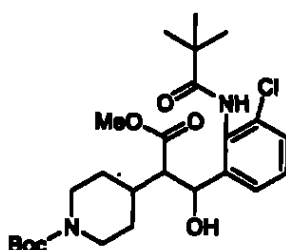
Intermediate 206



N-(3-Chloro-2-formylphenyl)pivalamide. Pyridinium chlorochromate (1.19g, 5.5mmol) was added to a solution of *N*-(2-chloro-6-(hydroxymethyl) phenyl)
25 pivalamide (884mg, 3.67mmol) in CH₂Cl₂ (100mL) at 0 °C. 5 min later the mixture was allowed stirring at room temperature for 3 hrs. The reaction mixture was passed

through a thin pad layer of silica gel with CH₂Cl₂(2x100mL), concentrated on rotary vacuo, and purified on a flash chromatography column eluting with 20~50% EtOAc/hexanes (1000mL) to afford the expected product as a white solid(414 mg, 47% yield); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.37 (s, 9 H), 7.30 (t, *J*=7.81 Hz, 1 H), 7.64 (dd, *J*=7.93, 1.39 Hz, 1 H), 7.77 (dd, *J*=7.55, 1.51 Hz, 1 H), 8.25 (s, 1 H), 9.84 (s, 1 H); Mass spec. 240.08 (MH⁺), Calc. for C₁₂H₁₄ClNO₂ 239.07.

Intermediate 207

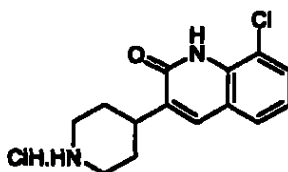


10

tert-butyl 4-(1-(3-Chloro-2-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate. The reaction procedure was the same as the synthesis of *tert-butyl 4-(1-(6-fluoro-2-pivalamidopyridin-3-yl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl) piperidine-1-carboxylate*. The reaction afforded an inseparable stereo isomer mixture of *tert-butyl 4-(1-(3-chloro-2-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl) piperidine-1-carboxylate*, as a white solid (56% yield) after purification on flash chromatography. Mass spec. 497.22(MH⁺), Calc. for C₂₅H₃₇ClN₂O₆ 496.23.

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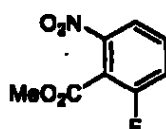
Intermediate 208



8-Chloro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride. The procedure was the same as the synthesis of 7-fluoro-3-(piperidin-4-yl)-1, 8-naphthyridin-2(1H)-

one. After reaction, partial of the solvent was removed on rotary vacuum, the expected product came out as a solid from the solution, filtration and washing with ethanol to gave the expected product, 8-chloro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride, a white solid (71% yield); ¹H NMR (400 MHz, MeOD) δ ppm 1.85 - 1.96 (m, 2 H), 2.17 (d, *J*=13.85 Hz, 2 H), 3.10 - 3.20 (m, 4 H), 3.46 - 3.54 (m, 2 H), 7.23 (t, *J*=7.81 Hz, 1 H), 7.59 - 7.64 (m, 2 H), 7.81 (s, 1 H); Mass spec. 263.08 (MH⁺), Calc. for C₁₄H₁₅ClN₂O 262.09.

Intermediate 209

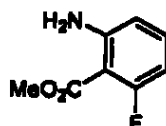


10

Methyl 2-fluoro-6-nitrobenzoate. To 2-fluoro-6-nitrobenzoic acid (712mg, 3.85 mmol) in methanol/acetonitrile (10 mL/10mL) was dropwise added TMSCHN₂ at 0 °C under N₂ until yellow color persistent, and stirred additional 30 min. Then the reaction was quenched with HOAc at 0 °C until the yellow color disappears. Partial of the solvent was removed on rotary vacuum, the residue was dissolved in small amount of EtOAc, purified on flash chromatography eluting with 30~50% EtOAc/hexanes (600mL) to afford the expected product, methyl 2-fluoro-6-nitrobenzoate, (716mg, 94% yield) which was used in step-2; ¹H NMR (400 MHz, CDCl₃) δ ppm 3.96 (s, 3 H), 7.40 - 7.48 (m, 1 H), 7.58 (td, *J*=8.31, 5.54 Hz, 1 H), 7.94 (d, *J*=8.31 Hz, 1 H); Mass spec. 200.05 (MH⁺), Calc. for C₈H₆FNO₄ 199.03.

20

Intermediate 210

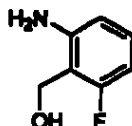


25

Methyl 2-amino-6-fluorobenzoate. Methyl 2-fluoro-6-nitrobenzoate (715 mg, 3.59 mmol) was dissolved in EtOH/HOAc/(10mL/10mL), followed by addition of

iron powder(602mg, 10.8mmol) at room temperature. The resulting mixture was refluxed under N₂ for 2 hrs. After cooling down to room temperature, the brown suspension was partitioned between H₂O (30mL) and Et₂O (100mL). After separation, the aqueous solution was extracted with Et₂O (50mL). The combined
5 organic layers were washed with 1N NaOH (3x50mL), brine (50mL), dried on MgSO₄, and concentrated on rotary vacuum to afford the expected product, methyl 2-amino-6-fluorobenzoate ,an colorless oil which became wax-type solid on standing. The crude compound was pure enough to be used in next step without further purification; ¹H NMR (400 MHz, CDCl₃) δppm 3.89 (s, 3 H), 5.67 (s, 2 H), 6.34
10 (ddd, J=11.58, 8.06, 1.01 Hz, 1 H), 6.41 (d, J=8.31 Hz, 1 H), 7.13 (td, J=8.18, 5.79 Hz, 1 H); Mass spec. 170.06 (MH⁺), Calc. for C₈H₈FNO₂ 169.05.

Intermediate 211

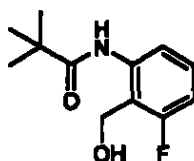


15

(2-Amino-6-fluorophenyl)methanol. Methyl 2-amino-6-fluorobenzoate, a crude compound obtained in the last step, dissolved in THF (15mL) was dropwise added to the suspension of LAH (204mg, 5.39mmol) at room temperature over 5 minutes. The mixture was stirred for 1hr, then cooled down to 0 ° C, quenched with
20 saturated Na₂SO₄ and extracted with Et₂O (2x50mL). The combined organic layers were washed with brine (30mL). dried on MgSO₄, concentrated on rotary vacuum to give an expected crude product, (2-amino-6-fluorophenyl)methanol, as a brown solid(268.1mg), which was pure enough to be used in the next step without further purification; ¹H NMR (400 MHz, CDCl₃) δppm 1.64 (s, 1 H), 4.30 (s, 2 H), 4.75 (s,
25 2 H), 6.39 - 6.47 (m, 2 H), 7.02 (td, J=8.18, 6.30 Hz, 1 H); Mass spec. 142.08 (MH⁺), Calc. for C₇H₈FNO 141.06.

30

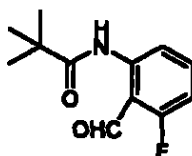
Intermediate 212



N-(3-Fluoro-2-(hydroxymethyl)phenyl)pivalamide. Trimethylacetyl chloride (0.25mL, 1.99mmol) was added to a solution of (2-amino-6-fluorophenyl) methanol (268mg, 1.90 mmol) in CH₂Cl₂ (10mL) at 0 °C, followed by the addition of DIEA (1.0 mL, 5.7 mmol). The mixture was stirred for 1 hr, followed by normal aqueous work-up to afford the expected crude product, *N*-(3-fluoro-2-(hydroxymethyl)phenyl)pivalamide, as a colorless oil (415mg, 97% yield), which was used directly in the next step; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.29 (s, 9 H), 2.64 (s, 1 H), 4.78 (d, *J*=4.78 Hz, 2 H), 6.75 - 6.84 (m, 1 H), 7.23 (td, *J*=8.62, 5.92 Hz, 1 H), 7.86 (d, *J*=8.31 Hz, 1 H), 8.97 (s, 1 H); Mass spec. 226.11 (MH⁺), Calc. for C₁₂H₁₆FNO₂ 225.12.

15

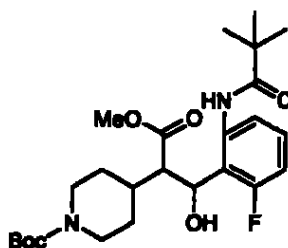
Intermediate 213



N-(3-Fluoro-2-formylphenyl)pivalamide. Pyridinium chlorochromate (596mg, 2.76 mmol) was added to a solution of *N*-(3-fluoro-2-(hydroxymethyl)phenyl) pivalamide (415mg, 1.84 mmol) in CH₂Cl₂ (50mL) at 0 °C. 5 min later the mixture was allowed stirring at room temperature for 3 hrs. The reaction mixture was passed through a thin pad layer of silica gel with CH₂Cl₂ (2x50mL), concentrated on rotary vacuum, and purified on a flash chromatography column eluting with 20~50% EtOAc/hexanes (600mL) to afford the expected product, *N*-(3-fluoro-2-formylphenyl)pivalamide, as a white solid (396 mg, 46% yield after five steps); ¹H NMR (400 MHz, CDCl₃) δ ppm 1.33 (s, 9 H), 6.76 - 6.83 (m, 1 H), 7.54 (td, *J*=8.44,

6.55 Hz, 1 H), 8.56 (d, $J=8.56$ Hz, 1 H), 10.38 (s, 1 H), 11.57 (s, 1 H); Mass spec. 224.11 (MH⁺), Calc. for C₁₂H₁₄FNO₂ 223.1.

Intermediate 214

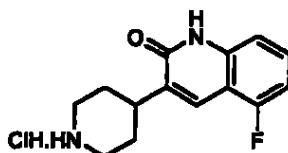


5

tert-butyl 4-(1-(2-Fluoro-6-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate. The reaction procedure was the same as the synthesis of *tert-butyl 4-(1-(6-fluoro-2-pivalamidopyridin-3-yl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate*. The reaction afforded a stereo isomer mixture of the expected crude product, *tert-butyl 4-(1-(2-fluoro-6-pivalamidophenyl)-1-hydroxy-3-methoxy-3-oxopropan-2-yl)piperidine-1-carboxylate*, as a colorless oil which was used directly in the next step without further purification. Mass spec. 481.24 (MH⁺), Calc. for C₂₅H₃₇FN₂O₆ 480.26.

15

Intermediate 215



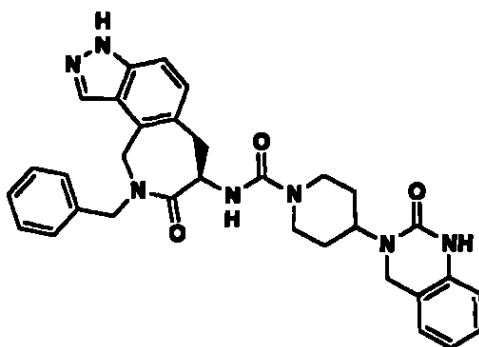
5-Fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride. The procedure was the same as the synthesis of 7-fluoro-3-(piperidin-4-yl)-1, 8-naphthyridin-2(1H)-one. After reaction, partial of the solvent was removed on rotary vacuum, the expected product came out as a solid from the solution, filtration and washing with ethyl ethanol to gave the expected product, 5-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride, a white solid (43% yield after two steps); ¹H NMR (400 MHz, MeOD) δ ppm 1.85 - 1.96 (m, 2 H), 2.16 (d, $J=14.10$ Hz, 2 H), 3.16 (td, $J=13.03, 2.90$ Hz, 3 H), 3.51 (dd, $J=10.58, 2.01$ Hz, 2 H), 4.55 (s, 1 H), 6.94 - 6.99

25

(m, 1 H), 7.13 (d, $J=8.31$ Hz, 1 H), 7.48 (td, $J=8.31, 5.79$ Hz, 1 H), 7.90 (s, 1 H);

Mass spec. 247.11 (MH^+), Calc. for $C_{14}H_{15}FN_2O$ 246.12.

EXAMPLE 1

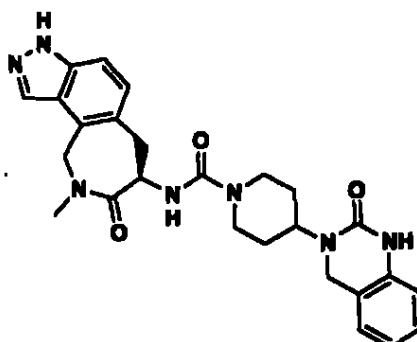


5

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (9-benzyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-amide. Potassium carbonate (25 mg, 0.18 mmol) was added to a solution of 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (3-acetyl-9-benzyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-amide (19 mg, 0.03 mmol). Reaction was stirred at room temperature for 1.25 hours. Reaction was quenched with 1N hydrochloric acid (5 mL). Methanol was removed from the mixture *in vacuo*. Remaining aqueous was made basic with sodium bicarbonate. Mixture was extracted with dichloromethane (3 X 10 mL). Combined extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as an off-white solid in 90% yield. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (s, 1H), 7.18 (m, 6H), 7.06 (m, 1H), 6.96 (t, $J=7.1$, 1H), 6.84 (m, 2H), 6.67 (m, 1H), 6.24 (d, $J=5.9$, 1H), 5.40 (m, 1H), 4.96 (d, $J=14.6$, 1H), 4.76 (d, $J=17.2$, 1H), 4.58 (m, 2H), 4.15 (m, 5H), 3.83 (d, $J=13.2$, 1H), 3.46 (dd, $J=3.1, J_2=16.7$, 1H), 2.98 (m, 3H), 1.78 (m, 4H). MS m/e ($M+H$) $^+$ = 564.3.

25

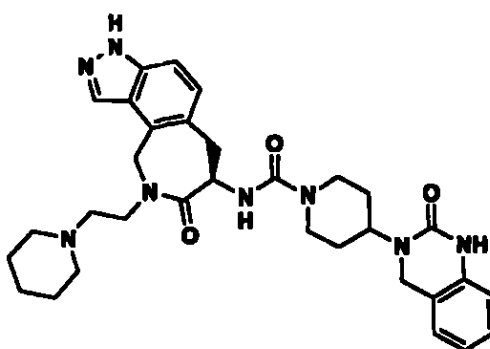
EXAMPLE 2



4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (9-methyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-amide. A catalytic amount of 10% palladium on carbon was added to a mixture of (3-acetyl-9-methyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester (30 mg, 0.07 mmol), and acetic acid (20 μ L, 0.35 mmol) in methanol (6 mL) and ethyl acetate (3 mL). Reaction vessel was placed on a Parr hydrogenation apparatus and charged with 50 psi of hydrogen gas. Reaction mixture was allowed to shake at room temperature for 1.5 hours. Mixture was filtered. Filtrate was concentrated. Residue was treated with dichloromethane (3 mL) and saturated aqueous sodium bicarbonate (1 mL). 20 % phosgene in toluene (48 μ L, 0.09 mmol) was added to the mixture. Reaction was stirred at room temperature for 5 minutes. 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidinium acetate (25 mg, 0.09 mmol) was added to the mixture. Reaction mixture was allowed to stir at room temperature for 1 hour. Another 20 μ L of phosgene solution was added to the mixture followed after 15 minutes by another 20 mg of 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidinium acetate. Reaction mixture was stirred at room temperature for 30 minutes. Reaction layers were partitioned. Organic was washed successively with 1N hydrochloric acid (2X 5mL), and brine (5 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was dissolved in methanol (3 mL). Potassium carbonate (25 mg, 0.18 mmol) was added to the mixture. Reaction mixture was stirred at room temperature for 1 hour. Reaction was quenched with a couple of drops of trifluoroacetic acid. C18 preparatory HPLC (acetonitrile-water-trifluoroacetic acid)

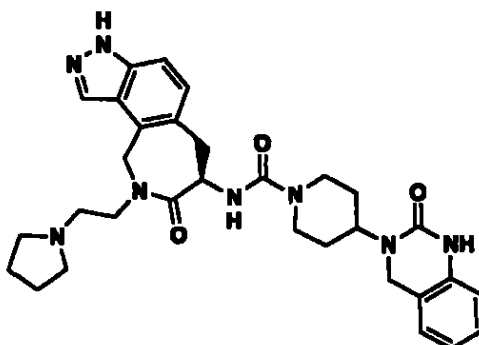
yielded the title compound as a white solid in 16% yield. ¹H NMR (300 MHz, CDCl₃): δ= 7.94 (s, 1H), 7.17 (m, 2H), 7.06 (t, *J*= 7.1, 2H), 6.93 (m, 2H), 6.82 (d, *J*= 9.2, 1H), 6.66 (d, *J*= 7.3, 1H), 6.19 (d, *J*= 5.9, 1H), 5.37 (m, 1H), 5.16 (m, 1H), 5.03 (d *J*= 17.2, 1H), 4.59 (m, 1H), 4.34 (s, 3H), 4.19 (m, 2H), 3.42 (m, 1H), 2.94 (m, 4H), 1.80 (m, 4H). MS *m/e* (M+H)⁺= 488.4.

EXAMPLE 3



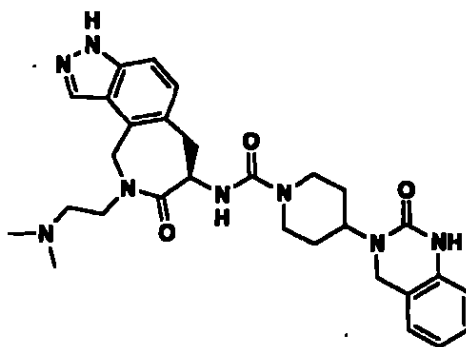
10 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. *N,N'*-Disuccinimidyl carbonate (55 mg, 0.21 mmol) was added to a mixture of 7-(R)-amino-9-(2-piperidin-1-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one (60 mg, 0.18 mmol) and
15 triethylamine (150 μL, 1.1 mmol) in dichloromethane (3 mL). Reaction was stirred at room temperature for 30 minutes. 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidinium acetate (65 mg, 0.22 mmol) was added to the reaction mixture. Reaction was stirred until judged complete by HPLC (1.75 hours). Mixture was washed successively with water (2 X 5 mL) and brine (1 X 5 mL). Organic was
20 concentrated *in vacuo*. C18 preparatory HPLC (acetonitrile-water-trifluoroacetic acid) afforded the desired product as a tan solid in 34% yield. ¹H NMR (300 MHz, DMSO-*d*₆): δ= 9.23 (s, 1H), 8.34 (s, 1H), 7.43 (d, *J*= 8.8, 1H), 7.13 (m, 2H), 6.86 (t, *J*= 7.0, 1H), 6.77 (d, *J*= 7.7, 1H), 6.68 (d, *J*= 7.7, 1H), 5.26 (m, 2H), 4.71 (d, *J*= 17.2, 1H), 4.36 (m, 1H), 4.13 (m, 4H), 3.48 (m, 2H), 3.26 (m, 2H), 3.08 (m, 1H), 2.92 (m, 2H), 2.80 (m, 2H), 1.80 (m, 2H), 1.62 (m, 4H). MS *m/e* (M+H)⁺= 585.4.

EXAMPLE 4



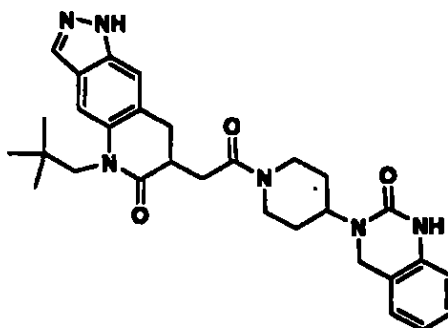
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-pyrrolidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. 7-(R)-Amino-9-(2-pyrrolidin-1-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one (27 mg, 0.09 mmol) was reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. Title compound was obtained as a white solid in 20% yield. ¹H NMR (300 MHz, DMSO-D₆): δ= 9.23 (s, 1H), 8.34 (s, 1H), 7.43 (d, *J*= 8.4, 1H), 7.13 (m, 2H), 6.86 (t, *J*= 7.3, 1H), 6.76 (d, *J*= 7.7, 1H), 6.67 (d, *J*= 7.0, 1H), 5.26 (m, 2H), 4.70 (d, *J*= 17.2, 1H), 4.37 (m, 2H), 4.12 (m, 6H), 3.62 (m, 2H), 3.36 (m, 4H), 3.04 (m, 3H), 2.80 (m, 2H), 2.00 (m, 2H), 1.86 (m, 2H), 1.70 (m, 2H), 1.57 (m, 2H). MS *m/e* (M+H)⁺= 571.4.

EXAMPLE 5



4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [9-(2-dimethylamino-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. 7-(R)-Amino-9-(2-dimethylamino-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one (11 mg, 0.04 mmol) was reacted
 5 in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. Desired compound was obtained as a white solid in 34% yield. ¹H NMR (300 MHz, DMSO-D₆): δ = 9.23 (s, 1H), 8.34 (s, 1H), 7.42 (d, J = 8.4, 1H), 7.12 (m, 2H), 6.87 (t, J = 7.5, 1H), 6.77 (d, J =
 10 8.1, 1H), 6.64 (d, J = 7.3, 1H), 5.26 (m, 2H), 4.69 (d, J = 17.2, 1H), 4.36 (m, 1H), 4.13 (m, 6H), 3.37 (m, 2H), 3.21 (m, 2H), 3.05 (m, 2H), 2.82 (m, 8H), 1.71 (m, 2H), 1.57 (m, 2H). MS m/e (M+H)⁺ = 545.4.

EXAMPLE 6

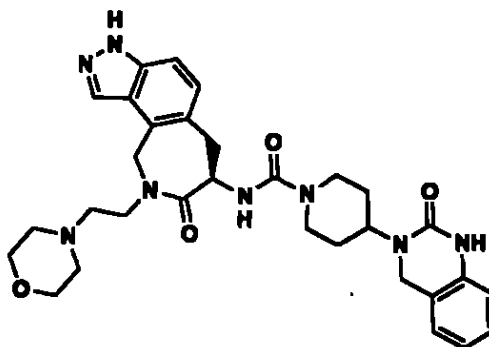


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5-Neopentyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidin-1-yl)ethyl)-7,8-dihydro-1H-pyrazolo[3,4-g]quinolin-6(5H)-one. O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (116 mg,
 20 0.3 mmol) was added to a solution of 2-(1-neopentyl-2-oxo-2,3,4,7-tetrahydro-1H-pyrazolo[3,4-h]quinolin-3-yl)acetic acid (95 mg, 0.3 mmol) and N,N-diisopropylethylamine (158 μ L, 0.9 mmol) in dichloromethane (5.0 mL). Mixture was stirred at room temperature for 45 minutes. 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidine (70 mg, 0.3 mmol) was then added to the mixture. After
 25 3 h stirring at room temperature, the crude reaction mixture was purified by prep HPLC starting from 30% methanol in water to 90% methanol in water over a period

of 8 min and at a flow rate of 40 ml/min. Removal of solvent furnished the desired. MS (ESI) 529 (M+H); R_f = 1.57.

EXAMPLE 7



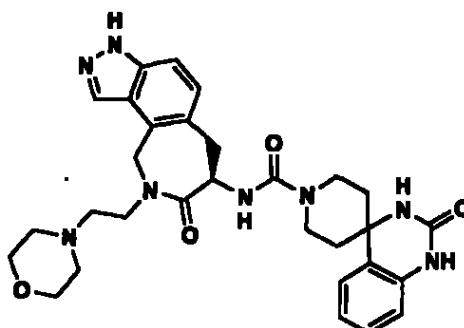
5

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [9-(2-morpholin-4-yl-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. 7-(R)-Amino-9-(2-morpholin-4-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one (18 mg, 0.05 mmol) was reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. The title compound was obtained as a light yellow solid in 43% yield. ^1H NMR (300 MHz, DMSO- D_6): δ = 9.23 (s, 1H), 8.33 (s, 1H), 7.44 (d, J = 8.4, 1H), 7.13 (t, J = 8.4, 2H), 6.86 (t, J = 7.5, 1H), 6.77 (d, J = 8.4, 1H), 6.66 (d, J = 7.0, 1H), 5.27 (m, 2H), 4.71 (d, J = 17.2, 1H), 4.38 (m, 1H), 4.16 (m, 4H), 3.98 (m, 2H), 3.61 (m, 4H), 3.42 (m, 4H), 3.29 (m, 2H), 3.10 (m, 4H), 2.79 (m, 2H), 1.72 (m, 2H), 1.56 (m, 2H), 1.56 (m, 2H). MS m/e (M+H) $^+$ = 587.4.

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EXAMPLE 8



*'H-Spiro[piperidine-4,4'-quinazolin]-2'(3'H)-one-1-carboxylic acid [9-(2-morpholin-4-yl-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. N,N'-Disuccinimidyl carbonate (21 mg, 0.08 mmol) was added to a mixture of 7-(R)-Amino-9-(2-morpholin-4-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one (22 mg, 0.07 mmol) and triethylamine (40 μ L, 0.29 mmol) in dichloromethane (1 mL). Reaction was stirred at room temperature for 30 minutes. 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)piperidinium acetate (65 mg, 0.22 mmol) was added to the reaction mixture. Reaction was stirred until judged complete by HPLC (1.5 hours). Mixture was concentrated *in vacuo*. C18 preparatory HPLC (acetonitrile-water-trifluoroacetic acid) afforded the desired product as a white solid in 34% yield. ^1H NMR (300 MHz, DMSO- D_6): δ = 9.26 (s, 1H), 8.34 (s, 1H), 7.43 (d, J = 8.8, 1H), 7.18 (m, 3H), 6.91 (t, J = 7.0, 1H), 6.83 (d, J = 8.1, 1H), 6.66 (d, J = 7.0, 1H), 5.28 (m, 2H), 4.70 (d, J = 17.6, 1H), 3.62 (m, 6H), 3.62 (m, 4H), 3.41 (m, 4H), 3.27 (m, 4H), 3.09 (m, 2H), 1.86 (m, 2H), 1.72 (m, 2H). MS m/e ($M+H$) $^+$ = 573.4.*

C[C@H](c1ccccc1)N2C(=O)C[C@H](C2NC(=O)N3CC[C@H](C3c4ccccc4N5C(=O)N5)c5ccccc5)C6=CC=CC=C6N7C=NC=C7

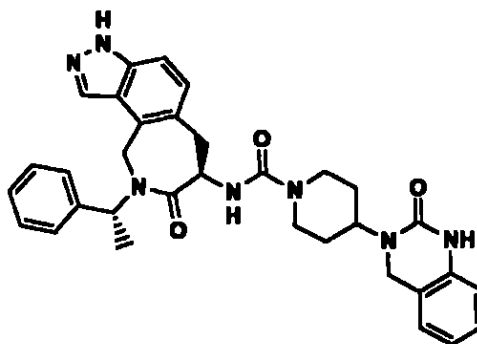
15

107 164

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(1-(S)-phenyl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. 7-Amino-9-(1-(S)-phenyl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-8-one (27 mg, 0.08 mmol) was
 5 reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. Title compound was obtained as a white solid in 20% yield. ¹H NMR (300 MHz, CD₃OD):
 8 = 7.92 (s, 1H), 7.47 (m, 5H), 7.43 (d, J = 8.8, 1H), 7.21 (d, J = 8.8, 1H), 7.12 (m,
 10 2H), 6.95 (t, J = 7.0, 1H), 6.78 (d, J = 7.7, 1H), 5.98 (d, J = 7.0, 1H), 5.44 (dd, J = 4.4, J₂ = 13.7, 1H), 4.98 (d, J = 17.2, 1H), 4.49 (m, 1H), 4.41 (m, 3H), 4.31 (m, 4H), 3.36 (m, 1H), 3.24 (m, 1H), 2.99 (m, 2H), 1.93 (m, 2H), 1.73 (m, 2H), 1.24 (d, J = 7.0, 3H). MS m/e (M+H)⁺ = 578.2.

15

EXAMPLE 11

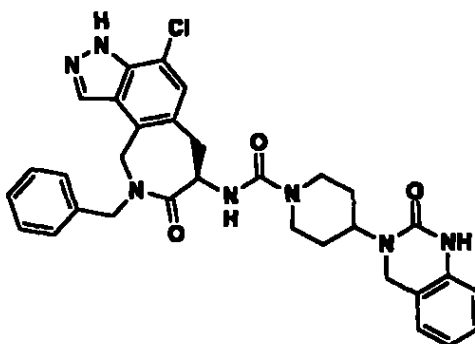


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(1-(R)-phenyl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. 7-Amino-9-(1-(R)-phenyl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-8-one (48 mg, 0.15 mmol) was
 20 reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. Title
 25 compound was obtained as an off-white solid in 10% yield. ¹H NMR (300 MHz, CD₃OD): δ = 7.50 (s, 21H), 7.25 (d, J = 8.4, 1H), 7.14 (m, 2H), 7.07 (m, 4H), 6.93 (t,

$J=7.5$, 1H), 6.83 (m, 2H), 6.78 (d, $J=7.7$, 1H), 5.97 (q, $J=6.7$, 1H), 5.40 (dd, $J_1=4.6$, $J_2=13.0$, 1H), 5.05 (d, $J=17.6$, 1H), 4.49 (m, 3H), 4.42 (s, 2H), 4.30 (m, 3H), 3.37 (m, 1H), 3.24 (m, 1H), 2.99 (m, 2H), 1.93 (m, 2H), 1.76 (m, 2H), 1.70 (d, $J=7.3$, 3H). MS m/e ($M+H$) $^+=578.1$.

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EXAMPLE 12

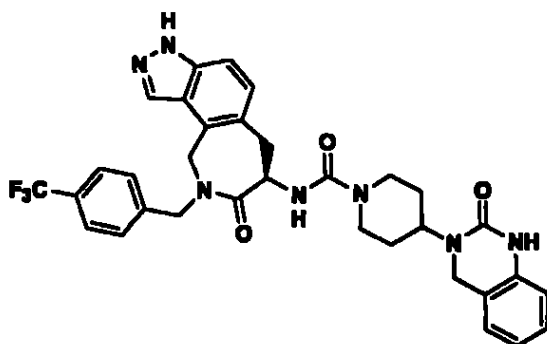


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (9-benzyl-4-chloro-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-amide. *N,N'*-Disuccinimidyl carbonate (63 mg, 0.25 mmol) was added to a mixture of 7-(R)-Amino-9-(2-morpholin-4-yl-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one (120 mg, 0.24 mmol) and triethylamine (500 μ L, 3.6 mmol) in dichloromethane (5 mL). Reaction was stirred at room temperature for 30 minutes. 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidine (54 mg, 0.23 mmol) was added to the reaction mixture. Reaction was stirred until judged complete by HPLC (0.5 hours). Mixture was washed successively with water (2 X 5 mL) and brine (5 mL). Organic layer was concentrated *in vacuo*. Residue was purified by C18 preparatory HPLC (acetonitrile-water-trifluoroacetic acid). Acetonitrile was removed from the product containing fractions *in vacuo*. Remaining aqueous was made basic with sodium bicarbonate. Mixture was extracted with ethyl acetate (2 x 20 mL). Combined extracts were washed with brine (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated. Desired product was obtained as a white solid in 24% yield. ^1H NMR (500 MHz, CD_3OD): $\delta=7.91$ (s, 1H), 7.16 (m, 4H), 7.10 (d, $J=7.3$, 1H), 7.04 (m, 3H), 6.92 (t, $J=7.5$, 1H), 6.79 (d, $J=7.9$, 1H), 5.45 (dd, $J_1=4.4$, $J_2=13.3$, 1H), 5.29 (d, $J=16.8$, 1H), 4.99 (d, $J=14.7$, 1H), 4.60 (m,

2H), 4.49 (m, 3H), 4.39 (s, 2H), 4.28 (t, $J=12.7$, 2H), 3.36 (m, 1H), 3.19 (dd, $J_1=14.0$, $J_2=16.2$, 1H), 2.98 (m, 2H), 1.91 (m, 2H), 1.71 (m, 2H). MS m/e ($M+H$) $^+$ = 598.1.

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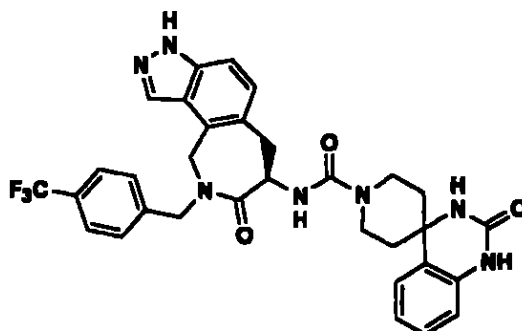
EXAMPLE 13



4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(4-trifluoromethyl-benzyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. 7-Amino-9-(4-trifluoromethyl-benzyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-8-one bismethanesulfonate was reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. Title compound was obtained as a white solid in 19% yield. ^1H NMR (500 MHz, DMSO- D_6): δ = 9.19 (s, 1H), 8.09 (s, 1H), 7.48 (d, $J=7.9$, 1H), 7.38 (d, $J=8.4$, 1H), 7.34 (d, $J=8.5$, 1H), 7.10 (m, 3H), 6.85 (t, $J=7.0$, 1H), 6.77 (d, $J=7.9$, 1H), 6.66 (d, $J=6.4$, 1H), 5.35 (m, 2H), 4.71 (m, 3H), 4.36 (m, 2H), 4.29 (s, 2H), 4.18 (d, $J=12.8$, 2H), 3.29 (m, 1H), 3.13 (dd, $J_1=13.6$, $J_2=16.6$, 1H), 2.81 (m, 2H), 1.72 (m, 2H), 1.56 (d, $J=11.3$, 2H). MS m/e ($M+H$) $^+$ = 632.1.

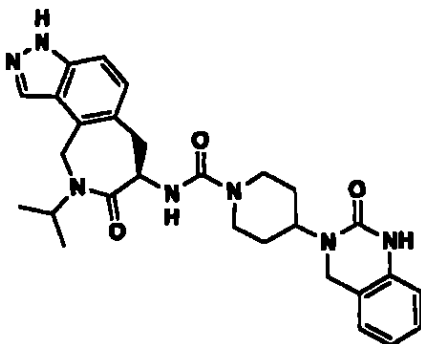
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EXAMPLE 14



- 'H*-spiro[piperidine-4,4'-quinazolin]-2'(3'H)-one-1-carboxylic acid [8-oxo-9-(4-trifluoromethyl-benzyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. 7-Amino-9-(4-trifluoromethyl-benzyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-8-one bismethanesulfonate was reacted in a manner analogous to the preparation of 'H-spiro[piperidine-4,4'-quinazolin]-2'(3'H)-one-1-carboxylic acid [9-(2-morpholin-4-yl-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. The title compound was obtained as a white solid in 6% yield. ¹H NMR (500 MHz, CD₃OD): δ = 7.91 (s, 1H), 7.46 (d, *J* = 8.2, 1H), 7.35 (d, *J* = 8.6, 1H), 7.30 (m, 5H), 7.17 (m, 2H), 7.01 (t, *J* = 7.6, 1H), 6.84 (d, *J* = 8.2, 1H), 5.51 (dd, *J*₁ = 4.6, *J*₂ = 13.1, 1H), 5.40 (d, *J* = 17.1, 1H), 5.07 (d, *J* = 15.3, 1H), 4.64 (d, *J* = 4.9, 1H), 4.61 (s, 1H), 4.43 (s, 1H), 4.09 (m, 2H), 3.42 (m, 3H), 3.35 (m, 1H), 3.22 (m, 1H), 2.16 (m, 1H), 2.07 (m, 1H), 1.92 (d, *J* = 13.4, 2H). MS *m/e* (M+H)⁺ = 618.1.

EXAMPLE 15

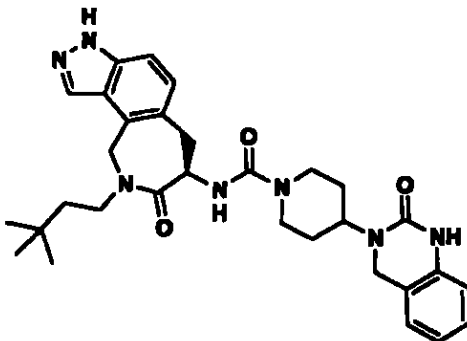


171 168

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (9-isopropyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-amide. 7-(R)-Amino-9-isopropyl-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one bismethanesulfonate was reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. The desired product was obtained as light yellow solid in 28% yield. ¹H NMR (400 MHz, DMSO-D₆): δ= 9.21 (s, 1H), 8.45 (s, 1H), 7.37 (d, J= 8.6, 1H), 7.10 (m, 3H), 6.86 (m, 1H), 6.77 (d, J= 7.6, 1H), 6.56 (m, 1H), 5.26 (m, 1H), 5.00 (d, J= 17.1, 1H), 4.74 (m, 2H), 4.65 (d, J= 17.4, 1H), 4.36 (m, 1H), 4.29 (s, 2H), 4.15 (m, 2H), 3.25 (dd, J1= 3.7, J2= 16.9, 1H), 3.04 (dd, J1= 13.6, J2= 16.5, 1H), 2.80 (m, 2H), 1.71 (m, 2H), 1.57 (d, J= 11.7, 2H), 1.23 (d, J= 6.9, 3H), 0.80 (d, J= 6.9, 3H). MS m/e (M+H)⁺= 516.4.

15

EXAMPLE 16

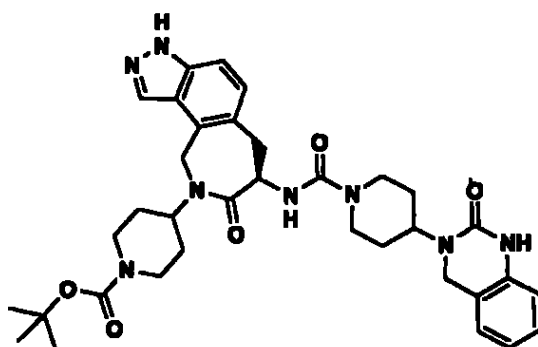


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (9-(3,3-dimethyl-butyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-amide. 7-(R)-Amino-9-(3,3-dimethyl-butyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one bismethanesulfonate was reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. The desired product was obtained as an off-white solid in 29% yield. ¹H NMR (500 MHz, DMSO-D₆): δ= 9.19 (s, 1H), 8.32 (s, 1H), 7.38 (d, J= 8.6, 1H), 7.10 (t, J= 9.2, 3H),

6.86 (t, $J=7.5$, 1H), 6.77 (d, $J=7.6$, 1H), 6.53 (s, 1H), 5.24 (d, $J=16.5$, 2H), 4.62 (d, $J=17.9$, 1H), 4.35 (m, 1H), 4.29 (s, 2H), 4.14 (m, 2H), 3.57 (m, 1H), 3.36 (m, 1H), 3.26 (dd, $J_1=2.8$, $J_2=17.1$, 1H), 3.01 (m, 1H), 2.80 (t, $J=12.4$, 2H), 1.72 (m, 2H), 1.56 (d, $J=11.3$, 2H), 1.27 (m, 1H), 1.15 (m, 1H), 0.79 (s, 9H). MS m/e ($M+H$) $^+=$

5 558.2.

EXAMPLE 17

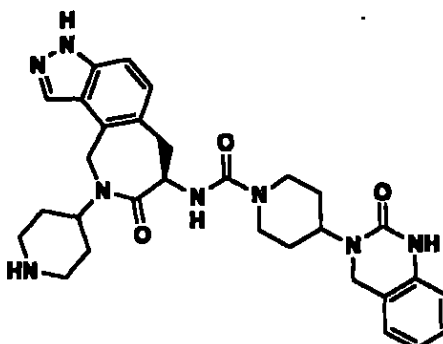


10

4-(8-Oxo-7-[[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino]-6,7,8,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-9-yl)-piperidine-1-carboxylic acid tert-butyl ester. 4-(7-(R)-Amino-8-oxo-6,7,8,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-9-yl)-piperidine-1-carboxylic acid
 15 tert-butyl ester acetate was reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. C18 preparatory HPLC gave the desired product as an off-white solid in 26% yield. ^1H NMR (500 MHz, DMSO- D_6): δ = 9.22 (s, 1H), 8.38 (s, 1H), 7.38 (d, $J=8.6$, 1H), 7.10 (m, 3H), 6.85 (m, 1H), 6.75 (d, $J=7.6$, 1H), 6.57 (s, 1H), 5.28 (m, 1H), 5.02 (d, $J=17.1$, 1H), 4.66 (d, $J=17.1$, 1H), 4.46 (m, 1H), 4.34 (m, 1H), 4.30 (s, 2H), 4.08 (m, 4H), 3.76 (m, 1H), 3.25 (d, $J=17.4$, 1H), 3.04 (m, 1H), 2.79 (m, 4H), 1.91 (m, 1H), 1.68 (n, 2H), 1.54 (m, 4H), 1.39 (s, 9H). MS m/e ($M+H$) $^+=$ 679.3.

25

EXAMPLE 18

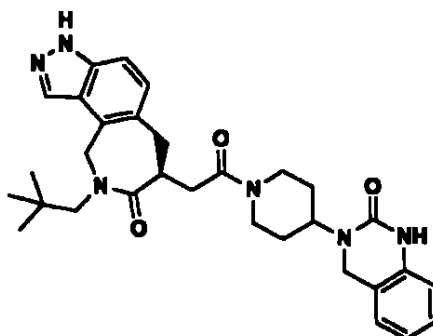


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (8-oxo-9-piperidin-4-yl-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl)-amide. Trifluoroacetic acid (250 μ L) was added to a chilled (water ice bath) solution of 4-(8-oxo-7-[[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino]-6,7,8,10-tetrahydro-3H-2,3,9-triaza-(R)-cyclohepta[e]inden-9-yl)-piperidine-1-carboxylic acid tert-butyl ester (60 mg, 0.08 mmol) in dichloromethane (1 mL). Reaction was stirred at 0°C for 1 hour. Mixture was concentrated *in vacuo*. The desired product was obtained as a light yellow solid in 65% yield. ^1H NMR (500 MHz, DMSO- D_6): δ = 9.23 (s, 1H), 8.32 (s, 1H), 7.41 (d, J = 8.6, 1H), 7.11 (m, 3H), 6.86 (t, J = 7.5, 1H), 6.76 (d, J = 7.9, 1H), 6.62 (d, J = 6.7, 1H), 5.29 (m, 1H), 5.11 (d, J = 16.8, 1H), 4.66 (t, J = 1H), 4.53 (d, J = 17.4, 1H), 4.35 (m, 1H), 4.29 (s, 2H), 4.16 (d, J = 12.5, 4H), 3.42 (d, J = 11.9, 1H), 3.26 (dd, J_1 = 3.8, J_2 = 16.3, 1H), 3.16 (d, J = 10.7, 1H), 3.05 (m, 2H), 2.83 (m, 3H), 2.15 (m, 1H), 1.70 (m, 4H), 1.57 (d, J = 10.7, 2H). MS m/e ($\text{M}+\text{H}$) $^+$ = 557.2.

20

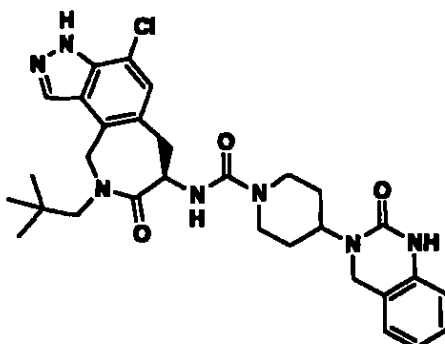
25

EXAMPLE 19



- 9-(2,2-Dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one. O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (62 mg, 0.16 mmol) was added to a solution of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid (45 mg, 0.14 mmol) and N,N-diisopropylethylamine (100 μ L, 0.57 mmol) in DMF (1.5 mL). Mixture was stirred at room temperature for 45 minutes. 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)piperidine (40 mg, 0.17 mmol) was then added to the mixture. Reaction was stirred at room temperature until it was judged complete by HPLC (45 minutes). C18 Preparatory HPLC (acetonitrile-water-trifluoroacetic acid) was performed on the crude mixture. Acetonitrile was removed from the fractions containing the desired product *in vacuo*. Remaining aqueous was made basic with sodium bicarbonate. Mixture was extracted with ethyl acetate (2 X 15 mL). Combined extracts were washed with saturated aqueous sodium bicarbonate (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as a white solid in 50% yield. ^1H NMR (500 MHz, DMSO- D_6): δ = 9.23 (s, 1H), 8.23 (s, 1H), 7.37 (d, J = 8.5, 1H), 7.10 (m, 3H), 6.86 (t, J = 7.3, 1H), 6.77 (d, J = 7.9, 1H), 5.38 (d, J = 16.2, 1H), 4.63 (d, J = 17.4, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 4.28 (s, 2H), 4.09 (m, 1H), 3.87 (m, 1H), 3.55 (t, J = 13.0, 1H), 3.10 (m, 2H), 3.01 (m, 3H), 2.88 (m, 1H), 2.59 (m, 1H), 2.34 (m, 1H), 1.84 (m, 1H), 1.59 (m, 3H), 0.74 (d, J = 19.2, 9H). MS m/e (M+H) $^+$ = 543.2.

EXAMPLE 20

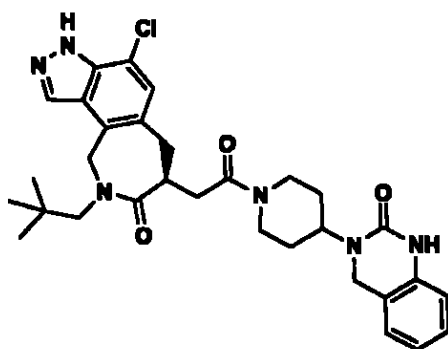


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. Methanesulfonic acid (250 μ L) was added to a solution of [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-carbamic acid benzyl ester (90 mg, 0.20 mmol) and anisole (70 μ L, 0.64 mmol) in dichloromethane (2 mL). Reaction stirred at room temperature for 2 hours. Mixture was diluted with diethyl ether (40 mL). Mixture was allowed to stand at room temperature for 30 minutes. Solvents were decanted off. Residue was washed with diethyl ether (30 mL) then dried *in vacuo*. Residue was dissolved in a mixture of triethylamine (250 μ L, 1.8 mmol) in dichloromethane (5 mL). *N,N'*-Disuccinimidyl carbonate (61 mg, 0.24 mmol) was added to the mixture. Reaction was stirred at ambient temperature for 30 minutes. 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidine (55 mg, 0.24 mmol) was then added to the mixture. Reaction was stirred at ambient temperature for 30 minutes. Mixture was washed successively with water (2 X 5 mL) and brine (5 mL). Organic was dried (magnesium sulfate), filtered and concentrated. C18 Preparatory HPLC (acetonitrile-water-trifluoroacetic acid) was performed on the residue. Acetonitrile was removed from the product containing fractions *in vacuo*. Remaining aqueous was made basic with sodium bicarbonate. Mixture was extracted with ethyl acetate (2 X 15 mL). Combined extracts were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as a white solid in 37% yield. ^1H NMR (500 MHz, CD_3OD): δ = 8.26 (s, 1H), 7.26 (s, 1H), 7.13 (m, 3H), 6.93 (t, J = 7.5, 1H), 6.78 (d, J = 7.9, 1H), 5.44 (d, J = 17.1, 1H), 5.34 (dd, J_1 = 3.5, J_2 = 13.0, 1H), 4.70 (d, J =

17.4, 1H), 4.47 (m, 1H), 4.40 (s, 2H), 4.26 (m, 2H), 3.82 (d, $J=13.4$, 1H), 3.19 (m, 1H), 3.08 (d, $J=13.7$, 1H), 2.94 (m, 2H), 1.90 (m, 2H), 1.71 (d, $J=12.2$, 2H), 0.81 (s, 9H). MS m/e ($M+H$)⁺ = 578.3.

5

EXAMPLE 21

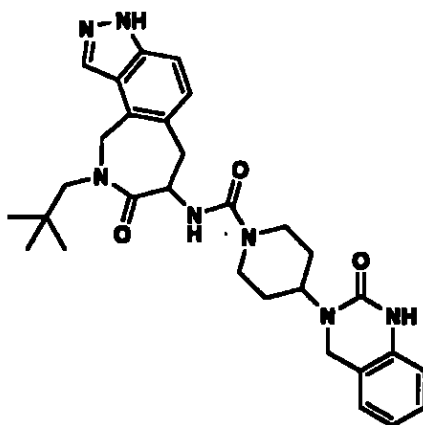


- 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one. O-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (90 mg, 0.28 mmol) was added to a solution of [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triazacyclohepta[e]inden-7-yl]-acetic acid (85 mg, 0.23 mmol) and N,N-diisopropylethyl amine (100 μ L, 0.57 mmol) in DMF (3 mL). Mixture was stirred at ambient temperature for 15 minutes.
- 15 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidine (65 mg, 0.28 mmol) was then added to the mixture. Reaction was stirred at ambient temperature for 1 hour. Mixture was diluted with ethyl acetate (20 mL). Mixture was washed successively with water (2 X 15 mL), and brine (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was purified by C18 preparatory HPLC
- 20 (acetonitrile-water-trifluoroacetic acid). Acetonitrile was removed from the product containing fractions *in vacuo*. Remaining aqueous was made basic with sodium bicarbonate. Mixture was extracted with ethyl acetate (2 X 20 mL). Combined extracts were washed with brine (10 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as a white solid in
- 25 37% yield. ¹H NMR (500 MHz, DMSO-D₆): δ = 13.55 (s, 1H), 9.21 (s, 1H), 8.36 (s, 1H), 7.25 (s, 1H), 7.09 (m, 2H), 6.86 (t $J=7.3$, 1H), 6.77 (d, $J=7.9$, 1H), 5.36 (d, $J=$

15.6, 1H), 4.63 (d, $J=17.1$, 1H), 4.51 (m, 1H), 4.40 (m, 1H), 4.29 (s, 2H), 4.10 (d, $J=13.2$, 1H), 3.87 (m, 1H), 3.57 (m, 1H), 3.11 (m, 2H), 3.00 (m, 2H), 2.88 (m, 1H), 2.59 (m, 1H), 2.32 (m, 1H), 1.85 (m, 1H), 1.59 (m, 3H), 0.74 (d, $J=18.3$, 9H). MS m/e (M+H)⁺ = 577.0.

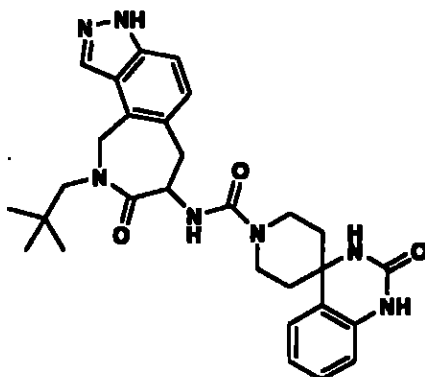
5

EXAMPLE 22



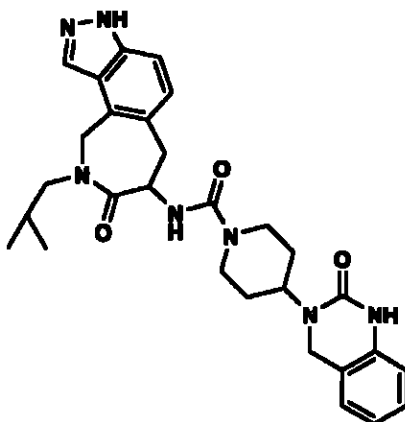
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl]-amide. In a manner similar to 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide, the title compound was prepared by reacting (7R)-7-amino-9-(2,2-dimethyl-propyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one, dihydrochloride with 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one, hydrochloride to give the title compound (80% yield). MS (ESI) 544 (M+H); $R_f=1.51$.

EXAMPLE 23



5 *N*-[9-(2,2-dimethylpropyl)-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-
e]indazol-7-yl]-2'-oxo-2',3'-dihydro-1*H*,1'*H*-spiro[piperidine-4,4'-quinazoline]-1-
 carboxamide. In a manner similar to 4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-
 piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-
 hexahydro-2,3,9-triaza-(*R*)-cyclohepta[*e*]inden-7-yl]-amide, the title compound was
 prepared by reacting (7*R*)-7-Amino-9-(2,2-dimethyl-propyl)-6,7,9,10-tetrahydro-3*H*-
 10 2,3,9-triaza-cyclohepta[*e*]inden-8-one, dihydrochloride with 1'*H*-spiro[piperidine-
 4,4'-quinazolin]-2'(3'*H*)-one, hydrochloride to give the title compound (80% yield).
 MS (ESI) 530 (*M*+*H*); *R*_f = 1.44.

EXAMPLE 24

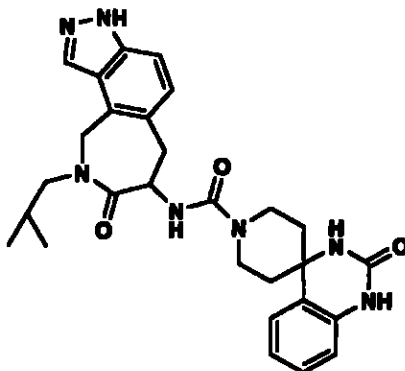


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (9-isobutyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-amide.

In a manner similar to 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide, the title compound was prepared by
5 reacting (7R)- 7-amino-9-isobutyl-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one, dihydrochloride with 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one, hydrochloride to give the title compound (80% yield). MS (ESI) 530 (M+H); R_f = 1.41.

10

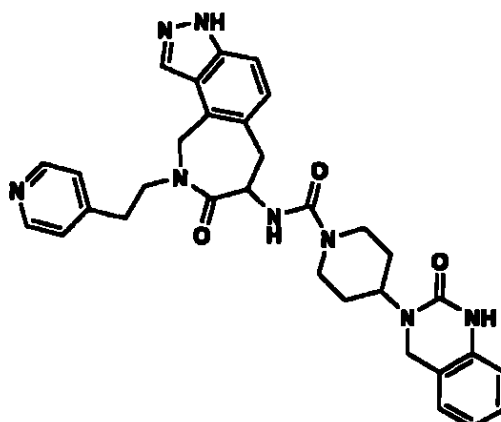
EXAMPLE 25



N-[9-(2-methylpropyl)-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl]-2'-oxo-2',3'-dihydro-1H,1'H-spiro[piperidine-4,4'-quinazoline]-1-carboxamide.

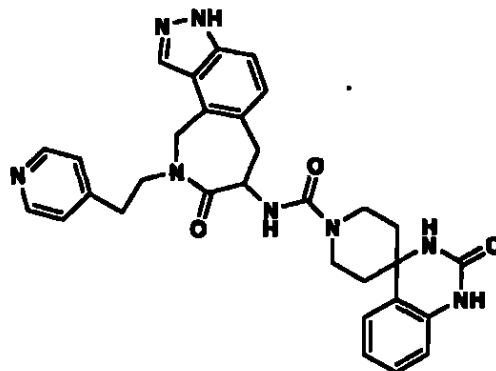
In a manner similar to 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide, the title compound was prepared by
15 reacting (7R)- 7-amino-9-isobutyl-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one, dihydrochloride with 1'H-spiro[piperidine-4,4'-quinazolin]-2'(3'H)-one, hydrochloride to give the title compound (80% yield). MS
20 (ESI) 516 (M+H); R_f = 1.35.

EXAMPLE 26



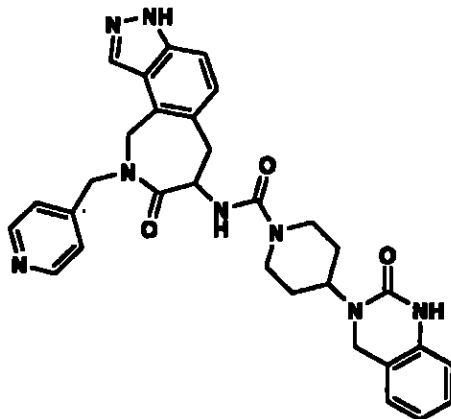
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-
 5 oxo-9-(2-pyridin-4-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-
 7-yl]-amide. In a manner similar to 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-
 piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-
 hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide, the title compound was
 prepared by reacting (7R)- 7-amino-9-(2-pyridin-4-yl-ethyl)-6,7,9,10-tetrahydro-3H-
 10 2,3,9-triaza-cyclohepta[e]inden-8-one, dihydrochloride with 3-piperidin-4-yl-3,4-
 dihydro-1H-quinazolin-2-one, hydrochloride to give the title compound (80% yield).
 MS (ESI) 530 (M+H); R_f = 1.41.

EXAMPLE 27



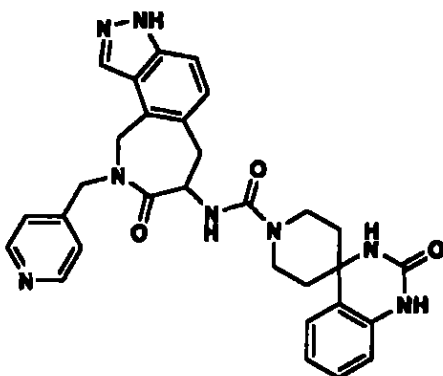
N-[9-(2-pyridin-4-yl-ethyl)-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl]-2'-oxo-2',3'-dihydro-1*H*,1'*H*-spiro[piperidine-4,4'-quinazoline]-1-carboxamide. In a manner similar to 4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(*R*)-cyclohepta[*e*]inden-7-yl]-amide, the title compound was prepared by reacting (7*R*)- 7-amino-9-(2-pyridin-4-yl-ethyl)-6,7,9,10-tetrahydro-3*H*-2,3,9-triaza-cyclohepta[*e*]inden-8-one, dihydrochloride with 1'*H*-spiro[piperidine-4,4'-quinazolin]-2'(3'*H*)-one, hydrochloride to give the title compound (80% yield). MS (ESI) 516 (M+H); *R*_f = 1.35.

EXAMPLE 28



4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid (8-oxo-9-pyridin-4-ylmethyl-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[*e*]inden-7-yl)-amide. In a manner similar to 4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(*R*)-cyclohepta[*e*]inden-7-yl]-amide, the title compound was prepared by reacting (7*R*)- 7-amino-9-pyridin-4-ylmethyl-6,7,9,10-tetrahydro-3*H*-2,3,9-triaza-cyclohepta[*e*]inden-8-one, dihydrochloride with 3-piperidin-4-yl-3,4-dihydro-1*H*-quinazolin-2-one, hydrochloride to give the title compound (80% yield). MS (ESI) 565 (M+H); *R*_f = 1.09.

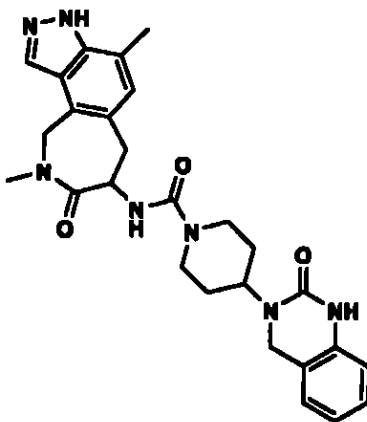
EXAMPLE 29



N-[9-pyridin-4-ylmethyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl]-2'-oxo-2',3'-dihydro-1H,1'H-spiro[piperidine-4,4'-quinazoline]-1-carboxamide.

In a manner similar to 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(*R*)-cyclohepta[*e*]inden-7-yl]-amide, the title compound was prepared by reacting (7*R*)-7-amino-9-pyridin-4-ylmethyl-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[*e*]inden-8-one, dihydrochloride with 1'H-spiro[piperidine-4,4'-quinazolin]-2'(3H)-one, hydrochloride to give the title compound (80% yield). MS (ESI) 551 (M+H); *R*_f = 1.07.

EXAMPLE 30



287 180

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (4,9-dimethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-amide.

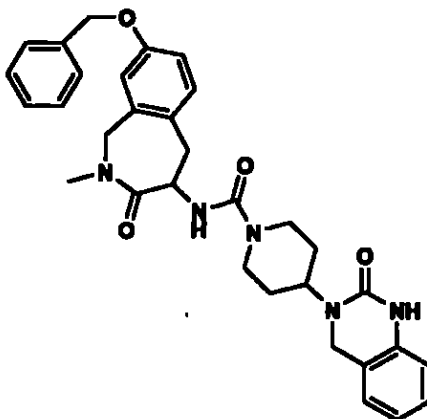
To a solution of (4,9-dimethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-carbamic acid benzyl ester (50 mg, 0.132 mmol) in

5 methanol and chloroform (0.5 mL) was added 10% palladium on carbon (20 mg) under nitrogen atmosphere. The reaction mixture was brought to hydrogen atmosphere (1 atm) and stirred for 3 h. The catalyst was filtered and the solvent was evaporated to give 7-amino-4,9-dimethyl-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one, hydrochloride in almost quantitative yield. To the amine

10 salt in dichloromethane was added disuccinimidyl carbonate (37 mg, 0.145 mmol) and triethylamine (0.11 mL, 0.8 mmol) at room temperature. After 120 min, 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one, hydrochloride (39 mg, 0.145 mmol) was added and stirring continued for 12 h. The solvent was evaporated and the crude product was purified by Prep HPLC to give 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-

15 yl)-piperidine-1-carboxylic acid (4,9-dimethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl)-amide in 59% overall yield. MS (ESI) 502 (M+H); R_f = 1.31.

EXAMPLE 31



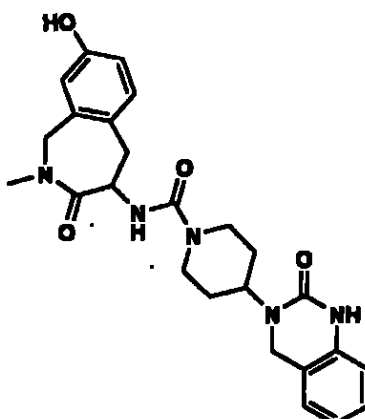
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4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (8-benzyloxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-amide. To a stirred solution of (8-benzyloxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-

25 benzo[c]azepin-4-yl)-carbamic acid tert-butyl ester (300 mg, 0.76 mmol) in

dichloromethane (2 mL) was added a 4.0 M solution of hydrogen chloride in dioxane (15 mL). The reaction mixture was stirred and removed the solvent to give the amine salt in quantitative yield. The amine salt was dissolved in dichloromethane (20 mL) followed by addition of N,N'-disuccinimidyl carbonate (214 mg, 0.83 mmol) and triethylamine (0.64 mL, 4.6 mmol). After 15 min, 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one, hydrochloride (225 mg, 0.84 mmol) was added and stirring continued for 12 h. The reaction mixture was then washed with aqueous sodium hydrogencarbonate, 1.0 M hydrochloric acid and dried (Na₂SO₄). The crude product was purified by flash chromatography using 5% methanol in dichloromethane to give 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (8-benzyloxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-amide in 66% yield. MS (ESI) 554 (M+H); R_f = 1.67.

EXAMPLE 32



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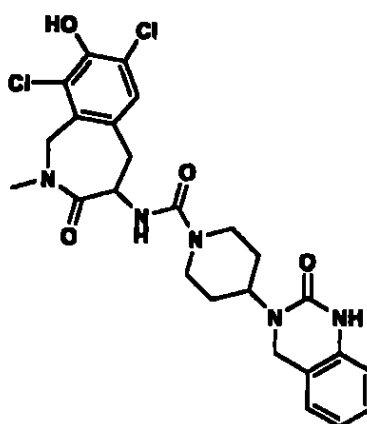
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-amide. To a stirred solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (8-benzyloxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-amide (187 mg, 0.34 mmol) in methanol (30 mL) followed by 10% palladium on carbon (30 mg) under nitrogen. The reaction mixture was brought to 1 atmosphere of hydrogen and stirred for 12 h. The catalyst was filtered and the solvent was evaporated to give 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-

carboxylic acid (8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-amide in quantitative yield.

MS (ESI) 464 (M+H); R_f = 1.34.

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EXAMPLE 33

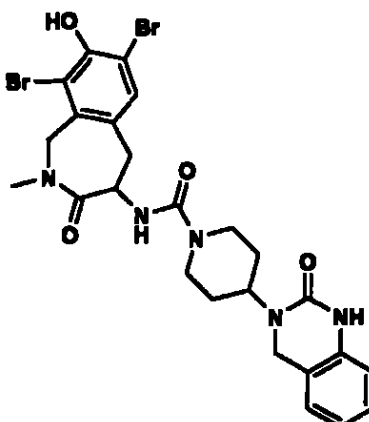


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (7,9-dichloro-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-
10 amide. To a stirred solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-amide (27 mg, 0.058 mmol) in dichloromethane (10 mL) was added methanol (2 mL), ether (3 mL) followed by sulfonyl chloride (70 μ L) at room temperature. The reaction mixture was stirred for additional 12 h and then concentrated. The crude
15 product was purified by Prep HPLC to give 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (7,9-dichloro-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-amide in 58% yield. MS (ESI) 532 (M+H); R_f = 1.40.

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EXAMPLE 34



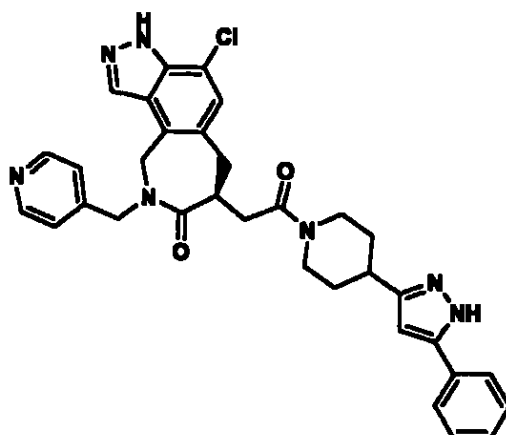
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (7,9-
5 dibromo-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-
amide. To a stirred solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-
1-carboxylic acid (8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-
4-yl)-amide (39 mg, 0.084 mmol) in dichloromethane (10 mL) was added
diisopropylamine (0.06 mL, 0.42 mmol) followed by N-bromosuccinimide (33 mg,
10 0.185 mmol) at room temperature. The reaction mixture was stirred for additional 1
h and then the solvent was removed. The crude product was purified by Prep HPLC
to give 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid (7,9-
dibromo-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-
amide in 74% yield. MS (ESI) 620 (M+H); R_f = 1.45.

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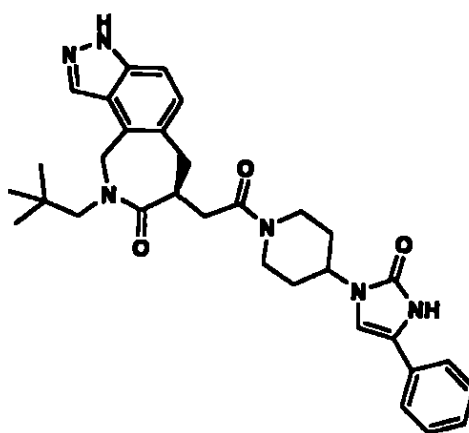
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EXAMPLE 35



5 *(S)*-4-Chloro-7-(2-oxo-2-(4-(5-phenyl-1*H*-pyrazol-3-yl)piperidin-1-yl)ethyl)-
 9-(pyridin-4-ylmethyl)-6,7,9,10-tetrahydroazepino[3,4-*e*]indazol-8(3*H*)-one. (*S*)-2-
 (4-chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-hexahydroazepino[3,4-
e]indazol-7-yl)acetic acid dihydrochloride (66 mg, 0.23 mmol) and 4-(5-phenyl-1*H*-
 pyrazol-3-yl)piperidine hydrochloride (40 mg, 0.15 mmol) were reacted following a
 procedure analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*S*)-
 10 {2-oxo-2-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-
 tetrahydro-3*H*-2,3,9-triaza-cyclohepta[*e*]inden-8-one. Title compound (34 mg) was
 obtained as white solid. MS (ESI) 594 (M+H); R_f = 1.99.

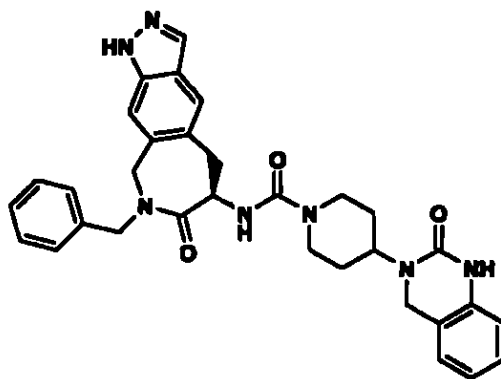
EXAMPLE 36



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(S)-9-Neopentyl-7-(2-oxo-2-(4-(2-oxo-4-phenyl-2,3-dihydroimidazol-1-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (62 mg, 0.16 mmol) was added to a solution of [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid (50 mg, 0.16 mmol) and N,N-diisopropylethylamine (85 μ L, 0.48 mmol) in DMF (2.0 mL). Mixture was stirred at room temperature for 45 minutes. 4-phenyl-1-(piperidin-4-yl)-1H-imidazol-2(3H)-one hydrochloride (53 mg, 0.19 mmol) was then added to the mixture. The desired compound was purified by prep HPLC. The title compound (49 mg) was obtained as a white foam. MS (ESI) 555 (M+H); R_f = 1.54.

EXAMPLE 37



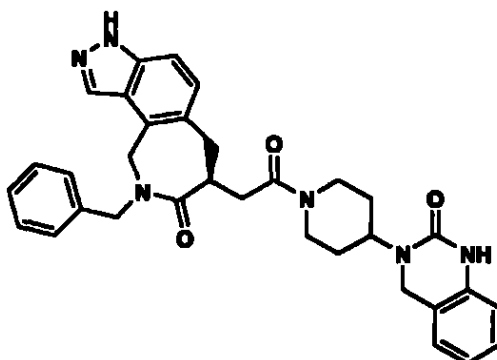
(R)-N-(8-Benzyl-7-oxo-1,5,6,7,8,9-hexahydroazepino[4,3-f]indazol-6-yl)-4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidine-1-carboxamide. (R)-Benzyl 1-acetyl-8-benzyl-7-oxo-1,5,6,7,8,9-hexahydroazepino[4,3-f]indazol-6-ylcarbamate (52 mg, 0.11 mmol) was dissolved in a mixture of methanol (7 mL) and acetic acid (100 μ L). A catalytic amount of 10% palladium on carbon was added to the mixture. Reaction was placed on a Parr apparatus under 60 psi of hydrogen gas. Reaction shook at room temperature for 2 hours. Mixture was filtered. Filtrate was concentrated. Residue was dissolved in dichloromethane (5 mL). Aqueous sodium bicarbonate (5 mL) was added to the mixture. 20% Phosgene in toluene (62 μ L, 0.12 mmol) was added to the mixture with vigorous stirring. Reaction was stirred vigorously at room temperature for 20 minutes. 4-(2-oxo-1,4-dihydro-2H-

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quinazolin-3-yl)piperidinium acetate was added to the mixture. Reaction stirred at room temperature for 1 hour. Layers were partitioned. Organics were washed twice with 1N hydrochloric acid and once with brine. Organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Residue was dissolved in methanol (5
5 mL). Potassium carbonate (20 mg, 0.14 mmol) was added to the mixture. Reaction stirred at room temperature for 1 hour. Reaction was quenched with trifluoroacetic acid. Mixture was purified by prep HPLC. Title compound was obtained as a white solid in 11% yield. MS m/e (M+H)⁺ = 564.3. R_f = 1.89 min.

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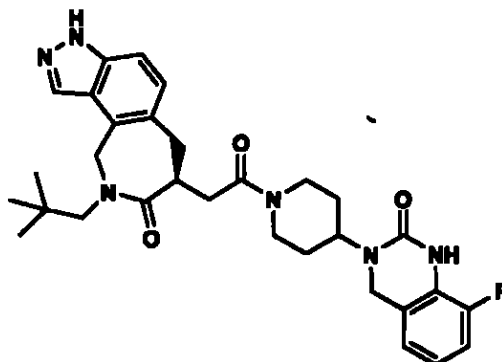
EXAMPLE 38



(S)-9-Benzyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound
15 was prepared in a manner analogous to the preparation of 4-chloro-9-(2,2-dimethylpropyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was
obtained as white solid in 18% yield. MS m/e (M+H)⁺ = 563.1. ¹H NMR (500 MHz, DMSO-D₆): δ = 12.93 (s, 1H), 9.23 (d, J = 6.71, 1H), 8.05 (d, J = 10.38, 1H), 7.33 (d, J = 8.55, 1H), 7.13 (m, 7H), 6.99 (d, J = 7.63, 1H), 6.84 (m, 1H), 6.76 (m, 1H), 5.34 (d, J = 17.4, 1H), 4.62 (m, 4H), 4.41 (m, 1H), 4.27 (d, J = 22.89, 2H), 4.11 (d, J = 12.82, 1H), 3.99 (m, 1H), 3.14 (d, J = 15.87, 2H), 3.07 (m, 1H), 2.61 (m, 1H), 2.42 (m, 1H), 1.84 (m, 1H), 1.62 (m, 3H).
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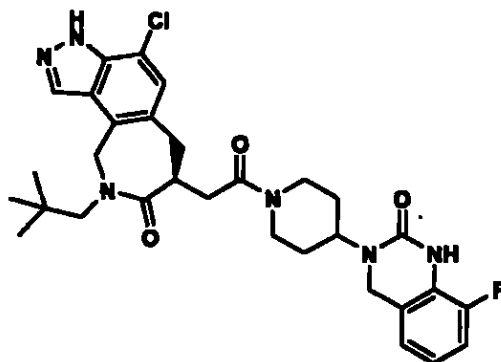
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EXAMPLE 39



- (S)-7-(2-(4-(8-Fluoro-2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidin-1-yl)-2-oxoethyl)-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound was prepared in a manner analogous to the preparation of 9-(2,2-Dimethyl-propyl)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as white solid in 35% yield. MS m/e ($M+H$)⁺ = 561.3. ¹H
- 10 NMR (500 MHz, DMSO-D₆): δ = 13.00 (s, 1H), 9.24 (s, 1H), 8.22 (s, 1H), 7.37 (d, J = 8.54, 1H), 7.11 (d, J = 7.63, 7H), 7.05 (m, 1H), 6.94 (m, 1H), 6.88 (m, 1H), 5.38 (d, J = 17.09, 1H), 4.62 (d, J = 17.09, 1H), 4.51 (m, 1H), 4.40 (m, 1H), 4.35 (s, 2H), 4.10 (d, J = 13.43, 2H), 3.88 (m, 1H), 3.55 (t, J = 12.67, 1H), 3.11 (m, 2H), 3.01 (m, 2H), 2.87 (m, 1H), 2.60 (m, 1H), 2.34 (m, 1H), 1.84 (m, 1H), 1.61 (m, 3H), 0.74 (d, J = 17.70, 9H).
- 15

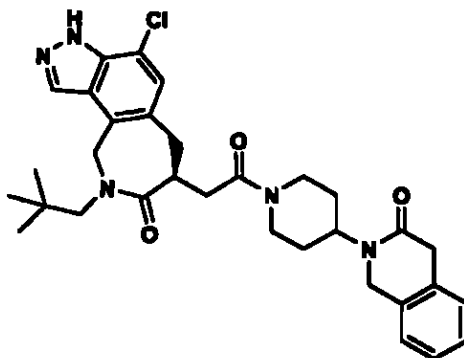
EXAMPLE 40



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(S)-4-Chloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidin-1-yl)-2-oxoethyl)-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound was prepared in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as white solid in 49% yield. MS m/e (M+H)⁺ = 595.2. ¹H NMR (500 MHz, DMSO-D₆): δ = 13.55 (s, 1H), 9.24 (s, 1H), 8.37 (s, 1H), 7.37 (d, J=8.54, 1H), 7.24 (s, 1H), 7.05 (m, 1H), 6.96 (m, 1H), 6.88 (dd, J1=12.21, J2=7.32, 1H), 5.36 (d, J=18.01, 1H), 4.63 (d, J=17.09, 1H), 4.50 (m, 1H), 4.42 (m, 1H), 4.35 (s, 2H), 4.10 (d, J=12.51, 1H), 3.88 (m, 1H), 3.57 (m, 1H), 3.09 (d, J=15.56, 2H), 3.00 (m, 2H), 2.88 (t, J=13.12, 1H), 2.60 (m, 1H), 2.33 (d, J=15.26, 1H), 1.85 (m, 1H), 1.60 (m, 3H), 0.73 (d, J=17.09, 9H).

EXAMPLE 41



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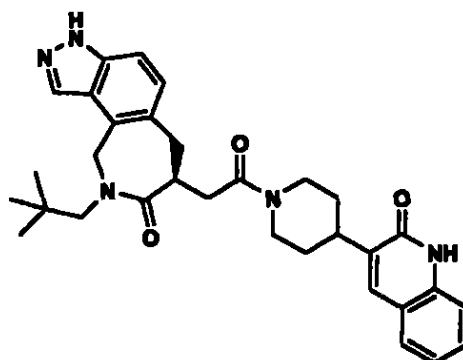
(S)-4-Chloro-9-neopentyl-7-(2-oxo-2-(4-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound was prepared from 2-(piperidin-4-yl)-1,2-dihydroisoquinolin-3(4H)-one hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as yellow solid in 35% yield. MS m/e (M+H)⁺ = 576.2. ¹H NMR (500 MHz, DMSO-D₆): δ = 13.55 (s, 1H), 8.37 (s, 1H), 7.29 (s, 1H), 7.23 (dd, J1=7.63, J2= 6.10, 4H), 5.37 (dd, J1=16.48, J2=7.63, 1H), 4.64 (d, J=17.70, 2H),

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4.48 (s, 1H), 4.38 (s, 2H), 4.09 (m, 1H), 3.57 (m, 1H), 3.54 (s, 2H), 3.11 (m, 3H), 3.00 (m, 2H), 2.89 (m, 1H), 2.61 (m, 1H), 2.36 (m, 1H), 1.54 (m, 2H), 0.74 (d, $J=28.08$, 9H).

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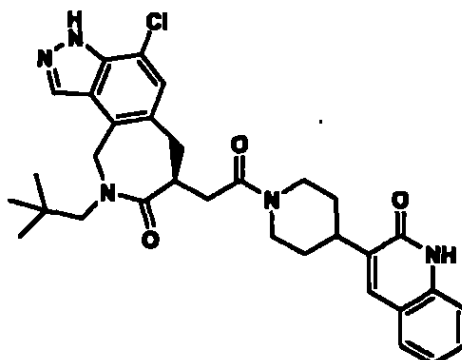
EXAMPLE 42



(*S*)-9-Neopentyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound was prepared from 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride in a manner analogous to the preparation of 9-(2,2-Dimethyl-propyl)-7-(*R*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as white solid in 31% yield. MS m/e ($M+H$) $^+$ = 540.2. ^1H NMR (500 MHz, DMSO- D_6): δ = 11.76 (s, 1H), 8.22 (s, 1H), 7.70 (d, $J=8.85$, 1H), 7.62 (s, 1H), 7.43 (t, $J=7.48$, 1H), 7.37 (d, $J=8.55$, 1H), 7.28 (d, $J=8.24$, 1H), 7.15 (t, $J=7.32$, 1H), 7.11 (d, $J=8.55$, 1H), 5.38 (d, $J=17.09$, 1H), 4.62 (d, $J=16.79$, 1H), 4.55 (d, $J=11.29$, 1H), 4.13 (s, 1H), 3.88 (s, 1H), 3.58 (s, 2H), 3.16 (m, 2H), 3.07 (m, 3H), 2.88 (t, $J=14.34$, 1H), 2.64 (m, 1H), 2.36 (m, 1H), 1.92 (d, $J=10.38$, 1H), 1.84 (d, $J=11.29$, 1H), 1.57 (m, 1H), 1.40 (m, 1H), 0.73 (s, 9H).

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EXAMPLE 43

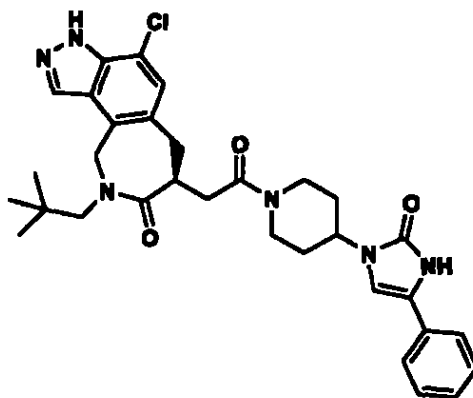


5 *(S)*-4-Chloro-9-neopentyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound was prepared from 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*S*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-
10 tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as off-white solid in 46% yield. MS m/e ($M+H$) $^+$ = 574.2. ^1H NMR (500 MHz, DMSO- D_6): δ = 13.54 (s, 1H), 11.76 (s, 1H), 8.36 (s, 1H), 7.70 (d, J =5.80, 1H), 7.61 (d, J =7.63, 1H), 7.43 (t, J =7.63, 1H), 7.28 (d, J =7.93, 1H), 7.24 (s, 1H), 7.15 (t, J =7.32, 1H), 5.37 (d, J =17.09, 1H), 4.63 (d, J =16.79, 1H), 4.55 (d, J =12.21, 1H), 4.13 (m, 1H),
15 3.87 (m, 1H), 3.58 (d, J =13.12, 1H), 3.15 (m, 2H), 3.03 (m, 3H), 2.88 (m, 1H), 2.63 (m, 1H), 2.34 (d, J =16.17 1H), 1.91 (d, J =1.22, 1H), 1.84 (d, J =11.29, 1H), 1.57 (m, 1H), 1.40 (m, 1H), 0.72 (s, 9H).

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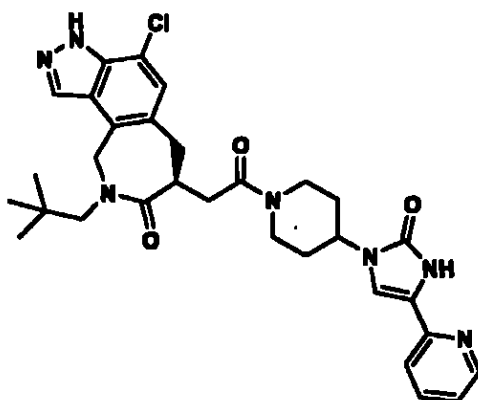
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EXAMPLE 44



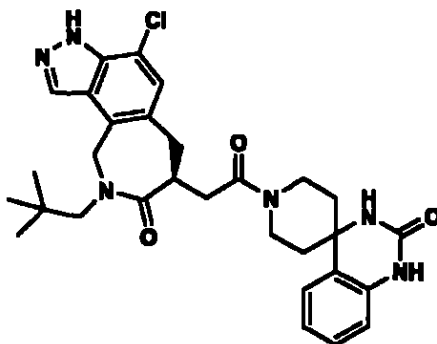
- (S)-4-Chloro-9-neopentyl-7-(2-oxo-2-(4-(2-oxo-4-phenyl-2,3-dihydroimidazol-1-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound was prepared from 4-phenyl-1-(piperidin-4-yl)-1H-imidazol-2(3H)-one in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one.
- Material was obtained as white solid in 46% yield. MS m/e ($M+H$)⁺ = 589.2. ¹H NMR (500 MHz, DMSO- D_6): δ = 13.55 (s, 1H), 10.68 (s, 1H), 8.37 (s, 1H), 7.50 (d, J = 7.63, 2H), 7.32 (t, J = 7.02, 2H), 7.24 (s, 1H), 7.16 (m, 2H), 5.37 (d, J = 14.34, 1H), 4.63 (d, J = 16.79, 1H), 4.51 (t, J = 10.83, 1H), 4.13 (m, 2H), 3.89 (m, 1H), 3.57 (m, 1H), 3.18 (m, 1H), 3.03 (m, 3H), 2.89 (t, J = 15.11, 1H), 2.66 (m, 1H), 2.34 (d, J = 16.17, 1H), 1.84 (m, 3H), 1.60 (m, 1H), 0.73 (d, J = 13.73, 9H).

EXAMPLE 45



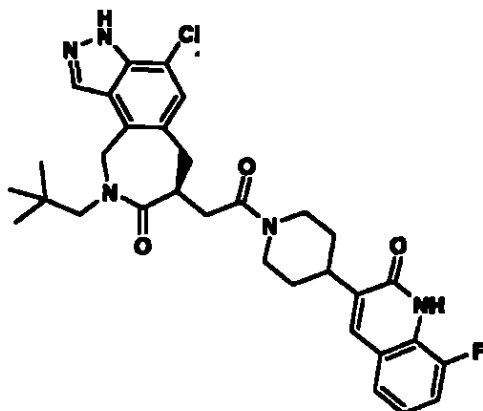
- (S)-4-Chloro-9-neopentyl-7-(2-oxo-2-(4-(2-oxo-4-(pyridin-2-yl)-2,3-dihydroimidazol-1-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound was prepared from 1-(piperidin-4-yl)-4-(pyridine-2-yl)-1H-imidazol-2(3H)-one in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one.
- 10 Material was obtained as white solid in 37% yield. MS m/e ($M+H$)⁺ = 590.2. ¹H NMR (500 MHz, DMSO- D_6): δ = 13.54 (s, 1H), 10.69 (d, 1H), 8.45 (s, 1H), 8.37 (s, 1H), 7.74 (s, 1H), 7.54 (d, J =8.24, 1H), 7.33 (d, J =4.88, 1H), 7.25 (s, 1H), 7.15 (dd, J_1 =6.71, J_2 =5.19, 1H), 5.37 (d, J =17.09, 1H), 4.63 (d, J =15.87, 1H), 4.50 (s, 1H), 4.12 (m, 2H), 3.87 (m, 1H), 3.56 (dd, J_1 =28.69, J_2 =13.43, 1H), 3.18 (t, J =13.73, 1H), 3.10 (d, J =14.65, 1H), 3.01 (m, 2H), 2.88 (t, J =15.26, 1H), 2.66 (m, 1H), 2.35 (d, J =14.95, 1H), 1.84 (m, 3H), 1.57 (m, 1H), 0.73 (d, J =16.17, 9H).

EXAMPLE 46



5 *(S)*-4-Chloro-9-neopentyl-7-(2-oxo-2-(4-(2-oxo-1'H-spiro(piperidine-4,4'-
 quinazoline)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title
 compound was prepared from 1'H-spiro(piperidine-4,4')quinazolin-2'(3'H)-one in a
 manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-(2-
 oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl)-6,7,9,10-
 tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as white
 10 solid in 37% yield. MS m/e ($M+H$)⁺ = 563.2. ¹H NMR (500 MHz, DMSO- D_6): δ =
 13.54 (s, 1H), 9.22 (d, J =10.68, 1H), 8.36 (s, 1H), 7.30 (m, 2H), 7.24 (s, 1H), 7.12
 (m, 1H), 6.85 (m, 2H), 5.36 (d, J =16.78, 1H), 4.62 (dd, J_1 =16.94, J_2 =9.31, 1H),
 4.26 (t, J =14.34, 1H), 3.89 (m, 2H), 3.63 (m, 1H), 3.52 (m, 1H), 3.09 (m, 3H), 2.98
 (m, 1H), 2.88 (m, 1H), 2.33 (dd, J_1 =51.12, J_2 =15.72, 1H), 1.96 (m, 1H), 1.74 (m,
 15 3H), 0.74 (d, J =16.48, 9H).

EXAMPLE 47

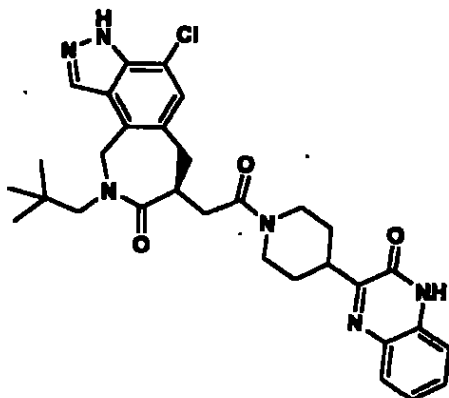


(S)-4-Chloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-*e*]indazol-8(3H)-one.

Title compound was prepared from 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*S*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[*e*]inden-8-one. Material was obtained as white solid in 36% yield. MS *m/e* (*M*+H)⁺ = 592.2. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 13.54 (s, 1H), 11.78 (s, 1H), 8.36 (s, 1H), 7.76 (d, *J*=5.19, 1H), 7.46 (d, *J*=7.93, 1H), 7.34 (dd, *J*₁=10.53, *J*₂=8.70, 1H), 7.24 (s, 1H), 7.14 (m, 1H), 5.36 (d, *J*=16.48, 1H), 4.63 (d, *J*=17.40, 1H), 4.55 (d, *J*=11.29, 1H), 4.12 (m, 1H), 3.87 (m, 1H), 3.58 (d, *J*=13.12, 1H), 3.17 (m, 1H), 3.05 (m, 4H), 2.88 (m, 1H), 2.65 (m, 1H), 2.34 (d, *J*=15.87, 1H), 1.92 (d, *J*=12.51, 1H), 1.84 (d, *J*=11.29, 1H), 1.57 (m, 1H), 1.40 (m, 1H), 0.72 (s, 9H).

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EXAMPLE 48

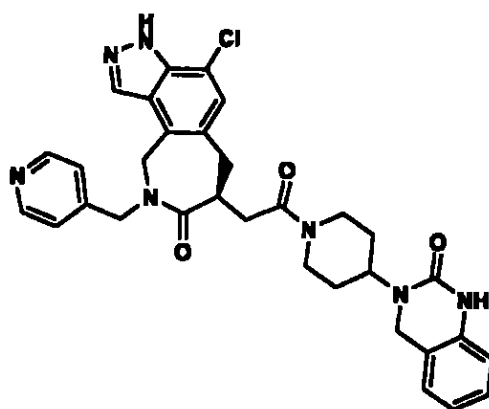


(S)-4-Chloro-9-neopentyl-7-(2-oxo-2-(4-(3-oxo-3,4-dihydroquinoxalin-2-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-*e*]indazol-8(3H)-one. Title compound was prepared from 3-(piperidin-4-yl)quinoxalin-2(1H)-one hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*S*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[*e*]inden-8-one. Material was obtained as white solid in 49% yield. MS *m/e* (*M*-H)⁻ = 573.2. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 13.53 (s, 1H), 12.35 (s, 1H), 8.36 (s, 1H), 7.72 (t, *J*=8.70, 1H), 7.48 (t, *J*=7.78, 1H),

25

7.28 (m, 2H), 7.24 (s, 1H), 5.37 (d, $J=17.09$, 1H), 4.63 (d, $J=17.09$, 1H), 4.49 (m, 1H), 4.12 (m, 1H), 3.86 (m, 1H), 3.59 (t, $J=12.36$, 1H), 3.45 (m, 1H), 3.22 (m, 1H), 3.10 (m, 1H), 2.99 (m, 1H), 2.87 (dd, $J_1=15.56$, $J_2=14.34$, 1H), 2.72 (m, 1H), 2.36 (m, 1H), 1.96 (d, $J=12.82$, 1H), 1.89 (d, $J=13.12$, 1H), 1.70 (m, 1H), 1.52 (m, 1H),
 5 0.72 (s, 9H).

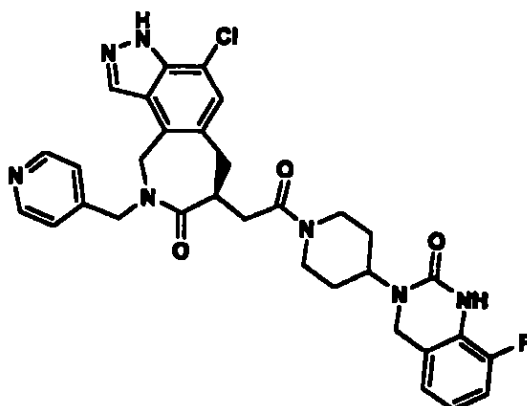
EXAMPLE 49



10 (S)-4-Chloro-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidin-1-yl)ethyl)-9-(pyridin-4-ylmethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. (S)-2-(4-Chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)acetic acid dihydrochloride (90 mg, 0.23 mmol) and 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidine hydrochloride (75
 15 mg, 0.28 mmol) were reacted following a procedure analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one. Title compound was obtained as white solid in 27% yield. MS m/e ($M+H$) $^+$ = 598.2. ^1H NMR (500 MHz, DMSO- D_6): δ = 13.47 (s, 1H), 9.19
 20 (s, 1H), 8.31 (s, 2H), 8.23 (s, 1H), 7.22 (s, 1H), 7.12 (s, 3H), 6.99 (m, 1H), 6.84 (m, 2H), 6.77 (s, 1H), 5.40 (d, $J=15.26$, 1H), 4.65 (m, 3H), 4.54 (d, $J=10.38$, 1H), 4.40 (m, 1H), 4.30 (s, 1H), 4.22 (s, 1H), 4.09 (m, 1H), 3.99 (m, 1H), 3.14 (m, 2H), 3.03 (m, 1H), 2.93 (m, 1H), 2.60 (m, 1H), 1.78 (m, 1H), 1.58 (m, 3H).

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EXAMPLE 50

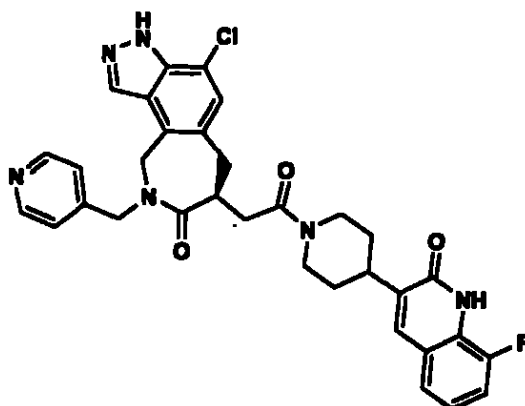


(S)-4-Chloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinazolin-3(4H)-
5 yl)piperidin-1-yl)-2-oxoethyl)-9-(pyridin-4-ylmethyl)-6,7,9,10-tetrahydroazepino[3,4-
e]indazol-8(3H)-one. (S)-2-(4-Chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-
hexahydroazepino[3,4-e]indazol-7-yl)acetic acid dihydrochloride (100 mg, 0.2
mmol) and 8-fluoro-3-(piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one
hydrochloride (61 mg, 0.2 mmol) were reacted in a manner analogous to the
10 preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-
dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-
triazacyclohepta[e]inden-8-one. Title compound was obtained as white solid in 16%
yield. MS m/e ($M+H$)⁺ = 616.2. ¹H NMR (500 MHz, DMSO-D₆): δ = 13.46 (s, 1H),
9.23 (d, J =6.41, 1H), 8.31 (m, 2H), 8.24 (d, J =6.10, 1H), 7.22 (s, 1H), 7.13 (dd,
15 J_1 =9.46, J_2 =4.88, 2H), 7.05 (m, 1H), 6.91 (m, 1H); 6.85 (s, 1H), 5.40 (d, J =17.09,
1H), 4.66 (m, 3H), 4.54 (d, J =11.90, 1H), 4.41 (m, 1H), 4.36 (s, 1H), 4.28 (d, J =4.58,
1H), 4.10 (d, J =12.51, 1H), 4.00 (m, 1H), 3.17 (m, 2H), 3.04 (m, 1H), 2.94 (m, 1H),
2.62 (d, J =11.29, 1H), 2.43 (m, 1H), 1.83 (m, 1H), 1.62 (m, 3H).

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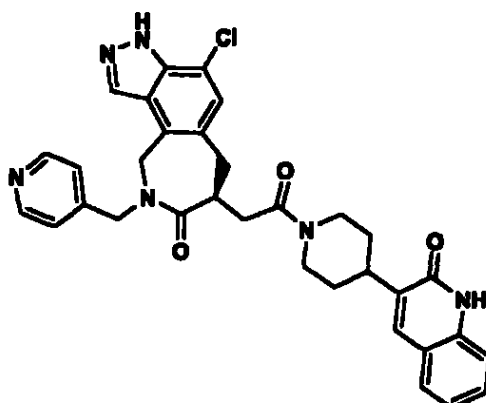
25

EXAMPLE 51



(S)-4-Chloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-9-(pyridin-4-ylmethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. (S)-2-(4-Chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)acetic acid dihydrochloride (100 mg, 0.22 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one acetate (90 mg, 0.29 mmol) were reacted following a procedure analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as tan solid in 13% yield. MS m/e ($M+H$)⁺ = 613.3. ¹H NMR (500 MHz, DMSO- D_6): δ = 13.46 (s, 1H), 11.78 (s, 1H), 8.30 (s, 2H), 8.23 (s, 1H), 7.75 (d, J =19.53, 1H), 7.45 (m, 1H), 7.34 (m, 1H), 7.21 (s, 1H), 7.12 (m, 3H), 5.40 (d, J =16.48, 1H), 4.64 (m, 4H), 4.13 (d, J =12.82, 1H), 4.00 (m, 1H), 3.17 (m, 2H), 3.04 (m, 2H), 2.94 (m, 1H), 2.67 (m, 1H), 2.44 (m, 1H), 1.94 (m, 1H), 1.86 (m, 1H), 1.57 (m, 1H), 1.42 (m, 1H).

EXAMPLE 52

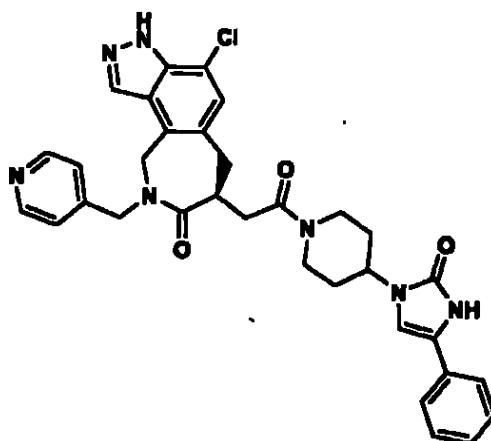


5 *(S)*-4-Chloro-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-9-(pyridin-4-ylmethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one.
(S)-2-(4-Chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)acetic acid dihydrochloride (100 mg, 0.23 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one (55 mg, 0.24 mmol) were reacted following a procedure analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*S*)-(2-oxo-2-[4-
 10 (2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 41% yield. MS m/e ($M+H$)⁺ = 595.2. ¹H NMR (500 MHz, DMSO-*D*₆): δ = 13.46 (s, 1H), 11.76 (s, 1H), 8.30 (d, J =5.19, 2H), 8.23 (s, 1H), 7.69 (d, J =19.84, 1H), 7.62 (m, 1H), 7.44 (m, 1H), 7.28 (d, J =7.93, 1H), 7.21 (s, 1H), 7.14 (m, 3H), 5.40 (d, J =17.09, 1H), 4.65 (m, 3H), 4.13 (d, J =13.43, 1H), 4.01 (m, 1H), 3.17 (d, J =14.95,
 15 2H), 3.04 (m, 2H), 2.94 (m, 1H), 2.66 (m, 1H), 2.45 (m, 2H), 1.93 (d, J =11.60, 1H), 1.85 (d, J =12.82, 1H), 1.56 (m, 1H), 1.41 (m, 1H).

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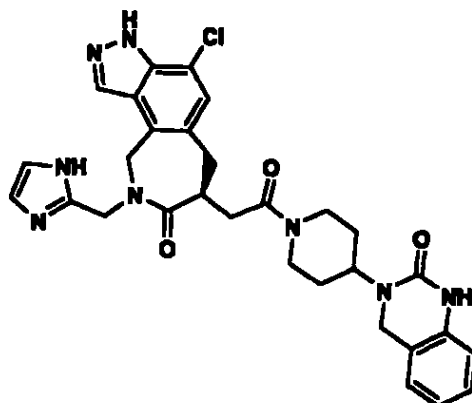
25

EXAMPLE 53



5 *(S)*-4-Chloro-7-(2-oxo-2-(4-(2-oxo-4-phenyl-2,3-dihydroimidazol-1-yl)piperidin-1-yl)ethyl)-9-(pyridin-4-ylmethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. *(S)*-2-(4-Chloro-8-oxo-9-(pyridin-4-ylmethyl)-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)acetic acid dihydrochloride (100 mg, 0.23 mmol) and 4-phenyl-1-(piperidin-4-yl)-1H-imidazol-2(3H)-one (60 mg, 0.28 mmol) were reacted following a procedure analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*S*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 30% yield. MS m/e ($M+H$)⁺ = 610.3. ¹H NMR (500 MHz, DMSO- D_6): δ = 13.46 (s, 1H), 10.68 (d, J =4.27, 1H), 8.30 (d, J =3.97, 2H), 8.23 (s, 1H), 7.50 (d, J =7.93, 1H), 7.45 (d, J =7.63, 1H), 7.31 (m, 2H), 7.22 (s, 1H), 7.14 (m, 4H), 5.41 (d, J =16.78, 1H), 4.66 (m, 3H), 4.55 (m, 1H), 4.13 (m, 2H), 3.99 (m, 1H), 3.33 (m, 1H), 3.18 (m, 1H), 3.05 (dd, J =16.02, J =8.70, 1H), 2.94 (m, 1H), 2.68 (m, 1H), 2.44 (m, 1H), 1.81 (m, 3H), 1.62 (m, 1H).

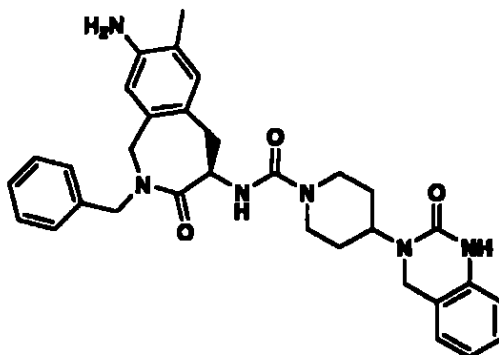
EXAMPLE 54



(S)-9-((1H-Imidazol-2-yl)methyl)-4-chloro-7-(2-oxo-2-(4-(2-oxo-1,2-
5 dihydroquinazolin-3(4H)-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-
e]indazol-8(3H)-one. (S)-Methyl 2-(9-((1H-imidazol-2-yl)methyl)-4-chloro-8-oxo-
3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)acetate (58 mg, 0.15 mmol) was
dissolved in a mixture containing methanol (2 mL), tetrahydrofuran (2 mL), and
water (2 mL). Lithium hydroxide monohydrate (20 mg, 0.48 mmol) was added to the
10 mixture. Reaction stirred at room temperature for 15 hours. Reaction was quenched
with 1N hydrochloric acid (0.5 mL). Mixture was concentrated *in vacuo*. Residue
was dissolved in DMF (2 mL). *N,N*-Diisopropylethylamine was added to the mixture
followed by *o*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium Tetrafluoroborate
(60 mg, 0.19 mmol). Mixture stirred at room temperature for 30 minutes. 4-(2-Oxo-
15 1,4-dihydro-2H-quinazolin-3-yl) piperidine hydrochloride (50 mg, 0.19 mmol) was
added to the mixture. Reaction stirred at room temperature for 3 hours. Reaction
mixture was purified by preparatory HPLC. Desired fractions were identified.
Acetonitrile was removed from the fractions *in vacuo*. Remaining aqueous was made
basic with sodium bicarbonate. Mixture was extracted twice with ethyl acetate.
20 Combined extracts were dried (magnesium sulfate), filtered and concentrated *in*
vacuo. Title compound was obtained as white solid in 28% yield. MS *m/e* (*M*+*H*)⁺=
587.2. ¹H NMR (500 MHz, DMSO-*d*₆): δ= 13.46 (s, 1H), 11.75 (s, 1H), 9.20 (s,
1H), 8.14 (s, 1H), 7.19 (s, 1H), 7.12 (m, 2H), 6.84 (m, 2H), 6.77 (d, *J*=7.93, 1H), 5.23
(d, *J*=15.16, 1H), 4.76 (m, 1H), 4.69 (dd, *J*₁=15.26, *J*₂=5.19, 1H), 4.53 (d, *J*=13.43,
25 1H), 4.47 (d, *J*=15.26, 1H), 4.40 (m, 1H), 4.29 (d, *J*=3.97, 2H), 4.08 (m, 1H), 3.89 (d,

$J=9.77$, 1H), 3.15 (m, 2H), 3.00 (m, 1H), 2.91 (m, 3H), 2.60 (m, 1H) 2.44 (m, 2H), 1.80 (m, 1H), 1.60 (m, 3H).

EXAMPLE 55



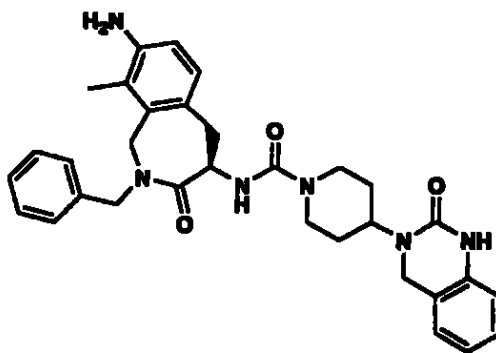
5

(R)-N-(8-Amino-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidine-1-carboxamide trifluoroacetate. (R)-N-(8-Amino-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-4-yl)-4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidine-1-carboxamide (95 mg, 0.15 mmol) was dissolved in dichloromethane (2 mL). Trifluoroacetic acid (1 mL) was added to the mixture. Reaction stirred at room temperature for 1 hour. Mixture was concentrated *in vacuo*. Residue was purified by preparatory HPLC. Solvent was lyophilized from the proper fractions.

