

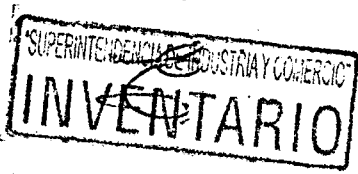


Organización
Digital

Industria y Comercio

SUPERINTENDENCIA

NOM
PCT



Delegatura de Propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

PCT

1/27

09-36257

1. EXPEDIENTE No.

4. TÍTULO

DERIVADOS DE QUINAZOLINONA E ISOQUINOLINONA ACETAMIDA

1. CLASIFICACIÓN INTERNACIONAL

1. SOLICITANTE

N.V. ORGANON Y PHARMACOPEIA, LLC.

DOMICILIO

AB OSS, HOLANDA y SAN DIEGO, CALIFORNIA, U.S.A.

4. APODERADO

EMILIO FERRERO
C.C. 438.019 de Usaquén

2. BOGOTÁ, D. C.,



PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-036257- -00000-0000

Fecha: 2009-04-08 13:31:50 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 379

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

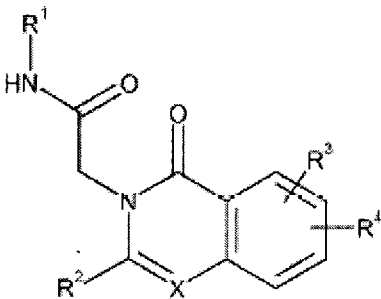
SOLICITUD DE:		
1	☒ Patente de Invención. ☒ Capítulo I.	☐ Patente de Modelo de Utilidad. ☐ Capítulo II.
2 SOLICITANTE (71)	Nombre: N. V. ORGANON y PHARMACOEPIA, LLC. sociedades constituidas y existentes bajo las leyes de Holanda y el Estado de California, Estados Unidos de América, respectivamente. Dirección: Kloosterstraat 6, 5349 AB Oss, Holanda Y 10275 Science Center Drive, San Diego, California 92121, Estados Unidos de América Domicilio: AB Oss, Holanda Y San Diego, California, Estados Unidos de América	IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax: 211 86 50 E-mail: clientes@cavelier.com Domicilio: Bogotá, Colombia.	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 438.019 T.P 31.929
4 INVENTOR (ES) (72)	1. Jeffrey LETOURNEAU 6 Bristol Way, East Windsor, New Jersey 08520, Estados Unidos de América 3. Susan Elizabeth NAPIER c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire ML1 5SH, Reino Unido 5. Michael OHLMEYER 6 Beechtree Lane, Plainsboro, New Jersey 08536, Estados Unidos de América	
	2. Patrick JOKIEL 2 Scarlet Oak Drive, Princeton, New Jersey 08540, Estados Unidos de América 4. Koc-Kan HO 77 Warwick Road, West Windsor, New Jersey 08850, Estados Unidos de América 6. Duncan Robert MCARTHUR c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire ML1 5SH, Reino Unido	

	7. Jeremiah FIONA c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire ML1 5SH, Reino Unido 9. Schulz JURGEN c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire ML1 5SH, Reino Unido	8. Paul David RATCLIFFE c/o Organon Laboratories Ltd., New Edinburgh Road, Newhouse, Lanarkshire ML1 5SH, Reino Unido		
5	PCT (86) Solicitud Internacional No. <u>PCT/US2007/078022</u> Fecha: <u>10 de septiembre de 2007</u> Publicación Internacional No. <u>WO 2008/033764 A3</u> Fecha: <u>20 de marzo de 2008</u>			
6	Título (54) <u>DERIVADOS DE QUINAZOLINONA E ISOQUINOLINONA ACETAMIDA</u>			
7	Clasificación Internacional (51) <u>C07D 239/070</u>			
8	Prioridad SI ☒ NO ☐	(33) País de Origen <u>US</u>	(32) Fecha <u>11 de septiembre de 2006</u>	(31) Número de Solicitud <u>60/843,718</u>
9	Comprobante de pago No.: <u>09-24,790</u>		Fecha: <u>30 de marzo de 2009</u>	
10	Anexos: ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 540.000.oo. ☐ Comprobante de pago por reivindicaciones adicionales después de la decimoquinta reivindicación por. ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica. ☒ Poderes, si fuere el caso de la Sociedad N. V. ORGANON. ☐ Documento de cesión del inventor al solicitante o a su causante. ☐ Declaraciones. ☒ 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. ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS			

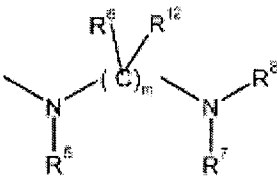
3

11

FIGURA CARACTERÍSTICA



I



II

12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA: 
C.C. 438.019 de Usaquén T.P. 31.929

JGG

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2008/033764 A3

Descripción:

Páginas 143 en el idioma original

Páginas 192 en español

Reivindicaciones: Número (s) 11

Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ **Forma PCT/ISA/237.** Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.

4. ☒ **Forma PCT/IB/306.** Notificación de la inscripción de un cambio en el Nombre de la Inventora **Elizabeth NAPIER** por **Susan Elizabeth NAPIER**.

5. ☒ Extracto de publicación.

**NO SE REALIZARON MODIFICACIONES EN
LA FASE INTERNACIONAL**

5

4449

GENERAL POWER OF ATTORNEY

CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 - COLOMBIA

179

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

N. V. ORGANON

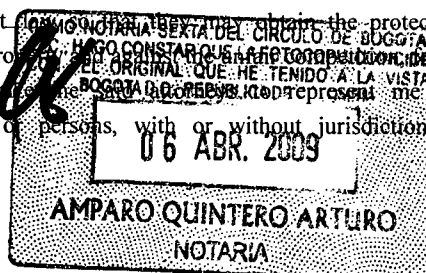
Domiciliado (S) En/Of Kloosterstraat 6, 5349 AB Oss, The Netherlands

por el presente nombramos a EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65.620, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and DANIEL PEÑA, tpa. 65.620, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporary or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternate in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombia Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact of its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys at law to obtain the protection of my (our) industrial property against unfair competition for which purpose (we) authorize the above-named attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those



administrativo, contencioso administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

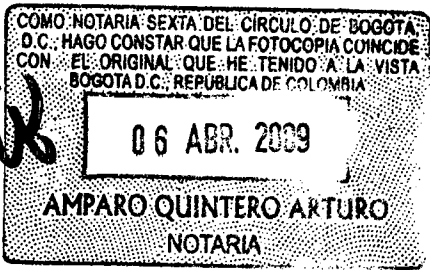
administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of ~~patents~~, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ of mandamus, the protection of trade secrets, and in general the civil, penal and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this August 22, 2007
in/in Oss, The Netherlands

for/by Dr. P.N.M. Konings
Holder of Proxy
Signature:

Dr. A.J.H. Pegt
Holder of Proxy
Signature:

Firma N.V. Organon



CERTIFICACION NOTARIAL (SOCIEDAD)

MAKELAAR

El infrascrito Notario/Certifica: Que la firma que antecede de
P.N.M. KONINGS & A.J.H.PEGT

es auténtica; que el signatario ^s desempeña actualmente el cargo
de apoderados
de la compañía N.V. Organon
sociedad que actualmente existe y está organizada de acuerdo a
las leyes de Países Bajos

que la dirección de dicha compañía es
Kloosterstraat 6, 5349 AB Oss, Holanda

y que el signatario ^s tiene facultad para otorgar este documento.

Todos los hechos anteriores le constan por haber examinado los
documentos respectivos y de todo ello da fe.

do y firmado en Bussum, Holanda

El 30 Agosto 2007

NOTARIAL CERTIFICATION (COMPANY)

BY "MAKELAAR"

"MAKELAAR"

The undersigned ~~Notary~~ ^{ies} certifies: That the preceding signature s
of

P.N.M. KONINGS & A.J.H. PEGT

are authentic, that the signatory ^{ies} currently acts in the position of

Holder of Proxy

of the company N.V. Organon

a company currently existing and organized under the laws of
The Netherlands

that the address is Kloosterstraat 6, 5349 AB Oss,
The Netherlands

and that the signatory ^{ies} has the power to grant this document.

"MAKELAAR"

The ~~Notary~~ ^{ies} Public is aware and attests to the above facts upon
examination of the corresponding documents.

Given and signed in Bussum, The Netherlands

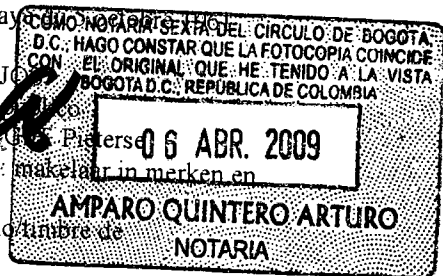
On 30 August 2007



APOSTILLE

Convention de La Haye

1. Pais: LOS PAISES BAJO
2. El presente documento
3. Ha sido firmado por: B.G.H. Pieterse
4. Actuando en calidad de: makelaar in merken en modellen te Bussum
5. Y está revestido del sello/timbre de B.G.H. Pieterse
6. Certificado
7. En Amsterdam
8. El día 31 Augustus 2007
9. Certificado por el Secretario Judicial del Tribunal de Distrito Amsterdam
10. Con el no: 053620
11. Sellado/timbrado



10. Firma
mw. H.H.S. Verhagen

[Signature]



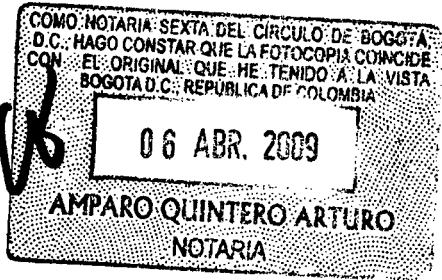
APOSTILLE
(Convention de La Haye du 5 octobre 1961)

- 1. Country:
This public document
- 2. has been signed by
- 3. acting in the capacity of
- 4. bears the seal/stamp of

Certified

- 5. at 6. the
 - 7. by
 - 8. No.
 - 9. Seal/stamp 10. Signature
-

PCQ\ID-105327\WPCL0299



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 C07D 243/08 (2006.01) A61K 31/4725 (2006.01)
 C07D 217/24 (2006.01) A61K 31/496 (2006.01)
 A61K 31/519 (2006.01) A61P 25/24 (2006.01)
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60/843,718 11 September 2006 (11.09.2006) US

(71) Applicant (for all designated States except US): N.V.
 ORGANON [NL/NL]; Kloosterstraat 6, NL-5349 AB Oss
 (NL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LETOURNEAU,

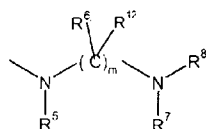
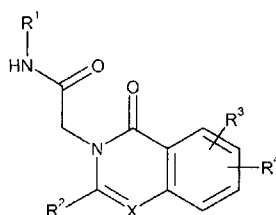
Jeffrey [US/US]; 6 Bristol Way, East Windsor, NJ 08520
 (US). JOKIEL, Patrick [US/US]; 2 Scarlet Oak Drive,
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 c/o Organon Laboratories Ltd., New Edinburgh Road,
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 Laboratories Ltd., New Edinburgh Road, Newhouse,
 Lanarkshire ML1 5SH (GB). RATCLIFFE, Paul, David
 [GB/GB]; c/o Organon Laboratories Ltd., New Edinburgh
 Road, Newhouse, Lanarkshire ML1 5SH (GB). JURGEN,
 Schulz [DE/GB]; c/o Organon Laboratories Ltd., New
 Edinburgh Road, Newhouse, Lanarkshire ML1 5SH (GB).

(74) Agent: HESS, Susan; Organon International Inc., 56 Liv-
 ington Avenue, Roseland, NJ 07068 (US).

(81) Designated States (unless otherwise indicated, for every
 kind of national protection available): AE, AG, AL, AM,
 AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH,

[Continued on next page]

(54) Title: QUINAZOLINONE AND ISOQUINOLINONE ACETAMIDE DERIVATIVES



(57) Abstract: The present invention relates to a quinazolinone or isoquinolinone derivative of formula I, wherein R¹ is C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, said C₁₋₆alkyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkylC₁₋₃alkyl being optionally substituted with hydroxy, C₁₋₆alkyloxy, cyano or one or more halogens; R² is C₆₋₁₀aryl optionally substituted with one to three substituents selected from halogen, hydroxy, cyano, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkyloxy and C₃₋₆cycloalkyloxy, said C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkyloxy and C₃₋₆cycloalkyloxy being optionally substituted with one or more halogens; or R² is a 5-10 membered heteroaryl ring system comprising a heteroatom selected from N, O and S and optionally substituted with a substituent selected from methyl, C₁₋₆alkyloxy and halogen; or R² is C₄₋₇cycloalkyl; R³ is an optional substituent selected from C₁₋₆alkyl, C₁₋₆alkyloxy and halogen, said C₁₋₆alkyl and C₁₋₆alkyloxy being optionally substituted with one or more halogens; R⁴ is a group located at the 6- or 7- position of the quinazolinone or isoquinolinone ring having the formula II, wherein R⁵ together with one of R⁶ forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR⁹, said

heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo or R⁵ together with one of R⁷ and R⁸ forms a 6-8 membered heterocyclic ring optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo; Each R⁶ is independently H, halogen or C₁₋₄alkyl optionally substituted with halogen or SO₂CH₃ or one of R⁶ together with R⁵ forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR⁹, said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo; R⁷ and R⁸ are independently H, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, cyanoC₁₋₃alkyl, C₆₋₁₀aryl, C₆₋₁₀arylC₁₋₃alkyl, C₁₋₃alkyloxyC₁₋₃alkyl or C₁₋₆acyl said C₁₋₆alkyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkylC₁₋₃alkyl being optionally substituted with hydroxy, 1 or more halogens or diC₁₋₂alkylamino; or R⁷ and R⁸ together with the nitrogen to which they are bonded form a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR¹⁰, said heterocyclic ring being optionally substituted with one or two substituents selected from C₁₋₆alkyl, halogen, hydroxy,

WO 2008/033764 A3



CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

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- (88) **Date of publication of the international search report:**

18 December 2008

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 A61P 25/00 (2006.01)

(21) International Application Number:

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(22) International Filing Date:

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(72) Inventors; and

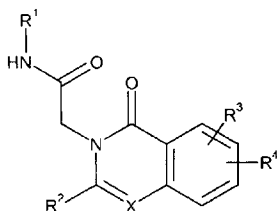
(75) Inventors/Applicants (for US only): LETOURNEAU,

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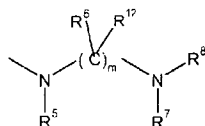
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(54) Title: QUINAZOLINONE AND ISOQUINOLINONE ACETAMIDE DERIVATIVES



I



II

(57) Abstract: The present invention relates to a quinazolinone or isoquinolinone derivative of formula I, wherein R¹ is C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, said C₁₋₆alkyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkylC₁₋₃alkyl being optionally substituted with hydroxy, C₁₋₆alkyloxy, cyano or one or more halogens; R² is C₆₋₁₀aryl optionally substituted with one to three substituents selected from halogen, hydroxy, cyano, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkyloxy and C₃₋₆cycloalkyloxy, said C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkyloxy and C₃₋₆cycloalkyloxy being optionally substituted with one or more halogens; or R² is a 5-10 membered heteroaryl ring system comprising a heteroatom selected from N, O and S and optionally substituted with a substituent selected from methyl, C₁₋₆alkyloxy and halogen; or R² is C₄₋₇cycloalkyl; R³ is an optional substituent selected from C₁₋₆alkyl, C₁₋₆alkyloxy and halogen, said C₁₋₆alkyl and C₁₋₆alkyloxy being optionally substituted with one or more halogens; R⁴ is a group located at the 6- or 7- position of the quinazolinone or isoquinolinone ring having the formula II, wherein R⁵ together with one of R⁶ forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR⁹, said

heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo or R⁵ together with one of R⁷ and R⁸ forms a 6-8 membered heterocyclic ring optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo; Each R⁶ is independently H, halogen or C₁₋₆alkyl optionally substituted with halogen or SO₂CH₃ or one of R⁶ together with R⁵ forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR⁹, said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo; R⁷ and R⁸ are independently H, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, cyanoC₁₋₃alkyl, C₆₋₁₀aryl, C₆₋₁₀arylC₁₋₃alkyl, C₁₋₃alkyloxyC₁₋₃alkyl or C₁₋₆acyl said C₁₋₆alkyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkylC₁₋₃alkyl being optionally substituted with hydroxy, 1 or more halogens or diC₁₋₂alkylamino; or R⁷ and R⁸ together with the nitrogen to which they are bonded form a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR¹⁰, said heterocyclic ring being optionally substituted with one or two substituents selected from C₁₋₆alkyl, halogen, hydroxy,



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QUINAZOLINONE AND ISOQUINOLINONE ACETAMIDE DERIVATIVES

The present invention relates to quinazolinone and isoquinolinone derivatives, to pharmaceutical compositions comprising these compounds and to their use in therapy, in particular to their use for the manufacture of a medicament for the treatment or prevention of disorders or diseases influenced by modulation of the activity of the HPA axis.