Title compound was obtained as white solid in 64% yield. MS m/e (M+H)⁺= 553.

15

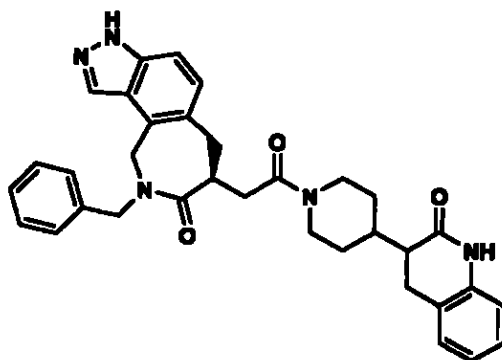
EXAMPLE 56



(R)-*N*-(8-Amino-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-yl)-4-(2-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)piperidine-1-carboxamide trifluoroacetate. *(R)*-tert-Butyl 2-benzyl-9-methyl-3-oxo-4-(4-(2-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ylcarbamate was reacted in a manner analogous with the preparation of *(R)*-*N*-(8-amino-2-benzyl-7-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-yl)-4-(2-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)piperidine-1-carboxamide trifluoroacetate. Title compound was obtained as off-white solid in 31% yield. MS *m/e* (*M*+*H*)⁺ = 553.

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EXAMPLE 57



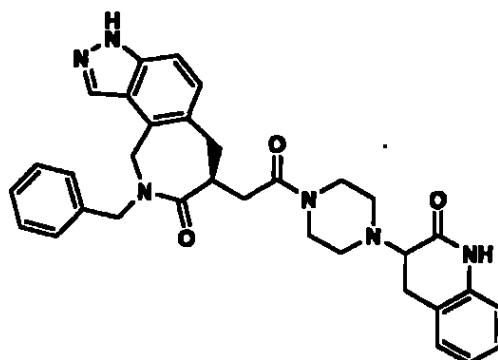
N-((*R*)-9-Benzyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl)-4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperidine-1-carboxamide. (*S*)-2-(9-Benzyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl)acetic acid (80 mg, 0.24 mmol) and 3-(piperidin-4-yl)-3,4-dihydroquinolin-2(1*H*)-one (75 mg, 0.33 mmol) were reacted in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethylpropyl)-7(*S*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3*H*-2,3,9-triaza-cyclohepta[*c*]inden-8-one. Material was obtained as white solid in 33% yield. MS *m/e* (*M*+*H*)⁺ = 542.3. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 13.01 (s, 1H), 10.11 (s, 1H), 8.21 (s, 1H), 7.36 (d, *J* = 7.93, 1H), 7.17 (m, 1H), 7.11 (m, 2H), 6.91 (m, 1H), 6.83 (d, *J* = 7.63, 1H), 5.35 (d, *J* = 17.09, 1H), 4.61 (d, *J* = 17.40, 1H), 4.38 (m, 1H), 4.02 (m, 1H), 3.83 (s, 1H), 3.55 (t, *J* = 12.36,

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1H), 2.95 (m, 6H), 2.79 (m, 1H), 2.42 (m, 1H), 2.31 (m, 2H), 1.90 (m, 1H), 1.63 (m, 2H), 1.17 (m, 1H), 0.72 (d, $J=9.77$, 9H).

EXAMPLE 58

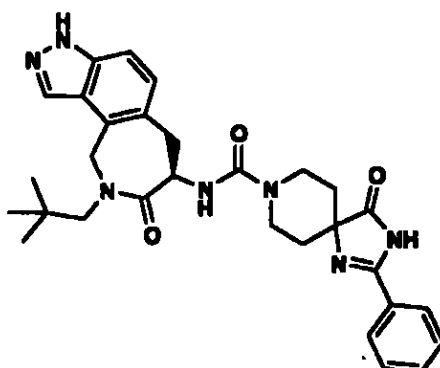


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(7S)-9-Benzyl-7-(2-oxo-2-(4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperazin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. (S)-2-(9-Benzyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)acetic acid (80 mg, 0.24 mmol) and 3-(piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (75 mg, 0.32 mmol) were reacted in a manner analogous to the preparation of 4-chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as white solid in 21% yield. MS m/e ($M+H$)⁺ = 543.3. ¹H NMR (500 MHz, DMSO- D_6): δ = 13.01 (s, 1H), 10.13 (s, 1H), 8.21 (s, 1H), 7.36 (d, $J=8.54$, 1H), 7.19 (d, $J=7.02$, 1H), 7.11 (m, 2H), 6.90 (t, $J=7.32$, 1H), 6.82 (d, $J=7.93$, 1H), 5.36 (d, $J=17.40$, 1H), 4.61 (d, $J=17.09$, 1H), 3.84 (m, 1H), 3.57 (d, $J=13.12$, 1H), 3.47 (m, 2H), 3.38 (m, 1H), 3.32 (m, 1H), 3.09 (m, 1H), 3.02 (d, $J=14.04$, 1H), 2.985 (m, 2H), 2.85 (m, 1H), 2.75 (m, 1H), 2.65 (m, 3H), 2.50 (m, 2H), 2.31 (d, $J=16.48$, 1H), 0.71 (s, 9H).

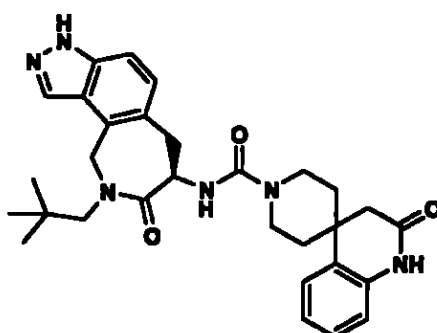
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EXAMPLE 59



4-Oxo-2-phenyl-1,3,8-triaza-spiro[4.5]dec-1-ene-8-carboxylic acid [(R)-9-
 5 (2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-
 7-yl]-amide. 2-Phenyl-1,3,8-triaza-spiro[4.5]dec-1-en-4-one trifluoroacetate (55 mg,
 0.16 mmol) and (R)-7-amino-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-
 8(3H)-one (40 mg, 0.14 mmol) were reacted in a manner analogous to the preparation
 of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-
 10 (2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-
 7-yl]-amide. C18 preparatory HPLC afforded the title compound as white solid in
 25% yield. High resolution MS m/e ($M+H$)⁺ = 542.2888.

EXAMPLE 60



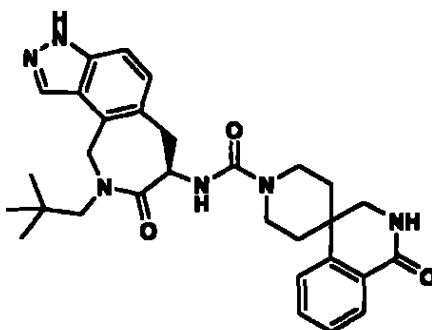
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Spiro[2,3-dihydro-1H-quinoline-2-one-4(1H),4'-piperidine]-1'-carboxylic
 acid [(R)-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-
 cyclohepta[e]inden-7-yl]-amide. Spiro[2,3-dihydro-1H-quinoline-2-one-
 20 4(1H),4'-piperidine] (32 mg, 0.15 mmol) and (R)-7-amino-9-neopentyl-6,7,9,10-

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tetrahydroazepino[3,4-e]indazol-8(3H)-one (35 mg, 0.12 mmol) were reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. C18 preparatory HPLC afforded the title compound as white solid in 46% yield. High resolution MS m/e (M+H)⁺ = 529.2924.

EXAMPLE 61

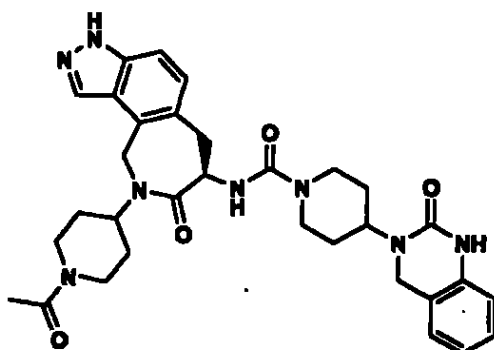


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Spiro[2,3-dihydro-1H-isoquinoline-1-one-4(1H),4'-piperidine]-1'-carboxylic acid [(R)-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohepta[e]inden-7-yl]-amide. Spiro[2,3-dihydro-1H-isoquinoline-1-one-4(1H),4'-piperidine] (32 mg, 0.15 mmol) and (R)-7-amino-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one (35 mg, 0.12 mmol) were reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. C18 preparatory HPLC afforded the title compound as white solid in 41% yield. High resolution MS m/e (M+H)⁺ = 529.2927.

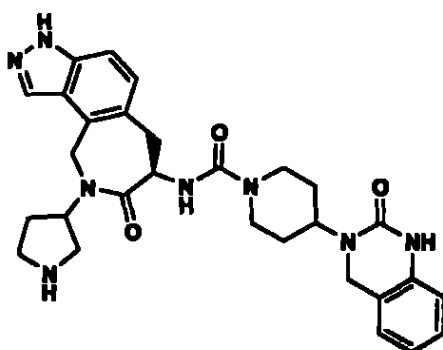
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EXAMPLE 62



5 *(R)*-*N*-(9-(1-acetylpiperidin-4-yl)-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-
e]indazol-7-yl)-4-(2-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)piperidine-1-carboxamide.
(R)-9-(1-acetylpiperidin-4-yl)-7-amino-6,7,9,10-tetrahydroazepino[3,4-*e*]indazol-
 8(3*H*)-one methanesulfonate (42 mg, 0.08 mmol) and 3-(piperidin-4-yl)-3,4-
 dihydroquinazolin-2(1*H*)-one acetate (30 mg, 0.10 mmol) were reacted in a manner
 analogous to the preparation of 4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-
 10 1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-
 triaza-(*R*)-cyclohepta[*e*]inden-7-yl]-amide. C18 preparatory HPLC afforded the title
 compound as white solid in 28% yield. High resolution MS m/e ($M+H$)⁺ = 599.3085.

EXAMPLE 63

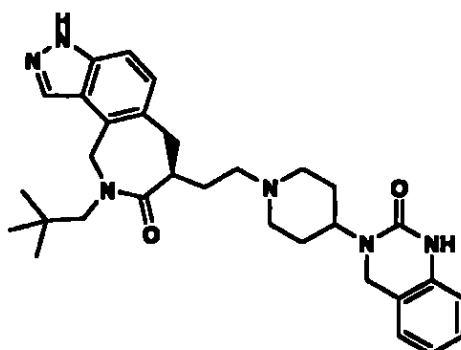


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4-(2-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)-*N*-((*R*)-8-oxo-9-(pyrrolidin-3-yl)-
 3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl)piperidine-1-carboxamide. (*R*)-
 tert-butyl 4-(8-oxo-7-(4-(2-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)piperidine-1-
 20 carboxamido)-7,8-dihydroazepino[3,4-*e*]indazol-9(3*H*,6*H*,10*H*)-yl)piperidine-1-

carboxylate (45 mg, 0.06 mmol) was dissolved in dichloromethane (1 mL). Trifluoroacetic acid (0.25 mL) was added to the mixture. Reaction stirred at room temperature for 1.5 hour. Reaction mixture was concentrated *in vacuo*. C18 preparatory HPLC purification afforded the title compound as yellow solid in 52% yield. High resolution MS m/e $(M+H)^+ = 543.2830$.

EXAMPLE 64

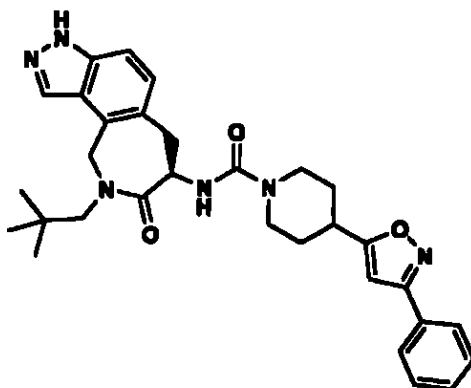


10 (S)-9-neopentyl-7-(2-(4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. (S)-7-(2-hydroxyethyl)-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one (15 mg, 0.04 mmol) was dissolved in dichloromethane (1 mL). Thionyl chloride (100 μ L) was added to the mixture. Reaction stirred at room temperature for 2 hours.

15 Thionyl chloride (500 μ L) was added to the mixture. Reaction stirred at room temperature for 2 hours and then was warmed to reflux for 2 hours. Reaction mixture was concentrated *in vacuo*. Residue was dissolved in acetonitrile (1 mL). Potassium carbonate (25 mg, 0.18 mmol) was added to the mixture followed by 3-(piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one (16 mg, 0.07 mmol). Reaction was heated at

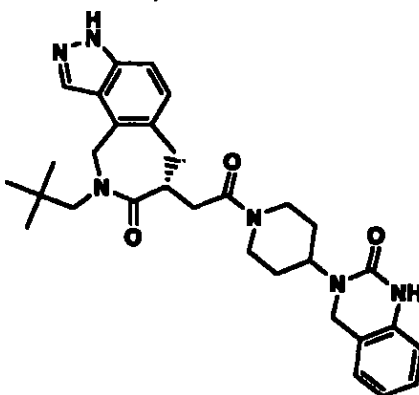
20 reflux for 2 hours. Preparatory HPLC purification afforded the title compound as white solid in 25% yield. High resolution MS m/e $(M+H)^+ = 529.3282$.

EXAMPLE 65



- 5 *(R)*-*N*-(9-neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-*e*]indazol-7-yl)-
 4-(3-phenylisoxazol-5-yl)piperidine-1-carboxamide. 4-(3-Phenylisoxazol-5-
 yl)piperidine (46 mg, 0.20 mmol) and (*R*)-7-amino-9-neopentyl-6,7,9,10-
 tetrahydroazepino[3,4-*e*]indazol-8(3H)-one (110 mg, 0.22 mmol) were reacted in a
 manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-
 piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-
 10 hexahydro-2,3,9-triaza-(*R*)-cyclohepta[*e*]inden-7-yl]-amide. C18 preparatory HPLC
 afforded the title compound as tan solid in 33% yield. High resolution MS *m/e*
 (*M*+*H*)⁺ = 541.2916.

EXAMPLE 66

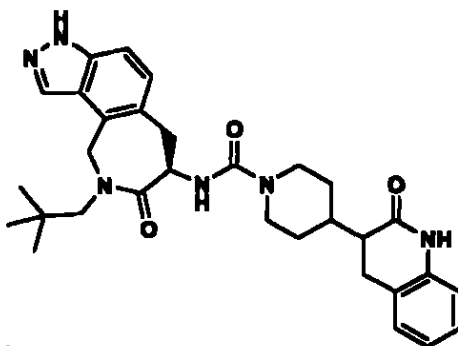


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9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-acetic acid (75 mg, 0.23 mmol) and 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidine (65 mg, 0.28 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as a white solid in 32% yield. High resolution MS m/e (M+H)⁺ = 543.3084.

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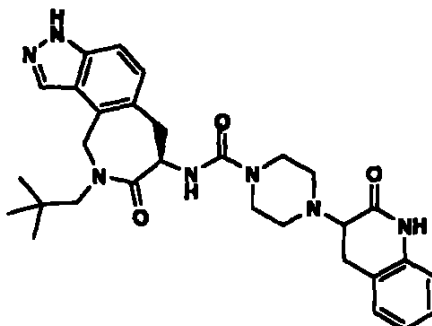
EXAMPLE 67



N-((R)-9-neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)-4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperidine-1-carboxamide. 3-(piperidin-4-yl)-3,4-dihydroquinolin-2(1H)-one (50 mg, 0.22 mmol) and (R)-7-amino-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one (110 mg, 0.22 mmol) were reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. C18 preparatory HPLC afforded the title compound as off-white solid in 25% yield. High resolution MS m/e (M+H)⁺ = 543.3084.

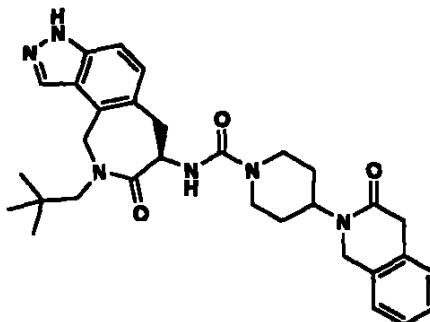
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EXAMPLE 68



N-((R)-9-Neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)-4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)piperazine-1-carboxamide. 3-(Piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (45 mg, 0.19 mmol) and (R)-7-amino-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one (75 mg, 0.15 mmol) were reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-yl-ethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. C18 preparatory HPLC afforded the title compound as white solid in 17% yield. High resolution MS m/e ($M+H$)⁺ = 544.3022.

EXAMPLE 69



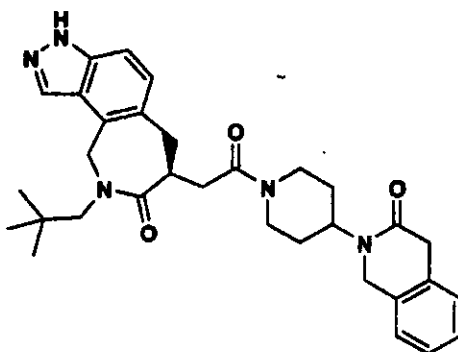
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(R)-N-(9-Neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)-4-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidine-1-carboxamide. 2-(Piperidin-4-yl)-1,2-dihydroisoquinolin-3(4H)-one (60 mg, 0.26 mmol) and (R)-7-amino-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one (100 mg,

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0.20 mmol) were reacted in a manner analogous to the preparation of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [8-oxo-9-(2-piperidin-1-ylethyl)-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(R)-cyclohepta[e]inden-7-yl]-amide. C18 preparatory HPLC afforded the title compound as yellow solid in 29% yield. High resolution MS m/e ($M+H$)⁺ = 543.3074.

EXAMPLE 70

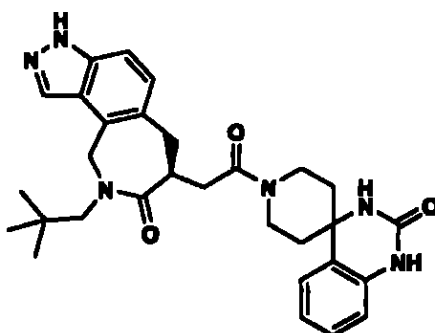


10 (S)-9-Neopentyl-7-(2-oxo-2-(4-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. 2-(Piperidin-4-yl)-1,2-dihydroisoquinolin-3(4H)-one (105 mg, 0.46 mmol) and [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (110 mg, 0.33 mmol) were combined in a manner analogous to the
15 preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as a white solid in 40% yield. High resolution MS m/e ($M+H$)⁺ = 541.3111.

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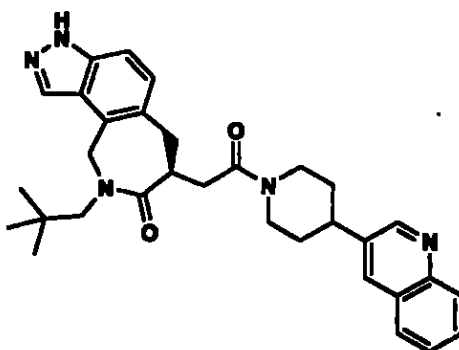
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EXAMPLE 71



1-[[7-(S)-9-(2,2-Dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-
 5 e]indazol-7-yl]acetyl]-spiro[piperidine-4,4'(1'H)-quinazolin]-2'(3'H)-one.
 Spiro[piperidine-4,4'(1'H)-quinazolin]-2'(3'H)-one hydrochloride (50 mg, 0.20
 mmol) and [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-
 cyclohepta[e]inden-7-yl]acetic acid (55 mg, 0.17 mmol) were combined in a manner
 analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-
 10 (2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-
 3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white
 solid in 35% yield. High resolution MS m/e (M+H)⁺ = 529.2921.

EXAMPLE 72



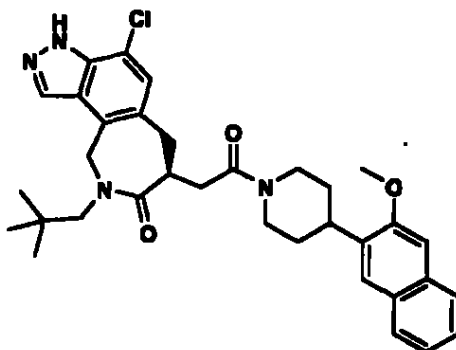
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1-[[7-(S)-9-(2,2-Dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-
 e]indazol-7-yl]acetyl]-4-(3-quinolinyl)piperidine. 3-(piperidin-4-yl)quinoline (75
 mg, 0.35 mmol) and [9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-
 20 triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (95 mg, 0.29 mmol) were combined in

a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as off-white solid in 50% yield. High resolution MS m/e (M+H)⁺ = 522.2878.

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EXAMPLE 73

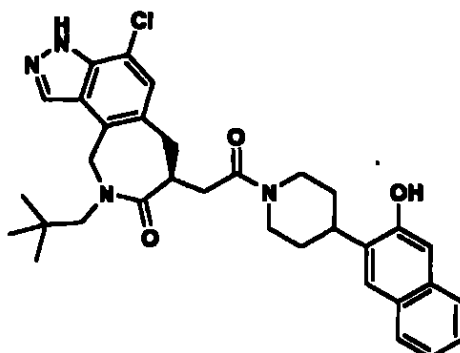


1-[[7-(S)-4-chloro-9-(2,2-Dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-4-(3-methoxy-2-naphthalenyl)piperidine. 4-(3-Methoxynaphthalen-2-yl)piperidine hydrochloride (78 mg, 0.28 mmol) and [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (88 mg, 0.24 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as tan solid in 88% yield. An analytical sample was prepared by C18 preparatory HPLC giving white solid with 30% recovery. High resolution MS m/e (M+H)⁺ = 587.2791.

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EXAMPLE 74



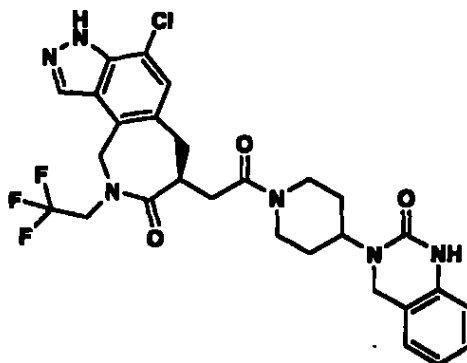
1-[[7-(S)-4-chloro-9-(2,2-Dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-4-(3-hydroxy-2-naphthalenyl)piperidine. A
5 1M solution of boron tribromide in dichloromethane (580 μ L, 0.58 mmol) was added to a solution of 1-[[7-(S)-4-chloro-9-(2,2-Dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-4-(3-methoxy-2-naphthalenyl)piperidine (78 mg, 0.13 mmol) in dichloromethane (3 mL). Reaction stirred at room temperature for
10 4 hours. 1M Boron tribromide in dichloromethane (500 μ L, 0.5 mmol) was added to the mixture. Reaction stirred at room temperature for 30 minutes. Reaction mixture was concentrated *in vacuo*. Residue was purified by C18 preparatory HPLC. Major peak was isolated. Methanol was removed from the combined fractions *in vacuo*. Remaining aqueous was extracted with ethyl acetate (30 mL). Organic layer was
15 washed with aqueous sodium bicarbonate (2x15 mL). Organic was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Title compound was obtained as tan solid in 37% yield. High resolution MS m/e (M+H)⁺ = 573.2636.

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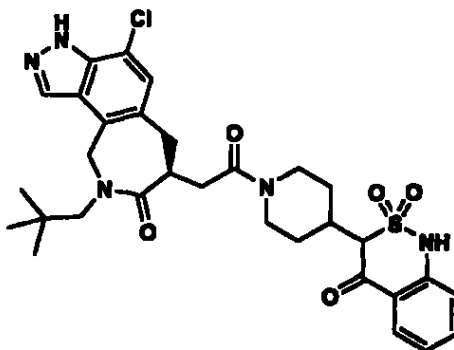
EXAMPLE 75



- 1-[[[(7S)-4-Chloro-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-
5 trifluoroethyl)azepino[3,4-e]indazol-7-yl]acetyl]-4-(1,4-dihydro-2-oxo-3(2H)-
quinazolin-3-yl)-piperidine. [4-Chloro-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-
trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (105 mg, 0.28
mmol) and 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl) piperidine hydrochloride (85
mg, 0.32 mmol) were combined in a manner analogous to the preparation of 4-
10 Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-
quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-
cyclohepta[e]inden-8-one. Title compound was obtained as pale yellow solid in 58%
yield. High resolution MS m/e (M+H)⁺ = 589.1932.

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EXAMPLE 76

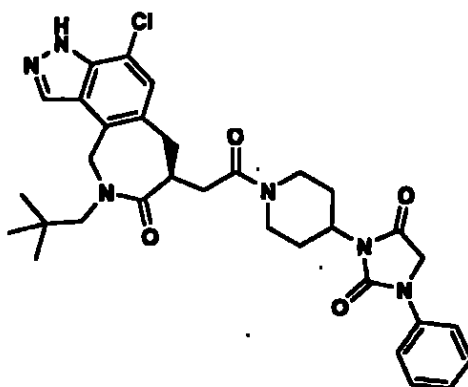


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1-[[7-(S)-4-chloro-9-(2,2-Dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-4-(3,4-dihydro-2,2-dioxo-4-oxo-1H-2,1-benzothiazin-3-yl)piperidine. 2,2-Dioxo-3-piperidin-4-yl-2,3-dihydro-1H-2,1-benzothiazin-4-one (86 mg, 0.27 mmol) and [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (85 mg, 0.23 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as tan solid in 37% yield.

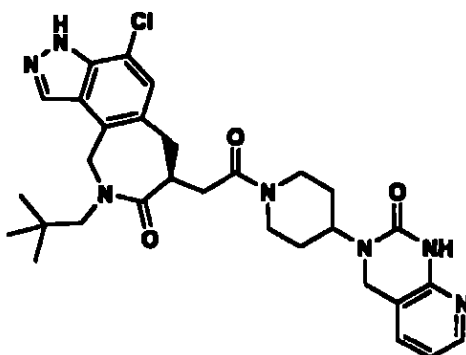
High resolution MS m/e $(M+H)^+ = 626.2217$.

EXAMPLE 77



1-[[7-(S)-4-chloro-9-(2,2-Dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-4-(2,5-dioxo-3-phenyl-1-imidazolidinyl)piperidine. 5-Phenyl-3-(piperidin-4-yl)imidazolidine-2,4-dione hydrochloride (46 mg, 0.16 mmol) and [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (46 mg, 0.13 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as yellow solid in 67% yield. High resolution MS m/e $(M+H)^+ = 605.2645$.

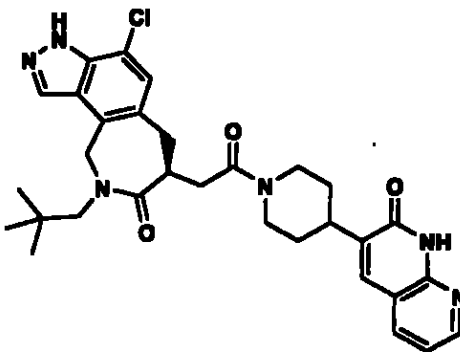
EXAMPLE 78



1-[[7-(S)-4-chloro-9-(2,2-Dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-4-(1,4-dihydro-2-oxopyrido[2,3-d]pyrimidin-3(2H)-yl)-piperidine. 3-(Piperidin-4-yl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one dihydrochloride (64 mg, 0.21 mmol) and [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (63 mg, 0.17 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 41% yield. High resolution MS m/e (M+H)⁺ = 578.2630.

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EXAMPLE 79



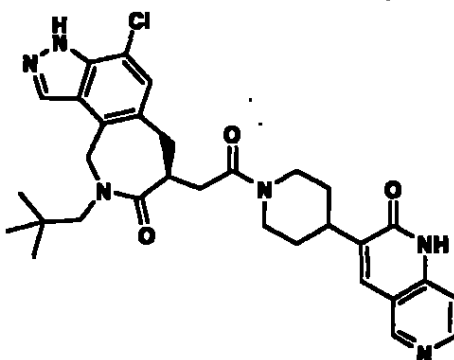
1-[[7(S)-4-chloro-9-(2,2-dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-4-(1,2-dihydro-2-oxo-1,8-naphthyridin-3-yl)-piperidine. 3-(piperidin-4-yl)-1,8-naphthyridin-2(1H)-one (57 mg, 0.19 mmol) and

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[4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (60 mg, 0.16 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 64% yield. High resolution MS m/e (M+H)⁺ = 575.2538.

EXAMPLE 80



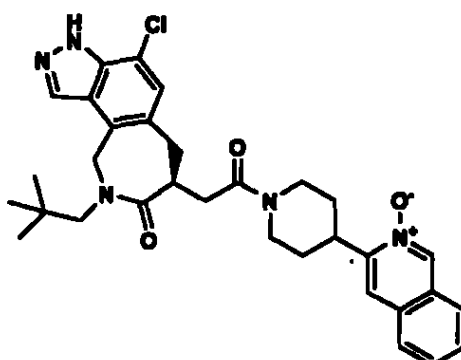
10

1-[[[(7S)-4-chloro-9-(2,2-dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-4-(1,2-dihydro-2-oxo-1,6-naphthyridin-3-yl)-piperidine. 3-(piperidin-4-yl)-1,6-naphthyridin-2(1H)-one (89 mg, 0.29 mmol) and [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (95 mg, 0.26 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 27% yield. High resolution MS m/e (M+H)⁺ = 575.2538.

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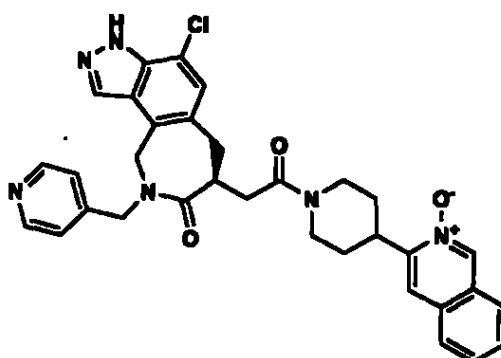
EXAMPLE 81



5 *(S)*-1-[[[(7*S*)-4-chloro-9-(2,2-dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-*e*]indazol-7-yl]acetyl]-4-(2-oxido-3-isoquinoliny)]-piperidine. Title compound was prepared from 3-piperidin-4-ylisoquinoline hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*S*)-(2-oxo-2-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-ethyl)-6,7,9,10-tetrahydro-3*H*-2,3,9-triaza-cyclohepta[*e*]inden-8-one. Material was obtained as light

10 brown solid. MS (ESI) 574 (*M*+*H*) ; *R*_f= 2.39 (3 min gradient run).

EXAMPLE 82



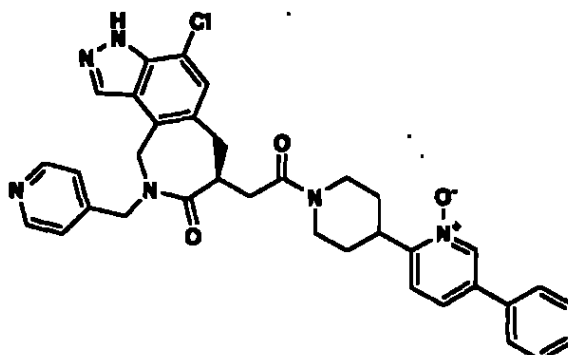
15 *(S)*-1-[[[(7*S*)-4-chloro-3,6,7,8,9,10-hexahydro-8-oxo-9-(4-pyridinylmethyl)azepino[3,4-*e*]indazol-7-yl]acetyl]-4-(2-oxido-3-isoquinoliny)]-piperidine. Title compound was prepared from 3-piperidin-4-ylisoquinoline

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hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as white solid. MS (ESI) 595 (M+H) ; R_f= 1.73 (3 min gradient run).

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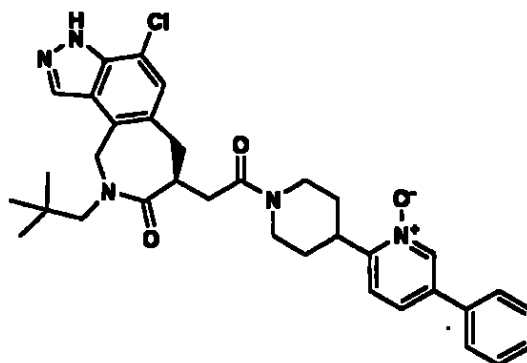
EXAMPLE 83



- (S)-1-[[[(7S)-4-chloro-3,6,7,8,9,10-hexahydro-8-oxo-9-(4-pyridinylmethyl)azepino[3,4-e]indazol-7-yl]acetyl]-4-(1-oxido-5-phenyl-2-pyridinyl)-piperidine. Title compound was prepared from 5-phenyl-2-piperidin-4-ylpyridine 1-oxide hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as white solid. MS (ESI) 621 (M+H) ; R_f= 1.87 (3 min gradient run).

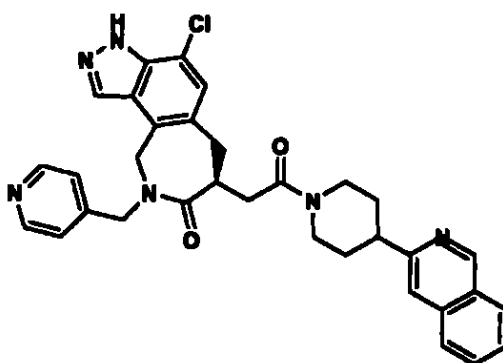
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EXAMPLE 84



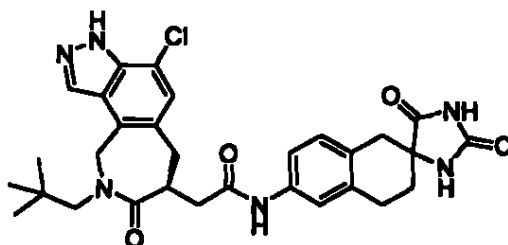
- 5 *(S)*-1-[[[(7*S*)-4-chloro-9-(2,2-dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-*e*]indazol-7-yl]acetyl]-4-(1-oxido-5-phenyl-2-pyridinyl)-piperidine. Title compound was prepared from 2-(piperidin-4-yl)-1,2-dihydroisoquinolin-3(4*H*)-one hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*S*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3*H*-2,3,9-triaza-cyclohepta[*e*]inden-8-one.
- 10 Material was obtained as white solid. MS (ESI) 600 (*M*+*H*) ; *R*_f= 2.51 (3 min gradient run).

EXAMPLE 85



(S)-4-chloro-7-(2-(4-(isoquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-9-(pyridin-4-ylmethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. Title compound was prepared from 3-(piperidin-4-yl)isoquinoline hydrochloride in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-
 5 (2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as white solid. MS (ESI) 579 (M+H) ; R_f = 1.43 (3 min gradient run).

EXAMPLE 86

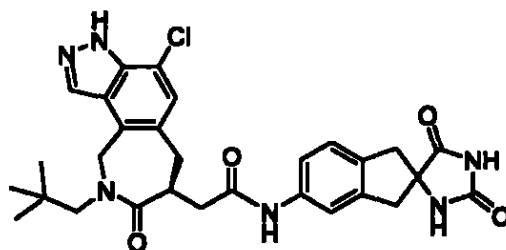


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(+/-)-1-[[[(7S)-4-chloro-9-(2,2-dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-Amino-3',4'-dihydro-1'H-spiro[imidazolidine-4,2'-naphthalene]-2,5-dione. Title compound was prepared from (+/-)-6'-Amino-
 15 3',4'-dihydro-1'H-spiro[imidazolidine-4,2'-naphthalene]-2,5-dione in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as a white solid. ¹H-NMR (CD₃OD, 400 MHz) δ 0.78(s, 9H), 1.80-1.89 (m, 1H), 2.07-2.15(m, 1H),
 20 2.53 (dd, J= 15.61,5.04 Hz,1H), 2.76 (d, J=16.87 Hz, 1H), 2.92-3.18 (m, 8H), 3.62-3.70 (m,1H), 3.90-4.07 (m, 1H), 4.64 (d, J=17.37 Hz, 1H), 5.47 (d, J=17.37 Hz,1H), 7.02 (d, J=8.31 Hz, 1H), 7.21(s, 1H), 7.22-7.30 (m, 1H), 7.35-7.45 (m 1H), 8.22 (d, J= 2.52 Hz,1H); Mass spec. 577.25(MH⁺), Calc. for C₃₀H₃₃ClN₆O₄ 576.23; R_f=2.15 (4 min gradient run)

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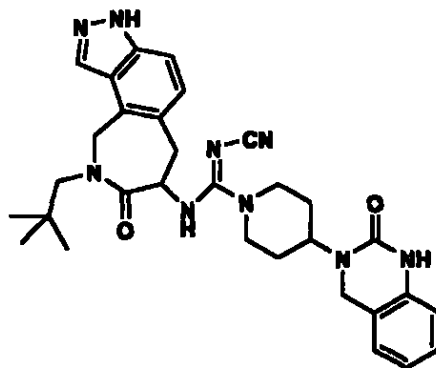
EXAMPLE 87



(+/-)-1-[[[(7S)-4-chloro-9-(2,2-dimethylpropyl)-3,6,7,8,9,10-hexahydro-8-oxoazepino[3,4-e]indazol-7-yl]acetyl]-Amino-spiro[imidazolidine-4,2'-indane]-2,5-dione. Title compound was prepared from (+/-)-5'-Amino-spiro[imidazolidine-4,2'-indane]-2,5-dione in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Material was obtained as a white solid. ¹H-NMR (CD₃OD, 400 MHz) δ 0.79 (s, 9H), 2.53 (dd, J=15.61, 5.04 Hz, 1H), 2.92-3.3 (m, 6H), 3.46 (dd, J= 16.49, 9.44 Hz, 2H), 3.66 (d, J=13.60 Hz, 1H), 3.98-4.08 (m, 1H), 4.63 (d, J=17.37 Hz, 1H), 5.47 (d, J=16.87 Hz, 1H), 7.15 (d, J=8.06 Hz, 1H), 7.21 (s, 1H), 7.25-7.35 (m, 1H), 7.50 (d, J=16.12 Hz, 1H), 8.23 (s, 1H); Mass spec. 563.24 (MH⁺), Calc. for C₂₉H₃₁ClN₆O₄ 562.21; R_f=2.15 (4 min gradient run)

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EXAMPLE 88

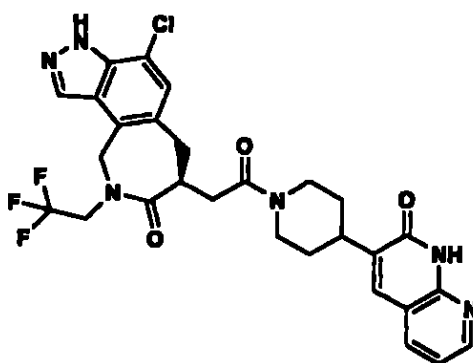


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(E, Z)-N'-cyano-N-(9-neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)-4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidine-1-carboxamidine. To a solution of 7-amino-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one, methanesulfonate (300 mg, 0.78 mmol) in CH₂Cl₂ (20 mL) was added diphenyl N-cyanocarbonimidate (221 mg, 0.93 mmol) followed by triethylamine (1 mL). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then washed with aqueous sodium hydrogencarbonate to give (E, Z)-1-cyano-3-(9-neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)-2-phenylisourea in 95% yield. MS (ESI) 431 (M+H)⁺; R_t = 2.22 (3 min gradient run).

To a solution of (E, Z)-1-cyano-3-(9-neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)-2-phenylisourea (301 mg, 0.7 mmol) in isopropanol (25 mL) was added 3-(piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one (323 mg, 1.4 mmol) and the reaction mixture was refluxed for 72 h. The solvent was evaporated and the crude product was purified by flash chromatography to give (E, Z)-N'-cyano-N-(9-neopentyl-8-oxo-3,6,7,8,9,10-hexahydroazepino[3,4-e]indazol-7-yl)-4-(2-oxo-1,2-dihydroquinazolin-3(4H)-yl)piperidine-1-carboxamidine (130 mg) in 33% yield. MS (ESI) 568 (M+H)⁺; R_t = 2.19 (3 min gradient run).

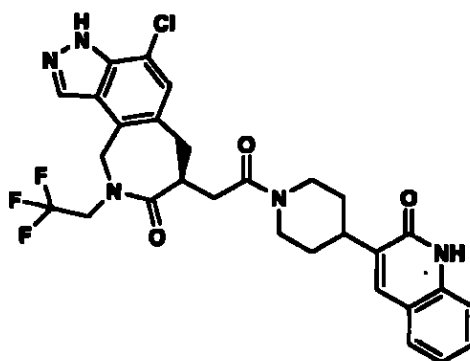
EXAMPLE 89



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(S)-4-chloro-7-(2-oxo-2-(4-(2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)piperidin-1-yl)ethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Chloro-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (120 mg, 0.32 mmol) and 3-(piperidin-4-yl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one dihydrochloride (120 mg, 0.40 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as pale yellow solid in 43% yield. High resolution MS m/e (M+H)⁺ = 587.1785.

EXAMPLE 90

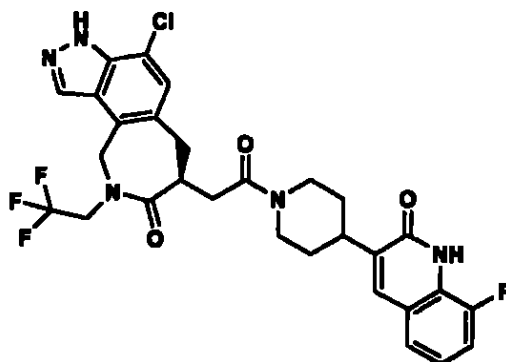


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(S)-4-chloro-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Chloro-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (115 mg, 0.31 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (96 mg, 0.36 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 65% yield. High resolution MS m/e (M+H)⁺ = 586.1811.

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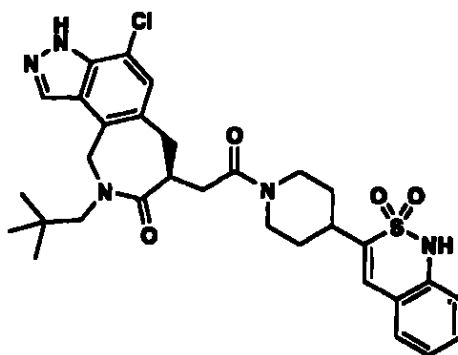
EXAMPLE 91



5 *(S)*-4-chloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Chloro-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(*S*)-cyclohepta[e]inden-7-yl]acetic acid (115 mg, 0.31 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (96 mg, 0.36 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*R*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 55% yield. High resolution MS m/e ($M+H$)⁺ = 604.1760.

15

EXAMPLE 92

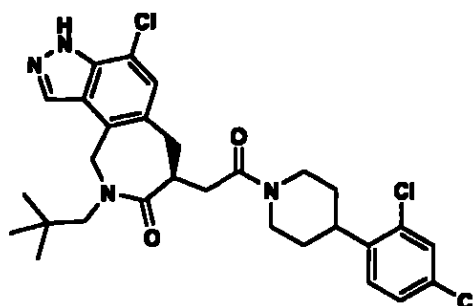


3-Piperidin-4-yl-1H-2,1-benzothiazine 2,2-dioxide *p*-toluenesulfonate (55 mg, 0.13 mmol) and [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-

227 227

2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (40 mg, 0.11 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title
5 compound was obtained as tan solid in 57% yield. High resolution MS m/e (M+H)⁺= 610.2268.

EXAMPLE 93



10

(S)-4-chloro-7-(2-(4-(2,4-dichlorophenyl)piperidin-1-yl)-2-oxoethyl)-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. 4-(2,4-Dichlorophenyl)-piperidine (32 mg, 0.08 mmol) and [4-chloro-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic
15 acid (25 mg, 0.07 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as off-white solid in 40% yield. High resolution MS m/e (M+H)⁺= 575.1747.

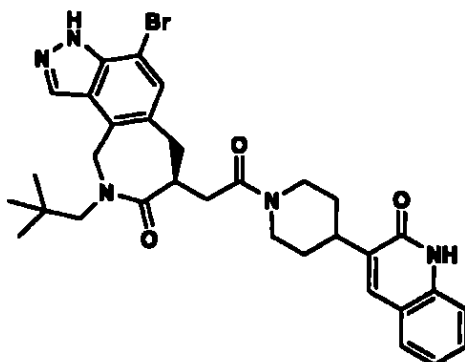
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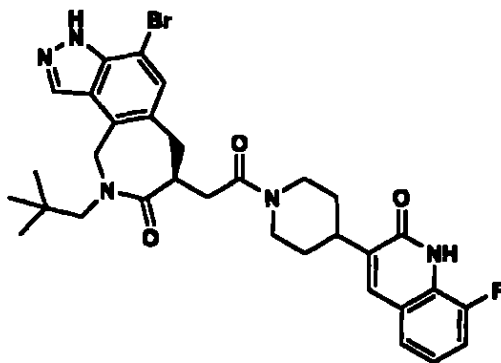
228 228

EXAMPLE 94



5 *(S)*-4-bromo-9-neopentyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid (56 mg, 0.14 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (35 mg, 0.15 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 61% yield. High resolution MS m/e ($M+H$)⁺ = 618.2064.

EXAMPLE 95



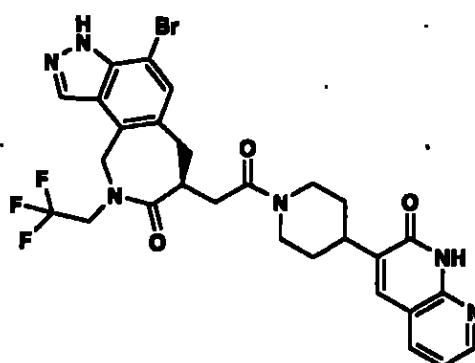
15

(S)-4-bromo-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-

232
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Bromo-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid (65 mg, 0.16 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (45 mg, 0.16 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 57% yield. High resolution MS m/e (M+H)⁺= 636.1973.

EXAMPLE 96



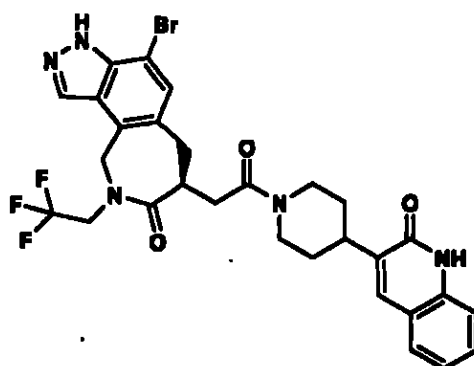
10

(S)-4-bromo-7-(2-oxo-2-(4-(2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)piperidin-1-yl)ethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (69 mg, 0.16 mmol) and 3-(piperidin-4-yl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one dihydrochloride (120 mg, 0.40 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 55% yield. High resolution MS m/e (M+H)⁺= 631.1279.

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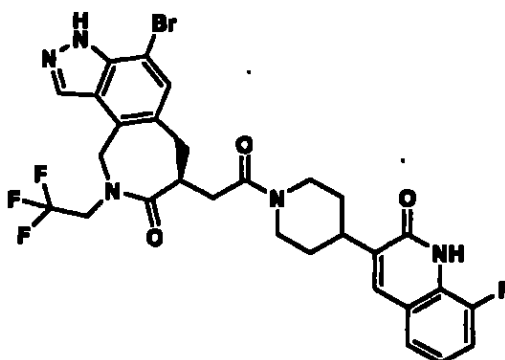
237/230

EXAMPLE 97



5 *(S)*-4-bromo-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-*(S)*-cyclohepta[e]inden-7-yl]acetic acid (73 mg, 0.17 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (50 mg, 0.19 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(*R*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained
 10 as yellow solid in 62% yield. High resolution MS m/e $(M+H)^+ = 630.1315$.

EXAMPLE 98

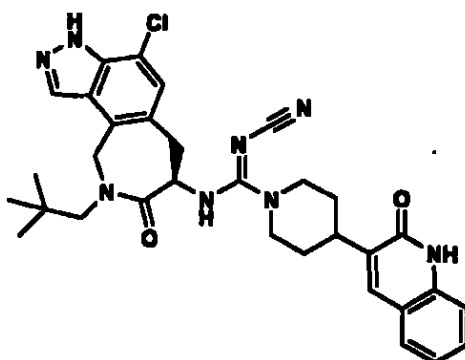


15

(S)-4-bromo-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Bromo-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-

25 triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (80 mg, 0.19 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (61 mg, 0.22 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as off-white solid in 64% yield. High resolution MS m/e (M+H)⁺ = 648.1217.

EXAMPLE 99

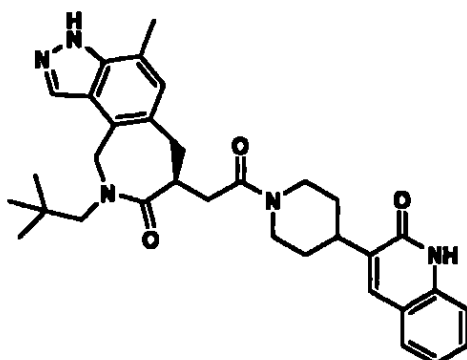


10

(R)-7-Amino-4-chloro-9-(2,2-dimethyl-propyl)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one (108 mg, 0.34 mmol) was dissolved in *N,N*-dimethylformamide (1.8 mL). *N,N*-Diisopropylethylamine (200 μ L, 1.1 mmol) was added to the mixture followed by diphenyl cyanocarbonimidate (86 mg, 0.36 mmol). Mixture was held at room temperature with stirring for 1.25 hours. 3-(Piperidin-4-yl)quinolin-2(1H)-one hydrochloride (100 mg, 0.38 mmol) was added to the mixture with *N,N*-dimethylformamide (2.0 mL). Reaction was warmed to 110°C and held with stirring for 5.5 hours. Mixture was cooled to 80°C and held with stirring for 20 hours. Reaction was quenched with 1:1 acetonitrile:water. Material was purified by preparatory HPLC (C18, acetonitrile-water-ammonium acetate). Major peak was isolated. Acetonitrile was removed from the proper fractions *in vacuo*. Material was extracted from the remaining aqueous twice with ethyl acetate. Organic phase was dried (magnesium sulfate), filtered and concentrated to dryness. Title compound was obtained as pale yellow solid in 40% yield. High resolution MS m/e (M+H)⁺ = 599.2622.

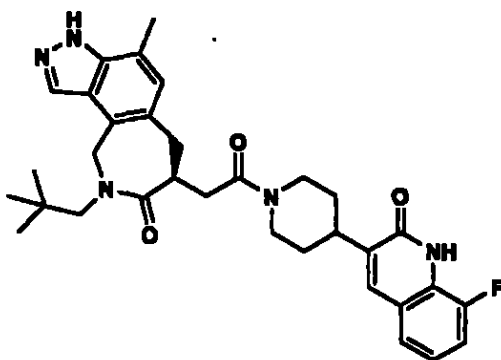
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EXAMPLE 100



(S)-4-methyl-9-neopentyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Methyl-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid (37 mg, 0.11 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (32 mg, 0.12 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 55% yield. High resolution MS m/e $(M+H)^+ = 554.3121$.

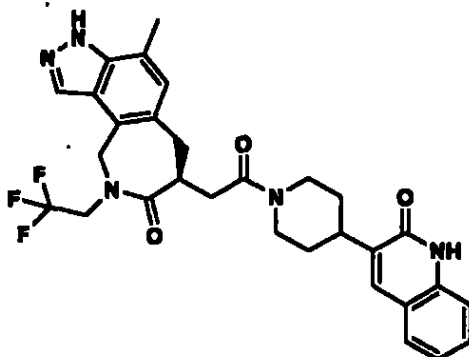
EXAMPLE 101



(S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-4-methyl-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Methyl-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid (60 mg, 0.18 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (60 mg, 0.21 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 48% yield. High resolution MS m/e (M+H)⁺ = 572.3021.

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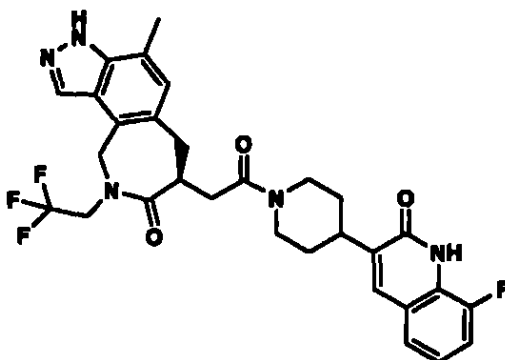
EXAMPLE 102



(S)-4-methyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Methyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (65 mg, 0.18 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (55 mg, 0.21 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 58% yield. High resolution MS m/e (M+H)⁺ = 566.2364

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EXAMPLE 103



(S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-4-methyl-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Methyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (65 mg, 0.18 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (62 mg, 0.22 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 53% yield. High resolution MS m/e (M+H)⁺ = 584.2302.

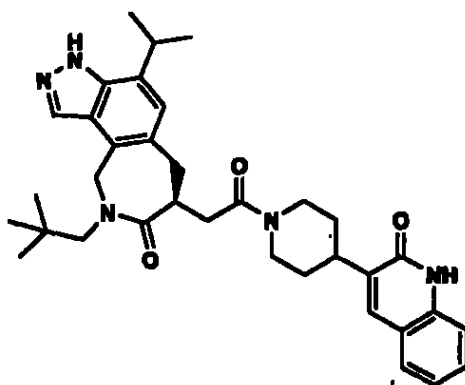
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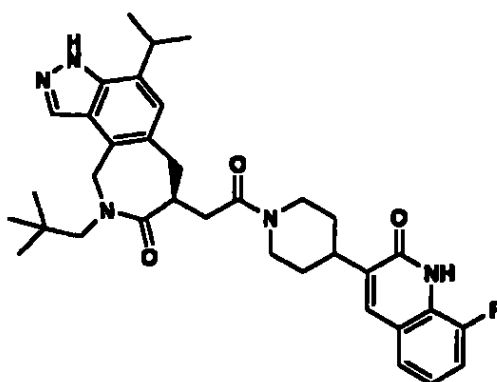
231

EXAMPLE 104



(S)-4-isopropyl-9-neopentyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Isopropyl-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid (42 mg, 0.11 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (36 mg, 0.14 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 33% yield. High resolution MS m/e ($M+H$)⁺ = 582.3466.

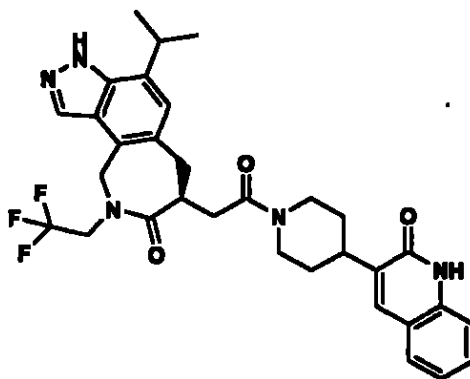
EXAMPLE 105



1.27
236

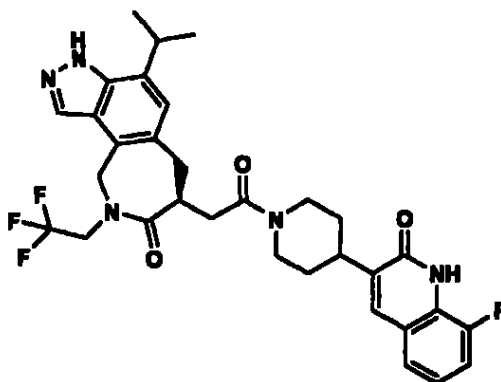
(S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-4-isopropyl-9-neopentyl-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Isopropyl-9-(2,2-dimethyl-propyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]-acetic acid (80 mg, 0.22 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (70 mg, 0.25 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 60% yield. High resolution MS m/e (M+H)⁺ = 600.3372.

EXAMPLE 106



(S)-4-isopropyl-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Isopropyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (50 mg, 0.13 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (41 mg, 0.15 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 62% yield. High resolution MS m/e (M+H)⁺ = 594.2682.

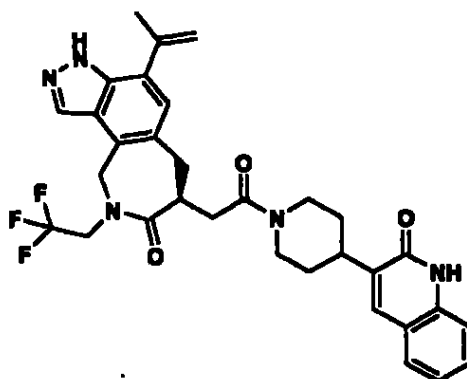
EXAMPLE 107



5 *(S)*-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-4-isopropyl-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-*e*]indazol-8(3*H*)-one. [4-Isopropyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(*S*)-cyclohepta[*e*]inden-7-yl]acetic acid (50 mg, 0.13 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1*H*)-one hydrochloride (43 mg, 0.15 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-
 10 dimethyl-propyl)-7-(*R*)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3*H*-2,3,9-triaza-cyclohepta[*e*]inden-8-one. Title compound was obtained as white solid in 66% yield. High-resolution MS *m/e* (*M*+*H*)⁺ = 612.2578.

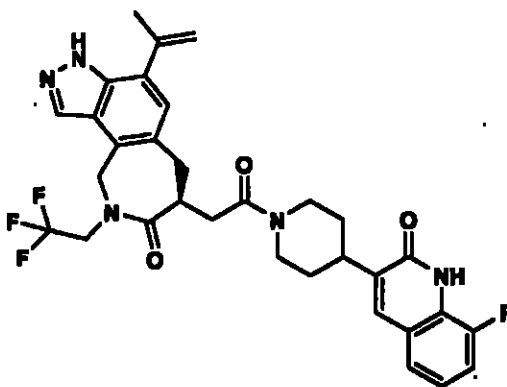
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EXAMPLE 108



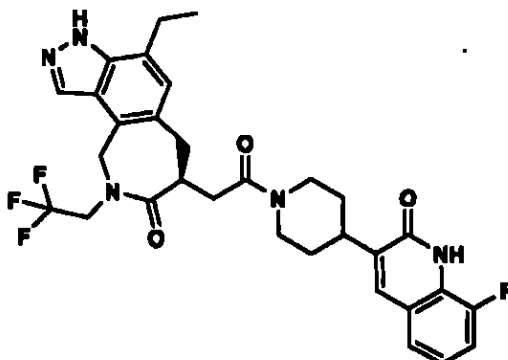
5 (S)-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-4-(prop-1-en-2-yl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Isopropenyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (47 mg, 0.12 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (42 mg, 0.16 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 55% yield. High resolution MS m/e
 10 (M+H)⁺= 592.2544.

EXAMPLE 109



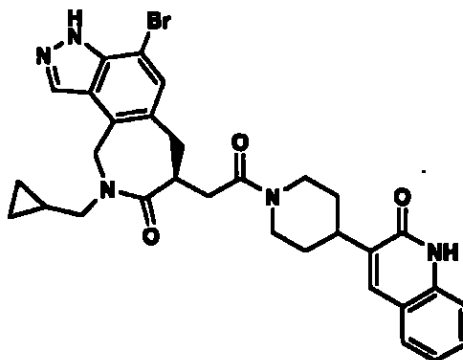
15 (S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-4-(prop-1-en-2-yl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [4-Isopropenyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-cyclohepta[e]inden-7-yl]acetic acid (47 mg, 0.12 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (44 mg, 0.16
 20 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 60% yield. High resolution MS m/e
 25 (M+H)⁺= 610.2457.

EXAMPLE 110



(S)-4-ethyl-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-
 2-oxoethyl)-9-(2,2,2-trifluoroethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-
 one. [4-Ethyl-3,6,7,8,9,10-hexahydro-8-oxo-9-(2,2,2-trifluoroethyl)-2,3,9-triaza-(S)-
 cyclohepta[e]inden-7-yl]acetic acid (25 mg, 0.07 mmol) and 8-fluoro-3-(piperidin-4-
 yl)quinolin-2(1H)-one hydrochloride (24 mg, 0.09 mmol) were combined in a
 manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-
 oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-
 tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained
 as white solid in 49% yield. High resolution MS m/e $(M+H)^+ = 598.2465$.

EXAMPLE 111



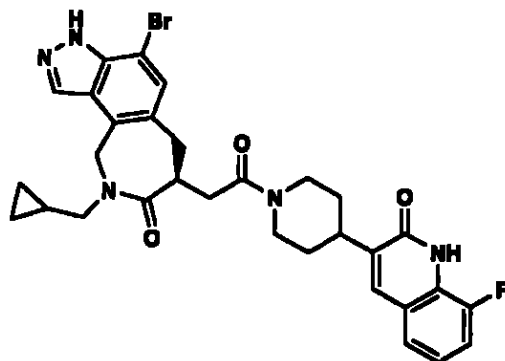
15

(S)-4-bromo-9-(cyclopropylmethyl)-7-(2-oxo-2-(4-(2-oxo-1,2-
 dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-

47
240

8(3H)-one. ((S)-4-Bromo-9-cyclopropylmethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl)-acetic acid (90 mg, 0.23 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (80 mg, 0.30 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 32% yield. High resolution MS m/e (M+H)⁺ = 602.1776.

EXAMPLE 112

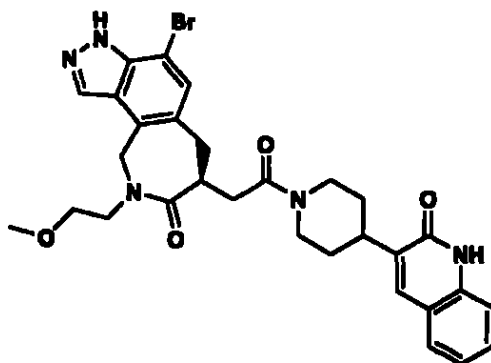


10

(S)-4-bromo-9-(cyclopropylmethyl)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. ((S)-4-Bromo-9-cyclopropylmethyl-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triaza-cyclohept[e]inden-7-yl)-acetic acid (90 mg, 0.23 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (80 mg, 0.28 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 56% yield. High resolution MS m/e (M+H)⁺ = 620.1665.

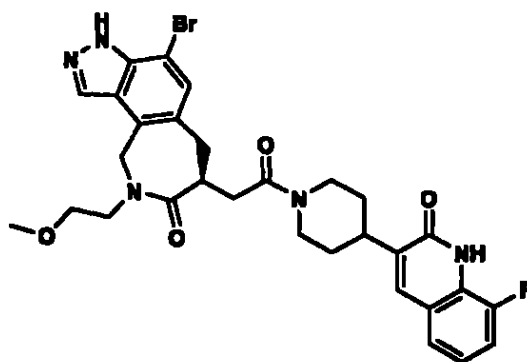
25

EXAMPLE 113



5 *(S)*-4-bromo-9-(2-methoxyethyl)-7-(2-oxo-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)ethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [(*S*)-4-Bromo-9-(2-methoxy-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triazacyclohept[e]inden-7-yl]-acetic acid (100 mg, 0.25 mmol) and 3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (80 mg, 0.30 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one. Title compound was obtained
 10 as white solid in 35% yield. High resolution MS m/e ($M+H$)⁺ = 606.1730.

EXAMPLE 114



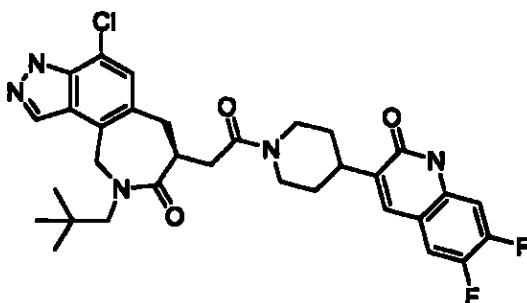
15

(S)-4-bromo-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-yl)-2-oxoethyl)-9-(2-methoxyethyl)-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-one. [(*S*)-4-Bromo-9-(2-methoxy-ethyl)-8-oxo-3,6,7,8,9,10-hexahydro-2,3,9-triazacyclohepta[e]inden-7-yl]-acetic acid (100 mg, 0.25 mmol) and 3-(piperidin-4-yl)-8-fluoroquinolin-2(1H)-one hydrochloride (80 mg, 0.30 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triazacyclohepta[e]inden-8-one. Title compound was obtained
 15 as white solid in 35% yield. High resolution MS m/e ($M+H$)⁺ = 606.1730.

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cyclohept[e]inden-7-yl]-acetic acid (100 mg, 0.25 mmol) and 8-fluoro-3-(piperidin-4-yl)quinolin-2(1H)-one hydrochloride (85 mg, 0.30 mmol) were combined in a manner analogous to the preparation of 4-Chloro-9-(2,2-dimethyl-propyl)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-6,7,9,10-tetrahydro-3H-2,3,9-triaza-cyclohepta[e]inden-8-one. Title compound was obtained as white solid in 56% yield. High resolution MS m/e ($M+H$)⁺ = 624.1631.

EXAMPLE 115

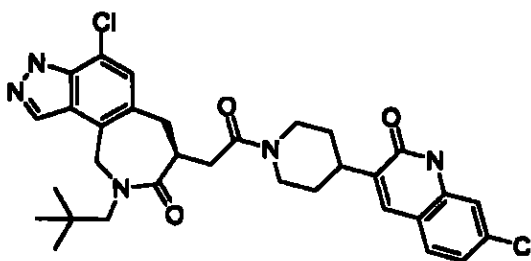


10

¹H NMR (400 MHz, MeOD) δ ppm 0.79 (s, 9H), 1.45-1.52 (m, 2 H), 1.83-2.02 (m, 2 H), 2.37-2.42 (m, 1 H), 2.68- 2.76 (m, 1 H), 3.04- 3.17 (m, 4 H), 3.64 - 3.68 (m, 2 H), 3.92- 4.06 (m, 1 H), 4.18- 4.25 (m, 1 H), 4.63- 4.74 (m, 3 H), 5.46- 5.54 (m, 1 H), 7.23 (s, 1 H), 7.12-7.23(m, 1H), 7.53 - 7.59 (m, 1 H), 7.75 (s, 1 H), 8.23 (s, 1 H); Mass spec. 610.25 (MH⁺), Calc. for C₃₂H₃₄ClF₂N₅O₃ 609.23

15

EXAMPLE 116



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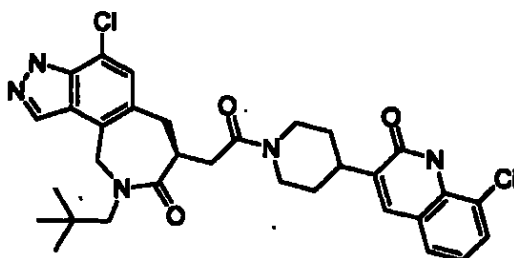
¹H NMR (400 MHz, MeOD) δ ppm 0.80 (s, 9 H), 1.47-1.60 (m, 2H), 1.75-1.80 (m, 1 H), 1.88-2.03 (m, 2H), 2.32-2.48 (m, 1 H), 2.68-2.78 (m, 1 H), 3.07- 3.18 (m, 4 H), 3.66-3.68 (m, 1 H), 3.96-4.05 (m, 1H), 4.13-4.24 (m, 1H), 4.53 (s, 2 H),

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4.62-4.72 (m, 2 H), 5.45-5.60 (m, 1 H), 7.17 - 7.24 (m, 1 H), 7.33 (s, 1 H), 7.61 (d, $J=8.31$ Hz, 1 H), 7.75 (d, $J=14.86$ Hz, 1 H), 8.23 (s, 1 H); Mass spec. 608.23 (MH⁺),
Calc. for C₃₂H₃₅Cl₂N₅O₃ 607.21

5

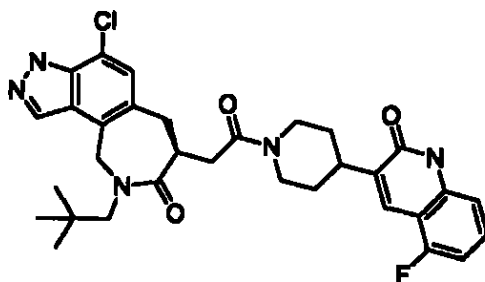
EXAMPLE 117



¹H NMR (400 MHz, MeOD) δ ppm 0.79 (s, 9 H), 1.46-1.70 (m, 2 H), 1.73 - 1.85 (m, 1 H), 1.90 - 2.08 (m, 2 H), 2.36 - 2.51 (m, 1 H), 2.73 - 2.81 (m, 1 H), 2.97 - 2.06 (s, 1 H), 3.09 - 3.20 (m, 4 H), 3.60 - 3.68 (m, 1 H), 3.95 - 4.08 (s, 1 H), 4.21 - 4.27 (m, 1 H), 4.66 - 4.73 (m, 2 H), 5.46 - 5.54 (m, 1 H), 7.15 - 7.23 (m, 2 H), 7.55 - 7.62 (m, 2 H), 7.79 (d, $J=15.86$ Hz, 1 H), 8.23 (s, 1 H); Mass spec. 608.26 (MH⁺),
Calc. for C₃₂H₃₅Cl₂N₅O₃ 607.21.

15

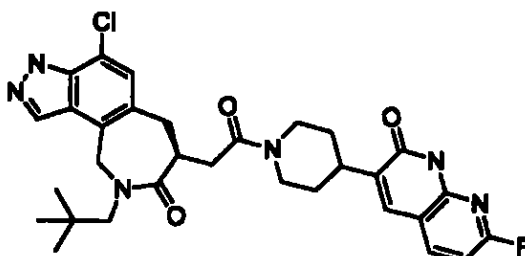
EXAMPLE 118



¹H NMR (400 MHz, MeOD) δ ppm 0.80 (s, 9 H), 1.46 - 1.56 (m, 1 H), 1.57 - 1.74 (m, 1 H), 1.80 - 2.08 (m, 2 H), 2.35 - 2.50 (m, 1 H), 2.69 - 2.80 (m, 1 H), 2.89 - 3.04 (m, 1 H), 3.09 - 3.20 (m, 4 H), 3.63 (dd, $J=19.14, 13.85$ Hz, 1 H), 3.95 - 4.07 (m, 1 H), 4.20 - 4.32 (m, 1 H), 4.60 - 4.72 (m, 3 H), 5.47 (d, $J=19.14$ Hz, 1 H), 6.88 - 6.96 (m, 1 H), 7.12 (t, $J=8.94$ Hz, 1 H), 7.22 (s, 1 H), 7.39 - 7.47 (m, 1 H), 7.88 (d,

$J=21.66$ Hz, 1 H), 8.23 (s, 1 H); Mass spec. 592.28 (MH^+), Calc. for $C_{32}H_{35}ClFN_5O_3$ 591.24.

EXAMPLE 119

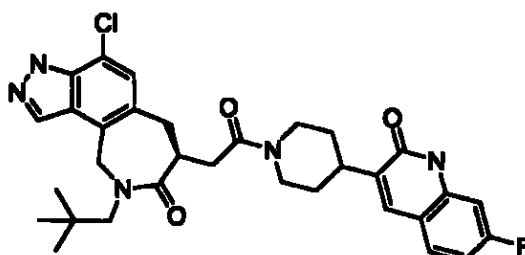


5

^1H NMR (400 MHz, MeOD) δ ppm 0.79 (s, 9 H), 1.45-1.66 (m, 2 H), 1.70-1.83 (m, 1 H), 1.90-2.07 (m, 2 H), 2.38 - 2.50 (m, 1 H), 2.69 - 2.80 (m, 1 H), 2.92-3.18 (m, 4 H), 3.60 - 3.69 (m, 1 H), 3.95- 4.07 (m, 1 H), 4.18-4.32(m, 1 H), 4.56-4.69 (m, 3 H), 5.43-5.58 (m, 1 H), 6.41 (s, 1 H), 7.23 (s, 1 H), 7.64-7.70 (m, 1 H), 7.80-7.84(m,1H), 8.23 (s, 1 H); Mass spec. 593.25 (MH^+), Calc. for $C_{31}H_{34}ClFN_6O_3$ 592.24.

10

EXAMPLE 120



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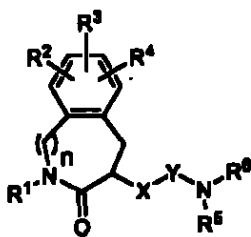
^1H NMR (400 MHz, MeOD) δ ppm 0.79 (s, 9 H), 1.45-1.68 (m, 2 H), 1.71-1.82 (m, 1 H), 1.90-2.07 (m, 2 H), 2.37 - 2.49 (m, 1 H), 2.68 - 2.79 (m, 1 H), 2.92-3.18 (m, 4 H), 3.59 - 3.68 (m, 1 H), 3.94- 4.06 (m, 1 H), 4.17-4.30(m, 1 H), 4.55-4.68 (m, 3 H), 5.43-5.58 (m, 1 H) 6.95 - 7.04 (m, 2 H) 7.22 (s, 1 H) 7.61 - 7.68 (m, 1 H) 7.75 (d, $J=14.60$ Hz, 1 H) 8.23 (s, 1 H); Mass spec. 592.28 (MH^+), Calc. for $C_{32}H_{35}ClFN_5O_3$ 592.24.

20

CLAIMS

We claim:

1. A compound of Formula I



I

wherein:

10

R¹ is C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkenyl, C₁₋₆(C₃₋₇cycloalkyl)alkyl, C₁₋₆haloalkyl, C₁₋₆(C₁₋₆alkoxy)alkyl, C₁₋₆(Ar¹)alkyl, C₁₋₆(NR⁷R⁸)alkyl, N-(R⁶)-pyrrolidinyl or N-(R⁶)-piperidinyl;

- 15 R² is hydrogen, halo, hydroxy, C₁₋₆alkyl, C₂₋₆alkenyl, benzyloxy, or NR⁷R⁸;

R³ is hydrogen, hydroxy, halo, C₁₋₆alkyl, or C₂₋₆alkenyl;

or R² and R³ taken together are CHNNR⁵;

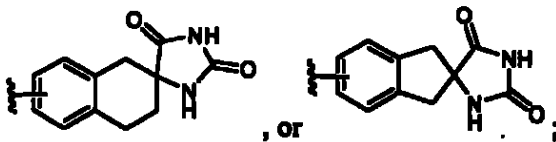
20

R⁴ is hydrogen, halo or C₁₋₆alkyl, or C₂₋₆alkenyl,;

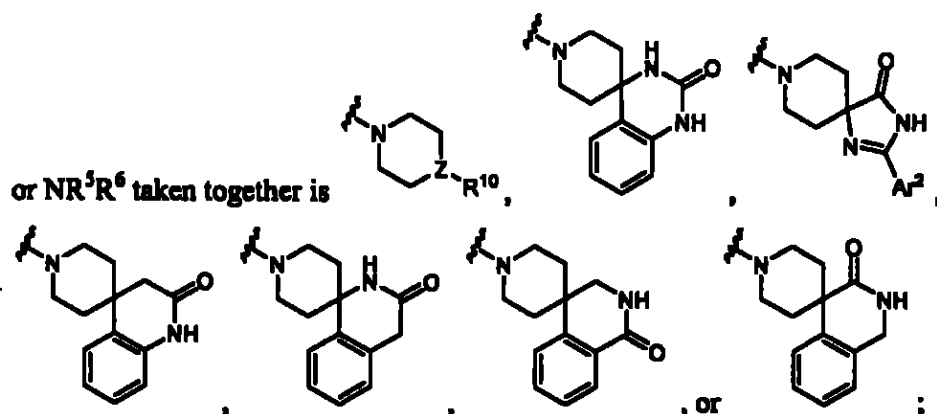
R⁵ is hydrogen or C₁₋₆alkyl;

25

R⁶ is hydrogen, C₁₋₆alkyl,



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R^7 is hydrogen or C_{1-6} alkyl;

5

R^8 is hydrogen or C_{1-6} alkyl; or

NR^7R^8 taken together is selected from the group consisting of pyrrolidinyl, piperidinyl, $\text{N-(R}^9\text{)-piperazinyl}$, morpholinyl, and thiomorpholinyl;

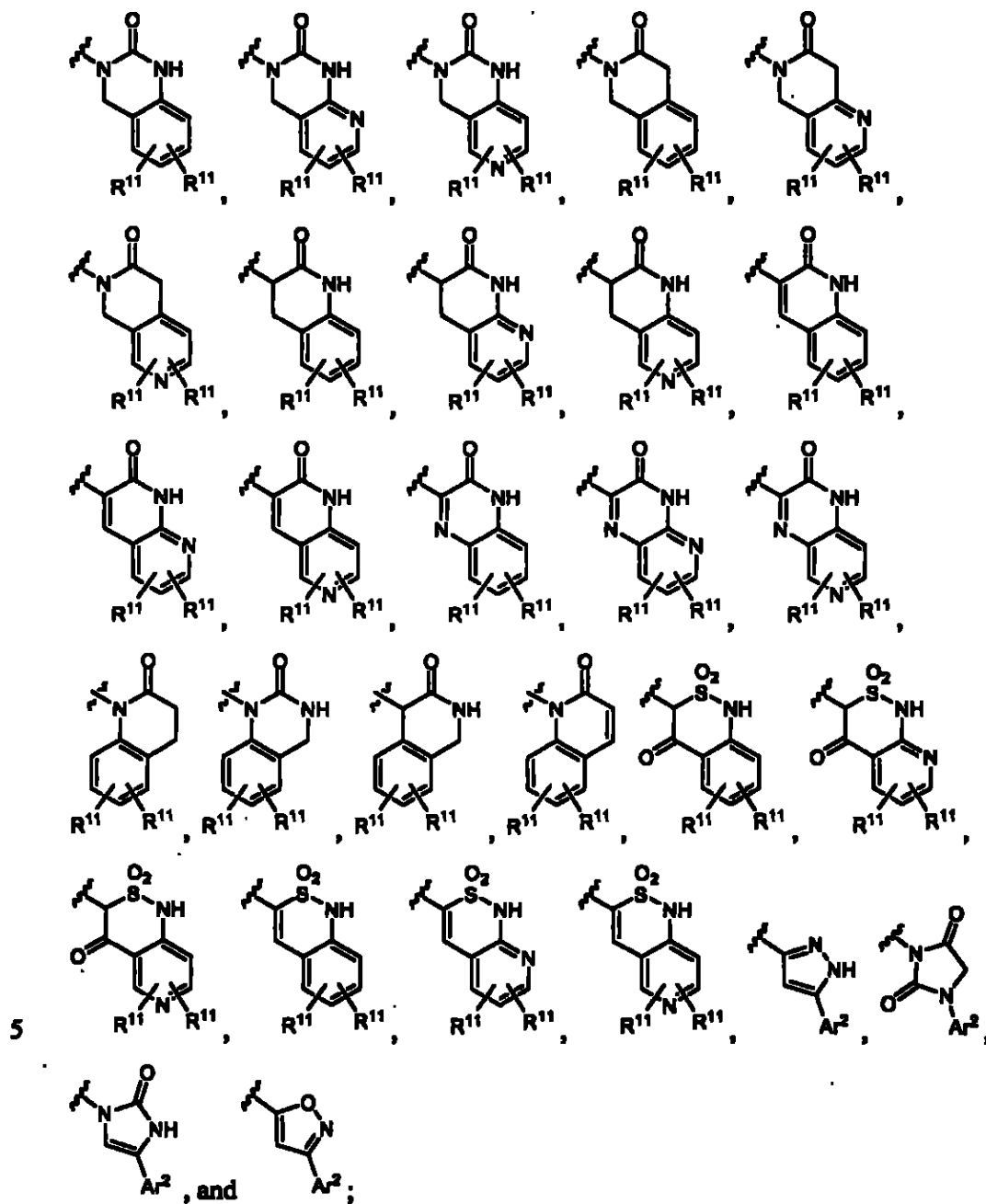
10

R^9 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, or C_{1-6} alkoxycarbonyl;

R^{10} is phenyl, naphthyl, pyridinyl, pyridinyl N-oxide, quinolinyl, quinolinyl N-oxide, isoquinolinyl, or isoquinolinyl N-oxide, and is substituted with 0-2 substituents selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, and phenyl;

15

or R^{10} is selected from the group consisting of



each R¹¹ is independently hydrogen, halo, C₁₋₆alkyl, C₁₋₆haloalkyl, or C₁₋₆alkoxy;

- 10 Ar¹ is phenyl, naphthyl, pyridinyl, or imidazolyl, and is substituted with 0-2 substituents selected from the group consisting of halo, C₁₋₆alkyl, and C₁₋₆haloalkyl;

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Ar^2 is phenyl, naphthyl, or pyridinyl, and is substituted with 0-2 substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

X-Y is aminocarbonyl, oxycarbonyl, methylenecarbonyl, ethylene, or
5 amino(cyano)iminomethyl;

Z is N or CH; and

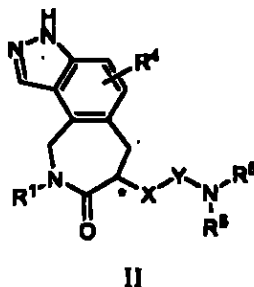
n is 0 or 1;

10

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of Formula II

15



where

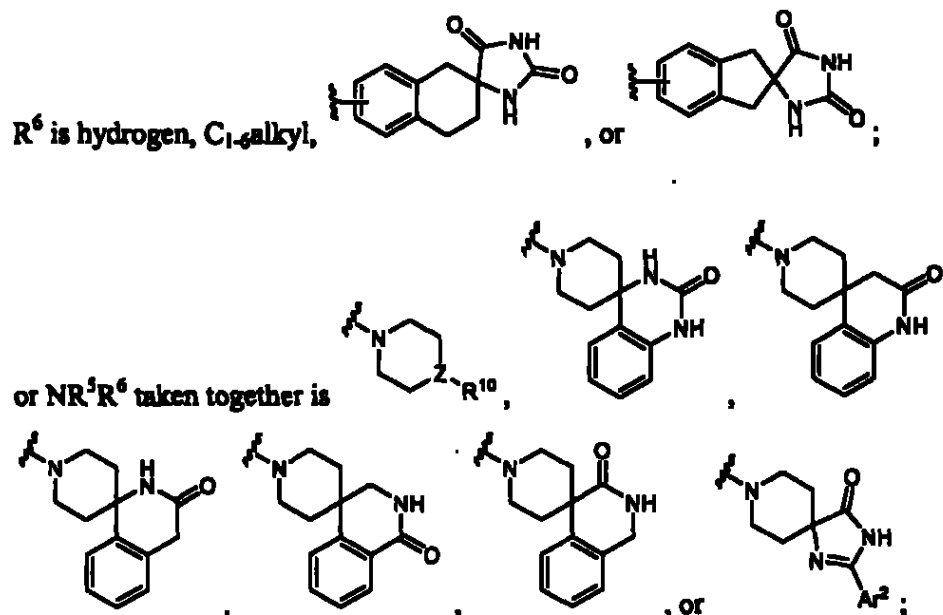
20

R^1 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{1-6} (C_{3-7} cycloalkyl)alkyl, C_{1-6} haloalkyl, C_{1-6} (C_{1-6} alkoxy)alkyl, C_{1-6} (Ar^1)alkyl, C_{1-6} (NR^7R^8)alkyl, N-(R^8)-pyrrolidinyl or N-(R^8)-piperidinyl;

25 R^4 is hydrogen, halo or C_{1-6} alkyl, or C_{2-6} alkenyl;

R^5 is hydrogen or C_{1-6} alkyl;

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5

R^7 is hydrogen or C_{1-6} alkyl;

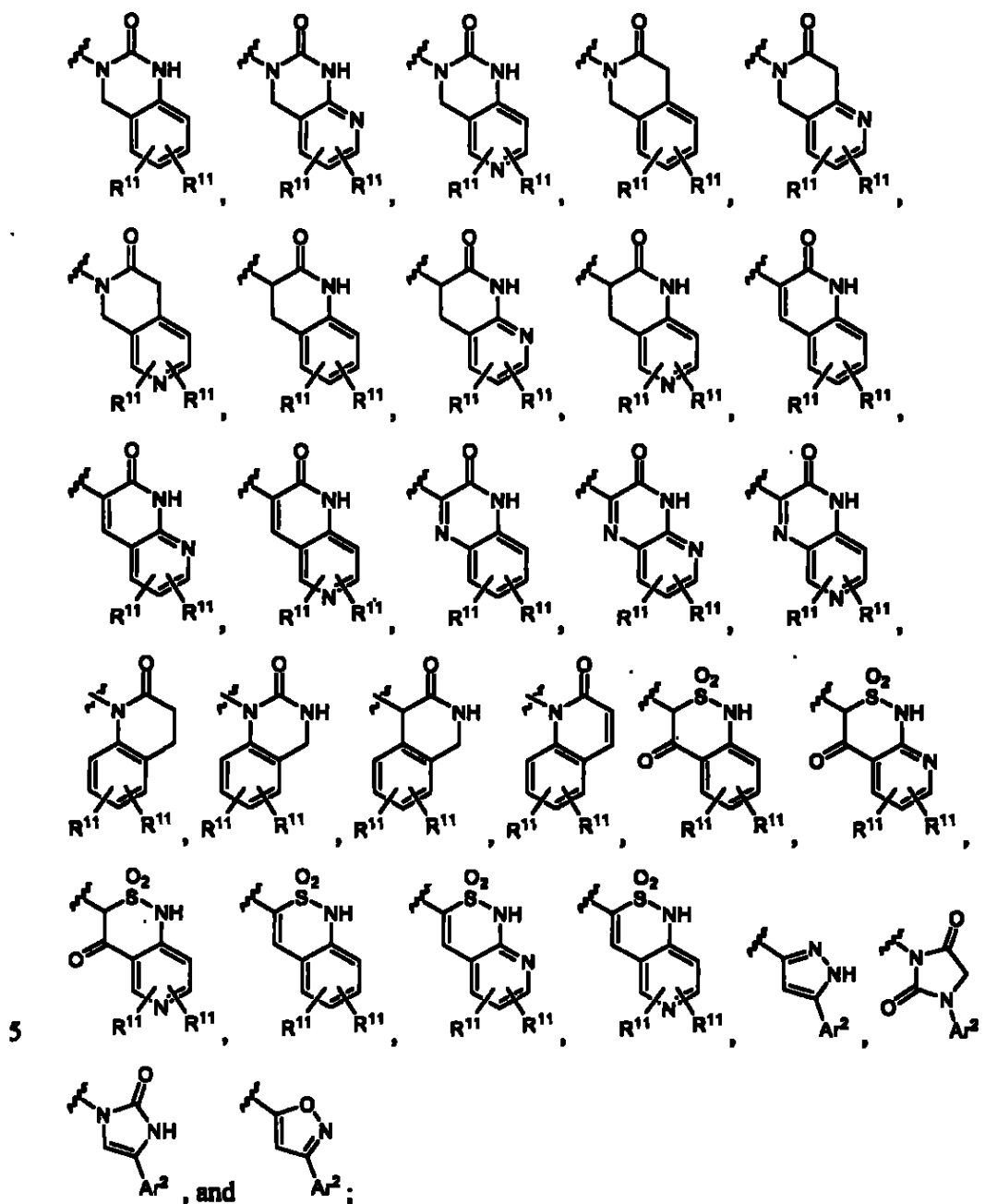
R^8 is hydrogen or C_{1-6} alkyl; or

- 10 NR^7R^8 taken together is selected from the group consisting of pyrrolidinyl, piperidinyl, $N-(R^9)$ -piperazinyl, morpholinyl, and thiomorpholinyl;

R^9 is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, or C_{1-6} alkoxycarbonyl;

- 15 R^{10} is phenyl, naphthyl, pyridinyl, pyridinyl N-oxide, quinolinyl, quinolinyl N-oxide, isoquinolinyl, or isoquinolinyl N-oxide, and is substituted with 0-2 substituents selected from the group consisting of halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, and phenyl;

- 20 or R^{10} is selected from the group consisting of



each R¹¹ is independently hydrogen, halo, C₁₋₆alkyl, C₁₋₆haloalkyl, or C₁₋₆alkoxy;

- 10 Ar¹ is phenyl, naphthyl, pyridinyl, or imidazolyl, and is substituted with 0-2 substituents selected from the group consisting of halo, C₁₋₆alkyl, and C₁₋₆haloalkyl;

Ar^2 is phenyl, naphthyl, or pyridinyl, and is substituted with 0-2 substituents selected from the group consisting of halo, C_{1-6} alkyl, and C_{1-6} haloalkyl;

X-Y is aminocarbonyl, oxycarbonyl, methylenecarbonyl, ethylene, or
5 amino(cyano)iminomethyl;

Z is N or CH; and

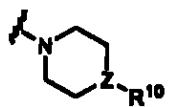
the carbon bearing the asterisk is either the (S) configuration or the (R) configuration;

10 or a pharmaceutically acceptable salt or solvate thereof.

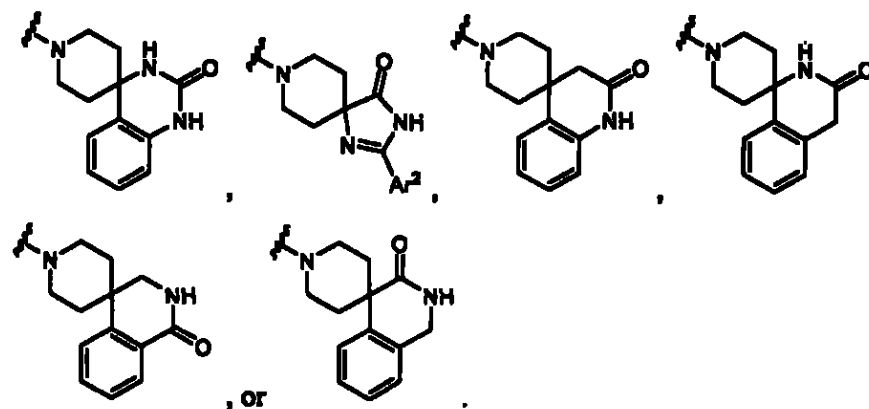
3. A compound of claim 2 where the carbon bearing the asterisk is of the (S) configuration.

4. A compound of claim 1 or 2 where R^4 is chloro, fluoro, or methyl.

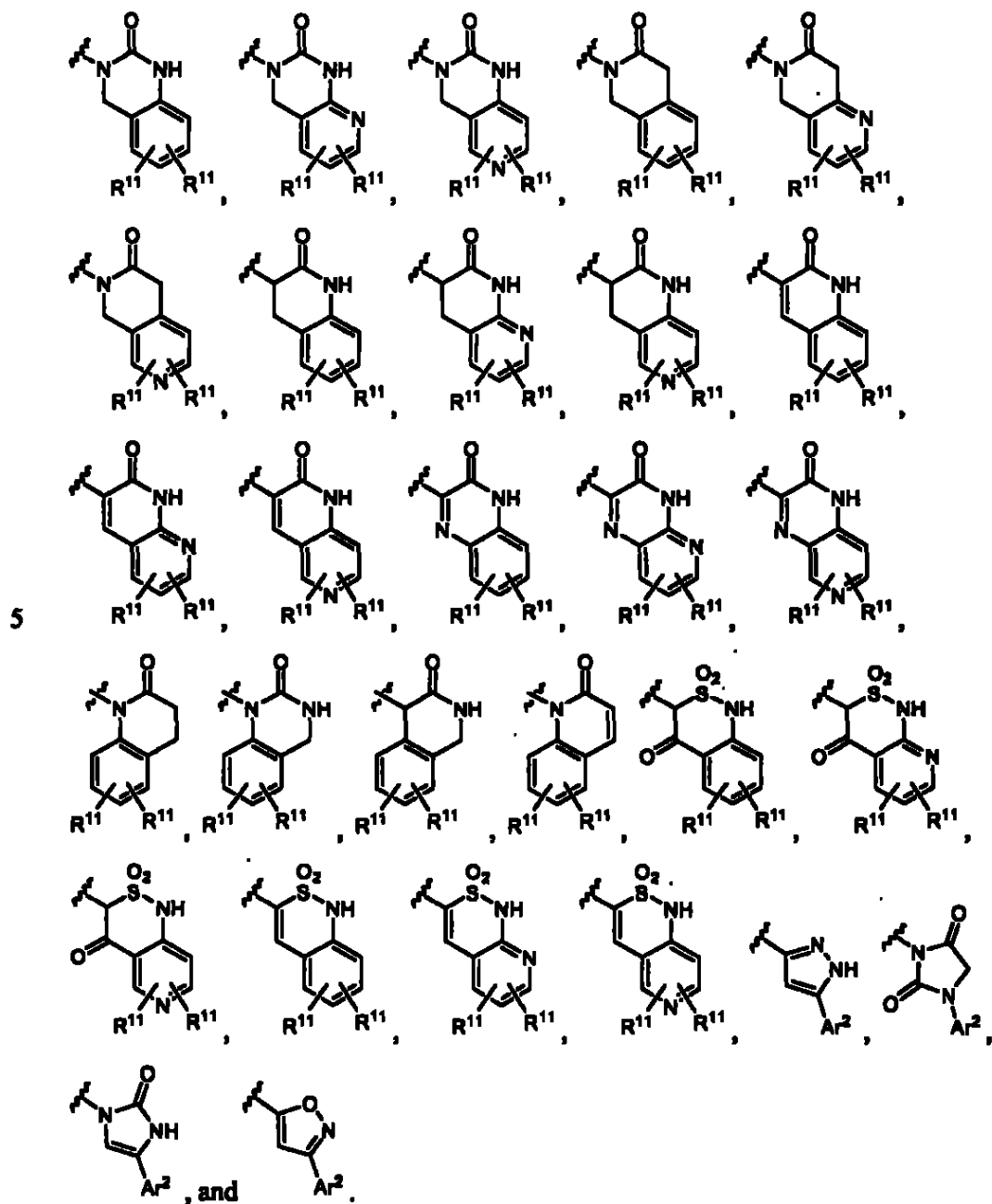
5. A compound of claim 1 or 2 where NR^5R^6 taken together is



6. A compound of claim 1 or 2 where NR^5R^6 taken together is



7. A compound of claim 1 or 2 where R^{10} is selected from the group consisting of



- 10 8. A compound of claim 1 or 2 where R^{11} is hydrogen, chloro, fluoro, or methyl.
9. A compound of claim 1 or 2 where Z is CH.

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10. A compound of claim 1 where n is 1.

11. A composition comprising a compound of claim 1 and a pharmaceutically acceptable adjuvant, carrier, or diluent.

5

12. A method of treating migraine comprising the administration of a therapeutically effective amount of a compound of claim 1 to a patient.

13. A composition comprising a compound of claim 2 and a pharmaceutically acceptable adjuvant, carrier, or diluent.

10

14. A method of treating migraine comprising the administration of a therapeutically effective amount of a compound of claim 2 to a patient.

15

(12) SOLICITUD INTERNACIONAL, PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

252

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GM,HR,HU,ID,IL,IN,IS,JP,KE,KO,KP,KR,KZ,LC,LK,LR,LS,
LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PH,PL,P
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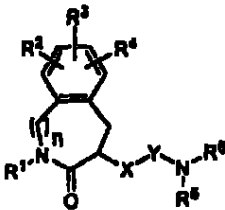
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Province Line Road, Princeton, NJ 08543-4000 (US).

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(54) Título: COMPUESTOS ARTIFICIALES COMO ANTAGONISTAS DEL RECEPTOR CGRP



(57) Extracto: La invención abarca antagonistas del receptor CGRP tricíclico y bicíclico restringidos, métodos para identificarlos, composiciones farmacéuticas que los comprenden, y métodos para su uso en terapia para el tratamiento de la migraña y otros dolores de cabeza, vasodilatación neurogénica, inflamación neurogénica, lesión térmica, choque circulatorio, bochornos asociados con la menopausia, enfermedades inflamatorias de las vías aéreas tales como asma y enfermedad pulmonar obstructiva crónica (COPD) y otras condiciones de tratamiento de las cuales se pueden efectuar por el antagonismo de los receptores CGRP.

**COMPUESTOS ARTIFICIALES COMO ANTAGONISTAS DEL RECEPTOR DEL
PEPTIDO RELACIONADO CON EL GEL DE CALCITONINA (CGRP)**

Antecedentes de la invención

El péptido relacionado con el gel de calcitonina (CGRP
5 por sus siglas en inglés) es un péptido de 37 aminoácidos que
se presenta naturalmente identificado primero en 1982 (Amara,
S. G. et al, Science 1982, 298, 240-244). Dos formas del
péptido se expresan (α CGRP y β CGRP) que difieren por uno y 3
aminoácidos en las ratas y humanos, respectivamente. El
10 péptido está ampliamente distribuido en el sistema nervioso
tanto periférico (PNS por sus siglas en inglés) como central
(CNS por sus siglas en inglés), localizado principalmente en
las neuronas sensoriales aferentes y centrales, y despliegan
diversos efectos biológicos, incluyendo la vasodilatación.

15 Cuando se libera de las células, el CGRP se enlaza a receptores
acoplados a la proteína G de superficie celular específicos y externalan
su acción biológica predominantemente por la activación de la
adenilato ciclasa intracelular (Poyner. D. R. et al, Br J
Pharmacol 1992, 105, 441-7; Van Valen, F. et al, Neurosci
20 Lett 1990, 119, 195-8.). Dos clases de receptores CGRP, CGRP₁
y CGRP₂, se han propuesto con base en las propiedades antagonistas del
fragmento de péptido CGRP(8-37) y la capacidad de análogos lineales de
CGRP para activar los receptores CGRP₂ (Juaneda, C. et al. TIPS 2000,
21, 432-438). Sin embargo, se carece de evidencia molecular
25 para los receptores CGRP₂ (Brain, S. D. et al, TIPS 2002, 23,

256 277

51-53). El receptor CGRP₁ tiene 3 componentes: (i) un receptor tipo receptor de calcitonina de transmembrana 7 (CRLR); (ii) la proteína que modifica la actividad del receptor de transmembrana sencillo de tipo 1 (RAMP1); y (iii) la proteína del componente del receptor intracelular (RCP) (Evans B. N. et al., J Biol Chem. 2000, 275, 31438-43). El RAMP1 se requiere para transportar el CRLR a la membrana de plasma y para enlace de ligando al receptor CGRP (McLatchie, L. M. et al, Nature 1998, 393, 333-339). RCP se requiere para la transducción de señal (Evans B. N. et al., J Biol Chem. 2000, 275, 31438-43). Se conocen diferentes especies específicas en el enlace de antagonistas de molécula pequeña para el receptor CGRP con una afinidad típicamente mayor apreciada por los antagonismos del receptor humano que para otras especies (Brain, S. D. et al, TIPS 2002, 23, 51-53). La secuencia de aminoácido de RAMP1 determina la selectividad de especie, en particular el residuo de aminoácido Trp74 es responsable para el fenotipo del receptor humano (Mallee et al. J Biol Chem 2002, 277, 14294-8).

Los inhibidores en el nivel del receptor para CGRP se postulan para ser útiles en condiciones patofisiológicas donde se presenta la activación excesiva del receptor CGRP. Algunas de estas incluyen la vasodilatación neurogénica, inflamación neurogénica, migraña, dolor de cabeza en grupo y otros dolores de cabeza, lesión térmica, choque circulatorio,

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bochornos menopáusicos y asma. La activación del receptor CGRP se ha implicado en la patogénesis de dolor de cabeza de 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.).
5 Varios niveles de CGRP son elevados durante la migraña (Goadsby PJ, et al. Ann Neurol 1990;28:183-7) y el tratamiento con fármacos anti-migraña regresa los niveles CGRP a normales coincidiendo con el alivio del dolor de cabeza (Gallai V. et
10 al. Cephalalgia 1995; 15: 384-90). Los que padecen migraña exhiben niveles CGRP basales elevados en comparación con los controles (Ashina M, et al. Pain 2000, 86(1-2): 133-8.2000). La infusión de CGRP intravenosa produce un dolor de cabeza tardío en los que padecen migraña (Lassen LH, et al.
15 Cephalalgia 2002 Feb; 22(1):54-61). Los estudios preclínicos en perros y ratas reportan que el bloqueo CGRP sistémico con el antagonista de péptido CGRP(8-37) no altera la hemodinámica sistémica en reposo ni el flujo sanguíneo regional (Shen, Y-T. et al, J Pharmacol Exp Ther 2001, 298,
20 551-8). De esta manera, los antagonistas del receptor CGRP pueden presentar un tratamiento novedoso para la migraña que evita las responsabilidades cardiovasculares de los vasoconstrictores activos asociados con un agonista 5-HT_{1B/1D} no selectivo, triptanos (por ejemplo, sumatriptano).

25 Se han reportado diversos antagonistas del receptor CGRP

258 243

de molécula pequeña, no péptidos. WO 04/091514, WO 04/092166
y WO 04/092168 describen compuestos cíclicos que contienen el
enlace amina en el anillo como antagonistas CGRP. WO '97/09046
y equivalentes describen *inter alia* compuestos relacionados
5 con quinina y quinidina que son ligandos, en particular
antagonistas, del receptor CGRP. WO 98/09630 y WO 98/56779 y
equivalentes describen *inter alia* compuestos de
nitrobenzamida, variadamente substituidos, como antagonistas
del receptor CGRP. WO 01/32649, WO 01/49676, y WO 01/32648 y
10 equivalentes describen *inter alia* una serie de 4-
oxobutanamidas y derivados de ciclopropano relacionados como
antagonistas del receptor CGRP. WO 00/18764, WO 98/11128 y WO
00/55154 y equivalentes describen *inter alia* piperidinas de
benzimidazolinilo como antagonistas del receptor CGRP. Sin
15 relacionarse a CGRP, una serie de antagonistas de
somatostatina se han descrito en WO 99/52875 y WO 01/25228 y
equivalentes. Ver también U.S. 6,344,449, U.S. 6.313,097,
U.S. 6 521 609, U.S. 6,552,043, US 20030181462, US
20030191068 y WO 03/076432 y solicitudes relacionadas. De
20 esta manera, los antagonistas del receptor CGRP novedosos
efectivos para el tratamiento de inflamación neurogénica,
migraña y otros trastornos, serían mayormente ventajosos.