The hypothalamo-pituitary-adrenal (HPA) axis is the major stress axis in humans and other mammals. A variety of stressors (and multiple other classes of stimuli) cause release of the hormone ACTH (adrenocorticotrophic hormone) from the anterior pituitary gland. ACTH enters the systemic circulation and acts on the adrenal cortex to promote synthesis and release of glucocorticoid hormone (the major endogenous glucocorticoid being cortisol in humans and corticosterone in rodents). The glucocorticoids exert a broad spectrum of effects, the main purpose of which is to mobilise energy sources for successful responsiveness and eventual adaptation to the stressor.

Abnormally elevated HPA axis activity in man is associated with the development of a variety of psychiatric disturbances, some of which are stress-related in aetiology. Elevated cortisol levels, which are indicative of HPA axis hyperactivity and loss of normal negative feedback regulatory processes, are a common finding in affective disorders and various other psychiatric disturbances, and are widely utilised as a diagnostic tool (Holsboer *et al.*, *Biol. Psych.*, 1986, **21**, 601-611). It is generally considered that dysregulation of the HPA axis is a reflection of enhanced vulnerability and poor adaptation to chronic stress and that chronic stress therefore plays a major role in the development of affective illness (Sperry and Carlson, DSM-IV diagnosis to treatment, 2nd Edition, Taylor & Francis, 1996). This central concept is supported by experimental evidence utilising animal models of chronic stress, where aberrant HPA function closely resembles that seen in clinical settings (De Goeij *et al.*, *Neuroendocrinology*, 1991, **53**, 150-159; Plotsky and Meaney, *Mol. Brain Res.*, 1993, **18**, 195-200).

The major secretagogues for ACTH in humans and rats are CRH (corticotropin releasing hormone) and AVP (arginine vasopressin). Within the HPA axis these peptide hormones are synthesised by the parvocellular neurones of the paraventricular nucleus (PVN) of the hypothalamus. The axons of these neurones project to the external zone of the median

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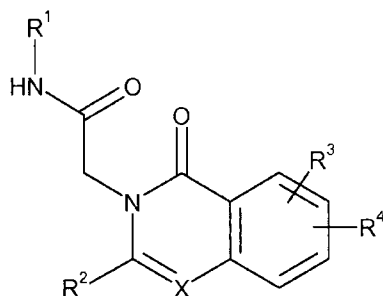
eminence, from where the hormone products enter the hypophyseal portal system to bathe the corticotrope cells that manufacture ACTH. CRH and AVP act synergistically at the corticotrope to regulate ACTH secretion in both rats (Rivier and Vale, *Nature*, 1983, **305**, 325-327) and in man (De Bold *et al.*, *J. Clin. Invest.*, 1984, **73**, 533-538).

The actions of AVP at the pituitary corticotrope are mediated by the vasopressin V_3 (or V_{1b}) receptor, which is known and has been cloned (human receptor: Sugimoto *et al.*, *J. Biol. Chem.*, 1994, **269**, 27088-27092). A report of clinical studies in depressed patients in which blunted ACTH responses to CRH could be restored by concomitant administration of desmopressin (dDAVP, an AVP agonist with V_3 affinity) confirms the involvement of the V_3 receptor in depression (Scott and Dinan, *Life Sciences*, 1998, **62**, 1985-1988). A study in rodents with non-selective peptide V_3 antagonists indicates that the V_3 receptor does play a functional role in control of pituitary ACTH release (Bernardini *et al.*, *Neuroendocrinology*, 1994, **60**, 503-508). Vasopressin antagonists are thus utilised to modulate and normalise pituitary ACTH release and subsequent HPA axis dysfunction in CNS disorders which are characterised by abnormal HPA axis negative feedback mechanisms.

In addition to the V_3 receptor, vasopressin also activates peripheral receptors, *i.e.*, the V_{1a} receptor, predominantly found on liver and vascular tissue and the V_2 receptor, predominantly found on kidney tissue. Interaction at these receptors mediate the pressor and antidiuretic actions of AVP.

Whilst there are several non-peptide low-molecular weight antagonists known which are selective for the V_{1a} or the V_2 receptor (for a recent review see Freidinger and Pettibone, *Medicinal Research Reviews*, 1997, **17**, 1-16), there are only a small number of non-peptide ligands known with selectivity for the V_3 receptor (see for example, WO 01/55130 and WO 04/009585). There exists therefore a need for further non-peptide V_3 selective antagonists which are both safe and effective.

In a first aspect, the present invention provides a quinazolinone or isoquinolinone derivative of formula I



formula I

wherein

R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, said C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl C_{1-3} alkyl being optionally substituted with hydroxy, C_{1-6} alkyloxy, cyano or more halogens;

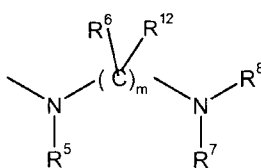
R^2 is C_{6-10} aryl optionally substituted with one to three substituents selected from halogen, hydroxy, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyloxy and C_{3-6} cycloalkyloxy, said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyloxy and C_{3-6} cycloalkyloxy being optionally substituted with one or more halogens;

or R^2 is a 5-10 membered heteroaryl ring system comprising a heteroatom selected from N, O and S and optionally substituted with a substituent selected from methyl, C_{1-6} alkyloxy and halogen;

or R^2 is C_{4-7} cycloalkyl;

R^3 is an optional substituent selected from C_{1-6} alkyl, C_{1-6} alkyloxy and halogen, said C_{1-6} alkyl and C_{1-6} alkyloxy being optionally substituted with one or more halogens;

R^4 is a group located at the 6- or 7- position of the quinazolinone or isoquinolinone ring having the formula II



formula II

wherein

R^5 together with one of R^6 forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR^9 , said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo or R^5 together with one of R^7 and R^8 forms a 6-8

membered heterocyclic ring optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo;

Each R^6 is independently H, halogen or C_{1-4} alkyl optionally substituted with halogen or SO_2CH_3 or one of R^6 together with R^5 forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR^9 , said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo;

R^7 and R^8 are independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-3} alkyl, cyano C_{1-3} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, C_{1-3} alkyloxy C_{1-3} alkyl or C_{1-6} acyl said C_{1-6} alkyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkyl C_{1-3} alkyl being optionally substituted with hydroxy, 1 or more halogens or di C_{1-2} alkylamino;

or R^7 and R^8 together with the nitrogen to which they are bonded form a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR^{10} , said heterocyclic ring being optionally substituted with one or two substituents selected from C_{1-6} alkyl, halogen, hydroxy, C_{1-6} alkyloxy, cyano and $COOR^{11}$;

or one of R^7 and R^8 is Y, CH_2Y or CH_2CH_2Y , wherein Y is a 4-6 membered saturated heterocyclic ring comprising a heterocyclic moiety selected from O, SO_2 and NR^{10} , said ring being optionally substituted with 1-2 substituents selected from methyl or halogen;

or one of R^7 or R^8 together with R^5 forms a 6-8 membered heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo

or one of R^7 and R^8 together with R^{12} forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR^{13} , said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, hydroxy and oxo;

R^9 and R^{10} are independently H, C_{1-6} alkyl or C_{1-6} acyl;

R^{11} is H or C_{1-6} alkyl;

Each R^{12} is independently H or C_{1-4} alkyl or one of R^{12} together with one of R^7 or R^8 forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR^{13} , said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, hydroxy and oxo;

R^{13} is H, C_{1-6} alkyl or C_{1-6} acyl;

m is 2-3 and

X is N or CH

or a pharmaceutically acceptable salt or solvate thereof.

IS

The term C_{1-6} alkyl, as used herein, represents a branched or unbranched alkyl group having 1-6 carbon atoms. Examples of such groups are methyl, ethyl, isopropyl, tertiary-butyl, pentyl and hexyl. Similarly the term C_{1-2} alkyl, as used herein, represents an alkyl group having 1-2 carbon atoms.

The term C_{2-6} alkenyl, as used herein, represents a branched or unbranched alkenyl group having 2-6 carbon atoms and at least one double bond. Examples of such groups are ethenyl and isopropenyl.

The term C_{2-6} alkynyl, as used herein, represents a branched or unbranched alkynyl group having 2-6 carbon atoms and at least one triple bond. Examples of such groups are ethynyl and 3-methyl-1-butylyl.

The term C_{3-6} cycloalkyl, as used herein, represents a branched or unbranched cyclic alkyl group having 3-6 carbon atoms. Examples of such groups are cyclopropyl, cyclopentyl and 2-methylcyclopentyl. Similarly the term C_{4-7} cycloalkyl, as used herein, represents a branched or unbranched cyclic alkyl group having 4-7 carbon atoms.

The term C_{3-6} cycloalkyl C_{1-3} alkyl, as used herein, represents a C_{1-3} alkyl group which is substituted with a C_{3-6} cycloalkyl group. Examples of such groups are cyclopropylmethyl and 2-cyclobutylethyl.

The term cyano C_{1-2} alkyl, as used herein, represents a C_{1-2} alkyl group which is substituted with a cyano group. Examples of such groups are cyanomethyl and cyanoethyl.

The term di C_{1-2} alkylamino, as used herein, represents an amino group which is substituted with two C_{1-2} alkyl groups. Examples of such groups are dimethylamine and diethylamine.

The term C_{1-6} alkyloxy, as used herein, represents a branched or unbranched alkyloxy group having 1-6 carbon atoms. Examples of such groups are methoxy, ethoxy, isopropoxy and tertiary-butyloxy.

The term C_{3-6} cycloalkyloxy, as used herein, represents a branched or unbranched cyclic alkyloxy group having 3-6 carbon atoms. Examples of such groups are cyclopropyloxy, cyclopentyloxy and 2-methylcyclopentyloxy.

The term C₁₋₆ acyl, as used herein, represents an acyl group derived from a carboxylic acid having 1-6 carbon atoms. The acyl group can comprise a hydrocarbon which may be branched, unbranched, saturated or unsaturated. Examples of such groups include formyl, acetyl, propionyl, acryloyl and pivaloyl. Also included within the definition of C₁₋₆ acyl are groups derived from dicarboxylic acids like groups derived from malonic acid.

The term C₆₋₁₀ aryl, as used herein, represents an aromatic group having 6-10 carbon atoms. Examples of such groups include phenyl and naphthyl.

The term C₆₋₁₀arylC₁₋₂alkyl, as used herein, represents a C₁₋₂ alkyl group which is substituted with a C₆₋₁₀ aryl group. Examples of such groups include benzyl and phenethyl.

The term halogen, as used herein, represents a fluorine, chlorine, bromine or iodine.

The term 5-10 membered heteroaryl ring system comprising a heteroatom selected from N, O and S, as used herein, represents a monocyclic or fused bicyclic 5-10 membered heteroaryl ring system comprising a heteroatom selected from N, O and S. Examples of such groups include furanyl, thienyl, pyrrolyl, pyridinyl, indolyl, benzthienyl and quinolinyl.

Examples of 4 - 8 membered saturated or unsaturated heterocyclic rings formed by R⁵ and R⁶ together with the nitrogen to which they are bonded and optionally comprising a further heteroatomic moiety selected from O, S and NR⁷ wherein R⁵ - R⁷ have the previously defined meanings include piperidine homopiperidine, morpholine, thiomorpholine, 4-methylpiperazine and tetrahydropyridine.

Examples of 4-6 membered saturated heterocyclic rings comprising a heterocyclic moiety selected from O, SO₂, and NR¹⁰, include tetrahydropyran and piperidine.

The term solvate, as used herein, refers to a complex of variable stoichiometry formed by a solvent and a solute (in this invention, a compound of formula I). Such solvents may not interfere with the biological activity of the solute. Examples of suitable solvents include, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent, such as water, ethanol and acetic acid.

In one embodiment of the present invention R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{3-6} cycloalkyl C_{1-3} alkyl. In a further embodiment R^1 is C_{3-4} alkyl, C_{3-4} cycloalkyl or C_{3-4} cycloalkyl C_{1-3} alkyl. In a further embodiment R^1 is isopropyl, isobutyl, tertiary-butyl, cyclopropylmethyl, cyclobutyl, 2,2,2-trifluoro-1-methylethyl or 2,2,2-trifluoro-1,1-dimethylethyl.

In another embodiment R^2 is C_{6-10} aryl, optionally substituted with one to three substituents selected from halogen, hydroxy, cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyloxy and C_{3-6} cycloalkyloxy, said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyloxy and C_{3-6} cycloalkyloxy being optionally substituted with one or more halogens. In a further embodiment R^2 is a phenyl ring. In a further embodiment R^2 is a 3-substituted phenyl ring. In a further embodiment R^2 is a 3-substituted phenyl ring substituted with one to three substituents selected from chloro, fluoro, C_{1-2} alkyl, trifluoromethyl, C_{1-3} alkyloxy, C_{1-4} cycloalkyloxy and trifluoromethoxy. In a further embodiment R^2 is a substituted phenyl ring selected from 3-chlorophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-trifluoromethoxyphenyl, 3-chloro-4-fluorophenyl, 4-fluoro-3-methoxyphenyl and 3,5-dimethoxyphenyl.

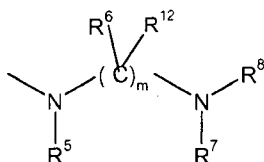
In another embodiment R^2 is a 5-10 membered heteroaryl ring system comprising a heteroatom selected from N, O and S and optionally substituted with a substituent selected from methyl, C_{1-6} alkyloxy and halogen. In a further embodiment R^2 is a 2-thienyl, 3-thienyl or 6-indolyl optionally substituted with chloro or methyl.

In another embodiment R^2 is C_{4-7} cycloalkyl

In another embodiment R^3 is a substituent selected from chloro, methyl and methoxy. In a further embodiment R^3 is a substituent at the 7-position of the quinazolinone.

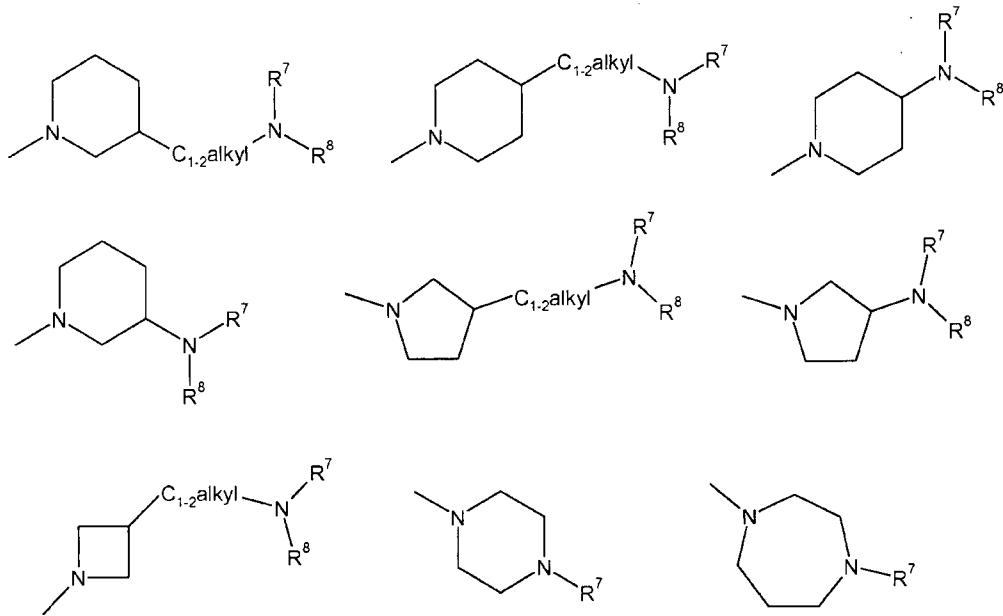
In a further embodiment R^3 is a substituent at the 6-position of the isoquinolinone.

In another embodiment, R^4 is the group



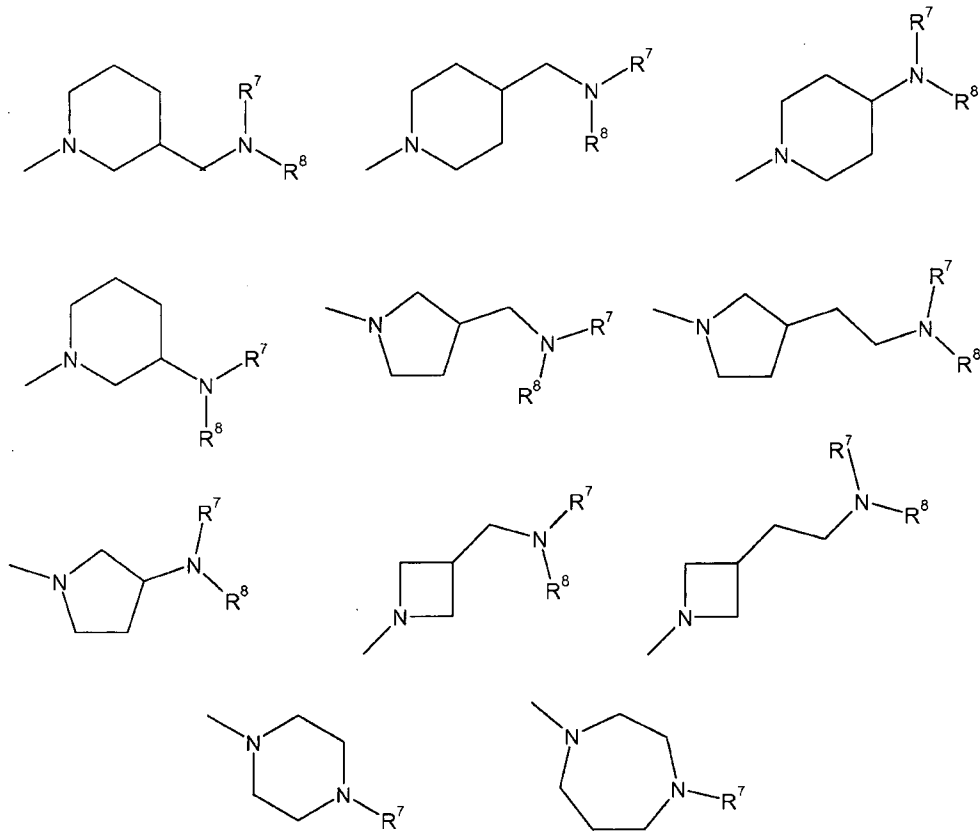
wherein $R^8 - R^{11}$ have the previously defined meanings. In a further embodiment R^4 is a group selected from

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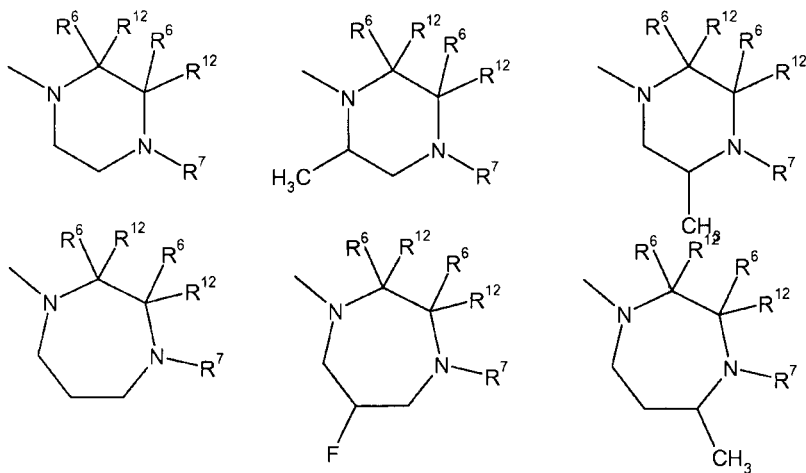
wherein R⁷ and R⁸ have the previously defined meanings

In a further embodiment R⁴ is a group selected from



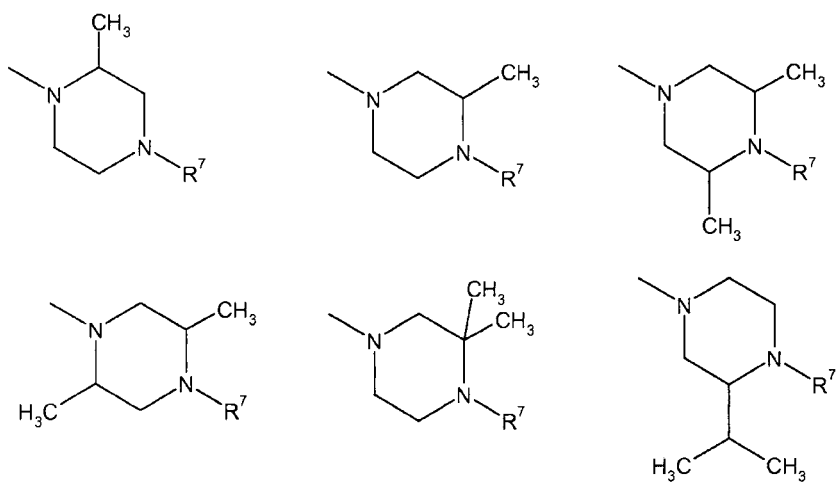
wherein R^7 and R^8 have the previously defined meanings.

In a further embodiment R^4 is a group selected from:



wherein R^6 , R^7 and R^{12} have the previously defined meanings.

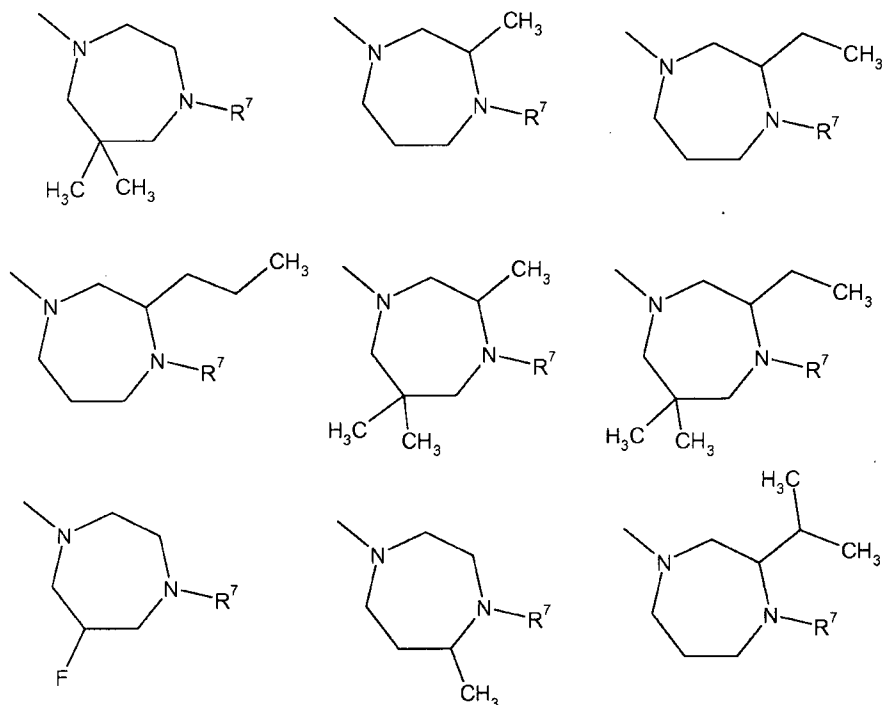
In a further embodiment R^4 is a group selected from:



wherein R^7 has the previously defined meaning.

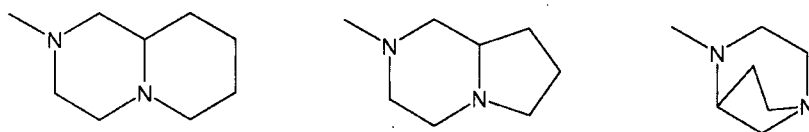
In a further embodiment R^4 is a group selected from:

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wherein R^7 has the previously defined meaning.

In a further embodiment R^4 is a group selected from:



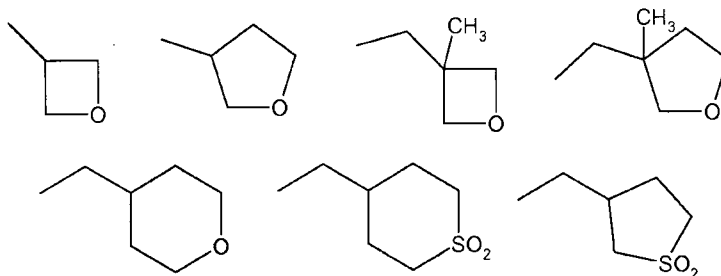
wherein R^7 has the previously defined meaning.

In a further embodiment, R^4 is a substituent at the 6-position of the quinazolinone. In a further embodiment R^4 is a substituent at the 7-position of the isoquinolinone.

In another embodiment, R^7 and R^8 are independently H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl C_{1-3} alkyl, C_{6-10} aryl or C_{6-10} aryl C_{1-3} alkyl. In a further embodiment R^7 and R^8 are independently H or C_{1-4} alkyl.

In another embodiment, R^7 and R^8 are independently H, methyl, ethyl, propyl, butyl, isopropyl, hydroxyethyl, methoxyethyl, cyclopropylmethyl, 1-cyclopropylethyl, cyclopentyl or cyclobutyl.

In another embodiment, R^7 and R^8 are independently selected from: H, methyl and



In another embodiment, R^7 and R^8 together with the nitrogen to which they are bonded form a 4 to 6 membered heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S or NR^{10} , said heterocyclic ring being optionally substituted with a hydroxyl substituent, wherein R^{10} has the previously defined meaning. In a further embodiment R^7 and R^8 together with the nitrogen to which they are bonded form a heterocyclic ring selected from pyrrolidine, piperidine, 3-hydroxypiperidine and morpholine.

In another embodiment m is 2. In a further embodiment m is 3.

In another embodiment X is N. In a further embodiment X is CH.

In a further embodiment is a quinazolinone selected from:

2-[2-(3-Chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;

N-*tert*-Butyl-2-[2-(3-chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]acetamide;

N-*tert*-Butyl-2-(2-(3-chloro-4-fluorophenyl)-6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)acetamide;

2-(2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)-*N*-isopropylacetamide;

2-(2-(3-Chloro-4-fluorophenyl)-6-(3-methyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)-*N*-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-(3-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-(dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;

2-[6-(Dimethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-((S)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chlorophenyl)-6-((S)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(4-Fluoro-3-methoxyphenyl)-6-((S)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chlorophenyl)-6-((R)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(4-Fluoro-3-methoxyphenyl)-6-((R)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chlorophenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chlorophenyl)-4-oxo-6-(4-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide;

N-*tert*-Butyl-2-[6-(4-ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide;

2-[2-(3-Chlorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(4-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

N-Isopropyl-2-[6-(4-isopropylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide;

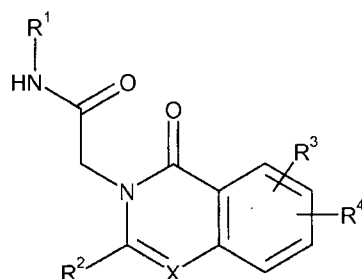
2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-5-trifluoromethylphenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3,5-Dimethoxyphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(1-cyclopropylethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazabicyclo[3.2.2]non-4-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(4-Fluoro-3-methoxyphenyl)-6-(4-isopropylpiperazin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylpiperazin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(3-Chloro-4-fluorophenyl)-6-((*S*)-3-isopropylpiperazin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(3-Chloro-4-fluorophenyl)-6-((*R*)-3-isopropylpiperazin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(3,5-dimethoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-(2,2,2-trifluoro-1,1-dimethylethyl)acetamide;
N-isopropyl-2-[6-(4-isopropyl-1,4-diazepan-1-yl)-2-(3-methoxyphenyl)-4-oxoquinazolin-3(4*H*)-yl]acetamide;
 2-(2-(3-Chlorophenyl)-6-(4-cyclopropylmethyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)-*N*-isopropylacetamide and
N-*tert*-Butyl-2-(2-(3-chlorophenyl)-6-(4-isopropyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)acetamide
 or a pharmaceutically acceptable salt or solvate thereof.

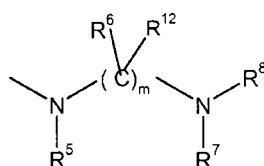
The quinazolinone and isoquinolinone derivatives of the present invention are prepared by methods well known in the art of organic chemistry. See, for example, J. March, '*Advanced Organic Chemistry*' 4th Edition, John Wiley and Sons. During synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This is achieved by means of conventional protecting groups, such as those described in T.W. Greene and P.G.M. Wuts, '*Protective Groups in Organic Synthesis*' 2nd

Edition, John Wiley and Sons, 1991. The protective groups are optionally removed at a convenient subsequent stage using methods well known in the art.



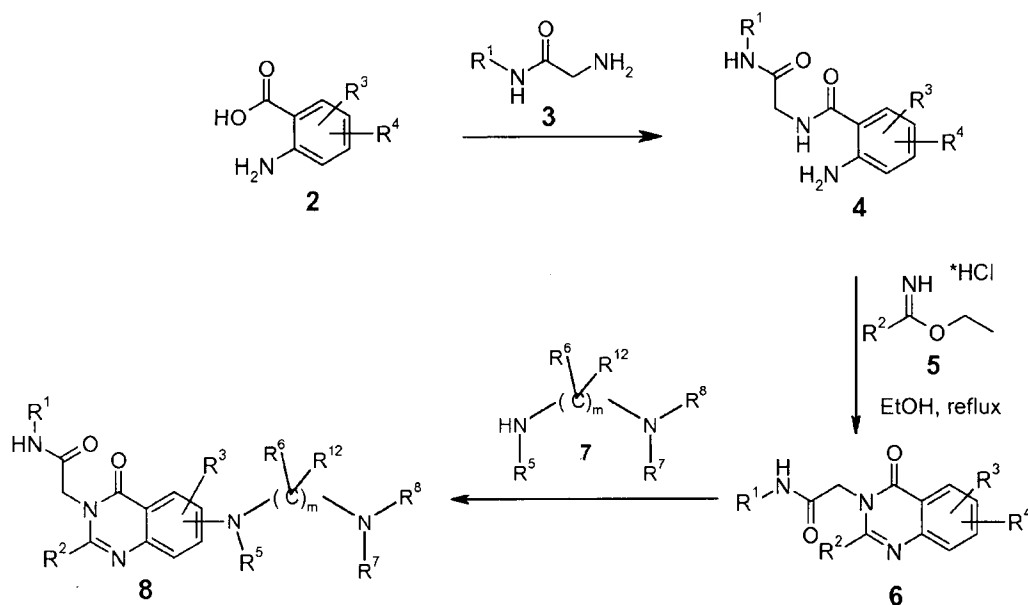
formula I

Quinazolinone and isoquinolinone derivatives of formula I wherein R^4 is the group



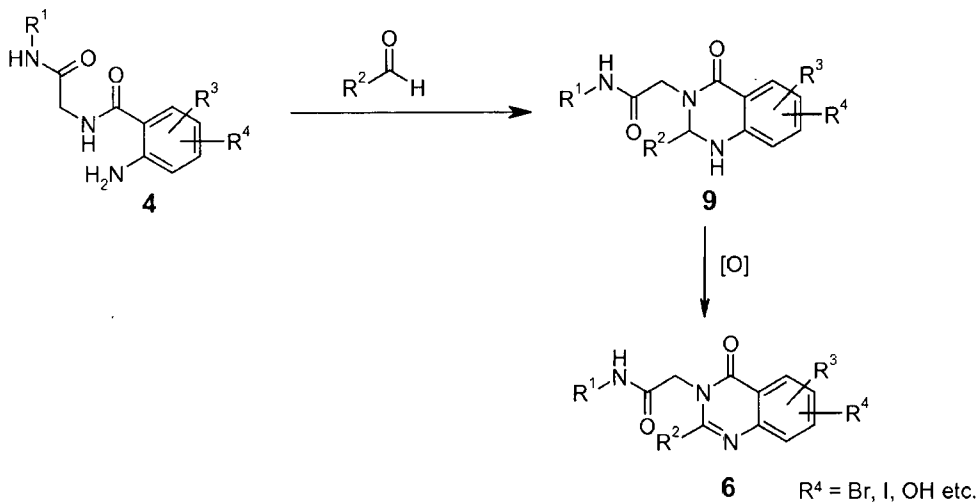
and X is N (shown as **8** below) can be prepared by the general three stage synthetic sequence shown in **Scheme 1**. Firstly an anthranilic acid of formula **2** wherein R^4 is OH or a suitably reactive group such as halogen (e.g. bromo or iodo) etc., is reacted with a glycine amide of formula **3** in the presence of a suitable amide bond coupling reagent to give the coupled product **4**. One example of such a coupling reagent would be EDCI. The coupling reagent is added either alone or in the presence of an additive such as HOBt and in a suitable inert solvent such as dichloromethane or DMF. The necessary anthranilic acids **2** and glycine amides **3** are either commercially available or they can readily be prepared by procedures well known in the art. The intermediate quinazolinones of general formula **6** can be made by condensation of the imidate salt **5** in a suitable solvent such as ethanol and at elevated temperatures such as at reflux. Intermediates **6** wherein R^4 is a reactive group such as triflate can be readily prepared from the corresponding intermediate **6** wherein R^4 is OH using procedures well known in the art, for example the triflate can be prepared by treatment of alcohols **6** with trifluoromethanesulfonic anhydride and pyridine. The intermediate quinazolinones **6** wherein R^4 is a suitably reactive group such as halogen (e.g. bromo or iodo), triflate, etc., can then be functionalised with diamines of formula **7** in the presence of a suitable catalyst system, such as $\text{Pd}_2(\text{dba})_3$ and BINAP, under conditions well known in the art to provide the desired product **8**. Diamines of formula **7** are either commercially available

or they can readily be prepared by procedures well known in the art.