Breve descripción de la invención

La invención abarca compuestos de la fórmula I y II que
25 son antagonistas CGRP. La invención también abarca

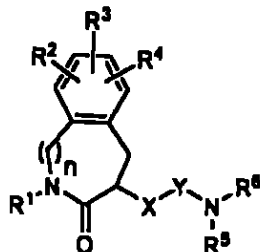
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composiciones que incorporan estos compuestos y métodos de uso de estos compuestos en un tratamiento terapéutico,

Un aspecto de la invención es un compuesto de la Fórmula

I

5



I

10 en donde:

R¹ es alquilo C₁₋₆, alquenilo C₂₋₆, cicloalquilo C₃₋₇, cicloalquenilo C₅₋₇, alquilo C₁₋₆(cicloalquilo C₃₋₇), haloalquilo C₁₋₆, alquilo C₁₋₆(alcoxi C₁₋₆), alquilo C₁₋₆(Ar¹), alquilo C₁₋₆(NR⁷R⁸), N-(R⁹-pirrolidinilo o N(R⁹)-piperidinilo;

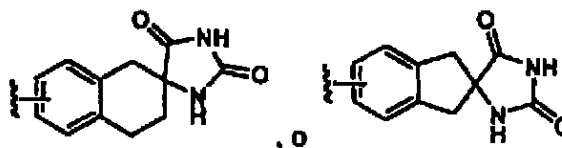
15 R² es hidrógeno, halo, hidroxilo, alquilo C₁₋₆, alquenilo C₂₋₆, benciloxi, o NR⁷R⁸;

R³ es hidrógeno, hidroxilo, halo, alquilo C₁₋₆, o alquenilo C₂₋₆;

o R² y R³ tomados juntos son CHNNR⁵;

20 R⁴ es hidrógeno, halo o alquilo C₁₋₆, o alquenilo C₂₋₆;

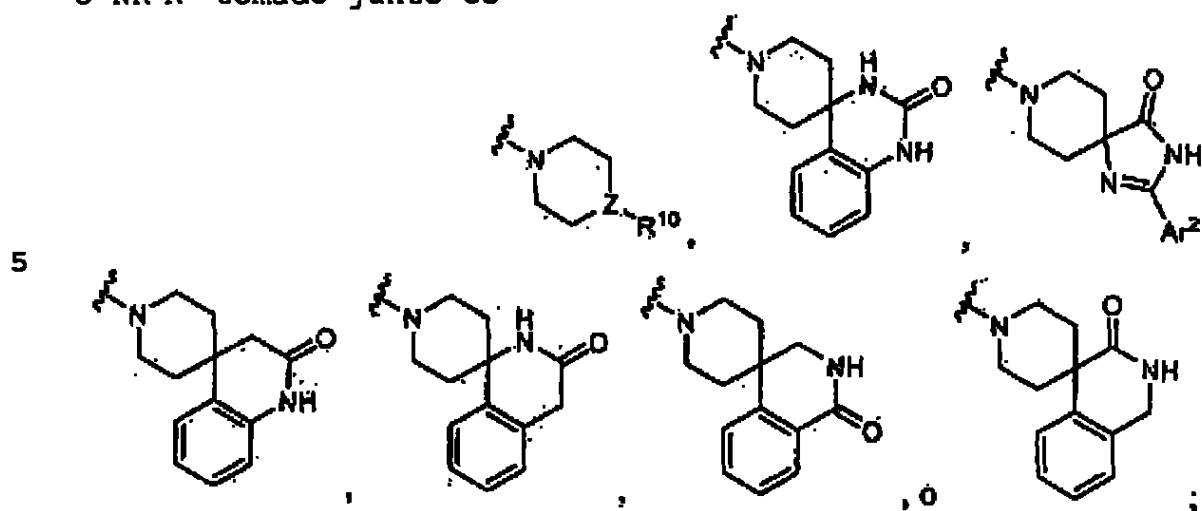
R⁵ es hidrógeno o alquilo C₁₋₆;



25 R⁶ es hidrógeno, alquilo C₁₋₆,

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o NR^5R^6 tomado junto es



R^7 es hidrógeno o alquilo C_{1-6} ;

R^8 es hidrógeno o alquilo C_{1-6} ; o

NR^7R^8 tomado junto se selecciona del grupo que
consiste de pirrolidinilo, piperidinilo, $\text{N}-(\text{R}^9)-$
15 piperazinilo, morfolinilo, y tiomorfolinilo;

R^9 es hidrógeno, alquilo C_{1-6} , alquilcarbonilo C_{1-6} , o
alcoxicarbonilo C_{1-6} ;

R^{10} es fenilo, naftilo, piridinilo, piridinil N-
óxido, quinolinilo, quinolinil N-óxido,
20 isoquinolinilo, o isoquinolinil N-óxido, y está
substituido con 0-2 substituyentse seleccionas del
grupo que consiste de halo, alquilo C_{1-6} , haloalquilo
 C_{1-6} , alcoxi C_{1-6} , hidroxil, y fenilo;

o R^{10} se selecciona del grupo que consiste de



R^{11} es hidrógeno, halo, alquilo C_{1-6} , haloalquilo C_{1-6} , o alcoxi C_{1-6} ;

Ar¹ es fenilo, naftilo, piridinilo, o imidazolilo, y esta substituido con 0-2 substituyentse seleccionas del grupo que consiste de halo,

25 alquilo C₁₋₆, y haloalquilo C₁₋₆;

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Ar^2 es fenilo, naftilo, o piridinilo, y esta substituido con 0-2 substituyentse seleccionas del grupo que consiste de halo, alquilo C_{1-6} , y haloalquilo C_{1-6} ;

X-Y es aminocarbonilo, oxicarbonilo, metilencarbonilo, etileno, o
5 amino(ciano)iminometilo;

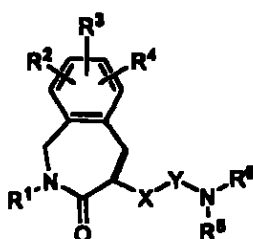
Z es N o CH; y

n es 0 o 1;

o una sal o solvato farmacéuticamente aceptable del mismo.

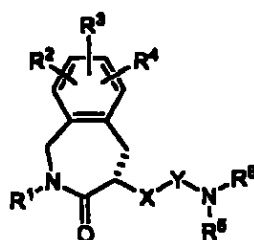
Otro aspecto de la invención es un compuesto de la Fórmula Ia.

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Otro aspecto de la invención es un compuesto de la

15 Fórmula Ib.

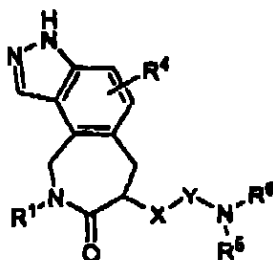


Ib

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Otro aspecto de la invención es un compuesto de la

Fórmula II.

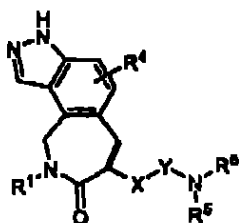


II

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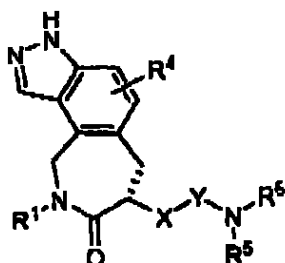
Otro aspecto de la invención es un compuesto de la
Fórmula IIa.



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IIa

Otro aspecto de la invención es un compuesto de la
Fórmula IIb.

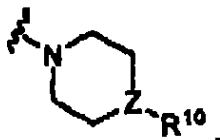


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IIb

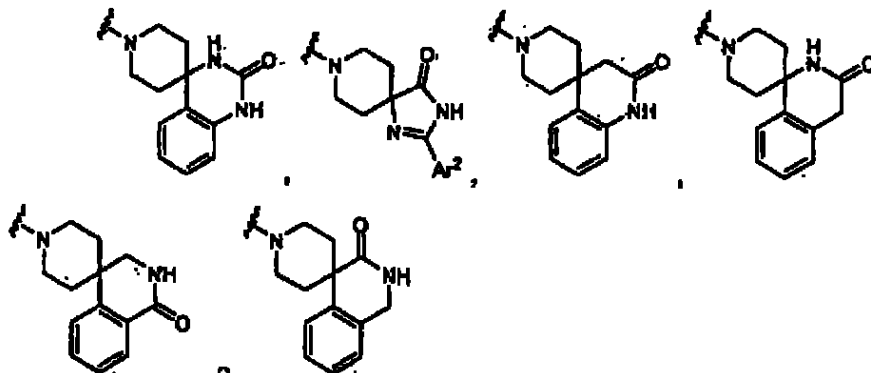
Otro aspecto de la invención es un compuesto de la
Fórmula I ó II, en donde R4 es cloro, fluoro o metilo.

Otro aspecto de la invención es un compuesto de la
Fórmula I ó II, en donde NR5R6 tomados juntos son



Otro aspecto de la invención es un compuesto de la
Fórmula I o II donde NR5R6 tomados juntos son

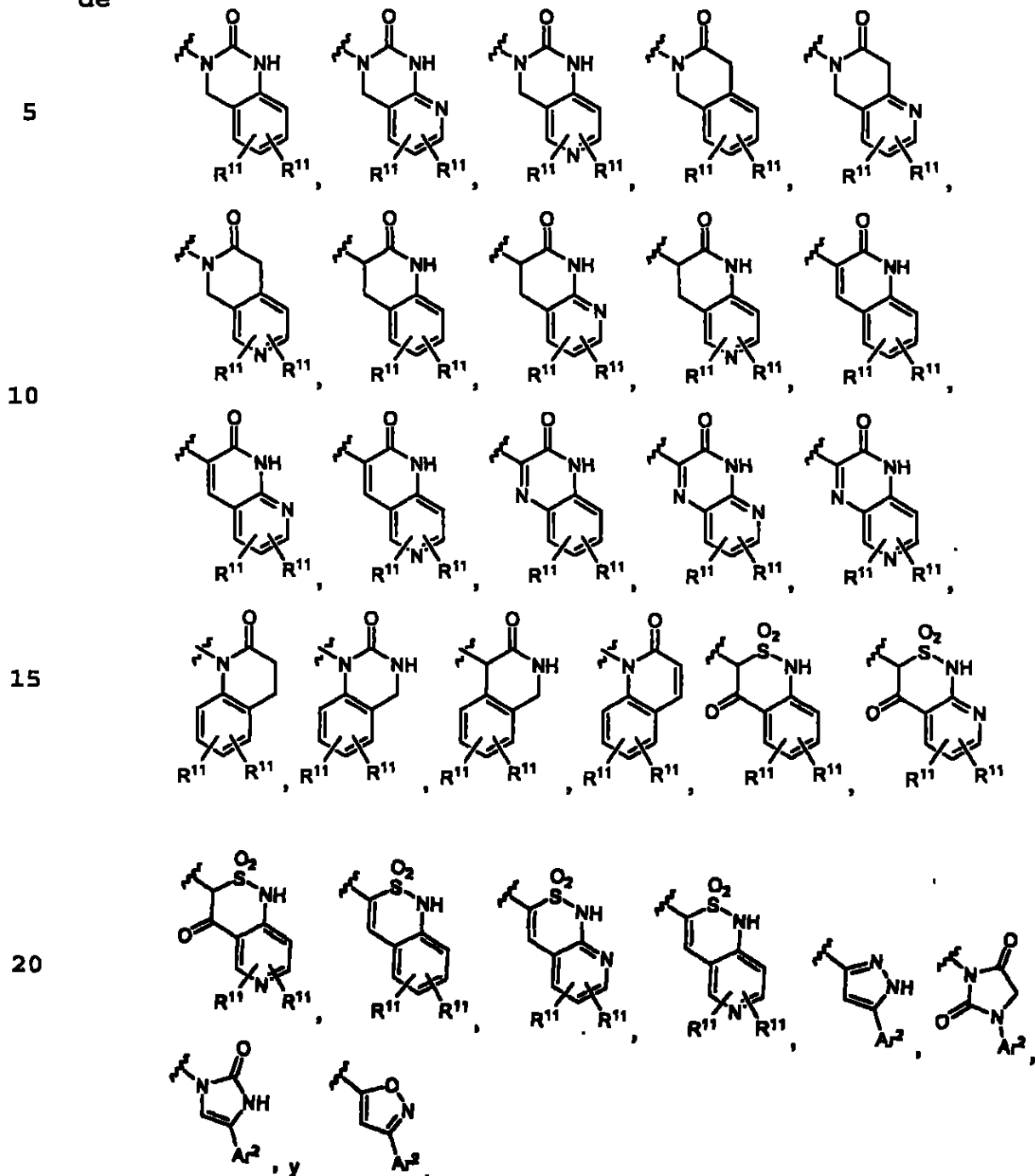
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Otro aspecto de la invención es un compuesto de la
Fórmula I o II donde R^{10} se selecciona del grupo que consiste
de



Otro aspecto de la invención es un compuesto de la

265 75p

Fórmula I o II donde R^{11} es hidrógeno, cloro, fluoro, o metilo.

Otro aspecto de la invención es un compuesto de la Fórmula I o II donde Z es CH.

5 Otro aspecto de la invención es un compuesto de la Fórmula I donde n es 1.

Otro aspecto de la invención es que cualquier alcance de las variables R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , Ar^1 , Ar^2 , X-Y, Z, y n pueden usarse con cualquier alcance de las
10 variables restantes

"Alquilo," "hidroxialquilo," "alcoxi" y terminus relacionados con la porción de alquilo incluye isómeros rectos o ramificados. "Alquenilo" significa un grupo alquilo lineal o ramificada con al menos un enlace doble. Un término
15 tal como alquilo $C_{1-6}(R)$ significa un grupo alquilo lineal o ramificado de uno a 6 carbonos substituido con el substituyente R. Un término tal como N-(R)-pirrolidinilo indica que el nitrógeno esta substituido con el substituyente R. "Haloalquilo" y "haloalcoxi" incluye todos los isómeros
20 halogenados de alquilo substituido por monohalo a alquilo substituido por perhalo. "Arilo" incluye sistemas de anilo aromático carbocíclico y heterocíclico. "Amino" incluye porciones primarias, secundarias, y terciarias. "Carbonilo" significa CO. "Oxi" significa -O-. "Aminocarbonilo" significa
25 -N(R)C(=O)-. "Oxicarbonilo" significa -OC(=O)-.

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"Metilencarbonilo"

significa

$-\text{CH}_2\text{C}(=\text{O})-$.

"Amino(ciano)iminometilo" significa $-\text{NHC}(=\text{NCN})-$.

La invención incluye todas las formas de sal farmacéuticamente aceptables de los compuestos. Las sales farmacéuticamente aceptables son aquellas en las cuales los contraiones no contribuyen de forma importante a la actividad o toxicidad fisiológica de los compuestos, y como tales funcionan como equivalentes farmacológicos. Estas sales pueden hacerse de conformidad con técnicas orgánicas comunes que emplean reactivos comercialmente disponibles. Algunas formas de sal aniónicas incluye acetato, acistrato, besilato, bromuro, cloruro, citrato, fumarato, glucouronato, bromohidrato, clorohidrato, yodohidrato, yoduro, lactato, maleato, mesilato, nitrato, pamoato, fosfato, succinato, sulfato, tartrato, tosilato, y xinofoato. Algunas formas de sal catiónicas incluyen amonio, aluminio, benztatina, bismuto, calcio, colina, dietilamina, dietanolamina, litio, magnesio, meglumina, 4-fenilciclohexilamina, piperazina, potasio, sodio, trometamina, y zinc.

La invención también incluye todas las formas de solvato de los compuestos, particularmente hidratos. Los solvatos no contribuyen de forma importante a la actividad o toxicidad fisiológica de los compuestos y como tales funcionan como equivalentes farmacológicos.

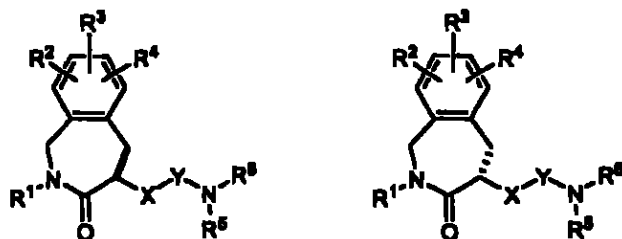
Los solvatos pueden formar en cantidades

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estoiquiometricas o pueden formarse de solventes recientes o una combinación de ambos. Un tipo de solvato es el hidrato, y algunas formas hidratadas incluyen monohidrato, hemihidrato, y dihidrato.

5 Algunos compuestos de la invención pueden existir en formas estereoisoméricas, un ejemplo de las cuales se muestra a continuación. La invención incluye todas las formas estereoisoméricas y tautoméricas de los compuestos.

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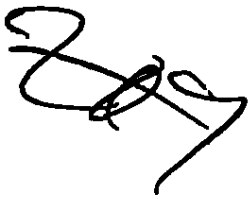


Métodos sintéticos

15 Los compuestos descritos en la presente invención pueden sintetizarse de conformidad con los esquemas 1-4 así como otros procedimientos conocidos en el arte. Los materiales de partida están comercialmente disponibles o se sintetizan por procedimientos sintéticos comunes. Las variaciones de los
20 compuestos y los procedimientos para hacer los que no se ilustran, están dentro de la experiencia de la técnica.

El esquema de reacción 1 describe como hacer ciertos compuestos de la invención. La introducción regio específica de yodo en un anillo aromático apropiadamente substituido
25 puede realizarse usando monocloruro de yodo. Los yoduros de

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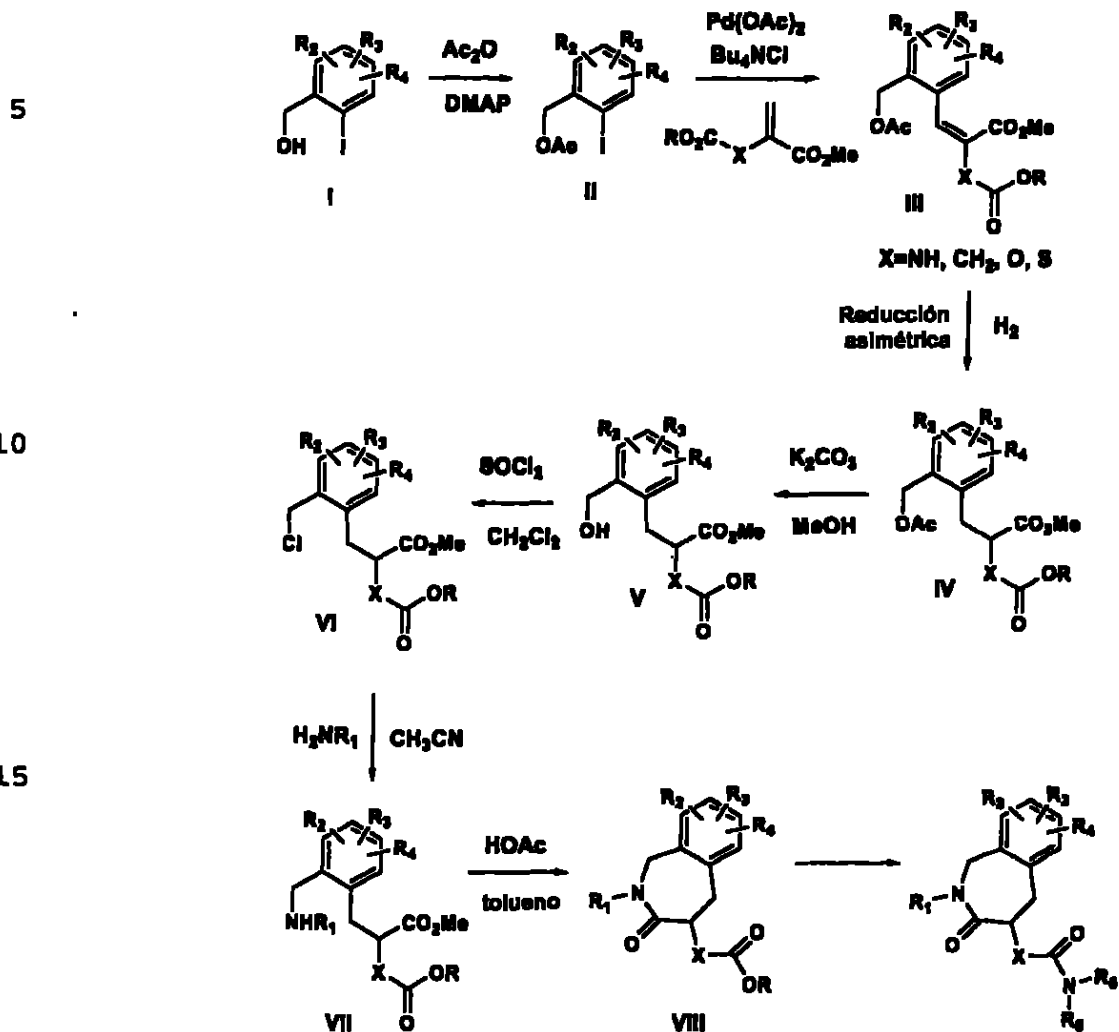
arilo (II) son buenos compañeros de acoplamiento en las reacciones Heck mediadas por paladio. Los productos Heck (III) pueden reducirse con hidrógeno mediado por varios catalizadores asimétricos para producir materiales enantioméricamente puros (IV). La hidrólisis posterior de la funcionalidad de acetato con carbonato de potasio metanólico seguido por el tratamiento del alcohol (V) con cloruro de tionilo, puede producir cloruros bencilícos (VI). El tratamiento de los cloruros bencilícos con varias aminas en acetonitrilo puede entregar las aminas requeridas (VII).

Las aminas (VII) pueden convertirse en azepinonas deseadas (VIII) en tolueno a reflujo mediado por ácido acético catalítico. Los intermediarios de azepinonas VII ($X = \text{NH}, \text{CH}_2, \text{O}$) pueden de nuevo elaborarse en productos finales. La hidrogenólisis de VII ($X = \text{NH}$) bajo Pd al 10 % en carbono produce el intermediario de amina IX (esquema II). La funcionalidad amina puede transformarse a la funcionalidad urea deseada (X) con la asistencia de fosgeno o dicarbonato de N,N'-disuccinimilo y varias aminas (esquema II). Alternativamente, el éster succínico VIII ($X = \text{CH}_2$) puede convertirse al ácido carboxílico (XI) con hidróxido de litio, seguido por la reacción con una amina apropiada bajo condiciones de acoplamiento TBTU para dar las amidas deseadas

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(XII) (esquema de reacción 3).

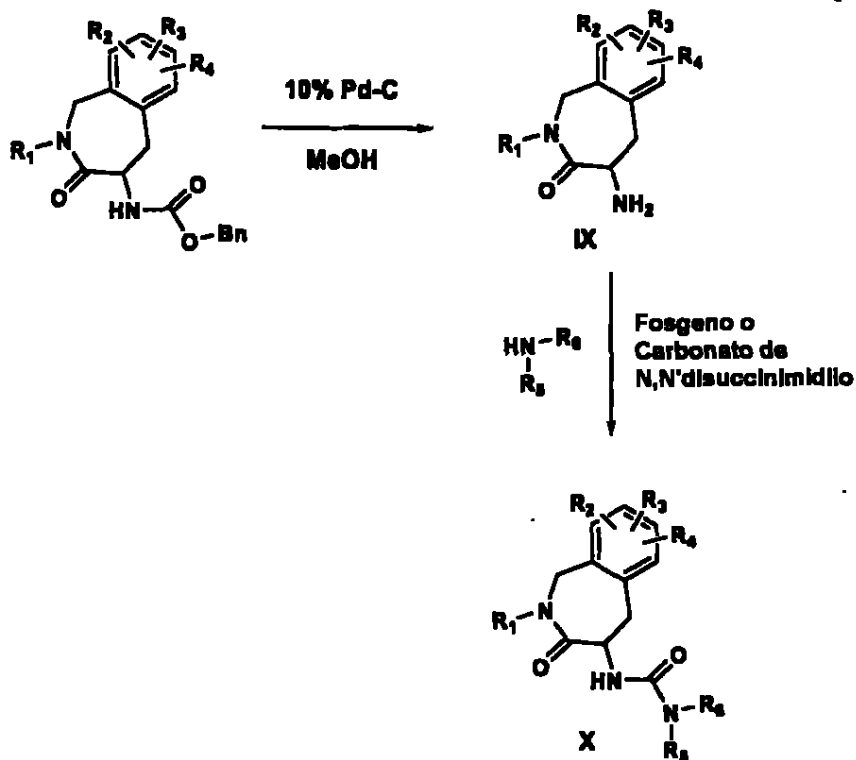
Esquema de reacción 1



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Esquema de reacción 2

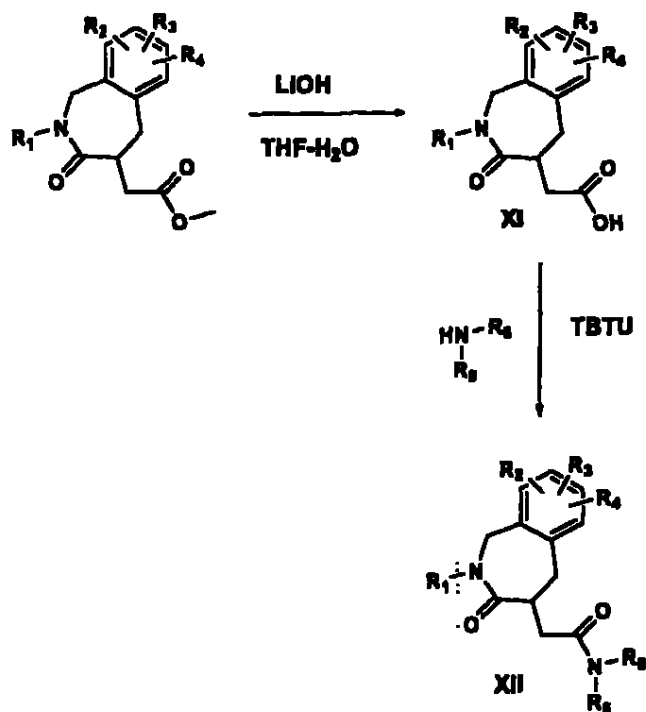
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Esquema de reacción 3

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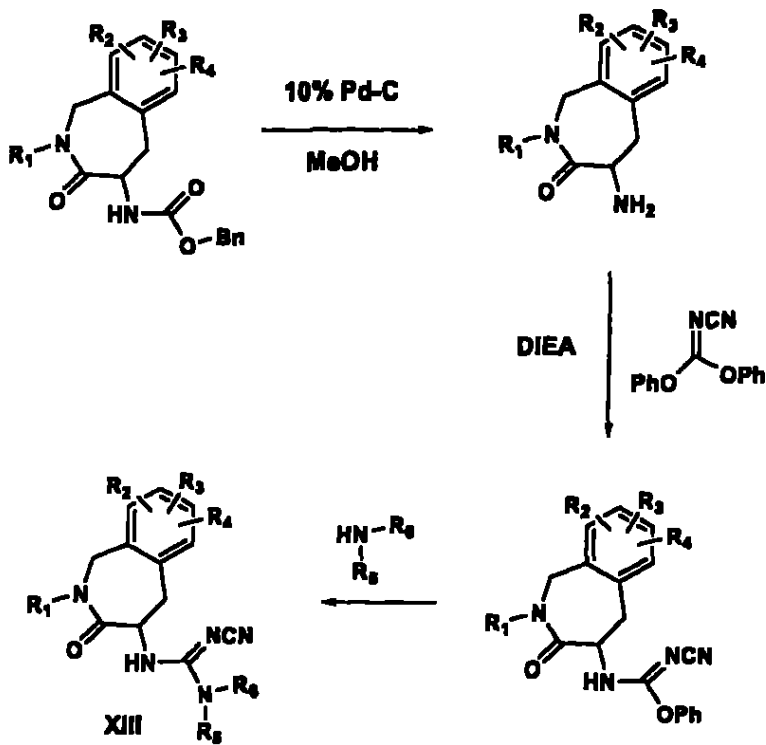
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De manera similar a la formación de urea, la cianoguanidina XII puede prepararse usando N-cianocarboimidato de difenilo y varias aminas substituidas (Esquema de reacción 4)

5 Esquema de reacción 4

10



Métodos biológicos

Ensayo de enlace CGRP. Cultivo de tejido. Se hacen
 20 crecer células SK-N-MC a 37°C CO₂ al 5% como una monocapa en
 un medio que consiste de MEM con sales Earle's y L-glutamina
 (Gibco) complementado con suero de bovino fetal al 10%
 (Gibco). Peletizados celulares. Las células se enjuagan 2
 veces con solución salina amortiguada en fosfato (NaCl 155
 25 mM, Na₂HPO₄ 3.3 mM, KH₂PO₄ 1.1 mM, pH 7.4), e incuban durante

5-10 minutos a 4°C en solución amortiguadora de lisis hipotónica que consiste de Tris 10 mM (pH 7.4) y EDTA 5 mM. Las células se transfieren de las placas a tubos de polipropileno (16 x 100 mm) y se homogenizan usando un 5 politrón. Los homogenados se centrifugan a 32,000 x g durante 30 minutos. Los peletizados se vuelven a suspender en solución amortiguadora de lisis hipotónica fría con un cocktail inhibidor de proteasa de mamífero al 0.1% (Sigma) y se evalúa para concentración de proteína. El homogenado SK-N- 10 MC se procesa en alícuota entonces y se almacena -80°C hasta que se necesite.

Ensayo de enlace de radioligando. Los compuestos de la invención se solubilizan y se llevan a través de diluciones en serie usando DMSO la 100%. Las 15 alícuotas de las diluciones en serie del compuesto se diluyen además 25 veces en solución amortiguadora de ensayo (Tris- Cl 50 mM pH 7.5, MgCl 5 mM, Triton X-100 al 0.005%) y se transfiere (volumen 50 µl) en placas de ensayo de 96 pozos. [¹²⁵I]-CGRP (Amersham 20 Biosciences) se diluye hasta 60 pM en solución amortiguadora de ensayo y un volumen de 50 µl se agrega a cada pozo. Los peletizados SK-N-MC se descongelan, se diluyen en solución amortiguadora de ensayo con el cocktail inhibidor de proteasa de 25 mamífero al 0.1% fresco (Sigma), y se homogenizan

2x3 2x4

nuevamente. El homogenado SK-N-MC (5 µl/posos) se
agrega en un volumen de 100 µl. Las placas de ensayo
se incuban entonces a temperatura ambiente durante 2
horas. Se detienen los ensayos por la adición de
5 solución amortiguadora de lavado fría en exceso
(Tris-Cl 20 mM pH 7.5, 0.1% BSA) inmediatamente
seguido por la filtración sobre filtros de fibra de
vidrio (Whatman GF/B) previamente mojados en PEI la
0.5%. Los enlaces no específicos se definen con 1 µM
10 beta-CGRP. La radioactividad enlace de proteína se
determina usando un contador gamma o de
escintilación. El IC₅₀ se define como la concentración
del compuesto de la invención requerida para
desplazar el 50% de enlace de radioligando.

15 Ensayo de antagonismo funcional AMP cíclico. El
antagonismo de los compuesto de invención se
determina al medir la formación de AMP cíclico
(monofosfato de adenosina 3'5'-cíclico) en células
SK-N-MC que expresan endogenamente el receptor CGRP
20 humano. El complejo del receptor CGRP se acopla con
la proteína Gs y el enlace de CGRP a este complejo
lleva a la producción de AMP cíclica por medio de la
activación dependiente de Gs de una adenilato ciclasa
(Juaneda C et al., TIS, 2000; 21:432-438; incorporado
25 para referencia en la presente). En consecuencia, los

274 25

antagonistas del receptor CGRP inhiben la formación de AMP cíclica inducida por CGRP en células SK-N-MC (Doods' H et al., Br J Pharmacol, 2000; 129(3):420-423); incorporado para referencia en la presnete).

5 Para mediciones AMP cíclicas, se incuban celulas SK-N-MC 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 preincuban con células
10 SK-N-MC durante 15 minutos antes de la adición de CGRP para permitir la ocupación del receptor (Edvinsson et al., Eur J Pharmacol, 2001, 415:39-44; incorporado para referencia en la presente). El AMP cíclico se extrae usando el reactivo de lisis y su
15 concentración se determina por radioinmuno ensayo usando el kit de ensayo de separación por exclusión directo RPA559 cAMP SPA (Amersham Pharmacia Biotech). Los valores IC₅₀ se calculan usando la colocación Excel. Los compuestos de prueba de la invención se
20 determinan para ser antagonistas ya que exhiben una inhibición dependiente de la dosis de la producción de AMP cíclica inducida por CGRP

En la tabla 4, los resultados se denotan como siguen: A 0.1-10 nM; B = 10-100 nM; C = 100-1000 nM; D > 1000 nM.

25 Tabla4. Enlace de CGRP y datos funcionales de cAMP

225- 27

Ejemplo	Enlace CGRP ¹ IC ₅₀ (nM)	Función cAMP ² IC ₅₀ (nM)
1	B	B
2	C	*
3	C	*
4	C	*
5	C	*
6	B	B
7	B	*
8	D	*
9	C	*
10	B	B
11	B	B
12	A	A
13	B	*
14	C	*
15	B	*
16	A	A
17	B	*
18	C	*
19	B	A
20	A	A
21	A	A
22	A	A
23	B	*
24	B	B
25	C	*
26	A	A
27	C	*
28	B	B
29	C	*
30	B	B
31	D	*
32	C	*
33	D	*

276

277

Ejemplo	Enlace CGRP ¹ IC ₅₀ (nM)	Función cAMP ² IC ₅₀ (nM)
34	C	*
35	B	*
36	B	B
37	A	B
38	C	*
39	B	B
40	A	A
41	A	A
42	B	B
43	A	A
44	A	A
45	A	A
46	A	A
47	B	B
48	B	*
49	A	A
50	A	A
51	A	*
52	A	A
53	A	A
54	A	A
55	C	*
56	C	*
57	C	*
58	C	*
59	C	*
60	D	*
61	D	*
62	B	*
63	C	*
64	D	*
65	D	*
66	B	*
67	B	*
68	C	*
69	B	*
70	C	*
71	C	*
72	D	*
73	D	*
74	D	*
75	A	*
76	B	*
77	B	*

5

10

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272

Ejemplo	Enlace CGRP ¹ IC ₅₀ (nM)	Función cAMP ² IC ₅₀ (nM)
78	A	*
79	A	*
80	B	B
81	B	*
82	A	*
83	C	*
84	C	*
85	B	B
86	A	*
87	B	*
88	A	*
89	A	*
90	A	*
91	A	*
92	B	*
93	C	*
94	A	*
95	B	*
96	A	*
97	A	*
98	B	*
99	A	*
100	A	*
101	B	*
102	A	*
103	B	*
104	B	*
105	B	*
106	B	*
107	C	*
108	B	*
109	C	*
110	B	*
111	A	*
112	B	*
113	A	*
114	B	*
115	B	*
116	A	*
117	C	*
118	B	*
119	D	*
120	A	*

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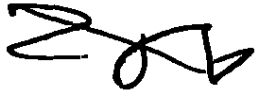
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Composiciones farmacéuticas y métodos de tratamiento

Los compuestos de la fórmula I inhiben el receptor CGRP. Como tales, son útiles para tratar trastornos asociados con los niveles CGRP aberrantes o donde los niveles CGRP
5 modulantes pueden tener un beneficio terapéutico.

En consecuencia, otro aspecto de la invención es una composición farmacéutica que comprende del compuesto de la fórmula I con un adyuvante, portador o diluyente farmacéuticamente aceptable.

10 Los compuestos sedan generalmente como composiciones farmacéuticas que comprenden una cantidad terapéuticamente efectiva de un compuesto de la fórmula I, o una sal farmacéuticamente aceptable y un portador farmacéuticamente aceptable y pueden contener excipientes convencionales. Una
15 cantidad terapéuticamente efectiva es la cantidad necesaria para proporcionar un beneficio importante al paciente como se determina por los practicantes en tal técnica. Los portadores farmacéuticamente aceptables son aquellos portadores conocidos convencionalmente que tienen perfiles de seguridad
20 aceptables. Las composiciones abarcan todas las formas sólidas y líquidas comunes incluyendo cápsulas, tabletas, pastillas y polvos así como suspensiones líquidas, jarabes, elixires, y soluciones. Las composiciones sólidas pueden formarse en formulaciones de liberación prolongada o
25 sostenida. Las composiciones se hacen usando técnicas de

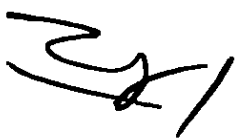
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formulación comunes y excipientes convencionales (tales como agentes humectantes y aglutinantes) y vehículos (tales como agua y alcoholes).

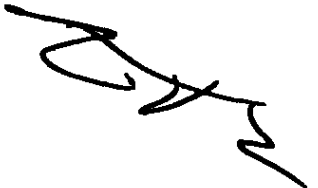
Las composiciones sólidas se formulan normalmente en unidades de dosis proporcionadas desde alrededor de 1 hasta alrededor de 1000 mg del ingrediente activo por dosis. Algunos ejemplos de unidades de dosis sólidas son 0.1 mg, 1 mg, 10 mg, 100 mg, 500 mg y 1000 mg. Las composiciones líquidas generalmente están en un rango de dosis unitaria de 1-100 mg/ml. Algunos ejemplos de unidades de dosis líquidas son 0.1 mg/ml, 1 mg/ml, 10 mg/ml, 25 mg/ml, 50 mg/ml y 100 mg/ml.

La invención abarca todos los modos convencionales de administración incluyendo métodos orales, parenterales, intranasales, sublinguales, y transdermales. Típicamente, la dosis diaria será 0.01-100 mg/kg de peso corporal diariamente. Generalmente, se requiere más compuesto oralmente y menos parenteralmente. El régimen de dosis específico, sin embargo, se determinara por un medico usando un juicio médico sólido.

Los inhibidores en el nivel del receptor para CGRP se postulan para ser útiles en condiciones patofisiológicas donde la activación del receptor CGRP excesiva se presenta. Algunos de estos incluyen vasodilatación neurogénica, inflamación neurogénica, migraña, dolor de cabeza en grupo, y otros

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dolores de cabeza, lesión térmica, choque circulatorio, bochornos menopausicos, y asma. La activación del receptor CGRP esta implicada en la patogenisis del color de cabeza de migraña (Edvinsson L. CNS Drugs 2001, 15 (10), 745-53; 5 Williamson, D. J. Microsc. Res. Tech. 2001, 53, 167-178; Grant, A. D. Brit. J. Pharmacol. 2002, 135, 356-362). Los niveles de suero de CGRP son elevados durante la migraña (Goadsby P. J. Et al. Ann. Neurol. 1990, 28, 183-7) y el tratamiento con fármacos antmigraña regresa los niveles CGRP 10 hasta una coincidencia normal que alivia el dolor de cabeza (Gallai V. Et al. Cephalalgia 1995, 15, 384-90). Los que padecen migraña exhiben niveles CGRP basales elevados en comparación con los controles (Ashina M. Et al., Pain 2000, 86 (1-2), 133-8). Los procedimientos de infusión CGRP 15 intravenosa retrasan los dolores de cabeza de los que padecen de migraña (Lassen L. H. et al. Cephalalgia. 2002, 22(1), 54-61). Los estudios preclínicos en perros y ratas reportan que el bloqueo CGRP sistémico con el antagonista de péptido CGRP (8-37) no altera la restauración de hemodinámica sistémica ni 20 el flujo sanguíneo regional (Shen, Y-T. Et al. J. Pharmacol. Exp. Ther. 2001, 298, 551-8). De esta manera, los antagonistas del receptor CGRP pueden presentar un tratamiento novedoso para la migraña que evita los obstáculos cardiovasculares de vasoconstricción activa asociada con 25 agonistas 5-HT_{1B/1D} no selectivos, "triptanos" (por ejemplo,

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sumatriptano).

Otro aspecto de la invención es un método para tratar la migraña o el dolor de cabeza.

5 "Migraña", "Dolor de cabeza" y términos relacionados se entiende por los practicantes en la medicina. La migraña abarca todas las clases de migraña incluyendo común, clásica, en grupo, fulgurante, hemipléjica, oftalmoplejica, y oftomálmica.

10 "Terapéuticamente efectivos" significa que hay un beneficio importante al paciente como se entiende por los practicantes en la medicina.

"Paciente" significa una persona que puede beneficiarse del tratamiento como se determina por los practicantes en la medicina.

15 Otro aspecto de la invención se refiere a un método para tratar la inflamación (particularmente inflamación neurogénica), dolor, lesión térmica, choque circulatorio, diabetes, síndrome de Reynaud, insuficiencia arterial periférica, hemorragia subaracnoide/creneal, crecimiento de
20 tumor, bochornos asociados con la menopausia, y otras condiciones, el tratamiento de las cuales puede efectuarse por el antagonismo del receptor CGRP por la administración de composiciones farmacéuticas que comprenden los compuestos de la fórmula (I) como se define en la presente.

25 Otro aspecto de la invención se refiere a métodos

seleccionados del grupo que consiste de (a) regulación inmune en la mucosa del intestino, (b) efecto protector contra lesión anafiláctica cardíaca, (c) estimulación o prevención de la estimulación de interleusina 1b(IL-1b)- de la resorción ósea, (d) modulación de la expresión de receptores NK1 en neuronas espinales y (e) enfermedades inflamatorias de las vías respiratorias y enfermedad pulmonar obstructiva crónica incluyendo el asma. Ver (a) Calcitonin Receptor-Like Receptor Is Expressed on Gastrointestinal Immune Cells, Hagner, Stefanie; Knauer, Jens; Haberberger, Rainer; Goeke, Burkhard; Voigt, Karlheinz; McGregor, Gerard Patrick. Institute of Physiology, Philipps University, Marburg, Alemania. Digestion (2002), 66(4), 197-203; (b) Protective effects of calcitonin gene-related peptide-mediated evodiamine on guinea-pig cardiac anaphylaxis. Rang, Wei-Qing; Du, Yan-Hua; Hu, Chang-Ping; Ye, Feng; Tan, Gui-Shan; Deng, Han-Wu; Li, Yuan-Jian. School of Pharmaceutical Sciences, Department of Pharmacology, Central South University, Xiang-Ya Road 88, Changsha, Hunan, Naunyn-Schmiedeberg's Archives of Pharmacology (2003), 367(3), 306-311; (c) The experimental study on the effect calcitonin gene-related peptide on bone resorption mediated by interleukin-1. Lian, Kai; Du, Jingyuan; Rao, Zhenyu; Luo, Huaican. Department of Orthopedics, Xiehe Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Peop. Rep.

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expression of neurokinin receptors by rat spinal neurons.
Seybold VS, McCarron KE, Mermelstein PG, Groth RD, Abrahams
5 LG. J. Neurosci. 2003 23 (5): 1816-1824. Department of
Neuroscience, University of Minnesota, Minneapolis, Minnesota
55455, and Department of Pharmacology, Toxicology, and
Therapeutics, University of Kansas Medical Center, Kansas
City. Kansas 66160 (e) Attenuation of antigen-induced airway
10 hyperresponsiveness in CGRP-deficient mice. Aoki-Nagase,
Tomoko; Nagase, Takahide; Oh-Hashi, Yoshio; Shindo, Takayuki;
Kurihara, Yukiko; Yamaguchi, Yasuhiro; Yamamoto, Hiroshi;
Tomita, Tetsuji; Ohga, Eihiro; Nagai, Ryozi; Kurihara,
Hiroki; Ouchi, Yasuyoshi. Department of Geriatric Medicine,
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L963-L970; (f) Calcitonin gene-related peptide as
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20 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,
25 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 para referencias en la
5 presente.

Otro aspecto de esta invención se refiere a un método de
tratamiento usando combinaciones de compuestos de la fórmula
I con uno o más agente seleccionas del grupo que consiste de
inhibidores COX-2, NSAIDS, aspirina, acetaminofen, triptanos,
10 ergotamina y cafeína para el tratamiento de migraña.

Descripción detallada de la invención

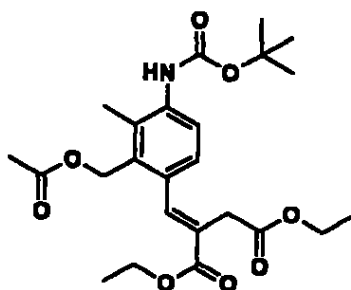
Los espectros de resonancia magnética de protones (^1H
RMN) se registran en un Bruker AC 300 ó AC 500. Todos los
espectros se determinan en los solventes indicados y los
15 cambios químicos se reportan en unidades δ de campo bajo del
tetrametilsilano estándar interno (TMS) y las constantes de
acoplamiento de interprotones se reportante en Hertz (Hz).
Los patrones de empalme se designan como sigue: s, singleta;
d, doblete; t, triplete; q, cuarteto; m, multiplete; br, pico
20 amplio. Los espectros de masa de baja resolución (EM) y el
molecular aparente (MH^+) o (M-H^+) se determinan en una
plataforma de micromasa. Los análisis elementales se reportan
como porcentaje en peso. Los productos se purifican por CLAR
preparativa usando la columna YMC S5 ODS (30 x 100 mm) en una
25 relación de flujo de 40.0 ml/min. y un tiempo de gradiente de

285 Z

8.0 min. Iniciando de la composición de solvente de 40% MeOH-
60% H₂O-0.1% TFA y terminando con la composición de solvente
95% MeOH-5% H₂O-0.1% TFA. Los productos se analizan por un
instrumento CLAR usando una columna XTERA (3.0 x 50 mm S7)
5 partiendo del solvente A (10% MeOH-90% agua -0.1% ácido
trifluoroacético (TFA)) y alcanzando el solvente B (10% agua
- 90% metanol - 0.1% TFA) sobre un tiempo de gradiente de 2
minutos. La relación de flujo es 5 ml/min y el tiempo de
retención (R_f) del producto se mide como longitud de onda 220
10 nm.

Intermediario 1

15



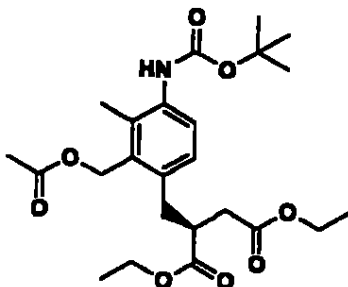
Éster de dietilo del ácido 2-(Acetoximetil-4-tert-
butoxicarbonilamino-3-metil-bencilideno)-succínico. El gas de
nitrógeno se burbujeó a través de una solución de éster 3-
20 tert-butoxicarbonilamino-6-yodo-2-metil-bencilo del ácido
acético (3.85 g, 9.5 mmol), éster de dietilo del ácido
itacónico (2.2 mL, 12 mmol), cloruro de tetrabutilamonio
(3.4 g, 12 mmol), y trietilamina (4.0 mL, 29 mmol) en N,N-
dimetilformamida (25 mL) durante 5 minutos. El acetato de
25 paladio (II) (0.32 g, 1.4 mmol) se agregó. La mezcla se

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calentó a 100°C durante 45 minutos. La mezcla se enfrió a temperatura ambiente luego se diluyó con éter de dietilo (100 ml). La mezcla se lavó sucesivamente con agua (3 X 50 mL), y salmuera (25 mL). El orgánico se secó (MgSO₄), filtró y
5 concentró in vacuo. La purificación de gel de sílice proporcionó el producto deseado en 99% de rendimiento como un aceite ámbar. ¹H RMN (300 MHz, CDCl₃): δ= 8.0 (s, 1H), 7.78 (d, J=8.4, 1H), 7.08 (d, J=8.4, 1H), 6.32 (s, 1H), 5.11 (s, 2H), 4.27 (q, J=7.3, 2H), 4.11 (q, J= 7.1, 2H), 3.30 (s, 2H),
10 2.24 (s, 3H), 2.04 (s, 3H), 1.55 (s, 3H), 1.51 (s, 9H), 1.32 (t, J= 7.1, 3H), 1.23 (t, J= 7.3, 3H). EM m/e (M-H)⁺= 462.0.

Intermediario 2

15



Éster de dietilo del ácido 2-(S)-(Acetoximetil-4-tert-butoxicarbonilamino-3-metil-bencil)-succínico. El éster de
20 dietilo del ácido 2-(S)-(acetoximetil-4-tert-butoxicarbonilamino-3-metil-bencilideno)-succínico (4.4 g, 9.5 mmol) y (-)-1,2-bis((2R,5R)-dietilfosfolano)benceno(ciclooctadieno)rodio (I) trifluorometano sulfonato (100 mg) se disolvió en etanol (80
25 mL). La mezcla se colocó en un aparato de hidrogenación Parr.

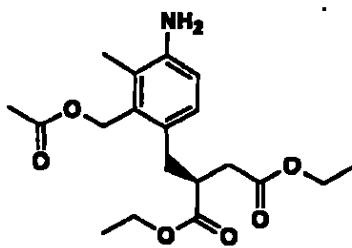
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El recipiente de reacción se cargó con 60 psi (4.218 kg/cm²) de gas de hidrógeno. La mezcla de reacción se permitió agitar a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró in vacuo. El residuo se pasó a través de un tapón de gel de sílice eluyendo 80% acetato de etilo-
5 hexanos (250 mL). El filtrado se concentró in vacuo para proporcionar el producto deseado en 97% de rendimiento como un aceite ámbar. ¹H RMN (300 MHz, CDCl₃): δ= 7.62 (d, J=8.1, 1H), 7.01 (d, J= 8.4, 1H), 6.20 (s, 1H), 5.20 (m, 2H), 4.09
10 (m, 4H), 3.14 (m, 1H), 2.69 (m, 2H), 2.38 (dd, J1= 16.8, J2=4.8, 1H), 2.23 (s, 3H), 2.07 (s, 3H), 1.56 (s, 3H), 1.50 (s, 9H), 1.22 (m, 6H). EM m/e (M-H)⁻= 464.0.

Intermediario 3

15



Éster de dietilo del ácido 2-(S)-(2-acetoximetil-4-
20 amino-3-metil-bencil)-succínico. El ácido trifluoroacético (10 mL) se agregó a una solución de éster de dietilo del ácido 2-(S)-(acetoximetil-4-tert-butoxicarbonilamino-3-metil-bencil)-succínico (4.6 g, 9.9 mmol) en diclorometano (40 mL). La mezcla de reacción se agitó a temperatura ambiente durante
25 1.5 horas. La mezcla se concentró in vacuo. El residuo se

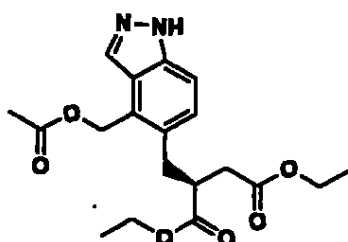
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disolvió en diclorometano (75 mL) y se lavó sucesivamente con bicarbonato de sodio acuoso saturado (2 X 50 mL) y salmuera (30 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró in vacuo hasta producir el producto deseado en 99% de rendimiento como un aceite ámbar. ^1H RMN (300 MHz, CDCl_3): δ = 6.85 (d, J = 8.1, 1H), 6.67 (d, J = 8.4, 1H), 5.18 (m, 2H), 4.09 (m, 4H), 3.09 (dd, J_1 = 6.2, J_2 = 13.9, 1H), 2.96 (m, 1H), 2.66 (m, 2H), 2.37 (dd, J_1 = 4.6, J_2 = 16.7, 1H), 2.15 (s, 3H), 2.06 (s, 3H), 1.20 (m, 6H). EM m/e ($\text{M}-\text{C}_2\text{H}_4\text{O}_2+\text{H}$) $^+$ = 306.2.

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Intermediario 4



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Éster de dietilo del ácido 2-(S)-(4-Acetoximetil-1H-indazol-5-ilmetil)-succínico. El nitrato de isoamilo (1.6 mL, 12 mmol) se agregó gota a gota a una solución fría (baño de hielo con agua) de éster de dietilo del ácido 2-(S)-(2-acetoximetil-4-amino-3-metil-bencil)-succínico en carbontetracloruro (80 mL) y ácido acético (4 mL). La mezcla se agitó a 0°C durante 2 horas. La mezcla se entibió y se agitó a temperatura ambiente durante 14 horas. La mezcla se concentró in vacuo. El residuo se disolvió en diclorometano (75 mL) luego se lavó sucesivamente con bicarbonato de sodio

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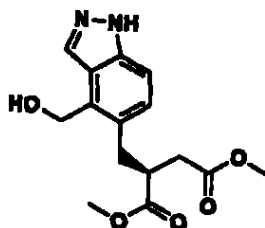
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acuoso saturado (2 X 50 mL), y salmuera (30 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró in vacuo. la cromatografía en gel de sílice (acetato de etilo-hexanos) proporcionó el producto en 55% de rendimiento como un aceite
5 ámbar. ^1H RMN (300 MHz, CDCl_3): δ = 8.19 (s, 1H), 7.44 (d, J = 8.8, 1H), 7.24 (d, J = 8.8, 1H), 5.49 (s, 2H), 4.06 (m, 4H), 3.25 (m, 1H), 3.11 (m, 1H), 2.97 (m, 1H), 2.72 (dd, J1 = 8.8, J2 = 16.5, 1H) 2.43 (dd, J1 = 5.1, J2 = 16.5), 2.09 (s, 3H), 1.19 (m, 6H). EM m/e $(\text{M}+\text{H})^+$ 377.1.

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Intermediario 5



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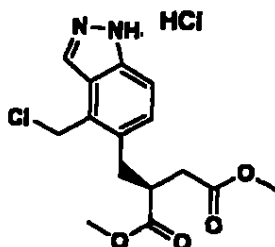
Éster de dimetilo del ácido 2-(S)-(4-hidroximetil-1H-indazol-5-ilmetil)-succínico. El carbonato de potasio (1.6 g, 11.6 mmol) se agregó a una solución de éster de dietilo del ácido 2-(S)-(4-acetoximetil-1H-indazol-5-ilmetil)-succínico
20 (2.0 g, 5.5 mmol) en metanol (60 mL). La mezcla se agitó a temperatura ambiente durante 1.5 horas. La reacción se apagó con la adición de ácido clorhídrico 1N (30 mL). El metanol se removi6 a partir de la mezcla in vacuo. El acuoso restante se hizo básico con bicarbonato de sodio. La mezcla se extrajo
25 con acetato de etilo (2 X 40 mL). Las capas orgánicas

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combinadas se lavaron sucesivamente con agua (30 mL) y salmuera (30 mL). El orgánico se secó (sulfato de magnesio), se filtró luego se concentró in vacuo. El producto deseado se obtuvo en 92% de rendimiento como un aceite ámbar. ^1H RMN (300 MHz, CDCl_3): δ = 8.21 ((s, 1H), 7.34 (d, J= 9.2, 1H), 7.17 (d, J= 8.8, 1H), 5.02 (dd, J1= 12.4, J2= 17.9, 1H) 3.63 (s, 6H), 3.23 (m, 1H), 2.98 (m, 1H), 2.77 (dd, J1= 7.7, J2= 16.8, 1H), 2.53 (dd, J1= 6.4, J2= 16.7, 1H). EM m/e $(\text{M}+\text{H})^+$ 307.0.

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Intermediario 6



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Clorohidrato de éster de dimetilo del ácido 2-(S)-(4-Clorometil-1H-indazol-5-ilmetil)-succínico. El cloruro de tionilo (5.0 mL) se agregó a una solución de éster de dimetilo del ácido 2-(S)-(4-hidroximetil-1H-indazol-5-ilmetil)-succínico (1.53 g, 5.0 mmol) en diclorometano (30 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se concentró in vacuo. El residuo se trituyó en tolueno (30 mL), luego se concentró in vacuo. El residuo se trató con diclorometano (30 mL) luego se concentró in vacuo. El producto deseado se obtuvo en 96% de

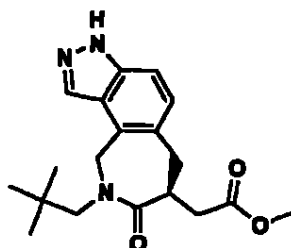
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rendimiento como un sólido anaranjado. ^1H RMN (300 MHz, CDCl_3): δ = 8.22 (s, 1H), 7.49 (d, J = 8.8, 1H), 7.15 (d, J = 8.8, 1H), 5.12 (s, 2H), 3.56 (s, 3H), 3.52 (s, 3H), 3.05 (m, 3H), 2.69 (dd, J_1 = 8.1, J_2 = 16.5), 2.54 (m, 1H). EM m/e
5 $(\text{M}+\text{H})^+ = 325.2$.

Intermediario 7

10



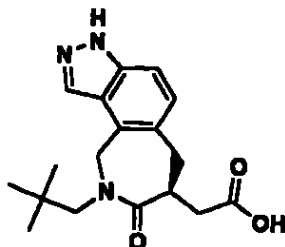
Éster de metilo del ácido [9-(2,2-Dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. La neopentilamina (2.0 mL, 17 mmol) se agregó a
15 una mezcla de carbonato de potasio (1.2 g, 8.7 mmol) y clorohidrato de éster de dimetilo del ácido 2-(S)-(4-clorometil-1H-indazol-5-ilmetil)-succínico (1.56 g, 4.3 mmol) en acetonitrilo (30 mL). La mezcla de reacción se calentó a reflujo hasta que el material de partida se consideró a ser
20 consumido por CLAR (1.5 horas). La mezcla se enfrió a temperatura ambiente luego se filtró. El filtrado se concentró in vacuo. El residuo se disolvió en una mezcla de tolueno (40 mL) y ácido acético (2 mL). La mezcla de reacción se calentó a reflujo hasta que se juzgó completa por CLAR (44
25 horas). La mezcla se concentró in vacuo. El residuo se

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disolvió en acetato de etilo (50 mL) y se lavó con bicarbonato de sodio acuoso saturado (2 X 25 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró in vacuo. La cromatografía en gel de sílice (acetato de etilo-hexanos) proporcionó el producto deseado en 90% de rendimiento como una espuma amarilla. ¹H RMN (300 MHz, CDCl₃): δ= 8.01 (s, 1H), 7.35 (d, J= 8.4, 1H), 7.13 (d, J= 8.4, 1H), 5.41 (d, J=16.8, 1H), 4.50 (d, J= 16.8, 1H), 3.90 (m, 1H), 3.70 (s, 3H), 3.62 (m, 1H), 3.50 (d, J= 13.9, 1H), 3.18 (d, J= 13.5, 1H), 3.05 (m, 2H), 2.43 (dd, J1= 16.7, J2= 5.3, 1H), 0.83 (s, 9H). EM m/e (M-H)⁺= 342.0.

Intermediario 8

15



Ácido [9-(2,2-Dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético.

20 El litio hidróxido monohidrato (335 mg, 8.0 mmol) se agregó a una solución de éster de metilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético (1.32 g, 3.8 mmol) en metanol (15 mL), tetrahidrofurano (15 mL) y agua (15 mL). La 25 mezcla de reacción se calentó a 50°C durante 1 hora. Los

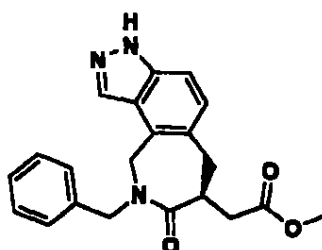
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solventes orgánicos se removieron a partir de la mezcla in vacuo. El acuoso restante se diluyó con agua (25 mL). La mezcla se neutralizó con ácido clorhídrico 1 N (8.0 mL). La mezcla se extrajo con acetato de etilo (2 X 30 mL). Las capas
5 orgánicas combinadas se lavaron con salmuera (20 mL) luego se secaron (sulfato de magnesio), filtraron y concentraron in vacuo. El producto deseado se obtuvo en 88% de rendimiento como un sólido amarillo ligero. ¹H RMN (300 MHz, CDCl₃): δ= 7.98 (s, 1H), 7.36 (d, J= 8.8, 1H), 7.10 (d, J= 8.8, 1H),
10 5.38 (d, J= 16.8, 1H), 4.48 (d, J= 16.8, 1H), 3.85 (m, 1H), 3.49 (d, J= 13.5, 1H), 3.18 (d, J= 13.9, 1H), 3.08 (s, 2H), 2.92 (dd, J₁=8.2, J₂= 16.3, 1H), 2.55 (dd, J₁= 16.5, J₂=4.8, 1H) 0.81 (s, 9H). EM m/e (M-H)⁻= 328.0.

Intermediario 9

15



20 *Éster de metilo del ácido (9-Bencil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il)-acético.*

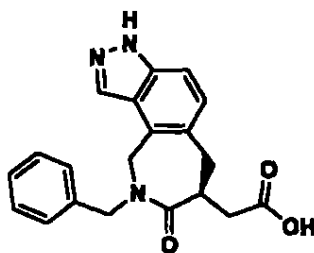
La bencilamina (250 µL, 2.3 mmol) y clorohidrato de éster de dimetilo del ácido 2-(S)-(4-Clorometil-1H-indazol-5-ilmetil)-succínico se convirtieron siguiendo un procedimiento análogo
25 a la preparación de éster de metilo del ácido [9-(2,2-

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Dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
(S)-ciclohepta[e]inden-7-il]-acético. La cromatografía de gel
de sílice (acetato de etilo-hexanos) proporcionó el producto
deseado en 62% de rendimiento como un aceite ámbar. ¹H RMN
5 (300 MHz, CDCl₃): δ= 7.77 (s, 1H), 7.28 (m, 6H), 7.09 (d, J= 8.4, 1H), 5.18 (d, J= 16.8, 1H), 4.99 (d, J= 15.0, 1H), 4.43 (d, J= 5.9, 1H), 4.39 (d, J= 1.8, 1H), 4.34 (d, J= 4.0, 1H), 3.74 (s, 3H), 3.13 (m, 2H), 2.51 (dd, J₁= 5.5, J₂= 16.8, 1H). EM m/e (M+H)⁺ 364.0.

10

Intermediario 10



15 Ácido (9-Bencil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il)-acético. El hidróxido de litio (32 mg, 0.76 mmol) y éster de metilo del ácido (9-bencil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il)-acético se hicieron reaccionar en
20 una manera análoga a la preparación del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El producto deseado se obtuvo como un aceite amarillo en 99% de rendimiento. ¹H RMN (300 MHz, DMSO, D₆): δ= 7.72 (s, 1H), 7.28 (m, 4H), 7.16 (m, 2H), 7.06 (d, J= 8.8, 1H), 5.15 (d, J= 16.8, 1H), 4.95 (d, J= 25

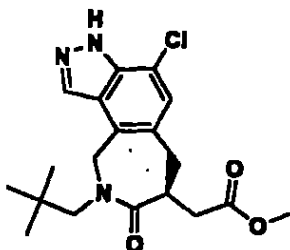
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15.0, 1H), 4.37 (m, 4H), 3.09 (m, 2H), 2.59 (dd, J1= 5.1, J2= 16.5, 1H). EM m/e (M+H)⁺= 350.0.

Intermediario 11

5



10 Éster de metilo del ácido [4-Cloro-9-(2,2-dimetil-
propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-
ciclohepta[e]inden-7-il]-acético. El carbonato de potasio
(190 mg, 1.4 mmol) se agregó a una solución de éster de
dietilo del ácido 2-(S)-(4-acetoximetil-7-cloro-1H-indazol-5-
15 ilmetil)-succínico (240 mg, 0.58 mmol) en metanol (10 mL) y
etanol (5 mL). La mezcla se agitó a temperatura ambiente
durante 1.5 horas. La reacción se apagó con la adición de
ácido clorhídrico 1 N (10 mL). Los solventes orgánicos se
removieron a partir de la mezcla in vacuo. El acuoso restante
20 se hizo básico con bicarbonato de sodio. La mezcla se extrajo
acetato de etilo 2X (15 mL). Las capas orgánicas combinadas
se secaron (sulfato de magnesio), filtraron y concentraron.
El residuo se disolvió en diclorometano (6 mL). El
cloruro de tionilo (2 mL) se agregó a la mezcla. La
25 reacción se agitó a temperatura ambiente durante 1.5

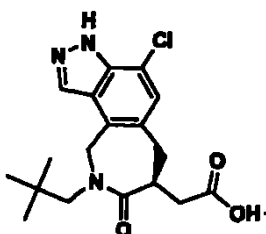
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horas. La mezcla se concentró in vacuo. El residuo se
trató con diclorometano (25 mL) luego se concentró in
vacuo. El residuo se suspendió en acetonitrilo (5
mL). El carbonato de potasio (200 mg, 1.4 mmol) se
5 agregó a la mezcla seguido por neopentilamina (150
μL, 1.3 mmol). La mezcla de reacción se calentó a
reflujo durante 1 hora. La mezcla se enfrió a
temperatura ambiente luego se filtró a través de una
membrana PTFE 0.45 μm. El filtrado se concentró. El
10 residuo se disolvió en una mezcla de tolueno (5 mL) y
ácido acético (250 μL). La mezcla de reacción se
calentó a 100°C durante 15 horas luego se enfrió a
reflujo durante 7 horas. La mezcla se enfrió a
temperatura ambiente luego se diluyó con acetato de
15 etilo (15 mL). La mezcla se lavó sucesivamente
bicarbonato de sodio acuoso saturado 2X (20 mL), agua
(15 mL) y salmuera (10 mL). El orgánico se secó
(sulfato de magnesio), filtró y concentró in vacuo.
La cromatografía en gel de sílice (acetato de etilo-
20 hexanos) proporcionó el producto deseado en 48% de
rendimiento como un aceite amarillo. ¹H RMN (300 MHz,
CDCl₃): δ= 8.02 (s, 1H), 7.13 (s, 1H), 5.37 (m, 1H), 4.42 (d,
J= 17.2, 1H), 3.88 (m, 1H), 3.70 (s, 3H), 3.53 (d, J= 13.9,
1H), 3.12 (d, J= 13.9, 1H), 3.03 (m, 3H), 2.44 (dd, J₁= 5.9,
25 J₂= 16.9, 1H), 0.81 (s, 9H). EM m/e (M+H)⁺= 378.1.

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Intermediario 12



Ácido

[4-Cloro-9-(2,2-dimetil-propil)-8-oxo-

3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El litio hidróxido monohidrato (30 mg, 0.71

10 mmol) se agregó a una solución de éster de metilo del ácido

[4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético (100 mg,

0.26 mmol) en metanol (2 mL), tetrahidrofurano (2 mL) y agua (2 mL). La mezcla de reacción se agitó a temperatura ambiente

15 durante dos horas seguido por el calentamiento a 50°C durante

40 minutos. Los solventes orgánicos se removieron a partir de

la mezcla in vacuo. El acuoso restante se neutralizó con

ácido clorhídrico 1N (750 µL). La mezcla se extrajo acetato

de etilo 2X (10 mL). Las capas orgánicas combinadas se

20 lavaron con salmuera (10 mL) luego se secaron (sulfato de

magnesio), filtraron y concentraron in vacuo. El producto

deseado se obtuvo en 93% de rendimiento como un sólido

anaranjado. ¹H RMN (300 MHz, CDCl₃): δ= 7.98 (s, 1H), 7.09 (s,

1H), 5.35 (d, J= 17.2, 1H), 4.41 (d, J=17.2, 1H), 3.82 (m,

25 1H), 3.48 (d, J= 13.9, 1H), 3.12 (d, J= 13.9, 1H), 3.02 (m,

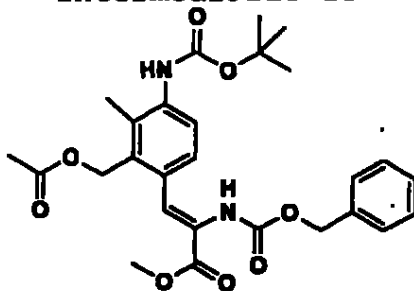
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2H), 2.92 (dd, $J_1 = 8.4$, $J_2 = 16.8$, 1H), 2.45 (dd, $J_1 = 5.1$, $J_2 = 16.8$, 1H), 0.78 (s, 9H). EM m/e (M-H)⁻ = 362.0.

Intermediario 13

5



Éster de metilo del ácido 3-(2-Acetoximetil-4-tert-
 10 butoxycarbonilamino-3-metil-fenil)-2-benciloxycarbonilamino-
 acrílico. El acetato de paladio (II) (105 mg, 0.43 mmol) se
 agregó a una mezcla del éster de 3-tert-butoxycarbonilamino-
 6-yodo-2-metil-bencilo del ácido acético (2.89 g, 7.1 mmol),
 éster de metilo Z-dehidroalanina (2.20 g, 9.4 mmol), hidrato
 15 de cloruro de tetrabutilamonio (2.70 g, 9.7 mmol), y
 bicarbonato de sodio (1.80 g, 21.4 mmol) en THF (100 mL). La
 reacción se calentó a reflujo durante 3.75 horas. La mezcla
 se enfrió a temperatura ambiente luego se filtró a través de
 un tapón de gel de sílice eluyendo acetato de etilo-hexanos
 20 70% (500 mL). El filtrado se concentró in vacuo. La
 cromatografía en gel de sílice proporcionó el compuesto del
 título como un sólido amarillo en 69% de rendimiento. ¹H RMN
 (300 MHz, CDCl₃): δ = 7.79 (d, $J = 8.4$, 1H), 7.42 (s, 1H), 7.27
 (m, 6H), 6.30 (s, 1H), 5.11 (s, 2H), 5.02 (s, 2H), 3.81 (s,
 25 3H), 2.21 (s, 3H), 2.02 (s, 3H), 1.51 (s, 9H). EM m/e (M-H)⁻ =

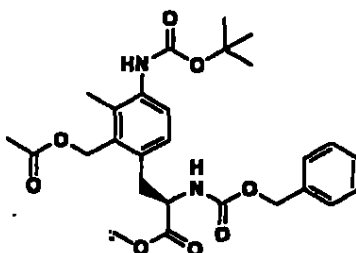
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Intermediario 14

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Éster de metilo del ácido 3-(2-Acetoximetil-4-tert-butoxicarbonilamino-3-metil-fenil)-2-(R)-

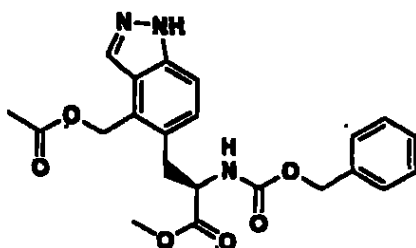
10 benciloxycarbonilamino-propiónico. Una solución de éster de metilo del ácido 3-(2-acetoximetil-4-tert-butoxicarbonilamino-3-metil-fenil)-2-benciloxycarbonilamino-acrílico (2.51 g, 4.9 mmol) en metanol (50 mL) y acetato de etilo (15 mL) se hizo reaccionar en una manera similar a la
15 preparación de éster de dietilo del ácido 2-(S)-(acetoximetil-4-tert-butoxicarbonilamino-3-metil-bencil)-succínico. El compuesto del título se obtuvo como un sólido blanco apagado en 97% de rendimiento. ^1H RMN (300 MHz, CDCl_3): δ = 7.66 (d, J= 7.9, 1H), 7.31 (m, 5H), 6.99 (d, J= 8.5, 1H),
20 6.21 (s, 1H), 5.31 (d, J= 7.6, 1H), 5.17 (d, J= 3.7, 2H), 5.04 (d, J= 5.80, 2H), 4.56 (m, 1H), 3.71 (s, 3H), 3.23 (dd, J1= 5.80, J2= 14.7, 1H), 3.07 (dd, J1= 7.8, J2= 14.2, 1H), 2.21 (s, 3H), 2.00 (s, 3H), 1.50 (s, 9H). EM m/e $(\text{M}-\text{H})^-$ = 513.0.

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Intermediario 15



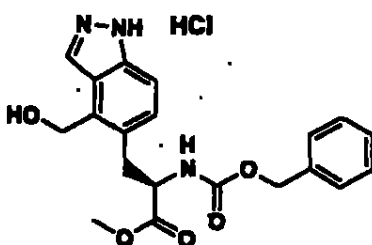
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Éster de metilo del ácido 3-(4-Acetoximetil-1H-indazol-5-il)-2-(R)-benciloxycarbonilamino-propiónico. El ácido trifluoroacético (2.5 mL) se agregó a una solución de éster de metilo del ácido 3-(2-acetoximetil-4-tert-butoxicarbonilamino-3-metil-fenil)-2-(R)-benciloxycarbonilamino-propiónico (770 mg, 1.5 mmol) en diclorometano (10 mL). La mezcla de reacción se agitó a temperatura ambiente durante 1.5 horas. La mezcla se concentró in vacuo. El residuo se trató con cloroformo (40 mL) luego se concentró in vacuo. El residuo se disolvió en ácido acético 5% en cloroformo (10 mL). El nitrato de isoamilo (240 µL, 1.8 mmol) se agregó a la mezcla. La mezcla de reacción se agitó a temperatura ambiente durante 20 minutos. El acetato de potasio (690 mg, 7.0 mmol) se agregó a la mezcla. La mezcla de reacción se agitó a temperatura ambiente durante 45 minutos. La mezcla se lavó sucesivamente con agua (10 mL), y bicarbonato de sodio acuoso saturado 2X (15 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró. El producto crudo se obtuvo en 81% de rendimiento

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como un aceite ámbar y se usó sin purificación adicional. ^1H RMN (300 MHz CDCl_3): δ = 8.17 (s, 1H), 7.41 (d, J = 8.4, 1H), 7.25 (m, 6H), 5.54 (d, J = 8.1, 1H), 5.44 (s, 2H), 5.03 (s, 2H), 4.67 (m, 1H), 3.78 (s, 3H), 3.37 (dd, J_1 = 5.9, J_2 = 14.3, 1H), 3.22 (dd, J_1 = 8.1, J_2 = 14.3, 1H), 1.98 (s, 3H). EM m/e $(\text{M}+\text{H})^+ = 426.0$.

Intermediario 16



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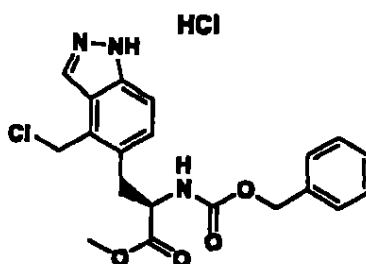
Clorohidrato del éster de metilo del ácido 2-(R)-
15 Benciloxycarbonilamino-3-(4-tert-butoxycarbonilamino-2-
hidroximetil-3-metil-fenil)-propiónico. El carbonato de
potasio (1.65 g, 12 mmol) se agregó a una solución de éster
de metilo del ácido 3-(4-acetoximetil-1H-indazol-5-il)-2-
benciloxycarbonilamino-propiónico (2.30 g, 5.4 mmol) en
20 metanol (70 mL). La mezcla de reacción se agitó a temperatura
ambiente durante 2 horas. La reacción se apagó con ácido
clorhídrico 1N (50 mL). El metanol se removió a partir de la
mezcla in vacuo. El acuoso restante se hizo básico con
bicarbonato de sodio. El acuoso se extrajo con acetato de
25 etilo (2 X 50 mL). Los extractos combinados se lavaron con

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agua (30 mL) y salmuera (20 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró. El residuo se disolvió en acetato de etilo:hexanos 1:1 (50 mL). El ácido clorhídrico 1N en 1,4 dioxano (1.4 mL), se agregó a la mezcla gota a gota causando un precipitado para formarse. La mezcla se agitó a temperatura ambiente durante 1 hora. Los sólidos se filtraron, se lavaron con acetato de etilo:hexanos 1:1, luego se secaron in vacuo. El producto se obtuvo en 61% de rendimiento como un sólido color canela. ^1H RMN (300 MHz, DMSO- D_6): δ = 8.67 (s, 1H), 7.49 (s, 2H), 7.22 (m, 5H), 4.99 (m, 4H), 4.50 (m, 1H), 3.73 (s, 3H), 3.41 (m, 1H), 3.13 (dd, J_1 = 9.9, J_2 = 13.9, 1H). EM m/e ($\text{M}+\text{H}$) $^+$ = 384.0.

Intermediario 17

15

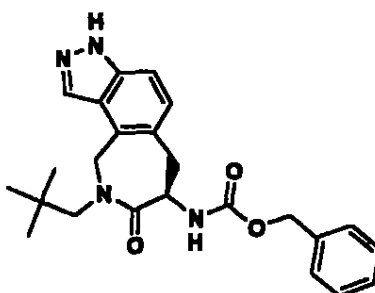


20 *Clorohidrato del éster de metilo del ácido 2-(R)-Benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)-propiónico.* El clorohidrato del éster de metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-tert-butoxicarbonilamino-2-hidroximetil-3-metil-fenil)-propiónico se hizo reaccionar en
25 una manera análoga a la preparación del clorohidrato del

303 ~~304~~

éster de dimetilo del ácido 2-(S)-(4-clorometil-1H-indazol-5-ilmetil)-succínico. El compuesto del título se obtuvo como un sólido anaranjado en 99% de rendimiento. ^1H RMN (300 MHz, CD_3OD): δ = 8.43 (s, 1H), 7.50 (d, J= 8.8, 1H), 7.38 (d, J= 8.4, 1H), 7.24 (m, 5H), 5.06 (d, J= 11.0, 1H), 4.98 (d, J= 4.8, 2H), 4.56 (dd, J1= 5.7, J2= 9.3, 1H), 3.71 (s, 3H), 3.42 (dd, J1= 5.5, J2= 14.3, 1H), 3.17 (dd, J1= 9.3, J2= 14.1, 1H). EM m/e $(\text{M}+\text{H})^+$ 402.0.

Intermediario 18



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Éster de bencilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico. La neopentilamina (600 μL , 4.5 mmol) y clorohidrato del éster de metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)propiónico se hicieron reaccionar en una manera análoga a la preparación de éster de metilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. La cromatografía en gel de sílice proporcionó el compuesto del título como un aceite

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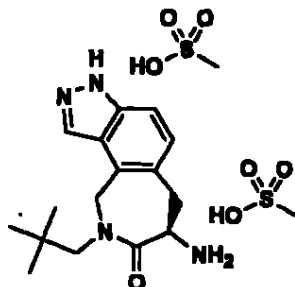
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ligeramente de color en 88% de rendimiento. ^1H RMN (300 MHz, CDCl_3); δ = 7.97 (d, J = 2.9, 1H), 7.38 (d, J = 4.0, 3H), 7.31 (m, 3H), 7.06 (dd, J_1 = 3.7, J_2 = 8.8, 6.32 (d, J = 6.3, 1H), 5.24 (m, 2H), 5.15 (s, 2H), 4.42 (dd, J_1 = 5.5, J_2 = 17.2, 1H), 3.56 (d, J = 13.9, 1H), 3.45 (d, J = 16.5, 1H), 3.07 (m, 2H), 0.82 (s, 9H). (M+H) $^+$ =421.0.

Intermediario 19

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Bismetansulfonato de 7-(R)-Amino-9-(2,2-dimetil-propil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.
El ácido metansulfónico (1 mL) se agregó a una solución de éster de bencilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico (145 mg, 0.34 mmol) y anisol (100 μL , 0.92 mmol) en diclorometano (4 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2.5 horas. La mezcla se diluyó con éter de dietilo (25 mL). La mezcla se permitió que reposara a temperatura ambiente durante 30 minutos. Los solventes se decantaron completamente. El residuo restante se lavó con éter de dietilo (25 mL) luego se secó in vacuo. El

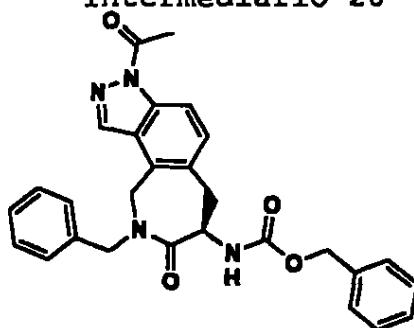
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producto crudo se obtuvo como un aceite anaranjado en
rendimiento cuantitativo, y se usó sin purificación
adicional. ^1H RMN (300 MHz, CD_3OD): δ = 8.50 (s, 1H), 7.56 (d,
 J = 8.8, 1H), 7.39 (s, J = 8.8, 1H), 5.42 (d, J = 17.9, 1H),
5 5.10 (dd, J_1 =4.4, J_2 = 12.4, 1H), 4.75 (d, J = 17.6, 1H), 3.84
(d, J = 13.5, 1H), 3.42 (m, 3H), 3.10 (d, J = 13.9, 1H), 2.71
(s, 6H), 0.82 (s, 9H). $(\text{M}+\text{H})^+=287.1$.

Intermediario 20

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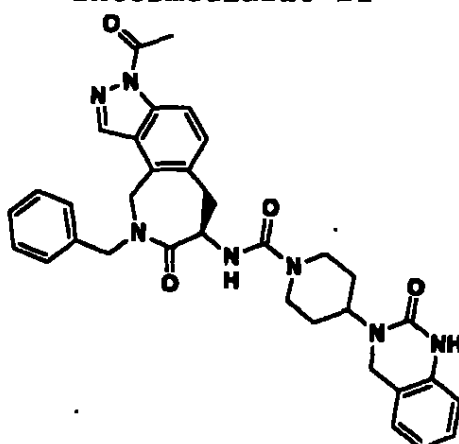


Éster de bencilo del ácido (3-acetil-9-bencil-8-oxo-3,6,7,8,9,10-
15 hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il)-carbámico. La
bencilamina (53 μL , 0.49 mmol) se agregó a una mezcla de éster de
metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-clorometil-1H-
indazol-5-il)-propiónico (125 mg, 0.31 mmol) y carbonato de potasio (50
mg, 0.36 mmol) en acetonitrilo (5 mL). La reacción se calentó a reflujo
20 durante 1 hora. La mezcla se enfrió a temperatura ambiente luego se
filtró. El filtrado se concentró. El residuo se disolvió en una mezcla
de tolueno (5 mL) y ácido acético (50 μL). La mezcla se calentó a
reflujo durante 2 horas. La mezcla se enfrió a temperatura ambiente. El
anhídrido acético (500 μL) se agregó a la mezcla. La reacción se agitó
25 a temperatura ambiente durante 2 horas. La mezcla se diluyó con acetato

30.6
~~30.6~~

de etilo (20 mL). La mezcla se lavó sucesivamente con agua (15 mL), ácido clorhídrico 1N (2 X 10 mL), y salmuera (10 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró. La cromatografía en gel de sílice (acetato de etilo - hexanos) proporcionó el compuesto del
 5 título en 43% de rendimiento como un aceite ámbar. ^1H RMN (300 MHz, CDCl_3): δ = 8.33 (s, 1H), 7.47 (d, J = 8.8, 1H), 7.33 (m, 5H), 7.17 (m, 5H), 7.02 (d, J = 9.2, 1H), 6.28 (d, J = 6.6, 1H), 5.34 (m, 1H), 5.16 (s, 2H), 5.00 (m, 1H), 4.84 (m, 1H), 5.43 (d, J = 14.5, 1H), 4.43 (d, J = 5.9, 1H), 4.32 (d, J = 16.8, 1H), 4.11 (m, 1H), 2.02 (s, 3H). EM m/e ($\text{M}+\text{H}$)⁺
 10 =483.2.

Intermediario 21



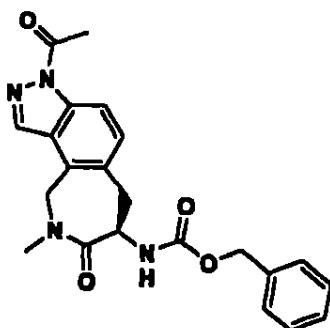
(3-acetil-9-bencil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-
 20 triaza-(R)-ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. Una cantidad catalítica de paladio en carbono al 10% se agregó a una mezcla de ácido acético (200 μL) y éster de bencilo del ácido (3-acetil-9-bencil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-
 25 triaza-(R)-ciclohepta[e]inden-7-il)-carbámico (65 mg, 0.13

307 282

mmol) en metanol (10 mL). El recipiente de reacción se cargó con 50 psi (3.51 Kg/cm²) de gas de hidrógeno y se colocó en un aparato de hidrogenación Parr. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se
5 filtró. El filtrado se concentró. El residuo se dividió entre diclorometano (10 mL) y bicarbonato de sodio acuoso saturado (5 mL). El fosgeno al 20% en tolueno (170 µL, 0.32 mmol) se agregó a la mezcla con agitación vigorosa. El acetato de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidinio (110 mg,
10 0.38 mmol) se agregó a la mezcla. La mezcla de reacción se agitó vigorosamente durante 45 minutos. Las capas se separaron. El orgánico se lavó con salmuera (10 mL) luego se secó (sulfato de magnesio) y se concentró in vacuo. La CLAR de fase inversa preparatoria (acetonitrilo - agua, ácido
15 trifluoroacético al 0.2%) seguido por la remoción del acetonitrilo in vacuo proporcionó una solución acuosa que contiene el compuesto del título. Se extrajo de la solución acuosa con diclorometano (20 mL). Los extractos combinados se lavaron con salmuera (20 mL). El orgánico se secó (sulfato de
20 magnesio), filtró y concentró. El producto deseado se obtuvo como un sólido blanco en 23% de rendimiento. EM m/e (M+H)⁺ 606.4. rf= 2.09 min.

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J. J. J.

Intermediario 22



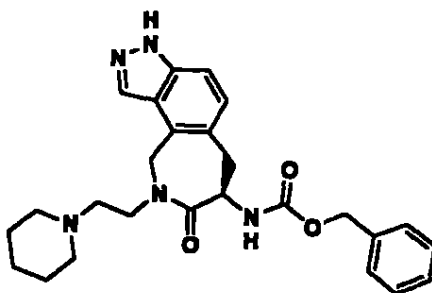
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Éster de bencilo del ácido (3-acetil-9-metil-8-oxo-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-
10 il)-carbámico. Una solución de metilamina en metanol (2M, 2
mL, 4 mmol) se agregó a una mezcla de carbonato de potasio
(130 mg, 0.94 mmol) y éster de metilo del ácido 2-(R)-
benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)-
propiónico (165 mg, 0.41 mmol) en acetonitrilo (5 mL). La
15 mezcla se calentó a 40°C durante 1 hora. La mezcla se enfrió
a temperatura ambiente. La mezcla se filtró. El filtrado se
concentró. El residuo se trató con una mezcla de tolueno (5
mL) y ácido acético (200 µL). La mezcla se calentó a reflujo
durante 45 minutos. La mezcla se enfrió a temperatura
20 ambiente luego el anhídrido acético se agregó (2 mL). La
reacción se agitó a temperatura ambiente durante 16 horas. La
mezcla se diluyó con acetato de etilo (10 mL) luego se lavó
sucesivamente con agua (10 mL), bicarbonato de sodio acuoso
saturado (2X15 mL) y salmuera (10 mL). El orgánico se secó
25 (sulfato de magnesio), filtró y concentró. La cromatografía

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en gel de sílice (acetato de etilo - hexanos) proporcionó el producto deseado como un sólido amarillo en 18% de rendimiento. ^1H RMN (300 MHz, CDCl_3): δ = 8.70 (s, 1H), 7.51 (d, J = 9.2, 1H), 7.34 (m, 5H), 7.05 (d, J = 9.2, 1 H), 6.19 (m, 1H), 5.23 (s, 2H), 5.13 (s, 2H), 4.18 (d, J = 17.2, 1H), 3.46 (d, J =17.2, 1H), 3.11 (s, 3H), 2.95 (m, 1H), 2.89 (s, 2H). EM m/e $(\text{M}+\text{H})^+=407.2$

Intermediario 23



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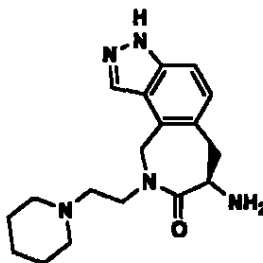
15 Éster de bencilo del ácido [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico. La 1-(2-Aminoetil)piperidina (150 μL , 1.1 mmol) se agregó a una mezcla de carbonato de potasio (150 mg, 1.1 mmol) y
20 clorohidrato del éster de metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)-propiónico (220 mg, 0.50 mmol) en acetonitrilo (5 mL). La reacción se calentó a reflujo durante 1 hora. La mezcla se enfrió a temperatura ambiente luego se concentró. El residuo
25 se disolvió en una mezcla de diclorometano (10 mL) y ácido

310 ~~310~~

acético (200 μ L). La mezcla se calentó at 40 °C for 32 horas y heated a reflujo for 8 horas. La mezcla se enfrió a temperatura ambiente then se lavó sucesivamente con bicarbonato de sodio acuoso saturado (2 X 10 mL), agua (10 mL) y salmuera (10 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró. El producto crudo se obtuvo como un sólido color canela en 86% de rendimiento. El material se llevó a cabo sin purificación adicional. EM m/e (M+H)⁺= 462.4. CLAR rf= 1.19 min.

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Intermediario 24



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7-(R)-Amino-9-(2-piperidin-1-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El ácido metansulfónico (1 mL) se agregó a una mezcla de anisol (100 μ L, 0.92 mmol) y éster de bencilo del ácido [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico (200 mg, 0.43 mmol) en diclorometano (4 mL). La reacción se agitó a temperatura ambiente durante 1 hora. La mezcla se diluyó con éter de dietilo (30 mL). La mezcla se permitió que reposara a temperatura ambiente durante 15 minutos. Los solventes se decantaron completamente. El residuo restante se disolvió en agua (5 mL). La

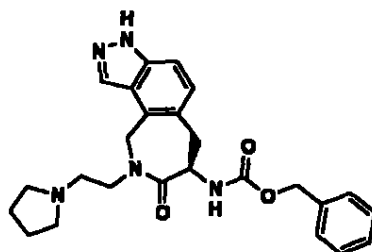
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mezcla se lavó con éter de dietilo (2X10 mL). La acuosa se hizo básico con hidróxido de sodio 1N (2 mL). La mezcla se extrajo con acetato de etilo (2X15 mL). Los extractos combinados se lavaron con salmuera (5 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró. El compuesto del título se obtuvo como un aceite ámbar en 42% de rendimiento. El material se llevó a cabo sin purificación adicional. ¹H RMN (300 MHz, CDCl₃): δ= 8.06 (s, 1H), 7.35 (d, J= 8.4, 1H), 7.11 (d, J= 8.4, 1H), 5.16 (d, J= 16.8, 1H), 4.57 (d, J= 16.8, 1H), 4.40 (dd, J₁= 12.8, J₂= 4.4, 1H), 3.77 (m, 1H), 3.54 (m, 1H), 3.29 (m, 1H), 3.03 (m, 1H), 2.36 (m, 6H), 2.14 (m, 2H), 1.38 (m, 4H). EM m/e (M+H)⁺ 328.3.

Intermediario 25



15

Éster de bencilo del ácido [8-oxo-9-(2-pirrolidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico. La 1-(2-aminoetil)pirrolidina (90 µL, 0.71 mmol) se agregó a una mezcla de éster de metilo del ácido 2-(R)-benciloxycarbonilamino-3-(4-clorometil-1H-indazol-5-il)-propiónico (100 mg, 0.23 mmol) y carbonato de potasio (120 mg, 0.87 mmol) en acetonitrilo (5 mL). La reacción se calentó a reflujo hasta que la CLAR sugiere que el material de

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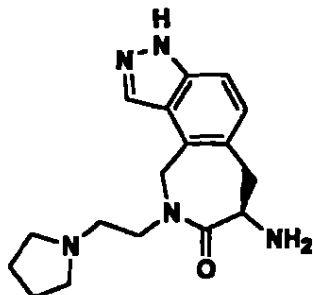
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partida se ha consumido (2 horas). La mezcla se enfrió a temperatura ambiente luego se filtró. El ácido acético (200 µL) se agregó al filtrado. La reacción se calentó a reflujo hasta que se juzgó completa por CLAR (1 hora). La mezcla se diluyó con acetato de etilo (20 mL) luego se lavó sucesivamente con bicarbonato de sodio acuoso saturado (15 mL), agua (10 mL) y salmuera (10 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró. El producto crudo se obtuvo en 69% de rendimiento como un aceite amarillo. El material se llevó a cabo sin purificación adicional. ¹H RMN (300 MHz, CDCl₃): δ= 8.04 (s, 1), 7.38 (m, 5H), 7.28 (d, J= 8.4, 1H), 7.02 (d, J= 8.8, 1H), 6.25 (d, J= 6.2, 1H), 5.25 (m, 1H), 5.15 (s, 2H), 4.56 (d, J= 16.8, 1H), 3.70 (m, 2H), 3.47 (dd, J1= 3.5, J2= 16.7, 1H), 3.01 (m, 1H), 2.62 (m, 2H), 2.48 (m, 3H), 1.74 (m, 4H). EM m/e (M+H)⁺= 448.4.

Intermediario 26



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7-(R)-Amino-9-(2-pirrolidin-1-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

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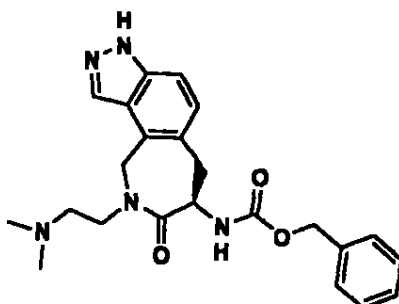
El compuesto del título se obtuvo a partir del éster de bencilo del ácido [8-oxo-9-(2-pirrolidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico siguiendo un
5 procedimiento análogo a la preparación de la 7-(R)-amino-9-(2-piperidin-1-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

El material se obtuvo como un aceite ámbar en 52% de rendimiento y se usó sin purificación adicional.

10 ^1H RMN (300 MHz, DMSO- D_6): δ = 8.06 (s, 1H), 7.33 (d, J= 8.8, 1H), 7.10 (d, J= 8.8, 1H), 5.16 (d, J= 16.8, 1H), 5.48 (d, J= 16.8, 1H), 4.40 (dd, J1= 13.0, J2= 4.2, 1H), 3.67 (m, 2H), 3.29 (dd, J1= 3.11, J2= 17.0, 1H), 3.01 (dd, J1= 16.8, J2= 12.8, 1H), 2.58
15 (m, 2H), 1.87 (m, 4H), 1.67 (m, 4H). EM m/e (M+H) $^+$ = 422.4.

Intermediario 27

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éster de bencilo del ácido [9-(2-dimetilamino-etil)-8-
25 oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-

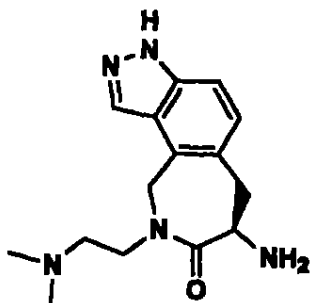
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ciclohepta[e]inden-7-il]-carbámico. La N,N-etilendiamina (70
µL, 0.66 mmol) y éster de metilo del ácido 2-(R)-
benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)-
propiónico (100 mg, 0.23 mmol) se convirtieron al compuesto
5 del título siguiendo un procedimiento análogo a la
preparación del éster de bencilo del ácido [8-oxo-9-(2-
pirrolidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
(R)-ciclohepta[e]inden-7-il]-carbámico.

El producto crudo se obtuvo como un aceite ámbar en 52%
10 de rendimiento. El material se llevó a cabo sin purificación
adicional. ¹H RMN (300 MHz, CDCl₃): δ= 7.99 (s, 1H), 7.36 (m,
6H), 6.27 (d, J= 6.2, 1H), 5.25 (m, 1H), 5.16 (s, 2H), 5.13
(m, 1H), 5.06 (d, J= 18.7, 1H), 4.52 (d, J= 17.2, 1H), 3.61
(t, J=6.8, 2H), 3.45 (dd, J₁= 2.4, J₂= 16.7, 1H), 3.01 (m,
15 1H), 2.38 (m, 2H), 2.11 (s, 6H). EM m/e (M+H)⁺= 422.4.

Intermediario 28

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7-(R)-Amino-9-(2-dimetilamino-etil)-6,7,9,10-
25 tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

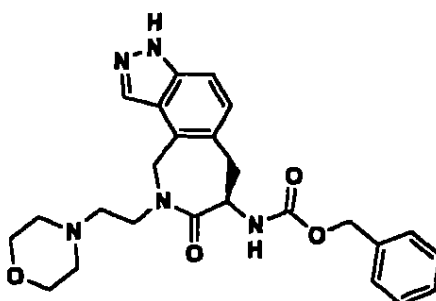
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El éster de bencilo del ácido [9-(2-dimetilamino-
 etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-
 ciclohepta[e]inden-7-il]-carbámico (65 mg, 0.15 mmol)
 se convirtió al producto deseado en una manera
 5 análoga a la preparación de la 7-(R)-amino-9-(2-
 pirrolidin-1-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-
 triaza-ciclohepta[e]inden-8-ona.

El material crudo se obtuvo como un aceite
 amarillo en 25% de rendimiento. El material se llevó
 10 a cabo sin purificación adicional. ^1H RMN (300 MHz,
 CDCl_3): δ = 8.07 (s, 1H), 7.35 (d, J = 8.4, 1H), 7.12
 (d, J = 8.4, 1H), 5.15 (d, J = 16.8, 1H), 4.58 (d, J =
 16.8, 1H), 4.42 (dd, J_1 = 4.8, J_2 = 12.8, 1H), 3.62 (m,
 2H), 3.30 (m, 1H), 3.01 (dd, J_1 = 13.0, J_2 = 16.7, 1H),
 15 2.37 (m, 2H), 2.15 (s, 6H). EM m/e ($M+H$) $^+$ = 288.3.

Intermediario 29

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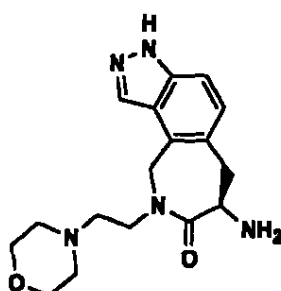
Éster de bencilo del ácido [9-(2-morfolin-4-il-etil)-8-
 oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-
 7-il]-carbámico. 4-(2-Aminoetil)morfolina (90 μL , 0.69 mmol) y éster de
 25 metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-clorometil-1H-

3/6

indazol-5-il)-propiónico (100 mg, 0.23 mmol) se convirtieron dentro del compuesto del título siguiendo un procedimiento análogo a la preparación de éster de bencilo del ácido [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico. El material crudo se obtuvo como un aceite ámbar en 92% de rendimiento. El producto se llevó adelante sin purificación adicional. EM m/e (M+H)⁺ = 464.4. CLAR rf = 1.15 min.

Intermediario 30

10



7-(R)-Amino-9-(2-morfolin-4-il-etil)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El éster de bencilo del ácido [9-(2-morfolin-4-il-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico (95 mg, 0.20 mmol) se convirtió dentro del compuesto del título siguiendo un procedimiento análogo a la preparación de 7-(R)-amino-9-(2-piperidin-1-il-etil)-6,7,9,10-tetrahydro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El producto crudo se obtuvo como un aceite ambar en 62% de rendimiento. El material se llevó a cabo sin purificación adicional. ¹H RMN (300 MHz, CDCl₃): δ = 8.06 (s, 1H), 7.34 (d, J = 8.4, 1H), 7.15 (d, J = 8.8, 1H), 5.22 (d, J = 16.8, 1H),

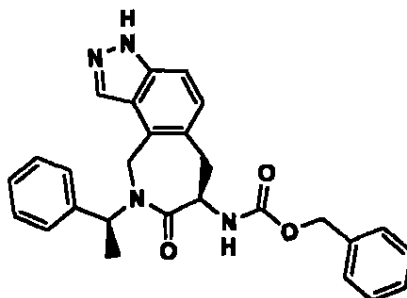
317

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4.51 (d, $J = 17.2$, 2H), 4.44 (m, 1H), 4.02 (m, 1H), 3.40 (t, $J = 4.8$, 4H), 3.31 (m, 3H), 3.07 (m, 1H), 2.32 (m, 4H), 1.95 (m, 2H). EM m/e $(M+H)^+$ 330.3.

Intermediario 31

5

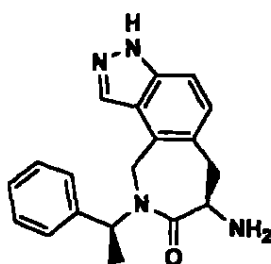


10 *Éster de bencilo del ácido [8-Oxo-9-(1-(S)-fenil-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico.* (S)-(-)- α -Metilbencilamina (85 μ L, 0.67 mmol) y éster de metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)-propiónico (100 mg, 0.23 mmol)
15 se convirtieron dentro del producto deseado siguiendo un procedimiento análogo a la preparación de éster de metilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El
producto crudo se obtuvo como un aceite oscuro en
20 rendimiento cuantitativo. El material se llevó a cabo sin purificación adicional. EM m/e $(M+H)^+$ 455.3. CLAR r_f = 1.68 min.

25

318 JH

Intermediario 32

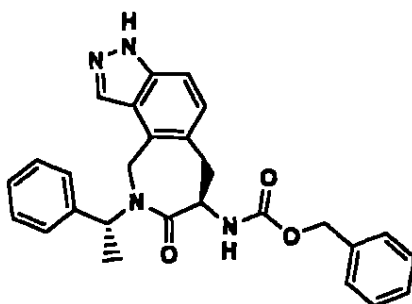


5

7-Amino-9-(1-(S)-fenil-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-(R)-ciclohepta[e]inden-8-ona. El éster de bencilo del ácido [8-Oxo-9-(1-(S)-fenil-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico (105 mg, 0.23 mmol) se hizo reaccionar en una manera análoga a la preparación de 7-(R)-amino-9-(2-piperidin-1-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

15 El producto crudo se obtuvo como un aceite oscuro en 82% de rendimiento. El material se llevó a cabo sin purificación adicional. EM m/e (M-H)⁺= 319.3. CLAR rf= 1.49 min.

Intermediario 33



20

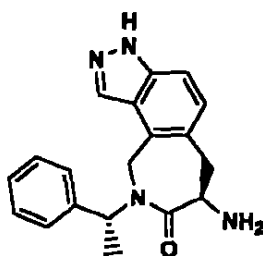
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319 } 20

Éster de bencilo del ácido [8-Oxo-9-(1-(R)-fenil-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico. La (R)-(+)- α -Metilbencilamina (85 μ L, 0.67 mmol) y éster de metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)-propiónico (100 mg, 0.23 mmol) se convirtieron dentro del compuesto del título en una manera similar a la preparación de éster de metilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El material crudo se obtuvo como una espuma oscura en rendimiento cuantitativo. El material se llevó a cabo sin purificación adicional. EM m/e (M-H)⁺ = 453.4. CLAR rf = 1.98 mm.

Intermediario 34

15



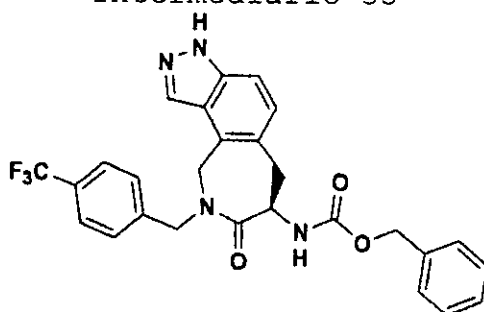
7-Amino-9-(1-(R)-fenil-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-(R)-ciclohepta[e]inden-8-ona. El éster de bencilo del ácido [8-Oxo-9-(1-(R)-fenil-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico (105 mg, 0.23 mmol) se hizo reaccionar en una manera análoga a la preparación de 7-(R)-amino-9-(2-piperidin-1-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El producto crudo se obtuvo como un sólido color canela en 78% de rendimiento. El material se llevó a cabo sin

320

321

purificación adicional. ^1H RMN (300 MHz, CDCl_3): δ = 7.88 (s, 1H), 7.40 (m, 6H), 7.14 (d, J = 8.8, 1H), 6.85 (m, 1H), 6.09 (m, 1H), 4.67 (d, J = 16.8, 1H), 4.47 (dd, J_1 = 4.6, J_2 = 12.6, 1H), 4.25 (d, J = 17.2, 1H), 1.48 (d, J = 7.0, 3H). EM m/e (M^+) = 319.3.

Intermediario 35



10

Éster de bencilo del ácido [8-oxo-9-(4-trifluorometilbencil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico.

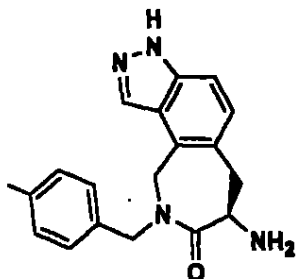
4-

15 Trifluorometilbencilamina (72 μL , 0.51 mmol) y éster de metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)-propiónico (100 mg, 0.23 mmol) se convirtieron dentro del compuesto del título en una manera similar a la preparación de éster de metilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El material
20 crudo se obtuvo como un sólido café oscuro en rendimiento cuantitativo. El material se llevó a cabo sin purificación adicional. EM m/e (M^+) = 509.4. CLAR rf = 1.67 min.

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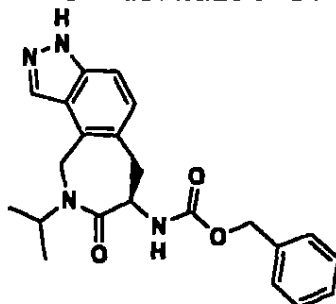
Intermediario 36



5

Bis-metansulfonato 7-Amino-9-(4-trifluorometil-bencil)-
6,7,9,10-tetrahidro-3H-2,3,9-triaza-(R)-ciclohepta[e]inden-8-
ona. El éster de bencilo del ácido [8-oxo-9-(4-
10 trifluorometil-bencil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
(R)-ciclohepta[e]inden-7-il]-carbámico se convirtió dentro
del compuesto del título en una manera análoga a la
preparación del bismetansulfonato 7-(R)-amino-9-(2,2-dimetil-
propil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
15 ciclohepta[e]inden-8-ona. El material crudo se obtuvo como
una espuma oscura en rendimiento cuantitativo. El material
se llevó a cabo sin purificación adicional. EM m/e (M+H)⁺=
375.2. CLAR rf= 1.00 min.

Intermediario 37



20

25 Éster de bencilo del ácido (9-Isopropil-8-oxo-

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3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-

ciclohepta[e]inden-7-il)-carbámico. La isopropilamina

(300 µL, 3.5 mmol) y éster de metilo del ácido 2-(R)-

benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-

5 il)-propiónico se convirtieron dentro del compuesto

del título siguiendo un procedimiento análogo a la

preparación de éster de metilo del ácido [9-(2,2-

dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-

triaza-(S)-ciclohepta[e]inden-7-il]-acético. El

10 producto crudo se obtuvo como un aceite oscuro en

rendimiento cuantitativo. El material se llevó a cabo

sin purificación adicional. ¹H RMN (500 MHz, CDCl₃):

δ= 8.09 (s, 1H), 7.39 (m, 3H), 7.23 (m, 2H), 7.17 (m,

1H), 6.32 (d, J= 5.8, 1H), 5.25 (m, 1H), 5.15 (m,

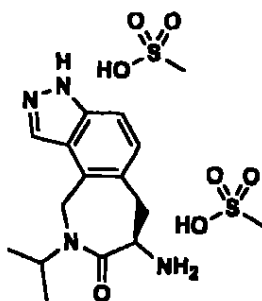
15 2H), 4.90 (m, 1H), 4.82 (d, J= 17.4, 1H), 4.51 (m,

1H), 3.51 (m, 1H), 3.05 (t, J= 13.6, 1H), 1.56 (s,

6H). EM m/e (M+H)⁺= 393.4.

Intermediario 38

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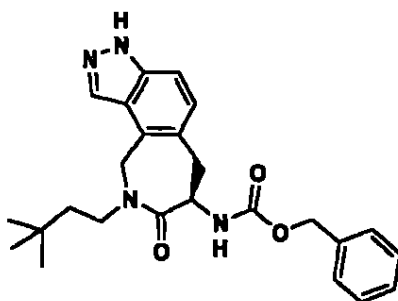
Bismetansulfonato 7-(R)-Amino-9-isopropil-6,7,9,10-tetrahidro-3H-

324/323

2,3,9-triaza-ciclohepta[e]inden-8-ona. El éster de bencilo del ácido (9-Isopropil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il)-carbámico (90 mg, 0.23 mmol) se convirtió dentro del compuesto del título siguiendo un procedimiento análogo a la síntesis de bismetansulfonato 7-(R)-amino-9-(2,2-dimetil-propil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El producto crudo se obtuvo como un aceite obscuro en rendimiento cuantitativo. El material crudo se llevó adelante sin purificación adicional. EM m/e (M+H)⁺= 259.2. CLAR rf= 0.60 min.