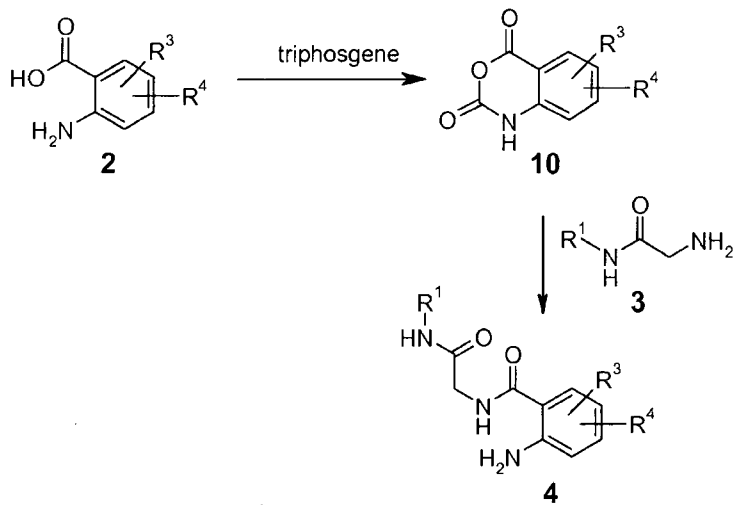
Scheme 1

Alternatively, the quinazolinone intermediates **6** can be formed by condensation of intermediate **4** with a suitable aldehyde, R^2CHO , followed by subsequent oxidation of the resultant dihydroquinazolinone intermediate **9** with a suitable oxidant such as MnO_2 , DDQ, or $CuCl_2$ (Scheme 2). Aldehydes R^2CHO are either commercially available or they can readily be prepared by procedures well known in the art.



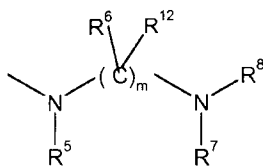
Scheme 2

The amide intermediate 4 can alternatively be prepared by reaction of an isatoic anhydride of general formula 10 with a glycine amide of formula 3 in a polar aprotic solvent such as acetonitrile. The isatoic anhydrides 10 are either commercially available or can readily be prepared by reaction of a suitable anthranilic acid of formula 2 with a carbonylating reagent such as phosgene or triphosgene (Scheme 3).

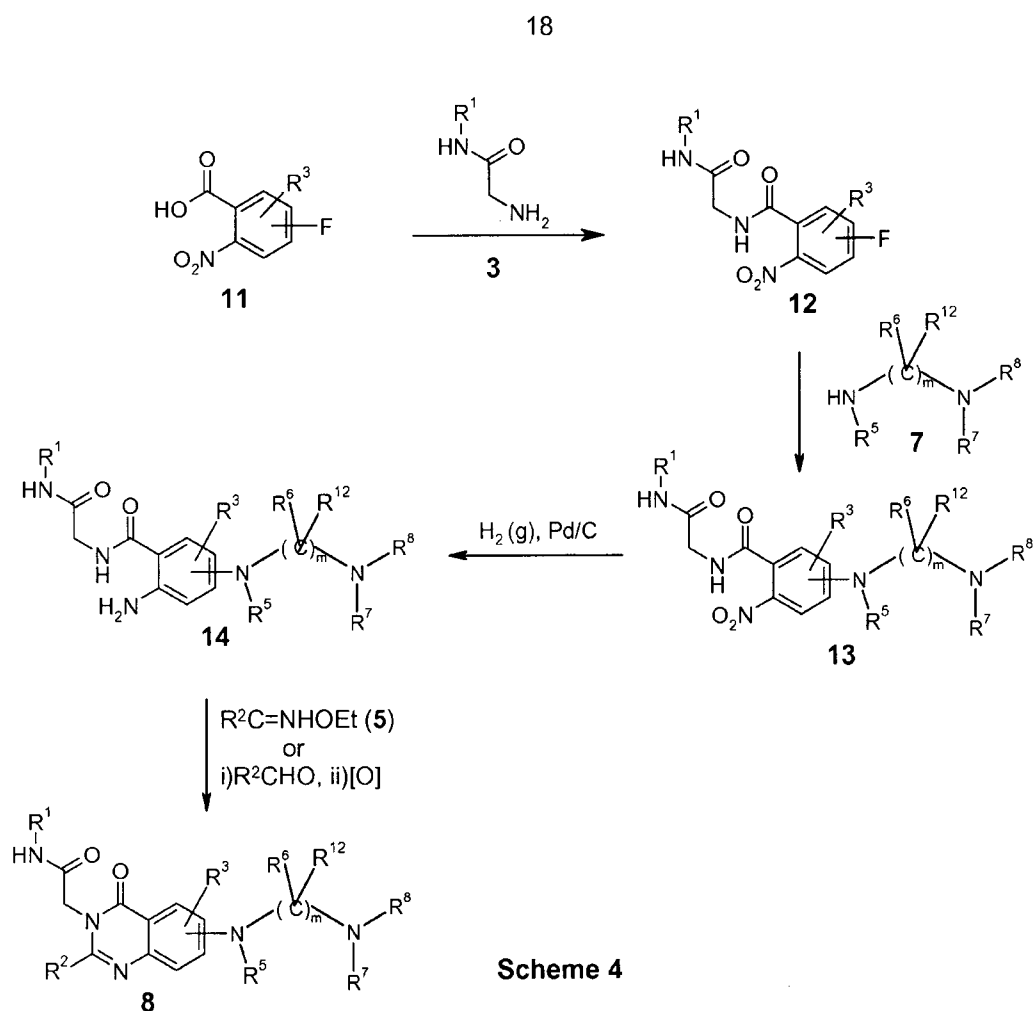


Scheme 3

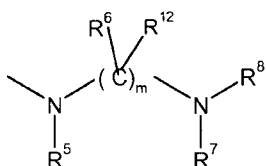
Compounds of formula I wherein R⁴ is the group



and X is N can also be prepared in four stages from the required fluoro-2-nitrobenzoic acid **11** as shown in **Scheme 4**. The fluoro-2-nitrobenzoic acid derivatives are either commercially available or can be prepared using procedures well known in the art of organic chemistry. The acid **11** can be coupled with a glycine amide of formula **3** using analogous procedures to those indicated previously (see **Scheme 1**) to yield the amide **12**. This in turn can then be treated with amine **7** in an inert polar, aprotic solvent such as DMF, DMSO or DMP at elevated temperatures and in the presence of a suitable base (for example, potassium or cesium carbonate) to afford the adduct **13**. Amines **7** are either commercially available or they can readily be prepared by procedures well known in the art. The nitro group is then reduced to give the aniline **14** using methods well known in the art, for example, reduction under a hydrogen atmosphere and in the presence of a suitable catalyst such as palladium on carbon. Finally, the desired quinazolinones **8** can be prepared upon reaction of **14** with an imidate* HCl salt of formula **5** (as previously described – **Scheme 1**) or upon reaction of **14** with an aldehyde R^2CHO followed by oxidation (as previously described – **Scheme 2**).



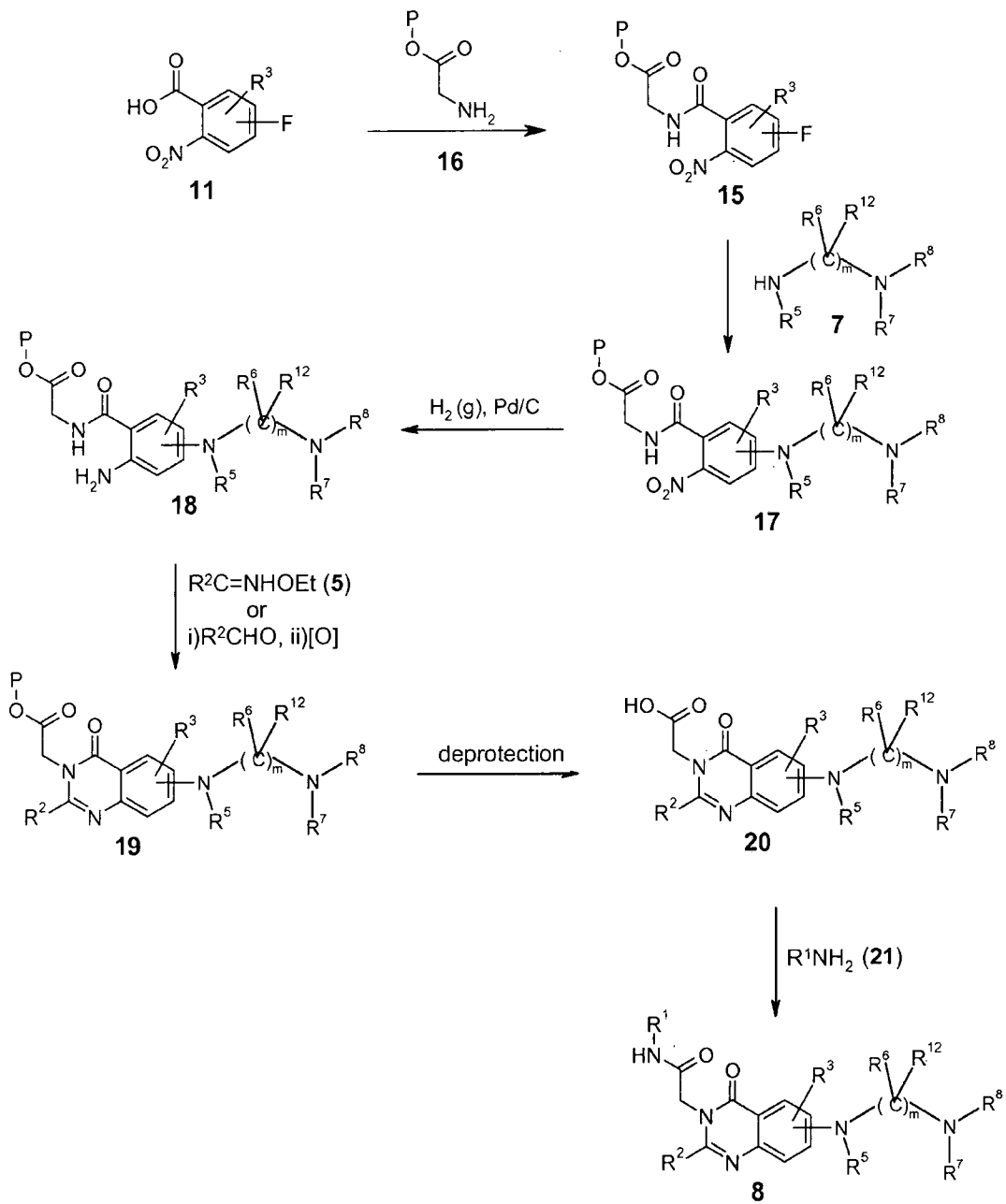
Compounds of formula I wherein R^4 is the group



and X is N can also be prepared in 6 stages from the required fluoro-2-nitrobenzoic acid **15** as shown in **Scheme 5**. The fluoro-2-nitrobenzoic acid derivatives **11** are either commercially available or can be prepared using procedures well known in the art of organic chemistry. The acid **11** can be coupled with suitably protected glycine of formula **16**, for example glycine *tert*-butyl ester or glycine methyl ester, using analogous procedures to those indicated previously (see **Scheme 1**) to yield the amide **15**. Suitably protected glycine

of formula **16** is either commercially available or can be prepared using procedures well known in the art of organic chemistry. Amide **15** can in turn be treated with amine **7** in an inert polar, aprotic solvent such as DMF, DMSO or DMP at elevated temperatures and in the presence of a suitable base (for example, potassium or cesium carbonate) to afford the adduct **17**. Amines **7** are either commercially available or they can readily be prepared by procedures well known in the art of organic chemistry. The nitro group can then be reduced to give the aniline **18** using methods well known in the art, for example, reduction under a hydrogen atmosphere and in the presence of a suitable catalyst such as palladium on carbon. Quinazolinones **19** are prepared upon reaction of **18** with an imidate* HCl salt of formula **5** (as previously described – **Scheme 1**) or upon reaction of **14** with an aldehyde R^2CHO followed by oxidation (as previously described – **Scheme 2**). Removal of the carboxylic acid protecting group can be readily achieved using procedures well known in the art of organic chemistry, for example *tert*-butyl ester can be removed under acidic conditions for example trifluoroacetic acid in an aprotic solvent such as DMF or DCM, to give the carboxylic acids **20**. Finally, the desired quinazolinones **8** can be prepared by reaction of carboxylic acid **20** with amine **21** using procedures well known in the art, for example a suitable amide coupling reagent. One example of such a coupling reagent would be EDCI. The coupling agent is added either alone or in the presence of an additive such as HOBt and in a suitable inert solvent such as DMF or DCM.

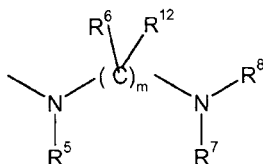
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Scheme 5

Compounds of formula I wherein R⁴ is the group

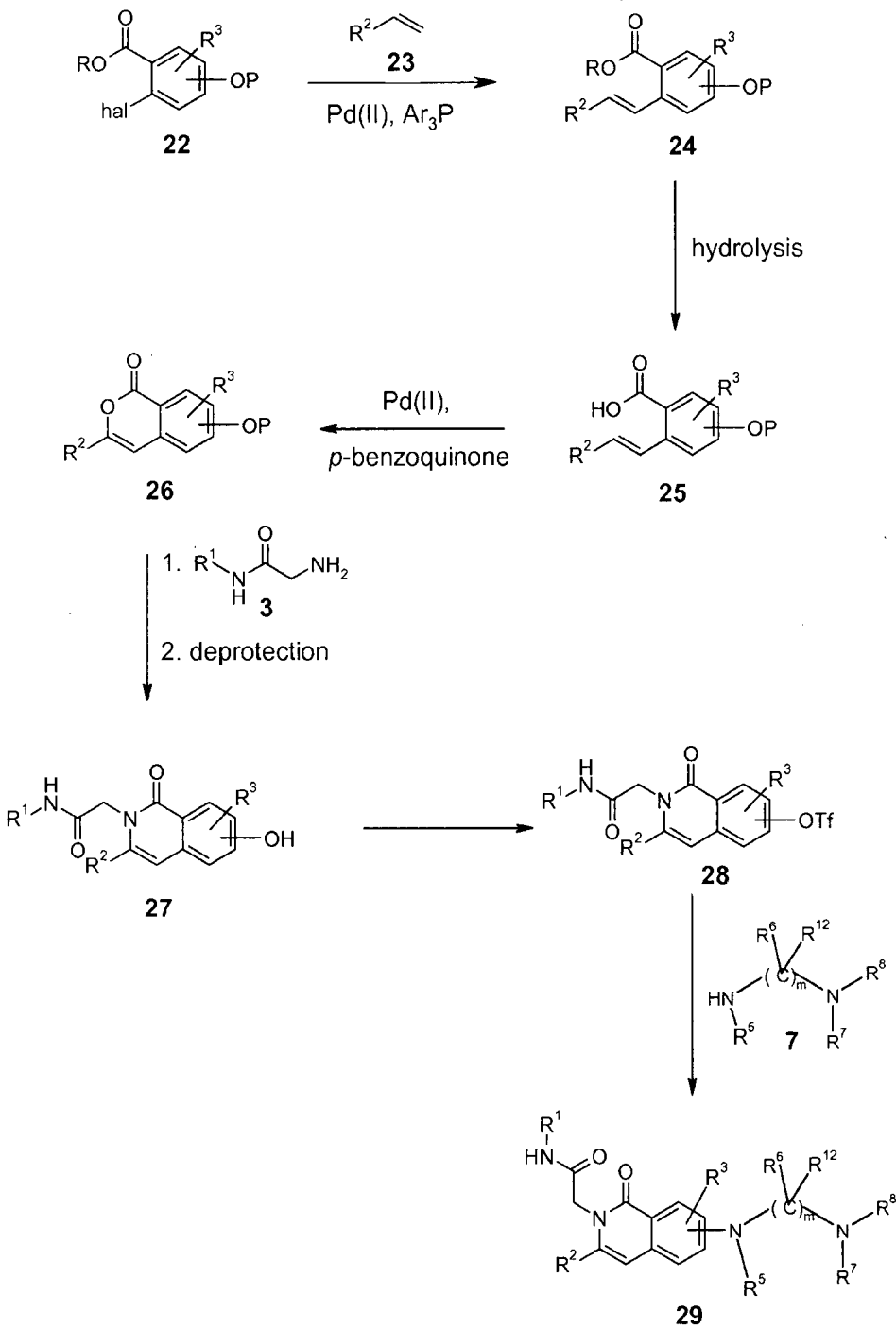
21



and X is CH (shown as **29** below) can be prepared by the general six stage synthetic sequence shown in **Scheme 6**. Firstly a suitably functionalised 2-halobenzoic acid ester of formula **22**, can be reacted with a suitably functionalised styrene of formula **23** in the presence of a suitable Pd(II) catalyst (for example palladium diacetate), a triarylphosphine ligand (for example tri(*o*-tolyl)phosphine) and a tertiary amine base (for example triethylamine) in a polar aprotic solvent (for example acetonitrile) to give the coupled product **24**. P represents a suitable protecting group, for example methyl. The 2-halobenzoic acids **22** and styrenes **23** are either commercially available or they can readily be prepared by procedures well known in the art. The carboxylic acid ester **24** can then be hydrolysed to the carboxylic acid **25** using either acid or base in a suitable solvent such as ethanol. The carboxylic acid intermediate **25** can subsequently be cyclised to the isocoumarin **26** using a palladium(II) catalyst, for example, bis(acetonitrile)dichloropalladium(II) and an oxidant, for example, *p*-benzoquinone, in an inert solvent, for example, tetrahydrofuran. The isocoumarin **26** thus obtained can be heated together with a glycine amide **3** to provide the isoquinolinone which can subsequently be deprotected to give isoquinolinone **27**. The free alcohol **27** thus obtained can be converted to the corresponding triflate using procedures well known in the art, for example by treatment of alcohol **27** with trifluoromethanesulfonic anhydride and pyridine. Triflate **28** can be reacted with diamines of formula **7** in the presence of a suitable catalyst system, such as Pd₂(dba)₃ and BINAP, under conditions well known in the art to afford desired isoquinolones **29** (**Scheme 6**).

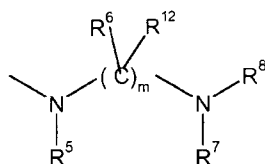
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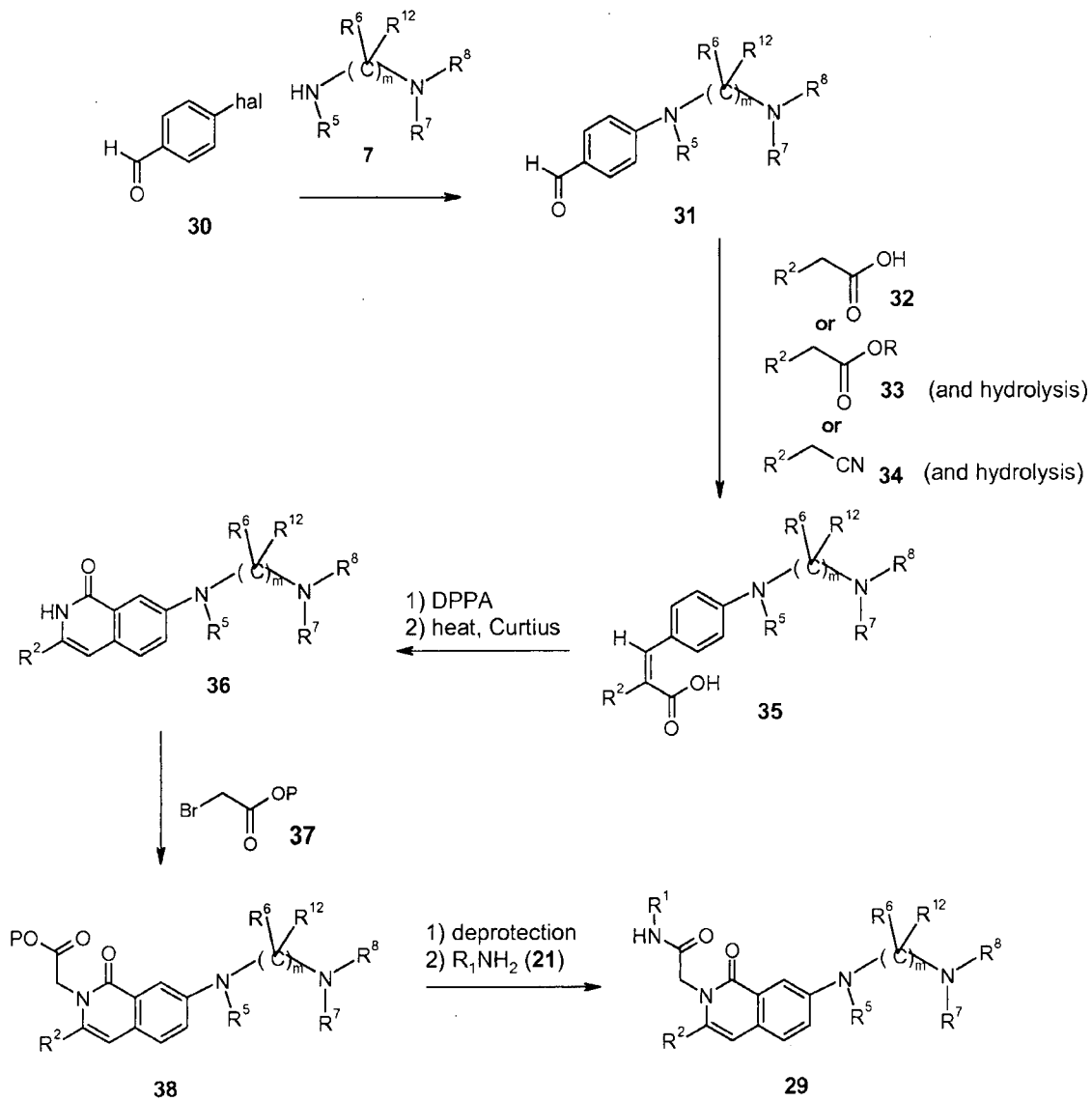
Scheme 6

Compounds of formula I wherein R⁴ is the group



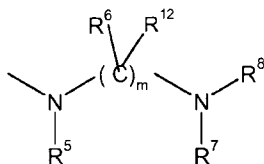
and X is CH (shown as **29** below) can alternatively be prepared by the general five stage synthetic sequence shown in **Scheme 7**. Firstly a 4-halobenzaldehyde of formula **30**, halo can be for example fluoro, can be reacted with amine **7** in an inert polar, aprotic solvent such as DMF, DMSO or DMP at elevated temperatures and in the presence of a suitable base (for example, potassium or cesium carbonate) to afford the aldehyde **31**. Aldehyde **31** can be reacted with a suitably functionalised carboxylic acid (**32**), carboxylic acid ester (**33**) or nitrile (**34**) to afford carboxylic acid **35**. Carboxylic acid **35** can be formed directly when using a suitably functionalised carboxylic acid **32** or following subsequent hydrolysis of the carboxylic acid ester or nitrile when using carboxylic acid ester **33** or nitrile **34** respectively. Hydrolysis can be achieved using procedures well known in the art of organic chemistry. Subsequent treatment of adduct **35** with, for example, DPPA at elevated temperatures can afford isoquinolone **36** via a Curtius reaction. Alkylation of isoquinolone **36** with a suitably protected bromoacetic acid derivative **37** (P represents a suitable protecting group, for example methyl) can afford ester **38**. Hydrolysis of ester **38** using procedures well known in the art of organic chemistry and subsequent reaction with amine **21** using procedures well known in the art (as previously described – **Scheme 7**) can afford the desired isoquinolones **29**.

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Scheme 7

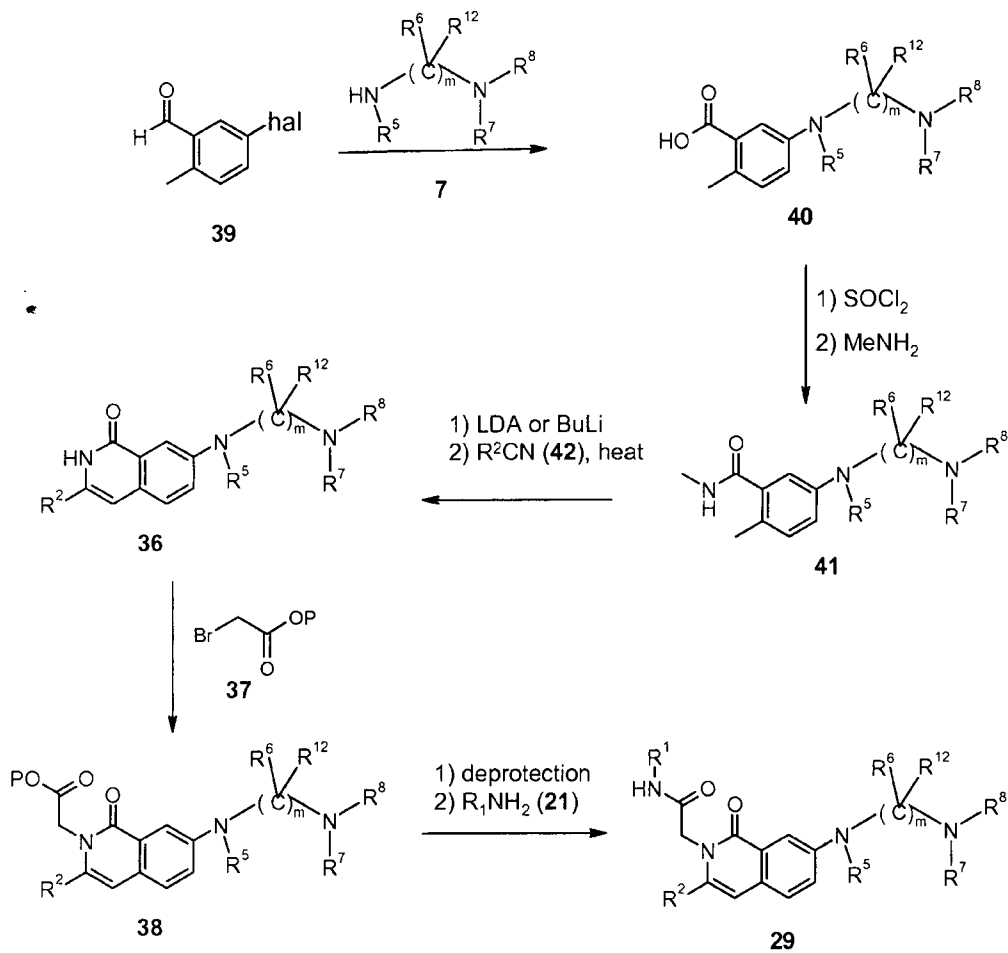
Compounds of formula I wherein R⁴ is the group



and X is CH (shown as **29** below) can alternatively be prepared by the general five stage synthetic sequence shown in **Scheme 8**. A 3-halo-6-methylbenzoic acid of formula **39**, halo can be for example fluoro, can be reacted with diamines of formula **7** in an inert polar, aprotic solvent such as DMF, DMSO or DMP at elevated temperatures and in the presence of a base such as potassium carbonate can afford carboxylic acid **40**. Carboxylic acid **40** can be converted to amide **41** by reaction with methylamine using procedures well known in the art of organic chemistry, for example converting to the acid chloride with thionyl chloride or oxalyl chloride and subsequent reaction with methylamine. Amide **41** can be treated with a suitable base, for example LDA or BuLi, and subsequently reacted with an appropriately substituted nitrile **42** in a suitable solvent to provide isoquinolone **36**. Isoquinolones **38** can be prepared upon reaction of **36** with a suitably protected bromoacetic acid derivative **37** in an inert polar, aprotic solvent such as DMF and in the presence of a suitable base such as potassium carbonate. P represents a protecting group for example methyl. The carboxylic acid ester can then be hydrolysed to the carboxylic acid using either acid or base in a suitable solvent and subsequently reacted with amine **21** (as previously described – **Scheme 7**) to afford isoquinolones **29**.

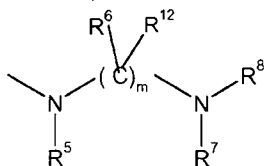
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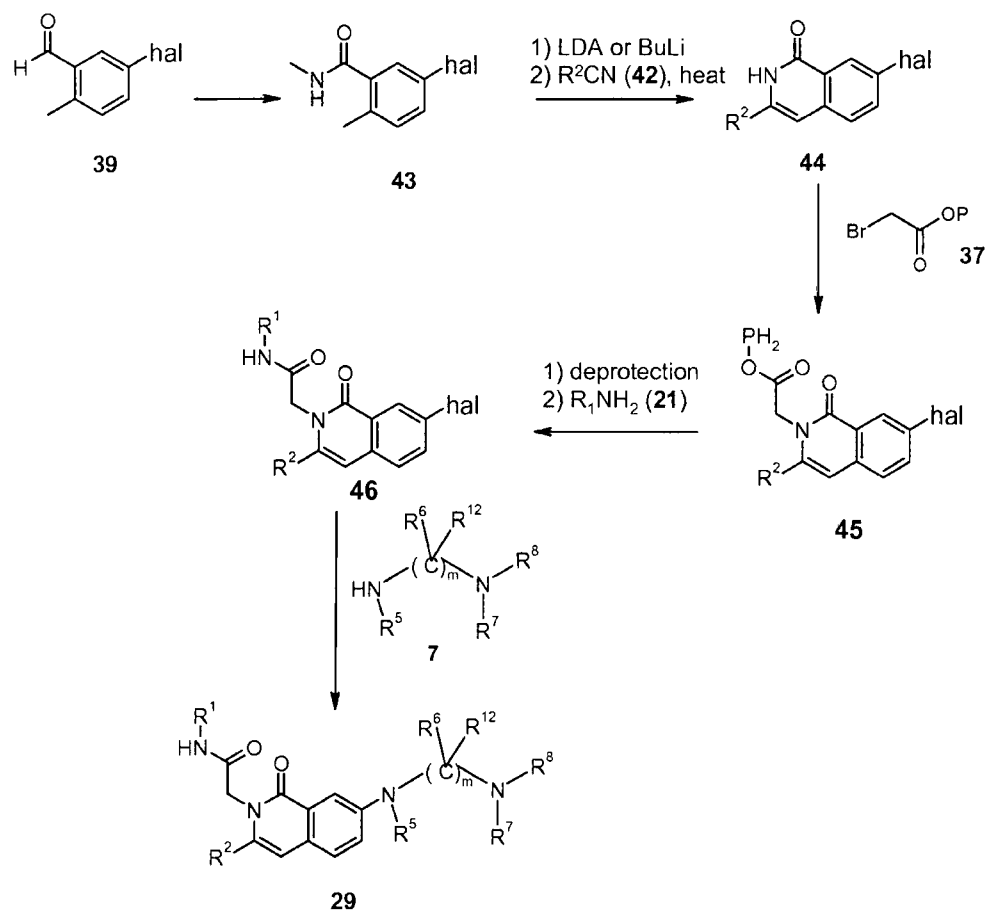
Scheme 8

Compounds of formula I wherein R⁴ is the group



and X is CH (shown as **29** below) can alternatively be prepared by the general five stage synthetic sequence shown in **Scheme 9**. A 3-halo-6-methylbenzoic acid of formula **39**, where halo can for example chloro or bromo, can be reacted with methylamine using procedures well known in the art of organic chemistry to provide amide **43**. For example

acid **39** can be converted to the acid chloride by reaction with, for example, thionyl chloride or oxalyl chloride at elevated temperature. The acid chloride can then be treated with methylamine. Amide **43** can be reacted with a suitable base, for example LDA or BuLi, in a suitable solvent such as THF and subsequently treated with an appropriately substituted nitrile of formula **42** to provide isoquinolone **44**. Isoquinolone **45** can be prepared by alkylation of isoquinolone **44** with a bromoacetic acid ester derivative **37** in a polar aprotic solvent such as DMF and in the presence of a suitable base such as potassium carbonate. P is a protecting group for example methyl. Deprotection using procedures well known in the art of organic chemistry followed by reaction with amine **21** can provide isoquinolones of formula **46**. Isoquinolones of formula **29** can be prepared by reacting isoquinolones **46** with diamines of formula **7** at elevated temperatures in a suitable solvent and in the presence of a suitable catalyst system, such as [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride.



Scheme 9

It will be readily appreciated by one skilled in the art that the quinazolinones and isoquinolinones of general formula I can be prepared using the general procedures and/or reaction sequences described above in any suitable order. For example, whereas the processes detailed above describe introduction of the R⁴ groups later in the syntheses utilizing preformed quinazolinone and isoquinolinone intermediates, it will be recognized that, in some cases, the R⁴ groups can be introduced before the formation of the quinazolinone and isoquinolinone ring system.

The present invention also includes within its scope all stereoisomeric forms of quinazolinone and isoquinolinone derivatives resulting, for example, because of configurational or geometrical isomerism. Such stereoisomeric forms are enantiomers, diastereoisomers, *cis* and *trans* isomers etc. For example, in the case where R¹ is 2-methylcyclopropylamine the compound exists as a pair of enantiomers. In the case where R⁴ comprises an alkene fragment, both (*Z*) and (*E*) stereoisomeric forms of the compound are possible. In the case of the individual enantiomers of quinazolinone and isoquinolinone derivatives of formula I or salts or solvates thereof, the present invention includes the aforementioned stereoisomers substantially free, i.e., associated with less than 5%, preferably less than 2% and in particular less than 1% of the other enantiomer. Mixtures of stereoisomers in any proportion, for example a racemic mixture comprising substantially equal amounts of two enantiomers are also included within the scope of the present invention.

For chiral compounds, methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, e.g., synthesis with chiral induction, synthesis starting from chiral intermediates, enantioselective enzymatic conversions, separation of stereoisomers using chromatography on chiral media. Such methods are described in *Chirality In Industry* (edited by A.N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley). Likewise methods for synthesis of geometrical isomers are also well known in the art.

The present invention also includes within its scope all isotopically labelled forms of the compounds of the invention. For example, compounds isotopically labelled with ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³¹I, ¹²⁵I, ¹²³I and ¹⁸F. The labelled compounds are useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods and for *in vivo* receptor imaging.