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Intermediario 39



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Éster de bencilo del ácido [9-(3,3-Dimetil-butyl)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico. La 3,3-Dimetilbutilamina (100 µL, 0.74 mmol) y éster de metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-clorometil-1H-indazol-5-il)-propiónico se convirtieron dentro del compuesto del título siguiendo un procedimiento análogo a la preparación de éster de bencilo del ácido [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico. El material crudo se obtuvo como un aceite obscuro en rendimiento cuantitativo. El

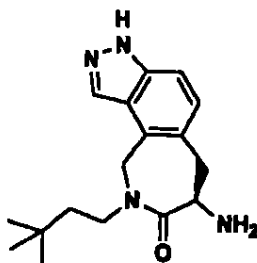
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material se llevó a cabo sin purificación adicional. ^1H RMN (300 MHz, CDCl_3): δ = 8.03 (m, 1H), 4.38 (m, 4H), 7.31 (m, 2H), 7.06 (d, J = 8.4, 1H), 6.26 (d, J = 6.2, 1H), 5.23 (m, 1H), 5.14 (s, 2H), 5.08 (m, 1H), 4.35 (dd, J_1 = 8.8, J_2 = 17.2, 1H), 3.50 (m, 2H), 1.33 (dd, J_1 = 6.2, J_2 = 11.0, 2H), 0.91 (m, 2H), 0.85 (s, 9H). EM m/e ($\text{M}+\text{H}$) $^+$ = 435.1.

Intermediario 40

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Bismetansulfonato 7-(R)-Amino-9-(3,3-dimetil-butil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

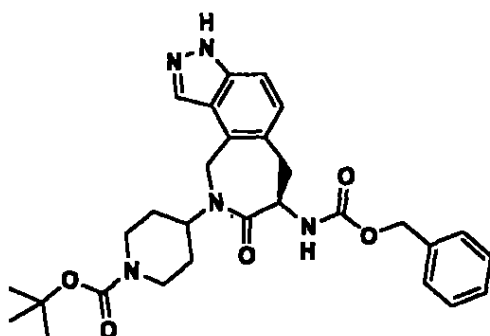
15 El éster de bencilo del ácido [9-(3,3-Dimetil-butil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico (100 mg, 0.23 mmol) se convirtió dentro del compuesto del título siguiendo un procedimiento análogo a la preparación de bismetansulfonato 7-(R)-amino-9-(2,2-dimetil-

20 propil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material crudo se obtuvo como un aceite oscuro en rendimiento cuantitativo. El material se llevó adelant sin purificación adicional. EM m/e ($\text{M}+\text{H}$) $^+$ = 301.2. CLAR rf= 1.11 min.

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Intermediario 41



5

Éster de tert-butilo del ácido 4-(7-(R)-

Benciloxycarbonilamino-8-oxo-6,7,8,10-tetrahidro-3H-2,3,9-

triazza-ciclohepta[e]inden-9-il)-piperidin-1-carboxílico. La

10 4-Amino-1-N-Boc-piperidina (110 mg, 0.55 mmol) y éster de

metilo del ácido 2-(R)-benciloxycarbonilamino-3-(4-

clorometil-1H-indazol-5-il)-propiónico (150 mg, 0.34 mmol) se

convirtió dentro del compuesto del título en una manera

análoga a la preparación de éster de metilo del ácido [9-

15 (2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-

triazza-(S)-ciclohepta[e]inden-7-il]-acético. El producto

crudo se obtuvo como una espuma oscura en rendimiento

cuantitativo. El material se llevó a cabo sin purificación

adicional. ¹H RMN (300 MHz, CDCl₃): δ= 8.05 (m, 1H), 7.35 (m,

20 6H), 7.15 (m, 1H), 6.27 (m, 1H), 5.28 (m, 1H), 5.15 (s, 2H),

4.87 (d, J= 16.5, 1H), 4.63 (m, 1H), 4.47 (m, 1H), 4.24 (m,

1H), 3.99 (m, 1H), 3.49 (m, 1H), 3.04 (m, 1H), 2.83 (m, 2H),

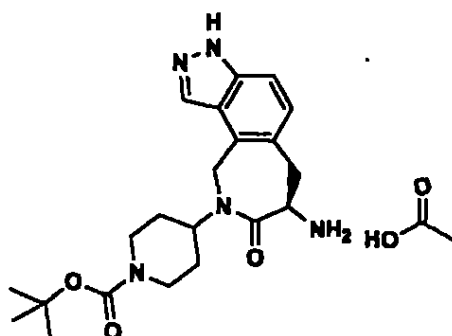
2.63 (m, 1H), 1.90 (m, 1H), 1.74 (m, 2H), 1.58 (s, 9H). EM

m/e (M-H)⁺= 532.1.

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32X 326

Intermediario 42



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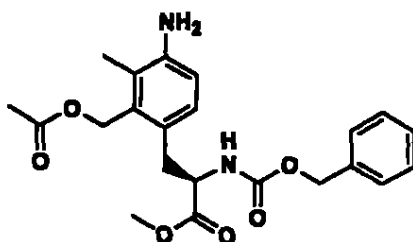
Acetato de éster de tert-butilo del ácido 4-(7-(R)-
Amino-8-oxo-6,7,8,10-tetrahidro-3H-2,3,9-triaza-
10 ciclohepta[e]inden-9-il)-piperidin-1-carboxílico. Una
cantidad catalítica de paladio en carbono al 10% se agregó a
una solución de éster de tert-butilo del ácido 4-(7-(R)-
Benciloxycarbonilamino-8-oxo-6,7,8,10-tetrahidro-3H-2,3,9-
triaz-a-ciclohepta[e]inden-9-il)-piperidin-1-carboxílico (200
15 mg, 0.37 mmol) y ácido acético (100 µL, 1.7 mmol) en metanol
(10 mL). El recipiente de reacción se colocó en un aparato
Parr y se cargó con 30 psi (2.10 kg/cm²) de gas de hidrógeno.
La mezcla se permitió agitar a temperatura ambiente durante 3
horas. La mezcla se filtró. El filtrado se concentró in
20 vacuo. El compuesto crudo se obtuvo como un aceite oscuro en
rendimiento cuantitativo. El material se llevó a cabo sin
purificación adicional. ¹H RMN (300 MHz, CDCl₃): δ= 8.06 (s,
1H), 7.36 (d, J= 8.8, 1H), 7.12 (d, J= 8.8, 1H), 4.92 (d,
J=17.6, 1H), 4.67 (m, 1H), 4.49 (d, J= 17.2, 1H), 4.26 (m,
25 1H), 3.98 (m, 2H), 3.05 (m, 1H), 2.83 (m, 2H), 2.64 (m, 1H),

322 327

1.89 (m, 1H), 1.73 (m, 1H), 1.45 (d, J= 2.9, 9H), 1.25 (m, 2H). EM m/e (M-C₄H₉+H)⁺= 344.2.

Intermediario 43

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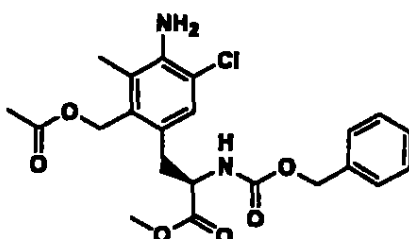


Éster de metilo del ácido 3-(2-Acetoximetil-4-amino-3-
 10 metil-fenil)-2-(R)-benciloxycarbonilamino-propiónico. El
 éster de metilo del ácido 3-(2-Acetoximetil-4-tert-
 butoxycarbonilamino-3-metil-fenil)-2-(R)-
 benciloxycarbonilamino-propionico se convirtió en éster de
 metilo del ácido 3-(2-Acetoximetil-4-amino-3-metil-fenil)-2-
 15 benciloxycarbonilamino-(R)-propionico siguiendo un
 procedimiento análogo para la síntesis de éster de dietilo
 del ácido 2-(2-Acetoximetil-4-amino-3-metil-bencil)-(S)-
 succínico. El producto deseado se obtuvo como un aceite
 amarillo en 95% de rendimiento. ¹H RMN (300 MHz, CDCl₃): δ =
 20 7.31 (m, 5H); 6.81 (d, J= 8.1. 1H); 6.65 (d, J= 8.4, 1H);
 5.35 (d, J= 8.1, 1H); 5.15 (s, 2H); 5.04 (s, 2H); 4.53 (m,
 1H); 3.71 (s, 3H); 3.16 (m, 1H); 3.01 (m, 1H); 2.12 (s, 3H);
 1.99 (s, 3H). EM m/e (M+H)⁺ = 415.2.

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328

Intermediario 44



5

Éster de metilo del ácido 3-(2-Acetoximetil-4-amino-5-

cloro-3-metil-fenil)-2-(R)-benciloxicarbonilamino-propiónico.

El producto deseado se obtuvo de éster de metilo del ácido 3-

10 (2-Acetoximetil-4-amino-3-metil-fenil)-2-(R)-

benciloxicarbonilamino-propiónico en una manera análoga para

la preparación de éster de dietilo del ácido 2-(2-

Acetoximetil-4-amino-5-cloro-3-metil-bencil)-(S)-succínico.

La cromatografía en gel de sílice (acetato de etilo -

15 hexanos) proporcionó el producto como un aceite amarillo en

40% de rendimiento. ^1H RMN (300 MHz, CDCl_3): δ = 7.31 (m, 5H);

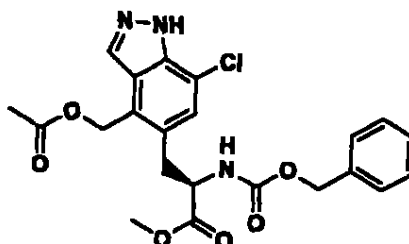
6.96 (s, 1H); 5.36 (d, J = 8.4, 1H); 5.12 (s, 2H); 5.05 (s,

2H), 4.53 (m, 1H); 3.72 (s, 3H); 3.15 (m, 1H), 2.99 (m, 1H);

2.15 (s, 3H); 1.99 (s, 3H). EM m/e ($\text{M}-\text{C}_2\text{H}_4\text{O}_2+\text{H}$) $^+$ = 398.3.

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Intermediario 45



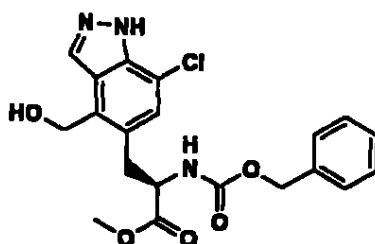
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Éster de metilo del ácido 3-(4-Acetoximetil-7-cloro-1H-indazol-5-il)-2-(R)-benciloxicarbonilamino-propiónico. El ácido trifluoroacético (70 µL, 0.91 mmol) se agregó a una solución de 3-(2-acetoximetil-4-amino-5-cloro-3-metil-fenil)-
5 2-(R)-benciloxicarbonilamino-propiónico (345 mg, 0.77 mmol) en 5% de ácido acético en cloroformo (5.2 mL). El isoarnil nitrito (120 µL, 0.89 mmol) se agregó a la mezcla gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 40 minutos. El acetato de potasio (300 mg, 3.1 mmol)
10 se agregó a la mezcla. La mezcla de reacción se agitó a temperatura ambiente durante 45 minutos. La mezcla se diluyó con diclorometano (10 mL) luego se lavó sucesivamente con agua (2 X 10 mL), y bicarbonato de sodio acuoso saturado (2X10 mL). El orgánico se secó (sulfato de magnesio), filtró
15 y concentró in vacuo. El producto crudo se obtuvo como un sólido anaranjado en 83% de rendimiento. El material se llevó a cabo sin purificación adicional. ¹H RMN (300 MHz, CDCl₃): δ = 8.20 (s, 1H); 7.29 (m, 5H); 7.21 (s, 1H); 5.53 (d, J=7.7, 1H); 5.40 (s, 2H); 5.04 (s, 2H); 4.67 (m, 1H); 3.74 (s, 3H);
20 3.34 (m, 1H); 3.21 (m, 1H); 2.02 (s, 3H). EM m/e (M+H)⁺ = 460.1.

337 330

Intermediario 46

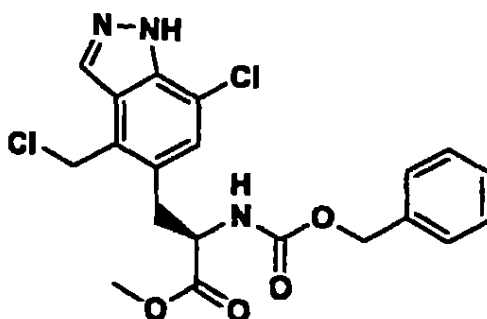


5

Éster de metilo del ácido 2-(R)-Benciloxicarbonilamino-3-(7-cloro-4-hidroximetil-1H-indazol-5-il)-propiónico. El éster de metilo del ácido 3-(4-Acetoximetil-7-cloro-1H-indazol-5-il)-2-(R)-benciloxicarbonilamino-propiónico (290 mg, 0.63 mmol) se convierte en el producto deseado en una manera análoga a la preparación del éster de metilo del ácido 2-(R)-benciloxicarbonilamino-3-(4-tert-butoxicarbonilamino-2-hidroximetil-3-metil-fenil)-propiónico. El producto crudo se obtuvo como un sólido naranja en 95% de rendimiento. El material se llevó a cabo sin purificación adicional. ^1H RMN (300 MHz, CDCl_3): δ = 8.15 (s, 1H); 7.27 (m, 5H); 7.14 (s, 1H); 6.10 (m, 1H); 5.01 (d, $J=4.8$, 2H); 4.95 (s, 2H); 4.75 (m, 1H); 3.79 (s, 3H); 3.34 (m, 1H); 3.09 (m, 1H). EM m/e $(\text{M}+\text{H})^+ = 418.0$.

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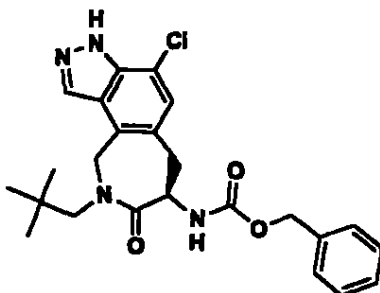
Intermediario 47



25

El compuesto del título se obtuvo como un sólido anaranjado en 86% de rendimiento. El material se llevó a cabo sin purificación adicional. ^1H RMN (300 MHz, CDCl_3): δ = 8.19 (s, 1H), 7.32 (m, 5H), 7.16 (s, 1H), 5.49 (d, J= 7.3, 2H), 5.07 (d, J= 4.4, 2H), 4.85 (s, 2H), 4.68 (d, J= 7.0, 1H), 3.72 (s, 3H), 3.27 (m, 2H). EM m/e $(\text{M}+\text{H})^+$ 436.1.

20

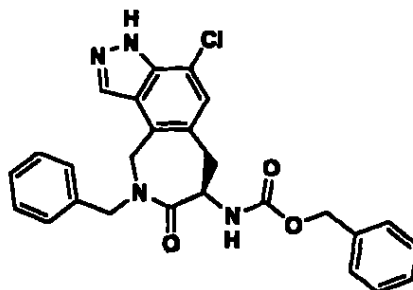


27 32

propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-
ciclohepta[e]inden-7-il]-carbámico. La neopentilamina (200
µL, 1.7 mmol) se agregó a una mezcla de éster de metilo del
ácido 2-(R)-benciloxicarbonilamino-3-(7-cloro-4-clorometil-
5 1H-indazol-5-il)-propiónico (180 mg, 0.41 mmol) y carbonato
de potasio (160 mg, 1.2 mmol) en acetonitrilo (5 mL). La
reacción se calentó a reflujo durante 1 hora. La mezcla se
enfrió a temperatura ambiente luego se filtró a través un
sistema de filtrado 0.45 µm PTFE syringeless. El filtrado se
10 concentró. El residuo se disolvió en una mezcla de tolueno (5
mL) y ácido acético (200 µL). La mezcla se calentó a 110°C
durante la noche. La mezcla se diluyó con acetato de etilo
(15 mL) luego se lavó sucesivamente con agua (15 mL),
bicarbonato de sodio acuoso saturado (2X15 mL) y salmuera (10
15 mL). El orgánico se secó (sulfato de magnesio), filtró y
concentró. La cromatografía en gel de sílice proporcionó el
compuesto del título en 52% de rendimiento como un sólido
amarillo. ¹H RMN (300 MHz, CDCl₃): δ = 7.89 (d, J= 10.6, 1H),
7.38 (m, 5H), 6.96 (d, J= 10.3, 1H), 6.35 (d, J=5.9, 1H),
20 5.25 (m, 1H), 5.19m, 2H), 4.28 (m, 1H), 3.66 (m, 1H), 3.40
(m, 1H), 2.96 (dd, J₁= 13.9, J₂= 5.5, 2H), 0.76 (d, J=2.6,
9H). EM m/e(M+H)⁺ = 455.2.

324 333

Intermediario 49



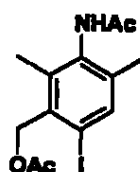
5

Éster de bencilo del ácido (9-Bencil-4-cloro-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il)-carbámico. El compuesto del título se obtuvo de bencilamina (100 μ L, 0.92 mmol) y éster de metilo del ácido 2-(R)-Benciloxicarbonilamino-3-(7-cloro-4-clorometil-1H-indazol-5-il)-propiónico (210 mg, 0.48 mmol) siguiendo un procedimiento análogo a la preparación del éster de bencilo del ácido [4-Cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-tnaza-(R)-ciclohepta[e]inden-7-il]-carbámico. La cromatografía en gel de sílice (acetato de etilo - hexanos) proporcionó el producto deseado como un sólido amarillo en 52% de rendimiento. ^1H RMN (300 MHz, CDCl_3): δ = 7.64 (s, 1H), 7.38 (m, 5H), 7.19 (m, 3H), 7.12 (m, 2H), 7.00 (s, 1H), 6.36 (d, J = 6.2 1H), 5.28 (m, 1H), 5.21 (s, 2H), 5.19 (m, 1H), 4.88 (m, 1H), 4.75 (d, J = 16.8, 1H), 4.34 (d, J = 14.6, 1H), 3.49 (m, 1H), 3.03 (m, 1H). EM m/e $(\text{M}+\text{H})^+$ = 475.0.

25

235 334

Intermediario 50



5

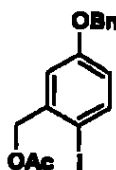
Éster de 3-acetilamino-6-yodo-2,4-dimetil-bencilo del ácido acético. A una solución bien agitada de (3-amino-2,4-dimetil-fenil)-metanol (1.5 g) en metanol (70 mL) y carbonato de hidrógeno de sodio sólido (4.0 eq) se agregó a una
10 solución 1.0 M de monocloruro de yodo gota a gota durante un periodo de 5 minutos a 0°C. El baño de enfriamiento se removió después de la adición de monocloruro de yodo. La mezcla de reacción se llevó a cabo a temperatura ambiente y se agito continuamente durante otra 1 h. La mezcla de
15 reacción se concentró para remover más del metanol, se diluyó con diclorometano (50 mL) y se lavó con 10% de solución de tiosulfato de sodio y se secó (Na₂SO₄). El compuesto deseado se purificó por trituración con diclorometano y hexano para dar 1.9 g de yoduro. El yoduro luego se trató con
20 diclorometano (100 mL) seguido por el anhídrido acético (4 eq) y una cantidad catalítica de dimetilaminopiridina y se agitó por un periodo de 12 h a temperatura ambiente. La mezcla de reacción luego se lavó con carbonato ácido de sodio acuoso, ácido clorhídrico 1.0 M y se secó (Na₂SO₄). El
25 compuesto deseado se trituró con diclorometano y hexano para

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dar el éster de 3-acetilamino-6-yodo-2,4-dimetil-bencilo del ácido acético en 95% de rendimiento. ^1H RMN (300 MHz, CDCl_3): en δ 7.68 (s, 1 H), 6.68 (s, 1 H), 2.28 (s, 3 H), 2.25 (s, 3 H), 2.18 (s, 3 H), 2.07 (s, 3 H); EM (ESI) 384 ($\text{M}+\text{Na}$); R_f =

5 1.12.

Intermediario 51



10 Éster de 5-benciloxi-2-yodo-bencilo del ácido acético.

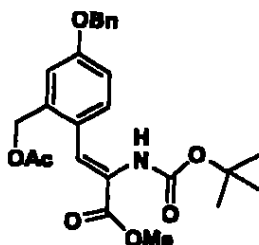
A una solución bien agitada del alcohol 3-benciloxibencilico (5.5 g, 25.7 mmol) en metanol (100 mL) y carbonato ácido de sodio (8.4 g, 100 mmol) se agregó a una solución 1.0 M de monoclóruo de yodo en diclorometano (30 mL) a 0°C. La mezcla
15 de reacción se llevó a cabo a temperatura ambiente y se agitó continuamente durante 1h adicional. La mezcla de reacción se concentró y luego se diluyó con diclorometano (150 mL), se lavó con 10% de tiosulfato de sodio acuoso y se secó (Na_2SO_4). El compuesto deseado se purificó por cromatografía
20 instantánea (sílice) usando 20% de acetato de etilo en hexano para dar el alcohol 5-benciloxi-2-yodobencilico (6.2 g, 71% de rendimiento). El alcohol (4.2 g, 12.4 mmol) se disolvió en diclorometano (100 mL) se agregó el anhídrido acético (2.52 g, 24.7 mmol) y una cantidad catalítica de 4-
25 dimetilaminopiridina. La mezcla de reacción luego se agitó

247 336

durante 12 h, se lavó con carbonato ácido de sodio acuoso y luego se secó (Na_2SO_4) para dar el éster 5-benciloxi-2-yodo-bencilo del ácido acético en rendimiento cuantitativo. EM (ESI) 405 ($\text{M}+\text{Na}$); $R_f = 2.27$.

5

Intermediario 52

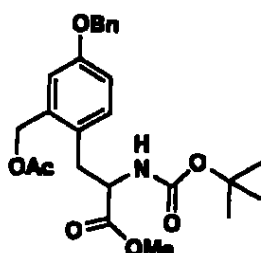


10

Éster de metilo del ácido 3-(2-Acetoximetil-4-benciloxi-fenil)-2-tert-butoxicarbonilamino-acrílico. En una manera similar el éster de dietilo el ácido 2-(acetoximetil-4-tert-butoxicarbonilamino-3-metil-bencilideno)-succínico, el éster de metilo del ácido 3-(2-acetoximetil-4-benciloxi-fenil)-2-tert-butoxicarbonilamino-acrílico se preparó por hacer reaccionar el éster 5-benciloxi-2-yodo-bencilo del ácido acético con éster de metilo del ácido 2-tert-butoxicarbonilamino-acrílico en 74% de rendimiento. EM (ESI) 456 ($\text{M}+\text{H}$); $R_f = 1.87$.

20

Intermediario 53

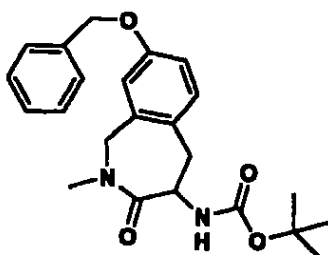


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332

Éster de metilo del ácido 3-(2-Acetoximetil-4-benciloxi-fenil)-2-tert-butoxicarbonilamino-propiónico. A una solución de éster de metilo del ácido 3-(2-acetoximetil-4-benciloxi-fenil)-2-tert-butoxicarbonilamino-acrílico (1.9 g, 4.2 mmol) en metanol anhidro bajo una atmósfera de nitrógeno se agregó trifluorometansulfonato de 1,2-bis((2R,5R)-2,5-dietilfosfolano)benceno(ciclotadieno)rodio(I)trifluorometansulfonato (50 mg) y se agitó en un agitador Parr a 50 psi (3.515 kg/cm²) de una atmosfera de hidrógeno durante 18 h. El solvente se evaporó y el producto deseado se cristalizó de acetato de etilo-hexano en 90% de rendimiento. EM (ESI) 458 (M+H); R_f = 1.81.

Intermediario 54



15

Éster de tert-butilo del ácido (8-Benciloxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-carbámico. A una solución de éster de metilo del ácido 3-(2-acetoximetil-4-benciloxi-fenil)-2-tert-butoxicarbonilamino-propiónico (1.85 g, 4.0 mmol) en metanol (40 mL) se agregó carbonato de potasio (560 mg, 4.0 mmol) a temperatura ambiente y se agitó durante 1 h. La mezcla de reacción se diluyó con

20

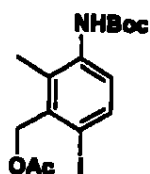
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324 338

diclorometano (150 mL), se lavó con cloruro de hidrógeno acuoso 1.0 M y se secó (Na_2SO_4) para dar el éster de metilo del ácido 3-(4-benciloxi-2-hidroximetil-fenil)-2-tert-butoxicarbonilamino-propiónico puro en casi un rendimiento 5 cuantitativo. al alcohol (800 mg, 1.93 mmol) en diclorometano (50 mL) se agregó cloruro de metansulfonilo (0.18 mL, 2.3 mmol) seguido por trietilamina (0.38 mL, 2.70 mmol) a 0°C y luego se llevó a temperatura ambiente. Después de 1h, la mezcla de reacción se lavó con carbonato ácido de sodio 10 acuoso, se secó (Na_2SO_4). El solvente se removió, se disolvió el producto crudo en THF anhidro (20 mL) seguido por la adición de una solución 2.0 M de metilamina en THF (10 mL) en un tubo sellado. El tubo sellado se calentó a 80 °C por un periodo de 12 h y luego se removió el solvente. El producto 15 crudo se purificó por cromatografía instantánea usando 30% de acetato de etilo en hexano para dar el éster de tert-butilo del ácido (8-benciloxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-carbámico en 39% de rendimiento general. ^1H RMN (500 MHz, CDCl_3): en δ 7.40 - 7.31 (m, 5H), 7.01 - 7.00 20 (m, 1H), 6.83 - 6.82 (m, 1H), 6.66 (s, 1H), 5.91 - 5.90 (m, 1H), 5.13 - 5.01 (m, 4H), 3.50 - 3.46 (m, 1H), 3.03 (s, 3H), 2.85-2.78 (m, 1H), 1.45 (s, 9H).

7/10 359

Intermediario 55



5

Éster 3-tert-butoxicarbonilamino-6-yodo-2-metil-bencilo del ácido acético. A una solución bien agitada de alcohol 3-amino-2-metilbencílico (10 g, 72.9 mmol) en metanol (250 mL) se agregó a una solución 1.0 M de monocloruro de yodo en diclorometano (76.6 mL) gota a gota durante un periodo de 5 minutos a 0°C. La mezcla de reacción luego se llevó a temperatura ambiente y se agitó continuamente durante 2h adicionales. La mezcla de reacción luego se concentró, se diluyó con diclorometano (250 mL), se lavó con 10% de tiosulfato de sodio acuoso y se secó (Na₂SO₄). El solvente se evaporó y el producto crudo se disolvió en THF (200 mL). El di-tert-butil dicarbonato (15.9 g, 72.9 mmol) se agregó y la mezcla de reacción se puso a reflujo durante 48 h. La mezcla de reacción luego se diluyó con éter (400 mL) se lavó con 1 M HCl (2 x 100 mL) seguido por salmuera y se secó (Na₂SO₄). El solvente se removió y el producto deseado se cristalizó a partir de 20% de acetato de etilo en hexano para dar el éster de tert-butilo del ácido (3-hidroximetil-4-yodo-2-metil-fenil)-carbámico (12.5 g). El filtrado luego se concentró y el producto deseado se purificó por cromatografía instantánea (sílice) usando 30% de acetato de etilo para dar 2.5 g adicionales de éster de tert-butilo del ácido (3-hidroximetil-4-yodo-2-metil-fenil)-carbámico. A una solución agitada de éster de tert-butilo

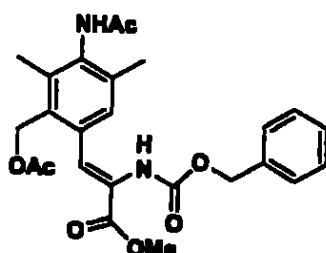
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341 340

del ácido 3-hidroximetil-4-yodo-2-metil-fenil)-carbámico (14.5 g, 40 mmol) en diclorometano (150 mL) se agregó el anhídrido acético (7.5 mL, 80 mmol) y una cantidad catalítica de 4-dimetilaminopiridina y se agitó durante 12 h a temperatura ambiente. La mezcla de reacción luego se
5 apagó con carbonato ácido de sodio acuoso, salmuera y se secó (Na₂SO₄). El solvente se removió y el producto crudo se purificó por cristalización de diclorometano y hexano para dar el éster 3-tert-butoxicarbonilamino-6-yodo-2-metil-bencilo del ácido acético (15.5 g, 94%). ¹H RMN (500 MHz, CDCl₃): en δ 7.71 (d, J= 8.5 Hz, 1H), 7.25 (d, J= 8.5 Hz, 1H), 5.30 (s, 2 H), 2.28 (s, 3H), 2.08 (s, 3H), 1.50 (s, 9H);
10 EM (ESI) 428 (M+Na); R_f = 1.59.

Intermediario 56

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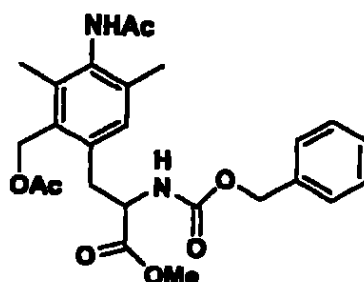
Éster de metilo del ácido 3-(2-Acetoximetil-4-acetilamino-3,5-dimetil-fenil)-2-benciloxycarbonilamino-
20 acrílico. En una manera similar al éster de dietilo del ácido 2-(acetoximetil-4-tert-butoxicarbonilamino-3-metil-bencilideno)-succínico, el éster de metilo del ácido 3-(2-acetoximetil-4-acetilamino-3,5-dimetil-fenil)-2-benciloxycarbonilamino-acrílico se preparó por hacer
25 reaccionar el éster de 3-acetilamino-6-yodo-2,4-dimetil-

341

bencilo del ácido acético con éster de metilo del ácido 2-benciloxycarbonilamino-acrílico en 74% de rendimiento. EM (ESI) 491 (M+H); $R_f = 1.87$.

Intermediario 57.

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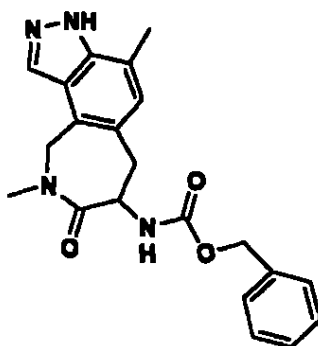
Éster de metilo del ácido 3-(2-Acetoximetil-4-acetilamino-3,5-dimetil-fenil)-2-benciloxycarbonilamino-propiónico. En una manera similar al éster de metilo del ácido 3-(2-acetoximetil-4-benciloxi-fenil)-2-tert-butoxicarbonilamino-acrílico, el éster de metilo del ácido 3-(2-acetoximetil-4-acetilamino-3,5-dimetil-fenil)-2-benciloxycarbonilamino-propiónico se preparó a partir del éster de metilo del ácido 3-(2-acetoximetil-4-acetilamino-3,5-dimetil-fenil)-2-benciloxycarbonilamino-acrílico (1.5 g) usando trifluorometansulfonato de 1,2-bis((2R,5R)-2,5-dietilfosfolano)benceno(ciclotadieno)rodio(I) (25 mg) en 98% de rendimiento. EM (ESI) 491 (M+H); $R_f = 1.87$.

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343 342

Intermediario 58

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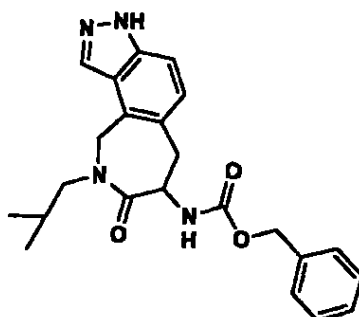
Éster de bencilo del ácido (8-Acetilamino-2,7,9-
 10 trimetil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-
 carbámico. En una manera similar al clorohidrato del éster de
 metilo del ácido 2-(R)-benciloxycarbonilamino-3-(4-tert-
 butoxycarbonilamino-2-hidroximetil-3-metil-fenil)-propiónico,
 el compuesto del título se preparó por hidrolizar el éster de
 15 metilo del ácido 3-(2-acetoximetil-4-acetilamino-3,5-dimetil-
 fenil)-2-benciloxycarbonilamino-propiónico (1.84 g, 3.78
 mmol) con carbonato de potasio (525 mg, 3.8 mmol) en MeOH (40
 mL). El alcohol se disolvió en diclorometano (100 mL) y luego se trató
 con cloruro de metansulfonilo (0.35 mL, 4.5 mmol) y trietilamina (0.68
 20 mL, 4.9 mmol). La mezcla de reacción se agitó durante 12 h, se lavó con
 carbonato ácido de sodio acuoso, cloruro de hidrógeno acuoso 1.0 M y se
 secó (Na₂SO₄). El solvente se removió para dar el éster de metilo del
 ácido 3-(4-acetilamino-2-clorometil-3,5-dimetil-fenil)-2-
 benciloxycarbonilamino-propiónico puro en casi un rendimiento
 25 cuantitativo. El cloruro (480 mg, 1.08 mmol) se trató con una solución

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de metilamina 1.0 M en THF en un tubo sellado durante 3h a 90°C. El
solvente se removió y el producto crudo se disolvió en tolueno y ácido
acético (0.5 mL) y se puso a reflujo durante 2 h para dar éster de
bencilo del ácido (8-acetilaraino-2,7,9-trimetil-3-oxo-2,3,4,5-
5 tetrahidro-1H-benzo[c]azepin-4-il)-carbámico en 68% de rendimiento. al
acetato en cloroformo (20 mL) se agregó ácido acético (0.5 mL) seguido
por isoamilnitrito (1.0 mL) y 18-crown-6 (50 mg). La mezcla de reacción
se puso a reflujo durante 12 h y se removió el solvente. El producto
crudo se purificó por cromatografía instantánea usando acetato de etilo
10 como eluyente para dar éster de bencilo del ácido (4,9-dimetil-8-oxo-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il)-carbámico
como un producto mayor en 37% de rendimiento general. ¹H RMN (500 MHz,
CDCl₃): en δ 7.96 (s, 1H), 7.35 - 7.24 (m, 5H), 6.7 (s, 1H), 6.43 -
6.41 (m, 1H), 5.25 - 5.05 (m, 3H), 4.18-4.10 (m, 2H), 3.07 - 3.05 (m,
15 2H), 3.00 (s, 3 H), 2.40 (s, 3H).

Intermediario 59

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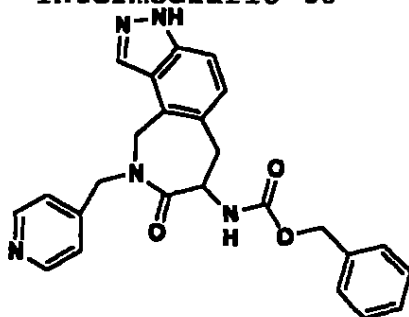


Éster de bencilo del ácido (9-Isobutil-8-oxo-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il)-
carbámico. En una manera similar al éster de bencilo del
25 ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-

344

2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico, el
compuesto del título se preparó al tratar éster de metilo del
ácido 2-benciloxycarbonilamino-3-(4-clorometil-1H-indazol-5-
il)-propiónico, el clorohidrato con isobutilamina seguido por
5 el tratamiento con ácido acético en tolueno a reflujo para
dar éster de bencilo del ácido (9-Isobutil-8-oxo-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il)-
carbámico en 91% de rendimiento. EM (ESI) 407 (M+H); R_f =1.58.

Intermediario 60



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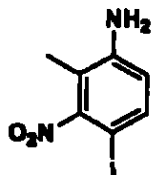
15 Éster de bencilo del ácido (8-oxo-9-piridin-4-ilmetil-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il)-
carbámico. En una manera similar al éster de bencilo del
ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-
2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-carbámico, el
20 compuesto del título se preparó al tratar éster de metilo del
ácido 2-benciloxycarbonilamino-3-(4-clorometil-1H-indazol-5-
il)-propiónico, clorohidrato con 4-(aminometil)piridina
seguido por el tratamiento con ácido acético en tolueno a
reflujo para dar éster de bencilo del ácido (8-oxo-9-piridin-
25 4-ilmetil-3,6,7,8,9,10-hexahidro-2,3,9-triaza-

346 - 345

ciclohepta[e]inden-7-il)-carbámico en 65% de rendimiento. EM
(ESI) 442 (M+H); R_f = 1.10.

Intermediario 61

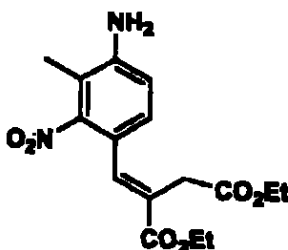
5



4-Yodo-2-metil-3-nitrobenzenamina. A una solución bien
agitada de 2-metil-3-nitroanilina (10 g, 66 mmol) en metanol
10 (150 mL) se agregó carbonato ácido de sodio (264 mmol)
seguido por solución 1.0 M de monocloruro de yodo (72 mmol) a
temperatura ambiente. Después de agitar durante 1 hora, El
solvente se removió, se diluyó con éter, se lavó con solución
de tiosulfato de sodio acuoso al 10%. El solvente se removió
15 y el yoduro crudo fue en la siguiente etapa.

Intermediario 62

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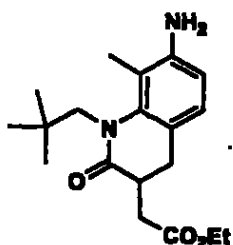


2-(4-Amino-3-metil-2-nitrobencilideno)succinato de (E)-
Dietilo. A una solución de 4-yodo-2-metil-3-nitrobencenamina
(59 mmol) en dimetilformamida (100 mL) se agregó itaconato de
25 dietilo (13.2 g, 71 mmol), cloruro de tetrabutylamonio (16.4

346

g, 59 mmol), trietilamina (236 mmol) y acetato de paladio (675 mg, 3 mmol) bajo nitrógeno. La mezcla de reacción se calentó a 80°C durante 2 horas. La mezcla de reacción cruda se filtró luego, se diluyó con éter (250 mL), se lavó con
5 agua (2 X 300 mL). El producto crudo se purificó por cromatografía instantánea usando acetato de etilo al 20% en hexano para dar 8.5 g del compuesto del título. ¹H RMN (500 MHz, CDCl₃): en δ 7.58 (s, 1 H), 7.10 (d, J = 8.5 Hz, 1 H), 6.73 (d, J = 8.5 Hz, 1 H), 4.24-4.15 (m, 4H), 3.40 (s, 2 H),
10 2.06 (s, 3 H), 1.30-1.23 (m, 6 H).

Intermediario 63



15

2-(7-Amino-8-metil-1-neopentil-2-oxo-1,2,3,4-tetrahydroquinolin-3-il)acetato de etilo. A una solución de 2-(4-amino-3-metil-2-nitrobencilideno)succinato de (E)-
20 dietilo (4.5 g, 13.4 mmol) en THF (100 mL) se agregó (Boc)₂O (16 mmol) seguido por una cantidad catalítica de dimetilaminopiridina (10 mg). La mezcla de reacción se calentó en un tubo sellado durante 3 horas a 100°C. La mezcla de reacción se enfrió, se removió el solvente, se diluyó con
25 éter y luego se lavó con carbonato ácido de sodio acuoso (50

mL). El producto crudo se encontró que contenía compuestos protegidos tanto mono- como bi-Boc. El producto crudo se disolvió en metanol (200 mL) y se agregó agua (150 ml) seguido por cloruro de amonio (14.3 g, 268 mmol) y polvo de fierro (8.9 g, 160 mmol). La mezcla de reacción se calentó a 50°C durante 1 hora, se enfrió y luego se filtró sobre una almohadilla de celite. El solvente se removi6, se extrajo con acetato de etilo y luego se lav6 con salmuera y se sec6 (Na₂SO₄). El producto crudo se purific6 por cromatografía instantánea usando acetato de etilo al 30% en hexano como eluyente para dar la amina. La amina (4.1 g, 10 mmol) se disolvió en dicloroetano (100 mL) seguido por la adición de ácido acético (10 mL), trimetilacetaldehído (11 mmol) y sulfato de magnesio (5.0 g). La mezcla de reacción se agitó durante 2 horas y luego se filtró. A la mezcla de reacción filtrada se agregó triacetoxiborohidruro de sodio (2.33 g, 11 mmol) y continuo la agitación durante 2 horas adicionales. La mezcla de reacción se diluyó con hexano (150 mL), se lavó con agua (2 X 100 mL), solución NaHCO₃ acuosa y se secó (Na₂SO₄). El solvente se removi6 y el producto crudo se disolvió en metanol (100 mL) seguido por la adición de ácido acético (5 mL) y se hidrogenó en una botella parr a una presión de 50 psi (3.51 kg/cm²) de hidrógeno. El catalizador se removi6 por filtración y el solvente se removi6. El producto crudo se disolvió en tolueno (100 mL) seguido por la adición de ácido

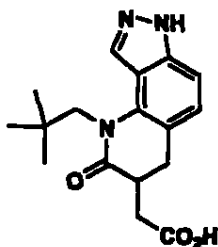
344 348

tósico (100 mg) y cianuro de sodio (50 mg). La mezcla de reacción se puso a reflujo durante 12 horas y el producto crudo se purificó por cromatografía instantánea usando acetato de etilo al 50% en hexano para dar 2-(7-amino-8-metil-1-neopentil-2-oxo-1,2,3,4-tetrahidroquinolin-3-il)acetato de etilo.

EM (ESI) 333 (M+H); R_f = 1.29.

Intermediario 64

10



Ácido 2-(1-Neopentil-2-oxo-2,3,4,7-tetrahidro-1H-pirazolo[3,4-h]quinolin-3-il)acético. A una solución de 2-(7-amino-8-metil-1-neopentil-2-oxo-1,2,3,4-tetrahidroquinolin-3-il)acetato de etilo (170 mg, 0.51 mmol) en tetracloruro de carbono (4.5 mL) se agregó ácido acético (0.5 mL) seguido por isoamilnitrato (0.04 mL) y la mezcla de reacción se agitó durante 2 horas a temperatura ambiente. La mezcla de reacción se diluyó con diclorometano (40 mL), se lavó con NaHCO_3 acuoso y se secó. El solvente se removió y el producto crudo se disolvió en THF (15 mL) seguido por la adición de hidróxido de litio (43 mg, 1 mmol) y agua (5 mL). Después de agitar durante 12 horas, el solvente se removió, se hizo

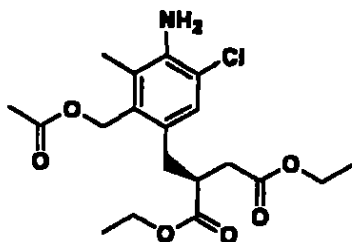
272 344

ácido con HCl 6 M y se extrajo con acetato de etilo para dar
ácido 2-(1-neopentil-2-oxo-2,3,4,7-tetrahidro-1H-
pirazolo[3,4-h]quinolin-3-il)acético.

EM (ESI) 316 (M+H); R_f = 1.31.

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Intermediario 65



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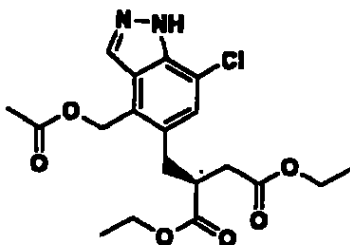
Éster de dietilo del ácido 2-(S)-(2-Acetoximetil-4-
amino-5-cloro-3-metil-bencil)-succínico. El éster de dietilo
del ácido 2-(S)-(2-Acetoximetil-4-amino-3-metil-bencil)-
succínico (3.0 g, 8.2 mmol) se disolvió en acetonitrilo (40
mL). La mezcla se entibió a 60°C. La N-clorosuccinimida (1.29
15 g, 9.7 mmol) se agregó a la solución tibia. La mezcla de
reacción se calentó a reflujo durante 10 minutos. La mezcla
se enfrió a temperatura ambiente luego se diluyó con acetato
de etilo (20 mL). La mezcla se lavó sucesivamente con
bicarbonato de sodio acuoso saturado (40 mL), y salmuera (20
20 mL). El orgánico se secó (sulfato de magnesio), filtró y
concentró in vacuo. La cromatografía de gel de sílice
(acetato de etilo-hexanos) proporcionó el producto deseado en
59% de rendimiento como un aceite ámbar. ^1H RMN (300 MHz,
 CDCl_3): δ = 6.98 (s, 1H), 5.15 (d, J = 3.3, 2H), 4.09 (m, 4H),
25 2.99 (m, 2H), 2.69 (m, 2H), 2.39 (dd, J_1 = 4.8, J_2 = 16.5, 1H),

350

2.17 (s, 3H), 2.06 (s, 3H), 1.20 (m, 6H). EM m/e (M-C₂H₄O₂+H)⁺ = 340.0.

Intermediario 66

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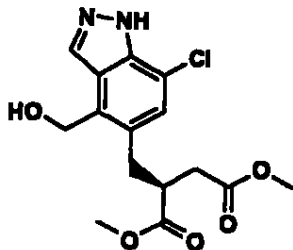
Éster de dietilo del ácido 2-(S)-(4-Acetoximetil-7-cloro-1H-indazol-5-ilmetil)-succínico. El nitrato de isoamilo
 10 (700 µL, 5.2 mmol), se agregó gota a gota a una solución enfriada en hielo de éster de dietilo del ácido 2-(S)-(2-Acetoximetil-4-amino-5-cloro-3-metil-bencil)-succínico (1.91 g, 4.8 mmol) en ácido acético al 5% en toluno (81.2 mL). La mezcla se agitó a 0°C durante 45 minutos. El acetato de
 15 potasio (1.50 g, 15.3 mmol) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 14 horas. La mezcla se apagó con agua. La mezcla se extrajo con acetato de etilo (30 mL). La mezcla se lavó bicarbonato de sodio acuoso saturado 2X. El orgánico se secó (sulfato de magnesio) filtró
 20 y concentró. La cromatografía en gel de sílice (acetato de etilo-hexanos) proporcionó el producto deseado en 80% de rendimiento como un aceite ámbar. ¹H RMN (300 MHz, CDCl₃): δ = 8.23 (s, 1H), 7.26 (s, 1H), 5.45 (s, 2H), 4.09 (q, J = 7.0, 4H), 3.20 (dd, J₁ = 7.32, J₂ = 13.2, 1H), 3.10 (m, 1H), 2.97
 25 (dd, J₁ = 7.0, J₂ = 13.3, 1H), 2.73 (dd, J₁ = 8.4, J₂ = 16.8,

372 351

1H), 2.44 (dd, J1=5.5, J2= 16.8, 1H), 2.08 (s, 3H), 1.18 (m, 6H). EM m/e (M+H)⁺= 411.0.

Intermediario 67

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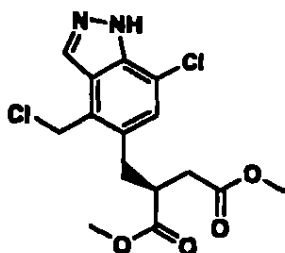


2-((7-Cloro-4-(hidroximetil)-1H-indazol-5-

il)metil)succinato de (S)-Dimetilo. El éster de dietilo del
 10 ácido 2-(S)-(2-Acetoximetil-4-amino-5-cloro-3-metil-bencil)-
 succínico (2.21 g, 5.4 mmol) se convirtió al compuesto del
 título en una manera análoga a la preparación de éster de
 dimetilo del ácido 2-(S)-(4-Hidroximetil-1H-indazol-5-
 ilmetil)-succínico. El material se obtuvo como un sólido
 15 ámbar en 99% de rendimiento. EM m/e (M+H)⁺= 241.2.

Intermediario 68

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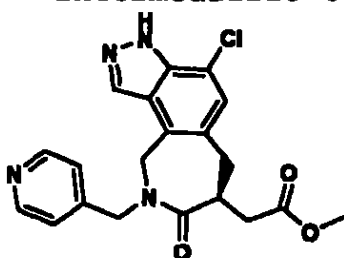
2-((7-Cloro-4-(clorometil)-1H-indazol-5-

il)metil)succinato de (S)-Dimetilo. El 2-((7-cloro-4-
 (hidroximetil)-1H-indazol-5-il)metil)succinato de (S)-
 Dimetilo (2.0 g, 5.9 mmol) se disolvió en diclorometano (35
 25 mL). El cloruro de tionilo (5.0 mL) se agregó a la mezcla. La

327 352

reacción se agitó a temperatura ambiente durante 1.5 horas. La mezcla se concentró. El residuo se disolvió en acetato de etilo. La mezcla se lavó dos veces con bicarbonato de sodio acuoso y una vez con salmuera. El orgánico se secó (sulfato de magnesio), filtró y concentró in vacuo. El compuesto del título se obtuvo como un sólido ámbar en 89% de rendimiento. EM m/e (M+H)⁺ = 359.1.

Intermediario 69



10

2-(4-Cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)acetato de (S)-Metilo. El 2-((7-cloro-4-(clorometil)-1H-indazol-5-il)metil)succinato de (S)-Dimetilo (120 mg, 0.33 mmol) se disolvió en DMF (1.0 mL). La 4-aminometilpiridina (100 µL, 1.0 mmol) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 24 horas. La mezcla se diluyó con acetato de etilo. La mezcla se lavó dos veces con agua y una vez con salmuera. El orgánico se secó (sulfato de magnesio), filtró y concentró in vacuo. El residuo se disolvió en tolueno (4 mL). ácido acético (1 mL) se agregó a la mezcla. La reacción se calentó a reflujo durante 3.5 horas. La mezcla se enfrió a temperatura ambiente luego se diluyó con acetato de etilo. El

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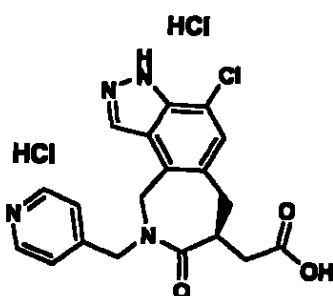
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27/11 253

material se lavó una vez con agua y dos veces con bicarbonato de sodio acuoso. La acuosa se hizo básica con bicarbonato de sodio. Nuevamente se extrajo de la acuosa dos veces con acetato de etilo. Los orgánicos combinados se secaron
5 (sulfato de magnesio), filtraron y concentraron in vacuo. El residuo se purificó con cromatografía de gel de sílice eluyendo diclorometano y amoniaco en metanol. El compuesto del título se obtuvo como un sólido amarillo en 48% de rendimiento. EM m/e (M+H)⁺= 399.2.

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Intermediario 70



15

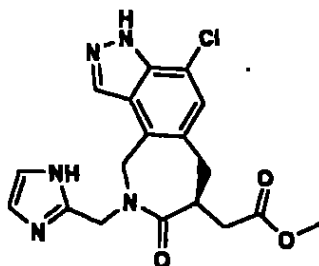
Diclorohidrato del ácido (S)-2-(4-Cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)acético. El 2-(4-cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)acetato de (S)-Metilo (21 mg, 0.05 mmol) se disolvió en ácido clorhídrico 1N (1.0 mL). La reacción se calentó a 50°C durante 5 horas. Otro 1 mL de ácido clorhídrico 1N se agregó a la mezcla. La reacción se calentó a 50°C durante 17 horas. La mezcla se concentró in vacuo. El residuo se trató con
20 acetónitrilo y luego el material se concentró. El compuesto
25

951 359

del título se obtuvo como un sólido amarillo oscuro en 83% de rendimiento. EM m/e (M+H)⁺ = 385.2.

Intermediario 71

5



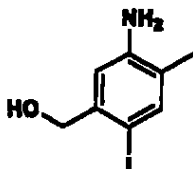
2-(9-((1H-Imidazol-2-il)metil)-4-cloro-8-oxo-

10 3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)acetato de
(S)-Metilo. El 2-((7-cloro-4-(clorometil)-1H-indazol-5-
il)metil)succinato de (S)-Dimetilo (250 mg, 0.63 mmol) y
diclorohidrato (1H-imidazol-2-il)metanamina (170 mg, 1.0
mmol) se combinaron y suspendieron en acetonitrilo (10 mL).
15 La trietilamina (800 µL, 5.7 mmol) se agregó a la mezcla. La
reacción se entibió a reflujo durante 3 horas. El ácido
acético (1.5 mL) se agregó a la mezcla. La reacción se
calentó a reflujo durante 20 horas. La mezcla se enfrió a
temperatura ambiente luego se diluyó con diclorometano. La
20 mezcla se extrajo dos veces con agua. La capa acuosa se
concentró in vacuo. El residuo se purificó por CLAR
preparatoria. El agua se liofilizó completamente. El residuo
restante se pasó a través de una columna de Dowex 1x4-200
resina de intercambio de iones eluyendo con metanol. El
25 compuesto del título se recuperó como un residuo ámbar en 24%

327 355

de rendimiento. EM m/e (M+H)⁺= 388.1.

Intermediario 72



5

Alcohol 5-amino-2-yodo-4-metilbencilo. A una solución enfriada en hielo de alcohol 3-amino-4-metilbencilo (10.0 g, 72.9 mmol) en metanol (200 mL) yodomonocloruro 1M en diclorometano (80.0 mL, 80.0 mmoles) se agregó gota a gota durante 30 minutos. El baño de hielo se removió. La reacción se agitó a temperatura ambiente durante 40 minutos. La mezcla se concentró in vacuo. El residuo se trató con diclorometano (250 mL). Los sólidos se filtraron completamente y se lavaron con diclorometano. Los sólidos se dividieron entre acetato de etilo e hidróxido de sodio acuoso 1N. Las capas se dividieron. La capa orgánica se lavó con hidróxido de sodio acuoso 1N. Las capas acuosas combinadas nuevamente se extrajeron dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera. Los extractos combinados se secaron (sulfato de magnesio), filtraron y concentraron in vacuo. El producto deseado se obtuvo como un sólido color canela en 81% de rendimiento. EM m/e (M+H)⁺= 264.

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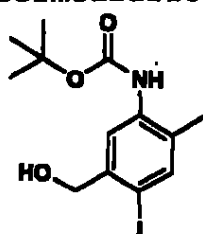
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Intermediario 73

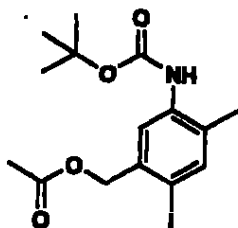


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5-(Hidroximetil)-4-yodo-2-metilfenilcarbamato de tert-Butilo. El alcohol 5-amino-2-yodo-4-metilbencilo (4.60 g, 17.5 mmoles) se disolvió en tetrahidrofurano (80 mL). El bicarbonato de di-tert-butilo (5.30 g, 24.3 mmoles) se agregó a la mezcla. La reacción se calentó a 60°C durante 20 horas. La mezcla se concentró. El residuo se purificó por cromatografía de gel de sílice eluyendo acetato de etilo-hexanos. El compuesto del título se obtuvo como un sólido blanco apagado. EM m/e $(M-C_4H_9O+H)^+ = 290$.

15

Intermediario 74



20

Acetato de 5-(tert-Butoxicarbonil)-2-yodo-4-metilbencilo. El 5-(hidroximetil)-4-yodo-2-metilfenilcarbamato de tert-Butilo (4.32 g, 11.9 mmol) se disolvió en diclorometano (60 mL). El anhídrido acético (2.6 mL, 27.6 mmol) se agregó a la mezcla seguido por acetato de potasio (2.0 g, 20.4 mmol). La reacción se agitó a

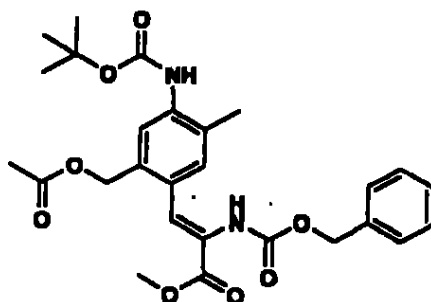
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temperatura ambiente durante 15 horas. La mezcla se entibió a 50°C y manteniendo durante 1 hora. La mezcla se enfrió a temperatura ambiente luego se diluyó con diclorometano. La mezcla se lavó dos veces con agua, y una vez con bicarbonato de sodio acuoso saturado. La capa orgánica se secó (sulfato de magnesio), filtró y se concentró in vacuo. El residuo se trató con acetato de etilo-hexanos al 10% (100 mL). El material se concentró in vacuo. el compuesto deseado se obtuvo como un sólido blanco en 98% de rendimiento. ¹H RMN (300 MHz, CD₃OD): δ= 7.64 (s, 1H), 7.54 (s, 1H), 4.51 (s, 2H), 2.19 (s, 3H), 1.51 (s, 9H).

Intermediario 75

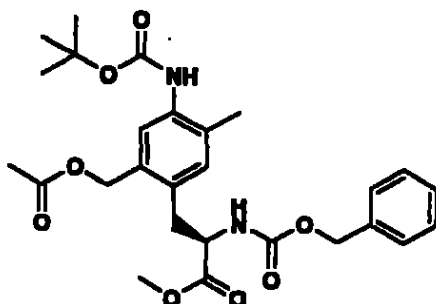
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Éster de metilo del ácido 3-(2-Acetoximetil-4-tert-butoxicarbonilamino-5-metil-fenil)-2-benciloxicarbonilamino-acrílico. El compuesto del título se preparó en manera análoga a la preparación de éster de metilo del ácido 3-(2-Acetoximetil-4-tert-butoxicarbonilamino-3-metil-fenil)-2-benciloxicarbonilamino-acrílico. El material se obtuvo como un sólido blanco en 65% de rendimiento. EM m/e (M+H)⁺= 513.

757 358

Intermediario 76



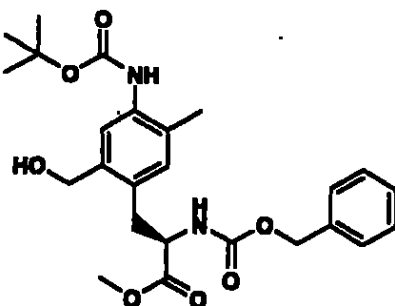
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Éster de metilo del ácido 3-(2-Acetoximetil-4-tert-butoxicarbonilamino-5-metil-fenil)-2-(R)-benciloxycarbonilamino-propiónico. El compuesto del título se preparó en una manera análoga a la preparación de éster de dietilo del ácido 2-(S)-(acetoximetil-4-tert-butoxicarbonilamino-3-metil-bencil)-succínico. El material se obtuvo como un aceite incoloro claro en 99% de rendimiento. EM m/e (M-H)⁻ = 513.

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Intermediario 77



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Éster de metilo del ácido 3-(2-Hidroximetil-4-tert-butoxicarbonilamino-5-metil-fenil)-2-(R)-benciloxycarbonilamino-propiónico. El compuesto del título se obtuvo en una manera análoga a la preparación de éster de metilo del ácido 2-(R)-Benciloxycarbonilamino-3-(4-tert-

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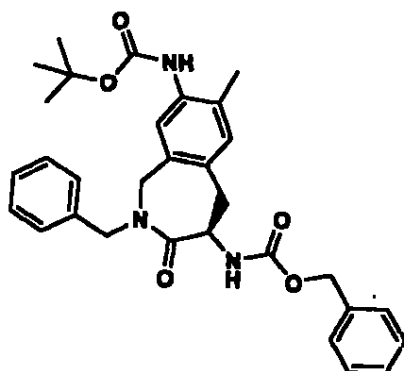
372 359

butoxicarbonilamino-2-hidroximetil-3-metil-fenil)-propiónico.

El material se obtuvo como un sólido blanco en 94% de rendimiento.

Intermediario 78

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10

Éster de metilo del ácido 3-(2-Clorometil-4-tert-butoxicarbonilamino-5-metil-fenil)-2-(R)-

benciloxycarbonilamino-propiónico. El éster de metilo del

15 ácido 3-(2-Hidroximetil-4-tert-butoxicarbonilamino-5-metil-

fenil)-2-(R)-benciloxycarbonilamino-propiónico (510 mg, 1.1

mmol) se disolvió en diclorometano (5 mL). La trietilamina

(250 µL, 1.8 mmol) se agregó a la mezcla seguido por cloruro

de metansulfonilo (100 µL, 1.3 mmol). La mezcla se agitó a

20 temperatura ambiente durante 1.5 horas. La mezcla se diluyó

con diclorometano luego se lavó una vez con agua, dos veces

con ácido clorhídrico 1N, y una vez con salmuera. Los

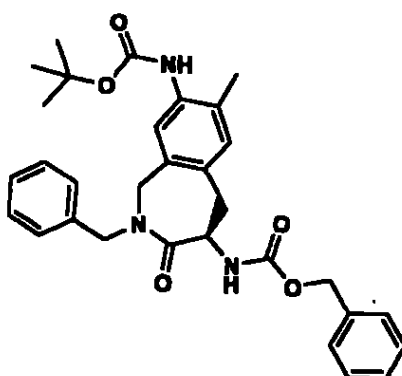
orgánicos se secaron (sulfato de magnesio), filtraron y

concentraron in vacuo. El compuesto del título se obtuvo como

25 un sólido blanco en 91% de rendimiento. EM m/e (M+H)⁺ = 491.

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Intermediario 79

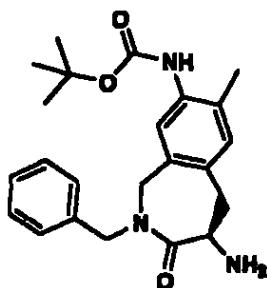


5

8-Tert-butoxicarbonilamido-2-bencil-7-metil-3-oxo-
2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-ilcarbamato de (R)-
10 Bencilo. El éster de metilo del ácido 3-(2-Clorometil-4-tert-
butoxicarbonilamino-5-metil-fenil)-2-(R)-
benciloxicarbonilamino-propiónico (335 mg, 0.72 mmol) se
disolvió en acetonitrilo (10 mL). El carbonato de potasio
(220 mg, 1.6 mmol) se agregó a la mezcla seguido por
15 bencilamina (150 µL, 1.4 mmol). La reacción se calentó a
reflujo durante 4.5 horas. La mezcla se enfrió a temperatura
ambiente. La mezcla se filtró sobre celite. El filtrado se
concentró. El residuo se disolvió en tolueno (15 mL). El
ácido acético (100 µL) se agregó a la mezcla. La reacción se
20 calentó a reflujo durante 3 horas. La mezcla se enfrió a
temperatura ambiente. La mezcla se concentró. El residuo se
purificó por cromatografía de gel de sílice eluyendo acetato
de etilo-hexanos. El compuesto del título se obtuvo como un
aceite incoloro claro en 81% de rendimiento. EM m/e (M+H)⁺=
25 530.

757 361

Intermediario 80



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4-Amino-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-8-ilcarbamato de (R)-tert-Butilo. El 8-tert-butoxicarbonilamido-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-ilcarbamato de (R)-Bencilo (305 mg, 0.58 mmol) se disolvió en metanol.

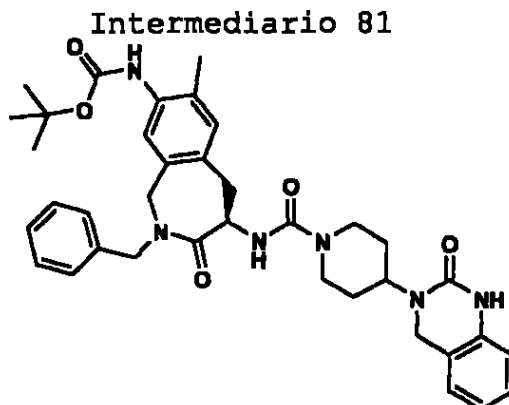
Una cantidad catalítica de paladio en carbono al 10% se agregó a la mezcla. La reacción se colocó en un aparato Parr bajo 50 psi (3.51 kg/cm²) de gas de hidrógeno.

La reacción se agitó a temperatura ambiente durante 1 hora. La reacción se removi6 del aparato. El catalizador se filtr6 completamente. El filtrado se concentr6 in vacuo. El compuesto del título se obtuvo como un aceite incoloro claro en 97% de rendimiento. EM m/e (M+H)⁺= 396.

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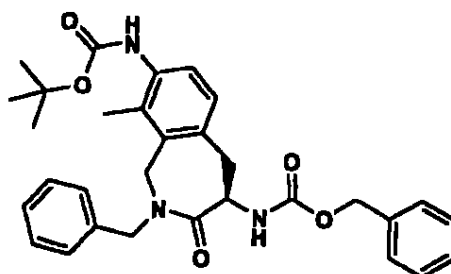
5



2-Bencil-7-metil-3-oxo-4-(4-(2-oxo-1,2-
dihidroquinazolin-3(4H)-il)piperidin-1-carboxamido)-2,3,4,5-
10 tetrahidro-1H-benzo[c]azepin-8-ilcarbamato de (R)-tert-
Butilo. El 4-amino-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-
1H-benzo[c]azepin-8-ilcarbamato de (R)-tert-Butilo (155 mg,
0.39 mmol) se disolvió en diclorometano (10 mL). El
bicarbonato de sodio acuoso (10 mL) se agregó a la mezcla.
15 Una solución de fosgeno al 20% en tolueno (230 µL, 0.43 mmol)
se agregó a la mezcla con agitación vigorosa. La reacción se
agitó a temperatura ambiente durante 20 minutos. El acetato
de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (140
mg, 0.48 mmol) se agregó a la mezcla. La reacción se agitó a
20 temperatura ambiente durante 1 hora. Las capas de reacción se
dividieron. La capa orgánica se lavó sucesivamente con ácido
clorhídrico 1N y salmuera. El orgánico se secó (sulfato de
magnesio), filtró y se concentró in vacuo. El compuesto del
título se obtuvo como un sólido blanco apagado en 94% de
25 rendimiento. EM m/e (M+H)⁺= 653.

357 363

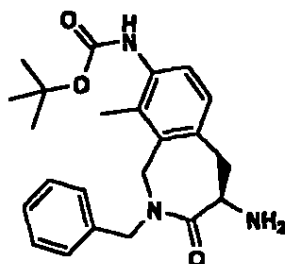
Intermediario 82



5

8-Tert-butoxicarbonilamido-2-bencil-9-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-ilcarbamato de (R)-Bencilo. El éster de metilo del ácido 3-(2-Clorometil-4-tert-butoxicarbonilamino-3-metil-fenil)-2-(R)-benciloxicarbonilamino-propiónico se hizo reaccionar en una manera análoga a la preparación de 8-tert-butoxicarbonilamido-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-ilcarbamato de (R)-bencilo. El compuesto del título se obtuvo como un sólido blanco en 78% de rendimiento. EM m/e (M+H)⁺ = 530.

Intermediario 83



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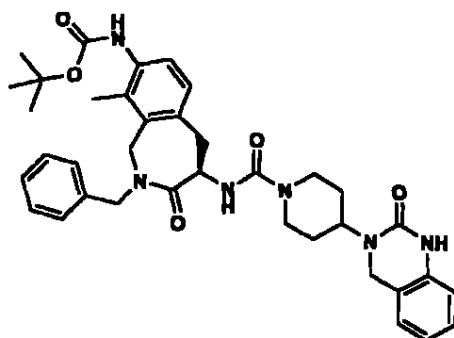
4-Amino-2-bencil-9-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-8-ilcarbamato de (R)-tert-Butilo. El 8-tert-butoxicarbonilamido-2-bencil-9-metil-3-oxo-2,3,4,5-

25

tetrahidro-1H-benzo[c]azepin-4-ilcarbamato de (R)-Bencilo se hizo reaccionar en una manera análoga a la preparación de 4-amino-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-8-ilcarbamato de (R)-tert-butilo. El compuesto
5 del título se obtuvo como un aceite incoloro claro en 99% de rendimiento. EM m/e (M+H)⁺= 340.

Intermediario 84

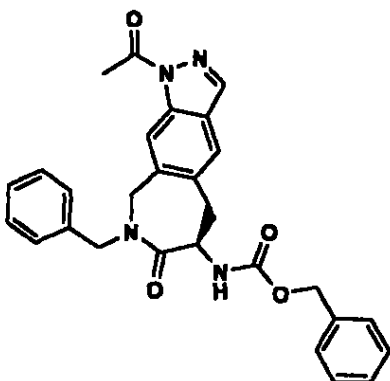
10



2-bencil-9-metil-3-oxo-4-(4-(2-oxo-1,2-
15 dihidroquinazolin-3(4H)-il)piperidin-1-carboxamido)-2,3,4,5-
tetrahidro-1H-benzo[c]azepin-8-ilcarbamato de (R)-tert-
Butilo. El 4-amino-2-bencil-9-metil-3-oxo-2,3,4,5-
tetrahidro-1H-benzo[c]azepin-8-ilcarbamato de (R)-
tert-Butilo se hizo reaccionar en una manera análoga
20 a la preparación de 2-bencil-7-metil-3-oxo-4-(4-(2-
oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-
carboxamido)-2,3,4,5-tetrahidro-1H-benzo[c]azepin-8-
ilcarbamato de (R)-tert-butilo. El compuesto del
título se obtuvo como un sólido blanco apagado en 94%
25 de rendimiento.

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Intermediario 85



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1-Acetil-8-bencil-7-oxo-1,5,6,7,8,9-

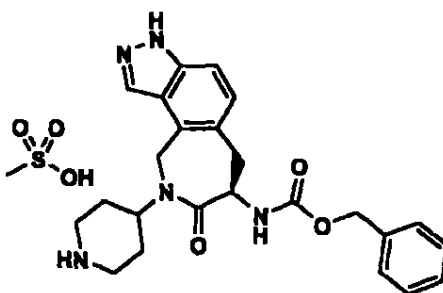
hexahidroazepino[4,3-f]indazol-6-ilcarbamato de (R)-Bencilo.

- 10 El éster de metilo del ácido 3-(2-clorometil-4-tert-butoxicarbonilamino-5-metil-fenil)-2-(R)-benciloxycarbonilamino-propiónico (160 mg, 0.33 mmol) se disolvió en diclorometano (3 mL). El ácido trifluoroacético (1 mL) se agregó a la mezcla. La reacción se agitó a
- 15 temperatura ambiente durante 45 minutos. La mezcla se concentró hasta un aceite amarillo. El residuo se disolvió en cloroformo (3 mL). El ácido acético (100 µL) se agregó a la mezcla seguido por nitrato de isoamilo (50 µL, 0.37 mmol) luego acetato de potasio (65 mg, 0.66 mmol). La reacción se
- 20 calentó a reflujo durante 30 minutos. La mezcla se enfrió a temperatura ambiente luego se diluyó con diclorometano. La mezcla se lavó una vez con agua, y dos veces con bicarbonato de sodio acuoso. Los orgánicos se secaron (sulfato de magnesio), filtraron y concentraron in vacuo. El residuo se
- 25 disolvió en acetonitrilo (3 mL). La bencilamina (100 µL, 0.92

mmol) se agregó a la mezcla seguido por carbonato de potasio (50 mg, 0.36 mmol). La reacción se calentó a reflujo durante 1 hora. La mezcla se enfrió a temperatura ambiente. Los sólidos se filtraron. El filtrado se concentró in vacuo. El
5 residuo se trató con tolueno (3 mL) y ácido acético (100 µL). La reacción se calentó a reflujo durante 1 hora. La mezcla se enfrió a temperatura ambiente. El anhídrido acético (1 mL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 1 hora. La mezcla se concentró. El residuo
10 se purificó por cromatografía de gel de sílice eluyendo acetato de etilo-hexanos. El compuesto del título se obtuvo como aceite ámbar en 27% de rendimiento. EM m/e (M+H)⁺= 483.

Intermediario 86

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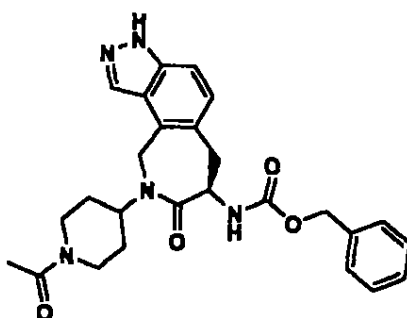
Metansulfonato de 8-oxo-9-(piperidin-4-il)-3,6,7,8,9,10-
20 *hexahidroazepino[3,4-e]indazol-7-ilcarbamato de (R)-bencilo.*
El éster de tert-butilo del ácido 4-(7-(R)-
Benciloxicarbonilamino-8-oxo-6,7,8,10-tetrahidro-3H-2,3,9-
triazaciclohepta[e]inden-9-il)-piperidin-1-carboxílico (100
mg, 0.19 mmol) se disolvió en diclorometano (2 mL). El anisol
25 (100 µL, 0.92 mmol) se agregó a la mezcla seguido por ácido

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367

metansulfónico (200 µL). La reacción se agitó a temperatura ambiente durante 30 minutos. La mezcla se diluyó con éter de dietilo, y la mezcla se agitó a temperatura ambiente durante 30 minutos. Los solventes se decantaron completamente. El residuo se secó in vacuo. El compuesto del título se obtuvo como un aceite oscuro en rendimiento cuantitativo. EM m/e (M+H)⁺ = 434.

Intermediario 87

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9-(1-Acetyl-4-piperidin-4-il)-8-oxo-3,6,7,8,9,10-

15 hexahidroazepino[3,4-e]indazol-7-ilcarbamato de (R)-bencilo.
El metansulfonato 8-oxo-9-(piperidin-4-il)-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-ilcarbamato de (R)-bencilo (100 mg, 0.19 mmol) se disolvió en una mezcla de diclorometano (4 mL) y trietilamina (500 µL, 3.6 mmol). El anhidrido acético (500 µL, 5.3 mmol) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se lavó sucesivamente agua 1x, ácido clorhídrico 2x 1N, hidróxido de sodio 2x 1N, y salmuera 1x. El orgánico se secó (sulfato de magnesio), y filtró. El filtrado se concentró in vacuo. El residuo se trató con

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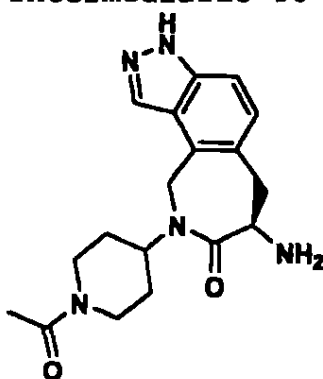
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metanol (3 mL). El carbonato de potasio (40 mg, 0.29 mmol) se
agregó a la mezcla. La reacción se agitó a temperatura
ambiente durante 2 horas. La reacción se apagó con ácido
clorhídrico 1N (6 mL). El metanol se removió de la mezcla in
5 vacuo. La mezcla acuosa restante se hizo básica con
bicarbonato de sodio. La mezcla se extrajo con acetato de
etilo. La capa orgánica se secó (sulfato de magnesio), filtró
y concentró. El compuesto del título se obtuvo como un sólido
amarillo en 43% de rendimiento. EM m/e (M+H)⁺= 476.

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Intermediario 88

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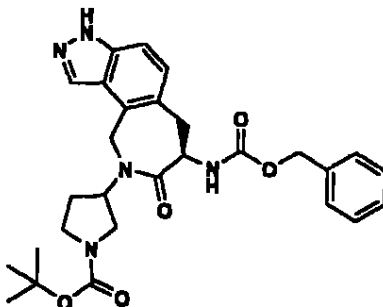
Metansulfonato (R)-9-(1-acetilpiperidin-4-il)-7-amino-
6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El 9-(1-
acetilpiperidin-4-il)-8-oxo-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-ilcarbamato de (R)-bencilo
(38 mg, 0.08 mmol) se disolvió en diclorometano (1 mL). El
anisol (30 µL, 0.27 mmol) se agregó a la mezcla seguido por
ácido metansulfónico (250 µL). La reacción se agitó a
temperatura ambiente durante 2 horas. La mezcla se diluyó con
éter de dietilo. La mezcla se saturó a temperatura ambiente

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durante 30 minutos. Los solventes se decantaron completamente. El residuo restante se secó in vacuo. El compuesto del título se obtuvo como un aceite oscuro en rendimiento cuantitativo. EM m/e (M+H)⁺= 342.

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Intermediario 89



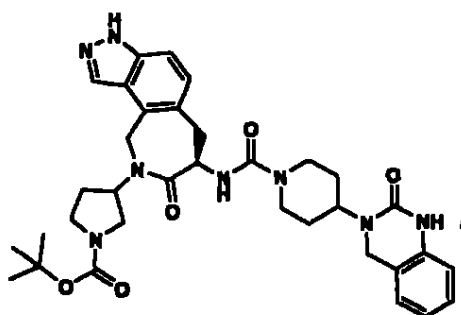
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3-((R)-7-(benciloxycarbonil)-8-oxo-7,8-dihidroazepino[3,4-e]indazol-9(3H,6H,10H)-il)pirrolidin-1-carboxilato de tert-butilo. El clorohidrato de éster de metilo del ácido 2-(R)-Benciloxycarbonilamino-3-(4-clorometil-1H-indazol-5-il)-propiónico (150 mg, 0.31 mmol) y R,S-3-amino-1-N-Boc-pirrolidina (90 µL, 0.48 mmol) se hicieron reaccionar en una manera análoga a la preparación de éster de metilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El compuesto del título se obtuvo son purificación como una espuma oscura en 96% de rendimiento. EM m/e (M+H)⁺= 342.

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Intermediario 90



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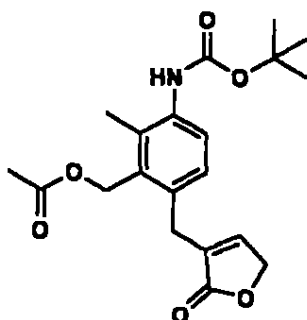
3-((R)-8-oxo-7-(4-(2-oxo-1,2-dihidroquinazolin-3(4H)-
il)piperidin-1-carboxamido)-7,8-dihidroazepino[3,4-e]indazol-
9(3H,6H,10H)-il)pirrolidin-1-carboxilato de tert-butilo. El
3-((R)-7-(benciloxicarbonil)-8-oxo-7,8-dihidroazepino[3,4-
e]indazol-9(3H,5H,10H)-il)pirrolidin-1-carboxilato de tert-
butilo se disolvió en metanol (10 mL). El ácido acético (300
μL) se agregó a la mezcla seguido por paladio en carbono al
10%. El recipiente de reacción se colocó en un aparato Parr y
se cargó con 30 psi (2.10 kg/cm²) de gas de hidrógeno. La
reacción se agitó a temperatura ambiente durante 2 horas. La
mezcla de reacción se filtró. El filtrado se concentró in
vacuo. El residuo se disolvió en diclorometano (2 mL). La
triethylamina (500 μL, 3.6 mmol) se agregó a la mezcla seguido
por carbonato N,N'-disuccinimidilo (90 mg, 0.35 mmol). La
reacción se agitó a temperatura ambiente durante 30 minutos.
El acetato 3-(piperidin-4-il)-3,4-dihidroquinazolin-2(1H)-ona
(80 mg, 0.27 mmol) se agregó a la mezcla. La reacción se
agitó a temperatura ambiente durante 1 hora. La mezcla se
diluyó con diclorometano. La mezcla se lavó con agua. La capa

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orgánica se concentró. La purificación de CLAR preparativa C18 proporcionó el compuesto del título como un sólido amarillo en 24% de rendimiento. EM m/e $(M-C_5H_8O_2+H)^+= 543$.

Intermediario 91

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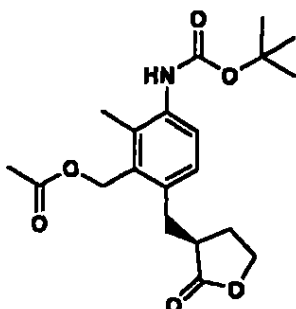
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Acetato 3-(tert-butoxicarbonil)-2-metil-6-((2-oxo-2,5-dihidrofuran-3-il)metil)bencilo. El éster de 3-tert-butoxicarbonilamino-6-yodo-2-metil-bencilo del ácido acético (575 mg, 1.4 mmol) se disolvió en N,N-dimetilformamida (2.5 mL). La α -Metilen- γ -butirolactona (190 μ L, 2.2 mmol) se
15 agregó a la mezcla seguido por acetato de potasio (420 mg, 4.3 mmol), y luego acetato de paladio (II) (16 mg, 0.07 mmol). La mezcla de reacción se calentó a 80°C durante 26 horas. La mezcla se enfrió a temperatura ambiente y se dividió entre acetato de etilo y bicarbonato de sodio acuoso.
20 Las capas se separaron. La capa orgánica se secó (sulfato de magnesio), filtró y concentró in vacuo. La cromatografía en gel de sílice proporcionó el compuesto del título como un sólido blanco apagado en 54% de rendimiento. EM m/e $(M-H)^-= 374$.

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Intermediario 92



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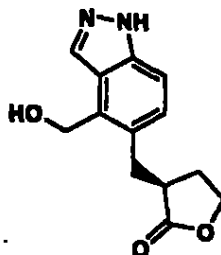
Acetato (S)-3-(tert-butoxicarbonil)-2-metil-6-((2-oxo-tetrahidrofuran-3-il)metil)bencilo. El acetato 3-(tert-butoxicarbonil)-2-metil-6-((2-oxo-2,5-dihidrofuran-3-il)metil)bencilo (280 mg, 0.75 mmol) se disolvió en una mezcla de acetato de etilo (10 mL) y metanol (10 mL). Una cantidad catalítica de tetrafluoroborato (-)-1,2-bis((2R,5R)-dietilfosfolano)benceno(ciclooctadieno)rodio(I) se agregó a la mezcla. El recipiente de reacción se colocó en un aparato Parr y se cargó con 50 psi (3.51 kg/cm²) de gas de hidrógeno. La reacción se agitó a temperatura ambiente durante 16 horas. Una porción fresca de tetrafluoroborato (-)-1,2-bis((2R,5R)-dietilfosfolano)benceno(ciclooctadieno)rodio (I) se agregó a la mezcla. El recipiente de reacción se cargó con 50 psi (3.51 kg/cm²) de gas de hidrógeno. La reacción se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se concentró in vacuo. El residuo se pasó a través de un tapón de gel de sílice eluyendo 80% acetato de etilo-hexanos. El filtrado se concentró in vacuo. El compuesto del título se obtuvo como un aceite incoloro claro en 69% de rendimiento.

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EM m/e (M-H)⁻ = 376.

Intermediario 93



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(S)-3-((4-(hidroximetil)-1H-indazol-5-il)metil)-

dihidrofuran-2(3H)-ona. El acetato (S)-3-(tert-butoxicarbonil)-2-metil-6-((2-oxo-tetrahidrofuran-3-

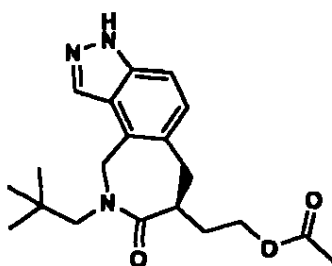
10 il)metil)bencilo (190 mg, 0.50 mmol) se disolvió en diclorometano (4 mL). El ácido trifluoroacético (1 mL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 30 minutos. La mezcla se diluyó con diclorometano y luego se concentró in vacuo. El residuo se
15 disolvió en cloroformo (5 mL). El ácido acético (250 µL) se agregó a la mezcla seguido por nitrato de isoamilo (80 µL, 0.60 mmol). La reacción se agitó a temperatura ambiente durante 20 minutos. El acetato de potasio (400 mg, 4.1 mmol) se agregó a la mezcla. La reacción se agitó a temperatura
20 ambiente durante 1 hora. La mezcla se diluyó con diclorometano. La mezcla se lavó sucesivamente agua 1x, bicarbonato de sodio acuoso 2x. La capa orgánica se secó (sulfato de magnesio), filtró y concentró in vacuo. El residuo se disolvió en metanol (5 mL). El carbonato de
25 potasio (120 mg, 0.87 mmol) se agregó a la mezcla. La

~~271~~ 374

reacción se agitó a temperatura ambiente durante 1 hora. La reacción se apagó con ácido clorhídrico 1N. El metanol se removió de la mezcla in vacuo. El acuoso restante se extrajo éter de dietilo 2x, se hizo básico con bicarbonato de sodio, y luego se extrajo nuevamente éter de dietilo 2x. Los extractos combinados se secaron (sulfato de magnesio), filtraron, y concentraron in vacuo. El compuesto del título se obtuvo como aceite ámbar en 73% de rendimiento. EM m/e (M+H)⁺ = 247.

10

Intermediario 94



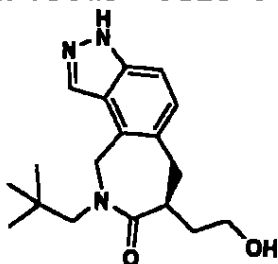
15

Acetato de (S)-2-(9-neopentil-8-oxo-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)etilo. La (S)-3-((4-(hidroximetil)-1H-indazol-5-il)metil)-dihidrofuran-2(3H)-ona (70 mg, 0.28 mmol), se disolvió en diclorometano (1.5 mL). El cloruro de tionilo (500 µL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 45 minutos. La mezcla se concentró. El residuo se trató con diclorometano y se reconcentró. El residuo se disolvió en acetonitrilo (3 mL). El carbonato de potasio (150 mg, 1.1 mmol) se agregó a la mezcla seguido por neopentilamina (100 µL, 0.85 mmol). La

372 375

mezcla se calentó a reflujo durante 45 minutos. La mezcla se enfrió a temperatura ambiente y se filtró. El filtrado se concentró in vacuo. El residuo se disolvió en tolueno (5 mL). El ácido acético (200 µL) se agregó a la mezcla. La reacción
5 se calentó a reflujo durante 5.5 horas. La mezcla se concentró in vacuo. La purificación de CLAR preparatoria dio el compuesto del título como un sólido amarillo en 19% de rendimiento. EM m/e (M-H)⁺ = 356.

Intermediario 95



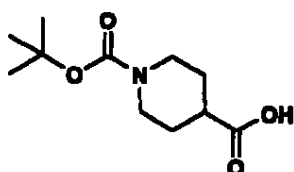
10

15 (S)-7-(2-hidroxietil)-9-neopentil-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El acetato (S)-2-(9-neopentil-8-oxo-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)etilo (18 mg, 0.05 mmol) se disolvió en metanol (1 mL). El carbonato de potasio (20 mg, 0.14 mmol) se
20 agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 1 hora. La resina de intercambio de iones Amberlite IR-50 se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 15 minutos. La mezcla se filtró. El filtrado se concentró in vacuo. El compuesto del título se
25 obtuvo como un residuo amarillo en 94% de rendimiento. EM m/e

37 376

(M+H)⁺ = 316.

Intermediario 96

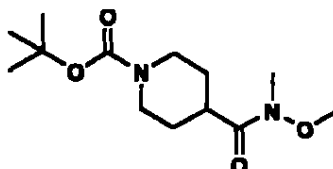


5

Ácido 1-(*tert*-butoxicarbonil)piperidin-4-carboxílico. El ácido isonipecótico (1.05 g, 8.1 mmol) se suspendió en una mezcla de tetrahidrofurano (20 mL) y hidróxido de sodio 1N (20 mL). El bicarbonato di-*tert*-butilo se agregó a la mezcla.

10 La reacción se agitó a temperatura ambiente durante 2.5 horas. La mezcla se hizo ácida con ácido clorhídrico 1N. La mezcla se extrajo con acetato de etilo 2x. Los orgánicos combinados se lavaron con salmuera y luego se secaron (sulfato de magnesio), filtraron y concentraron in vacuo. El
15 compuesto del título se obtuvo como un sólido blanco en 94% de rendimiento. EM m/e (M-H)⁻ = 228.0.

Intermediario 97



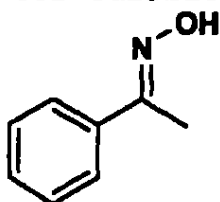
20

4-(Metoxi(metil)carbamoil)piperidin-1-carboxilato de *tert*-Butilo. El 4-(metoxi(metil)carbamoil)piperidin-1-carboxilato de *tert*-Butilo (640 mg, 2.8 mmol) y tetrafluoroborato *o*-benzotriazol-1-il-N,N',N'-
25 tetrametiluronio (1.0 g, 3.1 mmol) se combinaron y disolvieron

371 377

en N,N-dimetilformamida (12 mL). La N,N-Diisopropiletilamina se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 45 minutos. El clorohidrato de N,O-Dimetilhidroxilamina (450 mg, 4.6 mmol) se agregó a la
5 mezcla. La reacción se agitó a temperatura ambiente durante 1.5 horas. La mezcla se diluyó con éter de dietilo y luego se lavó 3x agua, de ácido clorhídrico 1N 1x. La capa orgánica se secó (sulfato de magnesio), filtró y se concentró in vacuo. El compuesto del título se obtuvo como un aceite incoloro
10 claro en 70% de rendimiento. EM m/e $(M-C_4H_9+H)^+ = 217.1$.

Intermediario 98

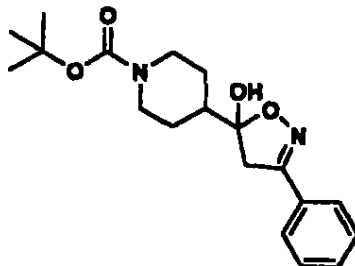


15 Oxima de acetofenona. La acetofenona (5.0 mL, 43 mmol) se disolvió en metanol (50 mL). El clorohidrato de hidroxilamina (6.1 g, 88 mmol) se agregó a la mezcla seguido por hidróxido de sodio 10N (10 mL, 100 mmol). La reacción se agitó a temperatura ambiente durante 20 minutos. El hidróxido
20 de sodio 10N (5 mL, 50 mmol) se agregó a la mezcla. La reacción se calentó a reflujo durante 1 hora. La mezcla se enfrió a temperatura ambiente y se agitó durante 4 horas. La mezcla de reacción se concentró in vacuo. El residuo se trató con agua. La mezcla se extrajo con éter de dietilo 2x. Los
25 extractos combinados se lavaron agua 1x, salmuera 1x. La capa

378

orgánica se secó (sulfato de magnesio), filtró y concentró. El compuesto del título se obtuvo como un sólido blanco en 76% de rendimiento. EM m/e (M+H)⁺= 136.0.

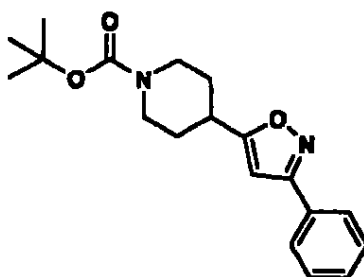
Intermediario 99



10 4-(5-Hidroxi-3-fenil-4,5-dihidroisoxazol-5-il)piperidin-1-carboxilato de tert-Butilo. La oxima de acetofenona (180 mg, 1.3 mmol) se disolvió en tetrahidrofurano (15 mL). La mezcla se enfrió a 0°C. El butillitio en pentanos (1.35 mL, 2.7 mmol) se agregó a la mezcla gota a gota. La reacción se
15 agitó a 0°C durante 1 hora. Una solución de 4-(metoxi(metil)carbamoil)piperidin-1-carboxilato de tert-Butilo (360 mg, 1.3 mmol) en tetrahidrofurano (5 mL) se agregó a la mezcla de reacción gota a gota. La reacción se agitó a 0°C durante 1 hora. La reacción se apagó con cloruro
20 de amonio acuoso. La mezcla se extrajo acetato de etilo 2x. Los extractos combinados se secaron (sulfato de magnesio), filtraron y concentraron in vacuo. La cromatografía de gel de sílice proporcionó el compuesto del título como un aceite incoloro claro en 71% de rendimiento. EM m/e (M-H)⁻= 345.1.

329

Intermediario 100



5

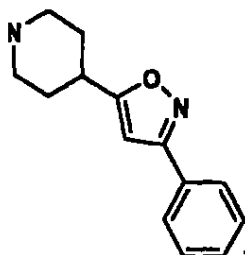
4-(3-Fenilisoxazol-5-il)piperidin-1-carboxilato de tert-Butilo.

El 4-(5-hidroxi-3-fenil-4,5-dihidroisoxazol-5-il)piperidin-1-carboxilato de tert-Butilo (320 mg, 0.92 mmol) se disolvió en metanol (10 mL). Una solución de carbonato de sodio (200 mg, 1.9 mmol) en agua (10 mL) se agregó a la mezcla. La reacción se agitó a reflujo durante 2 horas. El metanol se removió de la mezcla de reacción in vacuo. El acuoso restante se extrajo acetato de etilo 2x. Los extractos combinados se lavaron con salmuera. La capa orgánica se secó (sulfato de magnesio), filtró, y concentró. El compuesto del título se obtuvo como un sólido blanco apagado en 86% de rendimiento. $(M-C_4H_9+H)^+ = 273.1$.

10

15

Intermediario 101



20

4-(3-Fenilisoxazol-5-il)piperidina.

El

4-(3-

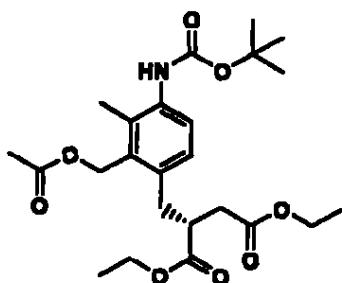
fenilisoxazol-5-il)piperidin-1-carboxilato de tert-Butilo (225 mg, 0.78 mmol) se diluyó en diclorometano (3 mL). El ácido trifluoroacético (3 mL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 1 hora. La

25

377 380

mezcla se diluyó con diclorometano y luego se concentró in vacuo. El residuo se trató con bicarbonato de sodio acuoso. La mezcla se extrajo acetato de etilo 2x. Los extractos combinados se lavaron agua 1x, salmuera 1x. La capa orgánica
5 se secó (sulfato de magnesio), filtró y concentró in vacuo. El compuesto del título se obtuvo como un sólido blanco en 76% de rendimiento. EM m/e (M+H)⁺= 229.1.

Intermediario 102

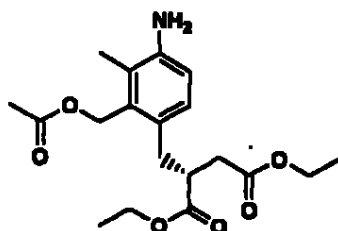


10

Éster de dietilo del ácido 2-(R)-(Acetoximetil-4-tert-
15 butoxycarbonilamino-3-metil-bencil)-succínico. El éster de dietilo del ácido 2-(S)-(acetoximetil-4-tert-butoxycarbonilamino-3-metil-bencilideno)-succínico (700 mg, 1.5 mmol). se hidrogenó en una manera análoga a la preparación de éster de dietilo del ácido 2-(S)-(acetoximetil-4-tert-
20 butoxycarbonilamino-3-metil-bencil)-succínico usando (+)-1,2-bis((2S,5S)-dietilfosfolano)benceno(ciclooctadieno)rodio(I) trifluorometano sulfonato como el catalizador. La cromatografía en gel de sílice proporcionó el compuesto del título como un aceite ligeramente coloreado en 75% de
25 rendimiento. EM m/e (M-H)⁻=464.0.

37:38

Intermediario 103



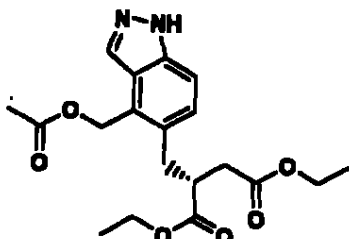
5

Ester de dietilo del ácido 2-(R)-(2-Acetoximetil-4-amino-3-metil-bencil)-succínico. Ácido trifluoroacético (2.5 mL) se agregó a una solución de éster de dietilo del ácido 2-(R)-(acetoximetil-4-tert-butoxicarbonilamino-3-metil-bencil)-succínico (525 mg, 1.1 mmol) en diclorometano (10 mL). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La mezcla se concentró in vacuo. El residuo se trató con bicarbonato de sodio acuoso y se extrajo con acetato de etilo (2x 20 mL). Las capas orgánicas combinadas se secaron (sulfato de magnesio), filtró y concentró in vacuo. El compuesto del título se obtuvo como aceite ámbar en 99% de rendimiento. EM m/e (M-C₂H₄O₂+H)⁺=306.1.

10

15

Intermediario 104



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Ester de dietilo del ácido 2-(R)-(4-Acetoximetil-1H-indazol-5-ilmetil)-succínico. Nitrito de isoamilo (170 µL, 1.3 mmol) se agregó gota a gota a una solución enfriada (baño de hielo con agua) de éster de dietilo del ácido 2-(R)-(2-

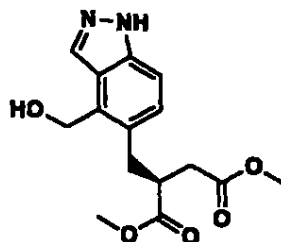
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acetoximetil-4-amino-3-metil-bencil)-succínico en ácido acético-cloroformo al 5% (5 mL). La mezcla se agitó a 0°C durante 1.5 horas. La mezcla se diluyó con diclorometano (20mL) y luego se lavó con bicarbonato de sodio acuoso saturado (2 X 20 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró in vacuo. El compuesto del título se obtuvo como un aceite ámbar en 99% de rendimiento. EM m/e (M+H)⁺ 377.1.

Intermediario 105

10



Ester de dimetilo del ácido 2-(R)-(4-Hidroximetil-1H-indazol-5-ilmetil)-succínico. Carbonato de potasio (380 mg, 2.7 mmol) se agregó a una solución de éster de dietilo del ácido 2-(R)-(4-acetoximetil-1H-indazol-5-ilmetil)-succínico (420 mg, 1.1 mmol) en metanol (10 mL). La mezcla se agitó a temperatura ambiente durante 2 horas. La reacción se apagó con ácido clorhídrico 1N. El metanol se removió de la mezcla in vacuo. El acuoso restante se hizo básico con bicarbonato de sodio. La mezcla se extrajo con acetato de etilo (2 X 20 mL). Las capas orgánicas combinadas se lavaron sucesivamente con agua (20 mL) y salmuera (20 mL). El orgánico se secó (sulfato de magnesio), filtró y concentró in vacuo. El

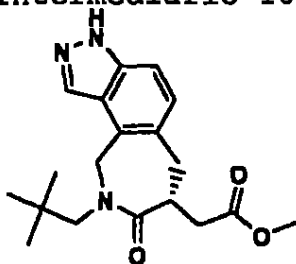
25

383

compuesto del título se obtuvo como un aceite ámbar en 92% de rendimiento. EM m/e (M+H)⁺ 307.1.

Intermediario 106

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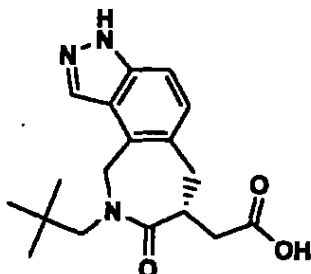


10 *Ester de metilo del ácido [9-(2,2-Dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-acético.* Cloruro de tionilo (2 mL) se agregó a una solución de éster de dimetilo del ácido 2-(R)-(4-hidroximetil-1H-indazol-5-ilmetil)-succínico (280 mg, 0.91 mmol) en diclorometano (4 mL). La reacción se agitó a temperatura ambiente durante 1 hora. La mezcla se diluyó con 15 diclorometano y luego se concentró in vacuo. El residuo se suspendió en acetonitrilo (5 mL). El carbonato de potasio (300 mg, 2.2 mmol) se agregó a la mezcla seguido por neopentilamina (250 µL, 2.1 mmol). La reacción se calentó a reflujo durante 30 minutos. Neopentilamina (150 µL, 1.3 mmol) 20 se agregó a la mezcla. La reacción se calentó a reflujo durante 20 minutos. La mezcla se enfrió a temperatura ambiente y filtró. El filtrado se concentró in vacuo. El residuo se disolvió en tolueno (5 mL). Acido acético (300 µL) se agregó a la mezcla. La reacción se calentó a reflujo 25 durante 16 horas. La mezcla se enfrió a temperatura ambiente

374 384

y se diluyó con acetato de etilo. La mezcla se lavó sucesivamente con bicarbonato de sodio acuoso (2x), agua, y salmuera. La capa orgánica se secó (sulfato de magnesio), filtró y concentró in vacuo. La cromatografía en gel de sílice proporcionó el compuesto del título como aceite ámbar en 29% de rendimiento. EM m/e(M-H)⁻ =342.1.

Intermediario 107



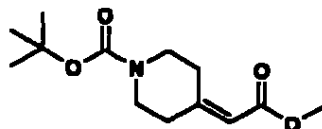
Acido [9-(2,2-Dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-acético.

Monohidrato de hidróxido de litio (31 mg, 0.74 mmol) se agregó a una solución de éster de metilo del ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-acético (90 mg, 0.26 mmol) en metanol (2.5 mL), tetrahidrofurano (2 mL) y agua (2.5 mL). La mezcla de reacción se calentó a 50 °C durante 1.5 horas. Los solventes orgánicos se removieron de la mezcla in vacuo. El acuoso restante se neutralizó con ácido clorhídrico 1N (730 µL). La mezcla se extrajo con acetato de etilo (2 X 20 mL). Las capas orgánicas combinadas se lavaron con salmuera (20 mL) y luego se secó (sulfato de magnesio), filtró y concentró in vacuo. El compuesto del título se obtuvo como un sólido

25 305

ámbar en 88% de rendimiento. EM m/e (M-H)⁺=328.1.

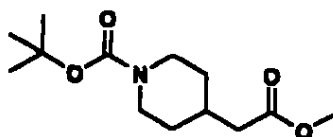
Intermediario 108



5 4-(2-metoxi-2-oxoetiliden)piperidin-1-carboxilato de
tert-butilo. Hidruro de sodio al 60% en aceite mineral (7.92
g, 198.02 mmoles) se lavó con hexanos, luego se suspendió en
N,N- dimetilformamida (220.00 mL). La mezcla se enfrió a 0°C.
Trimetil fosfonoacetato (29.0 mL, 189.82 mmoles) se agregó
10 gota a gota a la reacción. La mezcla se mantuvo a 0°C con
agitación y se mantuvo durante 20 min. Una solución de N-
tert-butoxicarbonil-4-piperidona (30.41 g, 152.62 mmoles) en
80 mL de N,N-dimetilformamida se agregó a la mezcla gota a
gota. La reacción se agitó a temperatura ambiente durante 3
15 horas. La mezcla se diluyó con éter de dietilo (650 mL). La
mezcla se lavó una vez con agua. La capa acuosa se volvió a
extraer con éter de dietilo. Las capas orgánicas se
combinaron. La mezcla se lavó 4 veces con agua y la fase
acuosa se descartó. La mezcla se lavó con salmuera y se
20 descartó la fase acuosa. El material se secó sobre MgSO₄, se
filtró, y se concentró hasta sequedad. El compuesto del
título se obtuvo como un sólido blanco en 92% de rendimiento.
¹H RMN (300 MHz, CDCl₃: δ= 5.68 (s, 1H), 3.66 (s, 3H), 3.40-
3.51 (m. 4H), 2.90 (t, 7=5.49, 2H), 2.25 (t, ,7=5.49, 2H),
25 1.44 (s, 9H).

386

Intermediario 109



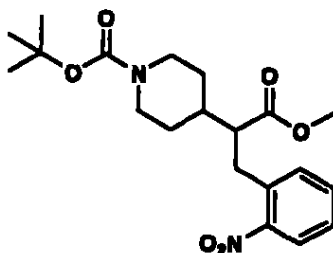
5

4-(2-metoxi-2-oxoetil)piperidina-1-carboxilato de tert-butilo. El 4-(2 metoxi-2-oxoetiliden)piperidina-1-carboxilato de tert-butilo (35.71 g, 140 mmol) se disolvió en una mezcla de acetato de etilo (110 mL) y metanol (110 mL). Paladio en carbono al 10% húmedo al 50% (3.3 g) se agregó a la mezcla. El recipiente de reacción se cargó con 55 psi (3.87 kg/cm²) de gas de hidrógeno. La reacción se agitó en un aparato Parr a temperatura ambiente durante 16 horas. La mezcla de reacción se filtró para remover el catalizador. El filtrado se concentró in vacuo. El compuesto del título se obtuvo como un aceite incoloro transparente en 97% de rendimiento. ¹H RMN (300 MHz, CDCl₃): δ= 4.04 (d, J=10.25, 2H), 3.64 (s, 3H), 2.68 (t, J=12.44, 2H), 2.21 (d, J=6.95, 2H), 1.98-1.77 (m, 1H), 1.64 (d, J=13.54, 2H), 1.41 (s, 9H), 1.25-0.99 (m, 2H).

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Intermediario 110



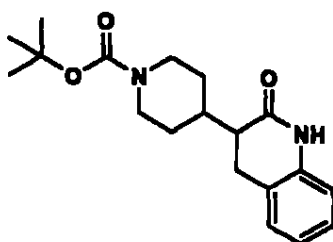
5

4-(1-metoxi-3-(2-nitrofenil)-1-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. El 4-(2-metoxi-2-oxoetil)piperidina-1-carboxilato de tert-butilo (240 mg, 0.93 mmol) se disolvió en tetrahidrofurano (7 mL). La mezcla se enfrió a -78°C. Una solución 0.5 M de bistrimetilsilil)amida de potasio en tolueno (2.2 mL, 1.1 mmol) se agregó a la mezcla gota a gota. La reacción se agitó a -78°C durante 20 minutos. Una solución de bromuro de 2-nitrobencilo (240 mg, 1.1 mmol) en tetrahidrofurano (2 mL) se agregó a la mezcla de reacción gota a gota. La reacción se agitó a -78°C durante 40 minutos.

El baño de hielo seco se removió y la mezcla de reacción se permitió entibiar a temperatura ambiente durante 30 minutos. La reacción se apagó con cloruro de amonio acuoso. La mezcla se extrajo con acetato de etilo (2x 20 mL). Los extractos combinados se secaron (sulfato de magnesio), filtraron y concentraron in vacuo. La cromatografía en gel de sílice proporcionó el compuesto del título como aceite amarillo en 41% de rendimiento. EM m/e (M-C₄H₉+H)⁺ =337.3.

2624
388

Intermediario 111

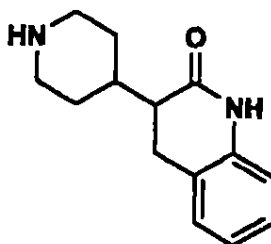


5

4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-il)piperidina-1-carboxilato de tert-butilo. El 4-(1-metoxi-3-(2-nitrofenil)1-oxopropan-2-il)piperidina-1-carboxilato de tert-butilo (660 mg, 1.7 mmol) se disolvió en una mezcla de acetato de etilo (15 mL) y metanol (15 mL). Acido acético (250 U.L, 4.4 mmol) se agregó a la mezcla. Una cantidad catalítica de paladio en carbono al 10% húmedo al 50% se agregó a la mezcla. El recipiente de reacción se cargó con 15 psi (1.05 kg/cm²) de gas de hidrógeno. La reacción se agitó en un aparato Parr a temperatura ambiente durante 2 horas. La mezcla de reacción se filtró y se removió el catalizador. El filtrado se concentró in vacuo. La cromatografía en gel de sílice dio el compuesto del título como espuma anaranjada en 47% de rendimiento. EM m/e (M-H)⁺ = 329.1.

20

Intermediario 112



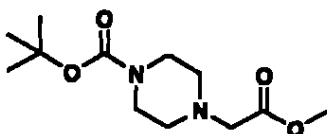
25

3-(piperidin-4-il)-3,4-dihidroquinolin-2(1H)-ona. Ácido

389

trifluoroacético (3 mL) se agregó a una solución de 4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-il)piperidina-1-carboxilato de tert-butilo (260 mg, 0.79 mmol) en diclorometano (3 mL). La reacción se agitó a temperatura ambiente durante 1 hora. La
5 mezcla de reacción se concentró in vacuo. El residuo se disolvió en metanol. La resina de intercambio de iones Dowex 1x4-200 se agregó a la mezcla para crear una suspensión espesa. La mezcla se agitó a temperatura ambiente por 30 minutos. La resina se filtró completamente y se lavó con
10 metanol. El filtrado se concentró. El compuesto del título se obtuvo como espuma oscura en rendimiento cuantitativo. MS $m/e (M+H)^+ = 231.1$.

Intermediario 113



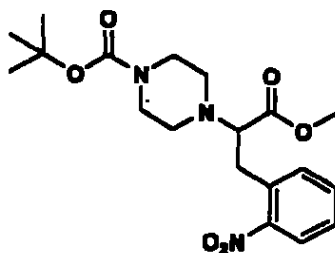
15

4-(2-metoxi-2-oxoetil)piperazina-1-carboxilato de de
tert-butilo. Carbonato de potasio (3.4 g, 25 mmol) se agregó
a una mezcla de N-Boc-piperazina (3.0 g, 16 mmol) en
20 acetonitrilo (20 mL). Metil bromoacetato (1.5 mL, 16 mmol) se
agregó a la mezcla. La reacción se agitó a temperatura
ambiente durante 1.5 horas. La mezcla se filtró sobre celite.
El filtrado se concentró in vacuo. El residuo se trató con
éter de dietilo (10 mL), filtró y concentró in vacuo. La
25 destilación bulbo a bulbo (165°C a 700 mtorr) dio el

223
390

compuesto del título como un aceite incoloro claro en 60% de rendimiento. EMm/e (M+H)⁺ 259.4.

Intermediario 114

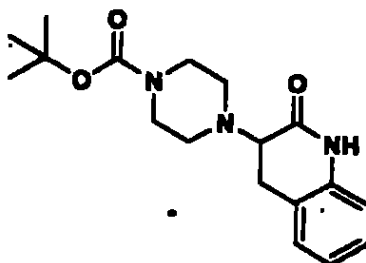


5

4-(1-metoxi-3-(2-nitrofenil)-1-oxopropan-2-il)piperazina-1-

10 carboxilato de tert-butilo. El 4-(2-metoxi-2-oxoetil)piperazina-1-carboxilato de tert-butilo (1.0 g, 3.9 mmol) y bromuro de 2-nitrobencilo (1.0 g, 4.6 mmol) se hicieron reaccionar en una forma análoga a la preparación de
15 4-(1-metoxi-3-(2-nitrofenil)-1-oxopropan-2-il)piperidina-1-carboxilato de tert-butilo. El compuesto del título se obtuvo como aceite ámbar en 51% de rendimiento. EM m/e (M+H)⁺ 394.4.

Intermediario 115



20

4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-il)piperazina-1-carboxilato de tert-butilo. 4-(1-metoxi-3-(2-nitrofenil)-1-oxopropan-2-il)piperazina-1-carboxilato de tert-butilo (770
25 mg, 2.0 mmol) se hizo reaccionar en una manera análoga a la

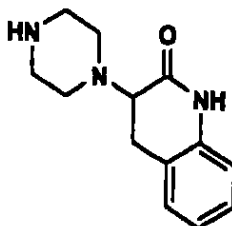
266

391

preparación de 4-(2-oxo-1,2,3,4-tetrahidroquinolin-3-il)piperidina-1-carboxilato de tert-butilo. El compuesto del título se obtuvo como aceite ámbar en rendimiento cuantitativo. EM m/e (M+H)⁺ =332.3.

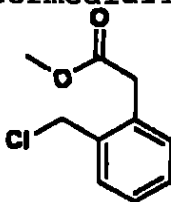
5

Intermediario 116



3-(Piperazin-1-il)-3,4-dihidroquinolin-2(1H)-ona. El 4-
10 (2-oxo-1,2,3,4-tetrahidroquinolin-3-il)piperazina-1-
carboxilato de tert-butilo (640 mg, 1.9 mmol) reaccionó en
una manera análoga a la preparación de 3-(piperidin-4-il)-
3,4-dihidroquinolin-2(1H)-ona. El compuesto del título se
obtuvo como un sólido café claro en rendimiento cuantitativo.
15 EM m/e (M+H)⁺ 232.4.

Intermediario 117

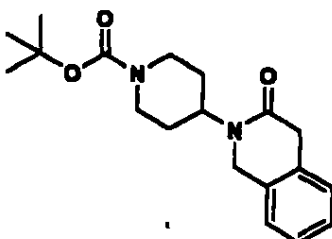


20 2-(2-(clorometil)fenil)acetato de metilo. Se burbujeó
gas de cloruro de hidrógeno a través de una solución de 3-
isocromanona (1.2 g, 8.1 mmol) en metanol (30 mL) durante 3
minutos. La reacción se agitó a temperatura ambiente durante
8 horas. La mezcla se diluyó con agua (70 mL). La mezcla se
25 extrajo con diclorometano (2x40 mL). Las capas orgánicas

214 392

combinadas se lavaron con salmuera (20 mL). La mezcla se secó (sulfato de magnesio), filtró y concentró in vacuo. El compuesto del título se obtuvo como un aceite incoloro claro en 90% de rendimiento. ^1H RMN (300 MHz, CDCl_3): δ =7.40-7.26 (m, 4H), 4.67 (s, 2H), 3.80 (s, 2H), 3.69 (s, 3H).

Intermediario 118



10

4-(3-oxo-3,4-dihidroisoquinolin-2(1H)-il)piperidina-1-carboxilato de tert-butilo. Carbonato de potasio (1.4 g, 10 mmol) se agregó a una solución de 2-(2-(clorometil)fenil)acetato de metilo (940 mg, 4.7 mmol) en acetonitrilo (20 mL). 4-Amino-N-Boc-piperidina (1.13 g, 5.6 mmol) se agregó a la mezcla. La reacción se calentó a reflujo durante 1 hora. La mezcla se enfrió a temperatura ambiente y luego se filtró sobre celite. El filtrado se concentró in vacuo. El residuo se trató con tolueno (29 mL). Acido acético (1.5 ml) se agregó a la mezcla. La reacción se calentó a reflujo durante 2 horas. La mezcla se concentró in vacuo. El residuo se trató con acetato de etilo (50 mL). La mezcla se lavó sucesivamente con bicarbonato de sodio acuoso (2x30 mL), ácido clorhídrico 1N (30 mL), y salmuera (20 mL). La capa orgánica se secó (sulfato de magnesio), filtró y concentró in

15

20

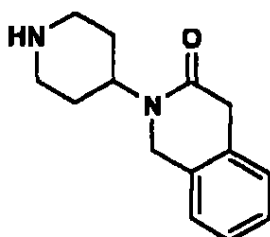
25

393

vacuo. La cromatografía en gel de sílice dio el compuesto del título como un aceite ligeramente coloreado en 40% de rendimiento. EM m/e (M+H)⁺=331.2.

Intermediario 119

5



2-(Piperidin-4-il)-1,2-dihidroisoquinolin-3(4H)-ona. El

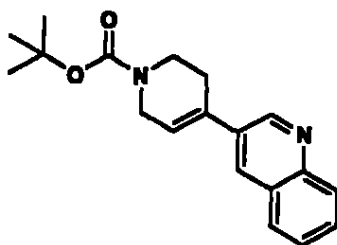
10

4-(3-oxo-3,4-dihidroisoquinolin-2(1H)-il)piperidina-1-carboxilato de tert-butilo (730 mg, 2.2 mmol) reaccionó en una manera análoga a la preparación de 3-(piperidin-4-il)-3,4-dihidroquinolin-2(1H)-ona. El compuesto del título se obtuvo como un sólido amarillo en 96% de rendimiento. EM m/e

15

(M+H)⁺ =231.4.

Intermediario 120



20

4-(quinolin-3-il)-5,6-dihidropiridina-1(2H)-carboxilato de tert-butilo. Acido 3-quinolinborónico (250 mg, 1.4 mmol) y 4-(trifluorometilsulfonilo)-5,6-dihidropiridina-1(2H)-carboxilato de tert-butilo (580 mg, 1.8 mmol) se combinaron y

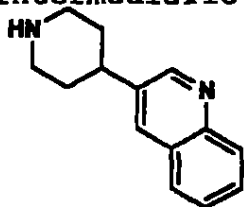
25

disolvieron en una mezcla de tolueno (10 mL) y etanol (1 mL).

294 394

Una solución 2M de bicarbonato de sodio acuoso (1.5 mL, 3.0 mmol) se agregó a la mezcla seguido por cloruro de litio (180 mg, 4.2 mmol). Gas de nitrógeno se burbujeó a través de la mezcla durante 10 minutos. Tetraquis(trifenilfosfina) paladio(0) (75 mg, 0.07 mmol) se agregó a la mezcla. La reacción se calentó a reflujo durante 3.5 horas. La mezcla se enfrió a temperatura ambiente y se diluyó con acetato de etilo (50 mL). La mezcla se lavó sucesivamente con agua (2x30 mL) y salmuera (20 mL). La capa orgánica se secó (sulfato de magnesio), filtró y concentró in vacuo. La cromatografía en gel de sílice proporcionó el producto deseado como un aceite ligeramente coloreado en 76% de rendimiento. EM m/e (M-C₄H₉+H)=255.1.

Intermediario 121

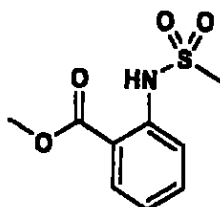


3-(Piperidin-4-il)quinolina. Una cantidad catalítica de 50% de paladio sobre carbono al 10% húmedo se agregó a una mezcla de 4-(quinolin-3-il)-5,6-dihidropiridina-1(2H)-carboxilato de tert-butilo (260 mg, 0.84 mmol) en metanol (10 mL). El recipiente de reacción se colocó en un aparato Parr y se cargó con 10 psi (0.7 kg/cm²) de gas de hidrógeno. La reacción se agitó a temperatura ambiente durante 4 horas. La mezcla se filtró y se removi6 el catalizador. El filtrado se

202
395

concentró in vacuo. El residuo se disolvió en diclorometano (4 mL). Ácido trifluoroacético (1 mL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró in vacuo. El residuo se
5 disolvió en diclorometano (20 mL). La mezcla se lavó con bicarbonato de sodio acuoso (20 mL). La capa acuosa se volvió a extraer con diclorometano (30 mL). Las capas orgánicas se combinaron, se secaron (sulfato de magnesio), filtraron y concentraron in vacuo. El compuesto del título se obtuvo como
10 un aceite amarillo en 45% de rendimiento. EM m/e(M+H)⁺=213.2.

Intermediario 122



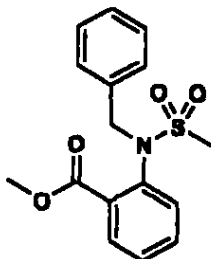
15 2-(metilsulfonamido)benzoato de metilo. Cloruro de metansulfonilo (3.4 mL, 44 mmol) se agregó a una solución de metil antranilato (5.0 mL, 39 mmol) en piridina (10 mL, 124 mmol). La mezcla se agitó a temperatura ambiente durante 16 horas. La reacción se apagó con ácido clorhídrico 1N (150
20 mL). La mezcla se extrajo con acetato de etilo (2x200 mL). Las capas orgánicas se lavaron sucesivamente con ácido clorhídrico 1N (2x100 mL) y salmuera (50 mL). La capa orgánica se secó (sulfato de magnesio), filtró y concentró in vacuo. El residuo se cristalizó a partir de 50 mL de alcohol
25 isopropílico. Los sólidos se filtraron, se lavó con alcohol

1196 396

isopropílico y se secó in vacuo. El compuesto del título se obtuvo como cristales color rosa en 75% de rendimiento. EM m/e (M-H)⁻=228.0.

Intermediario 123

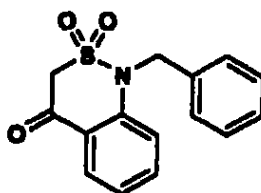
5



2-(N-bencilmetan-2-ilsulfonamido)benzoato de metilo. Hidruro de sodio al 60% en aceite mineral (650 mg, 16.3 mmol) se lavó con hexanos y luego se suspendió en N,N-dimetilformamida (50 mL). La mezcla se enfrió a 0°C. Una solución de metil 2-(metilsulfonamido)benzoato (3.1 g, 13.5 mmol) en N,N-dimetilformamida (10 mL) se agregó a la mezcla gota a gota con agitación. La reacción se mantuvo a 0°C con agitación durante 15 minutos. El bromuro de bencilo (1.9 mL, 15.9 mmol) se agregó a la mezcla gota a gota. La reacción se agitó a temperatura ambiente durante 16 horas. La reacción se apagó con ácido clorhídrico 1N (50 mL). La mezcla se extrajo con éter de dietilo (2x50 mL). Las capas orgánicas se combinaron y se lavó sucesivamente con agua (2x50 mL) y salmuera (30 mL). La capa orgánica se secó (sulfato de magnesio), filtró y concentró in vacuo. La cromatografía en gel de sílice proporcionó el compuesto del título como un aceite incoloro claro en 76% de rendimiento. EM m/e (M-CH₃O+H)⁺=288.1.

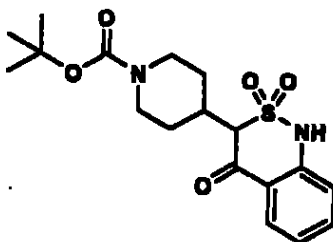
~~304~~ 397

Intermediario 124



5 1-Benzil-2,2-dioxo-2,3-dihidro-1H-2,1-benzotiazin-4-ona. Hidruro de sodio al 60% en aceite mineral (500 mg, 12.5 mmol) se lavó con hexanos y luego se suspendió en N,N-dimetilformamida (15 mL). La mezcla se enfrió a 0°C. Una solución de metil 2-(N-bencilmetan-2-ilsulfonamido)benzoato (3.25g, 10.2 mmol) en N,N-dimetilformamida (20
10 mL) se agregó a la mezcla gota a gota. La mezcla se entibió a temperatura ambiente. La reacción se agitó a temperatura ambiente durante 3 horas. La reacción se apagó con ácido clorhídrico 1N (40 mL). La mezcla se extrajo con éter de dietilo (2x40 mL). Las capas orgánicas combinadas se lavaron con agua (2x40mL). La capa orgánica se secó
15 (sulfato de magnesio), filtró y concentró in vacuo. El compuesto del título se obtuvo como un sólido amarillo ligero en 85% de rendimiento. EM m/e(M-H)⁻ = 286.1.

Intermediario 125



20

Éster de tert-butilo del ácido 4-(2,2,4-Trioxo-1,2,3,4-tetrahidro-2,1-benzotiazin-3-il)-piperidina-1-carboxílico. La
25

291 398

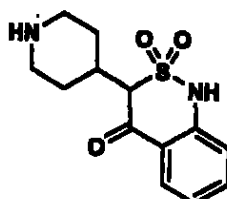
1-Bencil-2,2-dioxo-2,3-dihidro-1H-2,1-benzotiazin-4-ona (1.51 g, 5.26 mmol) se disolvió en piridina (50 mL). La N-tert-Butoxicarbonil-4-piperidinona (1.24 g, 6.33 mmol) se agregó a la mezcla seguido por piperidina (110 μ L, 1.11 mmol). El
5 tamiz molecular se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 40 horas. La mezcla de reacción se filtró sobre celite. El filtrado se concentró in vacuo. El residuo se purificó por cromatografía instantánea de sílice. El mayor componente se aisló y las fracciones se concentraron
10 in vacuo. El residuo se disolvió en metanol (50 mL). A una cantidad catalítica de 50% de paladio en carbono humedo al 10% se agregó a la mezcla. El recipiente de reacción se colocó en un aparato Parr apparatus y se cargó con 55 psi (3.8665 kg/cm²) de gas de hidrógeno. La reacción se agitó a
15 temperatura ambiente durante 2 horas. La mezcla de reacción se filtró sobre celite. El catalizador fresco se agregó al filtrado. El recipiente de reacción se colocó en un aparato Parr y se cargó con 55 psi (3.8665 kg/cm²) de gas de hidrógeno. La reacción se agitó a temperatura ambiente
20 durante 1 hora. La mezcla se filtró sobre celite. Un tercer lote de catalizadores fresco se agregó a la mezcla. El recipiente de reacción se colocó en un aparato Parr y se cargó con 55 psi (3.8665 kg/cm²) de gas de hidrógeno. La reacción se agitó a temperatura ambiente durante 7.5 horas.
25 El catalizador se filtró apagado. El filtrado se concentró in

399

vacuo. La cromatografía de Gel de sílice proporcionó el compuesto del título como un sólido amarillo pálido en 24% de rendimiento. EM m/e (M-H)⁻ = 379.1.

Intermediario 126
HCl

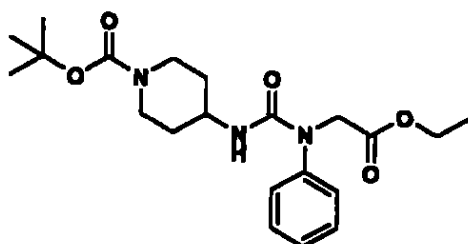
5



Clorohidrato de 2,2-Dioxo-3-piperidin-4-il-2,3-dihidro-1H-2,1-benzotiazin-4-ona. El éster de tert-butilo del ácido 4-(2,2,4-Trioxo-1,2,3,4-tetrahidro-2,1-benzotiazin-3-il)-piperidin-1-carboxílico (175 mg, 0.46 mmol) se disolvió en cloruro de hidrógeno 4M en 1,4-dioxana (3.0 mL, 12.0 mmol). La reacción se agitó a temperatura ambiente durante 45 minutos. La mezcla de reacción se concentró hasta secarse in vacuo. El compuesto del título se obtuvo como un sólido rosa en rendimiento cuantitativo. EM m/e (M+H)⁺ = 281.1.

Intermediario 127

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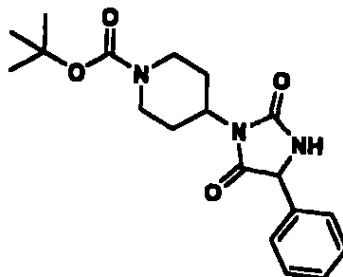


4-(3-(2-etoxi-2-oxoetil)-3-fenilureido)piperidina-1-carboxilato de tert-Butilo. La 4-Amino-1-N-Boc-piperidina (760 mg, 3.79 mmol) se disolvió en una mezcla de diclorometano (40 mL) y bicarbonato de sodio

34X 400

acuoso (30 mL). Una solución de fosgeno al 20% en tolueno (10 mL, 18.9 mmol) se agregó a la mezcla con agitación vigorosa. La reacción se agitó vigorosamente a temperatura ambiente durante 40 minutos. Las capas de reacción se dividieron. La capa orgánica se secó (sulfato de 5 magnesio), filtró y concentró in vacuo. El residuo se disolvió en tolueno (30 mL). El éter de etilo de N-fenilglicina se agregó a la mezcla. La reacción se calentó a reflujo durante 15 horas. La mezcla se enfrió a temperatura ambiente y se diluyó con acetato de etilo (50 mL). La mezcla se lavó sucesivamente con ácido clorhídrico 1N (3x50 mL) y 10 salmuera (30 mL). La capa orgánica se secó (sulfato de magnesio), se filtró y se concentró in vacuo. La cromatografía en gel de sílice proporcionó el compuesto del título como un sólido amarillo pálido en 63% de rendimiento. ¹H RMN (300 MHz, CDCl₃): δ = 7.47-7.26 (m, 5H), 4.30 (s, 1H), 4.16 (q, J=7.32, 2H), 3.88 (d, J=12.81, 2H), 3.81-3.69 (m, 15 1H), 2.89-2.70 (m, 2H), 1.83 (dd, J₁= 12.62, J₂=3.11, 2H), 1.38 (s, 9H), 1.23 (t, J= 7.14, 3H), 1.19-1.03 (m, 2H).

Intermediario 128



20

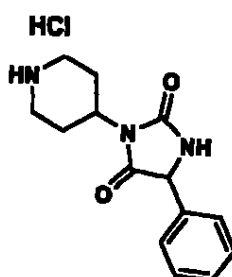
4-(2,5-dioxo-4-fenilimidazolidin-1-il)piperidina-1-carboxilato de tert-Butilo. La trietilamina (200 µL, 1.43 25 mmol) se agregó a una solución de 4-(3-(2-etoxi-2-

~~276~~ 401

oxoetil)-3-fenilureido)piperidina-1-carboxilato de
tert-butilo (90 mg, 0.22 mmol) en etanol (1.8 mL). La
reacción se mantiene a 60°C con agitación durante 3
horas. La mezcla de reacción se concentró in vacuo.
5 El residuo se trató con diclorometano (20 mL) y luego
se concentró in vacuo. El compuesto del título se
obtuvo como un sólido blanco en 81% de rendimiento.
EM m/e (M-C₄H₈+H)⁺ = 304.2.

Intermediario 129

10

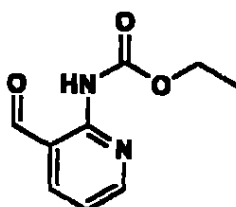


15 *Clorohidrato de 5-Fenil-3-(piperidin-4-il)imidazolidina-
2,4-diona.* El 4-(3-(2-etoxi-2-oxoetil)-3-
fenilureido)piperidina-1-carboxilato de tert-Butilo
(60 mg, 0.17 mmol) se disolvió en una solución de
cloruro de hidrógeno 4M en 1,4-dioxano (2.0 mL). La
20 reacción se agitó a temperatura ambiente durante 30
minutos. Los sólidos se filtraron apagados y se lavó
con éter de dietilo y se secaron. El compuesto del
título se obtuvo como un sólido blanco en rendimiento
cuantitativo. EM m/e (M+H)⁺ = 260.2.

25

3044 402

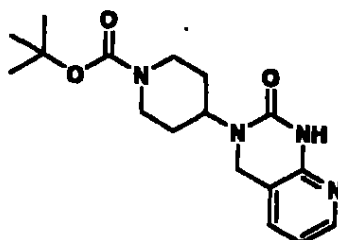
Intermediario 130



5

3-formilpiridin-2-ilcarbamato de etilo. El pirocarbonato de dietilo (570 μ L, 3.9 mmol) se agregó a una solución de 2-aminopiridina-3-carboxaldehído (400 mg, 3.3 mmol) en benceno (20 mL). La mezcla se entibió a 60°C y se mantuvo durante 4 horas. El Pirocarbonato de dietilo (1 mL, 6.8 mmol) se agregó a la mezcla. La reacción se mantuvo a 60°C y se mantuvo durante 1 hora. La mezcla se enfrió a temperatura ambiente. El pirocarbonato de dietilo (1 mL, 6.8 mmol) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 16 horas. La mezcla se concentró in vacuo. La cromatografía de gel de sílice proporcionó a el compuesto del título como un sólido blanco en 58% de rendimiento. EM m/e (M+H)⁺ = 195.1.

intermediario 131



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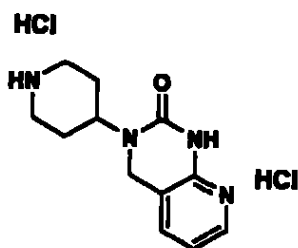
25 4-(2-oxo-1,2-dihidropirido[2,3-d]pirimidin-3(4H)-il)piperidina-1-

~~403~~ 403

carboxilato de *tert*-Butilo. La 4-Amino-1-N-Boc-piperidina (290 mg, 1.4 mmol) se agregó a una solución de 3-formilpiridin-2-ilcarbamato de etilo (240 mg, 1.2 mmol) en metanol (10 mL). La mezcla se entibió a 60°C y se mantuvo durante 1.5 horas. La mezcla se enfrió a temperatura ambiente. El borohidruro de sodio (62 mg, 1.6 mmol) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 30 minutos. El tolueno (20 mL) se agregó a la mezcla seguido por ácido acético (1.0 mL). La mezcla se entibió a 110°C. El metanol conduce de la mezcla de reacción y se colectó en una trampa Dean-Stark. La mezcla se mantuvo a 110°C durante 5 horas. La mezcla se enfrió a temperatura ambiente y se mantuvo durante 16 horas. La reacción se apagó con bicarbonato de sodio acuoso. La mezcla se extrajo con acetato de etilo (2x30 mL). Los orgánicos combinados se lavaron sucesivamente con agua (30 mL) y salmuera (20 mL). La capa orgánica se secó (sulfato de magnesio), filtró y concentró in vacuo. La cromatografía de gel de sílice proporcionó el compuesto del título como un sólido blanco en 44% de rendimiento. EM m/e (M-H)⁻ =311.2.

Intermediario 132

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Clorohidrato de 3-(Piperidin-4-il)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona. A una suspensión de

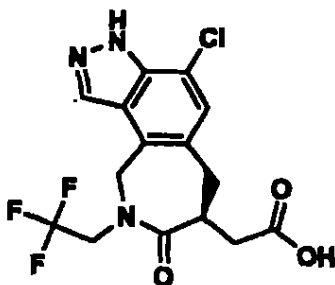
25

404

4-(2-oxo-1,2-dihidropirido[2,3-d]pirimidin-3(4H)-
il)piperidina-1-carboxilato de tert-butilo (220 mg, 0.66
mmol) en cloruro de hidrógeno 4N en 1,4-dioxano (5.0 mL) se
agitó a temperatura ambiente durante 45 minutos. La mezcla se
5 concentró in vacuo. La cristalización de etanol y acetato de
etilo proporciona el compuesto del título como un sólido
blanco en 62% de rendimiento. $(M+H)^+ = 233.2$.

Intermediario 133

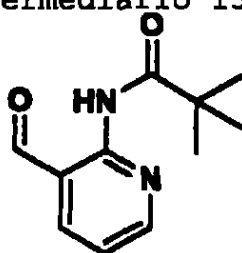
10



15 Ácido [4-Cloro-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-
trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-
il]acético. El éster de dietilo del ácido 2-(S)-(4-
acetoximetil-7-cloro-1H-indazol-5-ilmetil)-succínico (530 mg,
1.48 mmol) y 2,2,2-trifluoroetilamina (1 mL, 12.5 mmol) se
20 hizo reaccionar siguiendo el esquema y procedimiento análogos
a la preparación del ácido [4-Cloro-9-(2,2-dimetil-propil)-8-
oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-
ciclohepta[e]inden-7-il]-acético. El compuesto del título se
obtuvo como un sólido blanco en 20% de rendimiento. EM m/e
25 $(M-H)^- = 374.0$.

402 405

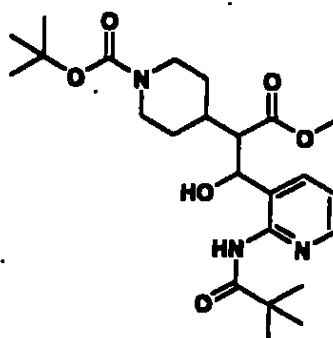
Intermediario 134



5

N-(3-Formilpiridin-2-il)pivalamida. La trietilamina (7.6 mL, 54 mmol), se agregó a una solución de 2-aminopiridina-3-carboxaldehído (4.45 g, 36 mmol) en diclorometano (70 mL). La mezcla se enfrió a 0°C. Una solución de cloruro de pivaloilo (5.3 mL, 43 mmol) en diclorometano (30 mL) se agregó a la mezcla. La reacción se entibió a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 63 horas. La mezcla se lavó sucesivamente con agua (2x50 mL) y salmuera (30 mL). La capa orgánica se secó (sulfato de magnesio), filtró y concentró in vacuo. La cromatografía en gel de sílice proporcionó el compuesto del título como un sólido blanco apagado en 90% de rendimiento. (M+H)⁺ = 207.1.

Intermediario 135



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4-(1-hidroxi-3-metoxi-2-oxo-1-(2-pivalamidopiridin-3-il)propan-2-il)piperidina-1-carboxilato de tert-butilo. Una

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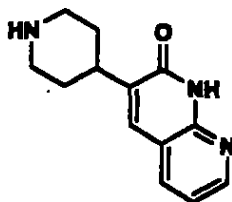
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solución de diisopropilamina (6.0 mL, 43 mmol) en tetrahidrofurano (200 mL) se enfrió a -78°C . Una solución 2.5M de n-butilitio en hexanos (17.0 mL, 43 mmol) se agregó a la mezcla gota a gota. La mezcla se mantuvo a -78°C con
5 agitación durante 20 minutos. Una solución de 4-(2-metoxi-2-oxoetil)piperidina-1-carboxilato de tert-butilo (9.3g, 36 mmol) en tetrahidrofurano (35 mL) se agregó a la mezcla gota a gota. La mezcla se mantuvo a -78°C durante 1.5 horas. En un
10 matraz separado, 60% de hidruro de sodio en aceite mineral (1.57 g, 39 mmol) se lavó en hexanos y luego se suspendió en tetrahidrofurano (70 mL). La mezcla se enfrió a 0°C . Una solución de N-(3-formilpiridin-2-il)pivalamida (6.74 g, 33 mmol) en tetrahidrofurano (20 mL) se agregó a la mezcla gota a gota. La reacción se mantuvo a -0°C con agitación durante 2
15 horas. La mezcla se entibió a temperatura ambiente y luego se agregó a el butillitio que contiene una solución gota a gota. La mezcla de reacción se mantuvo a -78°C con agitación durante 2 horas. La mezcla se permitió calentar lentamente a temperatura ambiente. La mezcla se agitó a temperatura
20 ambiente durante 14 horas. La reacción se apagó con cloruro de amonio acuoso. La mezcla se extrajo con acetato de etilo (2x100 mL). Los extractos orgánicos se combinaron, se secaron (sulfato de magnesio), filtraron y concentraron in vacuo. La cromatografía en gel de sílice proporcionó el compuesto del
25 título como una espuma blanca en 93% de rendimiento. $(\text{M}+\text{H})^{+} =$

404 407

464.2.

Intermediario 136

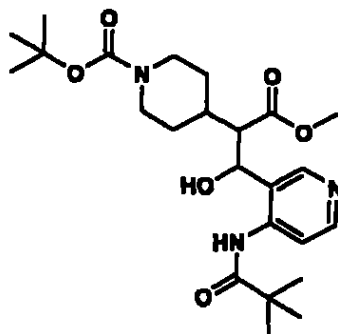


5

Diclorohidrato de 3-(Piperidin-4-il)-1,8-naftiridin-2(1H)-ona. El ácido clorhídrico concentrado (25 mL, 305 mmol) se agregó con agitación a una mezcla de 4-(1-hidroxi-3-metoxi-3-oxo-1-(2-pivalamidopiridin-3-il)propan-2-il)piperidina-1-carboxilato de tert-butilo (14.0 g, 30.2 mmol) y agua (75 mL). La reacción se calentó a reflujo y se mantuvo durante 25 horas. La mezcla se concentró in vacuo. El residuo se cristalizó a partir de etanol. El compuesto del título se obtuvo como un sólido blanco en 33% de rendimiento. $(M+H)^+ = 230.2$.

20

Intermediario 137



4-(1-hidroxi-3-metoxi-3-oxo-1-(4-pivalamidopiridin-3-il)propan-2-il)piperidina-1-carboxilato de tert-Butilo. 4-(2-

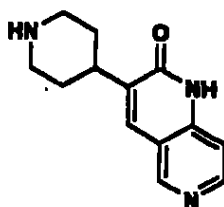
25

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metoxi-2-oxoetil)piperidina-1-carboxilato de tert-butilo (1.33g, 5.2 mmol) y N-(3-formil-4-piridinil-2,2-dimetilpropanamida (1.0 g, 4.7 mmol) se hicieron reaccionar en una manera análoga a la preparación de 4-(1-hidroxi-3-metoxi-3-oxo-1-(2-pivalamidopiridin-3-il)propan-2-il)piperidina-1-carboxilato de tert-butilo. El compuesto del título se obtuvo como una espuma blanca en 54% de rendimiento. $(M+H)^+ = 464.2$.

Intermediario 138

10



3-(piperidin-4-il)-1,6-naftiridín-2(1H)-ona. El ácido clorhídrico concentrado (8.0 mL, 97 mmol) se agregó con agitación a una mezcla de 4-(1-hidroxi-3-metoxi-3-oxo-1-(4-pivalamidopiridin-3-il)propan-2-il)piperidina-1-carboxilato de tert-butilo (1.2 g, 2.6 mmol) y agua (24 mL). La reacción se calentó a reflujo y se mantuvo durante 14 horas. La mezcla se concentró in vacuo.

20

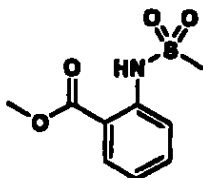
El residuo se trató con acetonitrilo (70 mL) y luego se concentró in vacuo. El residuo se cristalizó a partir de etanol.

El compuesto del título se obtuvo como un sólido blanco en 77% de rendimiento. $(M+H)^+ = 230.1$.

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~~409~~ 409

Intermediario 139

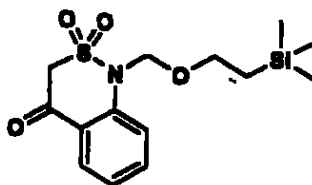


5

Metil 2-(metilsulfonamido)benzoato. El metil antranilato (11.73 g, 77.6 mmol) se disolvió en piridina (25 mL, 309 mmol). La mezcla se enfrió a 0°C. El cloruro de metansulfonilo (6.60 mL, 85.3 mmol) se agregó a la mezcla gota a gota. La mezcla de reacción se entibió a temperatura ambiente y se mantuvo con agitación durante la noche. La mezcla se diluyó con acetato de etilo. El material se lavó dos veces con agua y tres veces con ácido clorhídrico 1N. La capa orgánica se secó (sulfato de magnesio), se filtró y luego se concentró. El residuo se trituró con 50% de éter de dietilo en hexanos. Los sólidos se filtraron apagados, se lavaron con 50% de dietil éter-hexanos, se lavaron con hexanos y luego se secaron bajo alto vacío. El compuesto del título se obtuvo como un sólido blanco apagado en 88% de rendimiento. EM m/e (M-H)⁻ = 227.9.

Intermediario 140

20



2,2-Dioxo-1-(2-trimethylsilanyl-ethoxymetil)-2,3-clihidro-1H-2λ⁶-2,1-benzotiazin-4-ona. En un matraz de fondo redondo

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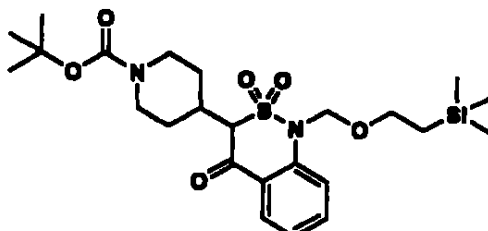
bajo un manto de nitrógeno 60% de hidruro de sodio en aceite mineral (1.05 g, 26 mmol) se lavó con hexanos y luego se suspendió en N,N-dimetilformamida (50 mL). La mezcla se enfrió a 0°C. Una solución de 2-(metilsulfonamido)benzoato de metilo (5.0 g, 22 mmol) en 10 mL de N,N-dimetilformamida se agregó a la mezcla gota a gota. La reacción se mantuvo a 0°C con agitación durante 25 minutos. El cloruro de 2-(Trimetilsilil)etoximetilo se agregó a la mezcla gota a gota. La reacción se agitó durante 2 horas, se calentó lentamente a temperatura ambiente. La reacción se apagó con ácido clorhídrico 1N. El material se extrajo dos veces con acetato de etilo. El material se lavó sucesivamente con agua y salmuera. La fase orgánica se secó (sulfato de magnesio), filtró y concentró hasta secarse. El residuo se disolvió en N,N-dimetilformamida (5 mL) y se agregó gota a gota a una mezcla de 60% de hidruro de sodio en aceite mineral (1.02 g, 26 mmol) que se lavó con hexanos, se suspendió en N,N-dimetilformamida (50 mL) y se enfrió a 0°C. El baño de hielo se removió y la mezcla se permitió calentar a temperatura ambiente. La reacción se mantuvo a temperatura ambiente durante la noche con agitación. La reacción se apagó con ácido clorhídrico 1N. El material se extrajo dos veces con acetato de etilo. La fase orgánica se lavó sucesivamente con agua y salmuera. La fase orgánica se secó (sulfato de magnesio), filtró y concentró hasta secarse. La cromatografía

408 411

de gel de sílice (acetato de etilo-hexanos) proporcionó el compuesto del título como un sólido blanco en 72% de rendimiento. EM m/e (M-H)⁻ = 326.0.

Intermediario 141

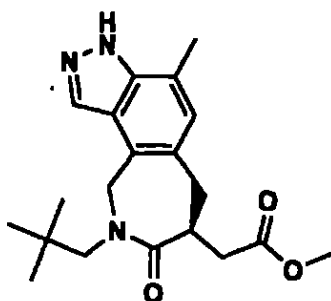
5



10 *Éster tert-butilo del ácido 4-[2,2,4-Trioxo-1-(2-trimethylsilanil-etoximetil)-1,2,3,4-tetrahidro-2λ⁶-2,1-benzotiazin-3-il]-piperidin-1-carboxílico.* La N-tert-Botoxicarbonil-4-piperidinona (2.44 g, 12 mmol) se disolvió en 1,2-dicloroetano (20 mL). La piperidina (1.2 mL, 12 mmol) se agregó a la mezcla. La reacción se calentó a 50°C y se
15 mantuvo con agitación durante 1.25 horas. La mezclase enfrió a temperatura ambiente. Una solución de 2,2-Dioxo-1-(2-trimethylsilanil-etoximetil)-2,3-dihidro-1H-2λ⁶-benzotiazin-ona (2.0 g, 6.1 mmol) en piridina (5.0 mL, 62 mmol) se agregó a la mezcla. La reacción se mantuvo durante la noche a
20 temperatura ambiente con agitación. El material se concentró por evaporación rotatoria. El residuo se disolvió en acetato de etilo. El material se lavó sucesivamente con tres porciones de ácido clorhídrico 1N y una porción de agua. La fase orgánica se secó (sulfato de magnesio), filtró y
25 concentró hasta secarse. El residuo se purificó por

444 422

Intermediario 153



5

Éster de metilo del ácido [4-metil-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El éster de metilo del

10 ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético (110 mg, 0.26 mmol) se disolvió en N,N-dimetilformamida (1.0 mL). Se burbujeó gas de nitrógeno a través de la mezcla durante 5 minutos. El tetraquis(trifenilfosfina)paladio(0)

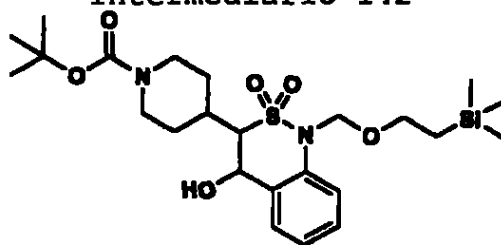
15 (6.0 mg, 0.01 mmol) se agregó a la mezcla seguido por tetrametilestaño (100 µL, 0.72 mmol). El recipiente de reacción se mojó con gas de nitrógeno y luego se selló. La reacción se sometió a calentamiento en microondas a 175°C durante 35 minutos. La mezcla se diluyó con acetato de etilo.

20 El material se lavó sucesivamente con agua y salmuera. La cromatografía en gel de sílice (acetato de etilo-hexanos) proporciona el compuesto del título como un sólido blanco en 83% de rendimiento. EM m/e (M+H)⁺ 358.2.

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413

Intermediario 142

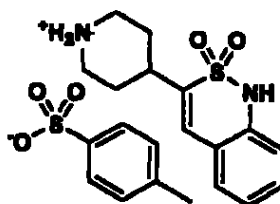


5

Éster tert-butilo del ácido 4-[4-Hidroxí-2,2-dioxo-1-(2-trimetilsilanil-etoximetil)-1,2,3,4-tetrahidro-2λ⁶-2,1-benzotiazin-3-il]-piperidin-1-carboxílico. El compuesto del título se obtuvo como un aceite amarillo en 85% de

10

Intermediario 143



15

2,2-dióxido para-toluenosulfonato de 3-Piperidin-4-il-1H-2,1-benzotiazina. El éster de tert-butilo del ácido 4-[2,2,4-Trioxo-1-(2-trimetilsilanil-etoximetil)-1,2,3,4-tetrahidro-2λ⁶,2,1-benzotiazin-3-il]-piperidin-1-carboxílico (865 mg, 1.7 mmol) se disolvió en metanol (25 mL). La mezcla se enfrió a 0°C. El borohidruro de sodio (100 mg, 2.6 mmol) se agregó a la mezcla en tres porciones. La reacción se agitó a 0°C durante 3 horas. La mezcla se concentró por evaporación rotatoria. El residuo se trató con ácido clorhídrico 1N. El material se extrajo dos veces con acetato de etilo. La fase

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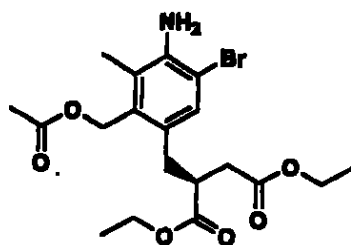
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orgánica se secó (sulfato de magnesio), filtró y concentró

44 44

hasta secarse. El residuo se disolvió en benceno (20 mL). El monohidrato del ácido p-toluensulfónico (475 mg, 2.5 mmol) se agregó a la mezcla. La reacción se calentó a reflujo y se mantuvo con agitación durante 1 hora. La mezcla se enfrió a temperatura ambiente. Los sólidos se filtraron apagados. El sólido pegajoso se trató con alcohol isopropílico caliente (10 mL). La mezcla se enfrió a temperatura ambiente y se permitió que reposara durante la noche. Los sólidos se filtraron apagados, se lavó con alcohol isopropílico y luego se secaron bajo alto vacío. El compuesto del título se obtuvo como un sólido color marrón en 65% de rendimiento. EM m/e $(M+H)^+ = 265.2$.

Intermediario 144



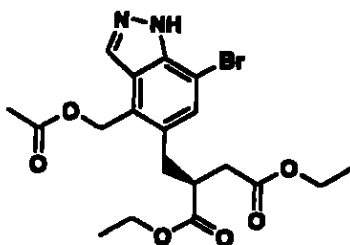
Éster de dietilo del ácido 2-(S)-(2-Acetoximetil-4-amino-5-bromo-3-metil-bencil)-succínico. El éster de dietilo del ácido 2-(S)-(2-Acetoximetil-4-amino-3-metil-bencil)-succínico (7.6 g, 21 mmol) se disolvió en ácido acético (100 mL). El acetato de sodio (4.2 g, 51 mmol) se agregó a la solución. El recipiente de reacción se colocó en un baño de agua frío para controlar la reacción exotérmica. El bromuro (1.1 mL, 22 mmol) se agregó a la mezcla en una porción. La

C/H 415

reacción se agitó a temperatura ambiente durante 10 minutos. La mezcla se vació en una solución de tiosulfato de sodio acuoso 1N (400 mL). El material se extrajo dos veces con acetato de etilo. La fase orgánica se lavó sucesivamente con
5 agua y salmuera. El orgánico se secó (sulfato de magnesio), filtró y concentró in vacuo. La cromatografía en gel de sílice (acetato de etilo-hexanos) proporcionó el producto deseado en 77% de rendimiento como un aceite ámbar. EM m/e $(M-H)^- = 440.0, 442.0$.

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Intermediario 145



15

Éster de dietilo del ácido 2-(S)-(4-Acetoximetil-7-bromo-1H-indazol-5-ilmetil)-succínico. El nitrito de isoamilo (2.3 mL, 17 mmol), se agregó gota a gota en una solución de hielo frío de éster de dietilo del ácido 2-(S)-(2-Acetoximetil-4-amino-5-bromo-3-metil-bencil)-succínico (7.14 g, 16 mmol) en 5% de ácido acético en tolueno (280 mL).

20

La mezcla se agitó a 0°C durante 40 minutos. El acetato de potasio (4.00 g, 41 mmol) se agregó a la mezcla. La mezcla se calentó lentamente a temperatura ambiente. La reacción se agitó a temperatura ambiente durante 14 horas. La mezcla se lavó dos veces con agua y una vez con salmuera. El orgánico se secó (sulfato de magnesio) filtró y

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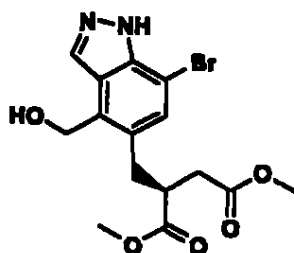
concentró. La cromatografía de gel de sílice (acetato de etilo-hexanos)

457 4/b

proporcionó el producto deseado en 77% de rendimiento como un aceite color ámbar. EM m/e (M+H)⁺ = 455.0, 457.0.

Intermediario 146

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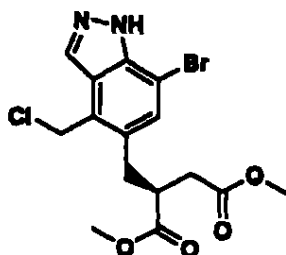
2-((7-bromo-4-(hidroximetil)-1H-indazol-5-

10 il)metil)succinato de (S)-dimetilo. El éster de dietilo del ácido 2-(S)-(2-Acetoximetil-4-amino-5-bromo-3-metil-bencil)-succínico (2.78 g, 6.1 mmol) se convirtió a el compuesto del título en una manera análoga a la preparación de éster de dimetilo del ácido 2-(S)-(4-Hidroximetil-1H-indazol-5-

15 ilmetil)-succínico. El material se obtuvo como un sólido ámbar en 96% de rendimiento. EM m/e (M-H)⁻ = 383.0, 385.0.

Intermediario 147

20



2-((7-bromo-4-(clorometil)-1H-indazol-5-

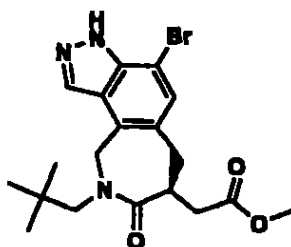
il)metil)succinato de (S)-dimetilo. El 2-((7-bromo-4-(hidrometil)-1H-indazol-5-il)metil)succinato de (S)-dimetilo

25

~~CH~~ 417

(2.25 g, 5.8 mmol) se disolvió en cloruro de tionilo 2M en diclorometano (42 mL, 84mmol). La reacción se agitó a temperatura ambiente durante 2.0 horas. La mezcla se concentró. El residuo se trató con tolueno y luego se concentró por evaporación rotatoria. El residuo se disolvió en acetato de etilo. La mezcla se lavó dos veces con bicarbonato de sodio acuoso. El orgánico se secó (sulfato de magnesio), se filtró y se concentró in vacuo. El compuesto del título se obtuvo como un sólido ámbar en 99% de rendimiento. EM m/e (M+H)⁺ = 404.9, 403.0, 406.9

Intermediario 148



Éster de metilo del ácido [4-Bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El 2-((7-bromo-4-

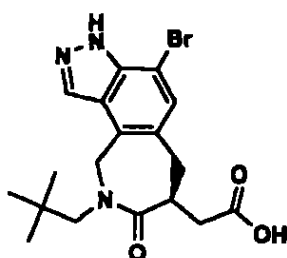
(clorometil)-1H-indazol-5-il)metil)succinato de (S)-dimetilo (860 mg, 2.1 mmol) se disolvió en acetonitrilo (50 mL). El carbonato de potasio (625 mg, 4.5 mmol) se agregó a la mezcla seguido por neopentilamina (800 µL, 6.78 mmol). La mezcla se calentó a reflujo y se mantuvo con agitación durante 1.5 horas. La mezcla se enfrió a temperatura ambiente. La mezcla

~~411~~ 418

se filtró sobre celite. El filtrado se concentró por evaporador rotatorio. El residuo se disolvió en una mezcla de tolueno (50 mL) y ácido acético (3 mL). La mezcla se calentó a reflujo y se mantuvo con agitación durante 37 horas. La
5 mezcla se concentró por evaporador rotatorio. La cromatografía en gel de sílice (acetato de etilo-hexanos) proporcionó el compuesto del título como un sólido color marrón en 75% de rendimiento. EM m/e (M-H)⁻ = 420.0, 422.0.

Intermediario 149

10



Ácido

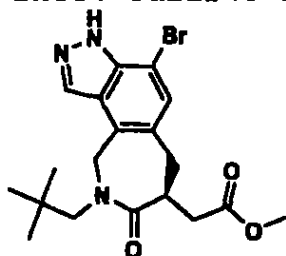
[4-bromo-9-(2,2-dimetil-propil)-8-oxo-

15 3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El éster de metilo del ácido [4-Bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza(S)-ciclohepta[e]inden-7-il]-acético (160 mg, 0.38 mmol) se disolvió en una mezcla de tetrahidrofurano (5.0 mL) y metanol
20 (5.0 mL). El agua (5.0 mL) se agregó a la mezcla seguido por monohidrato de hidróxido de litio (41 mg, 0.98 mmol). La mezcla se calentó hasta 50°C y se mantiene con agitación durante 5 horas. La mezcla se enfrió hasta temperatura ambiente. Los solventes orgánicos se removieron de la mezcla
25 in vacuo. El acuoso restante se diluyó con agua y luego se

~~416~~ 419

hace neutral con 1 mL de ácido clorhídrico 1N. El material se
extrajo dos veces con acetato de etilo. La fase orgánica se
secó (sulfato de magnesio), se filtró y se concentró hasta
secarse. El compuesto del título se obtiene como un sólido
5 color canela en rendimiento cuantitativo. ¹H RMN (300 MHz,
CDCl₃) δ=0.77 (s, 9 H) 2.31 - 2.60 (m, 3 H) 2.91 (dd,
J=16.47, 8.42 Hz, 1 H) 2.98 - 3.05 (m, 1 H) 3.09 (d, J=13.54
Hz, 1 H) 3.47 (d, J=13.91 Hz, 1 H) 3.71 - 3.89 (m, 1 H) 4.39
(d, J=17.20 Hz, 1 H) 5.30 (d, J=17.20 Hz, 1 H) 7.25 (s, 1 H)
10 8.00 (s, 1 H).

Intermediario 150



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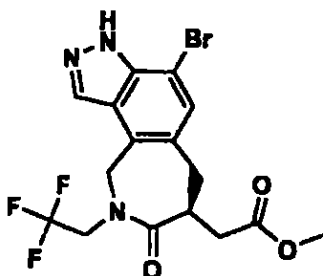
Éster de metilo del ácido [4-bromo-9-(2,2-dimetil-
propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-
ciclohepta[e]inden-7-il]-acético. El (S)-dimetil 2-((7-bromo-
4-(clorometil)-1H-imidazol-5-il)metil)succinato (860 mg, 2.1
20 mmol) se disolvió en acetonitrilo (50 mL). El carbonato de
potasio (625 mg, 4.5 mmol) se agregó a la mezcla seguido por
neopentilamina (800 µL, 6.78 mmol). La mezcla se calentó
hasta reflujo y se mantiene con agitación durante 1.5 hora.
La mezcla se enfrió hasta temperatura ambiente. La mezcla se
25 filtró sobre celite. El filtrado se concentró por evaporación

444 410

rotatoria. El residuo se disolvió en una mezcla de tolueno (50 mL) y ácido acético (3 mL). La mezcla se calentó hasta reflujo y se mantiene con agitación durante 37 horas. La mezcla se concentró por evaporación rotatoria. La cromatografía en gel de sílice (acetato de etilo-hexanos) proporciona el compuesto del título como un sólido color canela en 75% de rendimiento. EM m/e (M-H)⁺ = 420.0, 422.0.

Intermediario 151

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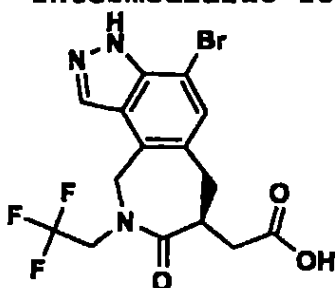
Éster de metilo del ácido [4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]. El éster de dietilo del ácido 2-(S)-(4-clorometil-7-bromo-1H-indazol-5-ilmetil)-succínico (325 mg, 0.81 mmol) se disolvió en acetonitrilo (10 mL). El carbonato de potasio (310 mg, 2.2 mmol) se agregó a la mezcla con 2,2,2-trifluoroetilamina (1.2 mL, 15 mmol). La mezcla se calentó a 60°C y se mantiene con agitación durante 15 horas. La mezcla se enfrió hasta temperatura ambiente. La mezcla se filtró sobre celite. El filtrado se concentró por evaporación rotatoria. El residuo se disolvió en una mezcla de tolueno (10 mL) y ácido acético (600 µL). La mezcla se calentó hasta

44.411

reflujo y se mantiene con agitación durante 22 horas. La mezcla se concentró por evaporación rotatoria. El residuo se disolvió en acetato de etilo. El material se lavó sucesivamente con agua y bicarbonato de sodio acuoso. La fase
5 orgánica se secó (sulfato de magnesio), se filtró y se concentró hasta secarse. El compuesto del título se obtiene como un residuo ámbar en 74% de rendimiento. EM m/e (M-H)⁻ = 431.9, 433.9.

Intermediario 152

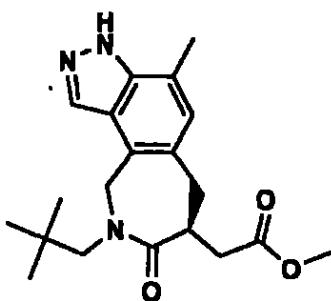
10



15 Ácido [4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El éster de metilo del ácido [4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (250 mg, 0.58
20 mmol) se hace reaccionar en una manera análoga a la preparación del ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El compuesto del título se obtiene como un sólido amarillo ligero en rendimiento cuantitativo. EM m/e
25 (M-H)⁻ = 417.9, 419.9.

144 412

Intermediario 153



5

Éster de metilo del ácido [4-metil-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-

ciclohepta[e]inden-7-il]-acético. El éster de metilo del

10 ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético

(110 mg, 0.26 mmol) se disolvió en N,N-dimetilformamida (1.0 mL). Se burbujeó gas de nitrógeno a través de la mezcla durante 5 minutos. El tetraquis(trifenilfosfina)paladio(0)

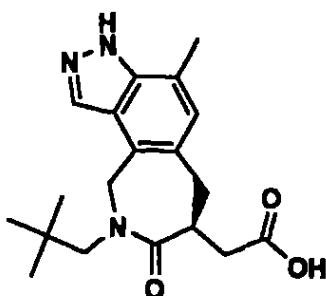
15 (6.0 mg, 0.01 mmol) se agregó a la mezcla seguido por tetrametilestaño (100 µL, 0.72 mmol). El recipiente de reacción se mojó con gas de nitrógeno y luego se selló. La reacción se sometió a calentamiento en microondas a 175°C durante 35 minutos. La mezcla se diluyó con acetato de etilo.

20 El material se lavó sucesivamente con agua y salmuera. La cromatografía en gel de sílice (acetato de etilo-hexanos) proporciona el compuesto del título como un sólido blanco en 83% de rendimiento. EM m/e (M+H)⁺ 358.2.

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Intermediario 154



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Ácido

[4-metil-9-(2,2-dimetil-propil)-8-oxo-

3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El éster de metilo del ácido [4-metil-9-(2,2-

10 dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-

(S)-ciclohepta[e]inden-7-il]-acético (70 mg, 196 μmol) se disolvió en tetrahidrofurano (2.0 mL). El metanol (2.0 mL) se agregó a la mezcla seguido por agua (2.0 mL) y luego hidrato

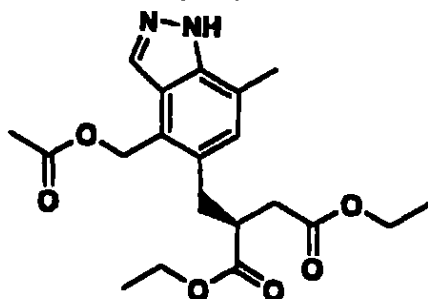
15 calentó hasta 50°C y se mantiene con agitación durante 1.5 hora. La mezcla se enfrió hasta temperatura ambiente. Los solventes orgánicos se removieron de la mezcla por evaporación rotatoria. El acuoso restante se diluyó con agua y luego se neutralizó con ácido clorhídrico 1N (500 μL). La

20 mezcla se extrajo dos veces con acetato de etilo. Los orgánicos se secaron en MgSO_4 , se filtraron y luego se concentraron hasta secarse. El compuesto del título se obtiene como un sólido blanco en 95% de rendimiento. EM m/e (M-H)⁻ = 342.2.

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447 (424)

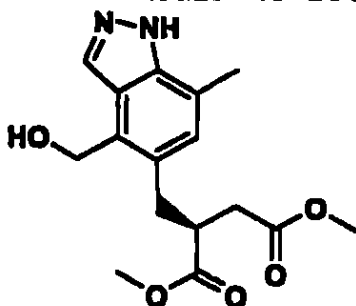
Intermediario 155



5

Éster de dietilo del ácido 2-(S)-(4-acetoximetil-7-metil-1H-indazol-5-ilmetil)-succínico. El éster de dietilo del ácido 2-(S)-(4-acetoximetil-7-bromo-1H-imidazol-5-ilmetil)-succínico (350 mg, 0.77 mmol) y tetrametilestaño (150 µL, 1.1 mmol) se hacen reaccionar en una manera análoga a la preparación del éster de metilo del ácido [4-metil-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El compuesto del título se obtiene como un sólido amarillo pálido en 68% de rendimiento. EM m/e (M-H)⁻ = 389.1.

Intermediario 156



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2-((7-metil-4-(hidroximetil)-1H-indazol-5-il)metil)succinato de (S)-dimetilo. El éster de dietilo del ácido 2-(S)-(2-acetoximetil-4-amino-5-metil-3-metil-bencil)-

25

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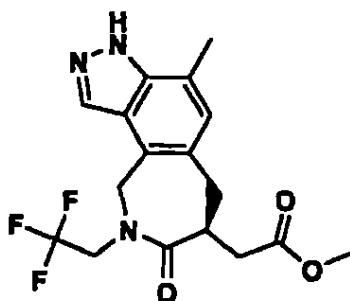
COC(=O)C[C@H](Cc1cc(Cl)cc2c1c[nH]n2)C(=O)OC

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427/426

Intermediario 159



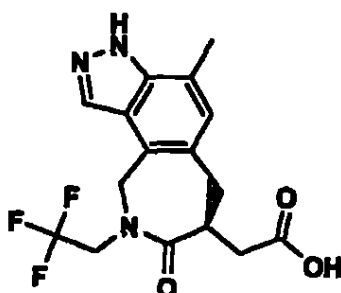
5

Éster de metilo del ácido [4-metil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El éster de dietilo del ácido 2-(S)-(4-clorometil-7-metil-1H-indazol-5-ilmetil)-succínico (190 mg, 0.56 mmol) y 2,2,2-trifluoroetilamina (45 µL, 0.56 mmol) se hacen reaccionar en una manera análoga a la preparación del éster de metilo del ácido [4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El compuesto del título se obtiene como un residuo ámbar en 76% de rendimiento. EM m/e (M+H)⁺ 370.1.

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Intermediario 160



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Ácido [4-metil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-

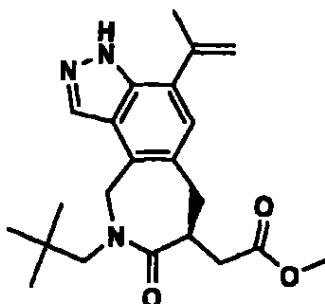
Yell 417

trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-

il]acético. El éster de metilo del ácido [4-metil-
3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-
triaza-(S)-ciclohepta[e]inden-7-il]acético (250 mg, 0.58
5 mmol) se hace reaccionar en una manera análoga a la
preparación del ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-
il]-acético. El compuesto del título se obtiene como un
sólido blanco en 97% de rendimiento. EM m/e (M-H)⁺ = 354.2.

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Intermediario 161



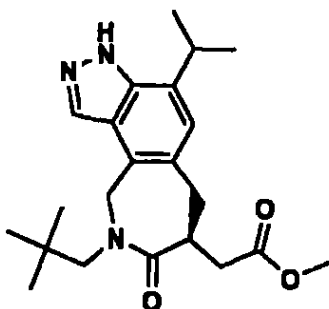
15

Éster de metilo del ácido [(S)-9-(2,2-dimetil-propil)-4-
isopropenil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
ciclohept[e]inden-7-il]-acético. El éster de metilo del ácido
[4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-
20 2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético (100 mg,
0.24 mmol) se disolvió en 2-propanol (1.0 mL). Se burbujeó
gas de nitrógeno a través de la mezcla durante 5 minutos. La
triethylamina (60 µL, 0.43 mmol) se agregó a la mezcla seguido
por cloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio(II)
25 (19 mg, 0.02 mmol) y 2-propeniltrifluoroborato de potasio (41

5/27 418

mg, 0.28 mmol). El recipiente de reacción se mojó con gas de nitrógeno y luego se selló. La reacción se sometió a calentamiento en microondas a 150°C durante 30 minutos. La cromatografía en gel de sílice (acetato de etilo-hexanos) proporciona el compuesto del título como un sólido ámbar en 73% de rendimiento. EM m/e (M+H)⁺= 384.4.

Intermediario 162



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Éster de metilo del ácido [(S)-9-(2,2-dimetil-propil)-4-isopropil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il]-acético. El éster de metilo del ácido [(S)-9-(2,2-dimetil-propil)-4-isopropenil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il]-acético (100 mg, 0.26 mmol) se disolvió en una mezcla de acetato de etilo (5.0 mL) y metanol (5.0 mL). Una cantidad catalítica de paladio en carbono al 10% se agregó a la mezcla. El recipiente de reacción se colocó en un aparato Parr y se cargó con 50 psi (3.51 kg/cm²) de gas de hidrógeno. La reacción se agitó a temperatura ambiente durante 1 hora. La mezcla se filtró y el filtrado se concentró hasta secarse. El compuesto del título se obtiene como un residuo café en 90%

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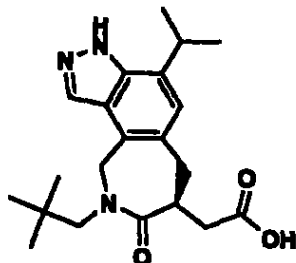
25

426 429

de rendimiento. EM m/e (M+H)⁺ = 386.3.

Intermediario 163

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Ácido [(S)-9-(2,2-dimetil-propil)-4-isopropil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-

10 il]acético. El éster de metilo del ácido [(S)-9-(2,2-dimetil-propil)-4-isopropil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-

triaza-ciclohept[e]inden-7-il]-acético (90 mg, 0.23 mmol) se hace reaccionar en una manera análoga a la preparación del

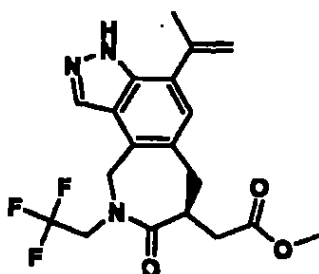
ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético.

15

El compuesto del título se obtiene como un sólido blanco en 92% de rendimiento. EM m/e (M-H)⁻ = 370.3.

Intermediario 164

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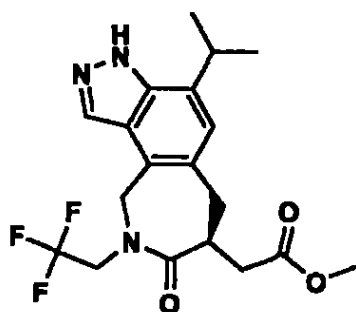
Éster de metilo del ácido [4-isopropenil-3,6,7,8,9,10-

25 hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-

42X 430

ciclohepta[e]inden-7-il]acético. El éster de metilo del ácido [4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (400 mg, 0.92 mmol) y 2-propeniltrifluoroborato de potasio (165 mg, 1.1 mmol) se hacen reaccionar en una manera análoga a la preparación del éster de metilo del ácido [(S)-9-(2,2-dimetil-propil)-4-isopropenil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il]-acético. El compuesto del título se obtiene como un aceite ámbar en 71% de rendimiento. EM m/e (M-H)⁺ = 394.1.

Intermediario 165



15

Éster de metilo del ácido [4-isopropil-5,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El éster de metilo del ácido [4-isopropenil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (150 mg, 0.38 mmol) se hace reaccionar en una manera análoga a la preparación del éster de metilo del ácido [(S)-9-(2,2-dimetil-propil)-4-isopropil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il]-acético. El

20

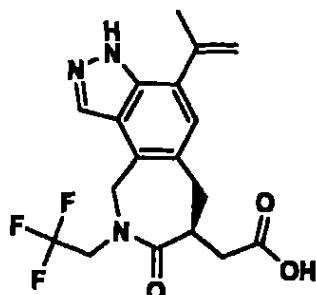
25

431

compuesto del título se obtiene como un sólido blanco en 73% de rendimiento. EM m/e (M+H)⁺=398.2.

Intermediario 166

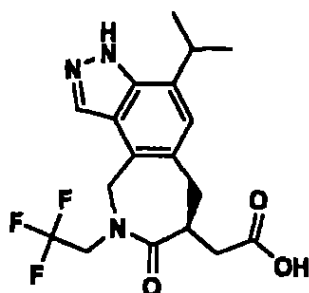
5



Ácido [4-isopropenil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El éster de metilo del ácido [4-isopropenil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (100 mg, 0.25 mmol) se hace reaccionar en una manera análoga a la preparación del ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El compuesto del título se obtiene como un sólido blanco opaco en 98% de rendimiento. EM m/e (M-H)⁻=380.2.

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Intermediario 167



25

Ácido

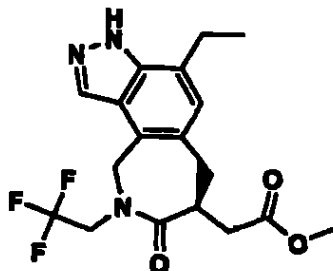
[4-isopropil-3,6,7,8,9,10-hexahidro-8-oxo-9-

422
432

(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El éster de metilo del ácido [4-isopropil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (105 mg, 0.26 mmol) se hace reaccionar en una manera análoga a la preparación del ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El compuesto del título se obtiene como un sólido blanco en 99% de rendimiento. EM m/e (M-H)⁻ = 382.2.

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Intermediario 168



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Éster de metilo del ácido [4-etil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El éster de metilo del ácido [4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-

20

trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (150 mg, 0.35 mmol) y tetraetilestano (200 µL, 1.0 mmol) se hacen reaccionar en una manera análoga a la preparación del éster de metilo del ácido [(S)-9-(2,2-dimetil-propil)-4-metil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-

25

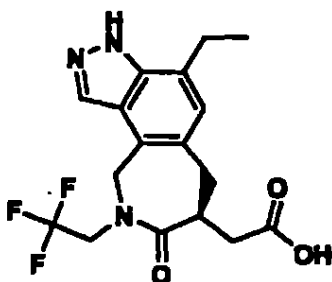
triaza-ciclohept[e]inden-7-il]-acético. El compuesto del

~~463~~ 463

título se obtiene como un aceite incoloro claro en 28% de rendimiento. EM m/e (M+H)⁺= 384.2.

Intermediario 169

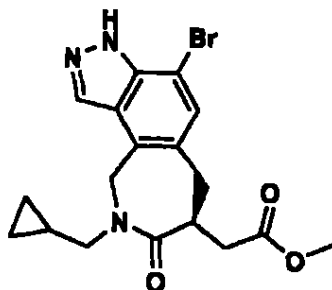
5



Ácido [4-etil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El éster de metilo del ácido [4-etil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (105 mg, 0.26 mmol) se hace reaccionar en una manera análoga a la preparación del ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El compuesto del título se obtiene como un sólido blanco en 73% de rendimiento. EM m/e (M-H)⁻= 368.3.

Intermediario 170

20



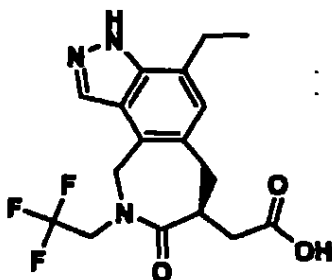
25 Éster de metilo del ácido ((S)-4-bromo-9-

434

título se obtiene como un aceite incoloro claro en 28% de rendimiento. EM m/e (M+H)⁺= 384.2.

Intermediario 169

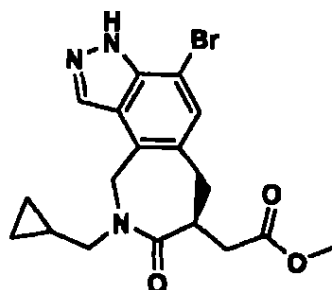
5



Ácido [4-etil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético. El éster de metilo del ácido [4-etil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (105 mg, 0.26 mmol) se hace reaccionar en una manera análoga a la preparación del ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El compuesto del título se obtiene como un sólido blanco en 73% de rendimiento. EM m/e (M-H)⁻= 368.3.

Intermediario 170

20



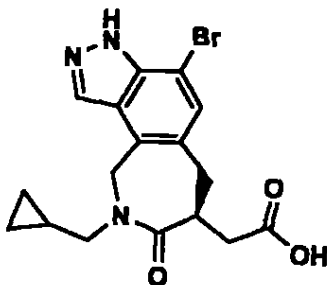
25 Éster de metilo del ácido ((S)-4-bromo-9-

437 435

ciclopropilmetil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
ciclohept[e]inden-7-il)-acético. El 2-((7-bromo-4-
(clorometil)-1H-indazol-5-il)metil)succinato de (S)-dimetilo
(630 mg, 1.6 mmol) se disolvió en acetonitrilo (5 mL). El
5 carbonato de potasio (560 mg, 4.1 mmol) se agregó a la mezcla
seguido por (aminometil)ciclopropano (700 µL, 8.1 mmol). La
mezcla se calentó hasta reflujo y se mantiene con agitación
durante 1.5 hora. La mezcla se enfrió hasta temperatura
ambiente. La mezcla se filtró. El filtrado se concentró por
10 evaporación rotatoria. El residuo se disolvió en una mezcla
de tolueno (10 mL) y ácido acético (1 mL). La mezcla se
calentó hasta reflujo y se mantiene con agitación durante 18
horas. La mezcla se concentró por evaporación rotatoria. La
cromatografía en gel de sílice (acetato de etilo-hexanos)
15 proporciona el compuesto del título como un sólido color
canela en 64% de rendimiento. EM m/e (M+H)⁺= 406.0, 408.0.

Intermediario 171

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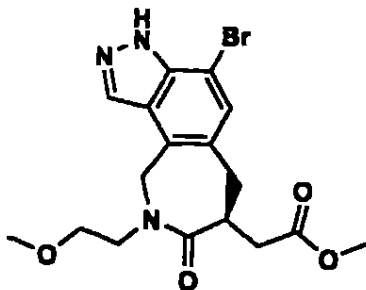
Ácido ((S)-4-bromo-9-ciclopropilmetil-8-oxo-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il)-
25 acético. El éster de metilo del ácido ((S)-4-bromo-9-

437 436

ciclopropilmetil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
ciclohept[e]inden-7-il)-acético (290 mg, 0.71 mmol) se hace
reaccionar en una manera análoga a la preparación del ácido
[4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-
5 2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El
compuesto del título se obtiene como un sólido amarillo en
96% de rendimiento. EM m/e (M-H)⁻ = 390.0, 392.0.

Intermediario 172

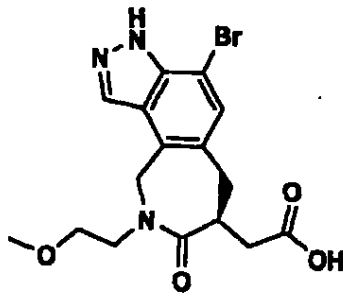
10



Éster de metilo del ácido [(S)-4-bromo-9-(2-
15 metoxi-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-
triaza-ciclohept[e]inden-7-il]-acético. El 2-((7-
bromo-4-(clorometil)-1H-indazol-5-
il)metil)succinato de (S)-dimetilo (400 mg, 0.99
mmol) y 2-metoxietilamina se hacen reaccionar en
20 una manera análoga a la preparación del éster de
metilo del ácido ((S)-4-bromo-9-ciclopropilmetil-
8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
ciclohept[e]inden-7-il)-acético. El compuesto del
título se obtiene como un sólido color canela en
25 66% de rendimiento. EM m/e (M-H)⁻ = 408.1, 410.0.

494 432

Intermediario 173



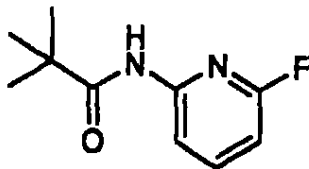
5

Ácido [(S)-4-bromo-9-(2-metoxi-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il]acético. El éster de metilo del ácido [(S)-4-bromo-9-(2-metoxi-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il]-acético (265 mg, 0.65 mmol) se hace reaccionar en una manera análoga a la preparación del ácido [4-bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético. El compuesto del título se obtiene como un sólido color canela en 89% de rendimiento. EM m/e (M-H)⁺ = 394.1, 396.0.

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Intermediario 174



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N-(6-Fluoropiridin-2-il)pivalamida. La 6-fluoropiridin-2-amina (13.1 g, 117mmol) se disolvió en piridina anhidra (100mL), y se enfrió hasta 0°C seguido por la adición gota a gota rápida de cloruro de trimetilacetilo (15.9mL, 129 mmol) durante 2 minutos. Cinco minutos después, la mezcla espesa

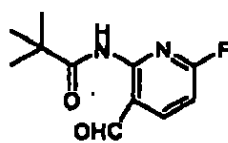
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~~521~~ 438

resultante se agitó durante la noche a temperatura ambiente. Una parte del solvente se removi6 al vacio rotatorio. El residuo se dividi6 entre cloruro de amonio saturado (200mL) y EtOAc (200mL). Después de la separaci6n, la capa orgánica se
5 lav6 con salmuera (50mL), se sec6 sobre MgSO₄, se concentr6 al vacio rotatorio, y se purific6 en cromatografía instantánea eluyendo con 25-75% EtOAc/Hexanos (1400mL) para proporcionar el producto esperado como un sólido blanco (21.4g, 93% de rendimiento); ¹H RMN (400 MHz, CDCl₃) δ ppm
10 1.29 (s, 9 H), 6.63 (dd, J=8.06, 2.01 Hz, 1 H), 7.76 (q, J=8.14 Hz, 1 H), 7.85 (s, 1 H), 8.09 (dd, J=8.06, 1.76 Hz, 1 H); Espectro de masa 197.15 (MH⁺), Calculado para C₁₀H₁₃FN₂O 196.1

Intermediario 175

15



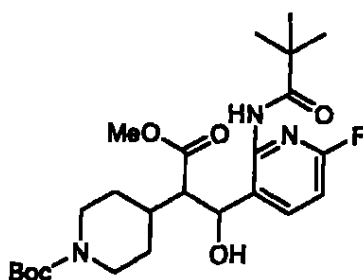
N-(6-fluoro-3-formilpiridin-2-il)pivalamida. La *N*-(6-fluoropiridin-2-il)pivalamida (1.67g, 8.5mmol) se disolvi6 en
20 THF (15mL) a temperatura ambiente, y la soluci6n incolora se enfri6 hasta -78°C, seguido por la adici6n gota a gota de *t*-BuLi (10.3mL, 1.7M en heptano, 17.4 mmol) bajo gas de nitr6geno durante 10 minutos. La soluci6n amarilla resultante se continu6 agitando a -78°C durante 3 horas, seguido por la
25 adici6n gota a gota de DMF (2.0 mL, 25.5 mmol) durante 5

439

minutos. La solución amarillo ligero se agitó durante 30 minutos adicionales a -78°C . De esta manera, la mezcla se apagó con NH_4Cl saturado (30 mL), se dividió entre $\text{H}_2\text{O}/\text{EtOAc}$ (100mL/100mL). Después de la separación, la fase orgánica se lavó con salmuera (30 mL), se secó sobre MgSO_4 , se concentró al vacío rotatorio, y se purificó en cromatografía instantánea eluyendo con 25-50% $\text{EtOAc}/\text{hexanos}$ (1400 mL) para proporcionar un producto esperado, como sólidos blancos (343mg, 18% de rendimiento), más el material de partida recuperado (622mg); ^1H RMN (400 MHz, CDCl_3) δ ppm 1.23 - 1.30 (s, 9 H), 8.12 (s, 1 H), 8.18 - 8.27 (m, 2 H), 10.13 (s, 1 H); Espectro de masa 225.13 (MH^+), Calculado para $\text{C}_{11}\text{H}_{13}\text{FN}_2\text{O}_2$ 224.1

Intermediario 176

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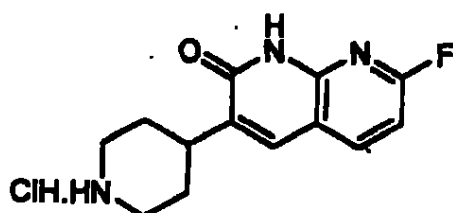
20 4-(1-(6-fluoro-2-pivalamidopyridin-3-yl)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. A la diisopropilamina (0.47mL, 3.35 mmol) en THF anhidro (10mL) se agregó gota a gota $n\text{-BuLi}$ (2.5 M en heptano, 1.4 mL, 3.48 mmol) a -78°C bajo N_2 durante 10 minutos. Quince minutos más tarde, el 4-(2-metoxi-2-oxoetil)piperidin-1-carboxilato de tert-butilo (861 mg, 3.35 mmol) en

25

49X 440

THF(10mL) se agregó gota a gota a -78°C durante 10 minutos. La mezcla resultante se agitó durante 45 minutos. A este mismo tiempo, la N-(6-fluoro-3-formilpiridin-2-il)pivalamida (500mg, 2.23 mmol), se disolvió en THF anhidro (10mL) en otro matraz de fondo redondo secado al horno, y se agregó gota a gota a NaH (60% en aceite mineral, 93.7mg, 2.34 mmol) en THF (10 mL) a 0°C . La suspensión amarilla resultante se agitó a 0°C bajo N_2 durante 1 hr, que luego se transfirió a la solución de anión anterior a -78°C a través de una jeringa durante 10 min. La suspensión resultante se continuó agitando a -78°C durante 1hr. Se apagó con NH_4Cl saturado (50 mL), se extrajo con EtOAc (2x100mL). Las capas orgánicas combinadas se lavaron con salmuera (30 mL), se secaron en MgSO_4 , se concentró al vacío rotatorio y se purificó en columna cromatografía instantánea eluyendo con 20-75% EtOAc/hexanos (600mL), 75-100% EtOAc/hexanos (600mL) para proporcionar la mezcla de estereoisómero inseparable esperada, como un producto blanco (536 mg, 50% de rendimiento), mas el material de partida recuperado, N-(6-fluoro-3-formilpiridin-2-il)pivalamida (140mg); Espectro de masa 482.23 (MH^+), Calculado para $\text{C}_{24}\text{H}_{36}\text{FN}_3\text{O}_6$ 481.26.

Intermediario 177



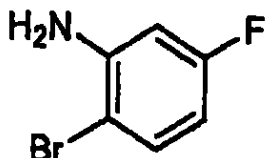
Clorohidrato de 7-fluoro-3-(piperidin-4-il)-1,8-

1578 441

naftiridin-2(1H)-ona. La mezcla de 4-(1-(6-fluoro-2-pivalamidopiridin-3-il)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo (238 mg, 0.494mmol), y HCl concentrado (1mL) en MeOH (1mL) y H₂O (1mL) se puso a reflujo bajo N₂ durante la noche. Los solventes se removieron al vacío rotatorio, el residuo, como un sólido amarillo, se trituroó con EtOH frío (2x3mL), se filtró y se secó bajo vacío para proporcionar un producto esperado, el sólido amarillo (139 mg, 99% de rendimiento); ¹H RMN (400 MHz, MeOD) δ ppm 1.27 (s, 1 H), 1.83 - 1.95 (m, 2 H), 2.13 (d, J=14.10 Hz, 2 H), 3.06 - 3.18 (m, 3 H), 3.49 (d, J=12.84 Hz, 2 H), 6.47 (d, J=8.81 Hz, 1 H), 7.69 (s, 1 H), 7.85 (d, J=9.06 Hz, 1 H); Espectro de masa 248.13 (MH⁺), Calculado para C₁₃H₁₄FN₃O 247.11.

15

Intermediario 178

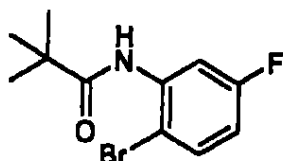


2-bromo-5-fluorobencenamina. A una solución de 1-bromo-4-fluoro-2-nitrobenceno (5.0g, 22.7 mmol) en HOAc/EtOH (20mL/20mL) se agregó polvo de fierro en una porción a temperatura ambiente. La mezcla se burbujeó con N₂ durante 5 minutos, y luego se puso a reflujo durante 2 hrs. Una parte de los solventes se removieron al vacío rotatorio, luego el residuo se dividió entre NaOH acuoso (10N, 200mL) y Et₂O

C654 442

(200mL). Después de la separación, la fase orgánica se lavó con H₂O (50 mL), salmuera (50 mL), se secó en MgSO₄, y se concentró al vacío rotatorio para proporcionar el producto esperado, como un aceite color canela ligero (rendimiento 5 cuantitativo), que fue lo suficientemente puro para usarse en la siguiente etapa sin purificación adicional; ¹H RMN (400 MHz, CDCl₃) δ ppm 4.15 (s, 1 H), 6.34 (td, J=8.44, 2.77 Hz; 1 H), 6.46 (dd, J=10.20, 2.90 Hz, 1 H), 7.31 (dd, J=8.81, 5.79 Hz, 1 H); Espectro de masa 189.94 (MH⁺), Calculado para 10 C₆H₅BrFN 188.96

Intermediario 179

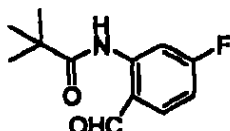


15 N-(2-bromo-5-fluorofenil)pivalamida. El cloruro de trimetilacetilo (4.2mL, 34.1mL) se agregó rápido gota a gota a una solución de 2-bromo-5-fluorobencenamina (4.31g, 22.7mmol) en CH₂Cl₂ (50 mL) a temperatura ambiente, seguido por la adición de DIEA (7.9 mL, 45.4mmol). La mezcla 20 resultante se agitó a temperatura ambiente durante 2 hrs, y luego se dividió entre HCl (1N, 200mL) y EtOAc (250mL). Después de la separación, la fase orgánica se lavó con salmuera (50mL), se secó en MgSO₄, se concentró al vacío rotatorio, y se purificó en cromatografía instantánea 25 eluyendo con 20-40% EtOAc/hexanos (1200mL) para proporcionar

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el producto esperado, como un aceite incoloro (6.07g, 98% de rendimiento); ^1H RMN (400 MHz, CDCl_3) δ ppm 1.33 (s, 9 H), 6.69 (ddd, $J=8.81$, 7.55, 3.02 Hz, 1 H), 7.45 (dd, $J=8.81$, 5.79 Hz, 1 H), 8.04 (s, 1 H), 8.28 (dd, $J=11.08$, 3.02 Hz, 1 H); Espectro de masa 274.04 (MH^+), Calculado para $\text{C}_{11}\text{H}_{13}\text{BrFNO}$ 273.02.

Intermediario 180



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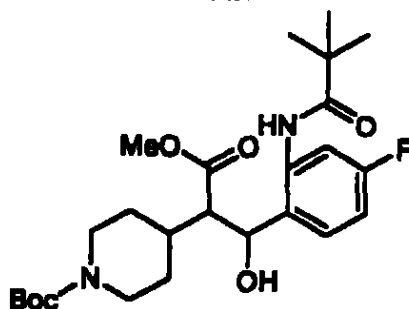
N-(5-fluoro-2-formilfenil)pivalamida. La *N*-(2-bromo-5-fluorofenil)pivalamida (2.4g, 8.75mmol) se disolvió en THF (30mL) a temperatura ambiente, y la solución incolora se enfrió hasta -78°C , seguido por la adición gota a gota rápida de *t*-BuLi (10.3mL, 1.7M en heptano, 17.4 mmol) bajo N_2 durante 10 minutos. La solución amarilla resultante se continuó agitando a -78°C durante 1 hr seguido por la adición gota a gota de DMF (2.7 mL, 35.0 mmol) durante 5 min. La solución amarillo ligero se agitó durante 30 minutos adicionales a -78°C . De esta manera la mezcla se apagó con NH_4Cl saturado (30 mL), se extrajo con Et_2O (2x150mL). La fase orgánica combinada se lavó con salmuera (30 mL), se secó sobre MgSO_4 , se concentró al vacío rotatorio, y se purificó en cromatografía instantánea eluyendo con 25-50% EtOAc/hexanos (1400 mL) para proporcionar un producto

25

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esperado, como sólidos blancos (1.03g, 53% de rendimiento);
 ^1H RMN (400 MHz, CDCl_3) δ ppm 1.30 (s, 9H), 6.80-6.86 (m, 1 H),
7.63 (dd, $J=8.56$, 6.04 Hz, 1 H), 8.53 (dd, $J=12.21$, 2.39 Hz,
1 H), 9.83 (s, 1 H), 11.54 (s, 1 H); Espectro de masa 224.16
5 (MH^+), Calculado para $\text{C}_{12}\text{H}_{14}\text{FNO}_2$ 223.1.

Intermediario 181

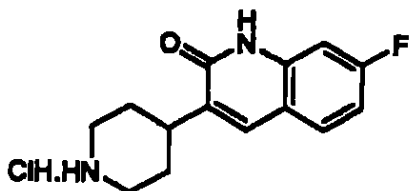


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4-(1-(4-fluoro-2-pivalamidofenil)-1-hidroxi-3-metoxi-3-
oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. El
procedimiento fue el mismo como la síntesis de 4-(1-(6-
15 fluoro-2-pivalamidopiridin-3-il)-1-hidroxi-3-metoxi-3-
oxopropan-2-il)piperidin-1-carboxilato de t-butilo. La
reacción dio una mezcla de estereoisómero inseparable, 4-(1-
(4-fluoro-2-pivalamidofenil)-1-hidroxi-3-metoxi-3-oxopropan-
2-il)piperidin-1-carboxilato de tert-butilo. El compuesto
20 crudo se usó directamente en la siguiente etapa sin
purificación adicional. Espectro de masa 481.25(MH^+),
Calculado para $\text{C}_{25}\text{H}_{37}\text{FN}_2\text{O}_6$ 480.26.

447 445

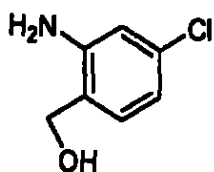
Intermediario 182



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Clorohidrato de 7-fluoro-3-(piperidin-4-il)quinolin-
2(1H)-ona. El procedimiento fue el mismo como la síntesis de
7-fluoro-3-(piperidin-4-il)-1,8-naftiridin-2(1H)-ona, y dio
el producto esperado, clorohidrato de 7-fluoro-3-(piperidin-
10 4-il)quinolin-2(1H)-ona, como un sólido blanco al 41% de
rendimiento después de dos etapas; ^1H RMN (400 MHz, MeOD)
 δ ppm 1.84 - 1.96 (m, 2 H), 2.15 (d, $J=14.10$ Hz, 2 H), 3.07 -
3.16 (m, 3 H), 3.50 (d, $J=12.84$ Hz, 2 H), 6.98 - 7.05 (m, 2
H), 7.69 (dd, $J=8.56, 5.79$ Hz, 1 H), 7.78 (s, 1 H); Espectro
15 de masa 247. (MH^+), Calculado para $\text{C}_{14}\text{H}_{15}\text{FN}_2\text{O}$ 246.12.

Intermediario 183

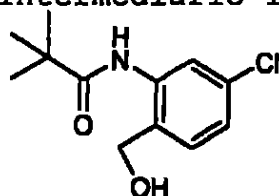


20 (2-Amino-4-clorofenil)metanol. El 2-amino-4-
clorobenzoato de metilo (1.5g, 8.08 mmol) en THF (15mL) se
agregó gota a gota a la suspensión de LAH (429mg, 11.3 mmol)
en THF (10mL) bajo N_2 a 0°C durante 10 min. La mezcla
resultante se agitó a temperatura ambiente durante 2 hrs,
25 luego la reacción se apagó a 0°C con Na_2SO_4 saturado (50 mL),

447.446

se extrajo con Et₂O (2x70 mL). Las soluciones orgánicas combinadas se lavaron con salmuera (30 mL), se secaron en MgSO₄, y se concentraron al vacío rotatorio para proporcionar el producto esperado como un sólido blanco (874 mg, 69% de rendimiento); ¹H RMN (400 MHz, MeOD) δppm 4.50 (s, 2 H), 6.58 (dd, J=8.06, 2.01 Hz, 1 H), 6.70 (d, J=2.01 Hz, 1 H), 7.01 (d, J=8.06 Hz, 1 H); Espectro de masa 157.06 (MH⁺), Calculado para C₇H₈ClNO 157.03.

Intermediario 184



10

N-(5-Cloro-2-(hidroximetil)fenil)pivalamida. El cloruro de trimetilacetilo (0.72 mL, 5.82 mmol) se agregó rápido gota a gota a (2-amino-4-clorofenil)metanol (874 mg, 5.55mmol) en CH₂Cl₂ (20mL) y THF(6mL) a 0°C, y se siguió por la adición de DIEA (2.41 mL, 13.9 mmol). La mezcla resultante se agitó durante 30 min. Luego la mezcla se dividió entre NaHCO₃ saturado (50mL) y CH₂Cl₂ (100mL). Después de la separación, la fase orgánica se lavó con salmuera (30mL), se secó en MgSO₄, y se concentró al vacío rotatorio para proporcionar el producto crudo esperado (1.34, 100% de rendimiento), el cual fue lo suficientemente puro para usarse en la siguiente etapa. Espectro de masa 242.08 (MH⁺) Calculado para C₁₂H₁₅ClNO₂ 241.09.

25

CC(C)(C)C(=O)Nc1ccc(Cl)cc1C=O

E1

se pasó a través de una almohadilla de gel de sílice delgada con CH_2Cl_2 (100mL), se concentró al vacío rotatorio y se purificó en cromatografía instantánea eluyendo con 20-40% EtOAc/hexanos (800mL) para proporcionar el producto esperado como un sólido blanco (937mg, 70% de rendimiento). ^1H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.28 - 1.34 (s, 9 H), 7.15 (dd, $J=8.31, 2.01$ Hz, 1 H), 7.53 - 7.59 (m, 1 H), 8.87 (d, $J=2.01$ Hz, 1 H), 9.84 - 9.88 (m, 1 H), 11.42 (s, 1 H); Espectro de masa 240.07 (MH^+), Calculado para $\text{C}_{12}\text{H}_{14}\text{ClNO}_2$ 239.07.

CC(C)(C)C(=O)Nc1ccc(Cl)cc1C(O)C(C(=O)OC)C2CCN(C2)C(=O)OC(C)(C)C

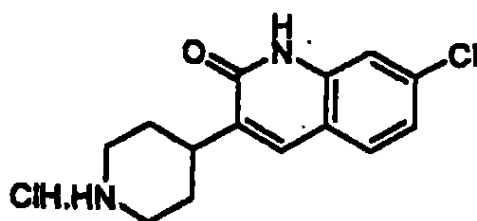
25

448

oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. El
procedimiento de reacción fue el mismo como la síntesis del
4-(1-(6-fluoro-2-pivalamidopiridin-3-il)-1-hidroxi-3-metoxi-
3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. La
5 reacción proporcionó la mezcla de estereoisómero de 4-(1-(4-
cloro-2-pivalamidofenil)-1-hidroxi-3-metoxi-3-oxopropan-2-
il)piperidin-1-carboxilato de tert-butilo como un sólido
blanco (73% de rendimiento total) después de la purificación
en cromatografía instantánea, que se usó directamente en la
10 siguiente etapa. Espectro de masa 497.19 (MH⁺), Calculado
para C₂₅H₃₇ClN₂O₆ 496.23.

Intermediario 187

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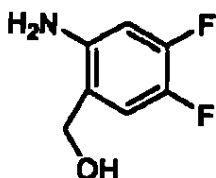


Clorohidrato de 7-cloro-3-(piperidin-4-
il)quinolin-2(1H)-ona. El procedimiento fue el mismo
20 como la síntesis de la 7-fluoro-3-(piperidin-4-il)-
1,8-naftiridin-2(1H)-ona. Después de la reacción, una
parte del solvente se removi6 al vacío rotatorio, el
producto esperado se sacó de la solución, se filtró y
se lavó con EtOH para dar un sólido blanco (71% de
25 rendimiento). ¹H RMN (400 MHz, MeOD) δppm 1.83 - 1.94

449

(m, 2 H), 2.14 (d, J=12.84 Hz, 2 H), 3.07 - 3.19 (m, 3 H), 3.48 (s, 1 H), 3.51 (d, J=3.02 Hz, 1 H), 7.18 - 7.23 (m, J=6.30, 4.34, 2.20, 2.01 Hz, 1 H), 7.30 - 7.35 (m, 1 H), 7.59 - 7.65 (m, 1 H), 7.74 - 7.78 (m, 1 H); Espectro de masa 263.07 (MH⁺), Calculado para C₁₄H₁₅ClN₂O 262.09.

Intermediario 188



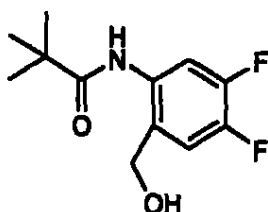
10

(2-Amino-4,5-difluorofenil)metanol. El ácido 2-amino-4,5-difluorobenzoico (5.37g, 31.0 mmol) en THF(50mL) se agregó gota a gota a la suspensión en LAH (1.65g, 43.5 mmol) en THF (15 mL) a temperatura ambiente bajo N₂ durante 10 minutos. La suspensión resultante se agitó a temperatura ambiente durante 1 hr. Luego la mezcla se enfrió hasta 0°C, se apagó con Na₂SO₄ saturado (100mL), y se extrajo con Et₂O (2x100mL), las capas orgánicas combinadas se lavaron con salmuera (60 mL), se secaron sobre MgSO₄, y se concentraron al vacío rotatorio para proporcionar el producto crudo esperado como un sólido café, que fue lo suficientemente puro para usarse en la siguiente etapa sin purificación adicional. ¹H RMN (400 MHz, CDCl₃) δppm 4.07 (s, 1 H), 4.56 (s, 2 H), 6.46 (dd, J=11.71, 6.92 Hz, 1 H), 6.87 (dd, J=10.58, 8.56 Hz, 1 H); Espectro de masa 160.04 (MH⁺), Calculado para C₇H₇F₂NO 159.05.

25

450

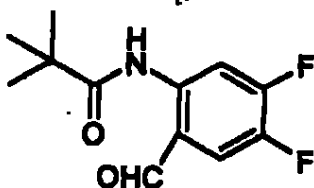
Intermediario 189



5 *N*-(4,5-difluoro-2-(hidroximetil)fenil)pivalamida. El
cloruro de trimetilacetilo (4.01mL, 32.55mmol) se agregó a la
solución del (2-amino-4,5-difluorofenil)metanol crudo en
CH₂Cl₂/THF (50mL/10mL) a 0°C, seguido por la adición de DIEA
(10.8mL, 62 mmol). La mezcla resultante se agitó durante 30
10 min, y luego se dividió entre NaHCO₃ saturado (100mL) y CH₂Cl₂
(150mL). Después de la separación, la fase orgánica se lavó
con salmuera (40 mL), se secó sobre MgSO₄, y se concentró al
vacío rotatorio para proporcionar el producto esperado, que
fue lo suficientemente puro para usarse en la siguiente etapa
15 sin purificación adicional; ¹H RMN (400 MHz, CDCl₃) δppm 1.28
(s, 9 H), 4.62 (s, 2 H), 6.94 (dd, J=10.20, 8.44 Hz, 1 H),
8.08 (dd, J=12.72, 7.68 Hz, 1 H), 9.04 (s, 1 H); Espectro de
masa 244.11 (MH⁺), Calculado para C₁₂H₁₅F₂NO₂ 243.11.

Intermediario 190

20



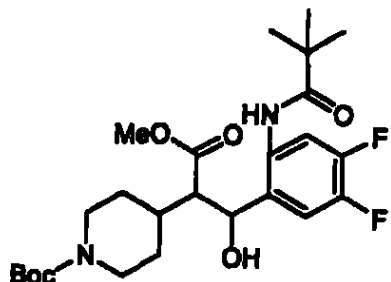
N-(4,5-Difluoro-2-formilfenil)pivalamida. El
25 piridiníoclorocromato (9.36g, 43.4 mmol) se agregó a la

449 451

solución de la N-(4,5-difluoro-2-(hidroximetil)fenil)pivalamida cruda en CH₂Cl₂ (150mL) a temperatura ambiente. La solución amarilla se volvió café oscura en 10 min, y la mezcla se continuó agitando durante 3hr, y luego se pasó a través de una almohadilla de gel de sílice delgada con CH₂Cl₂ (2x50mL). La solución orgánica combinada se concentró al vacío rotatorio, y se purificó en cromatografía instantánea eluyendo con 20~60% EtOAc/hexanos (1300 mL) para proporcionar el producto esperado como un sólido café (1.91g, 26% de rendimiento después de tres etapas); ¹H RMN (400 MHz, CDCl₃) δppm 1.29 (s, 9 H), 7.42 - 7.48 (m, 1 H), 8.75 (dd, J=13.35, 7.30 Hz, 1 H), 9.77 - 9.80 (m, 1 H), 11.40 (s, 1 H); Espectro de masa 242.08 (MH⁺), Calculado para C₁₂H₁₃F₂NO₂ 241.09

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Intermediario 200



20

4-(1-(4,5-Difluoro-2-pivalamidofenil)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. El procedimiento de reacción fue el mismo como la síntesis del 4-(1-(6-fluoro-2-pivalamidopiridin-3-il)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de

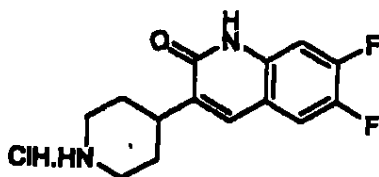
25

1452

tert-butilo. La reacción proporcionó una mezcla estereoisomérica de 4-(1-(4,5-difluoro-2-pivalamidofenil)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo inseparable, como un sólido blanco (70% de rendimiento total) después de la purificación en cromatografía instantánea, que se usó en la siguiente etapa. Espectro de masa 499.19 (MH^+), Calculado para $C_{25}H_{36}F_2N_2O_6$ 498.25

Intermediario 201

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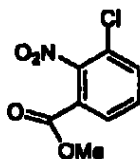


Clorohidrato de 6,7-difluoro-3-(piperidin-4-il)quinolin-2(1H)-ona. El procedimiento fue el mismo como la síntesis de la 7-fluoro-3-(piperidin-4-il)-1,8-naftiridin-2(1H)-ona. Después de la reacción, una parte del solvente se removió al vacío rotatorio, el producto esperado se sacó de la solución, se filtró y se lavó con etanol para dar un sólido blanco (77% de rendimiento); ^1H RMN (400 MHz, MeOD) δ ppm 1.81 - 1.93 (m, 2 H), 2.13 (d, $J=2.01$ Hz, 2 H), 3.07 - 3.19 (m, 4 H), 3.50 (d, $J=14.35$ Hz, 2 H), 7.16 - 7.23 (m, 1 H), 7.55 - 7.62 (m, 1 H), 7.71 - 7.77 (m, 1 H); Espectro de masa 265.07 (MH^+), Calculado para $C_{14}H_{14}F_2N_2O$ 264.11

25

457 453

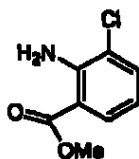
Intermediario 202



5 3-Cloro-2-nitrobenzoato de metilo. Al ácido 3-cloro-2-nitrobenzoico (3.15g, 15.6 mmol) en metanol/acetonitrilo (20mL/20mL) se le agregó gota a gota TMSCHN₂ (2N en hexanos, 11.7 mL, y 23.4 mmol) a 0°C bajo N₂ durante 10 min hasta que el color amarillo persiste. La mezcla se continuó agitando
10 durante 20 min, seguido por la adición gota a gota de HOAc hasta que el color amarillo desapareció para eliminar el TMSCHN₂ excesivo. Una parte del solvente se removió al vacío rotatorio, el producto se saca de la solución como un sólido amarillo ligero, que se filtró y se lavó con Et₂O (2x2mL)
15 para proporcionar el producto esperado como un sólido blanco (2.5g, 74% de rendimiento); ¹H RMN (400 MHz, CDCl₃) δppm 3.91 (s, 3 H), 7.51 (t, J=8.06 Hz, 1 H), 7.70 (dd, J=8.06, 1.26 Hz, 1 H), 7.97 (dd, J=7.81, 1.26 Hz, 1 H); Espectro de masa 216.02 (MH⁺), Calculado para C₉H₆ClNO₄ 215.00.

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Intermediario 203

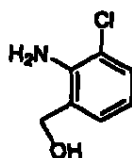


25 2-Amino-3-clorobenzoato de metilo. El polvo de fierro (1.94g, 34.8 mmol) se agregó a la solución de 3-cloro-2-

454

nitrobenzoato de metilo (2.5g, 11.6mmol) en EtOH/HOAc (100mL/100mL) a temperatura ambiente, y luego la suspensión se puso a reflujo bajo N₂ durante 2 hrs. Después de enfriar hasta temperatura ambiente, una parte de los solventes se
5 removió al vacío rotatorio, el residuo resultante se dividió entre H₂O/EtOAc (200mL/300mL). La fase orgánica separada se lavó con NaOH acuoso (1N, 50mL), salmuera (50 mL), se secó sobre MgSO₄, y se concentró al vacío rotatorio para proporcionar el producto esperado como un aceite color canela
10 (1.7g, 79% de rendimiento) que se volvió tipo cera durante el reposo en blanqueador. El producto crudo fue lo suficientemente puro para usarse en la siguiente etapa sin purificación adicional; ¹H RMN (400 MHz, CDCl₃) δppm 3.86 (s, 3 H), 6.25 (s, 2 H), 6.57 (t, J=7.93 Hz, 1 H), 7.39 (dd, J=7.81, 1.51 Hz, 1 H), 7.79 (dd, J=8.06, 1.51 Hz, 1 H);
15 Espectro de masa 185.95. (MH⁺), Calculado para C₈H₈ClNO₂ 185.02.