The quinazolinone and isoquinolinone derivatives of the present invention, in the form as a free base, are isolated from reaction mixtures as pharmaceutically acceptable salts. These salts are also obtained by treatment of said free base with an organic or inorganic acid, for example, hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulfonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid and ascorbic acid.

The quinazolinone and isoquinolinone derivatives of the present invention also exist as amorphous forms. Multiple crystalline forms are also possible. All these physical forms are included within the scope of the present invention.

In a further aspect, the quinazolinone and isoquinolinone derivatives of the present invention and their pharmaceutically acceptable salts and solvates are useful in therapy. As such the quinazolinone and isoquinolinone derivatives of the present invention are useful for the manufacture of a medicament for the treatment or prevention of diseases influenced by modulation of the activity of the HPA axis. In particular the quinazolinone and isoquinolinone derivatives are useful for the manufacture of a medicament for the treatment of schizophrenia, anxiety, hot flushes, addiction, anorexia nervosa, stress-related disorders and Alzheimer's dementia.

In a further aspect, the quinazolinone and isoquinolinone derivatives of the present invention are useful for the manufacture of a medicament for the treatment or prevention of depression. Depression states in the treatment of which the compounds of the present invention and their pharmaceutically acceptable salts and solvates are particularly useful are those classified as mood disorders in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition- Text Revised*, American Psychiatric Association, Washington D.C. (2000), including mood episodes, depressive disorders, bipolar disorders and other mood disorders.

The present invention further includes a method for the treatment of a mammal, including a human, suffering from or liable to suffer from depression or any of the aforementioned disorders, which comprises administering an effective amount of a quinazolinone or isoquinolinone derivative of the present invention or a pharmaceutically acceptable salt or solvate thereof.

The amount of a quinazolinone or isoquinolinone derivative of the present invention or a pharmaceutically acceptable salt or solvate thereof, also referred to herein as the active ingredient, which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated.

A suitable daily dose for any of the above mentioned disorders will be in the range of 0.001 to 50 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.01 to 20 mg per kilogram body weight per day. The desired dose may be presented as multiple sub-doses administered at appropriate intervals throughout the day.

Whilst it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. The present invention therefore also provides a pharmaceutical composition comprising a quinazolinone and isoquinolinone derivative according to the present invention in admixture with one or more pharmaceutically acceptable excipients, such as the ones described in Gennaro *et al.*, Remington: *The Science and Practice of Pharmacy*, 20th Edition, Lippincott, Williams and Wilkins, 2000; see especially part 5: pharmaceutical manufacturing. The term 'acceptable' means being compatible with the other ingredients of the composition and not deleterious to the recipients thereof. Suitable excipients are described e.g., in the Handbook of Pharmaceutical Excipients, 2nd Edition; Editors A. Wade and P.J.Weller, American Pharmaceutical Association, Washington, The Pharmaceutical Press, London, 1994. Compositions include those suitable for oral, nasal, topical (including buccal, sublingual and transdermal), parenteral (including subcutaneous, intravenous and intramuscular) or rectal administration.

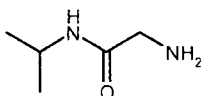
The mixtures of a quinazolinone and isoquinolinone derivative according to the present invention and one or more pharmaceutically acceptable excipient or excipients may be compressed into solid dosage units, such as tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g., a nasal or buccal spray. For making dosage units e.g., tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general, any pharmaceutically acceptable additive can be used. The compounds of the invention are also suitable for use in an implant, a patch, a gel or any other preparation for immediate and/or sustained release.

Suitable fillers with which the pharmaceutical compositions can be prepared and administered include lactose, starch, cellulose and derivatives thereof, and the like, or mixtures thereof used in suitable amounts.

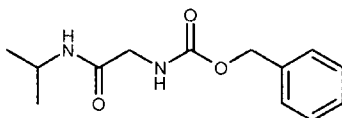
The following Examples further illustrate the compounds of the present invention and methods for their synthesis. In the following section, there is described the synthesis of precursors and common intermediates for compounds of the present invention

Procedure I

INTERMEDIATE I.1: 2-Amino-N-isopropylacetamide



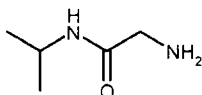
a) (Isopropylcarbamoylmethyl)carbamic acid benzyl ester



To a solution of *N*-Cbz-glycine (20.9 g, 100 mmol) in THF (400 mL) at 0 °C was added *N*-methylmorpholine (NMM) (12.1 mL, 110 mmol) and *i*-butylchloroformate (13 mL, 100 mmol). The resultant mixture was stirred at 0 °C for 2 min and then *i*-propylamine (9.4 mL, 110 mmol) was added. The reaction mixture was warmed to room temperature and stirred at this temperature for 16 h. The mixture was filtered through a pad of CELITE™ and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (500 mL) and washed with 1N HCl (aq.) (1 x 100 mL), sat. NaHCO₃ (aq.) (1 x 100 mL) and brine (1 x 100 mL). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to afford (isopropylcarbamoylmethyl)carbamic acid benzyl ester as a white solid (24.5 g, 98 mmol, 98%) which was used without further purification.

Data: ¹H NMR (300 MHz, CDCl₃): δ 7.37 (m, 5H), 5.78 (br s, 1H), 5.41 (br s, 1H), 5.15 (s, 2H), 4.07 (septet, 1H), 3.82 (d, 2H), 1.15 (d, 6H) ppm.

b) 2-Amino-N-isopropylacetamide



10% Pd/C (425 mg) was added to a solution of (isopropylcarbamoylmethyl)carbamic acid benzyl ester (10 g, 40 mmol) in ethanol (200 mL) and shaken in a Parr shaker under a hydrogen atmosphere (50 p.s.i.) for 16 h. The reaction mixture was filtered through a pad of CELITE™ and the solvent removed *in vacuo*. This afforded 2-amino-N-isopropylacetamide (INTERMEDIATE I.1) as a clear, colourless oil (5.1 g, 40 mmol, 100%).

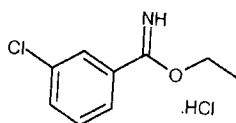
Data for 2-amino-N-isopropylacetamide (INTERMEDIATE I.1): ¹H NMR (300 MHz, CDCl₃): δ 7.05 (br s, 1H), 4.11 (septet, 1H), 3.33 (s, 2H), 1.48 (br s, 2H, amine NH₂), 1.15 (d, 6H) ppm.

Similarly prepared were:

INTERMEDIATE I.2: 2-Amino-N-tert-butylacetamide

Procedure II

INTERMEDIATE II.1: Ethyl 3-chlorobenzimidate hydrochloride



To a solution of 3-chlorobenzonitrile (50 g, 363 mmol) in anhydrous ethanol (500 mL), cooled to 0°C in an ice bath, was bubbled HCl (g) through a gas dispersion tube for approximately 20 minutes until the solution was saturated. The resulting reaction mixture was stirred at room temperature for 16 h. Volatiles were removed *in vacuo* and the residue was triturated with anhydrous ether (~200 mL). The white solid was collected by filtration and dried *in vacuo* overnight to afford ethyl 3-chlorobenzimidate hydrochloride (INTERMEDIATE II.1) (80 g, 363 mmol, 100%) which was used directly without further purification.

Data for ethyl 3-chlorobenzimidate hydrochloride (INTERMEDIATE II.1): ¹H NMR (300 MHz, DMSO): δ 12.0-11.8 (br s, 1H), 8.22-8.17 (t, 1H), 8.10-8.04 (dt, 1H), 7.90-7.85 (dt, 1H), 7.71-7.64 (t, 1H), 4.66-4.50 (q, 2H), 1.55-1.40 (t, 3H) ppm.

Similarly prepared were:

INTERMEDIATE II.2: Ethyl 3-methoxybenzimidate hydrochloride

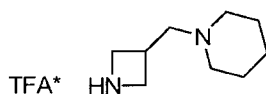
INTERMEDIATE II.3: Ethyl 4-fluoro-3-methoxybenzimidate hydrochloride

INTERMEDIATE II.4: Ethyl 3-chloro-4-fluorobenzimidate hydrochloride

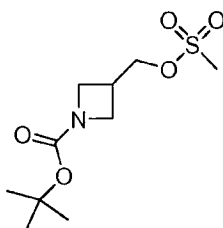
Procedure III

INTERMEDIATE III.1: 1-Azetidin-3-ylmethylpiperidine

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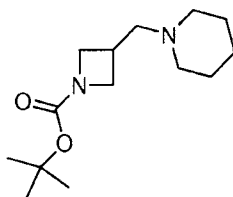
a) 3-Methanesulfonyloxymethylazetidine-1-carboxylic acid *tert*-butyl ester



To a solution of 3-hydroxymethylazetidine-1-carboxylic acid *tert*-butyl ester (for preparation see: Askew, B., *et al.*, US 20033225106) (0.3 g, 1.60 mmol) in DCM (3 mL) was added Et₃N (1 mL, 7.17 mmol), followed by methanesulfonyl chloride (0.5 mL, 6.46 mmol) and the reaction mixture stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo*, the residue dissolved in DCM and the organic phase washed with saturated sodium bicarbonate (aq.). The organic layer was dried (MgSO₄), and concentrated *in vacuo* to give 3-methanesulfonyloxymethylazetidine-1-carboxylic acid *tert*-butyl ester (0.36 g, 1.40 mmol, 85%) as an oil which was used in the next step without further purification.

Data for 3-methanesulfonyloxymethylazetidine-1-carboxylic acid *tert*-butyl ester: ¹H NMR (300MHz, CDCl₃): δ 4.36 (d, 2H), 4.05 (app t, 2H), 3.72 (dd, 2H), 3.05 (s, 3H), 2.92 (m, 1H), 1.42 (s, 9H) ppm.

b) 3-Piperidin-1-ylmethylazetidine-1-carboxylic acid *tert*-butyl ester



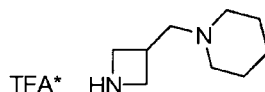
To a suspension of 3-methanesulfonyloxymethylazetidine-1-carboxylic acid *tert*-butyl ester (0.36 g, 1.40 mmol) in toluene (2 mL) was added piperidine (0.7 mL, 7.00 mmol) and the resultant mixture was heated to 110 °C in a sealed tube for 18 h. The solution was concentrated *in vacuo*, the crude residue dissolved in DCM and washed with 0.5 N KOH (aq.) (1 X) and brine (1 X). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resultant oil was purified by chromatography on silica gel with MeOH:DCM

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(1:19, v/v) as eluent to afford 3-piperidin-1-ylmethylazetidine-1-carboxylic acid *tert*-butyl ester (180 mg, 0.70 mmol, 50%) as an oil.

Data for 3-piperidin-1-ylmethylazetidine-1-carboxylic acid *tert*-butyl ester: ^1H NMR (300MHz, CDCl_3): δ 4.04 (app t, 2H), 3.60 (dd, 2H), 2.91 (br m, 1H), 2.72 (br m, 2 H), 2.48 (br m, 4 H), 1.71 (br m, 4 H), 1.49 (br m, 2H), 1.41 (s, 9H) ppm.

c) 1-Azetidin-3-ylmethylpiperidine



3-Piperidin-1-ylmethylazetidine-1-carboxylic acid *tert*-butyl ester (180 mg, 0.70 mmol) was treated with a solution of TFA:DCM (1:1 v/v, 5 mL) and the resultant solution stirred at room temperature for 1 h. The solution was concentrated *in vacuo* afford 1-azetidin-3-ylmethylpiperidine (INTERMEDIATE III.1) (190 mg, 0.70 mmol, 100%) as the trifluoroacetic acid salt which was used without further purification.

Data for 1-azetidin-3-ylmethylpiperidine (INTERMEDIATE III.1) trifluoroacetic acid salt: MS (ESI) m/z : 155 ($[\text{M}+\text{H}]^+$).

Similarly prepared were:

INTERMEDIATE III.2: 1-Pyrrolidin-3-ylmethylpiperidine (from commercially available *tert*-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate, Pharmacore)

INTERMEDIATE III.3: 1-Piperidin-3-ylmethylpiperidine (from commercially available *tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate, Pharmacore)

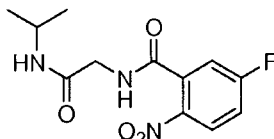
INTERMEDIATE III.4: (*R*)-1-Piperidin-3-ylmethylpiperidine (from commercially available (*R*)-*tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate, Astatech)

INTERMEDIATE III.5: (*S*)-1-Piperidin-3-ylmethylpiperidine (from commercially available (*S*)-*tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate, Astatech)

INTERMEDIATE III.6: 4-Piperidin-3-ylmethanmorpholine (from commercially available *tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate, Pharmacore)

INTERMEDIATE III.7: *N,N*-Dimethylpiperidin-3-ylmethanamine (from commercially available *tert*-butyl 3-(hydroxymethyl)piperidine-1-carboxylate, Pharmacore)

INTERMEDIATE III.8: 1-(2-Azetidin-3-ylethyl)piperidine (from *tert*-butyl 3-(2-hydroxyethyl)azetidine-1-carboxylate (prepared according to Duggan, M. E., *et al.*, US 5281585))

Procedure IVINTERMEDIATE IV.1: 5-Fluoro-N-(isopropylcarbamoylmethyl)-2-nitrobenzamide

To a solution of 5-fluoro-2-nitrobenzoic acid (370 mg, 2.0 mmol) in anhydrous DMF (5 mL) was added 1-hydroxybenzotriazole hydrate (330 mg, 2.4 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (460 mg, 2.4 mmol) and 2-amino-N-isopropylacetamide (INTERMEDIATE I.1) (230 mg, 2.0 mmol). The resultant mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*, the crude yellow residue dissolved in EtOAc (20 mL) and washed with dilute HCl (aq.) (3 X 5 mL), sat. NaHCO₃ (aq.) (3 X 5 mL) and brine (1 X 5 mL). The organic layer was dried (Na₂SO₄), concentrated *in vacuo* and purified by chromatography on silica gel with MeOH:DCM (1:19, v/v) as eluent to afford 5-fluoro-N-(isopropylcarbamoylmethyl)-2-nitrobenzamide (INTERMEDIATE IV.1) (400 mg, 1.4 mmol, 70%) as yellow solid.

Data for 5-fluoro-N-(isopropylcarbamoylmethyl)-2-nitrobenzamide (INTERMEDIATE IV.1): ¹H NMR (300 MHz, CDCl₃): δ 8.15 (dd, 1H), 7.2-7.3 (m, 2H), 6.94 (br s, 1H), 6.18 (br d, 1H), 4.07 (s, 2H), 4.06 (septet, 1H), 1.19 (d, 6H) ppm; MS (ESI) *m/z*: 283 ([M+H]⁺).

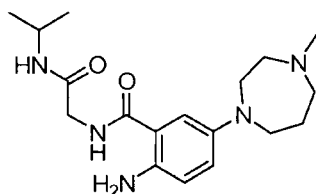
Similarly prepared were:

INTERMEDIATE IV.2: N-(*tert*-Butylcarbamoylmethyl)5-fluoro-2-nitrobenzamide (from INTERMEDIATE I.2)

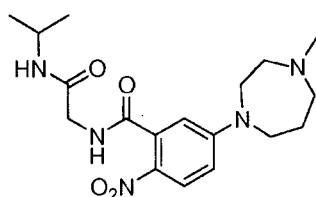
INTERMEDIATE IV.3: (5-Fluoro-2-nitrobenzoylamino)acetic acid *tert*-butyl ester (from glycine *tert*-butyl ester)

Procedure V

INTERMEDIATE V.1: 2-Amino-N-(isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)benzamide



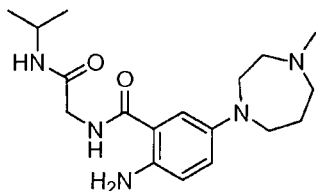
a) N-(Isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)-2-nitrobenzamide



A mixture of 5-fluoro-N-(isopropylcarbamoylmethyl)-2-nitrobenzamide (INTERMEDIATE IV.1) (400 mg, 1.4 mmol), 1-methylhomopiperazine (0.20 mL, 1.6 mmol) and potassium carbonate (1 g) in acetonitrile (20 mL) were heated at reflux temperature under an Argon atmosphere for 16 h. The mixture was cooled, filtered, the residue washed with DCM (2 X 1 mL) and the volatiles evaporated under reduced pressure. The red coloured residue was dissolved in DCM (15 mL), washed with 1 N NaOH (aq.) (2 X 5 mL) and brine (1 X 5 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford N-(isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)-2-nitrobenzamide (510 mg, 1.4 mmol, 100%) as an orange-red solid. This was used in the next step without further purification.

Data for N-(isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)-2-nitrobenzamide: MS (ESI) m/z: 378 ([M+H]⁺).

b) 2-Amino-N-(isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)benzamide



A mixture of N-(isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)-2-nitrobenzamide (510 mg, 1.4 mmol) and 10% Pd/C (60 mg) in MeOH (30 mL) was shaken

under 50 psi H₂ (g) in a Parr shaker for 5 h. The mixture was filtered through a pad of celite and the solvent removed *in vacuo* to afford 2-amino-*N*-(isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)benzamide (INTERMEDIATE V.1) (470 mg, 1.4 mmol, 100%) as a brownish-green glass.