Intermediario 204



20

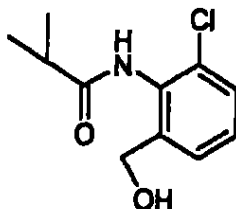
(2-Amino-3-clorofenil)metanol. Una solución de 2-amino-3-clorobenzoato de metilo (1.7g, 9.16 mmol) en THF (40 mL) se agregó gota a gota a una suspensión de LAH (521mg, 13.7 mmol)
25 en THF(15mL) a temperatura ambiente durante 10 minutos bajo

457 455 -

N₂, y se agitó durante 2 hrs. La reacción cuidadosamente se
apagó con Na₂SO₄ saturado (10 mL) a 0°C, se extrajo con Et₂O
(2x50mL). Las capas orgánicas combinadas se lavaron con
salmuera (30mL), se secaron en MgSO₄, y se concentraron al
5 vacío rotatorio para proporcionar el producto esperado como
un sólido amarillo (1.08g, 75%), que fue lo suficientemente
puro para usarse en la siguiente etapa sin purificación
adicional; ¹H RMN (400 MHz, CDCl₃) δppm 1.65 (s, 1 H), 4.59 -
4.70 (m, 4 H), 6.60 - 6.65 (m, 1 H), 6.96 (dd, J=7.55, 1.26
10 Hz, 1 H), 7.19 - 7.25 (m, 1 H); Espectro de masa 158.02
(MH⁺), Calculado para C₇H₈ClNO₂ 157.03.

Intermediario 205

15



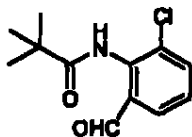
N-(2-Cloro-6-(hidroximetil)fenil)pivalamida. Al (2-
amino-3-clorofenil)metanol crudo (1.08g, 6.88mmol) en CH₂Cl₂
(15mL) se le agregó rápido gota a gota cloruro de
20 trimetilacetilo (.89mL, 7.23 mmol), seguido por DIEA (2.4mL,
13.8 mmol) a 0°C. Cinco minutos más tarde, la mezcla de
reacción se agitó a temperatura ambiente durante 1 hr. El
trabajo acuoso normal proporciona el producto esperado como
un sólido blanco (1.58g, 95% de rendimiento), el cual fue lo
25 suficientemente puro para usarse en la siguiente etapa; ¹H

452/456

RMN (400 MHz, CDCl₃) δ ppm 1.30 (s, 9 H), 3.35 (s, 2 H), 4.36 (d, J=6.29 Hz, 1 H), 7.06 - 7.22 (m, J=-7.81, 7.81 Hz, 1 H), 7.29 - 7.33 (m, 2 H), 7.58 (s, 1 H); Espectro de masa 242.08 (MH⁺), Calculado para C₁₂H₁₆ClNO₂ 241.09.

5

Intermediario 206



N-(5-Cloro-2-formilfenil)pivalamida.

El

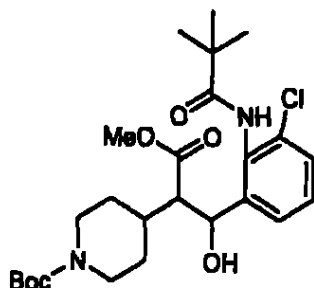
10 clorocromato de piridinio (1.19g, 5.5mmol) se agregó a una solución de N-(2-cloro-6-(hidroximetil)fenil)pivalamida (884mg, 3.67mmol) en CH₂Cl₂ (100mL) a 0°C. Cinco minutos más tarde, la mezcla se permitió agitarse a temperatura ambiente
15 durante 3 hrs. La mezcla de reacción se pasó a través de una capa de almohadilla delgada de gel de sílice con CH₂Cl₂ (2x100mL), se concentró en vacío rotatorio, y se purificó en una columna de cromatografía instantánea eluyendo con 20-50% EtOAc/hexanos
20 (1000mL) para proporcionar el producto esperado como un sólido blanco (414 mg, 47% de rendimiento); ¹H RMN (400 MHz, CDCl₃) δppm 1.37 (s, 9 H), 7.30 (t, J=7.81 Hz, 1 H), 7.64 (dd, J=7.93, 1.39 Hz, 1 H), 7.77 (dd, J=7.55, 1.51 Hz, 1 H), 8.25 (s, 1 H), 9.84 (s, 1 H);
25 Espectro de masa 240.08 (MH⁺), Calculado para

451 452

$C_{12}H_{14}ClNO_2$ 239.07.

Intermediario 207

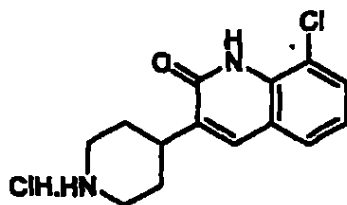
5



4-(1-(3-Cloro-2-pivalamidofenil)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. El
 10 procedimiento de reacción fue el mismo como la síntesis del
 4-(1-(6-fluoro-2-pivalamidopiridin-3-il)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. La
 reacción proporcionó una mezcla de estereoisómero inseparable
 de 4-(1-(3-cloro-2-pivalamidofenil)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo, como
 15 un sólido blanco (56% de rendimiento) después de la
 purificación en cromatografía instantánea. Espectro de masa
 497.22 (MH^+), Calculado para $C_{25}H_{37}ClN_2O_6$ 496.23.

Intermediario 208

20



Clorohidrato de 8-cloro-3-(piperidin-4-il)quinolin-
 25 2(1H)-ona. El procedimiento fue el mismo como la síntesis de

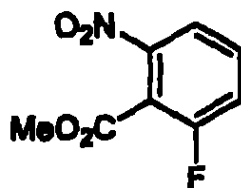
470 458

la 7-fluoro-3-(piperidin-4-il)-1,8-naftiridin-2(1H)-ona.

Después de la reacción, una parte del solvente se removió al vacío rotatorio, el producto esperado salió como un sólido de la solución, se filtró y se lavó con etanol para dar el

5 producto esperado, clorohidrato de 8-cloro-3-(piperidin-4-il)quinolin-2(1H)-ona, un sólido blanco (71% de rendimiento); ^1H RMN (400 MHz, MeOD) δ ppm 1.85 -1.96 (m, 2 H), 2.17 (d, $J=13.85$ Hz, 2 H), 3.10 - 3.20 (m, 4 H), 3.46 - 3.54 (m, 2 H), 7.23 (t, $J=7.81$ Hz, 1 H), 7.59 - 7.64 (m, 2 H), 7.81 (s, 1
10 H); Espectro de masa 263.08 (MH^+), Calculado para $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}$ 262.09.

Intermediario 209



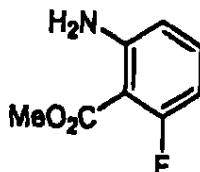
15

2-fluoro-6-nitrobenzoato de metilo. Al ácido 2-fluoro-6-nitrobenzoico (712mg, 3.85 mmol) en metanol/acetonitrilo (10 mL/10mL) se le agregó gota a gota TMSCHN_2 a 0°C bajo N_2 hasta
20 que el color amarillo persiste, y se agitó 30 minutos adicionales. Luego la reacción se apagó con HOAc a 0°C hasta que el color amarillo desapareció. Una parte del solvente se removió o vacío rotatorio, el residuo se disolvió en una cantidad pequeña de EtOAc, se purificó en cromatografía
25 instantánea eluyendo con 30~50% EtOAc/hexanos (600mL) para

~~447~~ 459

proporcionar el producto esperado, 2-fluoro-6-nitrobenzoato de metilo, (716mg, 94% de rendimiento) el cual se usó en la etapa 2; ^1H RMN (400 MHz, CDCl_3) δ ppm 3.96 (s, 3 H), 7.40 - 7.48 (m, 1 H), 7.58 (td, $J=8.31$, 5.54 Hz, 1 H), 7.94 (d, $J=8.31$ Hz, 1 H); Espectro de masa 200.05 (MH^+), Calculado para $\text{C}_8\text{H}_6\text{FNO}_4$ 199.03.

Intermediario 210



10

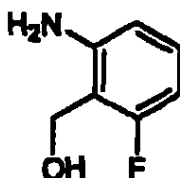
2-amino-6-fluorobenzoato de metilo. El 2-fluoro-6-nitrobenzoato de metilo (715 mg, 3.59 mmol) se disolvió en EtOH/HOAc/(10mL/10mL), seguido por la adición de polvo de fierro (602mg, 10.8mmol) a temperatura ambiente. La mezcla resultante se puso a reflujo bajo N_2 durante 2 hrs. Después de enfriar hasta temperatura ambiente, la suspensión café se dividió entre H_2O (30mL) y Et_2O (100mL). Después de la separación, la solución acuosa se extrajo con Et_2O (50mL). Las capas orgánicas combinadas se lavaron con NaOH 1N (3x50mL), salmuera (50mL), se secó en MgSO_4 , y se concentró al vacío rotatorio para proporcionar el producto esperado, 2-amino-6-fluorobenzoato de metilo, un aceite incoloro que se vuelve un sólido tipo cera durante el reposo. El compuesto crudo fue lo suficientemente puro para usarse en la siguiente

25

2478 460

etapa sin purificación adicional; ^1H RMN (400 MHz, CDCl_3) δ ppm 3.89 (s, 3 H), 5.67 (s, 2 H), 6.34 (ddd, $J=11.58$, 8.06, 1.01 Hz, 1 H), 6.41 (d, $J=8.31$ Hz, 1 H), 7.13 (td, $J=8.18$, 5.79 Hz, 1 H); Espectro de masa 170.06 (MH^+), Calculado para $\text{C}_8\text{H}_8\text{FNO}_2$ 169.05.

Intermediario 211



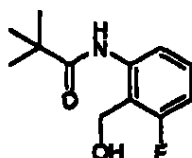
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(2-Amino-6-fluorofenil)metanol. El 2-amino-6-fluorobenzoato de metilo, el compuesto crudo obtenido en la última etapa, disuelto en THF (15mL) se agregó gota a gota a la suspensión de LAH (204mg, 5.39mmol) a temperatura ambiente durante 5 minutos. La mezcla se agitó durante 1 hr, luego se enfrió hasta 0°C , se apagó con Na_2SO_4 y se extrajo con Et_2O (2x50mL). Las capas orgánicas combinadas se lavaron con salmuera (30mL), se secaron en MgSO_4 , se concentraron al vacío rotatorio para dar un producto crudo esperado, (2-amino-6-fluorofenil)metanol, como un sólido café (268.1mg), que fue lo suficientemente puro para usarse en la siguiente etapa sin purificación adicional; ^1H RMN (400 MHz, CDCl_3) δ ppm 1.64 (s, 1 H), 4.30 (s, 2 H), 4.75 (s, 2 H), 6.39 - 6.47 (m, 2 H), 7.02 (td, $J=8.18$, 6.30 Hz, 1 H); Espectro de masa 142.08 (MH^+), Calculado para $\text{C}_7\text{H}_8\text{FNO}$ 141.06.

25

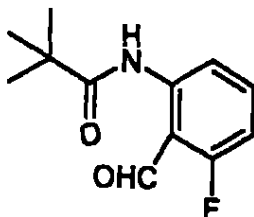
447.46

Intermediario 212



5 *N*-(3-fluoro-2-(hidroximetil)fenil)pivalamida. El cloruro de trimetilacetilo (.25mL, 1.99mmol) se agregó a una solución de (2-amino-6-fluorofenil)metanol (268mg, 1.90 mmol) en CH₂Cl₂ (10mL) a 0°C, seguido por la adición de DIEA (1.0 mL, 5.7 mmol). La mezcla se agitó durante 1 hr, seguido por trabajo acuoso normal para
10 proporcionar el producto crudo esperado, *N*-(3-fluoro-2-(hidroximetil)fenil)pivalamida, como un aceite incoloro (415mg, 97% de rendimiento), que se usó directamente en la siguiente etapa; ¹H RMN (400 MHz, CDCl₃) δppm 1.29 (s, 9 H), 2.64 (s, 1 H), 4.78 (d, J=4.78 Hz, 2 H), 6.75 - 6.84 (m, 1 H), 7.23 (td, J=8.62, 5.92 Hz, 1 H), 7.86 (d, 15 J=8.31 Hz, 1 H), 8.97 (s, 1 H); Espectro de masa 226.11 (MH⁺), Calculado para C₁₂H₁₆FO₂ 225.12.

Intermediario 213



20

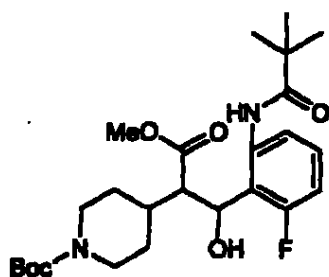
N-(3-fluoro-2-formilfenil)pivalamida. El clorocromato de piridinio (596mg, 2.76 mmol) se agregó a una solución de *N*-(3-fluoro-2-(hidroximetil)fenil)pivalamida (415mg, 1.84 mmol)
25 en CH₂Cl₂ (50mL) a 0°C. Cinco minutos más tarde, la mezcla se

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permitió agitarse a temperatura ambiente durante 3 hrs. La mezcla de reacción se pasó a través de una capa de almohadilla delgada de gel de sílice con CH_2Cl_2 (2x50mL), se concentró al vacío rotatorio, y se purificó en una columna de cromatografía instantánea eluyendo con 20-50% EtOAc/hexanos (600mL) para proporcionar el producto esperado, N-(3-fluoro-2-formilfenil)pivalamida, como un sólido blanco (396 mg, 46% de rendimiento después de cinco etapas); ^1H RMN (400 MHz, CDCl_3) δ ppm 1.33 (s, 9 H), 6.76 - 6.83 (m, 1 H), 7.54 (td, J=8.44, 6.55 Hz, 1 H), 8.56 (d, J=8.56 Hz, 1 H), 10.38 (s, 1 H), 11.57 (s, 1 H); Espectro de masa 224.11 (MH^+) Calculado para $\text{C}_{12}\text{H}_{14}\text{FNO}_2$ 223.1.

Intermediario 214

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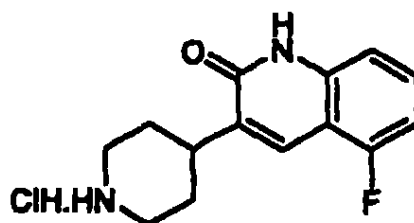


4-(1-(2-fluoro-6-pivalamidofenil)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. El procedimiento de reacción fue el mismo como la síntesis del 4-(1-(6-fluoro-2-pivalamidopiridin-3-il)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo. La reacción proporcionó una mezcla de

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estereoisómero del producto crudo esperado, 4-(1-(2-fluoro-6-pivalamidofenil)-1-hidroxi-3-metoxi-3-oxopropan-2-il)piperidin-1-carboxilato de tert-butilo, como un aceite incoloro el cual se usó
5 directamente en la siguiente etapa sin purificación adicional. Espectro de masa 481.24 (MH⁺), Calculado para C₂₅H₃₇FN₂O₆ 480.26.

Intermediario 215



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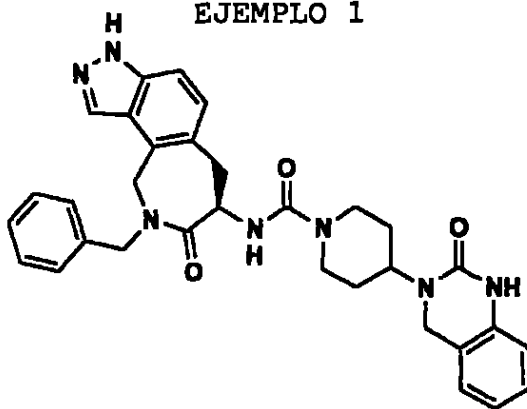
Clorohidrato de 5-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona. El procedimiento fue el mismo
15 como la síntesis de 7-fluoro-3-(piperidin-4-il)-1,8-naftiridin-2(1H)-ona. Después de la reacción, una parte del solvente se removió al vacío rotatorio, el producto esperado salió como un sólido de la
20 solución, se filtró y se lavó con etil etanol para dar el producto esperado, clorohidrato de 5-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona, un sólido blanco (43% de rendimiento después de dos etapas); ¹H RMN (400 MHz, MeOD) δppm 1.85 - 1.96 (m, 2 H), 2.16 (d, J=14.10 Hz, 2 H), 3.16 (td, J=13.03, 2.90 Hz, 3 H),
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3.51 (dd, $J=10.58$, 2.01 Hz, 2 H), 4.55 (s, 1 H), 6.94 - 6.99 (m, 1 H), 7.13 (d, $J=8.31$ Hz, 1 H), 7.48 (td, $J=8.31$, 5.79 Hz, 1 H), 7.90 (s, 1 H); Espectro de masa 247.11 (MH^+), Calculado para $C_{14}H_{15}N_2O$ 246.12.

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EJEMPLO 1



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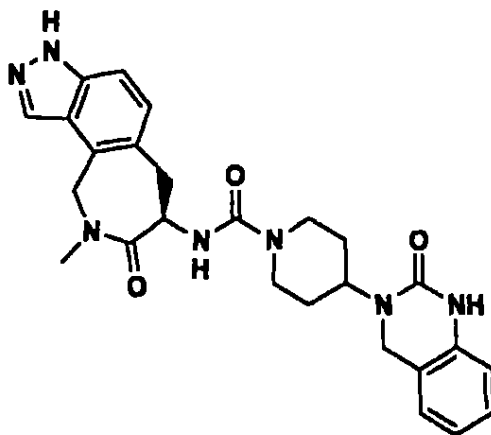
(9-bencil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El

15 carbonato de potasio (25 mg, 0.18 mmol) se agregó a una solución de (3-acetil-9-bencil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (19 mg, 0.03 mmol). La reacción se agitó a
20 temperatura ambiente durante 1.25 hora. La reacción se apagó con ácido clorhídrico 1N (5 mL). El metanol se removió de la mezcla in vacuo. El acuoso restante se hizo básico con bicarbonato de sodio. La mezcla se extrajo con diclorometano (3 X 10 mL). Los extractos combinados se secaron (sulfato de
25 magnesio), se filtraron y se concentraron in vacuo. El

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compuesto del título se obtiene como un sólido blanco
descolorido en 90% de rendimiento. ^1H RMN (300 MHz CDCl_3): δ =
7.64 (s, 1 H), 7.18 (m, 6H), 7.06 (m, 1 H), 6.96 (t, J = 7.1,
1 H), 6.84 (m, 2H), 6.67 (m, 1H), 6.24 (d, J = 5.9, 1H), 5.40
5 (m, 1H), 4.96 (d, J =14.6, 1H). 4.76 (d, J = 17.2, 1H), 4.58
(m, 2H), 4.15 (m, 5H), 3.83 (d, J = 13.2, 1H), 3.46 (dd, J_1 =
3.1, J_2 = 16.7, 1H), 2.98 (m, 3H), 1.78 (m, 4H). EM m/e $(M+H)^+$
564.3.

EJEMPLO 2



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(9-metil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-
ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-
dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. Una
20 cantidad catalítica de paladio en carbono al 10% se agregó a
la mezcla de éster de bencilo del ácido (3-acetil-9-metil-8-
oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-
ciclohepta[e]inden-7-il)-carbámico (30 mg, 0.07 mmol), y
ácido acético (20 μL , 0.35 mmol) en metanol (6 mL) y acetato
25 de etilo (3 mL). El recipiente de reacción se colocó en un

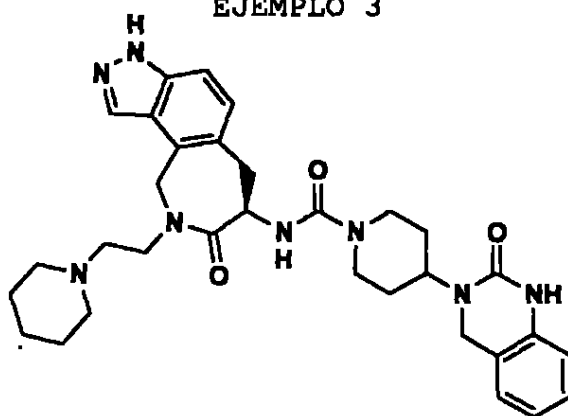
466

aparato de hidrogenación Parr y se cargó con 50 psi (3.51 kg/cm²) de gas de hidrógeno. La reacción la mezcla se permitió que se agitara a temperatura ambiente durante 1.5 hora. La mezcla se filtró. El filtrado se concentró. El
5 residuo se trató con diclorometano (3 mL) y bicarbonato de sodio acuoso saturado (1 mL). El fosgeno al 20% en tolueno (48 µL, 0.09 mmol) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 5 minutos. El acetato de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidinio (25 mg,
10 0.09 mmol) se agregó a la mezcla. La reacción la mezcla se permitió que se agitara a temperatura ambiente durante 1 hora. Otros 20 µL de solución de fosgeno se agregó a la mezcla seguido después de 15 minutos por otros 20 mg de acetato de acetato de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-
15 il)piperidinio. La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos. Las capas de reacción se dividieron. El orgánico se lavó sucesivamente con ácido clorhídrico 1N (2X 5mL), y salmuera (5 mL). El orgánico se secó (sulfato de magnesio), se filtró y se concentró in
20 vacuo. El residuo se disolvió en metanol (3 mL). El carbonato de potasio (25 mg, 0.18 mmol) se agregó a la mezcla. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La reacción se apagó con un par de gotas de ácido trifluoroacético. La CLAR preparatoria C18 (acetonitrilo-
25 agua-ácido trifluoroacético) proporciona el compuesto del

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título como un sólido blanco en 16% de rendimiento. ^1H RMN (300 MHz, CDCl_3): δ = 7.94 (s, 1H), 7.17 (m, 2H), 7.06 (t, J= 7.1, 2H), 6.93 (m, 2H), 6.82 (d J= 9.2, 1H), 6.66 (d, J= 7.3, 1H), 6.19 (d, J= 5.9, 1H), 5.37 (m, 1H), 5.16 (m, 1H) 5 03 (dJ= 17.2, 1H), 4.59 (m, 1H), 4.34 (s, 3H), 4.19 (m, 2H), 3.42 (m, 1H), 2.94 (m, 4H), 1.80 (m, 4H). EM m/e $(\text{M}+\text{H})^+$ 488.4.

EJEMPLO 3



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[8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El carbonato de N,N'-disuccinimidilo (55 mg, 0.21 mmol) se agregó a la mezcla de 7-(R)-amino-9-(2-piperidin-1-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona (60 mg, 0.18 mmol) y trietilamina (150 μL , 1.1 mmol) en diclorometano (3 mL). La reacción se agitó a temperatura ambiente durante 30 minutos. El acetato de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidinio (65 mg, 0.22 mmol) se

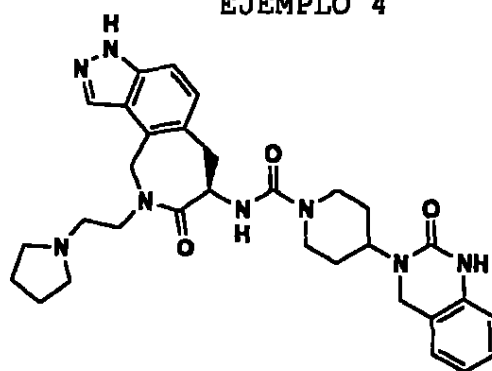
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agregó a la mezcla de reacción. La reacción se agitó hasta que se consideró completa por CLAR (1.75 hora). La mezcla se lavó sucesivamente con agua (2 X 5 mL) y salmuera (1 X 5 mL). El orgánico se concentró in vacuo. La CLAR preparatoria C18 (acetonitrilo-agua-ácido trifluoroacético) proporcionó el producto deseado como un sólido color canela en 34% de rendimiento. ¹H RMN (300 MHz, DMSO-D₆): δ= 9.23 (s, 1H), 8.34 (s, 1H), 7.43 (d, J= 8.8, 1H), 7.13 (m, 2H), 6.86 (t, J= 7.0, 1H), 6.77 (d, J= 7.7, 1H), 6.68 (d, J= 7.7, 1H), 5.26 (m, 2H), 4.71 (d, J= 17.2, 1H), 4.36 (m, 1H), 4.13 (m, 4H), 3.48 (m, 2H), 3.26 (m, 2H), 3.08 (m, 1H), 2.92 (m, 2H), 2.80 (m, 2H), 1.80 (m, 2H), 1.62 (m, 4H). EM m/e (M+H)⁺ 585.4.

EJEMPLO 4



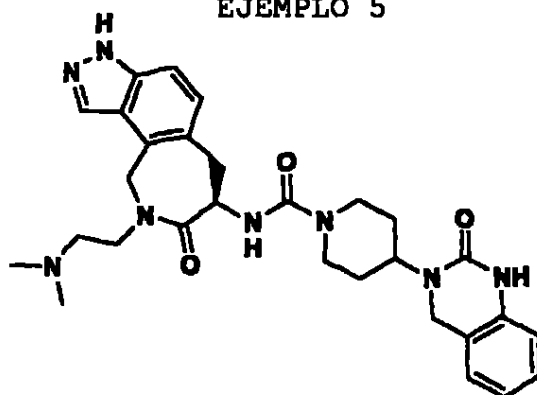
[8-oxo-9-(2-pirrolidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. La 7-(R)-amino-9-(2-pirrolidin-1-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona (27 mg, 0.09 mmol) se hace reaccionar en una manera análoga a

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la preparación de la [8-oxo-9-(2-piperidin-1-il-etil)-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-
il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
piperidin-1-carboxílico. El compuesto del título se obtiene
5 como un sólido blanco en 20% de rendimiento. ¹H RMN (300 MHz,
DMSO-D₆): δ= 9.23 (s, 1H), 8.34 (s, 1H), 7.43 (d, J= 8.4,
1H), 7.13 (m, 2H), 6.86 (t, J= 7.3, 1H), 6.76 (d, J= 7.7, 1
H), 6.67 (d, J= 7.0, 1H), 5.26 (m, 2H), 4.70 (d, J= 17.2,
1H), 4.37 (m, 2H), 4.12 (m, 6H), 3.62 (m, 2H), 3.36 (m, 4H),
10 3.04 (m, 3H), 2.80 (m, 2H), 2.00 (m, 2H), 1.86 (m, 2H), 1.70
(m, 2H), 1.57 (m, 2H). EM m/e (M+H)⁺ 571.4.

EJEMPLO 5

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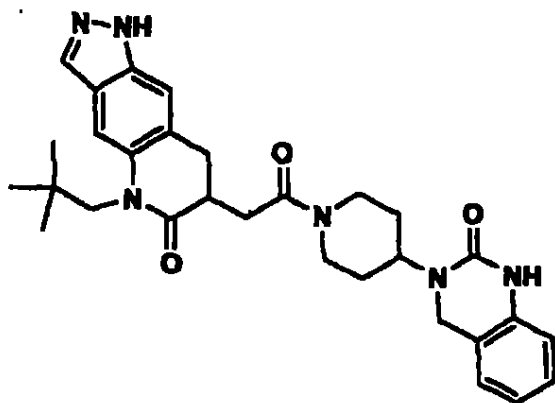


[9-(2-dimetilamino-etil)-8-oxo-3,6,7,8,9,10-hexahidro-
20 2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-
(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
carboxílico. 7(R)-amino-9-(2-dimetilamino-etil)-6,7,9,10-
tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona (11mg,
0.04 mmol) se hace reaccionar en una manera análoga a la
25 preparación de la [8-oxo-9-(2-piperidin-1-il-etil)-

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3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El compuesto deseado se obtiene como un sólido blanco en 34% de rendimiento. ¹H RMN (300 MHz, DMSO-D₆): δ= 9.23 (s, 1H), 8.34 (s, 1H), 7.42 (d, J= 8.4, 1H), 7.12 (m, 2H), 6.87 (t, J= 7.5, 1H), 6.77 (d, J= 8.1, 1H), 6.64 (d, J= 7.3, 1H), 5.26 (m, 2H), 4.69 (d, J= 17.2, 1H), 4.36 (m, 1H), 4.13 (m, 6H), 3.37 (m, 2H), 3.21 (m, 2H), 3.05 (m, 2H), 2.82 (m, 8H), 1.71 (m, 2H), 1.57 (m, 2H). EM m/e (M+H)⁺ 545.4.

EJEMPLO 6

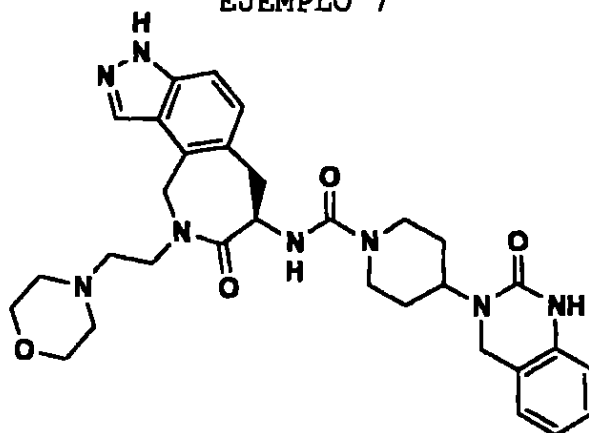


5-Neopentil-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-il)etil)-7,8-dihidro-1H-pirazol[3,4-g]quinolin-6(5H)-ona. El hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (116 mg, 0.3 mmol) se agregó a una solución de ácido 2-(1-neopentil-2-oxo-2,3,4,7-tetrahidro-1H-pirazol[3,4-h]quinolin-3-il)acético (95 mg, 0.3 mmol) y N,N-diisopropiletilamina (158 µL, 0.9 mmol)

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en diclorometano (5.0 mL). La mezcla se agitó a temperatura ambiente durante 45 minutos. La 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (70 mg, 0.3 mmol) se agregó entonces a la mezcla. Después de agitar 3 h a temperatura ambiente, la mezcla de reacción cruda se purificó por CLAR preparativa iniciando a partir de metanol al 30% en agua hasta metanol al 90% en agua durante un periodo de 8 minutos y a una relación de flujo de 40 ml/min. La remoción del solvente proporciona el deseado. EM (ESI) 529 (M+H); R_f= 1.57.

EJEMPLO 7

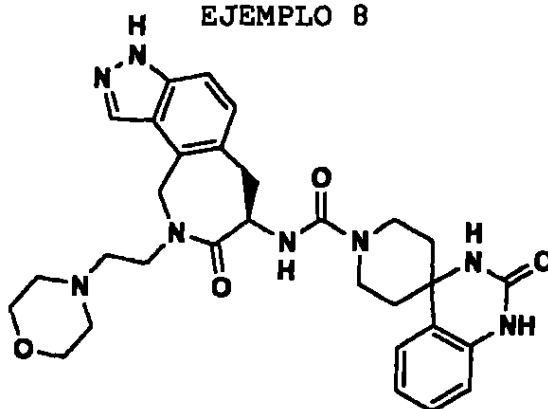


[9-(2-morfolin-4-il-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. La 7-(R)-amino-9-(2-morfolin-4-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona (18 mg, 0.05 mmol) se hace reaccionar en una manera análoga a la preparación de la [8-oxo-9-(2-piperidin-1-il-etil)-

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3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El compuesto del título se obtiene como un sólido amarillo ligero en 43% de rendimiento. ¹H RMN (300 MHz, DMSO-D₆): δ= 9.23 (s, 1H), 8.33 (s, 1H), 7.44 (d, J= 8.4, 1H), 7.13 (t, J= 8.4, 2H), 6.86 (t, J= 7.5, 1H), 6.77 (d, J= 8.4, 1H), 6.66 (d, J=7.0, 1H), 5.27 (m, 2H), 4.71 (d, J= 17.2, 1H), 4.38 (m, 1H), 4.16 (m, 4H), 3.98 (m, 2H), 3.61 (m, 4H), 3.42 (m, 4H), 3.29 (m, 2H), 3.10 (m, 4H), 2.79 (m, 2H), 1.72 (m, 2H), 1.56 (m, 2H), 1.56 (m, 2H). EM m/e (M+H)⁺ 587.4.

EJEMPLO 8

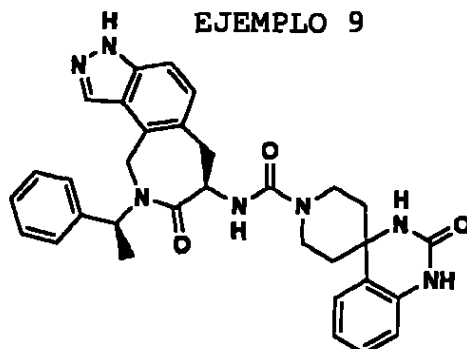


[9-(2-morfolin-4-il-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El carbonato de N,N'-disuccinimidilo (21 mg, 0.08 mmol) se agregó a la mezcla de 7-(R)-amino-9-(2-morfolin-4-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona (22 mg, 0.07 mmol) y trietilamina (40 µL, 0.29 mmol) en

443

diclorometano (1 mL). La reacción se agitó a temperatura ambiente durante 30 minutos. El acetato de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidinio (65 mg, 0.22 mmol) se agregó a la mezcla de reacción. La reacción se agitó hasta que se consideró completa por CLAR (1.5 hora). La mezcla se concentró in vacuo. La CLAR preparatoria C18 (acetonitrilo-agua-ácido trifluoroacético) proporcionó el producto deseado como un sólido blanco en 34% de rendimiento. ¹H RMN (300 MHz DMSO-D₆): δ= 9.26 (s, 1H), 8.34 (s, 1H), 7.43 (d, J= 8.8, 1H), 7.18 (m, 3H), 6.91 (t J= 7.0, 1H), 6.83 (d, J= 8.1, 1H), 6.66 (d, J= 7.0, 1H), 5.28 (m, 2H), 4.70 (d, J= 17.6, 1H), 3.62 (m, 6H), 3.62 (m, 4H), 3.41 (m, 4H), 3.27 (m, 4H), 3.09 (m, 2H), 1.86 (m, 2H), 1.72 (m, 2H). EM m/e (M+H)⁺ 573.4.

EJEMPLO 9



[8-oxo-9-(1-(S)-fenil-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 'H-espiro[piperidin-4,4'-quinazolin]-2' (3'H)-ona-1-carboxílico. La 7-amino-9-(1-(S)-fenil-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-(R)-ciclohepta[e]inden-8-ona (27 mg, 0.08 mmol) se hace reaccionar en una manera análoga a la preparación de la [9-(2-morfolin-4-il-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-

427 474

triazaz-(R)-ciclohepta[e]inden-7-il]-amida del ácido 1H-espiro[piperidin-4,4'-quinazolin]-2'-(3'H)-ona-1-carboxílico.

El compuesto del título se obtiene como un sólido blanco en

14% de rendimiento. ¹H RMN (300 MHz, CD₃OD): δ= 7.92 (s, 1H),

5 7.46 (m, 5H), 7.37 (m, 1H), 7.30 (m, 1H), 7.19 (m, 2H), 7.00

(t, J= 7.7, 1H), 6.85 (d, J= 7.7, 1H), 5.98 (q, J= 6.8, 1H),

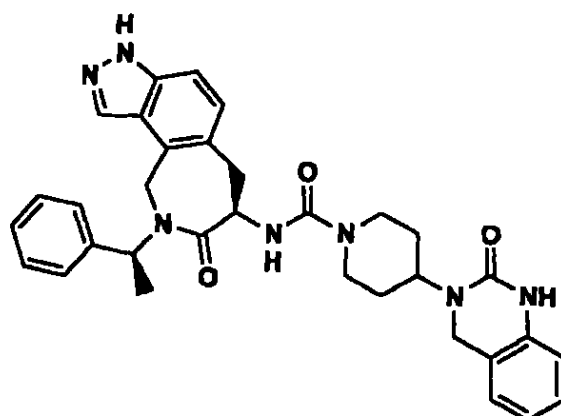
5.46 (dd, J₁= 4.6, J₂= 13.0, 1H), 4.98 (d, J= 17.2, 1H), 4.90

(m, 1H), 4.37 (d, J= 17.6, 1H), 4.11 (m, 2H), 3.40 (m, 4H),

3.22 (m, 2H), 2.12 (m, 2H), 1.92 (d, J= 13.5, 2H), 1.24 (d,

10 J= 7.3, 3H). EM m/e (M+H)⁺ 564.1.

EJEMPLO 10



[8-oxo-9-(1-(S)-fenil-etil)-3,6,7,8,9,10-hexahidro-

20 2,3,9-triazaz-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-

(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

carboxílico. La 7-amino-9-(1-(S)-fenil-etil)-6,7,9,10-

tetrahidro-3H-2,3,9-triazaz-(R)-ciclohepta[e]inden-8-ona (27

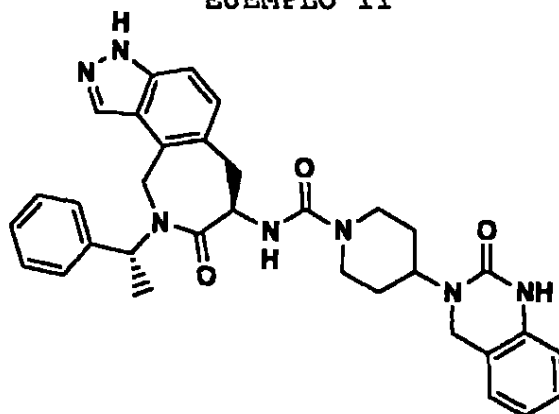
mg. 0.08 mmol) se hace reaccionar en una manera análoga a la

25 preparación de [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-

477 475

hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del
 ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
 carboxílico. El compuesto del título se obtiene como un
 sólido blanco en 20% de rendimiento. ¹H RMN (300 MHz, CD₃OD):
 5 δ= 7.92 (s, 1H), 7.47 (m, 5H), 7.43 (d, J= 8.8, 1H), 7.21 (d,
 J= 8.8, 1H), 7.12 (m, 2H), 6.95 (t, J= 7.0, 1H), 6.78 (d, J=
 7.7, 1H), 5.98 (d, J= 7.0, 1H), 5.44 (dd, J₁= 4.4, J₂= 13.7,
 1H), 4.98 (d, J=17.2, 1H), 4.49 (m, 1H), 4.41 (m, 3H), 4.31
 (m, 4H), 3.36 (m, 1H), 3.24 (m, 1H), 2.99 (m, 2H), 1.93 (m,
 10 2H), 1.73 (m, 2H), 1.24 (d, J= 7.0, 3H). EM m/e (M+H)⁺ 578.2.

EJEMPLO 11



15

[8-oxo-9-(1-(R)-fenil-etil)-3,6,7,8,9,10-hexahidro-
 20 2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-
 (2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
 carboxílico. La 7-amino-9-(1-(R)-fenil-etil)-6,7,9,10-
 tetrahidro-3H-2,3,9-triaza-(R)-ciclohepta[e]inden-8-ona (48
 mg. 0.15 mmol) se hace reaccionar en una manera análoga a la
 25 preparación de la [8-oxo-9-(2-piperidin-1-il-etil)-

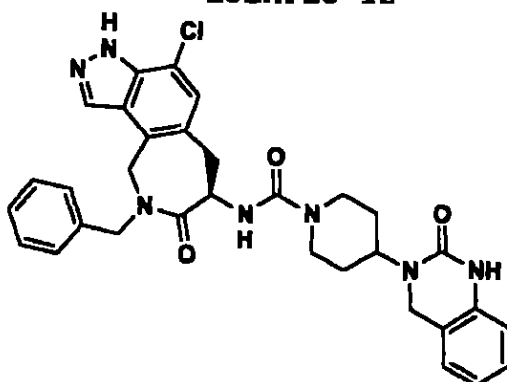
477/ 476

3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El compuesto del título se obtiene como un sólido blanco descolorido en 10% de rendimiento. ¹H

5 RMN (300 MHz, CD₃OD): δ= 7.50 (s, 2H), 7.25 (d, J= 8.4, 1H), 7.14 (m, 2H), 7.07 (m, 4H), 6.93 (t, J= 7.5, 1H), 6.83 (m, 2H), 6.78 (d, J= 7.7, 1H), 5.97 (q, J= 6.7, 1H), 5.40 (dd, J₁= 4.6, J₂= 13.0, 1H), 5.05 (d, J= 17.6, 1H), 4.49 (m, 3H), 4.42 (s, 2H), 4.30 (m, 3H), 3.37 (m, 1H), 3.24 (m, 1H), 2.99 (m, 2H), 1.93 (m, 2H), 1.76 (m, 2H), 1.70 (d, J= 7.3, 3H). EM m/e (M+H)⁺= 578.1.

EJEMPLO 12

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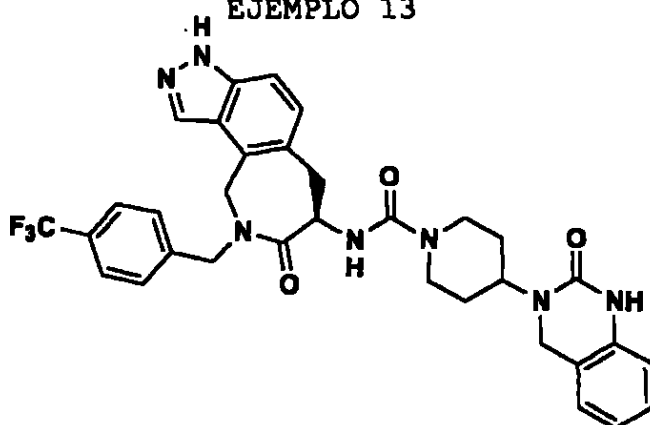
(9-benzil-4-cloro-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El carbonato de N,N'-disuccinimidilo (63 mg, 0.25 mmol) se agregó a la mezcla de 7-(R)-amino-9-(2-morfolin-4-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona (120 mg, 0.24 mmol) y trietilamina (500 µL, 3.6 mmol) en

475 477

diclorometano (5 mL). La reacción se agitó a temperatura ambiente durante 30 minutos. La 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (54 mg, 0.23 mmol) se agregó a la mezcla de reacción. La reacción se agitó hasta que se
5 consideró completa por CLAR (0.5 hora). La mezcla se lavó sucesivamente con agua (2 X 5mL) y salmuera (5 mL). La capa orgánica se concentró in vacuo. El residuo se purificó por CLAR preparatoria C18 (acetonitrilo-agua-ácido trifluoroacético). El acetonitrilo se removió de las
10 fracciones que contienen producto in vacuo. El acuoso restante se hizo básico con bicarbonato de sodio. La mezcla se extrajo con acetato de etilo (2 x 20 mL). Los extractos combinados se lavaron con salmuera (10mL). El orgánico se secó (sulfato de magnesio), se filtró y se concentró. El
15 producto deseado se obtiene como un sólido blanco en 24% de rendimiento. ^1H RMN (500 MHz, CD_3OD): δ = 7.91 (s, 1H), 7.16 (m, 4H), 7.10 (d, J= 7.3, 1H), 7.04 (m, 3H), 6.92 (t, J= 7.5, 1H), 6.79 (d, J= 7.9, 1H), 5.45 (dd, J1= 4.4, J2= 13.3, 1H), 5.29 (d, J= 16.8, 1H), 4.99 (d, J=14.7, 1H), 4.60 (m, 2H),
20 4.49 (m, 3H), 4.39 (s, 2H), 4.28 (t, J= 12.7, 2H), 3.36 (m, 1H), 3.19 (dd, J1= 4.0, J2= 16.2, 1H), 2.98 (m, 2H), 1.91 (m, 2H), 1.71 (m, 2H). EM m/e $(\text{M}+\text{H})^+$ 598.1.

4470 478

EJEMPLO 13



5

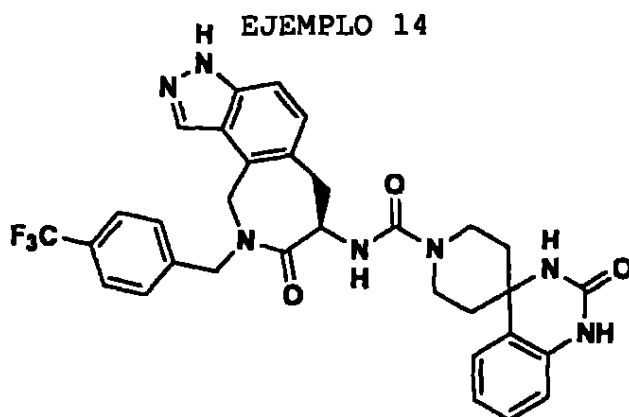
[8-oxo-9-(4-trifluorometil-bencil)-3,6,7,8,9,10-

10 hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del
ácido 4-(2-oxo-1,4-dihidro-2h-quinazolin-3-il)-piperidin-1-
carboxílico. El bismetansulfonato de 7-amino-9-(4-
trifluorometil-bencil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
(R)-ciclohepta[e]inden-8-ona se hace reaccionar en una manera
15 análoga a la preparación de la [8-oxo-9-(2-piperidin-1-il-
etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-
ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-
dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El
compuesto del título se obtiene como un sólido blanco en 19%
20 de rendimiento. ¹H RMN (500 MHz, DMSO-D₆): δ= 9.19 (s, 1H),
8.09 (s, 1H), 7.48 (d, J= 7.9, 1H), 7.38 (d, J= 8.4, 1H),
7.34 (d, J= 8.5, 1H), 7.10 (m, 3H), 6.85 (t, J= 7.0, 1H),
6.77 (d, J= 7.9, 1H), 6.66 (d, J= 6.4, 1H), 5.35 (m, 2H),
4.71 (m, 3H), 4.36 (m, 2H), 4.29 (s, 2H), 4.18 (d, J= 12.8,
25 2H), 3.29 (m, 1H), 3.13 (dd, J₁= 13.6, J₂= 16.6, 1H), 2.81

427 429

(m, 2H), 1.72 (m, 2H), 1.56 (d, J= 11.3, 2H). EM m/e (M+H)⁺ 632.1.

5



10

[8-oxo-9-(4-trifluorometil-bencil)-3,6,7,8,9,10-

hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 'H-espiro[piperidin-4,4'-quinazolin]-2' (3'H)-ona-1-carboxílico. El bismetansulfonato de 7-amino-9-(4-

trifluorometil-bencil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-

15

(R)-ciclohepta[e]inden-8-ona se hace reaccionar en una manera análoga a la preparación de [9-(2-morfolin-4-il-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 'H-espiro[piperidin-4,4'-quinazolin]-2' (3'H)-ona-1-carboxílico. El compuesto del título se obtiene

20

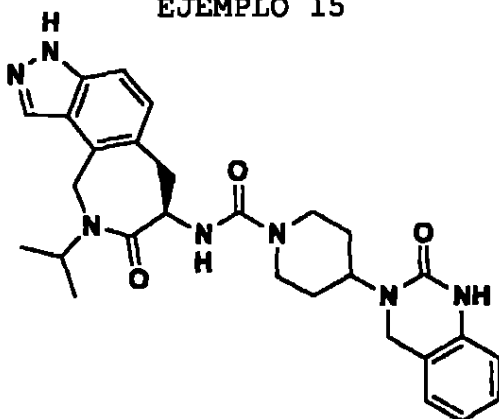
como un sólido blanco en 6% de rendimiento. ¹H RMN (500 MHz, CD₃OD): δ= 7.91 (s, 1H), 7.46 (d, J= 8.2, 1H), 7.35 (d, J= 8.6, 1H), 7.30 (m, 5H), 7.17 (m, 2H), 7.01 (t, J= 7.6, 1H), 6.84 (d, J= 8.2, 1H), 5.51 (dd, J₁= 4.6, J₂= 13.1, 1H), 5.40 (d, J= 17.1, 1H), 5.07 (d, J= 15.3, 1H), 4.64 (d, J= 4.9, 1H), 4.61 (s, 1H), 4.43 (s, 1H), 4.09 (m, 2H), 3.42 (m, 3H),

25

112 480

3.35 (m, 1H), 3.22 (m, 1H), 2.16 (m, 1H), 2.07 (m, 1H), 1.92 (d, J= 13.4, 2H). EM m/e (M+H)⁺ 618.1.

EJEMPLO 15



(9-isopropil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. La

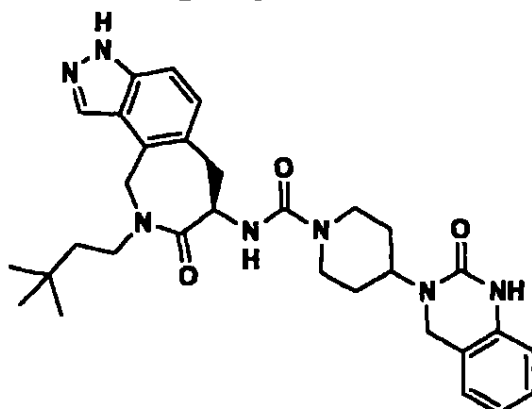
bismetansulfonato de 7-(R)-amino-9-isopropil-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona se hace reaccionar en una manera análoga a la preparación de la [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El

producto deseado se obtiene como un sólido amarillo ligero en 28% de rendimiento. ¹H RMN (400 MHz, DMSO-D₆): δ= 9.21 (s, 1H), 8.45 (s, 1H), 7.37 (d, J= 8.6, 1H), 7.10 (m, 3H), 6.86 (m, 1H), 6.77 (d, J= 7.6, 1H), 6.56 (m, 1H), 5.26 (m, 1H), 5.00 (d, J= 17.1, 1H), 4.74 (m, 2H), 4.65 (d, J= 17.4, 1H), 4.36 (m, 1H), 4.29 (s, 2H), 4.15 (m, 2H), 3.25 (dd, J1= 3.7,

474 481

J2= 16.9, 1H), 3.04 (dd, JJ= 13.6, J2= 16.5, 1H), 2.80 (m, 2H), 1.71 (m, 2H), 1.57 (d, J= 11.7, 2H), 1.23 (d, J= 6.9, 3H), 0.80 (d, J= 6.9, 3H). EM m/e (M+H)⁺ 516.4.

EJEMPLO 16



[9-(3,3-dimetil-butil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El bismetansulfonato de 7-(R)-amino-9-(3,3-dimetil-butil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona se hace reaccionar en una manera análoga a la preparación de la [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-

ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El

producto deseado se obtiene como un sólido blanco descolorido

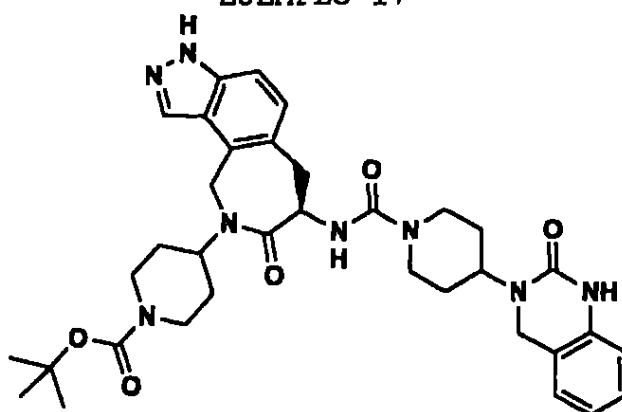
en 29% de rendimiento. ¹H RMN (500 MHz, DMSO-D₆): δ= 9.19 (s, 1H), 8.32 (s, 1H), 7.38 (d, J= 8.6, 1H), 7.10 (t, J= 9.2,

3H), 6.86 (t, J=7.5, 1H), 6.77 (d, J= 7.6, 1H), 6.53 (s, 1H),

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5.24 (d, J= 16.5, 2H), 4.62 (d, J= 17.9, 1H), 4.35 (m, 1H),
4.29 (s, 2H), 4.14 (m, 2H), 3.57 (m, 1H), 3.36 (m, 1H), 3.26
(dd, J7=2.8, J2=17.1, 1H), 3.01 (m, 1H), 2.80 (t, J= 12.4,
2H), 1.72 (m, 2H), 1.56 (d, J= 11.3, 2H), 1.27 (m, 1H), 1.15
5 (m, 1H), 0.79 (s, 9H). EM m/e (M+H)⁺= 558.2.

EJEMPLO 17

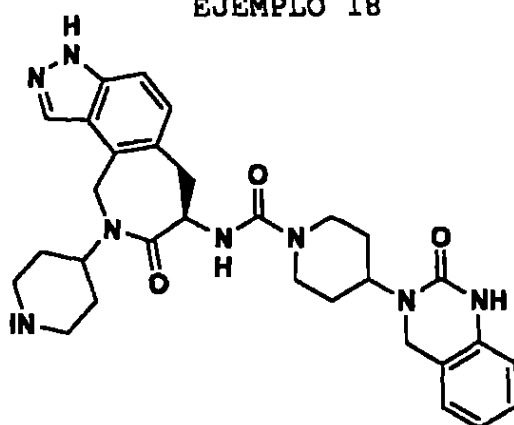


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Éster de *tert*-butilo del ácido 4-(8-oxo-7-[[4-(2-oxo-
15 1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino]-
6,7,8,10-tetrahidro-3H-2,3,9-triaza-(R)-ciclohepta[e]inden-9-
il)-piperidin-1-carboxílico. El acetato del éster de *tert*-
butilo del ácido 4-(7-(R)-amino-8-oxo-6,7,8,10-tetrahidro-3H-
2,3,9-triaza-ciclohepta[e]inden-9-il)-piperidin-1-carboxílico
20 se hace reaccionar en una manera análoga a la preparación de
la [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-
2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-
(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
carboxílico. La CLAR preparatoria C18 dio el producto deseado
25 como un sólido blanco descolorido en 26% de rendimiento. ¹H

RMN (500 MHz, DMSO-D₆: δ= 9.22 (s, 1H), 8.38 (s, 1H), 7.38 (d, J= 8.6, 1H), 7.10 (m, 3H), 6.85 (m, 1H), 6.75 (d, J= 7.6, 1H), 6.57 (s, 1H), 5.28 (m, 1H), 5.02 (d, J= 17.1, 1H), 4.66 (d, J= 17.1, 1H), 4.46 (m, 1H), 4.34 (m, 1H), 4.30 (s, 2H), 4.08 (m, 4H), 3.76 (m, 1H), 3.25 (d, J= 17.4, 1H), 3.04 (m, 1H), 2.79 (m, 4H), 1.91 (m, 1H), 1.68 (n, 2H), 1.54 (m, 4H), 1.39 (s, 9H). EM m/e (M+H)⁺ 679.3.

EJEMPLO 18



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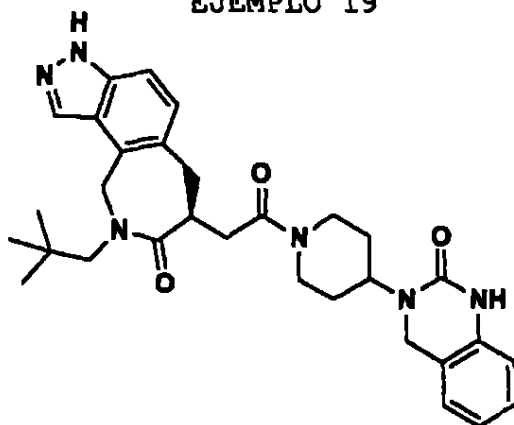
(8-oxo-9-piperidin-4-yl-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-yl)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-yl)-piperidin-1-carboxílico. El ácido trifluoroacético (250 µL) se agregó una solución enfriada (baño de hielo con agua) del éster de tert-butilo del ácido 4-(8-oxo-7-[[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-yl)-piperidin-1-carbonil]-amino]-6,7,8,10-tetrahidro-3H-2,3,9-triaza-(R)-ciclohepta[e]inden-9-yl)-piperidin-1-carboxílico (60 mg, 0.08 mmol) en diclorometano (1 mL). La reacción se agitó a 0°C durante 1 hora. La mezcla se

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concentró in vacuo. El producto deseado se obtiene como un sólido amarillo ligero en 65% de rendimiento. ¹H RMN (500 MHz, DMSO-D₆): δ= 9.23 (s, 1H), 8.32 (s, 1H), 7.41 (d, J= 8.6, 1H), 7.11 (m, 3H), 6.86 (t, J= 7.5, 1H), 6.76, d, J= 7.9, 1H), 6.62 (d, J= 6.7, 1H), 5.29 (m, 1H), 5.11 (d, J= 16.8, 1H), 4.66 (t, J= 1H), 4.53 (d, J= 17.4, 1H), 4.35 (m, 1H), 4.29 (s, 2H), 4.16 (d, J= 12.5, 4H), 3.42 (d, J= 11.9, 1H), 3.26 (dd, J₁= 3.8, J₂= 16.3, 1H), 3.16 (d, J= 10.7, 1H), 3.05 (m, 2H), 2.83 (m, 3H), 2.15 (m, 1H), 1.70 (m, 4H), 1.57 (d, J= 10.7, 2H). EM m/e (M+H)⁺= 557.2.

EJEMPLO 19

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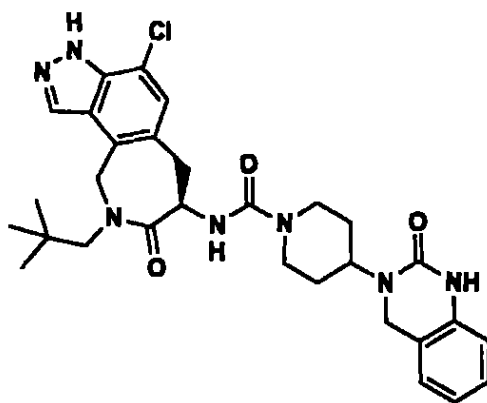
9-(2,2-Dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (62 mg, 0.16 mmol) se agregó a una solución de ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético

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(45 mg, 0.14 mmol) y N,N-diisopropiletilamina (100 μ L, 0.57 mmol) en DMF (1.5 mL). La mezcla se agitó a temperatura ambiente durante 45 minutos. La 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (40 mg, 0.17 mmol) luego se agregó a la mezcla. La reacción se agitó a temperatura ambiente hasta que se juzgó completa por la CLAR (45 minutos). La CLAR preparatoria C18 (acetonitrilo-agua-ácido trifluoroacético) se realizó en la mezcla cruda. El acetonitrilo se removió de las fracciones que contienen el producto deseado in vacuo. El acuoso restante se hizo básico con bicarbonato de sodio. La mezcla se extrajo con acetato de etilo (2X15 mL). Los extractos combinados se lavaron con bicarbonato de sodio acuoso saturado (10 mL). El orgánico se secó (sulfato de magnesio), se filtró y se concentró in vacuo. El compuesto del título se obtiene como un sólido blanco en 50% de rendimiento. ^1H RMN (500 MHz, DMSO- D_6): δ = 9.23 (s, 1H), 8.23 (s, 1H), 7.37 (d, J= 8.5, 1H), 7.10 (m, 3H), 6.86 (t, J= 7.3, 1H), 6.77 (d, J= 7.9, 1H), 5.38 (d, J= 16.2, 1H), 4.63 (d, J= 17.4, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 4.28 (s, 2H), 4.09 (m, 1H), 3.87 (m, 1H), 3.55 (t, J= 13.0, 1H), 3.10 (m, 2H), 3.01 (m, 3H), 2.88 (m, 1H), 2.59 (m, 1H), 2.34 (m, 1H), 1.84 (m, 1H), 1.59 (m, 3H), 0.74 (d, J= 19.2, 9H). EM m/e (M+H) $^+$ = 543.2.

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EJEMPLO 20



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- [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-
 10 hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del
 ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
 carboxílico. El ácido metansulfónico (250 µL) se agregó a una
 solución del éster de bencilo del ácido [4-cloro-9-(2,2-
 dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
 15 (R)-ciclohepta[e]inden-7-il]-carbámico (90 mg, 0.20 mmol) y
 anisol (70 µL, 0.64 mmol) en diclorometano (2 mL). La
 reacción se agitó a temperatura ambiente durante 2 horas. La
 mezcla se diluyó con éter de dietilo (40 mL). La mezcla se
 permitió reposar a temperatura ambiente durante 30 minutos.
 20 Los solventes se decantaron completamente. El residuo se lavó
 con éter de dietilo (30 mL) luego se secó in vacuo. El
 residuo se disolvió en una mezcla de trietilamina (250 µL,
 1.8 mmol) en diclorometano (5 mL). El carbonato de N,N'-
 disuccinimidilo (61 mg, 0.24 mmol) se agregó a la mezcla. La
 25 reacción se agitó a temperatura ambiente durante 30 minutos.

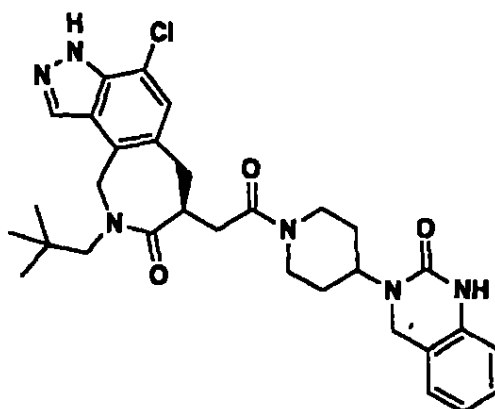
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La 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (55 mg, 0.24 mmol) se agregó entonces a la mezcla. La reacción se agitó a temperatura ambiente durante 30 minutos. La mezcla se lavó sucesivamente con agua (2X5 mL) y salmuera (5 mL). El orgánico se secó (sulfato de magnesio), se filtró y se concentró. La CLAR preparatoria C18 (acetonitrilo-agua-ácido trifluoroacético) se realizó en el residuo. El acetonitrilo se removió de las fracciones que contienen producto in vacuo. El acuoso restante se hizo básico con bicarbonato de sodio. La mezcla se extrajo con acetato de etilo (2X15 mL). Los extractos combinados se secaron (sulfato de magnesio), se filtraron y se concentraron in vacuo. El compuesto del título se obtiene como un sólido blanco en 37% de rendimiento. ¹H RMN (500 MHz, CD₃OD): δ= 8.26 (s, 1H), 7.26 (s, 1H), 7.13 (m, 3H), 6.93 (t, J= 7.5, 1H), 6.78 (d, J= 7.9, 1H), 5.44 (d, J= 17.1, 1H), 5.34 (dd, J₁= 3.5, J₂= 13.0, 1H), 4.70 (d, J= 17.4, 1H), 4.47 (m, 1H), 4.40 (s, 2H), 4.26 (m, 2H), 3.82 (d, J= 13.4, 1H), 3.19 (m, 1H), 3.08 (d, J= 13.7, 1H), 2.94 (m, 2H), 1.90 (m, 2H), 1.71 (d, J= 12.2, 2H), 0.81 (s, 9H). EM m/e (M+H)⁺= 578.3.

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EJEMPLO 21

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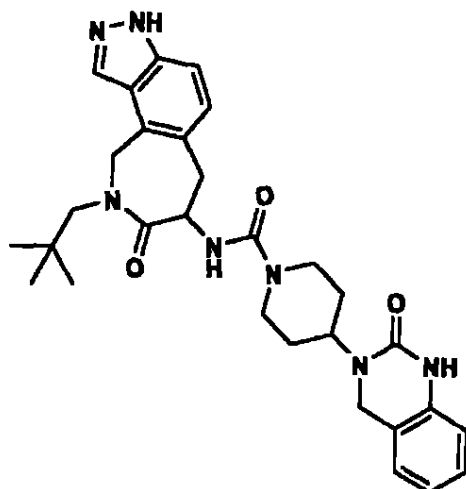


4-Cloro-9-(2,2-dimetil-propil)-7-(S)-(2-oxo-2-[4-(2-oxo-
10 1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-
6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.
El tetrafluoroborato de O-(1H-benzotriazol-1-il)-N,N,N',N'-
tetrametiluronio (90 mg, 0.28 mmol) se agregó a una solución
de ácido [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-
15 hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético
(85 mg, 0.23 mmol) y N,N-diisopropiletil amina (100 µL, 0.57
mmol) en DMF (3 mL). La mezcla se agitó a temperatura
ambiente durante 15 minutos. La 4-(2-oxo-1,4-dihidro-2H-
quinazolin-3-il)piperidina (65 mg, 0.28 mmol) se agregó
20 entonces a la mezcla. La reacción se agitó a temperatura
ambiente durante 1 hora. La mezcla se diluyó con acetato de
etilo (20 mL). La mezcla se lavó sucesivamente con agua (2X15
mL), y salmuera (10 mL). El orgánico se secó (sulfato de
magnesio), se filtró y se concentró in vacuo. El residuo se
25 purificó por CLAR preparatoria C18 (acetonitrilo-agua-ácido

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trifluoroacético). El acetonitrilo se removió de las fracciones que contienen producto in vacuo. El acuoso restante se hizo básico con bicarbonato de sodio. La mezcla se extrajo con acetato de etilo (2 X 20 mL). Los extractos combinados se lavaron con salmuera (10 mL). El orgánico se secó (sulfato de magnesio), se filtró y se concentró in vacuo. El compuesto del título se obtiene como un sólido blanco en 37% de rendimiento. ¹H RMN (500 MHz, DMSO-D₆): δ= 13.55 (s, 1H), 9.21 (s, 1H), 8.36 (s, 1H), 7.25 (s, 1H), 7.09 (m, 2H), 6.86 (t, J= 7.3, 1H), 6.77 (d, J= 7.9, 1H), 5.36 (d, J= 15.6, 1H), 4.63 (d, J= 17.1, 1H), 4.51 (m, 1H), 4.40 (m, 1H), 4.29 (s, 2H), 4.10 (d, J= 13.2, 1H), 3.87 (m, 1H), 3.57 (m, 1H), 3.11 (m, 2H), 3.00 (m, 2H), 2.88 (m, 1H), 2.59 (m, 1H), 2.32 (m, 1H), 1.85 (m, 1H), 1.59 (m, 3H), 0.74 (d, J= 18.3, 9H). EM m/e (M+H)⁺= 577.0.

EJEMPLO 22

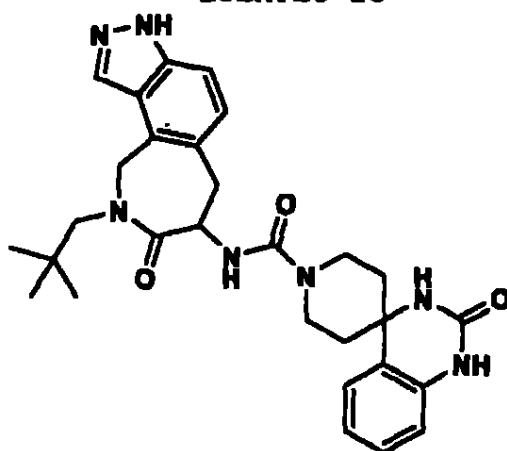


[9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico.

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En una manera similar a la [8-oxo-9-(2-piperidin-1-il-etil)-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-
il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
piperidin-1-carboxílico, el compuesto del título se preparó
5 al hacer reaccionar diclorohidrato de (7R)-7-amino-9-(2,2-
dimetil-propil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
ciclohepta[e]inden-8-ona con clorohidrato de 3-piperidin-4-
il-3,4-dihidro-1H-quinazolin-2-ona para dar el compuesto del
título (80% de rendimiento). EM (ESI) 544 (M+H); Rf=1.51.

EJEMPLO 23



N-[9-(2,2-dimetilpropil)-8-oxo-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-il]-2'-oxo-2',3'-dihidro-

1H,1'H-espiro[piperidin-4,4'-quinazolin]-1-carboxamida. En

una manera similar a la [8-oxo-9-(2-piperidin-1-il-etil)-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-
il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
piperidin-1-carboxílico, el compuesto del título se preparó

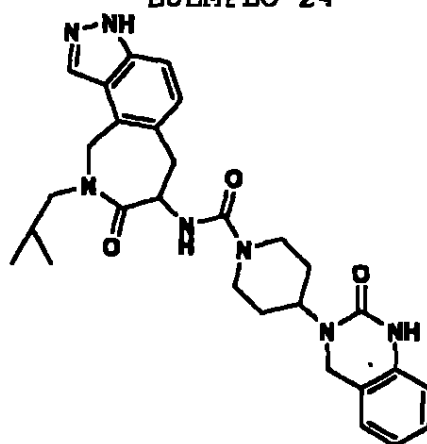
al hacer reaccionar el diclorohidrato de (7R)-7-amino-9-(2,2-

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dimetil-propil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
ciclohepta[e]inden-8-ona con clorohidrato de 1'H-
espiro[piperidin-4,4'-quinazolin]-2' (3'H)-ona para dar el
compuesto del título (80% de rendimiento). EM (ESI) 530
5 (M+H); R_f = 1.44.

EJEMPLO 24

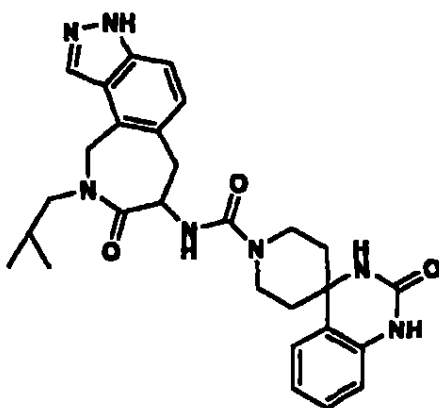
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(9-isobutil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-
15 ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-
dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. En una
manera similar a la [8-oxo-9-(2-piperidin-1-il-etil)-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-
il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
20 piperidin-1-carboxílico, el compuesto del título se preparó
al hacer reaccionar el diclorohidrato de (7R)-7-amino-9-
isobutil-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
ciclohepta[e]inden-8-ona con clorohidrato de 3-piperidin-4-
il-3,4-dihidro-1H-quinazolin-2-ona para dar el compuesto del
25 título (80% de rendimiento). EM (ESI) 530 (M+H); R_f = 1.41.

492

EJEMPLO 25

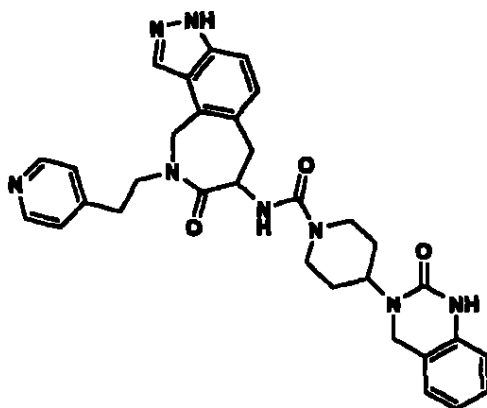


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10 *N*-[9-(2-metilpropil)-8-oxo-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-il]-2'-oxo-2',3'-
dihidro-1H,1'H-espiro[piperidin-4,4'-quinazolin]-1-
carboxamida. En una manera similar a la [8-oxo-9-(2-
piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-
15 triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido
4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
carboxílico, el compuesto del título se preparó al
hacer reaccionar el diclorohidrato de (7R)-7-amino-9-
isobutil-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
20 ciclohepta[e]inden-8-ona con clorohidrato de 1'H-
espiro[piperidin-4,4'-quinazolin]-2'(3'H)-ona para
dar el compuesto del título (80% de rendimiento). EM
(ESI) 516 (M+H); R_f =1.35.

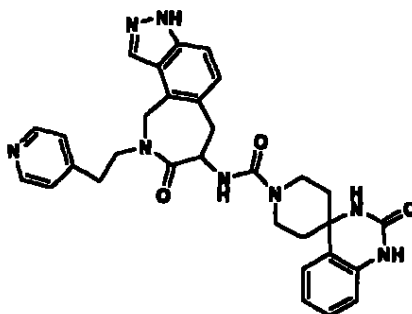
443

EJEMPLO 26



[8-oxo-9-(2-piridin-4-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. En una manera similar a la [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico, el compuesto del título se preparó al hacer reaccionar el diclorohidrato de (7R)-7-amino-9-(2-piridin-4-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona con clorohidrato de 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona para dar el compuesto del título (80% de rendimiento). EM (ESI) 530 (M+H); R_f = 1.41.

EJEMPLO 27

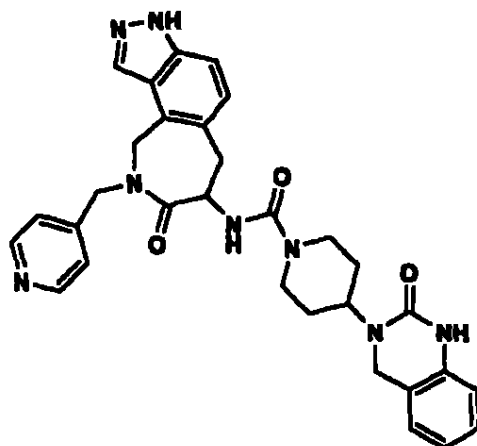


N-[9-(2-piridin-4-il-etil)-8-oxo-2,6,7,8,9,10-

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hexahidroazepino[3,4-e]indazol-7-il)-2'-oxo-2',3'-dihidro-
1H,1'H-espiro[piperidin-4,4'-quinazolin]-1-carboxamida. En
una manera similar a [8-oxo-9-(2-piperidin-1-il-etil)-
3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-
5 il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
piperidin-1-carboxílico, el compuesto del título se preparó
al hacer reaccionar el diclorohidrato de (7R)-7-amino-9-(2-
piridin-4-il-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
ciclohepta[e]inden-8-ona con clorohidrato de 1'H-
10 espiro[piperidin-4,4'-quinazolin]-2' (3'H)-ona para dar el
compuesto del título (80% de rendimiento). EM (ESI) 516
(M+H); R_f =1.35.

EJEMPLO 28



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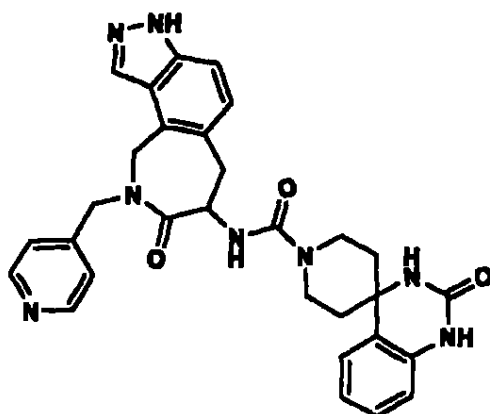
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(8-oxo-9-piridin-4-ilmetil-3,6,7,8,9,10-hexahidro-2,3,9-
triaza-ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-
dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. En una
manera similar a la [8-oxo-9-(2-piperidin-1-il-etil)-
25 3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-

495

il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
piperidin-1-carboxílico, el compuesto del título se preparó
al hacer reaccionar el diclorohidrato de (7R)-7-amino-9-
piridin-4-ilmetil-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
5 ciclohepta[e]inden-8-ona con clorohidrato de 3-piperidin-4-
il-3,4-dihidro-1H-quinazolin-2-ona para dar el compuesto del
título (80% de rendimiento). EM (ESI) 565 (M+H); R_f = 1.09.

EJEMPLO 29

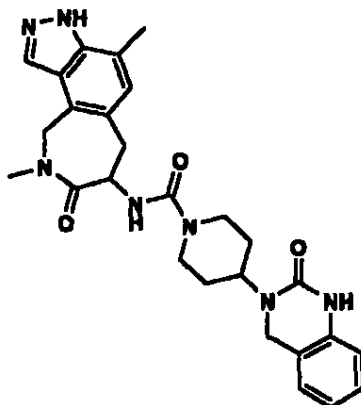


N-[9-piridin-4-ilmetil-8-oxo-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-il]-2'-oxo-2',3'-dihidro-
1H,1'H-espiro[piperidin-4,4'-quinazolin]-1-carboxamida. En
una manera similar a la [8-oxo-9-(2-piperidin-1-il-etil)-
20 3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-
il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
piperidin-1-carboxílico, el compuesto del título se preparó
al hacer reaccionar el diclorohidrato de (7R)-7-amino-9-
piridin-4-ilmetil-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
25 ciclohepta[e]inden-8-ona con clorohidrato de 1'H-

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espiro[piperidin-4,4'-quinazolin]-2' (3'H)-ona para dar el compuesto del título (80% de rendimiento). EM (ESI) 551 (M+H); $R_f=1.07$.

EJEMPLO 30

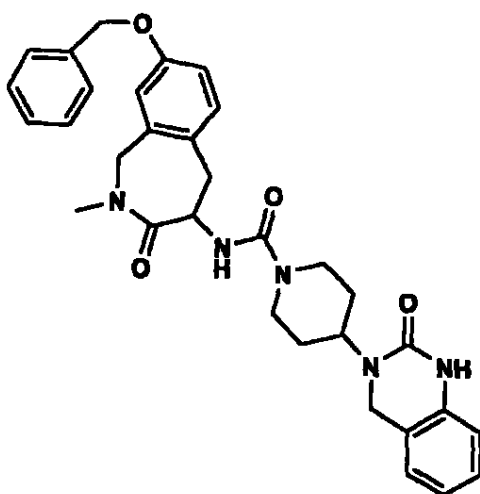


(4,9-etil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. A una solución del éster de bencilo del ácido (4,9-dimetil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il)-carbámico (50 mg, 0.132 mmol) en metanol y cloroformo (0.5 mL) se le agregó paladio en carbono al 10% (20 mg) bajo atmósfera de nitrógeno. La mezcla de reacción se llevó a atmósfera de hidrógeno (1 atm) y se agitó durante 3 h. El catalizador se filtró y el solvente se evaporó para dar el clorohidrato de 7-amino-4,9-dimetil-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona en un rendimiento casi cuantitativo. A la sal de amina en diclorometano se le agregó

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carbonato de disuccinimidilo (37 mg, 0.145 mmol) y trietilamina (0.11 mL, 0.8 mmol) a temperatura ambiente. Después de 120 min, el clorohidrato de 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (39 mg, 0.145 mmol) se agregó y la agitación continuó durante 12 h. El solvente se evaporó y el producto crudo se purificó por CLAR Preparativa para dar la (4,9-dimetil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triazaciclohepta[e]inden-7-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico en 59% de rendimiento general. EM (ESI) 502 (M+H); R_f =1.31.

EJEMPLO 31

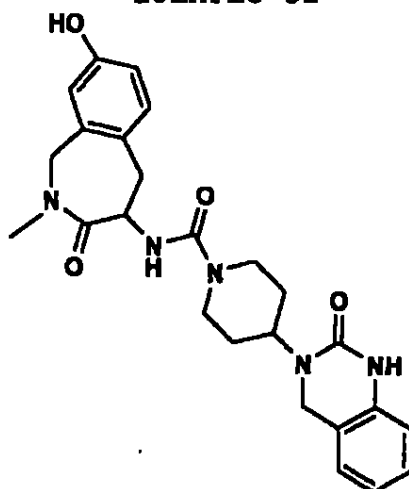


(8-benciloxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. A una solución agitada del éster de tert-butilo del ácido (8-benciloxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-carbámico (300 mg, 0.76 mmol) en diclorometano (2 mL) se agregó a una solución 4.0 M de cloruro de hidrógeno en dioxano

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498

(15 mL). La mezcla de reacción se agitó y se removió el solvente para dar la sal de amina en rendimiento cuantitativo. La sal de amina se disolvió en diclorometano (20 mL) seguido por la adición de carbonato de N,N'-disuccinimidilo (214 mg, 0.83 mmol) y trietilamina (0.64 mL, 4.6 mmol). Después de 15 minutos, el clorhidrato de 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (225 mg, 0.84 mmol) se agregó y la agitación continuó durante 12 h. La mezcla de reacción se lavó entonces con carbonato ácido de sodio acuoso, ácido clorhídrico 1.0 M y se secó (Na₂SO₄). El producto crudo se purificó por cromatografía instantánea usando metanol al 5% en diclorometano para dar la (8-benciloxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico en 66% de rendimiento. EM (ESI) 554 (M+H); R_f = 1.67.

EJEMPLO 32

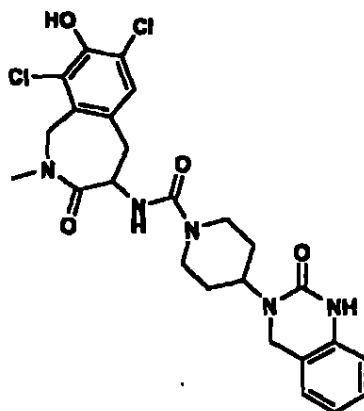


(8-hidroxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. A una solución

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agitada de (8-benciloxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (187 mg, 0.34 mmol) en metanol (30 mL) seguido por paladio en carbono al 10% (30 mg) bajo nitrógeno. La mezcla de reacción se llevó a 1 atmósfera de hidrógeno y se agitó durante 12 h. El catalizador se filtró y el solvente se evaporó para dar la (8-hidroxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico en rendimiento cuantitativo. EM (ESI) 464 (M+H); R_f = 1.34.

EJEMPLO 33

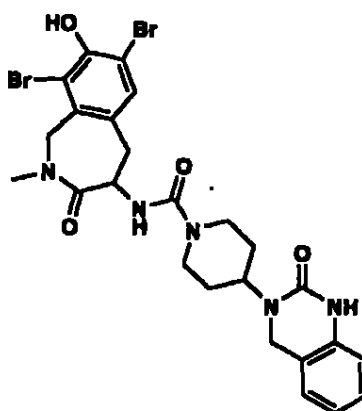


(7,9-dicloro-8-hidroxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. A una solución agitada de la (8-hidroxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-

328, 500

quinazolin-3-il)-piperidin-1-carboxílico (27 mg, 0.058 mmol)
en diclorometano (10 mL) se agregó metanol (2 mL), éter (3
mL) seguido por cloruro de sulfurilo (70 µL) a temperatura
ambiente. La mezcla de reacción se agitó durante 12 horas
5 adicionales y luego se concentró. El producto crudo se
purificó por CLAR Preparativa para dar la (7,9-dicloro-8-
hidroxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-
il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
piperidin-1-carboxílico en 58% de rendimiento. EM (ESI) 532
10 (M+H); $R_f = 1.40$.

EJEMPLO 34

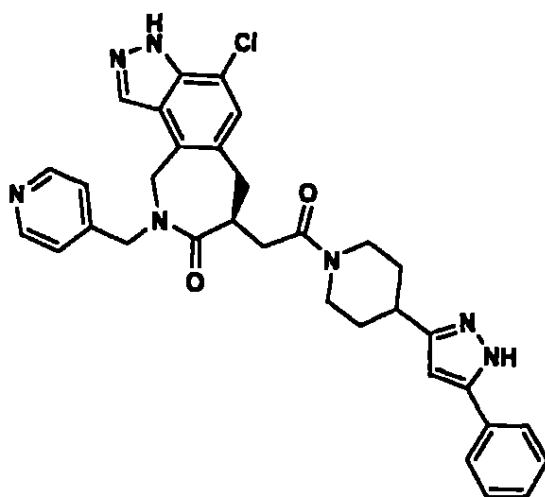


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20 (7,9-dibromo-8-hidroxi-2-metil-3-oxo-2,3,4,5-tetrahidro-
1H-benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-
2H-quinazolin-3-il)-piperidin-1-carboxílico. A una solución
agitada de la (8-hidroxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-
benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-
25 quinazolin-3-il)-piperidin-1-carboxílico (39 mg, 0.084 mmol)

501

en diclorometano (10 mL) se le agregó diisopropilamina (0.06 mL, 0.42 mmol) seguido por N-bromosuccinimida (33 mg, 0.185 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 1 hora adicional y luego el solvente se removió. El producto crudo se purificó por CLAR Preparativa para dar la (7,9-dibromo-8-hidroxi-2-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico en 74% de rendimiento. EM (ESI) 620 (M+H); R_f = 1.45.

EJEMPLO 35



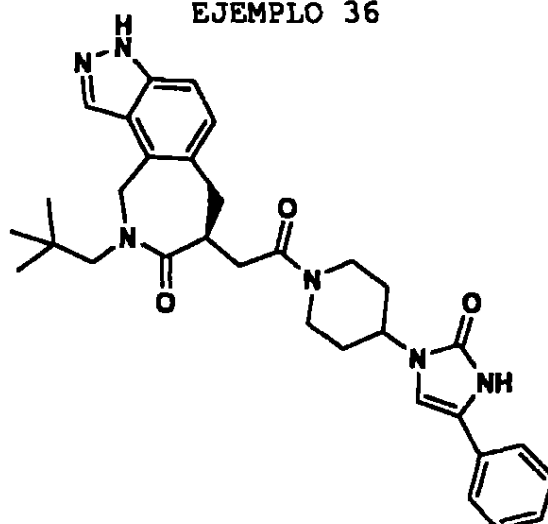
(S)-4-Cloro-7-(2-oxo-2-(4-(5-fenil-1H-pirazol-3-il)piperidin-1-il)etil)-9-(piridin-4-ilmetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El diclorohidrato del ácido (S)-2-(4-cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)acético (66 mg, 0.23 mmol) y clorohidrato de 4-(5-fenil-1H-pirazol-3-il)piperidina (40 mg, 0.15 mmol) se hacen reaccionar

3/20/502

siguiendo un procedimiento análogo a la preparación de la 4-cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El

5 compuesto del título (34 mg) se obtiene como un sólido blanco. EM (ESI) 594 (M+H); R_f = 1.99.

EJEMPLO 36



(S)-9-Neopentil-7-(2-oxo-2-(4-(2-oxo-4-fenil-2,3-dihidroimidazol-1-il)piperidin-1-il)etil)-6,7,9,10-tetrahidroazepin[3,4-e]indazol-8(3H)-ona. El

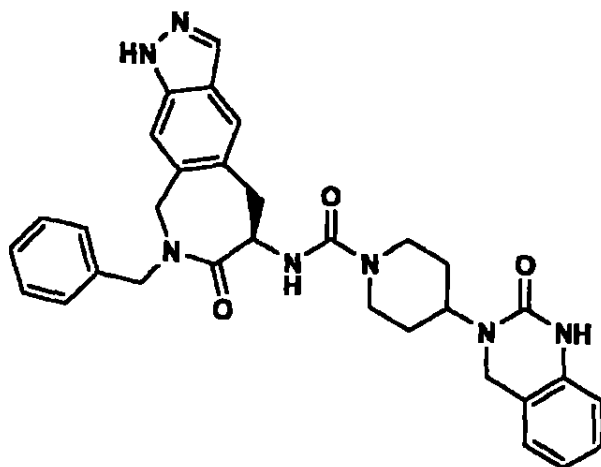
hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (62 mg, 0.16 mmol) se agregó a una solución de ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético (50 mg, 0.16 mmol) y N,N-diisopropiletilamina (85 μ L, 0.48 mmol) en DMF (2.0 mL). La mezcla se agitó a temperatura ambiente durante 45 minutos. El clorohidrato de 4-fenil-1-

30/503

(piperidin-4-il)-1H-imidazol-2(3H)-ona (53 mg, 0.19 mmol) se agregó entonces a la mezcla. El compuesto deseado se purificó por CLAR Preparativa. El compuesto del título (49 mg) se obtiene como una espuma blanca. EM (ESI) 555 (M+H); R_f = 1.54.

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EJEMPLO 37



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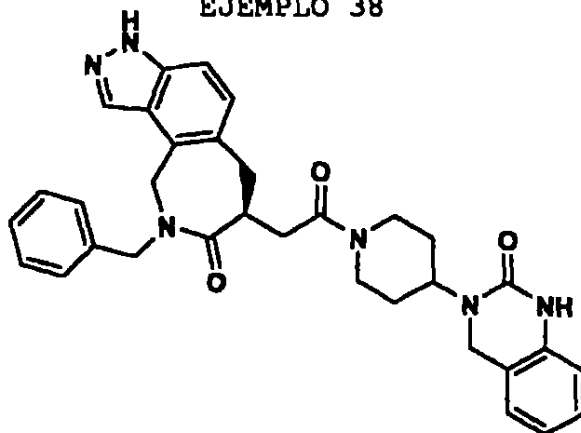
(R)-N-(8-Bencil-7-oxo-1,5,6,7,8,9-hexahidroazepino[4,3-f]indazol-6-il)-4-(2-oxo-1,2-dihidroquinazolin-3(4H)-

15 il)piperidin-1-carboxamida. El 1-acetil-8-bencil-7-oxo-1,5,6,7,8,9-hexahidroazepino[4,3-f]indazol-6-ilcarbamato de (R)-bencilo (52mg, 0.11 mmol) se disolvió en una mezcla de metanol (7 mL) y ácido acético (100 mL). Una cantidad catalítica de paladio en carbono al 10% se agregó a la
20 mezcla. La reacción se colocó en un aparato Parr bajo 60 psi (4.21 Kg/cm²) de gas de hidrógeno. La reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se filtró. El filtrado se concentró. El residuo se disolvió en diclorometano (5 mL). El bicarbonato de sodio acuoso (5 mL)
25 se agregó a la mezcla. El fosgeno al 20% en tolueno (62 µL,

50/509-

0.12 mmol) se agregó a la mezcla con agitación vigorosa. La
reacción se agitó vigorosamente a temperatura ambiente
durante 20 minutos. El acetato de 4-(2-oxo-1,4-dihidro-2H-
quinazolin-3-il)piperidinio se agregó a la mezcla. La
5 reacción se agitó a temperatura ambiente durante 1 hora. Las
capas se dividieron. Los orgánicos se lavaron dos veces con
ácido clorhídrico 1N y una vez con salmuera. La capa orgánica
se secó (sulfato de magnesio), se filtró y se concentró in
vacuo. El residuo se disolvió en metanol (5 mL). El carbonato
10 de potasio (20 mg, 0.14 mmol) se agregó a la mezcla. La
reacción se agitó a temperatura ambiente durante 1 hora. La
reacción se apagó con ácido trifluoroacético. La mezcla se
purificó por CLAR Preparativa. El compuesto del título se
obtiene como un sólido blanco en 11% de rendimiento. EM m/e
15 (M+H)⁺ = 564.3. R_f = 1.89 min.

EJEMPLO 38



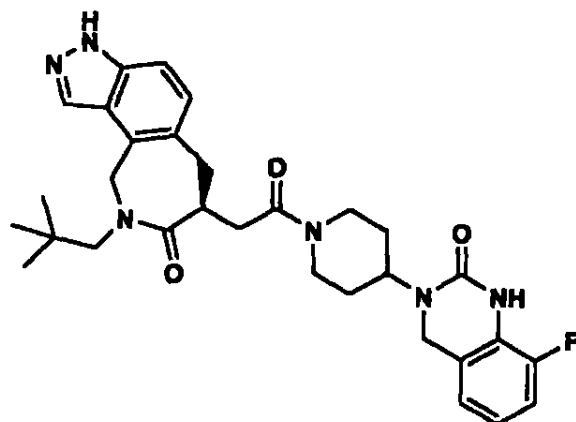
20

(S)-9-Bencil-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinazolin-
25 3(4H)-il)piperidin-1-il)etil)-6,7,9,10-tetrahidroazepin[3,4-

278 505

e]indazol-8(3H)-ona. El compuesto del título se preparó en una manera análoga a la preparación de la 4-cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-
 5 3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material se obtiene como un sólido blanco en 18% de rendimiento. EM m/e (M+H)⁺= 563.1. ¹H RMN (500 MHz, DMSO-D₆): δ= 12.93 (s, 1H), 9.23 (d, J=6.71, 1H), 8.05 (d, J=10.38, 1H), 7.33 (d, J=8.55, 1H), 7.13 (m, 7H), 6.99 (d, J=7.63, 1H), 6.84 (m, 1H), 6.76
 10 (m, 1H), 5.34 (d, J=17.4, 1H), 4.62 (m, 4H), 4.41 (m, 1H), 4.27 (d, J=22.89, 2H), 4.11 (d, J=12.82, 1H), 3.99 (m, 1H), 3.14 (d, J=15.87, 2H), 3.07 (m, 1H), 2.61 (m, 1H), 2.42 (m, 1H), 1.84 (m, 1H), 1.62 (m, 3H).

EJEMPLO 39

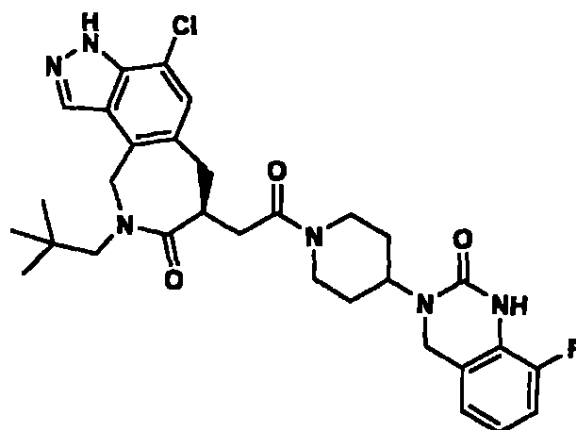


(S)-7-(2-(4-(8-Fluoro-2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-il)-2-oxoetil)-9-neopentil-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El compuesto del
 25 título se preparó en una manera análoga a la preparación de

504 506

9-(2,2-Dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-
2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-
tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El
material se obtiene como un sólido blanco en 35% de
rendimiento. EM m/e (M+H)⁺= 561.3. ¹H RMN (500 MHz, DMSO-D₆):
δ= 13.00 (s, 1H), 9.24 (s, 1H), 8.22 (s, 1H), 7.37 (d,
J=8.54, 1H), 7.11 (d, J=7.63, 7H), 7.05 (m, 1H), 6.94 (m,
1H), 6.88 (m, 1H), 5.38 (d, J=17.09, 1H), 4.62 (d, J=17.09,
1H), 4.51 (m, 1H), 4.40 (m, 1H), 4.35 (s, 2H), 4.10 (d,
J=13.43, 2H), 3.88 (m, 1H), 3.55 (t, J=12.67, 1H), 3.11 (m,
2H), 3.01 (m, 2H), 2.87 (m, 1H), 2.60 (m, 1H) 2.34 (m, 1H),
1.84 (m, 1H), 1.61 (m, 3H), 0.74 (d, J=1 7.70, 9H).

EJEMPLO 40



(S)-4-Cloro-7-(2-(4-(8-fluoro-2-oxo-1,2-
dihidroquinazolin-3(4H)-il)piperidin-1-il)-2-oxoetil)-9-
neopentil-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona.
El compuesto del título se preparó en una manera análoga a la
preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-

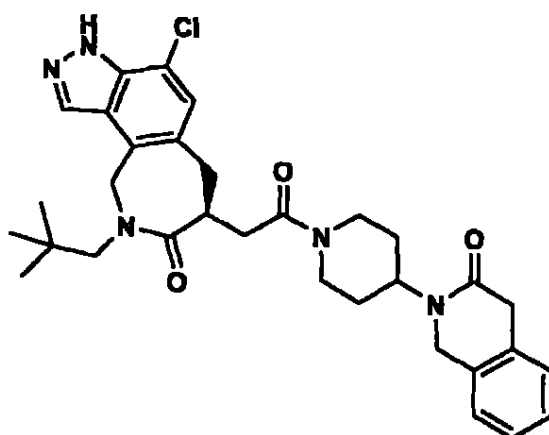
510 507

[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material se obtiene como un sólido blanco en 49% de rendimiento. EM m/e (M+H)⁺= 595.2. ¹H RMN (500 MHz, DMSO-D₆):

5 δ= 13.55 (s, 1H), 9.24 (s, 1H), 8.37 (s, 1H), 7.37 (d, J=8.54, 1H), 7.24 (s, 1H), 7.05 (m, 1H), 6.96 (m, 1H), 6.88 (dd, J₁=12.21, J₂=7.32, 1H), 5.36 (d, J=18.01, 1H), 4.63 (d, J=17.09, 1H), 4.50 (m, 1H), 4.42 (m, 1H), 4.35 (s, 2H), 4.10 (d, J=12.51, 1H), 3.88 (m, 1H), 3.57 (m, 1H), 3.09 (d, J=15.56, 2H), 3.00 (m, 2H), 2.88 (t, J=13.12, 1H), 2.60 (m, 1H) 2.33 (d, J=15.26, 1H), 1.85 (m, 1H), 1.60 (m, 3H), 0.73 (d, J=17.09, 9H).

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EJEMPLO 41



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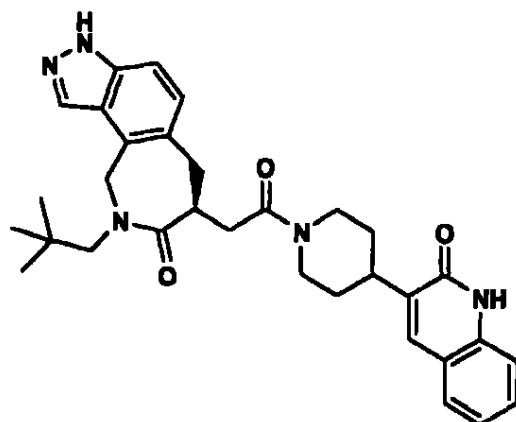
(S)-4-Cloro-9-neopentil-7-(2-oxo-2-(4-(3-oxo-3,4-dihidroisoquinolin-2(1H)-il)piperidin-1-il)etil)-6,7,9,10-tetrahidroazepin[3,4-e]indazol-8(3H)-ona. El compuesto del título se preparó a partir del clorohidrato de 2-(piperidin-4-il)-1,2-dihidroisoquinolin-3(4H)-ona en una manera análoga

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24 508

a la preparación de 4-cloro-9-(2,2-dimetil-propil)-7-(S)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material se obtiene como un sólido amarillo en 35% de rendimiento. EM m/e (M+H)⁺= 576.2. ¹H RMN (500 MHz, DMSO-D₆): δ= 13.55 (s, 1H), 8.37 (s, 1H), 7.29 (s, 1H), 7.23 (dd, J1=1.63, J2= 6.10, 4H), 5.37 (dd, J1=16.48, J2=7.63, 1H), 4.64 (d, J=17.70, 2H), 4.48 (s, 1H), 4.38 (s, 2H), 4.09 (m, 1H), 3.57 (m, 1H), 3.54 (s, 2H), 3.11 (m, 3H), 3.00 (m, 2H), 2.89 (m, 1H), 2.61 (m, 1H), 2.36 (m, 1H), 1.54 (m, 2H), 0.74 (d, J=28.08, 9H).

EJEMPLO 42



(S)-9-Neopentil-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)etil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El compuesto del título se preparó a partir del clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona en una manera análoga a la preparación de la 9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-

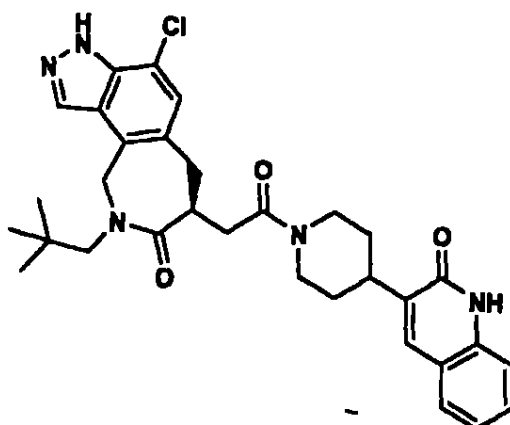
212/509

(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-
6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

El material se obtiene como un sólido blanco en 31% de
rendimiento. EM m/e (M+H)⁺ = 540.2. ¹H RMN (500 MHz, DMSO-D₆):

5 δ = 11.76 (s, 1H), 8.22 (s, 1H), 7.70 (d, J=8.85, 1H), 7.62
(s, 1H), 7.43 (t, J=7.48, 1H), 7.37 (d, J= 8.55, 1H), 7.28
(d, J=8.24, 1H), 7.15 (t, J= 7.32, 1H) 7.11 (d, J=8.55, 1H),
5.38 (d, J=17.09, 1H), 4.62 (d, J=16.79, 1H), 4.55 (d,
J=11.29, 1H), 4.13 (s, 1H), 3.88 (s, 1H), 3.58 (s, 2H), 3.16
10 (m, 2H), 3.07 (m, 3H), 2.88 (t, J=14.34, 1H), 2.64 (m, 1H),
2.36 (m, 1H), 1.92 (d, J=10.38, 1H), 1.84 (d, J= 11.29, 1H),
1.57 (m, 1H), 1.40 (m, 1H), 0.73 (s, 9H).

EJEMPLO 43



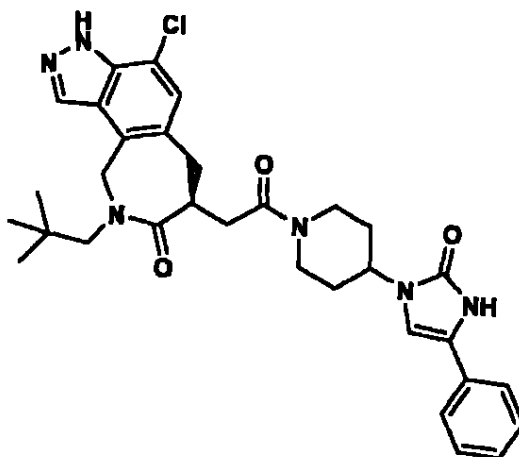
(S)-4-Cloro-9-neopentil-7-(2-oxo-2-(4-(2-oxo-1,2-
dihidroquinolin-3-il)piperidin-1-il)etil)-6,7,9,10-
tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El compuesto del
título se preparó a partir del clorohidrato de 3-(piperidin-
25 4-il)quinolin-2(1H)-ona en una manera análoga a la

510

preparación de la 4-cloro-9-(2,2-dimetil-propil)-7-(S)-(2-
 oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
 il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
 ciclohepta[e]inden-8-ona. El material se obtiene como un
 5 sólido blanco opaco en 46% de rendimiento. EM m/e (M+H)⁺=
 574.2. ¹H RMN (500 MHz, DMSO-D₆): δ= 13.54 (s, 1H), 11.76 (s,
 1H), 8.36 (s, 1H), 7.70 (d, J=5.80, 1H), 7.61 (d, J=7.63,
 1H), 7.43 (t, J=7.63, 1H), 7.28 (d, J=7.93, 1H), 7.24 (s,
 1H), 7.15 (t, J=7.32, 1H), 5.37 (d, J=17.09, 1H), 4.63 (d,
 10 J=16.79, 1H), 4.55 (d, J=12.21, 1H), 4.13 (m, 1H), 3.87 (m,
 1H), 3.58 (d, J=13.12, 1H), 3.15 (m, 2H), 3.03 (m, 3H), 2.88
 (m, 1H), 2.63 (m, 1H), 2.34 (d, J=16.17 1H), 1.91 (d, J=1.22,
 1H), 1.84 (d, J=11.29, 1H), 1.57 (m, 1H), 1.40 (m, 1H), 0.72
 (s, 9H).

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EJEMPLO 44



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(S)-4-Cloro-9-neopentil-7-(2-oxo-2-(4-(2-oxo-4-fenil-
 2,3-dihidroimidazol-1-il)piperidin-1-il)etil)-6,7,9,10-
 25 tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El compuesto del

5/4/51

título se preparó a partir de la 4-fenil-1-(piperidin-4-il)-
1H-imidazol-2(3H)-ona en una manera análoga a la preparación
de la 4-cloro-9-(2,2-dimetil-propil)-7-(S)-(2-oxo-2-[4-(2-
oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-

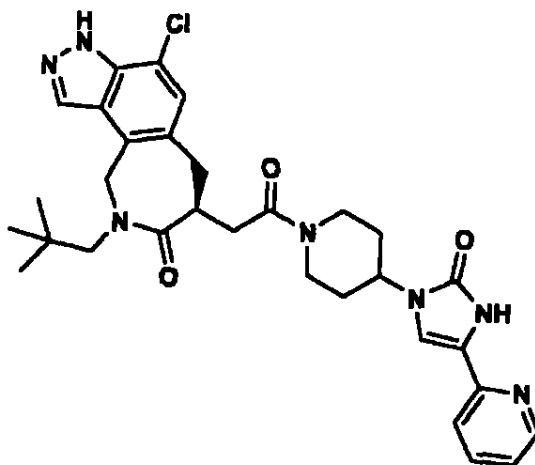
5 6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

El material se obtiene como un sólido blanco en 46% de
rendimiento. EM m/e (M+H)⁺= 589.2. ¹H RMN (500 MHz, DMSO-D₆):

δ= 13.55 (s, 1H), 10.68 (s, 1H), 8.37 (s, 1H), 7.50 (d,
J=7.63, 2H), 7.32 (t, J=7.02, 2H), 7.24 (s, 1H), 7.16 (m,
10 2H), 5.37 (d, J=14.34, 1H), 4.63 (d, J=16.79, 1H), 4.51 (t,
J=10.83, 1H), 4.13 (m, 2H), 3.89 (m, 1H), 3.57 (m, 1H), 3.18
(m, 1H), 3.03 (m, 3H), 2.89 (t, J=15.11, 1H), 2.66 (m, 1H),
2.34 (d, J=16.17 1H), 1.84 (m, 3H), 1.60 (m, 1H), 0.73 (d,
J=13.73, 9H).

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EJEMPLO 45



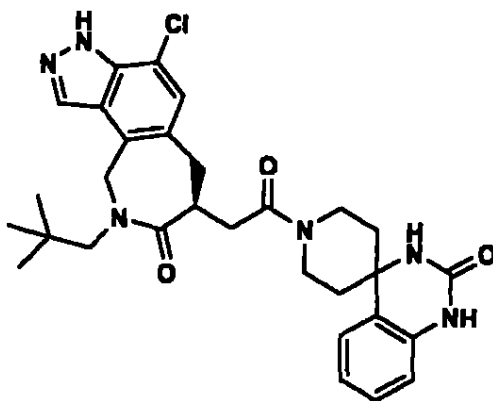
20

(S)-4-Cloro-9-neopentil-7-(2-oxo-2-(4-(2-oxo-4-(piridin-
2-il)-2,3-dihidroimidazol-1-il)piperidin-1-il)etil)-6,7,9,10-
25 tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El compuesto del

512

título se preparó a partir de la 1-(piperidin-4-il)-4-(piridin-2-il)-1H-imidazol-2(3H)-ona en una manera análoga a la preparación de la 4-Cloro-9-(2,2-dimetil-propil)-7(S)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material se obtiene como un sólido blanco en 37% de rendimiento. EM m/e (M+H)⁺= 590.2. ¹H RMN (500 MHz, DMSO-D₆): δ= 13.54 (s, 1H), 10.69 (d, 1H), 8.45 (s, 1H), 8.37 (s, 1H), 7.74 (s, 1H), 7.54 (d, J=8.24, 1H), 7.33 (d, J=4.88, 1H), 7.25 (s, 1H), 7.15 (dd, J₁=6.71, J₂=5.19, 1H), 5.37 (d, J=17.09, 1H), 4.63 (d, J=15.87, 1H), 4.50 (s, 1H), 4.12 (m, 2H), 3.87 (m, 1H), 3.56 (dd, J₁=28.69, J₂=13.43, 1H), 3.18 (t, J=13.73, 1H), 3.10 (d, J=14.65, 1H), 3.01 (m, 2H), 2.88 (t, J=15.26, 1H), 2.66 (m, 1H), 2.35 (d, J=14.95, 1H), 1.84 (m, 3H), 1.57 (m, 1H), 0.73 (d, J=16.17, 9H).

EJEMPLO 46



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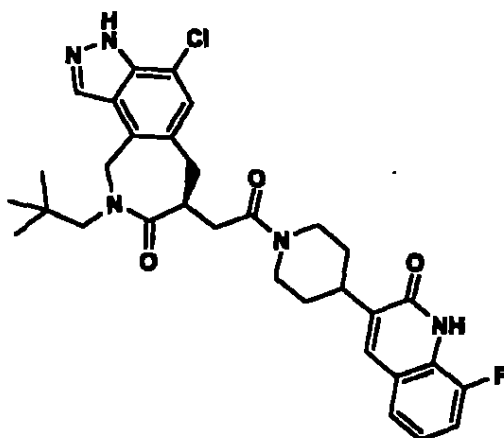
(S)-4-cloro-9-neopentil-7-(2-oxo-2-(4-(2-oxo-1'H-espiro(piperidin-4,4'-quinazolin)etil)-6,7,9,10-

25

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tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El compuesto del título se preparó a partir de la 1'H-espiro(piperidin-4,4')quinazolin)-2'(3'H)-ona en una manera análoga a la preparación de la 4-cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material se obtiene como un sólido blanco en 37% de rendimiento. EM m/e (M+H)⁺= 563.2. ¹H RMN (500 MHz, DMSO-D₆): δ= 13.54 (s, 1H), 9.22 (d, J=10.68, 1H), 8.36 (s, 1H), 7.30 (m, 2H), 7.24 (s, 1H), 7.12 (m, 1H), 6.85 (m, 2H), 5.36 (d, J=16.78, 1H), 4.62 (dd, J₁=16.94, J₂=9.31, 1H), 4.26 (t, J=14.34, 1H), 3.89 (m, 2H), 3.63 (m, 1H), 3.52 (m, 1H), 3.09 (m, 3H), 2.98 (m, 1H), 2.88 (m, 1H), 2.33 (dd, J₁=51.12, J₂= 15.72, 1H), 1.96 (m, 1H), 1.74 (m, 3H), 0.74 (d, J=16.48, 9H).

EJEMPLO 47



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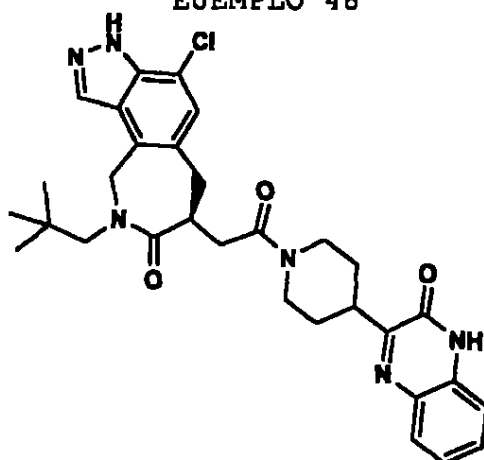
(S)-4-Cloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-9-neopentil-6,7,9,10-

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514

tetrahidroazepin[3,4-e]indazol-8(3H)-ona. El compuesto del título se preparó a partir del clorohidrato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona en una manera análoga a la preparación de la 4-Cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material se obtiene como un sólido blanco en 36% de rendimiento. EM m/e (M+H)⁺ = 592.2. ¹H RMN (500 MHz, DMSO-D₆): δ = 13.54 (s, 1H), 11.78 (s, 1H), 8.36 (s, 1H), 7.76 (d, J=5.19, 1H), 7.46 (d, J=7.93, 1H), 7.34 (dd, J₁=10.53, J₂=8.70, 1H), 7.24 (s, 1H), 7.14 (m, 1H), 5.36 (d, J=16.48, 1H), 4.63 (d, J=17.40, 1H), 4.55 (d, J=11.29, 1H), 4.12 (m, 1H), 3.87 (m, 1H), 3.58 (d, J=13.12, 1H), 3.17 (m, 1H), 3.05 (m, 4H), 2.88 (m, 1H), 2.65 (m, 1H), 2.34 (d, J=15.87, 1H), 1.92 (d, J=12.51, 1H), 1.84 (d, J=11.29, 1H), 1.57 (m, 1H), 1.40 (m, 1H), 0.72 (s, 9H).

EJEMPLO 48



(S)-4-Cloro-9-neopentil-7-(2-oxo-2-(4-(3-oxo-3,4-dihidroquinoxalin-2-il)piperidin-1-il)etil)-6,7,9,10-

tetrahidroazepin[3,4-e]indazol-8(3H)-ona. El compuesto del título se

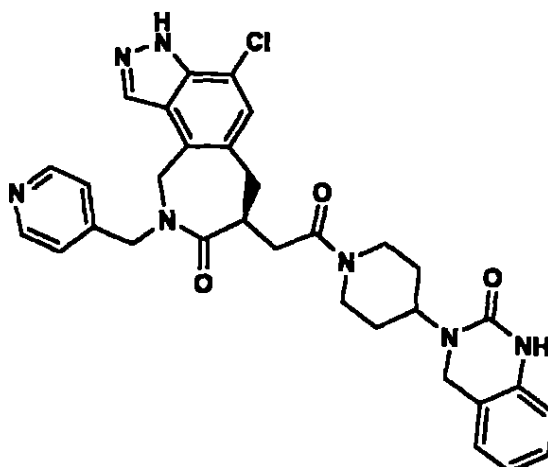
515

preparó a partir del clorohidrato de 3-(piperidin-4-il)quinoxalin-2(1H)-ona en una manera análoga a la preparación de la 4-Cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-

5 ciclohepta[e]inden-8-ona. El material se obtiene como un sólido blanco en 49% de rendimiento. EM m/e (M-H)⁺ = 573.2. ¹H RMN (500 MHz, DMSO-D₆): δ = 13.53 (s, 1H), 12.35 (s, 1H), 8.36 (s, 1H), 7.72 (t, J=8.70, 1H), 7.48 (t, J=7.78, 1H), 7.28 (m, 2H), 7.24 (s, 1H), 5.37 (d, J=17.09, 1H), 4.63 (d, J=17.09, 1H), 4.49 (m, 1H), 4.12 (m, 1H), 3.86 (m, 1H),
10 3.59 (t, J=12.36, 1H), 3.45 (m, 1H), 3.22 (m, 1H), 3.10 (m, 1H), 2.99 (m, 1H), 2.87 (dd, J₁=15.56, J₂=14.34, 1H), 2.72 (m, 1H), 2.36 (m, 1H), 1.96 (d, J=12.82, 1H), 1.89 (d, J=13.12, 1H), 1.70 (m, 1H), 1.52 (m, 1H), 0.72 (s, 9H).

EJEMPLO 49

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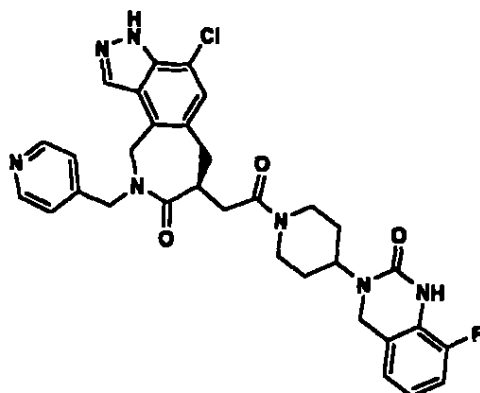
(S)-4-cloro-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-il)etil)-9-(piridin-4-ilmetil)-6,7,9,10-

25 tetrahidroazepin[3,4-e]indazol-8(3H)-ona. El diclorohidrato del ácido

516

(S)-2-(4-cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-hexahidroazepin[3,4-e]indazol-7-il)acético (90 mg, 0.23 mmol) y clorohidrato de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (75 mg, 0.28 mmol) se hacen reaccionar siguiendo un procedimiento análogo a la preparación de la 4-cloro-9-(2,2-dimetil-propil)-7-(S)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 27% de rendimiento. EM m/e (M+H)⁺= 598.2. ¹H RMN (500 MHz, DMSO-D₆): δ= 13.47 (s, 1H), 9.19 (s, 1H), 8.31 (s, 2H), 8.23 (s, 1H), 7.22 (s, 1H), 7.12 (s, 3H), 6.99 (m, 1H), 6.84 (m, 2H), 6.77 (s, 1H), 5.40 (d, J=15.26, 1H), 4.65 (m, 3H), 4.54 (d, J=10.38, 1H), 4.40 (m, 1H), 4.30 (s, 1H), 4.22 (s, 1H), 4.09 (m, 1H), 3.99 (m, 1H), 3.14 (m, 2H), 3.03 (m, 1H), 2.93 (m, 1H), 2.60 (m, 1H), 1.78 (m, 1H), 1.58 (m, 3H).

EJEMPLO 50



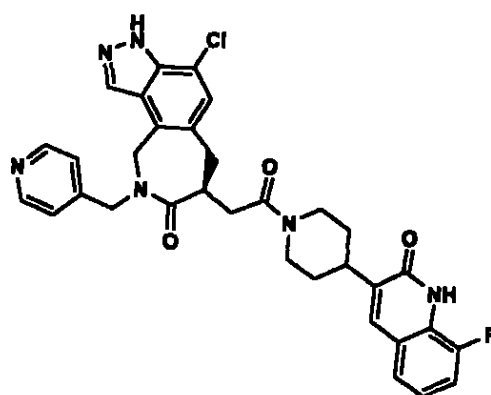
(S)-4-Cloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-il)-oxoetil)-9-(piridin-4-ilmetil)-6,7,9,10-

25 tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El diclorohidrato del ácido

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517

(S)-2-(4-Cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)acético (100 mg, 0.2 mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-il)-3,4-dihidroquinazolin-2(1H)-ona (61 mg, 0.2 mmol) se hacen reaccionar en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 16% de rendimiento. EM m/e (M+H)⁺ = 616.2. ¹H RMN (500 MHz, DMSO-D₆): δ = 13.46 (s, 1H), 9.23 (d, J=6.41, 1H), 8.31 (m, 2H), 8.24 (d, J=6.10, 1H), 7.22 (s, 1H), 7.13 (dd, J7=9.46, J2=4.88, 2H), 7.05 (m, 1H), 6.91 (m, 1H), 6.85 (s, 1H), 5.40 (d, J=17.09, 1H), 4.66 (m, 3H), 4.54 (d, J=11.90, 1H), 4.41 (m, 1H), 4.36 (s, 1H), 4.28 (d, J=4.58, 1H), 4.10 (d, J=12.51, 1H), 4.00 (m, 1H), 3.17 (m, 2H), 3.04 (m, 1H), 2.94 (m, 1H), 2.62 (d, J=11.29, 1H), 2.43 (m, 1H), 1.83 (m, 1H), 1.62 (m, 3H).

EJEMPLO 51



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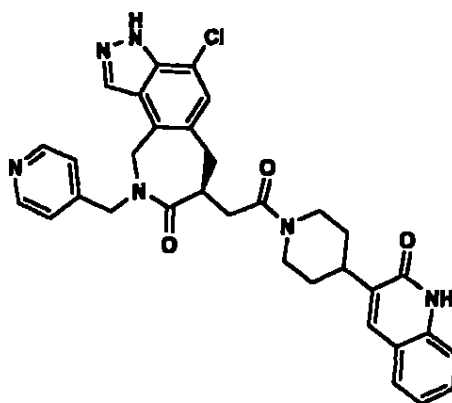
(S)-4-Cloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-9-(piridin-4-ilmetil)-6,7,9,10-

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51a

tetrahidroazepino[3.4-e]indazol-8(3H)-ona. Diclorohidrato del ácido
(S)-2-(4-Cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-il)acético (100 mg, 0.22 mmol) y
acetato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona (90 mg, 0.29
5 mmol) se hacen reaccionar siguiendo un procedimiento análogo a la
preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-
1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-
tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del
título se obtiene como un sólido color canela en 13% de rendimiento. EM
10 m/e (M+H)⁺ = 613.3. ¹H RMN (500 MHz, DMSO-D₆): δ= 13.46 (s, 1H), 11.78
(s, 1H), 8.30 (s, 2H), 8.23 (s, 1H), 7.75 (d, J=19.53, 1H), 7.45 (m,
1H), 7.34 (m, 1H), 7.21 (s, 1H), 7.12 (m, 3H), 5.40 (d, J=16.48, 1H),
4.64 (m, 4H), 4.13 (d, J=12.82, 1H), 4.00 (m, 1H), 3.17 (m, 2H), 3.04 (m,
2H), 2.94 (m, 1H), 2.67 (m, 1H), 2.44 (m, 1H), 1.94 (m, 1H), 1.86 (m,
15 1H), 1.57 (m, 1H), 1.42 (m, 1H).

EJEMPLO 52



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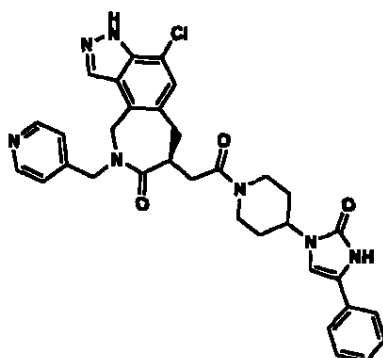
(S)-4-Cloro-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-
25 il)piperidin-1-il)etil)-9-(piridin-4-ilmetil)-6,7,9,10-

572
519

tetrahidroazepino[3,4-e]indazol-8(3H)-ona. Diclorohidrato del ácido
(S)-2-(4-Cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-il)acético (100 mg, 0.23 mmol) y 3-
(piperidin-4-il)quinolin-2(1H)-ona (55 mg, 0.24 mmol) se hacen
5 reaccionar siguiendo un procedimiento análogo a la preparación de 4-
Cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-
quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-
triazza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene
como un sólido blanco en 41% de rendimiento. EM m/e (M+H)⁺ = 595.2. ¹H
10 RMN (500 MHz. DMSO-D₆): δ= 13.46 (s, 1H), 11.76 (s, 1H), 8.30 (d,
J=5.19, 2H), 8.23 (s, 1H), 7.69 (d, J=19.84, 1H), 7.62 (m, 1H), 7.44
(m, 1H), 7.28 (d, J=7.93, 1H), 7.21 (s, 1H), 7.14 (m, 3H), 5.40 (d,
J=17.09, 1H), 4.65 (m, 3H), 4.13 (d, J=13.43, 1H), 4.01 (m, 1H), 3.17
(d, J=14.95, 2H), 3.04 (m, 2H), 2.94 (m, 1H), 2.66 (m, 1H), 2.45 (m,
15 2H), 1.93 (d, J=11.60, 1H), 1.85 (d, J=12.82, 1H), 1.56 (m, 1H), 1.41
(m, 1H).

EJEMPLO 53

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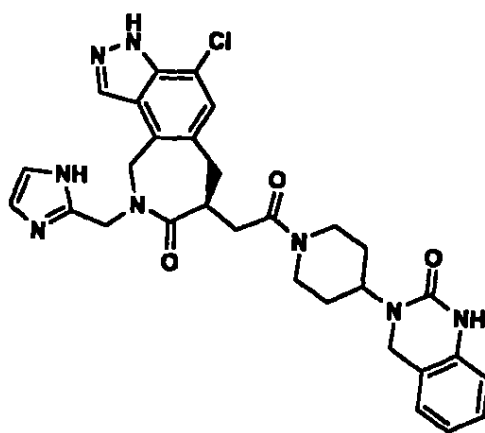


(S)-4-Cloro-7-(2-oxo-2-(4-(2-oxo-4-fenil-2,3-dihidroimidazol-1-
25 il)piperidin-1-il)etil)-9-(piridin-4-ilmetil)-6,7,9,10-

520

tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El diclorohidrato del ácido
(S)-2-(4-Cloro-8-oxo-9-(piridin-4-ilmetil)-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-il)acético (100 mg, 0.23 mmol) y 4-
fenil-1-(piperidin-4-il)-1H-imidazol-2(3H)-ona (60 mg, 0.28 mmol) se
5 hacen reaccionar siguiendo un procedimiento análogo a la preparación de
4-Cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-
quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-
triazaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene
como un sólido blanco en 30% de rendimiento. EM m/e (M+H)⁺= 610.3. ¹H
10 RMN (500 MHz, DMSO-D₆): δ= 13.46 (s, 1H), 10.68 (d, J=4.27, 1H), 8.30
(d, J=3.97, 2H), 8.23 (s, 1H), 7.50 (d, J=7.93, 1H), 7.45 (d, J=7.63,
1H), 7.31 (m, 2H), 7.22 (s, 1H), 7.14 (m, 4H), 5.41 (d, J=16.78, 1H),
4.66 (m, 3H), 4.55 (m, 1H), 4.13 (m, 2H), 3.99 (m, 1H), 3.33 (m, 1H),
3.18 (m, 1H), 3.05 (dd, J₁=16.02, J₂=8.70, 1H), 2.94 (m, 1H), 2.68 (m,
15 1H), 2.44 (m, 1H), 1.81 (m, 3H), 1.62 (m, 1H).

EJEMPLO 54



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(S)-9-((1H-Imidazol-2-il)metil)-4-cloro-7-(2-oxo-2-(4-
25 (2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-il)etil)-

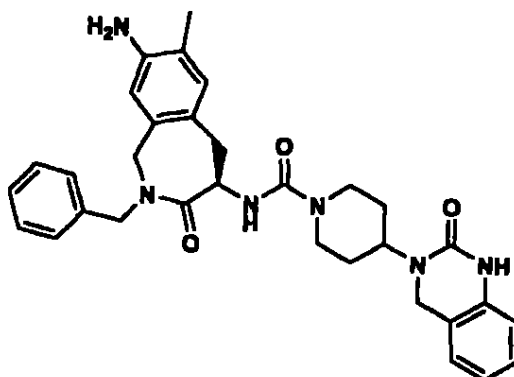
267
521

6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. 2-(9-
(1H-imidazol-2-il)metil)-4-cloro-8-oxo-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-il)acetato de (S)-Metilo (58
mg, 0.15 mmol) se disolvió en una mezcla que contiene metanol
5 (2 mL), tetrahidrofurano (2 mL), y agua (2 mL). El
monohidrato de hidróxido de litio (20 mg, 0.48 mmol) se
agregó a la mezcla. La reacción se agitó a temperatura
ambiente durante 15 horas. La reacción se apagó con ácido
clorhídrico 1N (0.5 mL). La mezcla se concentró in vacuo. El
10 residuo se disolvió en DMF (2 mL). La N,N-
Diisopropiletilamina se agregó a la mezcla seguido por
tetrafluoroborato de o-Benzotriazol-1-il-N,N,N',N'-
tetrametiluronio (60 mg, 0.19 mmol). La mezcla se agitó a
temperatura ambiente durante 30 minutos. El clorohidrato de
15 4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (50 mg,
0.19 mmol) se agregó a la mezcla. La reacción se agitó a
temperatura ambiente durante 3 horas. La mezcla de reacción
se purificó por CLAR preparatoria. La fracciones deseadas se
identificaron. El acetonitrilo se removió de las fracciones
20 in vacuo. El acuoso restante se hizo básico con bicarbonato
de sodio. La mezcla se extrajo dos veces con acetato de
etilo. Los extractos combinados se secaron (sulfato de
magnesio), se filtraron y se concentraron in vacuo. El
compuesto del título se obtiene como un sólido blanco en 28%
25 de rendimiento. EM m/e (M+H)⁺ = 587.2. ¹H RMN (500 MHz, DMSO-

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D₆): δ = 13.46 (s, 1H), 11.75 (s, 1H), 9.20 (s, 1H), 8.14 (s, 1H), 7.19 (s, 1H), 7.12 (m, 2H), 6.84 (m, 2H), 6.77 (d, J=7.93, 1H), 5.23 (d, J=15.16, 1H), 4.76 (m, 1H), 4.69 (dd, J₁=15.26, J₂=5.19, 1H), 4.53 (d, J=13.43, 1H), 4.47 (d, J=15.26, 1H), 4.40 (m, 1H), 4.29 (d, J=3.97, 2H), 4.08 (m, 1H), 3.89 (d, J=9.77, 1H), 3.15 (m, 2H), 3.00 (m, 1H), 2.91 (m, 3H), 2.60 (m, 1H), 2.44 (m, 2H), 1.80 (m, 1H), 1.60 (m, 3H).

EJEMPLO 55



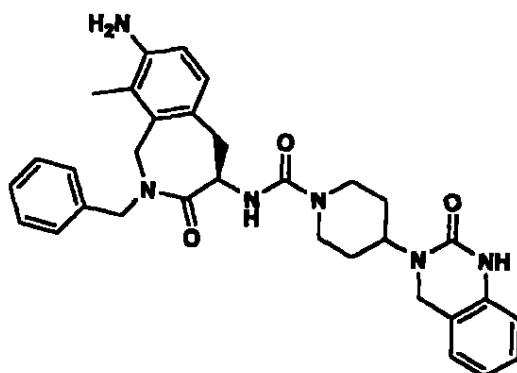
Trifluoroacetato de (R)-N-(8-amino-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-carboxamida. La (R)-N-(8-Amino-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-carboxamida (95 mg, 0.15 mmol) se disolvió en diclorometano (2 mL). El ácido trifluoroacético (1 mL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 1 hora. La mezcla se concentró in vacuo. El residuo se purificó por CLAR preparatoria. El solvente se

523

lío filizo de las fracciones apropiadas. El compuesto del título se obtiene como un sólido blanco en 64% de rendimiento. EM m/e (M+H)⁺ = 553.

EJEMPLO 56

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Trifluoroacetato de (R)-N-(8-Amino-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-1H-benzo[c]azepin-4-il)-4-(2-oxo-1,2-dihidroquinazolin-3(4H)-

15 il)piperidina-1-carboxamida. El 2-bencil-9-metil-3-oxo-4-(4-(2-oxo-1,2-dihidroquinazolin-3(4H)-

il)piperidín-1-carboxamido)-2,3,4,5-tetrahidro-1H-benzo[c]azepin-8-ilcarbamato de (R)-tert-butilo se hace reaccionar en una manera análoga con la

20 preparación de trifluoroacetato de (R)-N-(8-amino-2-bencil-7-metil-3-oxo-2,3,4,5-tetrahidro-1H-

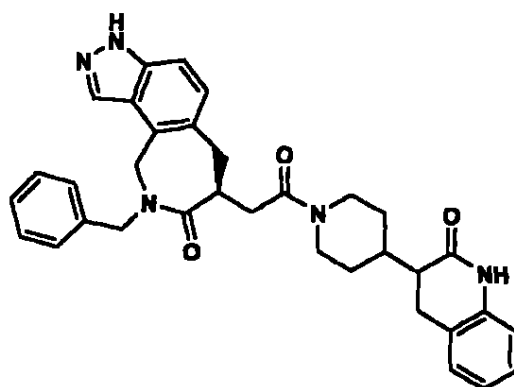
benzo[c]azepin-4-il)-4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidín-1-carboxamida. El compuesto del

título se obtiene como un sólido blanco opaco en 31% de rendimiento. EM m/e (M+H)⁺ = 553.

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EJEMPLO 57



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N-((R)-9-Bencil-8-oxo-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)-4-(2-oxo-1,2,3,4-tetrahidroquinolin-3-il)piperidin-1-carboxamida. El ácido (S)-2-(9-Bencil-8-oxo-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)acético (80 mg, 0.24 mmol) y 3-(piperidin-4-il)-3,4-dihidroquinolin-2(1H)-ona (75 mg, 0.33 mmol) se hacen reaccionar en una

15 manera análoga a la preparación de 4-Cloro-9-(2,2-dimetilpropil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material se obtiene como un sólido blanco en 33% de rendimiento. EM m/e (M+H)⁺ =

20 542.3. ¹H RMN (500 MHz, DMSO-D₆): δ= 13.01 (s, 1H), 10.11 (s, 1H), 8.21 (s, 1H), 7.36 (d, J=7.93, 1H), 7.17 (m, 1H), 7.11 (m, 2H), 6.91 (m, 1H), 6.83 (d, J=7.63, 1H), 5.35 (d, J=17.09, 1H), 4.61 (d, J=17.40, 1H), 4.38 (m, 1H), 4.02 (m, 1H), 3.83 (s, 1H), 3.55 (t, J=12.36, 1H), 2.95 (m, 6H), 2.79 (m,

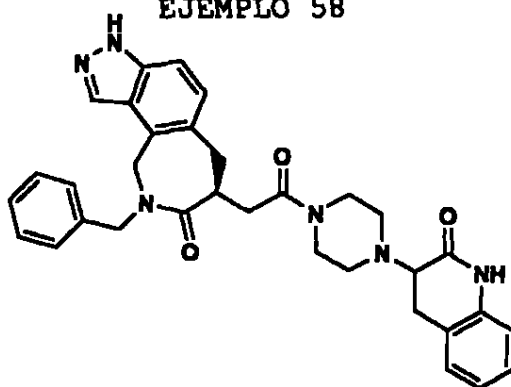
25 1H), 2.42 (m, 1H), 2.31 (m, 2H), 1.90 (m, 1H), 1.63 (m, 2H),

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1.17 (m, 1H), 0.72 (d, J=9.77, 9H).

EJEMPLO 58

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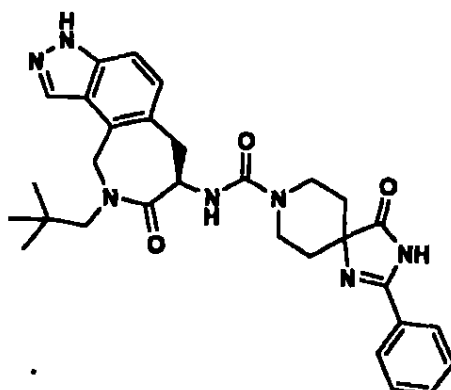


(7S)-9-Bencil-7-(2-oxo-2-(4-(2-oxo-1,2,3,4-
10 tetrahydroquinolin-3-il)piperazin-1-il)etil)-6,7,9,10-
tetrahidroazepino[2,4-e]indazol-8(3H)-ona. El ácido (S)-2-(9-
bencil-8-oxo-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-
il)acético (80 mg, 0.24 mmol) y 3-(piperazin-1-il)-3,4-
dihidroquinolin-2(1H)-ona (75 mg, 0.32 mmol) se hacen
15 reaccionar en una manera análoga a la preparación de 4-cloro-
9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-
2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-
tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El
material se obtiene como un sólido blanco en 21% de
20 rendimiento. EM m/e (M+H)⁺ = 543.3. ¹H RMN (500 MHz, DMSO-D₆):
δ= 13.01 (s, 1H), 10.13 (s, 1H), 8.21 (s, 1H), 7.36 (d,
J=8.54, 1H), 7.19 (d, J=7.02, 1H), 7.11 (m, 2H), 6.90 (t,
J=7.32, 1H), 6.82 (d, J=7.93, 1H), 5.36 (d, J=17.40, 1H), 4.61
(d, J=17.09, 1H), 3.84 (m, 1H), 3.57 (d, J=13.12, 1H), 3.47
25 (m, 2H), 3.38 (m, 1H), 3.32 (m, 1H), 3.09 (m, 1H), 3.02 (d,

526

J=14.04, 1H), 2.985 (m, 2H), 2.85 (m, 1H), 2.75 (m, 1H), 2.65 (m, 3H), 2.50 (m, 2H), 2.31 (d, J=16.48, 1H), 0.71 (s, 9H).

EJEMPLO 59



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[(R)-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il]-amida del ácido 4-oxo-2-fenil-1,3,8-triaza-spiro[4.5]dec-1-ene-8-carboxílico. El trifluoroacetato de 2-Fenil-1,3,8-triaza-spiro[4.5]dec-1-en-4-ona (55 mg, 0.16 mmol) y (R)-7-amino-9-neopentil-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona (40 mg, 0.14 mmol) se hacen reaccionar en una manera análoga a la preparación de [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. La CLAR preparatoria C18 proporciona el compuesto del título como un sólido blanco en 25% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 542.2888.

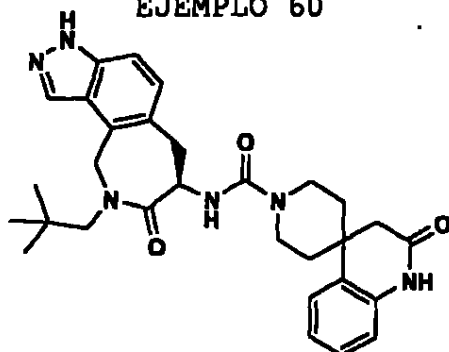
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EJEMPLO 60



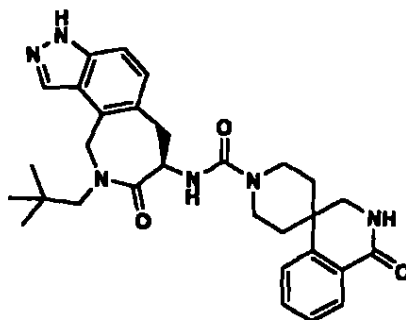
5

[(R)-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il]-amida del ácido espiro[2,3-dihidro-1H-quinolina-2-ona-4(1H),4'-piperidina]-1'-carboxílico. La espiro[2,3-dihidro-1H-quinolina-2-ona-4(1H),4'-piperidina] (32 mg, 0.15 mmol) y (R)-7-amino-9-neopentil-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona (35 mg, 0.12 mmol) se hacen reaccionar en una manera análoga a la preparación de [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. La CLAR preparatoria C18 proporciona el compuesto del título como un sólido blanco en 46% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 529.2924.

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EJEMPLO 61



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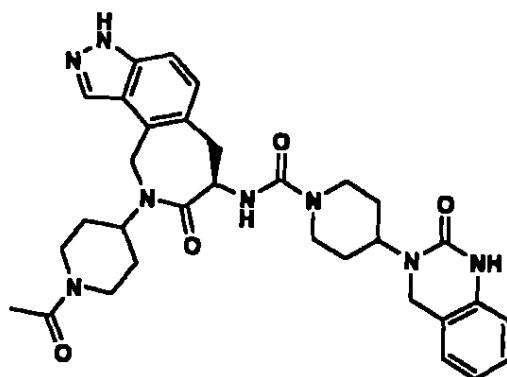
[(R)-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-

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778

hexahidro-2,3,9-triaza-ciclohepta[e]inden-7-il]-amida del
ácido espiro[2,3-dihidro-1H-isoquinolina-1-ona-
4(1H),4'piperidina]-1'-carboxílico. La espiro[2,3-dihidro-1H-
isoquinolina-1-ona-4(1H),4'piperidina] (32 mg, 0.15 mmol) y
5 (R)-7-amino-9-neopentil-6,7,9,10-tetrahidroazepino[3,4-
e]indazol-8(3H)-ona (35 mg, 0.12 mmol) se hacen reaccionar en
una manera análoga a la preparación de [8-oxo-9-(2-piperidin-
1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-
ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-
10 dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. La CLAR
preparatoria C18 proporciona el compuesto del título como un
sólido blanco en 41% de rendimiento. Alta resolución EM m/e
(M+H)⁺ = 529.2927.

EJEMPLO 62

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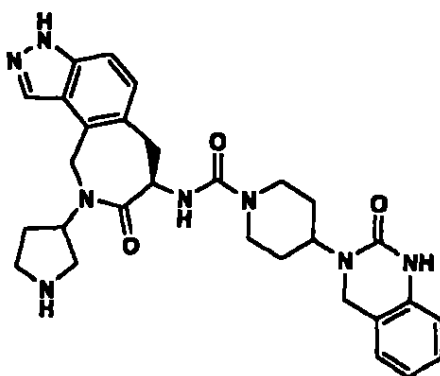
(R)-N-(9-(1-acetilpiperidin-4-il)-8-oxo-3,6,7,8,9,10-
hexahidroazepino[3,4-e]indazol-7-il)-4-(2-oxo-1,2-
dihidroquinazolin-3(4H)-il)piperidina-1-carboxamida. El
25 matansulfonato de (R)-9-(1-acetilpiperidin-4-il)-7-amino-

529
152

6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona (42 mg, 0.08 mmol) y acetato de 3-(piperidin-4-il)-3,4-dihidroquinazolin-2(1H)-ona (30 mg, 0.10 mmol) se hacen reaccionar en una manera análoga a la preparación de [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidina-1-carboxílico. La CLAR preparatoria C18 proporciona el compuesto del título como un sólido blanco en 28% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 599.3085.

EJEMPLO 63

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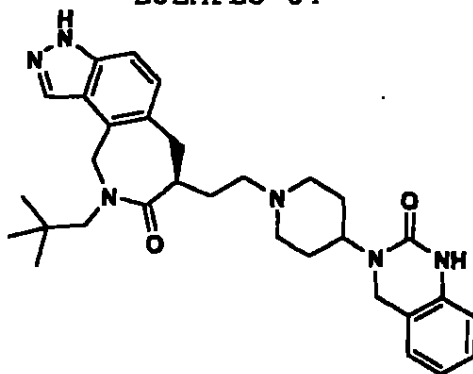


4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)-N-((R)-8-oxo-9-(pirrolidin-3-il)-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)piperidina-1-carboxamida. El 4-(8-oxo-7-(4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidina-1-carboxamido)-7,8-dihidroazepino[3,4-e]indazol-9(3H,6H,10H)-il)piperidina-1-carboxilato de (R)-tert-butilo (45 mg, 0.06 mmol) se disolvió en diclorometano (1 mL). El ácido trifluoroacético

538
47

(0.25 mL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 1.5 hora. La mezcla de reacción se concentró in vacuo. La purificación por CLAR preparatoria C18 proporciona el compuesto del título como un sólido amarillo en 52% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 543.2830.

EJEMPLO 64



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(S)-9-neopentil-7-(2-(4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-il)etil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. La (S)-7-(2-hidroxietil)-9-neopentil-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona (15 mg, 0.04 mmol) se disolvió en diclorometano (1 mL). El cloruro de tionilo (100 mL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 2 horas. El cloruro de tionilo (500 uL) se agregó a la mezcla. La reacción se agitó a temperatura ambiente durante 2 horas y luego se calentó hasta reflujo durante 2 horas. La mezcla de reacción se concentró in vacuo. El residuo se disolvió en acetonitrilo (1 mL). El carbonato de potasio (25 mg, 0.18 mmol) se agregó a la mezcla

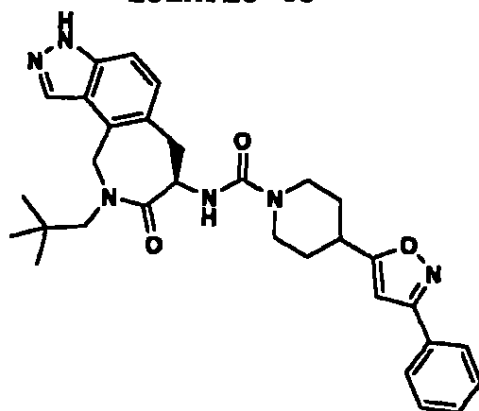
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seguido por 3-(piperidin-4-il)-3,4-dihidroquinazolin-2(1H)-
ona (16 mg, 0.07 mmol). La reacción se calentó a reflujo
durante 2 horas. La purificación por CLAR preparatoria
proporciona el compuesto del título como un sólido blanco en
5 25% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 529.3282.

EJEMPLO 65

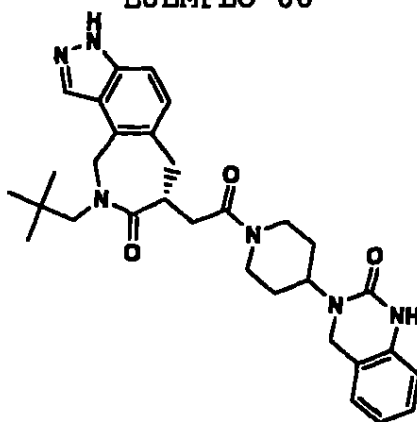


10

(R)-N-(9-neopentil-8-oxo-3,6,7,8,9,10-
15 hexahidroazepino[3,4-e]indazol-7-il)-4-(3-fenilisoxazol-5-
il)piperidina-1-carboxamida. La 4-(3-Fenilisoxazol-5-
il)piperidina (46 mg, 0.20 mmol) y (R)-7-amino-9-neopentil-
6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona (110 mg,
0.22 mmol) se hacen reaccionar en una manera análoga a la
20 preparación de [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-
hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del
ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
carboxílico. La CLAR preparatoria C18 proporciona el
compuesto del título como un sólido color canela en 33% de
25 rendimiento. Alta resolución EM m/e (M+N)⁺ = 541.2916.

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EJEMPLO 66



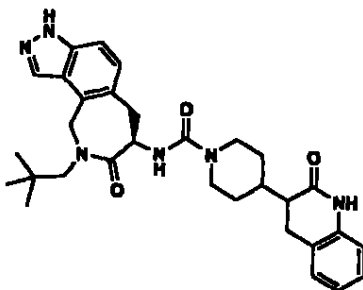
5

9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-acético (75 mg, 0.23 mmol) y 4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (65 mg, 0.28 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 32% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 543.3084.

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EJEMPLO 67



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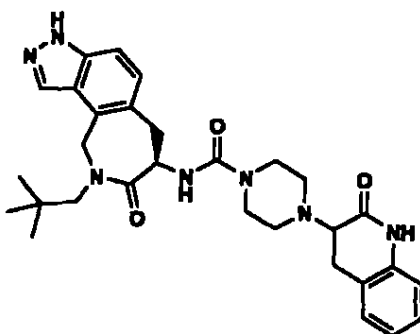
25

N-((R)-9-neopentil-8-oxo-3,6,7,8,9,10-

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hexahidroazepino[3,4-e]indazol-7-il)-4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-il)piperidin-1-carboxamida. La 3-(piperidin-4-il)-3,4-dihidroquinolin-2(1H)-ona (50 mg, 0.22 mmol) y (R)-7-amino-9-neopentil-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-ona (110 mg, 0.22 mmol) se hacen reaccionar m una manera análoga a la preparación de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílicoacid[8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida. La CLAR preparatoria C18 proporciona el compuesto del título como un sólido blanco opaco en 25% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 543.3084.

EJEMPLO 68



N-((R)-9-Neopentil-8-oxo-3,6,7,8,9,10-

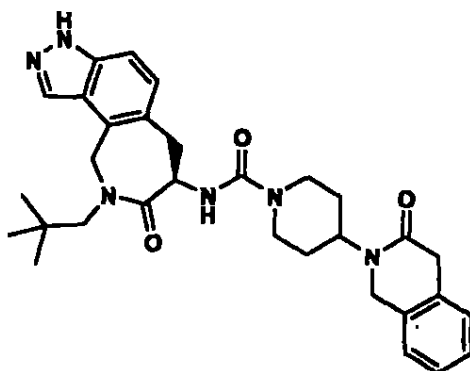
hexahidroazepino[3,4-e]indazol-7-il)-4-(2-oxo-1,2,3,4-tetrahydroquinolin-3-il)piperazina-1-carboxamida. La 3-(Piperazin-1-il)-3,4-dihidroquinolin-2(1H)-ona (45 mg, 0.19 mmol) y (R)-7-amino-9-neopentil-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-ona (75 mg, 0.15 mmol) se hacen reaccionar en una manera análoga a la preparación de

534 ✓

la [8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-
2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-
(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
carboxílico. La CLAR preparatoria C18 proporciona el
5 compuesto del título como un sólido blanco en 17% de
rendimiento. Alta resolución EM m/e (M+H)⁺ = 544.3022.

EJEMPLO 69

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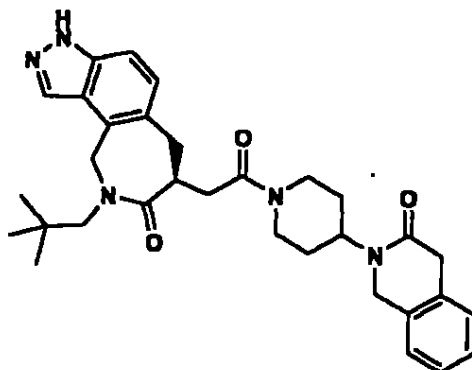


(R)-N-(9-Neopentil-8-oxo-3,6,7,8,9,10-
15 hexahidrozepino[3,4-e]indazol-7-il)-4-(3-oxo-3,4-
dihidroisoquinolin-2(1H)-il)piperidina-1-carboxamida. La 2-
(Piperidin-4-il)-1,2-dihidroisoquinolin-3(4H)-ona (60 mg,
0.26 mmol) y (R)-7-amino-9-neopentil-6,7,9,10-
tetrahidrozepino[3,4-e]indazol-8(3H)-ona (100mg, 0.20 mmol)
20 se hacen reaccionar en una manera análoga a la preparación de
[8-oxo-9-(2-piperidin-1-il-etil)-3,6,7,8,9,10-hexahidro-
2,3,9-triaza-(R)-ciclohepta[e]inden-7-il]-amida del ácido 4-
(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-
carboxílico. La CLAR preparatoria C18 proporciona el
25 compuesto del título como un sólido amarillo en 29% de

535

rendimiento. Alta resolución EM m/e (M+H)⁺ = 543.3074.

EJEMPLO 70



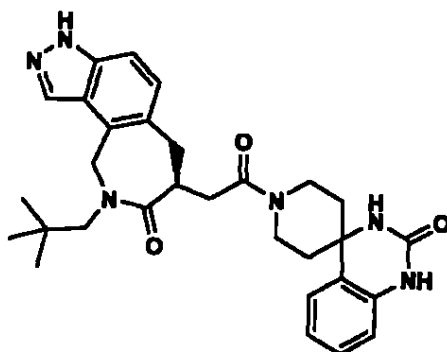
(S)-9-Neopentil-7-(2-oxo-2-(4-(3-oxo-3,4-dihidroisoquinolin-2(1H)-il)piperidin-1-il)etil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona.

La 2-(Piperidin-4-il)-1,2-dihidroisoquinolin-3(4H)-ona (105 mg, 0.46 mmol) y el ácido [9-(2,2-dimetilpropil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (110 mg, 0.33 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetilpropil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

El compuesto del título se obtiene como un sólido blanco in 40% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 541.3111.

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TMC

EJEMPLO 71



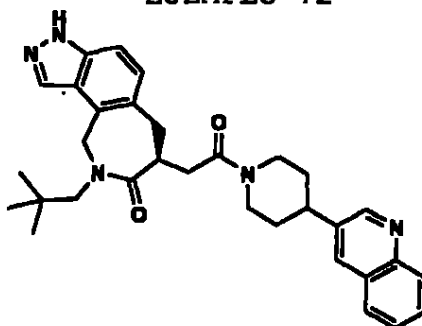
1-[[7-(S)-9-Dimetilpropil]-3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]indazol-7-il]acetil]-spiro[piperidin-4,4' (1'H)-

10 quinazolin]-2' (3'H)-ona. El clorohidrato de espiro[piperidin-4,4' (1'H)-quinazolin]-2' (3'H)-ona (50 mg, 0.20 mmol) y el ácido [9-(2,2-dimetilpropil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-

ciclohepta[e]inden-7-il]acético (55 mg, 0.17 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetilpropil)-7-

15 (R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco opaco en 35% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 529.2921.

EJEMPLO 72



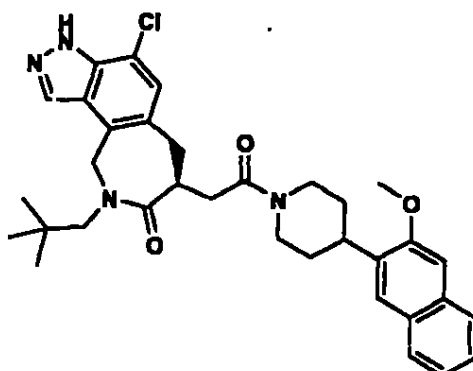
25 1-[[7-(S)-9-Dimetilpropil]-3,6,7,8,9,10-hexahidro-8-

537
240

oxoazepino[3,4-e]indazol-7-il]acetil]-4-(3-quinolinil)piperidina. La 3-(piperidin-4-il)quinolina (75 mg, 0.35 mmol) y el ácido [9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (95 mg, 0.29 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco opaco en 50% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 522.2878.

EJEMPLO 73

15



20 1-[[7-(S)-4-cloro-9-(2,2-Dimetilpropil)-3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]indazol-7-il]acetil]-4-(3-metoxi-2-naftalenil)piperidina. El clorohidrato de 4-(3-metoxinaftalen-2-il)piperidina (78 mg, 0.28 mmol) y ácido [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (88 mg, 0.24

25

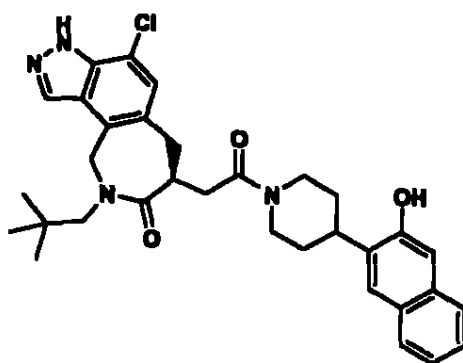
538 JH

mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4--(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El

5 compuesto del título se obtiene como un sólido color canela en 88% de rendimiento. Una muestra analítica se preparó por CLAR preparatoria C18 da un sólido blanco con 30% de recubrimiento. Alta resolución EM m/e (M+H)⁺ = 587.2791.

EJEMPLO 74

10



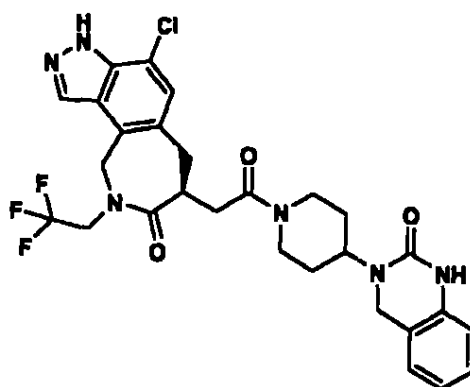
15

1-[[7-(s)-4-cloro-9-(2,2-Dimetilpropil)-3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]indazol-7-il]acetil]-4-(3-hidroxi-2-naftalenil)piperidina. Una solución 1M de
20 tribromuro de boro en diclorometano (580 aL, 0.58 mmol) se agregó a una solución de 1-[[7-(S)-4-cloro-9-(2,2-dimetilpropil)-3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]indazol-7-il]acetil]-4-(3-metoxi-2-naftalenil)piperidina (78 mg, 0.13 mmol) en diclorometano (3 mL). La reacción se
25 agitó a temperatura ambiente durante 4 horas. El tribromuro

539 ✓

de boro 1M en diclorometano (500 μ L, 0.5 mmol) se agregó a la
mezcla. La reacción se agitó a temperatura ambiente durante
30 minutos. La mezcla de reacción se concentró in vacuo. El
residuo se purificó por La CLAR preparatoria C18. El pico
5 mayor se aisló. El metanol se removió de las fracciones
combinadas in vacuo. El acuoso restante se extrajo con
acetato de etilo (30 mL). La capa orgánica se lavó con
bicarbonato de sodio acuoso (2x15 mL). El orgánico se secó
(sulfato de magnesio), se filtró y se concentró in vacuo. El
10 compuesto del título se obtiene como un sólido color canela
en 37% de rendimiento. Alta resolución EM m/e (M+H)⁺ =
573.2636.

EJEMPLO 75



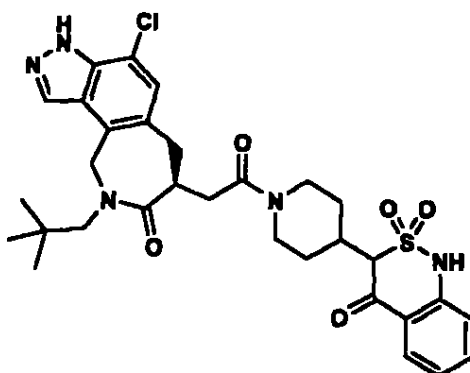
20

1-[[[(7S)-4-Cloro-3,6,7,8,9,10-hexahidro-8-oxo-9-
trifluoroetil)azepino[3,4-e]indazol-7-il]acetil]-4-(1,4-
dihidro-2-oxo-3(2H)-quinazolinil)-piperidina. El ácido [4-
Cloro-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-
25 2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (105 mg,

540
✓

0.28 mmol) y el clorohidrato de 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)piperidina (85 mg, 0.32 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido amarillo pálido en 58% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 589.1932.

EJEMPLO 76



1-[[7-(S)-cloro-9-(2,2-Dimetilpropil)-3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]imidazol-7-il]acetil]-4-(3,4-dihidro-2,2-dioxido-4-oxo-1H-2,1-benzotiazin-3-il)piperidina.

La 2,2-Dioxo-3-piperidin-4-il-2,3-dihidro-1H-2,1-benzotiazin-4-ona (86 mg, 0.27 mmol) y ácido [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-

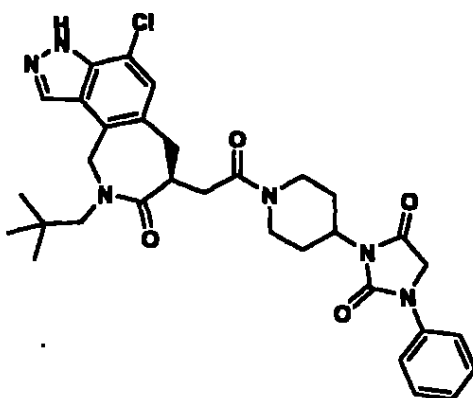
ciclohepta[e]inden-7-il]acético (85 mg, 0.23 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-

9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-

54b
S(14)

2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido color canela en 37% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 626.2217.

EJEMPLO 77



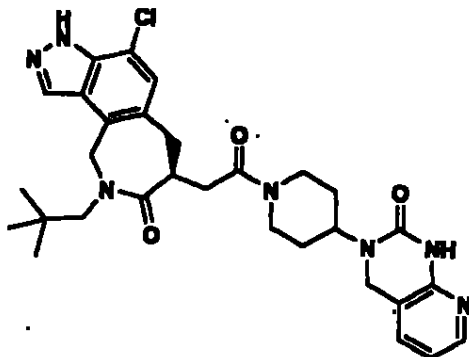
1-[[7-(S)-4-cloro-9-(2,2-Dimetilpropil)-3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]indazol-7-il]acetil]-4-(2,5-dioxo-3-fenil-1-imidazolidinil)piperidina. El clorohidrato de 5-Fenil-3-(piperidin-4-il)imidazolidina-2,4-diona (46 mg, 0.16 mmol) y ácido [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (46 mg, 0.13 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido amarillo en 67% de rendimiento. Alta

542

resolución EM m/e (M+H)⁺ = 605.2645.

EJEMPLO 78

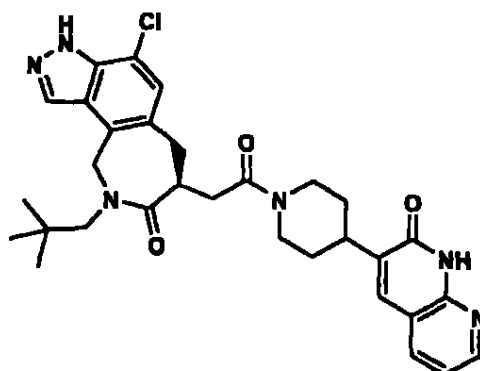
5



10 1-[[7-(S)-cloro-9-(2,2-Dimetilpropil)-
3,6,7,8,9,10-hexahidro-9-oxoazepino[3,4-e]indazol-7-
il]acetil]-4-(1,4-dihidro-2-oxopirido[2,3-
d]pirimidin-3(2H)-il)-piperidina. El diclorohidrato
de 3-(Piperidin-4-il)-3,4-dihidropirido[2,3-
15 d]pirimidin-2(1H)-ona (64 mg, 0.21 mmol) y ácido [4-
cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-
hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-
il]acético (63 mg, 0.17 mmol) se combinaron en una
manera análoga a la preparación de 4-Cloro-9-(2,2-
20 dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-
2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-
tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.
El compuesto del título se obtiene como un sólido
blanco en 41% de rendimiento. Alta resolución EM m/e
25 (M+H)⁺ = 578.2630.

543

EJEMPLO 79



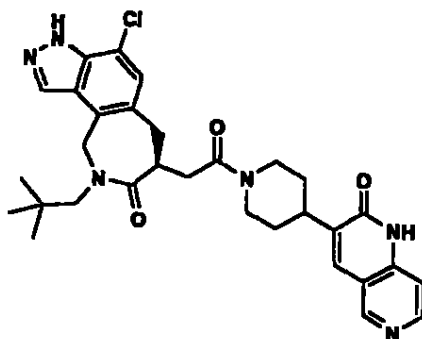
5

1-[[[(7S)-4-cloro-9-(2,2-dimetilpropil)-3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]indazol-7-il]acetil]-4-(1,2-dihidro-2-oxo-1,8-

10 naftiridin-3-il)-piperidina. La 3-(piperidin-4-il)-1,8-naftiridin-2(1H)-ona (57 mg, 0.19 mmol) y ácido [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (60 mg, 0.16 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 64% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 575.2538.

15

EJEMPLO 80



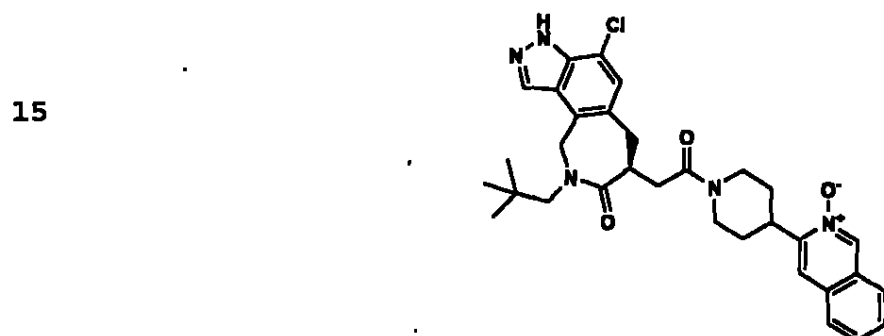
20

25 1-[[[(7S)-4-cloro-9-(2,2-dimetilpropil)-3,6,7,8,9,10-

544

hexahidro-8-oxoazepino[3,4-e]indazol-7-il]acetil]-4-(1,2-
 dihidro-2-oxo-1,6-naftiridin-3-il)-piperidina. La 3-
 (piperidin-4-il)-1,6-naftiridin-2(1H)-ona (89 mg, 0.29 mmol)
 y ácido [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-
 5 hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético
 (95 mg, 0.26 mmol) se combinaron en una manera análoga a la
 preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-
 [4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-
 etil]-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-
 10 8-ona. El compuesto del título se obtuvo como un sólido
 blanco en 27% de rendimiento. Alta resolución EM m/e (M+H)⁺ =
 575.2538.

EJEMPLO 81



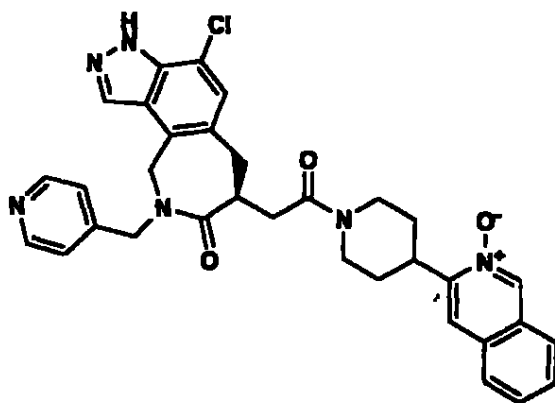
(S)-1-[[[(7S)-4-cloro-9-(2,2-dimetilpropil)-
 20 3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]indazol-7-
 il]acetil]-4-(2-oxido-3-isoquinolinil)-piperidina. El
 compuesto del título se preparó a partir de
 clorohidrato de 3-piperidin-4-ilisoquinolina en una
 manera análoga a la preparación de 4-Cloro-9-(2,2-
 25 dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-

✓
545

2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

El material se obtiene como un sólido café ligero. EM (ESI) 574 (M+H); $R_f = 2.39$ (corrida de gradiente de 3 5 minutos).

EJEMPLO 82



10

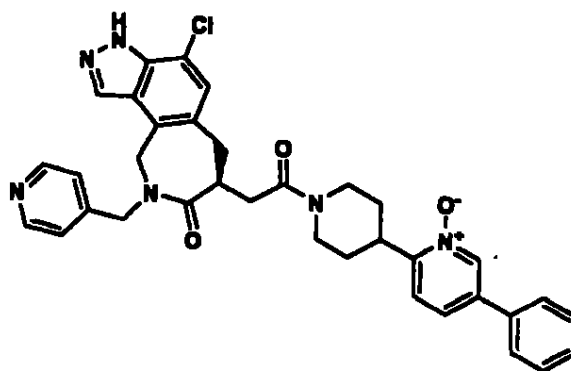
(S)-1-[[[(7S)-4-cloro-3,6,7,8,9,10-hexahidro-8-oxo-9-(4-piridnilmetil)azepino[3,4-e]indazol-7-il]acetil]-4-(2-oxido-3-isoquinolinil)-piperidina.

El compuesto del título se preparó a partir de clorohidrato de 3-piperidin-4-ilisoquinolina en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

El material se obtiene como un sólido blanco. EM (ESI) 595 (M+H); $R_f = 1.73$ (corrida de gradiente de 3 25 minutos).

546

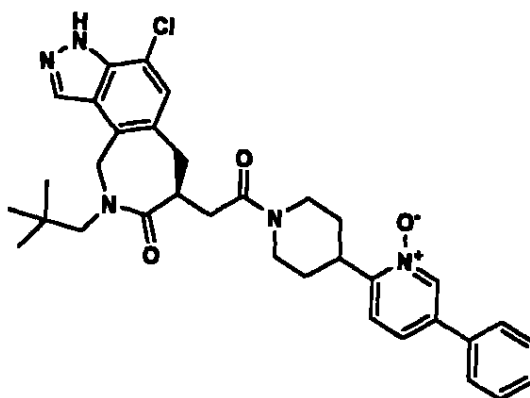
EJEMPLO 83



5

(S)-1-[[[(7S)-4-cloro-3,6,7,8,9,10-hexahidro-8-oxo-9-(4-
 10 Piridinilmetil)azepino[3.4-e]indazol-7-il]acetil]-4-(1-oxido-5-fenil-2-
 piridinil)-piperidina. El compuesto del título se preparó a partir del
 clorohidrato de 1-óxido de 5-fenil-2-piperidin-4-ilpiridina en una
 manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-
 (S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-
 15 etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El
 material se obtiene como un sólido blanco. EM (ESI) 621 (M+H); R_f =
 1.87 (corrida de gradiente de 3 minutos).

EJEMPLO 84



20

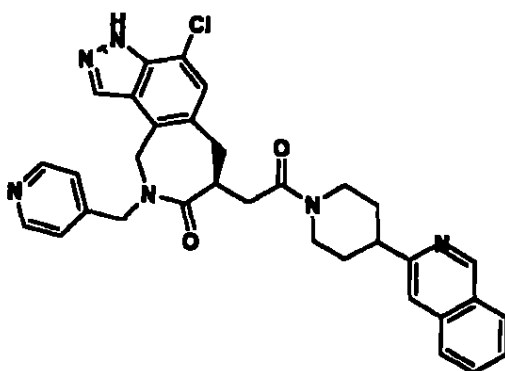
25 (S)-1-[[[(7S)-4-cloro-9-(2,2-dimetilpropil)-3,6,7,8,9,10-

547.

hexahidro-8-oxoazepino[3,4-e]indazol-7-il]acetil]-4-(1-oxido-5-fenil-2-piridinil)-piperidina. El compuesto del título se preparó a partir del clorohidrato de 2-(piperidin-4-il)-1,2-dihidroisoquinolin-3(4H)-ona en una manera análoga a la
5 preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(S)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El material se obtiene como un sólido blanco. EM (ESI) 600 (M+H); R_f = 2.51 (corrida de gradiente de 3 minutos).

10

EJEMPLO 85



15

(S)-4-cloro-7-(2-(4-(isoquinolin-3-il)piperidin-1-il)-2-oxoetil)-9-(piridin-4-ilmetil)-6,7,9,10-

tetrahydroazepino[3.4-e]indazol-8(3H)-ona. El compuesto del
20 título se preparó a partir del clorohidrato de 3-(piperidin-4-il)isoquinolina en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(S)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El

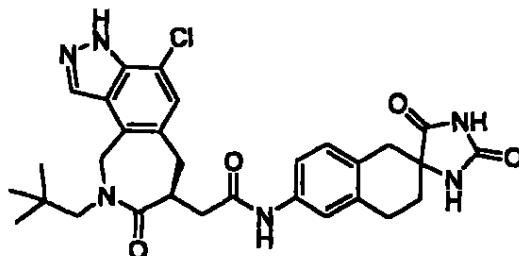
25 material se obtiene como un sólido blanco. EM (ESI) 579

548

(M+H); $R_f = 1.43$ (corrida de gradiente de 3 minutos).

EJEMPLO 86

5



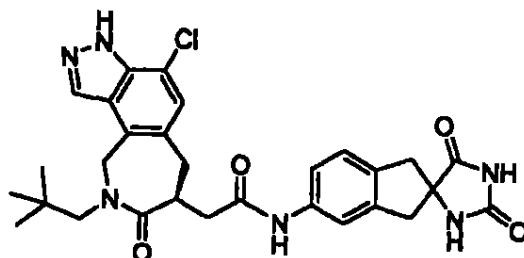
(+/-)-1-[[(7S)-4-cloro-9-(2,2-dimetilpropil)-
3,6,7,8,9,10-hexahidro-8-oxoazepino[3,4-e]indazol-7-
10 il]acetil]-amino-3',4'-dihidro-1'H-spiro[imidazolidina-4,2'-
naftaleno]-2,5-diona. El compuesto del título se preparó a
partir de la (+/-)-6'-Amino-3',4'-dihidro-1'H-
espiro[imidazolidina-4,2'-naftaleno]-2,5-diona en una manera
análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-
15 (S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
ciclohepta[e]inden-8-ona. El material se obtuvo como un
sólido blanco. ^1H RMN (CD_3OD , 400 MHz) δ 0.78 (s, 9H), 1.80-
1.89 (m, 1H), 2.07-2.15 (m, 1H), 2.53 (dd, $J=15.61$, 5.04 Hz,
20 1H), 2.76 (d, $J=16.87$ Hz, 1H), 2.92-3.18 (m, 8H), 3.62-3.70
(m, 1H), 3.90-4.07 (m, 1H), 4.64 (d, $J=17.37$ Hz, 1H), 5.47
(d, $J=17.37$ Hz, 1H), 7.02 (d, $J=8.31$ Hz, 1H), 7.21 (s, 1H),
7.22-7.30 (m, 1H), 7.35-7.45 (m, 1H), 8.22 (d, $J=2.52$ Hz,
1H); Espectrometría de masa. 577.25 (MH^+), calculado para
25 $\text{C}_{30}\text{H}_{33}\text{ClN}_6\text{O}_4$ 576.23; $R_f = 2.15$ (corrida de gradiente de 4

549. 73

minutos).

EJEMPLO 87

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(+/-)-1-[[[(7S)-4-cloro-9-(2,2-dimetilpropil)-3,6,7,8,9,10-hexahidro-8-oxoazepino[3.4-e]indazol-7-il]acetil]-amino-espiro[imidazolidina-4,2'-indano]-2,5-diona. El compuesto del título se preparó a partir de (+/-)-5'-amino-espiro[imidazolidina-4,2'-indano]-2,5-diona en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetilpropil)-7-(S)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

15

20

El material se obtiene como un sólido blanco. $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ 0.79 (s, 9H), 2.53 (dd, $J=15.61, 5.04$ Hz, 1H), 2.92-3.3 (m, 6H), 3.46 (dd, $J=16.49, 9.44$ Hz, 2H), 3.66 (d, $J=13.60$ Hz, 1H), 3.98-4.08 (m, 1H), 4.63 (d, $J=17.37$ Hz, 1H), 5.47 (d, $J=16.87$ Hz, 1H), 7.15 (d, $J=8.06$ Hz, 1H), 7.21 (s, 1H), 7.25-7.35 (m, 1H), 7.50 (d, $J=16.12$ Hz, 1H), 8.23 (s, 1H);

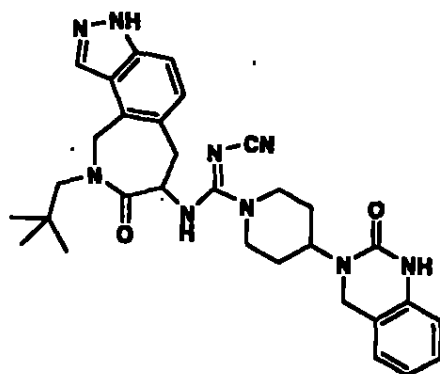
25

Espectro de masa 563.24 (MH^+), Calculado para $\text{C}_{29}\text{H}_{31}\text{ClN}_6\text{O}_4$ 562.21; $R_f = 2.15$ (corrida de gradiente de 4 minutos).

227
550.

EJEMPLO 88

5



(E,Z)-N'-ciano-N-(9-neopentil-8-oxo-3,6,7,8,9,10-
10 hexahidroazepino[3,4-e]indazol-7-il)-4-(2-oxo-1,2-
dihidroquinazolin-3(4H)-il)piperidin-1-carboxamidina. A una
solución de 7-amino-9-neopentil-6,7,9,10-
tetrahidroazepino[3,4-e]indazol-8(3H)-ona, metanosulfonato
15 (300 mg, 0.78 mmol) en CH₂Cl₂ (20 mL) se agregó difenil N-
cianocarbonimidato (221 mg, 0.93 mmol) seguido por
triethylamina (1 mL). La mezcla de reacción se agitó a
temperatura ambiente durante 12 h. La mezcla de reacción
luego se lavó con carbonato ácido de sodio acuoso para dar
20 (E,Z)-1-ciano-3-(9-neopentil-8-oxo-3,6,7,8,9,10-
hexahidróazepino[3,4-e]indazol-7-il)-2-fenilisourea en 95% de
rendimiento. EM (ESI) 431 (M+H); R_f = 2.22 (corrida de
gradiente de 3 minutos).

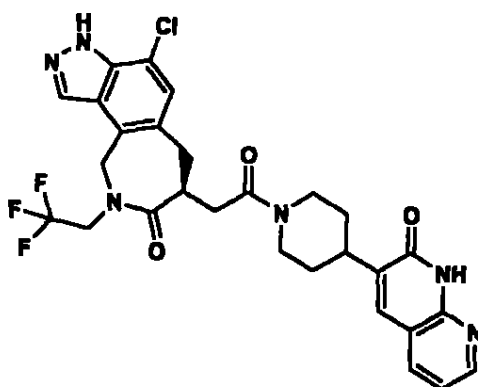
A una solución de (E,Z)-1-ciano-3-(9-neopentil-8-oxo-
3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)-2-
25 fenilisourea (301 mg, 0.7 mmol) en isopropanol (25 mL) se

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agregó 3-(piperidin-4-il)-3,4-dihidroquinazolin-2(1H)-ona (323 mg, 1.4 mmol) y la mezcla de reacción se puso a reflujo durante 72 h. El solvente se evaporó y el producto crudo se purificó por cromatografía instantánea para dar (E,Z)-N'-ciano-N-(9-neopentil-8-oxo-3,6,7,8,9,10-hexahidroazepino[3,4-e]indazol-7-il)-4-(2-oxo-1,2-dihidroquinazolin-3(4H)-il)piperidin-1-carboxamida (130 mg) en 33% de rendimiento. EM (ESI) 568 (M+H); R_f = 2.19 (corrida de gradiente de 3 minutos).

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EJEMPLO 89



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(S)-4-cloro-7-(2-oxo-2-(4-(2-oxo-1,2-dihidro-1,8-naftiridin-3-il)piperidin-1-il)etil)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-Cloro-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (120 mg, 0.32 mmol) y diclorohidrato de 3-(piperidin-4-il)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona (120 mg, 0.40 mmol) se combinaron en una manera análoga a la

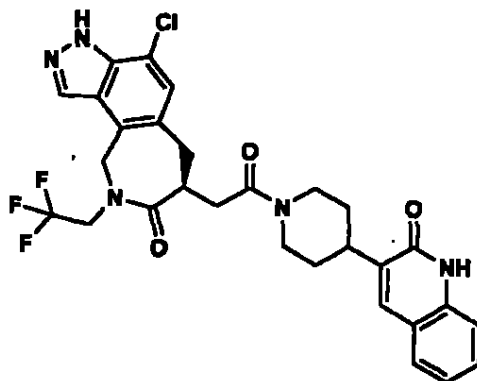
20

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552

preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido
5 amarillo pálido in 43% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 587.1785.

EJEMPLO 90

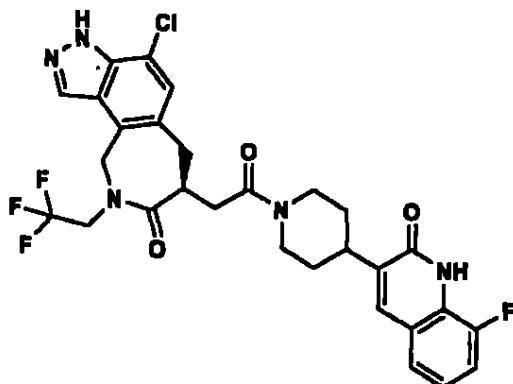


15 (S)-4-cloro-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)etil)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-Cloro-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (115 mg, 0.31
20 mmol) y clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona (96 mg, 0.36 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-
25 8-ona. El compuesto del título se obtiene como un sólido

553 30

blanco en 65% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 586.1811.

EJEMPLO 91



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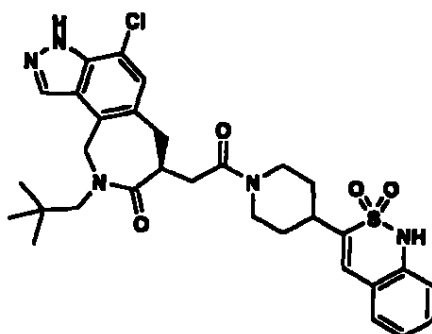
10

(S)-4-cloro-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-Cloro-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (115 mg, 0.31 mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona (96 mg, 0.36 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 55% de rendimiento.

25 Alta resolución EM m/e (M+H)⁺ = 604.1760.

554 *gsk*

EJEMPLO 92



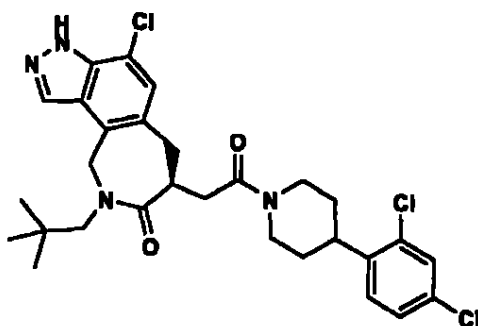
5

El 2,2-dióxido p-toluensulfonato de 3-Piperidin-4-il-1H-2,1-benzotiazina (55 mg, 0.13 mmol) y ácido [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (40 mg, 0.11 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido color canela en 57% de rendimiento. Alta resolución EM m/e (M+H)⁺ 610.2268.

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EJEMPLO 93



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(S)-4-cloro-7-(2-(4-(2,4-diclorofenil)piperidin-1-il)-2-oxoetil)-9-neopentil-6,7,9,10-tetrahidroazepino[3,4-

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302

e]indazol-8(3H)-ona. La 4-(2,4-Diclorofenil)-piperidina (32 mg, 0.08 mmol) y ácido [4-cloro-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-

ciclohepta[e]inden-7-il]acético (25 mg, 0.07 mmol) se

5 combinaron en una manera análoga a la preparación de 4-Cloro-

9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-

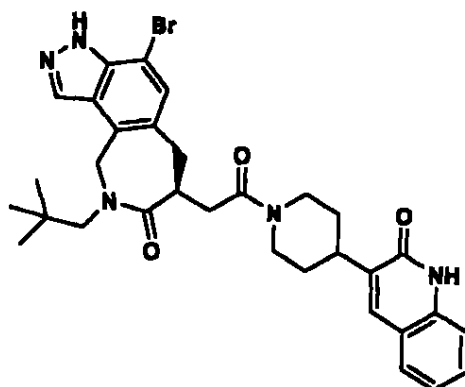
tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El

compuesto del título se obtiene como un sólido blanco opaco

10 en 40% de rendimiento. Alta resolución EM m/e $(M+H)^+ = 575.1747$.

EJEMPLO 94

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(S)-4-bromo-9-neopentil-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)etil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)ona. El ácido bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-

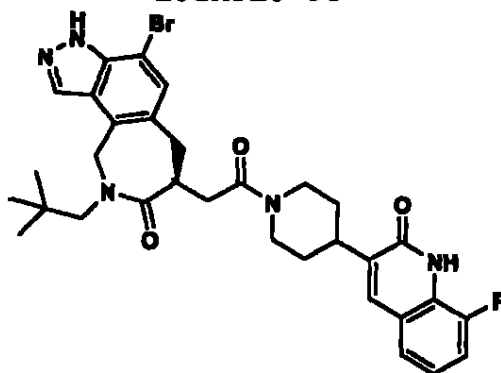
triaza-(S)-ciclohepta[e]inden-7-il]-acético (56 mg, 0.14 mmol) y clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona

25 (35 mg, 0.15 mmol) se combinaron en una manera análoga a la

556 107

preparación del 4-cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtuvo como un sólido blanco en 61% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 618.2064.

EJEMPLO 95



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(S)-4-bromo-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-9-neopentil-6,7,9,10-tetrahydroazepino[3,4-e]indazol-8(3H)-ona. El ácido bromo-9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético (65 mg, 0.16 mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona (45 mg, 0.16 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 57% de rendimiento. Alta resolución

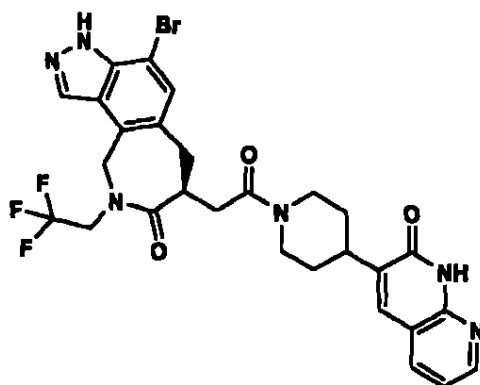
20

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557 70

EM m/e (M+H)⁺ 636.1973.

EJEMPLO 96



5

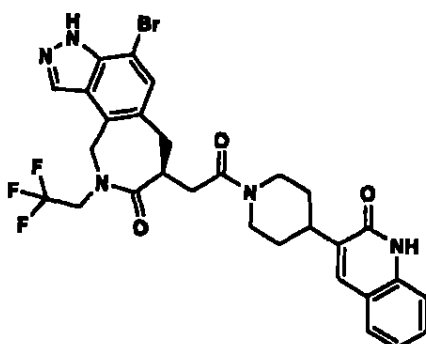
10 (S)-4-bromo-7-(2-oxo-2-(4-(2-oxo-1,2-dihidro-1,8-naftiridin-3-il)piperidin-1-il)etil)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-

15 il]acético (69 mg, 0.16 mmol) y diclorohidrato de 3-(piperidin-4-il)-3,4-dihidropirido[2,3-d]pirimidin-2(1H)-ona (120 mg, 0.40 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-

20 8-ona. El compuesto del título se obtiene como un sólido blanco en 55% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 631.1279.

558 60

EJEMPLO 97



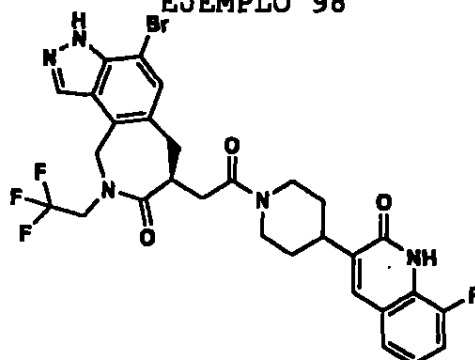
5

(S)-4-bromo-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)etil)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (73 mg, 0.17 mmol) y clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona (50 mg, 0.19 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido amarillo en 62% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 630.1315.

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EJEMPLO 98



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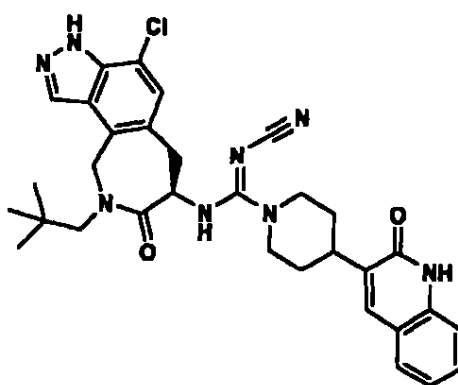
(S)-4-bromo-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-9-(2,2,2-trifluoroetil)-

25

55A 10

6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido
[4-bromo-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-
trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-
il]acético (80 mg, 0.19 mmol) y clorohidrato de 8-fluoro-3-
5 (piperidin-4-il)quinolin-2(1H)-ona (61 mg, 0.22 mmol) se
combinaron en una manera análoga a la preparación de 4-Cloro-
9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-
2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-
tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El
10 compuesto del título se obtiene como un sólido blanco opaco
en 64% de rendimiento. Alta resolución EM m/e (M+H)⁺ =
648.1217.

EJEMPLO 99



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La (R)-7-amino-4-cloro-9-(2,2-dimetil-propil)-6,7,9,10-
tetrahidro-3H-2,3,9-triaza-ciclohept[e]inden-8-ona (108 mg,
0.34 mmol) se disolvió en N,N-dimetilformamida (1.8 mL). La
N,N'-Diisopropiletilamina (200 µL, 1.1 mmol) se agregó a la
25 mezcla seguido por difenil cianocarbonimidato (86 mg, 0.36

10

EJEMPLO 100

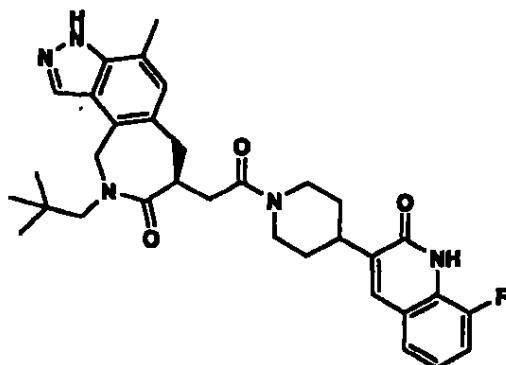


25

tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-Metil-
9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-
triazaz-(S)-ciclohepta[e]inden-7-il]-acético (37 mg, 0.11
mmol) y clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona
5 (32 mg, 0.12 mmol) se combinaron en una manera análoga a la
preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-
[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-
etil}-6,7,9,10-tetrahidro-3H-2,3,9-triazaz-ciclohepta[e]inden-
8-ona. El compuesto del título se obtuvo como un sólido
10 blanco en 55% de rendimiento. Alta resolución EM m/e (M+H)⁺ =
554.31.21

EJEMPLO 101

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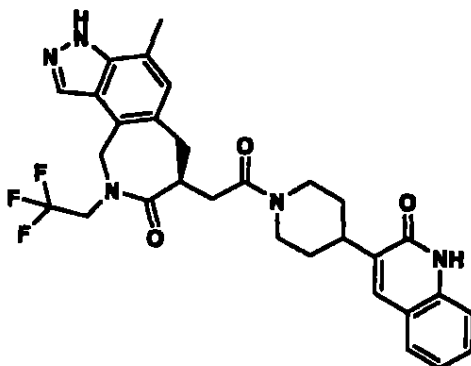
20 (S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-
il)piperidin-1-il)-2-oxoetil)-4-metil-9-neopentil-6,7,9,10-
tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-metil-
9-(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-
triazaz-(S)-ciclohepta[e]inden-7-il]acético (60 mg, 0.18 mmol)
25 y clorohidrato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-

562

ona (60 mg, 0.21 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-triaza-ciclohepta[e]inden-8-ona. El

5 compuesto del título se obtiene como un sólido blanco m 48% de rendimiento. Alta resolución EM m/e (M+H)* = 572.3021.

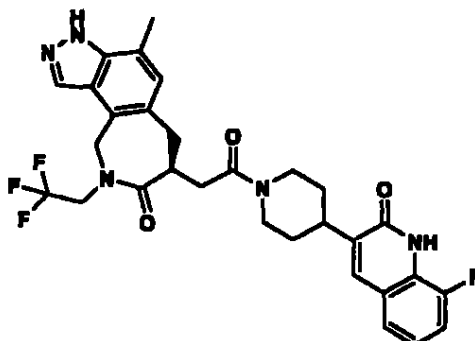
EJEMPLO 102



10
15 (S)-4-metil-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)etil)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-Metil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (65 mg, 0.18 mmol)
20 y clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona (55 mg, 0.21 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-
25 8-ona. El compuesto del título se obtiene como un sólido

blanco en 58% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 566.2364.

EJEMPLO 103



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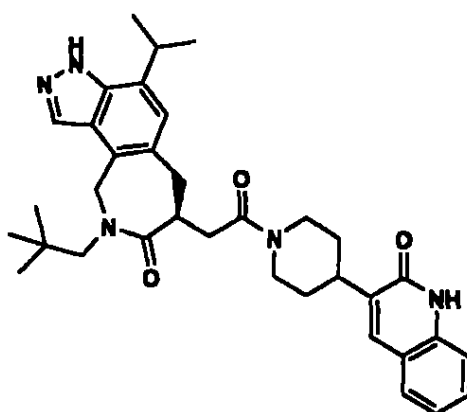
10

(S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-
il)piperidin-1-il)-2-oxoetil)-4-metil-9-(2,2,2-
trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-
e]indazol-8(3H)-ona. El ácido [4-Metil-3,6,7,9,10-
15 hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-
(S)-ciclohepta[e]inden-7-il]acético (65 mg, 0.18
mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-
il)quinolin-2(1H)-ona (62 mg, 0.22 mmol) se
combinaron en una manera análoga a la preparación de
20 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-
oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-
etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
ciclohepta[e]inden-8-ona. El compuesto del título se
obtiene como un sólido blanco en 53% de rendimiento.
25 Alta resolución EM m/e (M+H)⁺ = 584.2302.

564

27

EJEMPLO 104

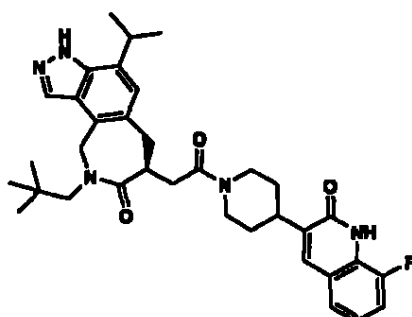


5

(S)-4-isopropil-9-neopentil-7-(2-oxo-2-(4-(2-oxo-1,2-
 10 ciihidroquinolin-3-il)piperidin-1-il)etil)-6,7,9,10-
 tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-
 isopropil-9(2,2-dimetil-propil)-8-oxo-3,6,7,8,9,10-hexahidro-
 2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-acético (42 mg,
 0.11 mmol) y clorohidrato de 3-(piperidin-4-il)quinolin-
 15 2(1H)-ona (36 mg, 0.14 mmol) se combinaron en una manera
 análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-
 (R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-
 piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-
 ciclohept[e]inden-8-ona. El compuesto del título se obtuvo
 20 como un sólido blanco en 33% de rendimiento. Alta resolución
 EM m/e (M+H)⁺ = 582.3466.

565 7A

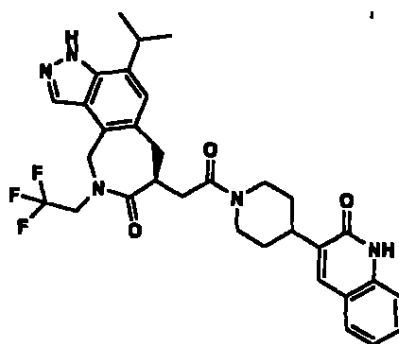
EJEMPLO 105



5

(S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)piperidin-1-
il)-2-oxoetil)-4-isopropil-9-neopentil-6,7,9,10-tetrahidroazepino[3,4-
e]indazol-8(3H)-ona. El ácido [4-isopropil-9-(2,2-dimetil-propil)-8-
10 oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]-
acético (80 mg, 0.22 mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-
il)quinolin-2(1H)-ona (70 mg, 0.25 mmol) se combinaron en una manera
análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-
oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-pipendin-1-il]-etil)-
15 6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El
compuesto del título se obtiene como un sólido blanco en 60% de
rendimiento. Alta resolución EM m/e (M+H)⁺ = 600.3372.

EJEMPLO 106



20

25

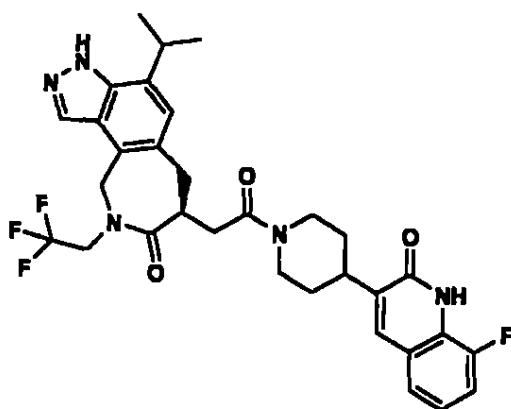
(S)-4-isopropil-7-(2-oxo-2-(4-(2-oxo-1,2-

dihidroquinolin-3-il)piperidin-1-il)etil)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-isopropil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-

5 ciclohepta[e]inden-7-il]acético (50 mg, 0.13 mmol) y clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona (41 mg, 0.15 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 62% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 594.2682.

EJEMPLO 107

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20

(S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-4-isopropil-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-

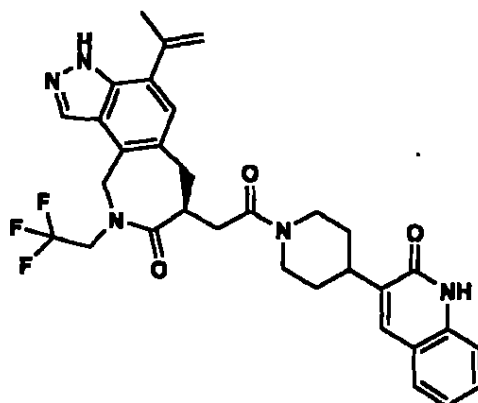
25

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8(3H)-ona. El ácido [4-isopropil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (50 mg, 0.13 mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona
5 (43 mg, 0.15 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido
10 blanco en 66% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 612.2578.

EJEMPLO 108

15

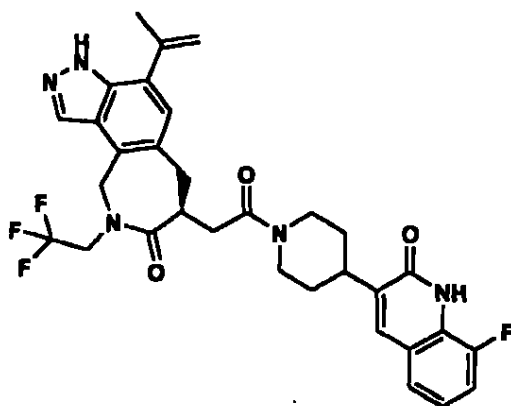


20 (S)-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)etil)-4-(prop-1-en-2-il)-9-(2,2,2-trifluoroetil)-6,7,9,10-teti-ahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-Isopropenil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-
25 ciclohepta[e]inden-7-il]acético (47 mg, 0.12 mmol) y

568

clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona (42 mg, 0.16 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 55% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 592.2544.

EJEMPLO 109

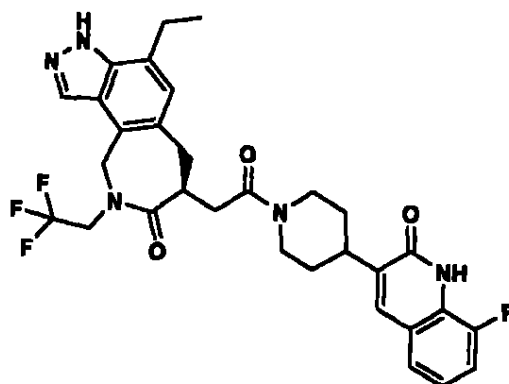


(S)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-4-(prop-1-en-2-il)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-Isopropenil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (47 mg, 0.12 mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona (44 mg, 0.16 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-

569

[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 60% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 610.2457.

EJEMPLO 110



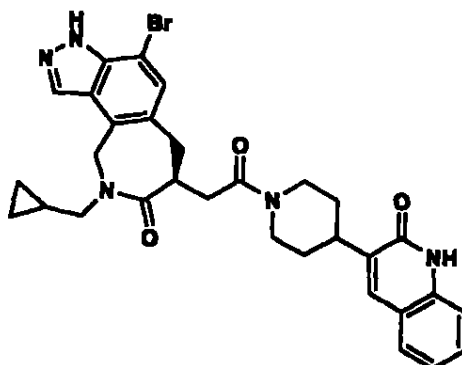
(S)-4-etil-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-9-(2,2,2-trifluoroetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [4-etil-3,6,7,8,9,10-hexahidro-8-oxo-9-(2,2,2-trifluoroetil)-2,3,9-triaza-(S)-ciclohepta[e]inden-7-il]acético (25 mg, 0.07 mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona (24 mg, 0.09 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del

570 25 1

título se obtuvo como un sólido blanco en 49% de
rendimiento. Alta resolución EM m/e (M+H)⁺ = 598.2465.

EJEMPLO 111

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10 (S)-4-bromo-9-(ciclopropilmetil)-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)etil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona.

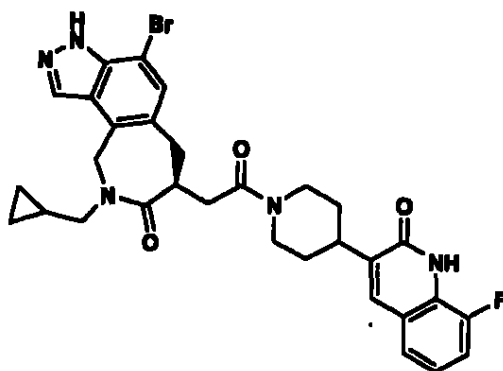
El ácido (S)-4-bromo-9-ciclopropilmetil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-

15 ciclohept[e]inden-7-il)-acético (90 mg, 0.23 mmol) y clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona (80 mg, 0.30 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetilpropil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona.

El compuesto del título se obtiene como un sólido blanco en 32% de rendimiento. Alta resolución EM m/e
25 (M+H)⁺ = 602.1776.

571

EJEMPLO 112

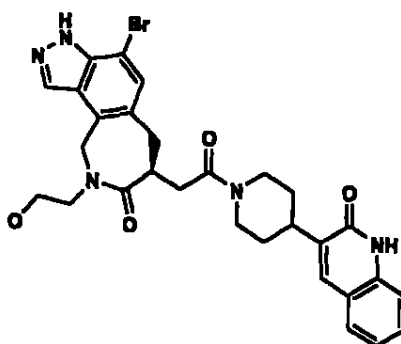


5

10 (S)-4-bromo-9-(ciclopropilmetil)-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)-2-oxoetil)-6,7,9,10-tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido ((S)-4-bromo-9-ciclopropilmetil-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il)-acético (90 mg, 0.23 mmol) y clorohidrato de 8-fluoro-3-(piperidin-4-il)quinolin-2(1H)-ona (80 mg, 0.28 mmol) se combinaron en una manera
15 análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 56% de rendimiento. Alta resolución
20 EM m/e (M+H)⁺ = 620.1665.

572 746

EJEMPLO 113



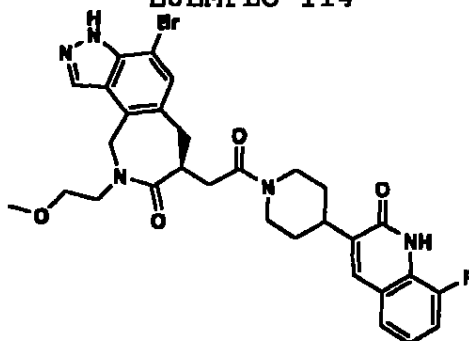
5

(S)-4-bromo-9-(2-metoxietil)-7-(2-oxo-2-(4-(2-oxo-1,2-dihidroquinolin-3-il)piperidin-1-il)etil)-6,7,9,10-

10 tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido Bromo-9-(2-metoxi-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-triaza-ciclohept[e]inden-7-il]-acético (100 mg, 0.25 mmol) y clorohidrato de 3-(piperidin-4-il)quinolin-2(1H)-ona (80 mg, 0.30 mmol) se combinaron en una manera análoga a la preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-(2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil)-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-8-ona. El compuesto del título se obtiene como un sólido blanco en 35% de rendimiento. Alta resolución EM m/e (M+H)⁺ = 606.1730.

15

EJEMPLO 114



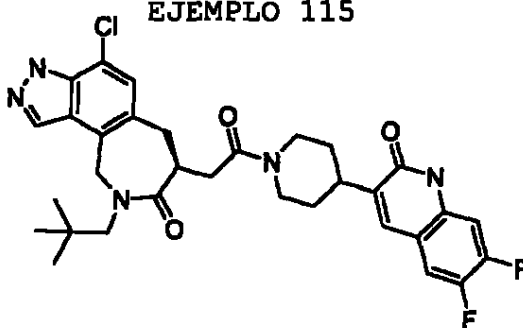
20

25 (S)-4-bromo-7-(2-(4-(8-fluoro-2-oxo-1,2-dihidroquinolin-

593

3-il)piperidin-1-il)-2-oxoetil)-9-(2-metoxietil)-6,7,9,10-
 tetrahidroazepino[3,4-e]indazol-8(3H)-ona. El ácido [(S)-4-
 bromo-9-(2-metoxi-etil)-8-oxo-3,6,7,8,9,10-hexahidro-2,3,9-
 triaza-ciclohept[e]inden-7-il]-acético (100 mg, 0.25 mmol) y
 5 clorohidrato de 8-fluoro-3-(piperidin-4-il)quinohn-2(1H)-ona
 (85 mg, 0.30 mmol) se combinaron en una manera análoga a la
 preparación de 4-Cloro-9-(2,2-dimetil-propil)-7-(R)-{2-oxo-2-
 [4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-
 etil}-6,7,9,10-tetrahidro-3H-2,3,9-triaza-ciclohepta[e]inden-
 8-ona. El compuesto del título se obtiene como un sólido
 10 blanco en 56% de rendimiento. Alta resolución EM m/e (M+H)⁺ =
 624.1631.

EJEMPLO 115

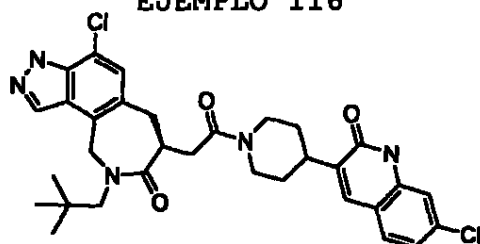


15

¹H RMN (400 MHz, MeOD) δ ppm 0.79 (s, 9H), 1.45-1.52 (m,
 20 2 H), 1.83-2.02 (m, 2 H), 2.37-2.42 (m, 1 H), 2.68-2.76 (m, 1
 H), 3.04-3.17 (m, 4 H), 3.64-3.68 (m, 2 H), 3.92-4.06 (m, 1
 H), 4.18-4.25 (m, 1 H), 4.63-4.74 (m, 3 H), 5.46-5.54 (m, 1
 H), 7.23 (s, 1 H), 7.12-7.23 (m, 1H), 7.53-7.59 (m, 1 H), 7.75
 (s, 1 H), 8.23 (s, 1 H); Espectro de masa 610.25 (MH⁺),
 25 Calculado para C₃₂H₃₄ClF₂N₅O₃ 609.23.

594

EJEMPLO 116

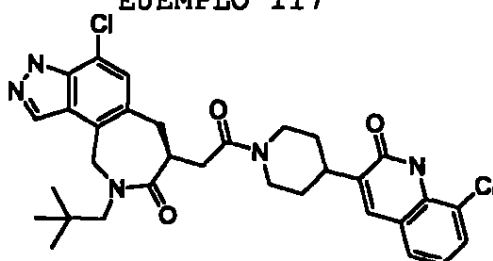


5

^1H RMN (400 MHz, MeOD) δ ppm 0.80 (s, 9 H), 1.47-1.60 (m, 2H), 1.75-1.80 (m, 1 H), 1.88-2.03 (m, 2H), 2.32-2.48 (m, 1 H), 2.68-2.78 (m, 1 H), 3.07-3.18 (m, 4 H), 3.66-3.68 (m, 1 H), 3.96-4.05 (m, 1H), 4.13-4.24 (m, 1H), 4.53 (s, 2 H), 4.62-4.72 (m, 2 H), 5.45-5.60 (m, 1 H), 7.17-7.24 (m, 1 H), 7.33 (s, 1 H), 7.61 (d, $J=8.31$ Hz, 1 H), 7.75 (d, $J=14.86$ Hz, 1 H), 8.23 (s, 1 H); Espectro de masa 608.23 (MH^+), Calculado para $\text{C}_{32}\text{H}_{35}\text{ClN}_5\text{O}_3$ 607.21.

15

EJEMPLO 117



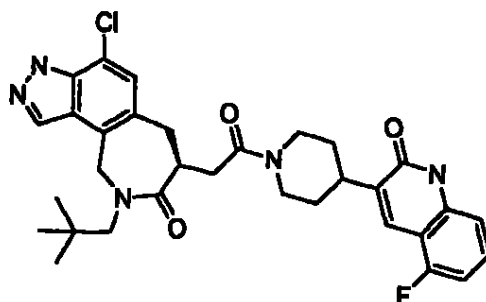
^1H RMN (400 MHz, MeOD) δ ppm 0.79 (s, 9 H), 1.46-1.70 (m, 2 H), 1.73-1.85 (m, 1 H), 1.90-2.08 (m, 2 H), 2.36-2.51 (m, 1 H), 2.73-2.81 (m, 1 H), 2.97-2.06 (s, 1 H), 3.09-3.20 (m, 4 H), 3.60-3.68 (m, 1 H), 3.95-4.08 (s, 1 H), 4.21-4.27 (m, 1 H), 4.66-4.73 (m, 2 H), 5.46-5.54 (m, 1 H), 7.15-7.23 (m, 2 H), 7.55-7.62 (m, 2 H), 7.79 (d, $J=15.86$ Hz, 1 H), 8.23 (s, 1 H); Espectro de masa 608.26 (MH^+), Calculado para $\text{C}_{32}\text{H}_{35}\text{Cl}_2\text{N}_5\text{O}_3$

575 ✓

607.21.

EJEMPLO 118

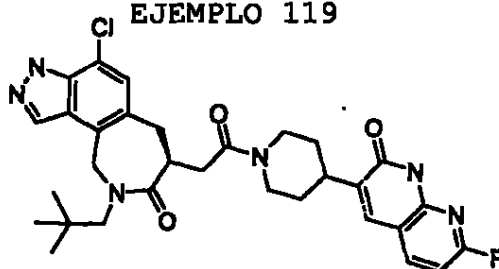
5



^1H RMN (400 MHz, MeOD) δ ppm 0.80 (s, 9 H), 1.46-1.56 (m, 1 H), 1.57-1.74 (m, 1H), 1.80-2.08 (m, 2H), 2.35-2.50 (m, 1 H), 2.69-2.80 (m, 1 H), 2.89-3.04 (m, 1 H), 3.09-3.20 (m, 4 H), 3.63 (dd, $J=19.14$, 13.85 Hz, 1 H), 3.95-4.07 (m, 1 H), 4.20-4.32 (m, 1 H), 4.60-4.72 (m, 3 H), 5.47 (d, $J=19.14$ Hz, 1 H), 6.88-6.96 (m, 1 H), 7.12 (t, $J=8.94$ Hz, 1 H), 7.22 (s, 1 H), 7.39-7.47 (m, 1 H), 7.88 (d, $J=21.66$ Hz, 1 H), 8.23 (s, 1 H); Espectro de masa 592.28 (MH^+), Calculado para $\text{C}_{32}\text{H}_{35}\text{ClFN}_5\text{O}_3$ 591.24.

EJEMPLO 119

20



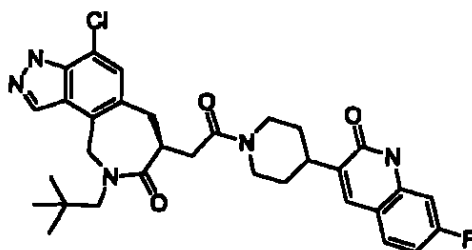
^1H RMN (400 MHz, MeOD) δ ppm 0.79 (s, 9 H), 1.45-1.66 (m, 2 H), 1.70-1.83 (m, 1 H), 1.90-2.07 (m, 2 H), 2.38-2.50 (m, 1 H), 2.69-2.80 (m, 1 H), 2.92-3.18 (m, 4 H), 3.60-3.69 (m, 1 H), 3.95-4.07 (m, 1 H), 4.18-4.32 (m, 1 H), 4.56-4.69

576 26

(m, 3 H), 5.43-5.58 (m, 1 H), 6.41 (s, 1 H), 7.23 (s, 1 H), 7.64-7.70 (m, 1 H), 7.80-7.84 (m, 1 H), 8.23 (s, 1 H); Espectro de masa 593.25 (MH^+), Calculado para $C_{31}H_{34}ClFN_6O_3$ 592.24.

EJEMPLO 120

5



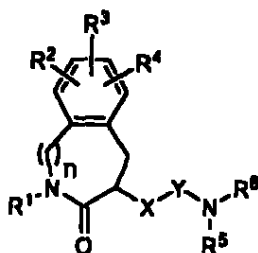
^1H RMN (400 MHz, MeOD) δ ppm 0.79 (s, 9 H), 1.45-1.68 (m, 2 H), 1.71-1.82 (m, 1 H), 1.90-2.07 (m, 2 H), 2.37-2.49 (m, 1 H), 2.68-2.79 (m, 1 H), 2.92-3.18 (m, 4 H), 3.59-3.68 (m, 1 H), 3.94-4.06 (m, 1 H), 4.17-4.30 (m, 1 H), 4.55-4.68 (m, 3 H), 5.43-5.58 (m, 1 H), 6.95-7.04 (m, 2 H) 7.22 (s, 1 H) 7.61-7.68 (m, 1 H) 7.75 (d, $J=14.60$ Hz, 1 H) 8.23 (s, 1 H); Espectro de masa 592.28 (MH^+), Calculado para $C_{32}H_{35}ClFN_5O_3$ 592.24.