Data for 2-amino-*N*-(isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)benzamide (INTERMEDIATE V.1): ¹H NMR (300 MHz, CDCl₃): δ 7.38 (br s, 1H), 6.6-6.8 (m, 3H), 6.22 (br d, 1H), 4.36 (br s, 2H, NH₂), 4.0-4.2 (m, 3H), 3.47-3.51 (m, 2H), 3.39 (t, 2H), 2.72 (dd, 2H), 2.60 (dd, 2H), 2.38 (s, 3H), 2.00 (m, 2H), 1.16 (d, 6H) ppm; MS (ESI) *m/z*: 348 ([M+H]⁺).

Similarly prepared were:

INTERMEDIATE V.2: 4-{4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE IV.1)

INTERMEDIATE V.3: 4-{4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}piperazine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE IV.1)

INTERMEDIATE V.4: 2-Amino-5-(3-dimethylaminopyrrolidin-1-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)

INTERMEDIATE V.5: 2-Amino-5-(3-dimethylaminomethylpiperidin-1-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE III.7)

INTERMEDIATE V.6: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(4-methylpiperazin-1-yl)benzamide (from INTERMEDIATE IV.1)

INTERMEDIATE V.7: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((S)-3-piperidin-1-ylmethylpiperidin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE III.5)

INTERMEDIATE V.8: 2-Amino-5-(4-dimethylaminopiperidin-1-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)

INTERMEDIATE V.9: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((R)-3-piperidin-1-ylmethylpiperidin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE III.4)

INTERMEDIATE V.10: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(3-piperidin-1-ylmethylpiperidin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE III.3)

INTERMEDIATE V.11: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(3-piperidin-1-ylmethylazetidin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE III.1)

INTERMEDIATE V.12: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(4-phenylperhydro-1,4-diazepin-1-yl)benzamide (from INTERMEDIATE IV.1)

- INTERMEDIATE V.13: 2-Amino-*N*-(*tert*-butylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)benzamide (from INTERMEDIATE IV.2)
- INTERMEDIATE V.14: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(3-piperidin-1-ylmethylpyrrolidin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE III.2)
- INTERMEDIATE V.15: 2-Amino-5-[1,4']bipiperidinyl-1'-yl-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.16: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-[3-(2-piperidin-1-ylethyl)azetidin-1-yl]benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE III.8)
- INTERMEDIATE V.17: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(3-morpholin-4-ylmethylpiperidin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE III.6)
- INTERMEDIATE V.18: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((*S*)-3-methylpiperazin-1-yl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.19: 2-Amino-5-(3,3-dimethylpiperazin-1-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.20: 2-Amino-5-(2,5-dimethylpiperazin-1-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.21: [2-Amino-5-(hexahydropyrrolo[1,2-*a*]pyrazin-2-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3)
- INTERMEDIATE V.22: 2-Amino-5-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.23: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(4-isopropylpiperazin-1-yl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.24: 2-Amino-5-(3,5-dimethylpiperazin-1-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.25: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((*R*)-3-methylpiperazin-1-yl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.26: 2-Amino-5-(3-ethylperhydro-1,4-diazepin-1-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE X.1)
- INTERMEDIATE V.27: 2-Amino-5-(3-fluoromethylpiperazin-1-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE XII.1)
- INTERMEDIATE V.28: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((*S*)-2-pyrrolidin-1-ylmethylpyrrolidin-1-yl)benzamide (from INTERMEDIATE IV.1)
- INTERMEDIATE V.29: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(5-methylperhydro-1,4-diazepin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE XI.1)

INTERMEDIATE V.30: [2-Amino-5-(4-ethylperhydro-1,4-diazepin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3)

INTERMEDIATE V.31: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(4-isopropylperhydro-1,4-diazepin-1-yl)benzamide (from INTERMEDIATE IV.1)

INTERMEDIATE V.32: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(3-propylperhydro-1,4-diazepin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE X.3)

INTERMEDIATE V.33: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-[3-(2-methanesulfonyl)ethyl]perhydro-1,4-diazepin-1-yl]benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE X.4)

INTERMEDIATE V.34: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((*S*)-3-isopropylperhydro-1,4-diazepin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE X.5)

INTERMEDIATE V.35: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((*R*)-3-isopropylperhydro-1,4-diazepin-1-yl)benzamide (from INTERMEDIATE IV.1 and INTERMEDIATE X.6)

INTERMEDIATE V.36: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((*R*)-3-isopropylpiperazin-1-yl)benzamide (from INTERMEDIATE IV.1)

INTERMEDIATE V.37: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-((*S*)-3-isopropylpiperazin-1-yl)benzamide (from INTERMEDIATE IV.1)

INTERMEDIATE V.38: 4-{4-Amino-3-[(*tert*-butylcarbamoylmethyl)carbamoyl]phenyl}perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE IV.2)

INTERMEDIATE V.39: [2-Amino-5-(6,6-dimethyl-3-propylperhydro-1,4-diazepin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3 and INTERMEDIATE X.9)

INTERMEDIATE V.40: [2-Amino-5-((*S*)-3-isopropylperhydro-1,4-diazepin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3 and INTERMEDIATE X.11)

INTERMEDIATE V.41: {2-Amino-5-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]benzoylamino}acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3)

INTERMEDIATE V.42: (*S*)-4-{4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}-2-isopropylpiperazine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE IV.1)

INTERMEDIATE V.43: [2-Amino-5-(6,6-dimethylperhydro-1,4-diazepin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3 and INTERMEDIATE X.10)

INTERMEDIATE V.44: [2-Amino-5-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3 and INTERMEDIATE X.7)

INTERMEDIATE V.45: [2-Amino-5-(3-ethyl-6,6-dimethylperhydro-1,4-diazepin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3 and INTERMEDIATE X.8)

INTERMEDIATE V.46: 2-Amino-*N*-(isopropylcarbamoylmethyl)-5-(octahydropyrido[1,2-*a*]pyrazin-2-yl)benzamide (from INTERMEDIATE IV.1)

INTERMEDIATE V.47: 2-Amino-5-(1,4-diazabicyclo[3.2.2]non-4-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)

INTERMEDIATE V.48: 2-Amino-5-(hexahydropyrrolo[1,2-*a*]pyrazin-2-yl)-*N*-(isopropylcarbamoylmethyl)benzamide (from INTERMEDIATE IV.1)

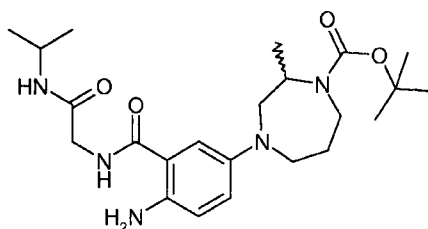
INTERMEDIATE V.49: 2-Amino-*N*-(*tert*-butylcarbamoylmethyl)-5-(4-isopropylperhydro-1,4-diazepin-1-yl)benzamide (from INTERMEDIATE IV.2)

INTERMEDIATE V.50: [2-Amino-5-((*R*)-3-methylpiperazin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3)

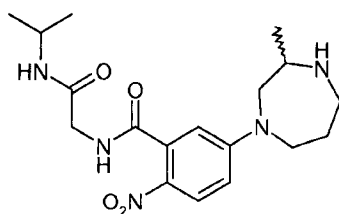
INTERMEDIATE V.51: [2-Amino-5-(1,4-diazabicyclo[3.2.2]non-4-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3)

INTERMEDIATE V.52: [2-Amino-5-(4-isopropylperhydro-1,4-diazepin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (from INTERMEDIATE IV.3)

INTERMEDIATE V.53: 4-{4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester



a) *N*-(Isopropylcarbamoylmethyl)-5-(3-methylperhydro-1,4-diazepin-1-yl)-2-nitrobenzamide

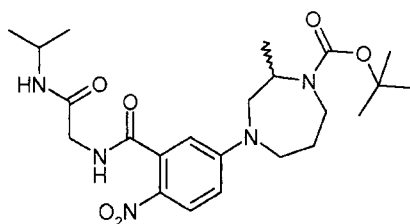


5-Fluoro-*N*-(isopropylcarbamoylmethyl)-2-nitrobenzamide (INTERMEDIATE IV.1) (150 mg, 0.530 mmol), 2-methylperhydro-1,4-diazepine (INTERMEDIATE X.2) (61 mg, 0.530 mmol) and potassium carbonate (220 mg, 1.589 mmol) in acetonitrile (3 mL) were stirred at room

temperature for 48 h followed by heating at 50-60°C for 2 h. The reaction mixture was filtered through a silica plug, solvent evaporated under reduced pressure and crude product purified by chromatography on silica gel with a gradient of DCM to DCM:MeOH (4:1, v/v) as eluent. This afforded *N*-isopropylcarbamoylmethyl)-5-(3-methylperhydro-1,4-diazepin-1-yl)-2-nitrobenzamide (72 mg, 0.191 mmol, 36%).

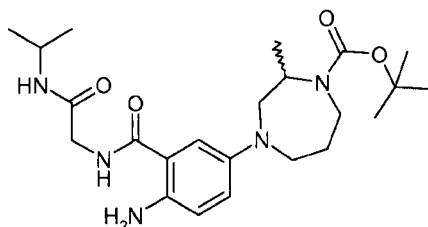
Data for *N*-isopropylcarbamoylmethyl)-5-(3-methylperhydro-1,4-diazepin-1-yl)-2-nitrobenzamide: MS (ESI) m/z : 379 ($[M+H]^+$).

b) 4-{3-[(isopropylcarbamoylmethyl)carbamoyl]-4-nitrophenyl}-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester



N-(isopropylcarbamoylmethyl)-5-(3-methylperhydro-1,4-diazepin-1-yl)-2-nitrobenzamide (72 mg, 0.191 mmol) and di-*tert*-butyldicarbonate (42 mg, 0.191 mmol) in DCM (5 mL) were stirred at room temperature overnight. Solvent was evaporated under reduced pressure to afford crude 4-{3-[(isopropylcarbamoylmethyl)carbamoyl]-4-nitrophenyl}-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (100 mg, 0.209 mmol, 100%) which was used directly in the next step.

c) 4-{4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester



4-{3-[(isopropylcarbamoylmethyl)carbamoyl]-4-nitrophenyl}-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (100 mg, 0.209 mmol) and 10% Pd/C (10 mg, 0.209 mmol) in MeOH (5 mL) was stirred under 4 bar H₂ (g) at room temperature overnight. The mixture was filtered through a pad of celite and the solvent removed *in vacuo* to afford 4-{4-amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}-2-methylperhydro-1,4-diazepine-1-carboxylic

acid *tert*-butyl ester (INTERMEDIATE V.53) (94 mg, 0.210 mmol, 100%). This was used directly without purification.

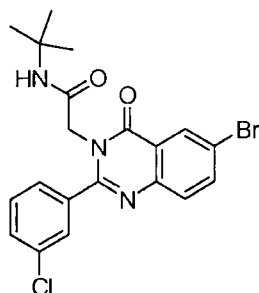
Similarly prepared was:

INTERMEDIATE V.54: 4-{4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}-6,6-dimethylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE IV.1 and INTERMEDIATE X.10)

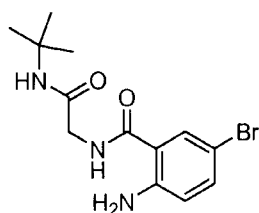
INTERMEDIATE V.55: 4-{4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}-6-fluoroperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE IV.1 and XII.2)

Procedure VI

INTERMEDIATE VI.1: 2-[6-Bromo-2-(3-chlorophenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-*tert*-butylacetamide



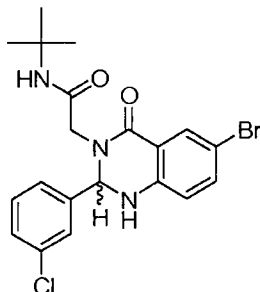
a) 2-Amino-5-bromo-*N*-(*tert*-butylcarbamoylmethyl)benzamide



A suspension of 5-bromoisatoic anhydride (1.2 g, 5.0 mmol) and 2-amino-*N*-*tert*-butylacetamide (INTERMEDIATE I.2) (0.78 g, 6.0 mmol) in acetonitrile (8 mL) was stirred at room temperature for 20 h. The white suspension was filtered, and the white precipitate washed cold EtOH to give 2-amino-5-bromo-*N*-(*tert*-butylcarbamoylmethyl)benzamide (1.06 g, 3.22 mmol, 65%).

Data for 2-amino-5-bromo-N-(tert-butylcarbamoylmethyl)benzamide: ^1H NMR (300 MHz, d^6 -DMSO): δ 8.44 (t, 1H), 7.68 (d, 1H), 7.49 (s, 1H), 7.27 (dd, 1H), 6.67 (d, 1H), 6.56 (br s, 1H), 3.73 (d, 1H), 3.33 (br s, 2H), 1.26 (s, 9H) ppm; MS (ESI) m/z : 328/330 ($[\text{M}+\text{H}]^+$).

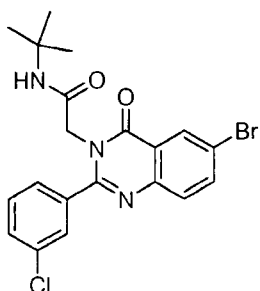
b) 2-[6-Bromo-2-(3-chlorophenyl)-4-oxo-1,4-dihydro-2H-quinazolin-3-yl]-N-tert-butylacetamide



In a capped 20 mL scintillation vial, a solution of 2-amino-5-bromo-N-(tert-butylcarbamoylmethyl)benzamide (0.65 g, 2.0 mmol), 3-chlorobenzaldehyde (0.27 mL, 2.4 mmol) and catalytic glacial acetic acid (2 drops) in anhydrous ethanol (10 mL) was heated with stirring at 85 °C for 16 h. The resulting white suspension was cooled to room temperature, the white solid collected by suction filtration and washed with cold EtOH to give 2-[6-bromo-2-(3-chlorophenyl)-4-oxo-1,4-dihydro-2H-quinazolin-3-yl]-N-tert-butylacetamide (0.53 g, 1.21 mmol, 58%).

Data for 2-[6-bromo-2-(3-chlorophenyl)-4-oxo-1,4-dihydro-2H-quinazolin-3-yl]-N-tert-butylacetamide: MS (ESI) m/z : 450/452 ($[\text{M}+\text{H}]^+$).

c) 2-[6-Bromo-2-(3-chlorophenyl)-4-oxoquinazolin-3(4H)-yl]-N-tert-butylacetamide



In a capped 20 mL scintillation vial, a mixture of 2-[6-bromo-2-(3-chlorophenyl)-4-oxo-1,4-dihydro-2H-quinazolin-3-yl]-N-tert-butylacetamide (0.51 g, 1.13 mmol) and manganese(IV) dioxide (0.44 g, 5.10 mmol) in chloroform (10 mL) was heated at 70 °C for 3 h. The black suspension was cooled to room temperature, filtered through a pad of celite and

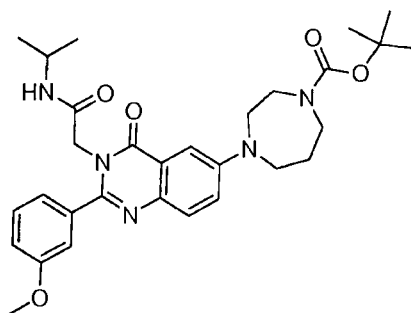
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concentrated *in vacuo* to provide 2-[6-bromo-2-(3-chlorophenyl)-4-oxo-4H-quinazolin-3-yl]-N-*tert*-butylacetamide (INTERMEDIATE VI.1) (0.51 g, 1.13 mmol, 100%) as a white solid.

Data for 2-[6-bromo-2-(3-chlorophenyl)-4-oxo-4H-quinazolin-3-yl]-N-*tert*-butylacetamide (INTERMEDIATE VI.1): ^1H NMR (300 MHz, CDCl_3): δ 9.44 (d, 1H), 7.86 (dd, 1H), 7.65-7.54 (m, 2H), 7.53-7.4 (m, 3H), 5.47 (s, 1H), 4.46 (s, 2H), 1.34 (s, 9H) ppm; MS (ESI) m/z : 448/450 ($[\text{M}+\text{H}]^+$).

Procedure VII

INTERMEDIATE VII.1: 4-[3-(Isopropylcarbamoylmethyl)-2-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester



A mixture of 4-{4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl}perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE V.2) (300 mg, 0.69 mmol) and ethyl 3-methoxybenzimidate hydrochloride (INTERMEDIATE II.2) (298 mg, 1.38 mmol) in EtOH (6 mL) was heated at reflux temperature for 16 h. The reaction mixture was cooled, filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by preparative HPLC to afford 4-[3-(isopropylcarbamoylmethyl)-2-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE VII.1) (50 mg, 0.09 mmol, 13%).