537

Reivindicaciones

1. Compuesto de la Fórmula I

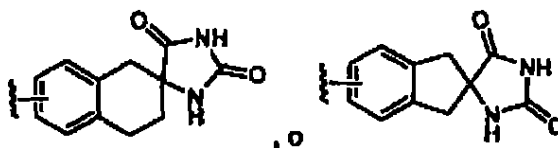
5



caraterizado porque:

I

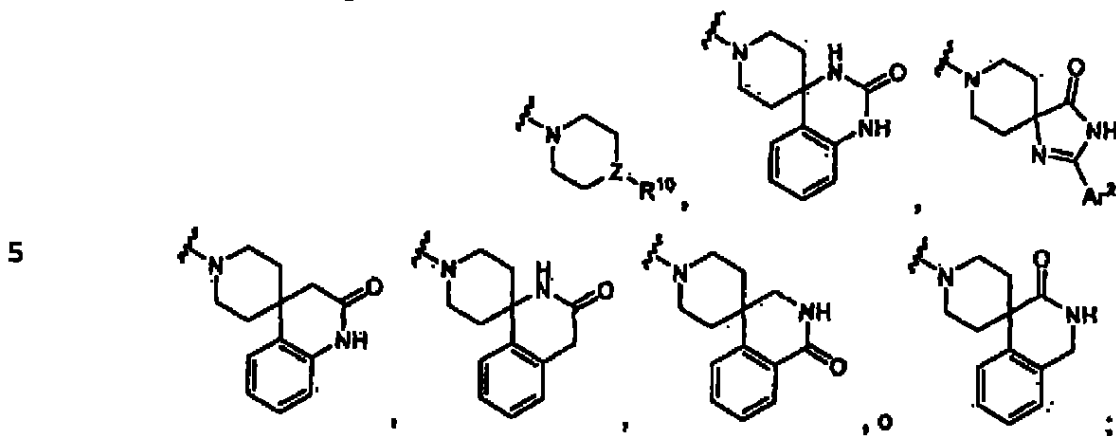
- 10 R^1 es alquilo C_{1-6} , alquenilo C_{2-6} , cicloalquilo C_{3-7} ,
cicloalquenilo C_{5-7} , alquilo C_{1-6} (cicloalquilo C_{3-7}),
haloalquilo C_{1-6} , alquilo C_{1-6} (alcoxi C_{1-6}), alquilo C_{1-6} (Ar^1),
alquilo C_{1-6} (NR^7R^8), N-(R^9 -pirrolidinilo o N(R^9)-piperidinilo;
 R^2 es hidrógeno, halo, hidroxilo, alquilo C_{1-6} , alquenilo C_{2-6} ,
15 benciloxi, o NR^7R^8 ;
 R^3 es hidrógeno, hidroxilo, halo, alquilo C_{1-6} , o alquenilo C_{2-6} ;
o R^2 y R^3 tomados juntos son $CHNNR^5$;
 R^4 es hidrógeno, halo o alquilo C_{1-6} , o alquenilo C_{2-6} ;
20 R^5 es hidrógeno o alquilo C_{1-6} ;
 R^6 es hidrógeno, alquilo C_{1-6} ,



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o NR^5R^6 tomado junto es



R^7 es hidrógeno o alquilo C_{1-6} ;

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R^8 es hidrógeno o alquilo C_{1-6} ; o

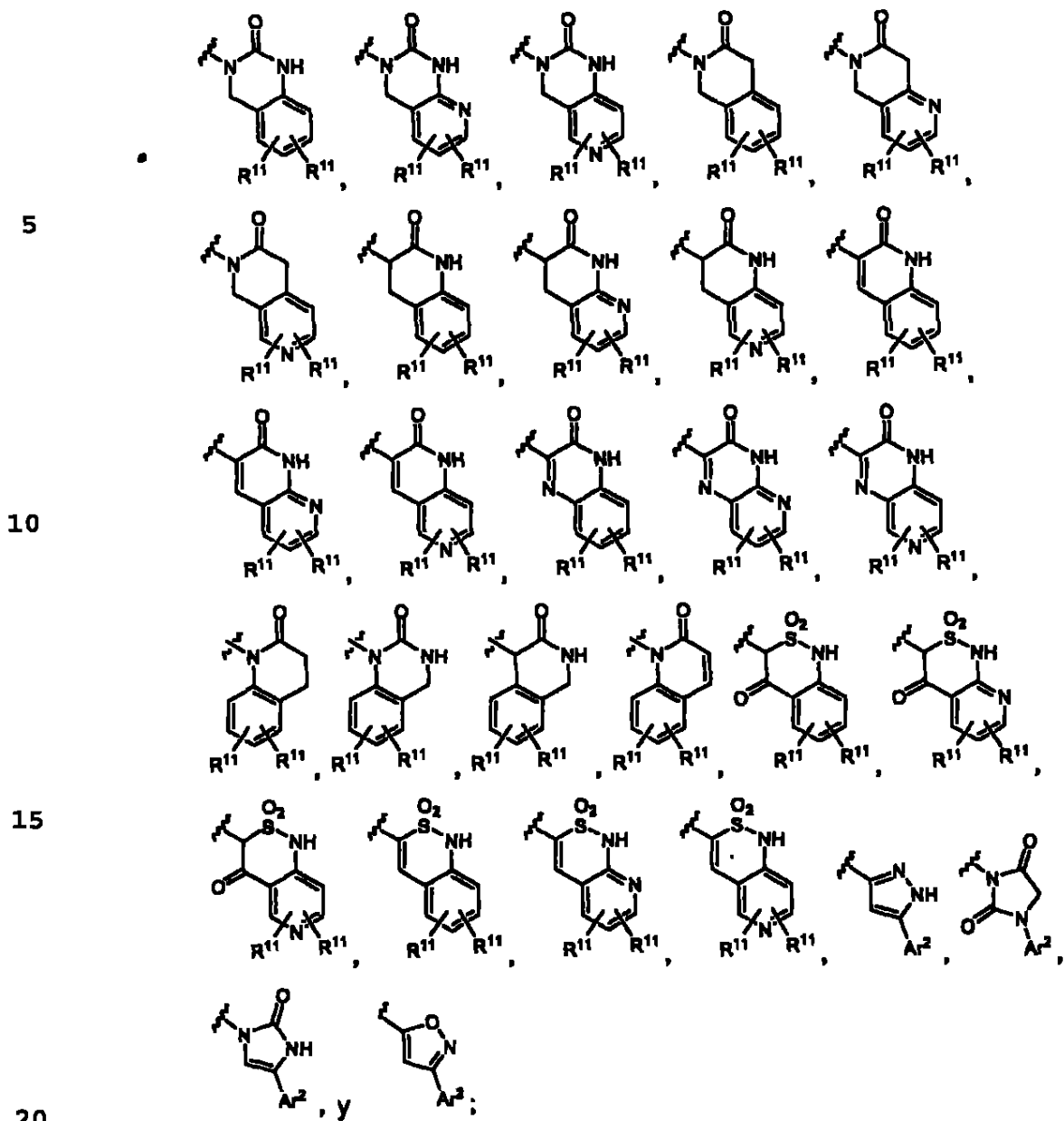
NR^7R^8 tomado junto se selecciona del grupo que
consiste de pirrolidinilo, piperidinilo, N-(R^9)-
15 piperazinilo, morfolinilo, y tiomorfolinilo;

R^9 es hidrógeno, alquilo C_{1-6} , alquilcarbonilo C_{1-6} , o
alcoxicarbonilo C_{1-6} ;

20 R^{10} es fenilo, naftilo, piridinilo, piridinil N-
óxido, quinolinilo, quinolinil N-óxido,
isoquinolinilo, o isoquinolinil N-óxido, y está
substituido con 0-2 substituyentes seleccionados del
grupo que consiste de halo, alquilo C_{1-6} , haloalquilo
25 C_{1-6} , alcoxi C_{1-6} , hidroxil, y fenilo;

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o R^{10} se selecciona del grupo que consiste de



cada R^{11} es hidrógeno, halo, alquilo C_{1-6} , haloalquilo C_{1-6} , o alcoxi C_{1-6} ;

Ar^1 es fenilo, naftilo, piridinilo, o imidazolilo, y está substituido con 0-2 substituyentes seleccionados del grupo que consiste de halo, alquilo C_{1-6} , y haloalquilo C_{1-6} ;

25 Ar^2 es fenilo, naftilo, o piridinilo, y está substituido con

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0-2 substituyentes seleccionados del grupo que consiste de halo, alquilo C₁₋₆, y haloalquilo C₁₋₆;

X-Y es aminocarbonilo, oxicarbonilo, metilencarbonilo, etileno, o amino(ciano)iminometilo;

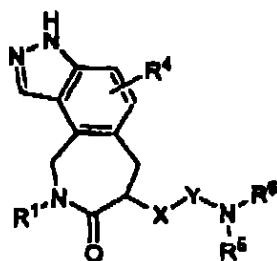
5 Z es N o CH; y

n es 0 o 1;

o una sal o solvato farmacéuticamente aceptable del mismo.

2. Compuesto de la Fórmula II.

10



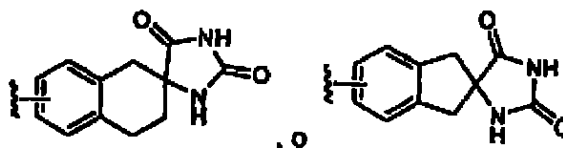
II

15 caracterizado porque

R¹ es alquilo C₁₋₆, alqueno C₂₋₆, cicloalquilo C₃₋₇, cicloalqueno C₅₋₇, alquilo C₁₋₆(cicloalquilo C₃₋₇), haloalquilo C₁₋₆, alquilo C₁₋₆(alcoxi C₁₋₆), alquilo C₁₋₆(Ar¹), alquilo C₁₋₆(NR⁷R⁸), N-(R⁹-pirrolidinilo o N(R⁹)-piperidinilo

20 R⁴ es hidrógeno, halo o alquilo C₁₋₆, o alqueno C₂₋₆;

R⁵ es hidrógeno o alquilo C₁₋₆;

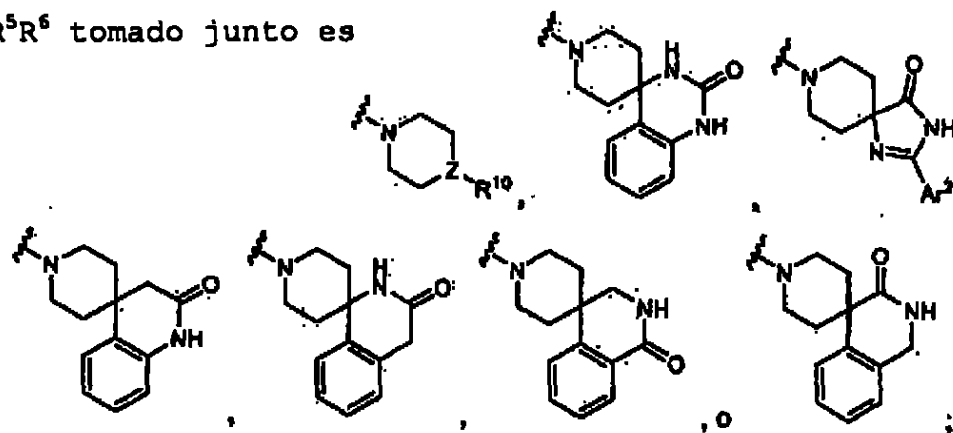


R⁶ es hidrógeno, alquilo C₁₋₆,

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o NR^5R^6 tomado junto es



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R^7 es hidrógeno o alquilo C_{1-6} ;

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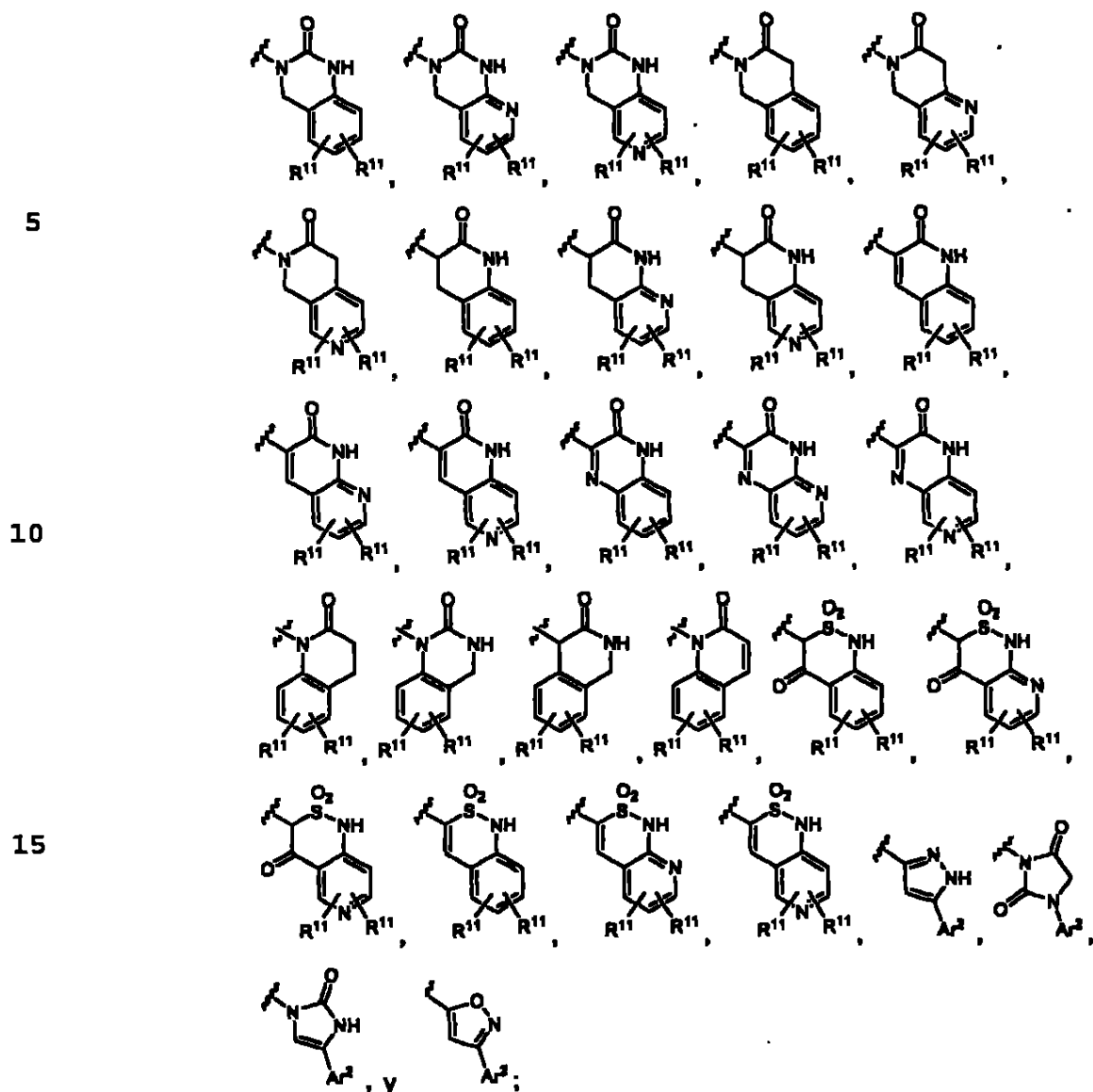
R^8 es hidrógeno o alquilo C_{1-6} ; o

NR^7R^8 tomado junto se selecciona del grupo que consiste de
 pirrolidinilo, piperidinilo, N-(R^9)-piperazinilo,
 15 morfolinilo, y tiomorfolinilo;

R^9 es hidrógeno, alquilo C_{1-6} , alquilcarbonilo C_{1-6} , o
 alcoxycarbonilo C_{1-6} ;

20 R^{10} es fenilo, naftilo, piridinilo, piridinil N-
 óxido, quinolinilo, quinolinil N-óxido,
 isoquinolinilo, o isoquinolinil N-óxido, y está
 substituido con 0-2 substituyentes seleccionados del
 grupo que consiste de halo, alquilo C_{1-6} , haloalquilo
 25 C_{1-6} , alcoxi C_{1-6} , hidroxil, y fenilo;

o R^{10} se selecciona del grupo que consiste de



cada R^{11} es hidrógeno, halo, alquilo C_{1-6} , haloalquilo C_{1-6} , o alcoxi C_{1-6} ;
 Ar^1 es fenilo, naftilo, piridinilo, o imidazolilo, y está
 substituido con 0-2 substituyentes seleccionados del grupo
 que consiste de halo, alquilo C_{1-6} , y haloalquilo C_{1-6} ;
 Ar^2 es fenilo, naftilo, o piridinilo, y está substituido con
 0-2 substituyentes seleccionados del grupo que consiste de halo,

583 *[Handwritten signature]*

alquilo C₁₋₆, y haloalquilo C₁₋₆;

X-Y es aminocarbonilo, oxicarbonilo, metilencarbonilo, etileno, o amino(ciano)iminometilo;

Z es N o CH; y

5 el carbono que soporta un asterisco es ya sea de la configuración (S) o de la configuración (R);

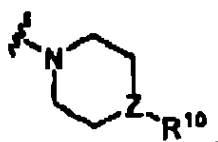
o una sal o solvato farmacéuticamente aceptable del mismo.

3. Compuesto de conformidad con la reivindicación 2, caracterizado porque el carbono que soporta un asterisco es
10 de la configuración (S).

4. Compuesto de conformidad con la reivindicación 1 ó 2, caracterizado porque R⁴ es cloro, fluoro o metilo.

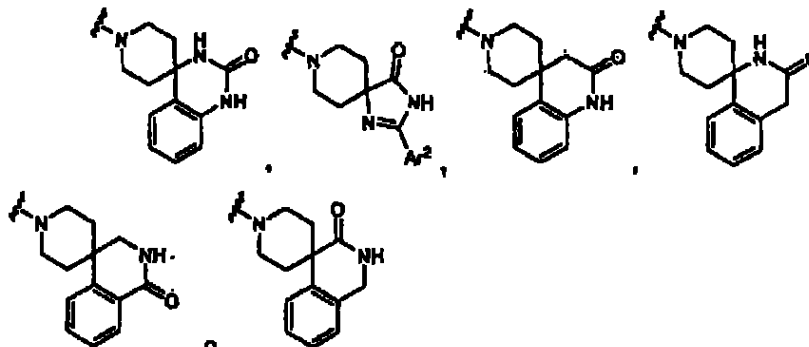
5. Compuesto de conformidad con la reivindicación 1 ó 2, caracterizado porque NR⁵R⁶ tomado junto es

15



6. Compuesto de conformidad con la reivindicación 1 ó 2, caracterizado porque NR⁵R⁶ tomado junto es

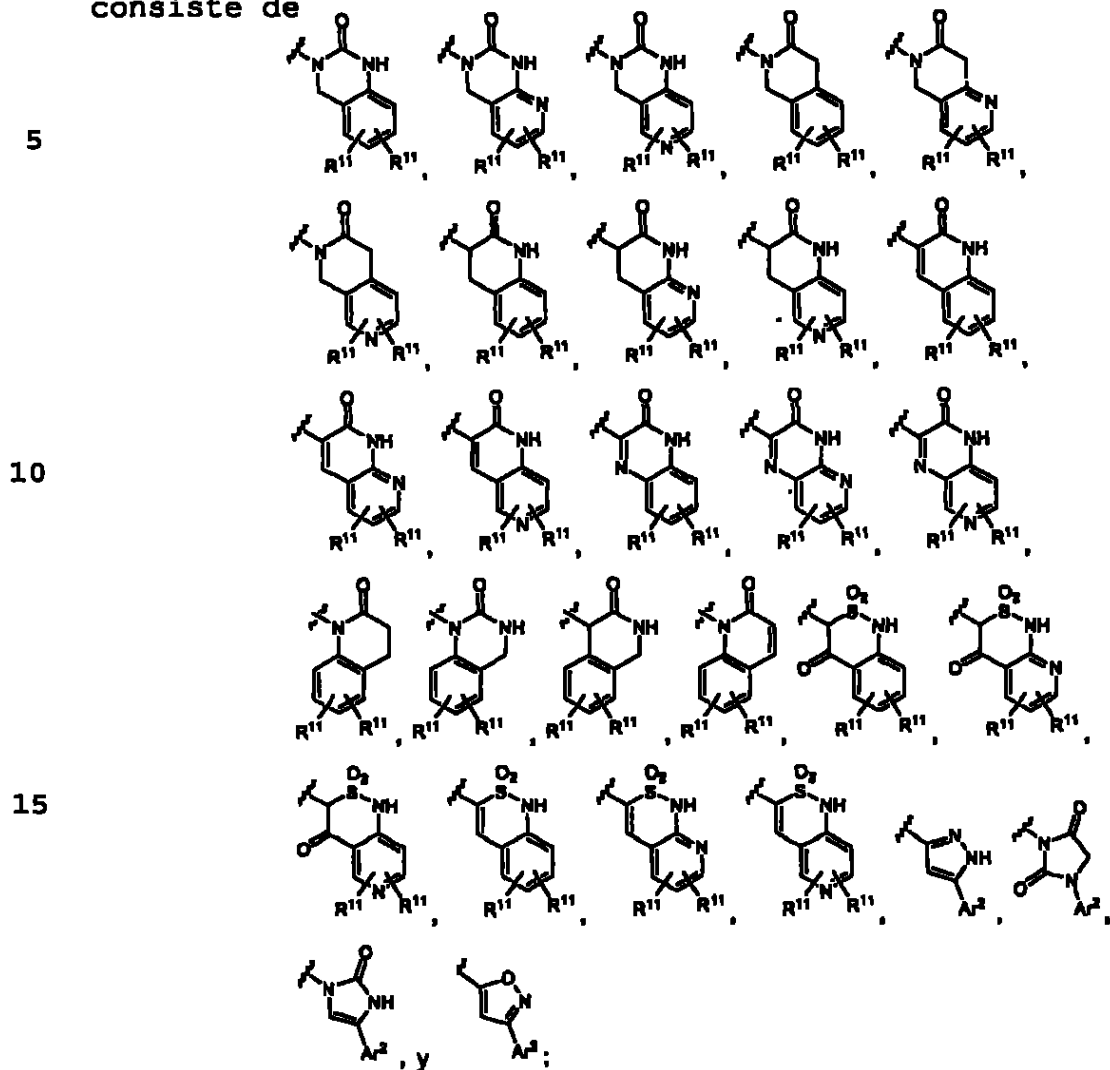
20



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7. Compuesto de conformidad con la reivindicación 1 ó 2, caracterizado porque R^{10} se selecciona del grupo que consiste de



20 8. Compuesto de conformidad con la reivindicación 1 ó 2, caracterizado porque R^{11} es hidrógeno, cloro, fluoro, o metilo.

9. Compuesto de conformidad con la reivindicación 1 ó 2, caracterizado porque Z es CH.

25 10. Compuesto de conformidad con la reivindicación 1,

585 Jhu

caracterizado porque n es 1.

11. Composición caracterizada porque comprende un compuesto de conformidad con la reivindicación 1 y un adyuvante, portador o diluyente farmacéuticamente aceptable.

5 12. Método para el tratamiento de la migraña caracterizado porque comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1, a un paciente en necesidad del mismo.

10 13. Composición caracterizada porque comprende un compuesto de conformidad con la reivindicación 2 y un adyuvante, portador o diluyente farmacéuticamente aceptable.

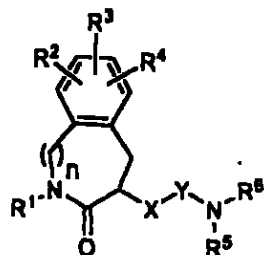
15 14. Método para el tratamiento de la migraña caracterizado porque comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 2, a un paciente en necesidad del mismo.

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Resumen de la invencion

La invención abarca antagonistas del receptor CGRP
tricíclico y bicíclico restringidos, métodos para
identificarlos, composiciones farmacéuticas que los
5 comprenden, y métodos para su uso en terapia para el
tratamiento de la migraña y otros dolores de cabeza,
vasodilatación neurogénica, inflamación neurogénica, lesión
térmica, choque circulatorio, bochornos asociados con la
menopausia, enfermedades inflamatorias de las vías aéreas
10 tales como asma y enfermedad pulmonar obstructiva crónica
(COPD) y otras condiciones de tratamiento de las cuales se
pueden efectuar por el antagonismo de los receptores CGRP.

15



I

INTERNATIONAL SEARCH REPORT

International application no
/US2005/036859

A. CLASSIFICATION OF SUBJECT MATTER

C07D487/04 C07D401/14 C07D519/00 A61P25/06 A61K31/55

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/092166 A (MERCK & CO., INC; BURGEY, CHRISTOPHER, S; DENG, ZHENGWU, J; NGUYEN, DI) 28 October 2004 (2004-10-28) cited in the application abstract; tables E-4	1-14
A	WO 2004/082602 A (MERCK & CO. INC; BELL, IAN, M; GALLICCHIO, STEVEN, N; STUMP, CRAIG, A;) 30 September 2004 (2004-09-30) examples 10,11,13	1-14
A	WO 2004/002960 A (SCHERING AKTIENGESELLSCHAFT; DUNNING, LAURA; JAROCH, STEFAN; KOCHANNY,) 8 January 2004 (2004-01-08) abstract; examples 182,183,196-262	1-14
	-/-	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubt 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
- *8* document member of the same patent family

Date of the actual completion of the international search

9 February 2006

Date of mailing of the international search report

21/02/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentkan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl
Fax (+31-70) 340-3016

Authorized officer

Eberhard, M

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INTERNATIONAL SEARCH REPORT

Patent application No
/US2005/036859

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/002495 A1 (SHER PHILIP ET AL) 1 January 2004 (2004-01-01) abstract; examples 31,32,44-47,56 -----	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/036859

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 12 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

international application No
/US2005/036859

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 2004092166	A	28-10-2004	AU	2004230926 A1	28-10-2004
			CA	2522220 A1	28-10-2004
			WO	2004092168 A1	28-10-2004
WO 2004082602	A	30-09-2004	AU	2004222378 A1	30-09-2004
			CA	2518830 A1	30-09-2004
			EP	1613368 A2	11-01-2006
WO 2004002960	A	08-01-2004	AU	2003247772 A1	19-01-2004
			BR	0312204 A	26-04-2005
			CA	2489560 A1	08-01-2004
			CN	1678586 A	05-10-2005
			EP	1534681 A1	01-06-2005
			JP	2005537247 T	08-12-2005
US 2004002495	A1	01-01-2004	NONE		

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BRISTOL-MYERS SQUIBB COMPANY
Attn: Epperson, James
P.O. Box 4000
Princeton, NJ 08453-4000
UNITED STATES OF AMERICA

PCT
NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

21/02/2006

Applicant's or agent's file reference

10243 PCT

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2005/036859

International filing date
(day/month/year)

12/10/2005

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 48):

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, 84 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 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 30 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 18 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.

RECEIVED

BMS PATENT LAW

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Petersilien 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

John De Bruijn

FEB 22 2006

Docketed Item Claims Amended

Due Date Int'l Exam 9/3/06

Attorney (See notes on accompanying sheet)

Epperson

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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume IA, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume IA, paragraph 286).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 18 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 10243 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 6 below.	
International application No. PCT/US2005/036859	International filing date (day/month/year) 12/10/2005	(Earliest) Priority Date (day/month/year) 03/11/2004
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 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the International search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.8(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
/US2005/036859

A. CLASSIFICATION OF SUBJECT MATTER

C07D487/04 C07D401/14 C07D519/00 A61P25/06 A61K31/55

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P A61K

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

Electronic data bases consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/092166 A (MERCK & CO., INC; BURGEY, CHRISTOPHER, S; DENG, ZHENGWU, J; NGUYEN, DI) 28 October 2004 (2004-10-28) cited in the application abstract; tables E-4	1-14
A	WO 2004/082602 A (MERCK & CO. INC; BELL, IAN, M; GALLICCHIO, STEVEN, N; STUMP, CRAIG, A;) 30 September 2004 (2004-09-30) examples 10,11,13	1-14
A	WO 2004/002960 A (SCHERING AKTIENGESELLSCHAFT; DUNNING, LAURA; JAROCH, STEFAN; KOCHANNY,) 8 January 2004 (2004-01-08) abstract; examples 182,183,196-262	1-14
	-/-	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

9 February 2006

Date of mailing of the international search report

21/02/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5518 Patentlaan 2
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Tel (+31-70) 340-2040, Tx 31 651 epo nl,
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Authorized officer

Eberhard, M

INTERNATI NAL SEARCH REPORT

International application No.
PCT/US2005/036859

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/002495 A1 (SHER PHILIP ET AL) 1 January 2004 (2004-01-01) abstract; examples 31,32,44-47,56	1-14

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Form PCT/ISA/210 (continuation of second sheet) (April 2000)

page 2 of 2

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/036859

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 12 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/036859

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004092166	A	28-10-2004	AU 2004230926 A1	28-10-2004
			CA 2522220 A1	28-10-2004
			WO 2004092168 A1	28-10-2004
WO 2004082602	A	30-09-2004	AU 2004222378 A1	30-09-2004
			CA 2518830 A1	30-09-2004
			EP 1613368 A2	11-01-2006
WO 2004002960	A	08-01-2004	AU 2003247772 A1	19-01-2004
			BR 0312204 A	26-04-2005
			CA 2489560 A1	08-01-2004
			CN 1678586 A	05-10-2005
			EP 1534681 A1	01-06-2005
			JP 2005537247 T	08-12-2005
US 2004002495	A1	01-01-2004	NONE	

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/US2005/036859	International filing date (day/month/year) 12.10.2005	Priority date (day/month/year) 03.11.2004

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, C07D401/14, C07D519/00, A61P25/06, A61K31/55

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Paternlaan 2
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Authorized Officer

Eberhard, M

Telephone No. +31 70 340-8519



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/036859

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/036859

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12 and 14

because:

☒ the said international application, or the said claims Nos. 12 and 14 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/036859

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	
Inventive step (IS)	Yes: Claims	1-14
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11, 13
	No: Claims	

2. Citations and explanations

see separate sheet

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/036859

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 For the assessment of the present claims 12 and 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

III.2 Claims 12 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Subject-matter

The present application describes benzazepan-derived compounds linked to other heterocyclic moieties and their use as CGRP antagonists.

V.2 Documents

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/036859

- D1: WO 2004/092166 A (MERCK & CO., INC; BURGEY, CHRISTOPHER, S; DENG, ZHENGWU, J; NGUYEN, DI) 28 October 2004 (2004-10-28)
D2: WO 2004/082602 A (MERCK & CO. INC; BELL, IAN, M; GALLICCHIO, STEVEN, N; STUMP, CRAIG, A;) 30 September 2004 (2004-09-30)
D3: WO 2004/002960 A (SCHERING AKTIENGESELLSCHAFT; DUNNING, LAURA; JAROCH, STEFAN; KOCHANNY,) 8 January 2004 (2004-01-08)
D4: US 2004/002495 A1 (SHER PHILIP ET AL) 1 January 2004 (2004-01-01)

V.3 Novelty

Documents D1-D4 disclose azepan-based compounds which are linked to other heterocyclic moieties and are useful as CGRP receptor antagonists (abstract, Table E-4, D1; examples 10, 11 and 13, D2; abstract, examples 182, 183, 196-262, D3) or for the treatment of diabetes (abstract, examples 31, 32, 44-47, 56; D4). The benzazepan compounds of the present application are structurally different to the ones disclosed in D1-D4 i.e. they comprise different linkers to other heterocyclic moieties and in none of the prior art documents is the benzazepan-ring fused with another heterocyclic ring. Thus, claims 1-14 of the present application can be considered novel with regard to D1-D4 (Article 33(2) PCT).

V.4 Inventive step

- Closest prior art:** Document D1 is considered to be the closest prior art. D1 discloses azepan-based compounds connected to an oxo-imidazo condensed pyridine via an amido-piperidine linker (abstract, Table E-4; D1).
- Difference:** The compounds are structurally different to the present application.
- Problem:** The provision of alternative azepan-based compounds useful as CGRP antagonists.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/036859

Solution: Compounds and use according to claims 1-14.

D1 does not provide an indication for the skilled person to use a benzazepan-ring or a benzazepan-ring fused with a heterocycle instead of an aryl-substituted azepan-ring and said compounds being useful as CGRP antagonists. Thus, claims 1-14 of the present application can be considered inventive with regard to D1 (Article 33(2) PCT).

PCT

REPORTE DE BUSQUEDA INTERNACIONAL
(Artículo 18 y Reglas 43 y 44)

Referencia de archivo del solicitante o agente 10243 PCT	PARA ACCION ADICIONAL Ver la Forma PCT/ISA/220
Solicitud internacional No. PCT/US2005/036859	Fecha de presentación internacional (día/mes/año) 12/10/2005
Fecha de prioridad (día/mes/año) 03/11/2004	
Solicitante BRISTOL - MYERS SQUIBB COMPANY	

Este reporte es el reporte de búsqueda internacional, establecido por esta Autoridad de Búsqueda Internacional y se transmite al solicitante de acuerdo al Artículo 18. Una copia del mismo ha sido transmitida a la Oficina Internacional

Este REPORTE consiste de un total de 5 hojas

☒ También ha sido acompañado por una copia de cada documento del arte previo citado en este reporte

1. Bases del Reporte

a. Con respecto al lenguaje, la búsqueda internacional ha sido llevada a cabo sobre la base de la solicitud internacional en el lenguaje en el cuál fue presentado, a menos que se indique lo contrario bajo este punto.

☒ la solicitud internacional en el idioma en el cual ha sido llenado

☐ La búsqueda Internacional ha sido llevada a cabo en base a la traducción de la solicitud internacional presentada a esta Autoridad (Regla 23.1(b)).

b. ☐ Con respecto a cualquier secuencia de nucleótidos y aminoácidos descrita en la Solicitud Internacional, ver recuadro I.

2. ☒ Ciertas reivindicaciones fueron encontradas como no sometidas a una búsqueda (Ver recuadro II).

3. ☐ Carecen de unidad de invención

4. Con respecto al título,

☒ el texto es aprobado como fue presentado por el solicitante

☐ el texto ha sido establecido por esta Autoridad para leerse como sigue:

5. Con respecto al resumen

☒ el texto es aprobado como fue presentado por el solicitante

☐ el texto ha sido establecido de acuerdo a la Regla 38.2(B), por esta autoridad como aparece en el recuadro IV. El solicitante puede, dentro de un mes de la fecha de envío de este reporte, presentar sus comentarios a esta Autoridad.

6. Con respecto a los dibujos

a. La figura de los dibujos ha ser publicada con el resumen en la Figura No. _____

☐ como se sugirió por el solicitante

☐ como se selecciono por esta Autoridad, debido a que el solicitante fallo al sugerir una figura.

☐ como se selecciono por esta Autoridad, debido a que esta figura caracteriza mejor la invención.

b. ☒ ninguna de estas figuras es publicada con el resumen

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US 2005/032859

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A. CLASIFICACION DEL TEMA

C07D487/04 C07D401/14 C07D519/00 A61P25/06 A61K31/55

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):
C07D A61P A61K

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos están incluidos en los campos buscados:

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):
EPO-Internal, WPI data, PAJ, CHEM ABS Data

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Relv. No.
A	WO 2004/092166 A (MERCK & CO., INC; BURGEY, CHRISTOPHER, S; DENG, ZHENGWU, J; NGUYEN, DI) 28 Octubre 2004 (2004-10-28) citada en la aplicación resumen; tablas E-4	1-14
A	WO 2004/082602 A (MERCK & CO. INC; BELL, IAN, M; GALLICCHIO, STEVEN, N; STUMP, CRAIG, A;) 30 Septiembre 2004 (2004-09-30) ejemplos 10,11,13	1-14
A	WO 2004/002960 A (SCHERING AKTIENGESELLSCHAFT; DUNNING, LAURA; JAROCH, STEFAN; KOCHANNY,) 8 Enero 2004 (2004-01-08) resumen; ejemplos 182,183,196-262	1-14

☒ Documentos adicionales se enlistan en la continuación del bloque C ☒ Véase familia de patentes anexa.

* Categorías especiales de los documentos citados

"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.

"E" documento anterior 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 presentación internacional pero después de la fecha de prioridad reivindicada.

"T" documento posterior publicado después de la fecha de presentación internacional o 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 reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada.

"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.

"Z" documento miembro de la misma familia de patentes.

Fecha de la terminación real de la búsqueda internacional
9 Febrero 2006

Fecha de envío del reporte de búsqueda internacional
21/02/2005

Nombre y dirección de correspondencia de la ISA
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Fax: (+31-70)340-3016

Funcionario Autorizado

Eberdhard, M

Forma PCT/ISA/210 (segunda hoja) (Enero 2004)

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US 2005/036859

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C(Continuación). DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
A	US 2004/002495 A1 (SHER PHILIP ET AL) 1 Enero 2004 (2004-01-01) resumen; ejemplos 31,32,44-47,56 -----	1-14

Forma PCT/ISA/210 (continuación segunda hoja) (Enero 2004)

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US 2005/036859

Bloque I Observaciones en donde ciertas reivindicaciones se encontraron inescrutables (Continuación del ítem 1 de la primera hoja)

Este reporte internacional no ha sido establecido con respecto a ciertas reivindicaciones bajo el Artículo 17(2) del PCT por las siguientes razones:

- ☒ Reivindicaciones Nos.:
debido a que se relacionan con temas que no requieren ser buscados por esta Autoridad, a saber:
Aunque las reivindicaciones 12 y 14 esta dirigida a un método de tratamiento del cuerpo humano/animal, la búsqueda ha sido llevada a cabo y basada en los efectos alegados de la composición.
- ☐ Reivindicaciones Nos.:
debido a que se relacionan con partes de la solicitud internacional que no cumplen con los requerimientos prescritos a tal extensión que ninguna búsqueda internacional significativa se puede llevar a cabo, específicamente:
- ☐ Reivindicaciones Nos.:
debido a que son reivindicaciones dependientes y no están redactadas de acuerdo con las segundas y terceras oraciones de la Regla 6.4(a).

Bloque II Observaciones en donde se carece de unidad de la invención (Continuación del ítem 2 de la primera hoja)

La Autoridad de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, como sigue:

- ☐ Ya que todas las cuotas de búsqueda adicionales fueron pagadas a tiempo por la solicitante, este reporte de búsqueda cubre todas las reivindicaciones escrutables.
- ☐ Ya que todas las reivindicaciones escrutables pudieron ser buscadas sin esfuerzo que justifique una cuota adicional, esta Autoridad no invita al pago de ninguna cuota adicional.
- ☐ Ya que solamente algunas de las cuotas de búsqueda adicionales requeridas fueron pagadas oportunamente por la Solicitante, este reporte de búsqueda internacional cubre solamente aquellas reivindicaciones para las cuales se pagaron Cuotas, específicamente las reivindicaciones Nos.:
- ☐ Ninguna cuota de búsqueda adicional requerida fue pagada oportunamente por la solicitante. Consecuentemente, este Reporte de búsqueda internacional está restringido a la invención primero mencionada en las reivindicaciones; está Cubierta por las reivindicaciones Nos.:

Observación en protesta ☐ Las cuotas de búsqueda adicionales estuvieron acompañadas por la protesta de la solicitante.
☐ Ninguna protesta acompañó el pago de las cuotas de búsqueda adicional.

REPORTE DE BUSQUEDA INTERNACIONAL

No. De solicitud internacional
PCT/US 2005/036859

Documento de patente citado en el Reporte de Búsqueda	Fecha de publicación	Miembro(s) de la familia de patente(s)	Fecha de publicación
WO 2004092166 A	28-10-2004	AU 2004230926 A1 CA 2522220 A1 WO 2004092168 A1	28-10-2004 28-10-2004 28-10-2004
WO 2004082602 A	30-09-2004	AU 2004222378 A1 CA 2518830 A1 EP 1613368 A2	30-09-2004 30-09-2004 11-01-2006
WO 2004002960 A	08-01-2004	AU 2003247772 A1 BR 0312204 A CA 2489560 A1 CN 1678586 A EP 1534681 A1 JP 2005537247 T	19-01-2004 26-04-2005 08-01-2004 05-10-2005 01-06-2005 08-12-2005
US 2004002495 A1	01-01-2004	NINGUNO	

TRATADO DE COOPERACION EN MATERIA DE PATENTES .

De la
AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL

610

Para: ver forma PCT/ISA/220		PCT OPINIÓN ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL (Regla 43bis.1 PCT)	
		Fecha de envío (día/mes/año) ver forma PCT/ISA/220 (segunda hoja)	
Referencia de archivo del solicitante o agente ver forma PCT/ISA/220		PARA ACCIÓN ADICIONAL Ver párrafo 2 siguiente	
No. de solicitud internacional PCT/US2005/036859	Fecha de presentación internacional (día/mes/año) 12.10.2005	Fecha de prioridad (día/mes/año) 03.11.2004	

Clasificación de Patente Internacional (IPC) o ambas clasificación nacional e IPC
C07D487/04, C07D401/14, C07D519/00, A61P25/06, A61K31/55

Solicitante
BRISTOL - MYERS SQUIBB COMPANY

1. Esta opinión contiene las indicaciones relacionadas a los siguientes incisos:
- ☒ Cuadro No. I Bases de la Opinión
 - ☐ Cuadro No. II Prioridad
 - ☒ Cuadro No. III Sin establecimiento de la opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial
 - ☐ Cuadro No. IV Carente de unidad de la invención
 - ☒ Cuadro No. V Declaración razonada bajo la Regla 43bis.1(a)(i) con respecto a la novedad, etapa inventiva y aplicabilidad industrial; citas y explicaciones que soportan esta declaración.
 - ☐ Cuadro No. VI Ciertos documentos citados
 - ☐ Cuadro No. VII Ciertos defectos en la solicitud internacional
 - ☐ Cuadro No. VIII Ciertas observaciones en la solicitud internacional

2. ACCIÓN ADICIONAL

Si se hace una demanda para el examen preliminar internacional, esta opinión será considerada ser una opinión escrita de la Autoridad de Examen Preliminar Internacional ("IPEA") a menos que ese esto no aplique donde el aspirante elige una Autoridad de otra manera que uno sea la IPEA y la IPEA elegida haya notificado a la Oficina Internacional bajo la Regla 66.1bis(b) donde las opiniones escritas de esta Autoridad de Búsqueda Internacional no serán así considera.

Si esta opinión es, como la provista anteriormente, considerada para ser una opinión escrita de la IPEA, se invita al solicitante a someter a la IPEA una respuesta escrita a la vez, cuando sea apropiado, con enmiendas, antes de la expiración de 3 meses a partir de la fecha del correo de la forma PCT/ISA/220 o antes de la expiración de 22 meses a partir de la fecha de prioridad, cualquiera expira más adelante.

Para otras opciones, ver Forma PCT/ISA/220.

3. Para otros detalles, ver notas para la Formar PCT/ISA/220.

Nombre y dirección de correspondencia de la ISA: European Patent Office .PB. 5818 Patentlaan 2 NL-2280 HV Rijswijk + Pays Bas Tel (+31-70)340-2040, Tx. 31 651 epo nl Fax: (+31-70)340-3016	Oficial autorizado Eberhard, M Teléfono No. +31 70 340 - 9519

Forma PCT/ISA/237 (carátula) (Enero2004)

Cuadro No. I Bases de la opinión

1. Con respecto al idioma, esta opinión se estableció basada sobre las bases de: la solicitud internacional en el idioma en el cual ha sido llenado

- ☐ Esta opinión se estableció basado en la traducción del idioma original en el siguiente idioma, que es el idioma de una traducción proporcionada para los propósitos de la búsqueda internacional (bajo las Reglas 12.3 y 23.1 (b)).

2. Con respecto a cualquier **secuencia nucleótido y amino ácido** publicada en la solicitud internacional y necesaria para la invención reivindicada esta opinión se estableció basada en:

a. tipo de material:

- ☐ un listado de secuencia
☐ tabla(s) relacionada con el listado de secuencia

b. formato de material:

- ☐ en formato escrito
☐ en forma legible en computadora

c. tiempo de limite/proporcionar:

- ☐ contenido en la solicitud internacional como se archivo.
☐ archivado junto con la solicitud internacional en forma legible en computadora.
☐ proporcionado subsecuencialmente para esta autoridad para el propósito de búsqueda.

3. ☐ Además, en el caso que más de una versión o copia del listado de secuencia y/o en relación a la misma tabla se archivo o proporciono, las declaraciones requeridas de la información en las copias subsecuentes o adicionales son idénticas a esa solicitud archivada o no va más allá de la solicitud archivada, como apropiadamente, fue proporcionada.

4. Comentarios adicionales:

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Cuadro No. III. Sin establecimiento de la opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial.

1. Las cuestiones de si la invención reivindicada parece que es nueva, que comprende una etapa inventiva (que sea obvio), o que es aplicable industrialmente no serán examinadas con respecto de:

- ☐ la solicitud Internacional completa
- ☒ reivindicaciones Nos. 13 y 14
debido a que:
- ☒ la solicitud Internacional, o las reivindicaciones Nos. 13-15 se relacionan al siguiente tema que no requiere un examen preliminar Internacional (*especifica*):
ver hoja separada
- ☐ la descripción, reivindicaciones o dibujos (indicar los elementos particulares a continuación) o las reivindicaciones Nos. _____ no son claras de modo que no se puede formar una opinión (*especifica*):
- ☐ las reivindicaciones, o las reivindicaciones Nos. ____ se soportan inadecuadamente por la descripción de modo que no se puede formar una opinión significativa.
- ☐ no se ha establecido ningún reporte de búsqueda Internacional para las reivindicaciones Nos.
- ☐ el listado de secuencias del nucleótido y/o aminoácidos no cumple con el estándar proporcionado para un Anexo C de las Instrucciones Administrativas en que:
 - la forma escrita ☐ no se ha suministrado
 - ☐ no cumple con el estándar
 - la forma legible por computadora ☐ no se ha suministrado
 - ☐ no cumple con el estándar
- ☐ las tablas relacionadas el listado de secuencias del nucleótido y/o aminoácidos, si solo en la forma legible por computadora, no cumplen con los requisitos técnicos proporcionados para el Anexo C – bis de las Instrucciones Administrativas
- ☐ ver hoja separada para detalles adicionales

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Recuadro III

Sin establecimiento de la opinión con respecto a la novedad, etapa inventiva y aplicabilidad Industrial.

III.1

III.2

Recuadro V

Declaración razonada con respecto a la novedad, etapa inventiva o aplicabilidad Industrial; citas y explicaciones que soportan esta declaración

V.1

V.2 Documentos

Referencia esta hecha a los siguientes documentos; la numeración sera adherida en el resto de el procedimiento.

OPINION ESCRITA DE
AUTORIDAD DE BUSQUEDA INTERNACIONAL

No. de Solicitud Internacional
PCT/US2005/036859

614

- D1: WO 2004/092166 A (MERCK & CO., INC; BURGEY, CHRISTOPHER, S; DENG, ZHENGWU, J; NGUYEN, DI) 28 Octubre 2004 (2004-10-28)
- D2: WO 2004/082602 A (MERCK & CO. INC; BELL, IAN, M; GALLICCHIO, STEVEN, N; STUMP, CRAIG, A;) 30 Septiembre 2004 (2004-09-30)
- D3: WO 2004/002960 A (SCHERING AKTIENGESELLSCHAFT; DUNNING, LAURA; JAROCH, STEFAN; KOCHANNY,) 8 Enero 2004 (2004-01-08)
- D4: US 2004/002495 A1 (SHER PHILIP ET AL) 1 Enero 2004 (2004-01-01)

V.3 Novedad

V.4 Etapa inventiva

Closets prior art:

Diferencia: Los compuestos son estructuralmente diferentes a la presente aplicación.

Problema: La provisión de alternativa de compuestos azepan-basados usados como antagonistas CGRP.

Solucion: Compuestos y usos acordados en las reivindicaciones 1-14.

PATENT COOPERATION TREATY

PCT/US2005/036859

10243-60-PCT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

To: **RECEIVED**
BMS PATENT LAW
EPPERSON, James
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
JAN 26 2006
Due Date
Attorney

(PCT Administrative Instructions, Section 4)

Date of mailing (day/month/year) 20 December 2005 (20.12.2005)	JAN 27 2006	Due Date	Attorney
Applicant's or agent's file reference 10243PCT	BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT	IMPORTANT NOTIFICATION	
International application No. PCT/US2005/036859	WALLINGFORD, VT	Filing date (day/month/year) 12 October 2005 (12.10.2005)	1/24/2006
International publication date (day/month/year)		Priority date (day/month/year) 03 November 2004 (03.11.2004)	
Applicant BRISTOL-MYERS SQUIBB COMPANY et al			

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, 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.
- (If applicable) 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) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) 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
03 November 2004 (03.11.2004)	80/824,855	US	05 December 2005 (05.12.2005)
05 May 2005 (05.05.2005)	80/878,099	US	05 December 2005 (05.12.2005)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Arunkumar NAIR Facsimile No. (41-22) 338.87.40 Telephone No. +41 22 338 8157

Facsimile No. +41 22 338 82 70
Form PCT/IB/304 (January 2004)

COT9983Y

PATENT COOPERATION TREATY

10243-WO-PCT

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 28bis.1 and 28bis.2 and Administrative Instructions, Sections 402(c) and 408)

From the INTERNATIONAL BUREAU

To:

BMS PATENT LAW

EPPERSON, James
 Bristol-Myers Squibb Company
 P.O. Box 4000
 Princeton, NJ 08540
 United States of America

FEB 07 2006

Discontinued Item

Due Date

Attorney

Date of mailing (day/month/year)

31 January 2006 (31.01.2006)

Applicant's or agent's file reference

10243PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US2005/036859

International filing date (day/month/year)

12 October 2005 (12.10.2005)

Applicant

BRISTOL-MYERS SQUIBB COMPANY et al

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

1. ☒ Correction of priority claim. In accordance with the applicant's notice received on: 08 January 2006 (08.01.2006), the following priority claim has been corrected, according to paragraph 178 of the PCT Receiving Guidelines where application, to read as follows:

US 11 October 2005 (11.10.2005) 11/247,697

- ☐ even though the indication of the number of the earlier application is missing.
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

2. ☐ Addition of priority claim. In accordance with the applicant's notice received on: FEB 15 2006, the following priority claim has been added:

- ☐ even though the indication of the number of the earlier application is missing.
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

3. ☐ As a result of the correction and/or addition of (s) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:

4. ☐ Priority claim considered not to have been made.

- ☐ The applicant failed to respond to the invitation under Rule 28bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 28bis.1(a).
☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 28bis.2(d) and the PCT Applicant's Guide, Volume I, Annex B2(18).

5. ☒ Where multiple priorities have been claimed, the above item(s) relate(s) to the following priority claim(s):

US 11 October 2005 (11.10.2005) 11/247,697

6. A copy of this notification has been sent to the receiving Office and

- ☒ to the International Searching Authority (where the international search report and the written opinion of the International Searching Authority have not yet been issued).
☐ the designated Offices (in accordance with Rule 93bis).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Authorized officer

Carine SEVILLANO (Fax 022 338 87 40)

Facsimile No. (41-22) 338.87.40

Telephone No. (41-22) 338 9254

Form PCT/IB/316 (January 2004)

006895087

617

Docket No.10243PCT

IN THE UNITED STATES RECEIVING OFFICE

International Application No.: PCT/US2005/036859
International Filing Date: 12 October 2005
Priority Date: 03 November 2004
Applicant: Bristol-Myers Squibb Company, et al.
For: Constrained Compounds As CGRP-Receptor Antagonists

Via Facsimile - No. 571-273-3201
PCT Operations
Alexandria, VA 22313-1450

Response to Notification Relating to Priority Claim

Dear Sir:

Reference is made to the Notification Relating to Priority Claim mailed on October 24, 2006 in the above international application (copy attached). The Notification mistakenly lists the corrected priority claim as 11/251,432. Please note, that the correct priority claim is 11/247,697 as is indicated on the Correction to Priority Claim (Rule 26 Bis) that Applicant submitted on December 21, 2005 (copy attached). Please correct the record of the PCT case accordingly.

Respectfully submitted,

BRISTOL-MYERS SQUIBB COMPANY

By: James Epperson
James Epperson, Agent for Applicant
Reg. No. 52,867
P.O. Box 4000
Princeton, New Jersey 08543-4000
Telephone: (203)677-6974

Dated: November 10, 2006

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PATENT COOPERATION TREATY

10243-WO-A7

From the RECEIVING OFFICE

To:
JAMES EPPERSON
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and
Administrative Instructions, Sections 302 and 314)

Date of mailing
(day/month/year) 24 OCT 2006

Applicant's or agent's file reference 10243PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2005/038858	International filing date (day/month/year) 12 Oct 2005
Applicant BRISTOL-MYERS SQUIBB COMPANY	

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

- ☒ Correction of priority claim. In accordance with the applicant's notice received on 08 JANUARY 2006 the following priority claim has been corrected to read as follows:
US 11 OCTOBER 2005 11/251,432 - not in final.
☒ even though the indication of the number of the earlier application is missing
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document
- ☐ Addition of priority claim. In accordance with the applicant's notice received on _____ the following priority claim has been added:
☐ even though the indication of the number of the earlier application is missing
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document
- ☒ As a result of the correction and/or addition of (s) priority claim(s) under items 1 and/or 2, the (corrected) priority date is: 03 NOVEMBER 2004
- ☐ The priority claim (see also item 5, below, if applicable) is considered not to have been made because:
☐ the applicant failed to respond to the invitation under Rule 26bis.2(a) (Form PCT/RO/110) within the prescribed time limit
☐ the applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a)
☐ the applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10
The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(a) and the PCT Applicant's Guide, Volume I, Annex B2(B).
- ☐ The priority claim cannot be corrected/added since the applicant's notice was received on _____ after expiration of the prescribed time limit under Rule 26bis.1(a).
- ☒ In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s): VI-3
- A copy of this notification has been sent to the International Bureau and ☒ in the International Searching Authority

Name and mailing address of the receiving Office
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450
Facsimile No. 571-373-3201

Authorized officer

Virginia Irbay

Telephone No. 703-305-9290 EX 107

RECEIVED
BMS PATENT LAW

Form PCT/RO/111 (April 2006)

OCT 26 2006

Docketed Item _____
Due Date _____
Attorney Epperson

Addressee's fax number: 203-677-6900

WORLD INTELLECTUAL PROPERTY ORGANIZATION (WIPO)
ORGANISATION MONDIALE DE LA PROPRIÉTÉ INTELLECTUELLE (OMPI)



PCT

(Patent Cooperation Treaty)

34, chemin des Colombettes - 1211 Geneva 20 - Switzerland
Tel (41-22) 338 9111 - Telex 412 912 ompl ch
PCT Facsimile (41-22) 338.87.40

Facsimile/Télécopie

Date : 29 December 2005 (29.12.2005) Fax: 203-677-6900

To : EPPERSON, James
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

ETATS-UNIS D'AMERIQUE

File Reference: 10243PCT

From : Carine SEVILLANO

Telephone: (41-22) 338 9254

Email address: carine.sevillano@wipo.int

Concerns: PCT/US2006/036859

Number of pages including cover sheet : 1

Dear Sir:

With reference to form PCT/RO/110 concerning the missing serial number for Item 3 of the priority claims sent to you by the receiving Office US on 29 November 2005, and in order for publication to appear correctly, please could you inform us of the missing serial number. If you have already sent a response to the receiving Office US, please send us a copy of your reply accompanied by the date-stamped receipt card.

Please respond by facsimile to +41 22 338 87 40.

Thanking you in advance for your kind cooperation, I remain.

With best regards,

Carine SEVILLANO
PCT Examination Section

Fax: (41-22) 338.87.40

Sevillano

SAI
620

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2005/036859

International filing date: 12 October 2005 (12.10.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 11/247,697
Filing date: 11 October 2005 (11.10.2005)

Date of receipt at the International Bureau: 15 March 2006 (15.03.2006)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

Handwritten signature

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10243PCT

1/0

PCT REQUEST

Original (for SUBMISSION)

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 Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.173)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	10243PCT
I	Title of invention	CONSTRAINED COMPOUNDS AS CORP-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	Route 206 and Province Line Road Princeton, New Jersey 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	CHATURVEDULA, Prasad, V.
III-1-5	Address	190 Lancaster Way Cheshire, Connecticut 06410 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

62X

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10243PCT

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PCT REQUEST

Original (for SUBMISSION)

III-2	Applicant and/or inventor	applicant and inventor US only MERCER, Stephen, E. 62 Sisk Street Middletown, Connecticut 06457 United States of America US US
III-2-1	This person is	
III-2-2	Applicant for	
III-2-4	Name (LAST, First)	
III-2-5	Address	
III-2-6	State of nationality	
III-2-7	State of residence	
III-3	Applicant and/or inventor	applicant and inventor US only FANG, Haiquan 304 County Road Madison, Connecticut 06443 United States of America CN US
III-3-1	This person is	
III-3-2	Applicant for	
III-3-4	Name (LAST, First)	
III-3-5	Address	
III-3-6	State of nationality	
III-3-7	State of residence	
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent EPPELSON, James Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America 203-677-6974 203-677-6900 52,867
IV-1-1	Name (LAST, First)	
IV-1-2	Address	
IV-1-3	Telephone No.	
IV-1-4	Facsimile No.	
IV-1-5	Agent's registration No.	
IV-2	Additional agent(s)	
IV-2-1	Name(s)	

10243PCT

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PCT REQUEST

Original (for SUBMISSION)

		GIBBONS, Maureen, S. (44,121); KILCOYNE, John, M. (33,100); KORSER, Elliott (32,705); LAMERDIN, John, A. (44,858); O'BRIEN, Maureen, P. (42,043); PROVOOST, Jonathan, H. (44,292); RODNEY, Burton (22,076); SHER, Audrey, F. (39,024); VANATTEN, Mary, K. (39,408); WINSLOW, Anastasia, P. (40,875); ALGERI, Aldo, A. (31,697); MAKUJIMA, Shab, R. (41,174); RYAN, Richard, P. (30,491); VOLLES, Warren, K. (33,810); MINGO, Pamela, A. (48,256); GREENBLATT, Gary, D. (47,609); CHIN, Jennifer, T. (47,487); WANG, Joseph, C. (44,391); WILLE, Louis, J. (32,954); FARLET, Mickel, L. (44,996); COHEN, Jacqueline, M. (51,574); KRIEGER, Stuart, E. (28,731); SCHMIDT, Richard, D. (31,301)
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.8(a), the designation of all Contracting States bound by the PCT on the International filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	03 November 2004 (03.11.2004)
VI-1-2	Number	60/624,655
VI-1-3	Country	US
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	05 May 2005 (05.05.2005)
VI-2-2	Number	60/678,099
VI-2-3	Country	US
VI-3	Priority claim of earlier national application	
VI-3-1	Filing date	11 October 2005 (11.10.2005)
VI-3-2	Number	
VI-3-3	Country	US
VI-4	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

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10243PCT

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PCT REQUEST

Original (for SUBMISSION)

VI-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VII	Declarations	Number of declarations	
VII-1	Declaration as to the identity of the inventor	-	
VII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	1	
VII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	2	
VII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

10249PCT

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PCT REQUEST

Original (for SUBMISSION)

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(i) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i) v)		an assignment from CHATURVEDULA, Prasad, V. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2005 (03.01.2005)
VIII-2-1(i) v)		an assignment from MERCER, Stephen, E. to BRISTOL-MYERS SQUIBB COMPANY, dated 30 December 2004 (30.12.2004)
VIII-2-1(i) v)		an assignment from CHATURVEDULA, Prasad, V. to BRISTOL-MYERS SQUIBB COMPANY, dated 31 May 2005 (31.05.2005)
VIII-2-1(i) v)		an assignment from MERCER, Stephen, E. to BRISTOL-MYERS SQUIBB COMPANY, dated 24 May 2005 (24.05.2005)
VIII-2-1(i) x)	This declaration is made for the purpose of:	all designations except the designation of the United States of America

10243PCT

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PCT REQUEST

Original (for SUBMISSION)

VII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(ii) and 51bis.1(a)(ii)) Name	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/624,655 by virtue of the following:
VIII-3-1(i) v)		an assignment from CHATURVEDULA, Prasad, V. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2005 (03.01.2005)
VIII-3-1(i) v)		an assignment from MERCER, Stephen, E. to BRISTOL-MYERS SQUIBB COMPANY, dated 30 December 2004 (30.12.2004)
VIII-3-1(i) x)	This declaration is made for the purposes of:	AP: (BW GH GN KE LS MN NX NA SD SL SZ TZ UG ZM ZW); EA: (AM AE BY KG KZ MD RU TU TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LT LU LV MC NL PL PT RO SE SI SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW NX NY SD SN SG SK SL SM SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

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10243PCT

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PCT REQUEST

Original (for SUBMISSION)

VIII-3-2	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(B) and 51bis.1(a)(B)) Name:	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/678,099 by virtue of the following:
VIII-3-2(v)		an assignment from CHATONVEDOLA, Prasad, V. to BRISTOL-MYERS SQUIBB COMPANY, dated 31 May 2005 (31.05.2005)
VIII-3-2(v)		an assignment from MERCHER, Stephen, E. to BRISTOL-MYERS SQUIBB COMPANY, dated 24 May 2005 (24.05.2005)
VIII-3-2(x)	This declaration is made for the purpose of:	AP: (BW GH GM KN LS MW MX NA SD SL SZ TZ UG ZM ZW); EA: (AM AE BY KG KE MD RU TJ TM); EP: (AT BE BG CH&LI CY CE DE DK EE ES FI FR GB GR HU IE IS IT LT LU LV MC NL PL PT RO SE SI SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AX BA BB BG BR BW BY BE CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HA HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MY NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

10243PCT

B/B

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	9	✓
IX-2	Description	240	-
IX-3	Claims	9	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	259	
	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-SAFE physical media	-	✓
IX-18	other		
IX-18	other	Postcard receipt; Certificate of Express Mailing; 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	<i>James Epperson</i>	
X-1-1	Name (LAST, First)	EPPERSON, James	
X-1-2	Name of signatory		
X-1-3	Capacity		

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/EP
10-6	Transmittal of search copy delayed until search fee is paid	

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10243PCT

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PCT REQUEST

Original (for SUBMISSION)

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

10243PCT

1/1

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(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/RQ/101 (Annex)	
0-4-1	PCT Fee Calculation Sheet Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.173)
0-9	Applicant's or agent's file reference	10243PCT
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (USD)
12-1	Transmittal fee T	⇒ 300
12-2-1	Search fee S	⇒ 2075
12-2-2	International search to be carried out by	EP
12-3	International filing fee (first 30 sheets) I1	1211
12-4	Remaining sheets	229
12-5	Additional amount (X) 13	
12-6	Total additional amount I2	2977
12-7	I1 + I2 = I	4188
12-12	EASY Filing reduction R	-87
12-13	Total international filing fee (I-R) I	⇒ 4101
12-14	Fee for priority document	
	Number of priority documents requested	3
12-15	Fee per document (X) 20	
12-16	Total priority document fee: P	⇒ 60
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒ 6536
12-19	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions	
	The receiving Office	United States Patent and Trademark Office (USPTO) (NO/US)
12-20-1	Authorization to charge the total fees indicated above	/
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	/
12-20-3	Authorization to charge the fee for priority document	/
12-21	Deposit account No.	19-3880
12-22	Date	12 October 2005 (12.10.2005)
12-23	Name and signature	EPPERSON, James <i>James Epperson</i>

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PCT

Original (for SUBMISSION)

13-1-1	Applicant Remarks	Please charge any additional fees to deposit account 19-3880.
13-1-2	Applicant Remarks	Abstract contains chemical structure.
13-2-4	Validation messages Priority	Yellow Priority 3: Application No. is missing
13-2-5	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
13-2-10	Validation messages Annotations	Green? All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

VII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(i) and 51bA.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i) v)		an assignment from CHATURVEDULA, Prasad, V. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2005 (03.01.2005)
VIII-2-1(i) v)		an assignment from MERCER, Stephen, E. to BRISTOL-MYERS SQUIBB COMPANY, dated 30 December 2004 (30.12.2004)
VIII-2-1(i) v)		an assignment from CHATURVEDULA, Prasad, V. to BRISTOL-MYERS SQUIBB COMPANY, dated 31 May 2005 (31.05.2005)
VIII-2-1(i) v)		an assignment from MERCER, Stephen, E. to BRISTOL-MYERS SQUIBB COMPANY, dated 24 May 2005 (24.05.2005)
VIII-2-1(i) d)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

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PCT/US2005/036859

VII-3-1	Declaration Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(ii) and 51bis.1(a)(ii)) Name	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/626,655 by virtue of the following:
VII-3-1(i)	v)	an assignment from CHATURVEDULA, Prasad, V. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2005 (03.01.2005)
VII-3-1(i)	v)	an assignment from MERCER, Stephen, E. to BRISTOL-MYERS SQUIBB COMPANY, dated 30 December 2004 (30.12.2004)
VII-3-1(ii)	This declaration is made for the purposes of:	AP: (EW GH GN KE LE MW NX NA SD SL SE TE UG EN ZW); EA: (AM AZ BY EG KE MD RU TJ TN); EP: (AT BE BG CHALI CY CE DE DK EE ES FI FR GE GR HU IE IS IT LT LU LV MC NL PL PT RO SE SI SK TR); OA: (BY BJ CF CG CI CM GA GN OQ OW XL MR NE SN TD TG); AE AG AL AN AT AU AX BA BB BG BR BW BY BE CA CHALI CN CO CR CU CE DE DK DM DE EC EE EG ES FI GE GO GN GH GR HU ID IL IN IS JP KE KG KM KP KR KE LC LK LA LE LT LU LV MA MD MG MK MN MW NX NE NA NG NI NO NZ OM PG PK PL PT RO RU SC SD SE SG SK SL SM SY TJ TN TM TR TT TE UA UG UZ VC VN TU VA XM ZW

524 634

PCT/US2005/036859

VII-3-2	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/678,099 by virtue of the following:
VIII-3-2(v)		an assignment from CHATURVEDULA, Prasad, V. to BRISTOL-MYERS SQUIBB COMPANY, dated 31 May 2005 (31.05.2005)
VIII-3-2(v)		an assignment from MERCER, Stephen, E. to BRISTOL-MYERS SQUIBB COMPANY, dated 24 May 2005 (24.05.2005)
VIII-3-2(v)	This declaration is made for the purposes of:	AP: (DW GH GM KE LE MN NE NA ND NL NE TE UG ZH ZW); EA: (AM AE BY KG KE MD RU TJ TH); EP: (AT BE BG CHALI CY CE DE DK EE ES FI FR GE GR HU IE IS IT LT LU LV MC NL PL PT RO SE SI SK TA); OA: (BF BJ CF CG CI CM GA GN GQ GW HL HA HE SN TD TG); AE AG AL AN AT AU AZ BA BB BG BR BW BY BE CA CHALI CN CO CR CU CE DE DK DN DE EC EE EG ES FI GE GO GH GI HA HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LA LS LT LU LV MA MD ME MK MN MW NX NE NA NG NI NO NZ OM PG PE PF PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TE UA UG UZ VC VN YU ZA ZN ZW

Petitorio PCT

0	Para uso de la Oficina receptora únicamente	
0-1	Solicitud internacional N°	
0-2	Fecha de presentación internacional	
0-3	Nombre de la oficina receptora y Solicitud internacional PCT	
0-4	Forma - PCT/RO/101 petitoria	
0-4-1	Preparado usando	PCT-SAFE [EASY model] versión 3.50 (construida 0002.173)
0-5	Petición El abajo firmante pide que la presente solicitud sea tramitada de conformidad con el Tratado de Cooperación en materia de Patentes.	
0-6	Oficina Receptora (especificada por el solicitante)	Oficina de Patentes y Marcas de los Estados Unidos (USPTO) (RO/US)
0-7	Referencia de archivo de solicitantes o agentes	10243 PCT
I	TITULO DE LA INVENCIÓN	COMPUESTOS ARTIFICIALES COMO ANTAGONISTAS DEL RECEPTOR CORP
II	Solicitante	
II-1	Esta persona es:	Solicitante únicamente
II-2	Solicitante para	Todos los estados designados excepto US
II-4	Nombre	BRISTOL-MYERS SQUIBB COMPANY
II-5	Dirección:	Route 206 and Province Line Road Princeton, New Jersey 08543-4000 Estados Unidos de América
II-6	Estado de Nacionalidad	US
II-7	Estado de Residencia	US
II-8	Teléfono No.	609-252-4000
II-9	Fax No.	609-252-4526
III-1	Solicitante y/o inventor	
III-1-1	Esta persona es:	Inventor y solicitante
III-1-2	Solicitante para:	Solo US
III-1-4	Nombre (primero y ultimo)	CHATURVEDULA, Prasad, V.
III-1-5	Dirección	190 Lancaster Way, Cheshire, Connecticut 06410 Estados Unidos de América
III-1-6	Estado de Nacionalidad	US
III-1-7	Estado de Residencia	US
III-2	Solicitante y/o inventor	
III-2-1	Esta persona es:	Inventor y solicitante
III-2-2	Solicitante para:	Solo US
III-2-4	Nombre (primero, ultimo)	MERCER, Stephen, E.
III-2-5	Dirección:	62 Sisk Street, Middletown, Connecticut 06457 Estados Unidos de América
III-2-6	Estado de Nacionalidad	US
III-2-7	Estado de Residencia	US
III-3	Solicitante y/o inventor	
III-3-1	Esta persona es:	Inventor y solicitante
III-3-2	Solicitante para:	Solo US
III-3-4	Nombre (primero, ultimo)	FANG, Haiquan
III-3-5	Dirección:	304 County Road Madison, Connecticut 06443

Petit rio PCT

III-3-6	Estado de Nacionalidad	Estados Unidos de América
III-3-7	Estado de Residencia	US
IV-1	La persona abajo identificada se designa/ha sido designada para actuar en nombre del/ de los solicitante(s) ante las administraciones internacionales competentes como:	US
IV-1-1	Nombre	Agente
IV-1-2	Dirección:	EPPERSON, James Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 Estados Unidos de América
IV-1-3	Teléfono No.	203-677-6974
IV-1-4	Faxsimile No.	203-677-6900
IV-1-5	Registro del Agente No.	52,867
IV-2	Agente adicional	Agente(s) adicional con misma dirección como primer nombre agente
IV-2-1	Nombre(s):	GOLIAN, Paul, D. (42,591); BABAJKO, Suzanne, E. (32,880); BAXAN, Deanna, L. (45,266); SUN, Jing, G. (45,914); BOGIE, Terence, J. (44,544); BERGEN, Briana, C. (39,123); D'AMICO, Stephen, C. (46,652); DAVIS, Stephen, B. (26,693); DUNCAN, Laureleer A. (44,096); DUNCAN, Sammy, G. Jr. (46,675);

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Petitorio PCT

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		GIBBONS, Maureen, S. (44,121); KILCOYNE, John, M. (33,100); KORSEN, Elliott (32,705); LAMERDIN, John, A. (44,858); O'BRIEN, Maureen, P. (42,043); PROVOOST, Jonathan, . (44,1292); RODNEY, Burton (22,076); SHER, Audrey, F. (39,024); VANATTEN, Mary, K. (39,408); WINSLOW, Anastasia, P. (40,875); ALGIERI, Aldo, A. (31,697); MAKUJINA, Shah, R. (41,174); RYAN, Richard, P. (30,491); VOLLES, Warren, K. (33,810); MINGO, Pamela, A. (48,256); GREENBLATT, Gary, D. (47,609); CHIN, Jennifer, T. (47,487); WANG, Joseph, C. (44,391); WILLE, Louis, J. (32,954); PARLET, Nickki, L. (44,996); COEEN, Jacqueline, M. (51,574); KRIEGER, Stuart, E. (28,731); SCHMIDT, Richard, D. (31,301)
V	Designaciones	
V-1	El llenado de este petitorio hechas bajo la Regla 4.9(b)	
VI-1	Solicitud de reivindicación de prioridad previa nacional	
VI-1-1	Fecha de presentación	03 Noviembre 2004 (03.11.2004)
VI-1-2	Solicitud N°	60/624,655
VI-2	Solicitud de reivindicación de prioridad previa nacional	
VI-2-1	Fecha de presentación	05 Mayo 2005 (05.05.2005)
VI-2-2	Solicitud N°	60/678,099
VI-2-3	País	US
VI-3	Solicitud de reivindicación de prioridad previa nacional	
VI-3-1	Fecha de presentación	11 Octubre 2005 (11.10.2005)
VI-3-2	Solicitud N°	
VI-3-3	País	US
VI-2	Prioridad documento petitorio Se ruega a la Oficina receptora que prepare y transmita a la Oficina Internacional una copia certificada de la solicitud anterior/de las solicitudes anteriores identificada(s) supra como punto o punto(s)	VI-1, VI-2, VI-3

Petit rio PCT

VII-1	Autoridad de Búsqueda Internacional Elegida	Oficina Estados Unidos de Patente y Marcas (EPO) (ISA/US)	
VIII	Declaraciones	Numero de declaraciones	
VIII-1	Declaración como para la identidad del inventor	-	
VIII-2	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para solicitar y garantizar una patente	1	
VIII-3	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para reivindicar la prioridad de la solicitud previa	2	
VIII-4	Declaración de los inventores (sólo para los propósitos de designación de los Estados Unidos de América)	-	
VIII-5	Declaración como descripciones o excepciones no perjudiciales para carecer de novedad	-	

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Petitorio PCT

237 639

VIII-2-1	Declaración: autorización para solicitar y otorgar una patente Declaración como autoriza el solicitante, como en la fecha de presentación internacional, para solicitar y otorgar una patente (Reglas 4.17(iii) y 51 bis. 1(a)(ii)), en caso donde la declaración bajo la Regla 4.17(iv) no sea apropiada: Nombre:	En relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY Se autoriza a reivindicar la prioridad de la solicitud previa en virtud de lo siguiente:
VIII-2-1 (iv)		Una cesión de CHATURVEDULA, Prasad, V. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 3 Enero 2005 (03.01.2005)
VIII-2-1 (iv)		Una cesión de MERCER, Stephen, E. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 30 Diciembre 2004 (30.12.2004)
VIII-2-1 (iv)		Una cesión de CHATURVEDULA, Prasad, V. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 Octubre 2004 (04.10.2004)
VIII-2-1 (iv)		Una cesión de MERCER, Stephen, E. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 24 Mayo 2005 (24.05.2005)
VIII-2-1 (ix)	Esta declaración esta hecha para el propósito de:	Todas las designaciones excepto la designación de los Estados Unidos de América

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VIII-2-1	Declaración: autorización para solicitar y otorgar una patente Declaración como autoriza el solicitante, como en la fecha de presentación internacional, para solicitar y otorgar una patente (Reglas 4.17(iii) y 51 bis. 1(a)(ii)), en caso donde la declaración bajo la Regla 4.17(iv) no sea apropiada: Nombre:	En relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY Se autoriza a reivindicar la prioridad de la solicitud No. 60/624,655 en virtud de lo siguiente:
VIII-2-1 (iv)		Una cesión de CHATURVEDULA, Prasad, V. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 3 Enero 2005 (03.01.2005)
VIII-2-1 (iv)		Una cesión de MERCER, Stephen, E. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 30 Diciembre 2004 (30.12.2004)
VIII-2-1 (ix)	Esta declaración esta hecha para el propósito de:	AP: (BW GH GM KE LS MW MZ NA SD SL SZ TZ UG WM ZW); EA: (AM AZ BY KG KE MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LT LU LV MC NL PL PT RO SE SI SK TR); OA: (BF Ba CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM WW

Petitorio PCT

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VIII-3-1	Declaración: autorización para solicitar y otorgar una patente Declaración como autoriza el solicitante, como en la fecha de presentación internacional, para solicitar y otorgar una patente (Reglas 4.17(iii) y 51 bis. 1(a)(ii)), en caso donde la declaración bajo la Regla 4.17(iv) no sea apropiada: Nombre:	En relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY Se autoriza a reivindicar la prioridad de la solicitud No. 60/678,099 en virtud de lo siguiente:
VIII-3-1 (iv)		Una cesión de CHATURVEDULA, Prasad, V. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 Mayo 2005 (31.05.2005)
VIII-3-1 (iv)		Una cesión de MERCER, Stephen, E. a BRISTOL-MYERS SQUIBB COMPANY, con fecha 24 Mayo 2005 (24.05.2005)
VIII-3-1 (ix)	Esta declaración esta hecha para el propósito de:	AP: (BW GH GM KE LS MW MZ NA SD SL SZ TZ UG WM ZW); EA: (AM AE BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LT LU LV MC NL PL PT RO SE SI SK TR); OA: (BF Ba CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM WW

Petitorio PCT

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IX	Lista de verificación	Número de hojas	Archivos electrónicos anexos
IX-1	Petitorio	9	✓
IX-2	Descripción	240	-
IX-3	Reivindicaciones	9	-
IX-4	Resumen	1	✓
IX-5	Dibujos	0	-
IX-7	Total	259	
	Puntos acompañantes	Papel de documento(s) anexos	Archivo(s) electrónico anexos
IX-8	Hoja de calculo de tasa	✓	-
IX-10	Original del poder general Protesta del Abogado	✓	-
IX-17	Diskette PCT-SAFE	-	✓
IX-18	Otro		
IX-18	Otro	Receptor de correo; Certificado de correo Express; Certificación	
IX-19	Figura de los dibujos para acompañar el resumen en el momento de su publicación.		
IX-20	Idioma de presentación de la solicitud internacional de patente	INGLES	
X-1	Firma del solicitante o del mandatario	Rúbrica	
X-1-1	Nombre	EPPERSON, James	
X-1-2	Nombre de signatura		
X-1-3	Capacidad		
PARA LA OFICINA RECEPTORA ÚNICAMENTE			
10-1	Fecha efectiva de recepción de la pretendida solicitud internacional		
10-2	Dibujos		
10-2-1	Recibidos		
10-2-2	No recibidos		
10-3	Fecha efectiva de recepción, rectificada de la recepción ulterior pero dentro del plazo, de documentos o de dibujos que completa la pretendida solicitud internacional		
10-4	Fecha de recepción, dentro del plazo de las correcciones solicitadas según el Artículo 11(2) del PCT		
10-5	Autoridad de búsqueda internacional	ISA/US	
10-6	Transmisión de la copia para la búsqueda diferida hasta que se pague la tasa de búsqueda		

Petitorio PCT

Handwritten signature

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PARA USO UNICAMENTE DE LA OFICINA INTERNACIONAL		
11-1	Fecha de recepción del ejemplar Original por la Oficina Internacional	

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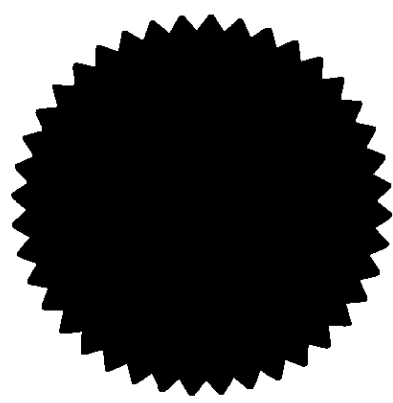
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

- 1. COUNTRY: UNITED STATES OF AMERICA
- 2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
EVELYN VAZQUEZ
- 3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
- 4. BEARS THE SEAL/STAMP OF:
EVELYN VAZQUEZ, NOTARY

CERTIFIED

- 5. AT TRENTON, NEW JERSEY
- 6. THE 23RD DAY OF APRIL 2007
- 7. BY: Bradley Abelow, NEW JERSEY TREASURER
- 8. NO. A289535
- 9. SEAL/STAMP:
- 10. SIGNATURE



Bradley Abelow

NOTARY CERTIFICATION

I, Evelyn Vazquez, Notary Public, do hereby certify that these Assignment documents were executed by the inventors and are notarized true and accurate copies of the original assignments signed by this inventors.

STATE OF NEW JERSEY

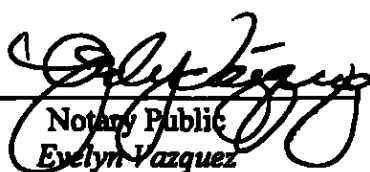
)

ss.

COUNTY OF MERCER

)

)


Notary Public
Evelyn Vazquez

Notary Public of New Jersey
No. 2106805

My Commission Expires December 9, 2007
Registered in Middlesex County

(SEAL)

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ASSIGNMENT

We,

Prasad V. Chaturvedula residing at **190 Lancaster Way
Cheeshire, Connecticut 08410
United States of America,**

Stephen E. Mercer residing at **62 Sisk Street
Middletown, Connecticut 08457
United States of America**

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at **Lawrenceville-Princeton Road, Princeton, NJ 08543-4000**, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

CONSTRAINED COMPOUNDS AS CGRP-RECEPTOR ANTAGONISTS

Invented by us and described in the non-provisional United States patent application executed on even date herewith including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said **Bristol-Myers Squibb Company** and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 31st day of January, 2005 by Prasad V. Chaturvedula
Prasad V. Chaturvedula

Signed this 30 day of December, 2004 by Stephen E. Mercer
Stephen E. Mercer

ACKNOWLEDGMENT

State of Connecticut
County of New Haven

) ss: Wallingford

On this 3rd day of January 2005, before me Nancy S. Turover,
the undersigned, personally appeared Prasad V. Chaturvedula, to me known to be the person
of that name mentioned in, and who executed the foregoing Assignment and acknowledged that
he executed it.

Nancy S. Turover
Notary Public

COMMISSION EXPIRES: NANCY S. TUROVER
NOTARY PUBLIC
MY COMMISSION EXPIRES FEB. 28, 2008

ACKNOWLEDGMENT

State of Connecticut
County of New Haven

) ss: Wallingford

On this 30th day of December 2004, before me Nancy S. Turover,
the undersigned, personally appeared Stephen E. Mercer, to me known to be the person of
that name mentioned in, and who executed the foregoing Assignment and acknowledged that
he executed it.

Nancy S. Turover
Notary Public

COMMISSION EXPIRES: NANCY S. TUROVER
NOTARY PUBLIC
MY COMMISSION EXPIRES FEB. 28, 2008

ASSIGNMENT

We,

Prasad V. Chaturvedula residing at 190 Lancaster Way
Cheshire, Connecticut 06410
United States of America

Stephen E. Mercer residing at 62 Sisk Street
Middletown, Connecticut 06457
United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Constrained Compounds as CGRP-Receptor Antagonists

Invented by us and described in the provisional United States patent application

Application No. 60/678,099, filed May 5, 2005.

including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

-2-

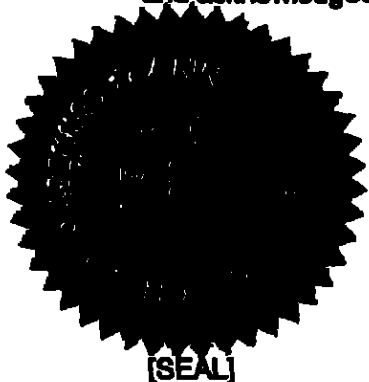
And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 31 day of May, 2005 by Prasad V. Chaturvedula
Prasad V. Chaturvedula

Signed this 24 day of May, 2005 by Stephen E. Mercer
Stephen E. Mercer

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 31 day of May, 2005, before me came Prasad V. Chaturvedula, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



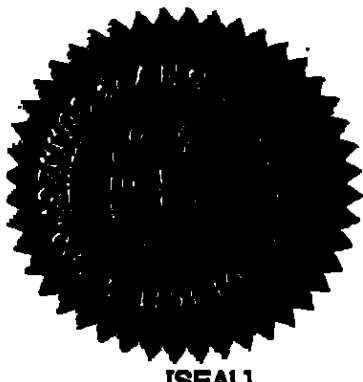
[SEAL]

Annamarie Rodisch
Notary Public

ANNE MARIE RODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 24 day of May, 2005, before me came Stephen E. Mercer, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



[SEAL]

Annamarie Rodisch
Notary Public

ANNE MARIE RODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

ASSIGNMENT

We,

Prasad V. Chaturvedi	residing at	190 Lancaster Way Cheshire, Connecticut 06410 United States of America
Stephen E. Mercer	residing at	62 Sisk Street Middletown, Connecticut 06457 United States of America
Halquan Fang	residing at	304 County Road Madison, Connecticut 06443 United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Constrained Compounds as CGRP-Receptor Antagonists

invented by us and described in the non-provisional United States patent application

Application No. 11/247,697, filed October 11, 2005,

Including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 15 day of November, 2005 by Prasad V. Chaturvedula
Prasad V. Chaturvedula

Signed this 14 day of November, 2005 by Stephen E. Mercer
Stephen E. Mercer

Signed this 11 day of Nov., 2005 by Halquan Fang
Halquan Fang

-3-

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 15 day of November, 2005, before me came Prasad V. Chaturvedula, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 14 day of November, 2005, before me came Stephen E. Mercer, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

-4-

STATE OF Connecticut)
) ss. Wallingford
COUNTY OF New Haven)

On the 11 day of November, 2005, before me came Helquan Fang, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.



[SEAL]

Annamarie Bodisch
Notary Public

ANNAMARIE BODISCH
NOTARY PUBLIC
MY COMMISSION EXPIRES MARCH 31, 2010

[Handwritten signature]

656

TRADUCCION AL ESPAÑOL del Documento de Cesión a **BRISTOL-MYERS SQUIBB COMPANY firmada por el cedente y el cesionario.**

APOSTILLA

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

1. País: Estados Unidos de América
2. Este documento público ha sido firmado por
Evelyn Vazquez
3. actuando en capacidad:
Notario Público del Estado de Nueva Jersey
4. lleva el sello/timbre de:
Evelyn Vazquez, NOTARIO

Certificado

5. en Trenton, New Jersey
6. el 23ro día de Abril de 2007
7. Por: Bradley Abelow, Tesorero de Nueva Jersey
8. No. A289535
9. Sello/timbre:
10. Firma

[sello]

(Firma)

Bradley Abelow

657

CERTIFICACIÓN NOTARIAL

Yo, Evelyn Vazquez, Notario Público, certifico que estos documentos de Cesión se ejecutaron por los inventores y son copias verdaderas y precisas de las cesiones originales firmadas por estos inventores.

ESTADO DE NUEVA JERSEY)
)
CONDADO DE MERCER) **ss.**

(firma)
Notario Público
Evelyn Vazquez
Notario Público de Nueva Jersey
No. 2106805
Mi Comisión vence Diciembre 9, 2007
Registrada en el Condado de Middlesex

(sello notarial)

658

CESIÓN

Nosotros,

Prasad V. Chaturvedula residente en 190 Lancaster Way
Cheshire, Connecticut 06410
Estados Unidos de América

Stephen E. Mercer residente en 62 Sisk Street
Middletown, Connecticut
Estados Unidos de América

según obligaciones contractuales desde ahora asumidas por nosotros y/o para buena y valiosa consideración, el recibimiento y legitimidad de la cual se reconoce aquí, por la presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una corporación de Delaware, con cede de negocios en Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, sus sucesores, cesionarios y representantes legales, todo nuestro derecho, título e interés, lo cual incluye el derecho a y el completo beneficio de dichas prioridades como puedan ahora o de ahora en adelante ser otorgadas a nosotros por leyes locales o por tratado, incluyendo cualquier convención internacional para la protección de la propiedad industrial, en y para todos los países del mundo, incluyendo los Estados Unidos y sus territorios y posesiones, en y para el invento titulado:

COMPUESTOS LIMITADOS COMO ANTAGONISTAS DE RECEPTOR CGRP

inventados por nosotros y descritos en la solicitud no provisional para patente ejecutada en la fecha aquí mencionada incluyendo dicha solicitud para patente de los Estados Unidos provisional y cualquier solicitud reivindicando prioridad de dicha solicitud no provisional, presentada en cualquier país, y cualquier patente que pueda ser expedida u otorgada en adelante, y todas las divisiones, continuaciones, reexpediciones, certificados de reexaminación y extensiones de los mismos en todos los países, dicho interés siendo la completa propiedad de dicha solicitud y de dichas solicitudes, patentes (incluyendo patentes de reexpedición), extensiones y certificados de reexaminación para ser tenidos y disfrutados por el mencionado Bristol-Myers Squibb Company y sus sucesores y cesionarios hasta el final de los términos para los cuales dichas patentes (incluyendo patentes de reexpedición), extensiones y certificados de reexaminación que puedan ser otorgados y/o expedidos, tan completa y enteramente como los mismos hubiesen sido tenidos y disfrutados por nosotros si esta venta, cesión y transferencia no se hubiese llevado a cabo;

Y acordamos por la presente comunicarle a dicho cesionario o sus representantes los hechos conocidos por nosotros con referencia a dicha invención, a testificar en cualquier procedimiento legal, a firmas y/o ejecutar cualquier documento y/o instrumento adicional que pueda ser necesario, legal y correcto en y/o para la presentación y/o persecución de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reexpedición, extensiones y certificados de reexaminación y/o la concesión y/o expedición de los mismos y/o para de otra manera asegurar el título por dicha invención y todas las dichas solicitudes,



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patentes, extensiones y certificados de reexaminación en dicho cesionario, y en general hacer todo lo posible para ayudar a dicho cesionario, sus sucesores y cesionarios y hacer cumplir la correcta protección de dicha invención en todos los países.

Firmado en este 3 día de Enero, 2005 por (firma)
Prasad V. Chaturvedula

Firmado en este 30 día de Diciembre, 2004 por (firma)
Stephen E. Mercer

660

RECONOCIMIENTO

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

En este día 3 de Enero, 2005, apareció personalmente ante mi, el abajo firmante, **Prasad V. Chaturvedula**, conocido por mi como la persona del nombre mencionado, y quien ejecutó la Cesión saliente y reconoció que el la ejecutó.

(firma)

Notario público

Hay un Sello que dice:

[SELLO]

NANCY S. TUROVER
NOTARIO PÚBLICO

Mi comisión vence Feb. 28, 2008

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

En este día 30 de Diciembre, 2004, apareció personalmente ante mi, el abajo firmante, **Stephen E. Mercer**, conocido por mi como la persona del nombre mencionado, y quien ejecutó la Cesión saliente y reconoció que el la ejecutó.

(firma)

Notario público

Hay un Sello que dice:

[SELLO]

NANCY S. TUROVER
NOTARIO PÚBLICO
Mi comisión vence Feb. 28, 2008

661

CESIÓN

Nosotros,

Prasad V. Chaturvedula residente en 190 Lancaster Way
Cheshire, Connecticut 06410
Estados Unidos de América

Stephen E. Mercer residente en 62 Sisk Street
Middletown, Connecticut
Estados Unidos de América

según obligaciones contractuales desde ahora asumidas por nosotros y/o para buena y valiosa consideración, el recibimiento y legitimidad de la cual se reconoce aquí, por la presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una corporación de Delaware, con sede de negocios en Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, sus sucesores, cesionarios y representantes legales, todo nuestro derecho, título e interés, lo cual incluye el derecho a y el completo beneficio de dichas prioridades como puedan ahora o de ahora en adelante ser otorgadas a nosotros por leyes locales o por tratado, incluyendo cualquier convención internacional para la protección de la propiedad industrial, en y para todos los países del mundo, incluyendo los Estados Unidos y sus territorios y posesiones, en y para el invento titulado:

COMPUESTOS LIMITADOS COMO ANTAGONISTAS DE RECEPTOR CGRP

inventados por nosotros y descritos en la solicitud provisional para patente de los Estados Unidos

Solicitud No. **60/678,099**, presentada en **Mayo 5, 2005**

incluyendo dicha solicitud para patente de los Estados Unidos no provisional y cualquier solicitud reivindicando prioridad de dicha solicitud no provisional, presentada en cualquier país, y cualquier patente que pueda ser expedida u otorgada en adelante, y todas las divisiones, continuaciones, reexpediciones, certificados de reexaminación y extensiones de los mismos en todos los países, dicho interés siendo la completa propiedad de dicha solicitud y de dichas solicitudes, patentes (incluyendo patentes de reexpedición), extensiones y certificados de reexaminación para ser tenidos y disfrutados por el mencionado Bristol-Myers Squibb Company y sus sucesores y cesionarios hasta el final de los términos para los cuales dichas patentes (incluyendo patentes de reexpedición), extensiones y certificados de reexaminación que puedan ser otorgados y/o expedidos, tan completa y enteramente como los mismos hubiesen sido tenidos y disfrutados por nosotros si esta venta, cesión y transferencia no se hubiese llevado a cabo;

Y acordamos por la presente comunicarle a dicho cesionario o sus representantes los hechos conocidos por nosotros con referencia a dicha invención, a testificar en

662

cualquier procedimiento legal, a firmas y/o ejecutar cualquier documento y/o instrumento adicional que pueda ser necesario, legal y correcto en y/o para la presentación y/o persecución de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reexpedición, extensiones y certificados de reexaminación y/o la concesión y/o expedición de los mismos y/o para de otra manera asegurar el título por dicha invención y todas las dichas solicitudes, patentes, extensiones y certificados de reexaminación en dicho cesionario, y en general hacer todo lo posible para ayudar a dicho cesionario, sus sucesores y cesionarios y hacer cumplir la correcta protección de dicha invención en todos los países.

Firmado en este 31 día de Mayo , 2005 por (firma)
Prasad V. Chaturvedula

Firmado en este 24 día de Mayo , 2005 por (firma)
Stephen E. Mercer

663

ESTADO DE Connecticut)
CONDADO DE New Haven) ss. Wallingford

En este día 31 de Mayo, 2005, apareció personalmente ante mi, el abajo firmante, Prasad V. Chaturvedula, conocido por mi como la persona del nombre mencionado, y quien ejecutó la Cesión saliente y reconoció que el la ejecutó.

(firma)
Notario público

Hay un Sello que dice:

[SELLO]

ANNAMARIE BODISH
NOTARIO PÚBLICO
MI COMISIÓN VENCE MARZO 31, 2010

ESTADO DE Connecticut)
CONDADO DE New Haven) ss. Wallingford

En este día 24 de Mayo, 2005, apareció personalmente ante mi, el abajo firmante, Stephen E. Mercer, conocido por mi como la persona del nombre mencionado, y quien ejecutó la Cesión saliente y reconoció que el la ejecutó.

(firma)
Notario público

Hay un Sello que dice:

[SELLO]

ANNAMARIE BODISH
NOTARIO PÚBLICO
MI COMISIÓN VENCE MARZO 31, 2010

664

CESIÓN

Nosotros,

Prasad V. Chaturvedula residente en 190 Lancaster Way
Cheshire, Connecticut 06410
Estados Unidos de América

Stephen E. Mercer residente en 62 Sisk Street
Middletown, Connecticut
Estados Unidos de América

Haiquan Fang residente en 304 County Road
Madison, Connecticut 06443
Estados Unidos de América

según obligaciones contractuales desde ahora asumidas por nosotros y/o para buena y valiosa consideración, el recibimiento y legitimidad de la cual se reconoce aquí, por la presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una corporación de Delaware, con sede de negocios en Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, sus sucesores, cesionarios y representantes legales, todo nuestro derecho, título e interés, lo cual incluye el derecho a y el completo beneficio de dichas prioridades como puedan ahora o de ahora en adelante ser otorgadas a nosotros por leyes locales o por tratado, incluyendo cualquier convención internacional para la protección de la propiedad industrial, en y para todos los países del mundo, incluyendo los Estados Unidos y sus territorios y posesiones, en y para el invento titulado:

COMPUESTOS LIMITADOS COMO ANTAGONISTAS DE RECEPTOR CGRP

inventados por nosotros y descritos en la solicitud no provisional para patente de los Estados Unidos

Solicitud No. 11/247,897, presentada en Octubre 11, 2005

incluyendo dicha solicitud para patente de los Estados Unidos no provisional y cualquier solicitud reivindicando prioridad de dicha solicitud no provisional, presentada en cualquier país, y cualquier patente que pueda ser expedida u otorgada en adelante, y todas las divisiones, continuaciones, reexpediciones, certificados de reexaminación y extensiones de los mismos en todos los países, dicho interés siendo la completa propiedad de dicha solicitud y de dichas solicitudes, patentes (incluyendo patentes de reexpedición), extensiones y certificados de reexaminación para ser tenidos y disfrutados por el mencionado Bristol-Myers Squibb Company y sus sucesores y cesionarios hasta el final de los términos para los cuales dichas patentes (incluyendo patentes de reexpedición), extensiones y certificados reexaminación que puedan ser otorgados y/o expedidos, tan completa y enteramente como los mismos hubiesen sido tenidos y

Handwritten signature 665

disfrutados por nosotros si esta venta, cesión y transferencia no se hubiese llevado a cabo;

Y acordamos por la presente comunicarle a dicho cesionario o sus representantes los hechos conocidos por nosotros con referencia a dicha invención, a testificar en cualquier procedimiento legal, a firmas y/o ejecutar cualquier documento y/o instrumento adicional que pueda ser necesario, legal y correcto en y/o para la presentación y/o persecución de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reexpedición, extensiones y certificados de reexaminación y/o la concesión y/o expedición de los mismos y/o para de otra manera asegurar el título por dicha invención y todas las dichas solicitudes, patentes, extensiones y certificados de reexaminación en dicho cesionario, y en general hacer todo lo posible para ayudar a dicho cesionario, sus sucesores y cesionarios y hacer cumplir la correcta protección de dicha invención en todos los países.

Firmado en este 15 día de Noviembre , 2005 por (firma)
Prasad V. Chaturvedula

Firmado en este 14 día de Noviembre , 2005 por (firma)
Stephen E. Mercer

Firmado en este 11 día de Noviembre , 2005 por (firma)
Haiquan Fang

67

666

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

En este día 15 de Noviembre, 2005, apareció personalmente ante mí, el abajo firmante, Prasad V. Chaturvedula, conocido por mí como la persona del nombre mencionado, y quien ejecutó la Cesión saliente y reconoció que el la ejecutó.

(firma)
Notario público

Hay un Sello que dice:

[SELLO]

ANNAMARIE BODISH
NOTARIO PÚBLICO
MI COMISIÓN VENCE MARZO 31, 2010

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

En este día 14 de Noviembre, 2005, apareció personalmente ante mí, el abajo firmante, Stephen E. Mercer, conocido por mí como la persona del nombre mencionado, y quien ejecutó la Cesión saliente y reconoció que el la ejecutó.

(firma)
Notario-público

Hay un Sello que dice:

[SELLO]

ANNAMARIE BODISH
NOTARIO PÚBLICO
MI COMISIÓN VENCE MARZO 31, 2010

667

ESTADO DE Connecticut)
) ss. Wallingford
CONDADO DE New Haven)

En este día 11 de Noviembre, 2005, apareció personalmente ante mí, el abajo firmante, Halquan Fang, conocido por mí como la persona del nombre mencionado, y quien ejecutó la Cesión saliente y reconoció que el la ejecutó.

(firma)

Notario público

Hay un Sello que dice:

[SELLO]

ANNAMARIE BODISH
NOTARIO PÚBLICO
MI COMISIÓN VENCE MARZO 31, 2010

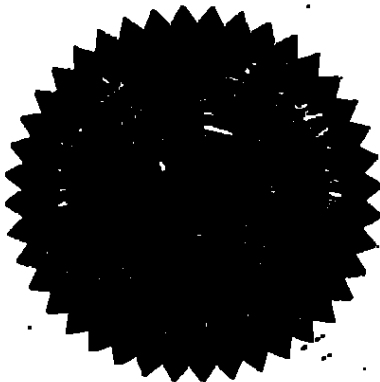
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

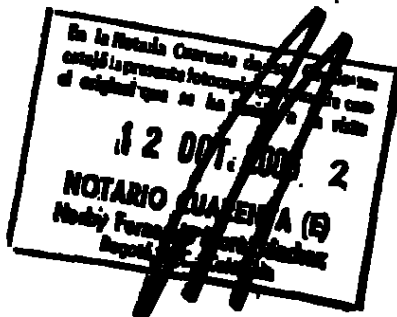
1. COUNTRY: UNITED STATES OF AMERICA . . .
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MAURA O KNOBL
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 13TH DAY OF JANUARY 2006
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A248886
9. SEAL/STAMP: .
10. SIGNATURE



John E McCormac



Brigard & Castro
BOGOTÁ - COLOMBIA

669

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) **BRISTOL-MYERS SQUIBB COMPANY**

domiciliado(s) en

domiciled in **Princeton, New Jersey, USA**

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o MARTIN E. TORRES CARDOZO**, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recibir de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseñanzas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

Hereby appoints **JUAN PABLO CADENA SARMIENTO and/or CARLOS H. PALACIO EASTMAN and/or MARTIN E. TORRES CARDOZO**, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and records of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

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.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o MARTIN E. TORRES CARDOZO**, domiciliado(s) en la Carrera 7 No. 16-58 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints **JUAN PABLO CADENA SARMIENTO and/or CARLOS H. PALACIO EASTMAN and/or MARTIN E. TORRES CARDOZO**, domiciled in Carrera 7 No. 16-58, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Otorgado y firmado en

Granted and signed in

hoy de 200_

1st day Jan of 2006

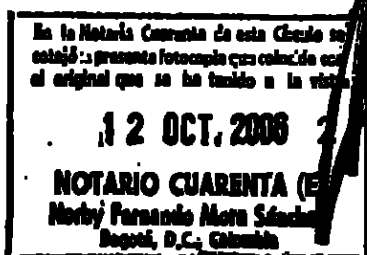
Firma

Signature

Nombre
Cargo

Name
Title

Suzanne E. Babajko
Senior Patent Counsel



CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

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Hoy de de
personalmente compareció ante mí

On this 11 day of January of 2006 personally
appeared before me SUZANNE E. BABAJKO

a quien conozco, y de quien me consta que firmó el anterior
documento, debidamente juramentado declaró y dijo que él
(ella) es

to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the
SENIOR PATENT COUNSEL

de

of BRISTOL-MYERS SQUIBB COMPANY

Sociedad legalmente constituida para un período de
duración que aún no ha terminado; que el declarante está
autorizado por dicha compañía para conferir este poder; que
el sello estampado por él al pie de tal poder, en nombre y
representación de la expresada compañía, es el sello oficial
de ella; y que el objeto para el cual se confiere este
instrumento está comprendido dentro del objeto social de la
sociedad.

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.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

The undersigned Notary Public attests that he has seen the
documents that prove the existence of the company.

Estado de
con fecha

State of
under date of

y que quien confiere el presente poder es su representante.

and that he (she) who grants the present power of attorney
is its Representative.

Notario Público (sello)

Public Notary (Seal)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

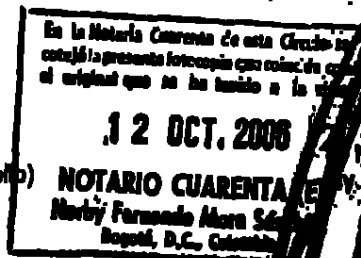
**NOTARIAL CERTIFICATE
NATURAL PERSON**

Hoy de de , compareció(eron) ante mí

On this 11th day of January of 2006
personally appeared before me
Suzanne E. Babajko

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.

who is(are) known to me and who I attest executed the
foregoing document and he (they) declared he (they)
grant(s) the document for the uses and purposes therein
expressed



Maura O. Knebl
Notary Public
MAURA O. KNOBL
NOTARY PUBLIC OF NEW JERSEY
Commission Expires July 19, 2006

Notario Público (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

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TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por
BRISTOL-MYERS SQUIBB COMPANY domiciliada en Princeton, New
Jersey, Estados Unidos de América.

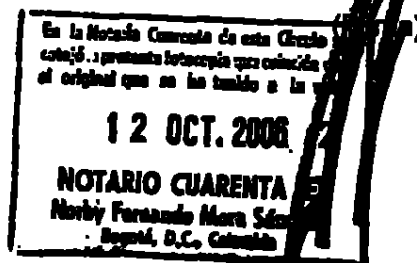
APOSTILLA

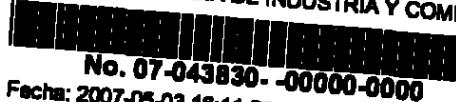
(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PUBLICO HA SIDO FIRMADO POR:
MAURA O KNOBL
3. ACTUANDO EN CAPACIDAD DE:
NOTARIO PUBLICO DE NEW JERSEY
4. LLEVA EL SELLO/TIMBRE DE:
MAURA O KNOBL, NOTARIO

CERTIFICADO

5. EN TRENTON, NEW JERSEY
6. EL 13 DE ENERO DE 2006
7. POR: John E. McCormac, CPA, TESORERO DE NEW JERSEY
8. NO. A248886
9. SELLO/TIMBRE:
10. FIRMA





No. 07-043830-00000-0000

Fecha: 2007-05-03 18:11:59 Dep. 2020 NUECREACIONE
Trs. 11 PATENTE Y II Eje: 378 FASENACIONAL
Act. 411 PRESENTACION Folios: 655



Industria y Comercio
SUPERINTENDENCIA

672

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION



MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente [X]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- ◆ Descripción de la invención [X]
- ◆ Dibujos de ser estos pertinentes [X]
- ◆ Comprobante de pago de las tasas establecidas [X]

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Firma Responsable

Fecha

10 3 MAYO 2007

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@slc.gov.co
www.slc.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

673
Folio 657

2020
Bogotá D.C.,

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
BRISTOL MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	07 43830
	Solicitud internacional	PCT/US2005/036859
	Fecha inicio fase nacional	03/06/2007
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	3335
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

16 JUL 2007

Clara C. de Jaimés
CLARA C. DE JAIMES
Jefe de la división de Nuevas Creaciones (E)

adpall