Similarly prepared were:

INTERMEDIATE VII.2: 4-[2-(3-Chlorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.2 and II.1)

INTERMEDIATE VII.3: 4-[2-(3-Chlorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]piperazine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.3 and II.1)

INTERMEDIATE VII.4: 4-[3-(*tert*-Butylcarbamoylmethyl)-2-(3-chloro-4-fluorophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.38 and II.4)

INTERMEDIATE VII.5: 4-[3-(*tert*-Butylcarbamoylmethyl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.38 and II.3)

INTERMEDIATE VII.6: 4-[2-(3-Chloro-4-fluorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.2 and II.4)

INTERMEDIATE VII.7: 4-[2-(4-Fluoro-3-methoxyphenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.2 and II.3)

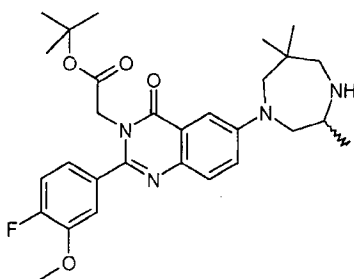
INTERMEDIATE VII.8: [2-(3-Chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.30 and II.4)

INTERMEDIATE VII.9: {2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl}acetic acid *tert*-butyl ester (from INTERMEDIATE V.41 and II.3)

INTERMEDIATE VII.10: 4-[2-(4-Fluoro-3-methoxyphenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-6,6-dimethylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.54 and II.3)

INTERMEDIATE VII.11: 4-[2-(3-Chloro-4-fluorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-6,6-dimethylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.54 and II.2)

INTERMEDIATE VII.12: [2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester



[2-Amino-5-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)benzoylamino]acetic acid *tert*-butyl ester (INTERMEDIATE V.44) (1.00 g, 2.56 mmol), 4-fluoro-3-methoxybenzaldehyde (414 mg, 2.69 mmol), ethanol (20 mL) and acetic acid (3 drops) were stirred overnight at reflux temperature. Solvent was evaporated under reduced pressure. The crude reaction mixture was purified by SCX with product eluted with 2N NH₃/MeOH. Solvent was evaporated under reduced pressure and the product dissolved in toluene (10 mL) and water (10 mL). Potassium hexacyanoferrate (III) (8.43 g, 25.6 mmol) was added and the reaction mixture stirred vigorously overnight. The reaction was then quenched by the addition of methanol (300 mL), the mixture filtered through a celite pad and the cake washed with further methanol (200 mL). The filtrate was evaporated to dryness and purified by chromatography on silica gel with a gradient of DCM to DCM:MeOH (3:1, v/v) as eluent to afford [2-(4-fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]acetic acid *tert*-butyl ester (INTERMEDIATE VII.12) (160 mg, 0.305 mmol, 12 %).

INTERMEDIATE VII.13: [2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazabicyclo[3.2.2]non-4-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.51)

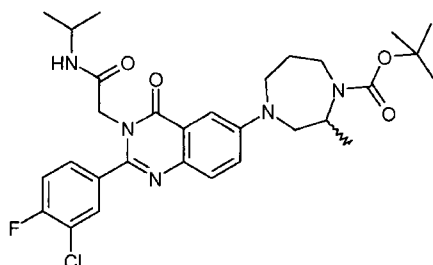
INTERMEDIATE VII.14: [6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(3,5-dimethoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.51)

INTERMEDIATE VII.15: [6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.51)

INTERMEDIATE VII.16: [6-(3-Ethyl-6,6-dimethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.45)

INTERMEDIATE VII.17: [2-(3-Chloro-4-fluorophenyl)-6-((R)-3-methylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.50)

INTERMEDIATE VII.18: 4-[2-(3-Chloro-4-fluorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester



4-[4-Amino-3-[(isopropylcarbamoylmethyl)carbamoyl]phenyl]-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE V.53) (94 mg, 0.201 mmol), 3-chloro-4-fluorobenzaldehyde (40 mg, 0.252 mmol) and acetic acid (3 μ L, catalytic) were dissolved in ethanol (3 mL) in a microwave vial and the vial sealed. The reaction mixture was stirred at 90 °C for 16 h. The reaction mixture was evaporated to dryness, crude material dissolved in DCM (3 mL) and manganese dioxide (80 mg, 0.840 mmol) was added. The reaction mixture was stirred in a sealed vial at 60 °C for 3h. TLC showed incomplete reaction so additional manganese dioxide (80 mg, 0.840 mmol) was added and the reaction mixture heated at 60 °C for a further 2h. Solvent was evaporated under reduced pressure and crude product purified by chromatography on silica gel with DCM:MeOH (9:1, v/v) as eluent. This afforded 4-[2-(3-chloro-4-fluorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE VII.18) (65 mg, 0.111 mmol, 53%).

Data for 4-[2-(3-chloro-4-fluorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2-methylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE VII.18): MS (ESI) *m/z*: 586/588 ([M+H]⁺).

INTERMEDIATE VII.19: (S)-4-[2-(3-Chloro-4-fluorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2-isopropylpiperazine-1-carboxylic acid *tert*-butyl ester ester (from INTERMEDIATE V.42)

INTERMEDIATE VII.20: [2-(3-Chloro-4-fluorophenyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2-yl)-4-oxo-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.21)

INTERMEDIATE VII.21: [2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.52)

INTERMEDIATE VII.22: [2-(3-Chloro-4-fluorophenyl)-6-(dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.43)

INTERMEDIATE VII.23: [2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.52)

INTERMEDIATE VII.24: [6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.30)

INTERMEDIATE VII.25: [6-(6,6-Dimethyl-3-propylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.39)

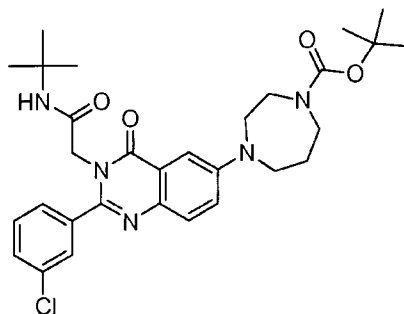
INTERMEDIATE VII.26: [2-(4-Fluoro-3-methoxyphenyl)-6-((S)-3-isopropyl-6,6-dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetic acid *tert*-butyl ester (from INTERMEDIATE V.40)

INTERMEDIATE VII.27: 4-[2-(3-Chloro-4-fluorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-6-fluoroperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.55)

INTERMEDIATE VII.28: 4-[2-(3-Chloro-4-fluorophenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]piperazine-1-carboxylic acid *tert*-butyl ester (from INTERMEDIATE V.3)

Procedure VIII

INTERMEDIATE VIII.1: 4-[3-(*tert*-Butylcarbamoylmethyl)-2-(3-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester

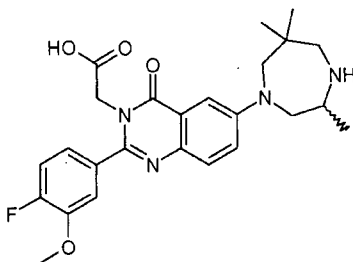


Racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (5 mg, 0.009 mmol) and anhydrous toluene (0.5 mL) was heated in a microwave vial with stirring at 80 °C under an Argon atmosphere until a homogeneous milky solution was obtained (~5 min). This solution was cooled to room temperature and palladium(II) acetate (2 mg, 0.006 mmol) was added. After stirring at room temperature for 2 min., 2-[6-bromo-2-(3-chlorophenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-*tert*-butylacetamide (INTERMEDIATE VI.1) (67 mg, 0.15 mmol), *tert*-butyl-1-homopiperazinecarboxylate (35 μ L, 0.18 mmol) and freshly ground cesium carbonate (68 mg, 0.21 mmol) were added to the red solution. Anhydrous dioxane (0.2 mL) was added to rinse down solid left on the side of the vial. The vial was capped and heated in a microwave at 120 °C for 40 min. The reaction mixture was diluted with DCM (3 mL), filtered and the filtrate concentrated *in vacuo*. This crude product was purified by preparative TLC on silica gel with hexane:EtOAc:CH₂Cl₂ (1:1:1, v/v) as eluent to give 4-[3-(*tert*-butylcarbamoylmethyl)-2-(3-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE VIII.1) (38.9 mg, 0.07 mmol, 46%) as a yellow solid.

Data for 4-[3-(*tert*-butylcarbamoylmethyl)-2-(3-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE VIII.1): ^1H NMR (300 MHz, CDCl_3): δ 7.7-7.4 (m, 6H), 7.3-7.2 (m, 1H), 5.70 (s, 1H), 4.43 (s, 2H), 3.7-3.6 (m, 6H), 3.3-3.2 (m, 2H), 2.02 (m, 2H), 1.33 (s, 18H) ppm; MS (ESI) m/z : 568/570 ($[\text{M}+\text{H}]^+$).

Procedure IX

INTERMEDIATE IX.1: [2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]acetic acid



[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]acetic acid *tert*-butyl ester (INTERMEDIATE VII.12) (160 mg, 0.305 mmol) was dissolved in DCM (10 mL) and TFA (3 mL) added. The reaction mixture was stirred at room temperature overnight. Crude reaction mixture was poured directly onto an SCX cartridge, the cartridge was washed with MeOH and product eluted with 2N NH_3/MeOH . Solvent was removed under reduced pressure to afford [2-(4-fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]acetic acid (INTERMEDIATE IX.1) which was used without further purification.

Data for [2-(4-fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]acetic acid (INTERMEDIATE IX.1): MS (ESI) m/z : 469 ($[\text{M}+\text{H}]^+$).

Similarly prepared from were:

INTERMEDIATE IX.2: [6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(3,5-dimethoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.14)

INTERMEDIATE IX.3: [6-(3-Ethyl-6,6-dimethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.16)

INTERMEDIATE IX.4: [2-(3-Chloro-4-fluorophenyl)-6-(dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.22)

INTERMEDIATE IX.5: [6-(6,6-Dimethyl-3-propylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.25)

INTERMEDIATE IX.6: [2-(4-Fluoro-3-methoxyphenyl)-6-((S)-3-isopropyl-6,6-dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.26)

INTERMEDIATE IX.7: [6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.15)

INTERMEDIATE IX.8: [2-(3-Chloro-4-fluorophenyl)-6-((R)-3-methylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.17)

INTERMEDIATE IX.9: [2-(3-Chloro-4-fluorophenyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.20)

INTERMEDIATE IX.10: [2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.21)

INTERMEDIATE IX.11: [6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.24)

INTERMEDIATE IX.12: [2-(3-Chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.8)

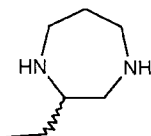
INTERMEDIATE IX.13: [2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.9)

INTERMEDIATE IX.14: [2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.23)

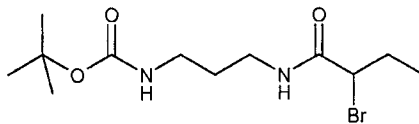
INTERMEDIATE IX.15: [2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazabicyclo[3.2.2]non-4-yl)-4-oxo-4H-quinazolin-3-yl]acetic acid (from INTERMEDIATE VII.13)

Procedure X

INTERMEDIATE X.1: 2-Ethylperhydro-1,4-diazepine



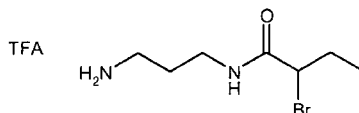
a) [3-(2-Bromobutylamino)propyl]carbamic acid *tert*-butyl ester



1-Propanephosphonic acid cyclic anhydride (4.11 g, 3.84 mL, 6.46 mmol) was added to a cooled solution of *tert*-butyl 3-aminopropylcarbamate (750 mg, 4.30 mmol), 2-bromobutanoic acid (791 mg, 0.51 mL, 4.73 mmol) and triethylamine (1.31 g, 1.82 mL, 12.91 mmol) in DCM

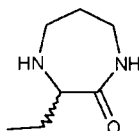
(5 mL). The reaction mixture was stirred at room temperature for 2 h followed by addition of Na_2CO_3 (aq.). This was stirred for 30 min and then the organic layer separated. Solvent was evaporated under reduced pressure and crude product purified by chromatography on silica gel with DCM:MeOH (9:1, v/v) as eluent. This afforded [3-(2-bromobutyrylamino)propyl]carbamic acid *tert*-butyl ester (1.41 g, 4.36 mmol, 100%).

b) N-(3-Aminopropyl)-2-bromobutyramide trifluoroacetic acid salt



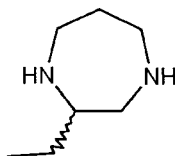
[3-(2-Bromobutyrylamino)propyl]carbamic acid *tert*-butyl ester (1.41 g, 4.36 mmol) was treated with TFA:DCM (1:1 (v/v), 20 mL) and the solution stirred at room temperature for 3 h. The volatiles were removed *in vacuo* and crude product, isolated as the trifluoroacetic acid salt, used directly in the next stage.

c) 3-Ethylperhydro-1,4-diazepin-2-one



N-(3-Aminopropyl)-2-bromobutyramide trifluoroacetic acid salt (1.8 g, 5.33 mmol), K_2CO_3 (2.94 g, 21.33 mmol) and acetonitrile (30 mL) were combined and stirred at 140°C in a microwave for 3500 seconds. Analysis showed presence of a considerable amount of starting material so the reaction mixture was subjected to a further 2000 seconds at 140°C. The reaction mixture was diluted with DCM (50 mL) and filtered through celite. Solvent was evaporated under reduced pressure and purified by chromatography on silica gel with a gradient of DCM to DCM:MeOH (3:1, v/v) as eluent. This afforded 3-ethylperhydro-1,4-diazepin-2-one (540 mg, 3.80 mmol, 71%).

d) 2-Ethylperhydro-1,4-diazepine



Lithium aluminium hydride (475 mg, 12.49 mmol) was added portionwise to a stirred solution of 3-ethylperhydro-1,4-diazepin-2-one (740 mg, 5.20 mmol) in THF (10 mL). After the resultant effervescence had subsided, the reaction mixture was heated at 50-60°C for 3 h. The reaction mixture was cooled and quenched by the slow addition of water and 10% NaOH (aq.). The reaction mixture was diluted with diethyl ether (20 mL) and filtered through celite. The filter cake was washed thoroughly with THF (50 mL), diethyl ether (50 mL), THF (50 mL) and diethyl ether (50 mL). Evaporation under reduced pressure afforded 2-ethylperhydro-1,4-diazepine (INTERMEDIATE X.1) (615 mg, 5.20 mmol), 92%).

Similarly prepared were:

INTERMEDIATE X.2: 2-Methylperhydro-1,4-diazepine

INTERMEDIATE X.3: 2-Propylperhydro-1,4-diazepine

INTERMEDIATE X.4: 2-(2-Methanesulfonyl)ethylperhydro-1,4-diazepine

INTERMEDIATE X.5: (S)-2-Isopropylperhydro-1,4-diazepine

INTERMEDIATE X.6: (R)-2-Isopropylperhydro-1,4-diazepine

INTERMEDIATE X.7: 2,6,6-Trimethylperhydro-1,4-diazepine

INTERMEDIATE X.8: 2-Ethyl-6,6-dimethylperhydro-1,4-diazepine

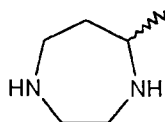
INTERMEDIATE X.9: 6,6-Dimethyl-2-propylperhydro-1,4-diazepine

INTERMEDIATE X.10: 6,6-Dimethylperhydro-1,4-diazepine

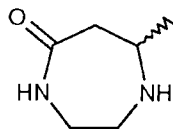
INTERMEDIATE X.11: 6,6-Dimethyl-(S)-2-isopropylperhydro-1,4-diazepine

Procedure XI

INTERMEDIATE XI.1: 5-Methyl-1,4-diazepane



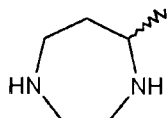
a) 7-Methyl-1,4-diazepan-5-one



Ethane-1,2-diamine (1.35 g, 22.44 mmol) and (E)-ethyl but-2-enoate (2.56 g, 22.44 mmol) in MeOH (22 mL) was stirred at room temperature overnight. Solvent was evaporated under reduced pressure and crude product purified by chromatography on silica gel with a gradient of DCM to DCM:2M NH₃/MeOH (4:1, v/v) as eluent. This afforded a mixture of desired product and uncyclised material. The mixture was diluted with MeOH (4 mL) and heated in

the microwave at 150 °C for 10 min followed by 160 °C for 10 min. Sodium bicarbonate (100 mg) was added and the reaction mixture stirred at room temperature for 48 h. The reaction mixture was filtered, solvent evaporated under reduced pressure and crude product purified by chromatography on silica gel with a gradient of DCM to DCM:2M NH₃/MeOH (4:1, v/v) as eluent to afford *7-methyl-1,4-diazepan-5-one* (310 mg, 2.42 mmol, 11%).

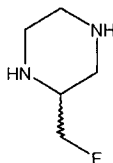
b) 5-Methyl-1,4-diazepane



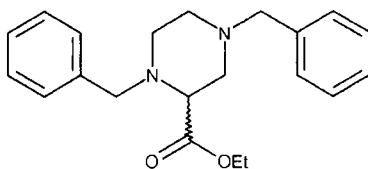
Similar procedure to INTERMEDIATE X.1 step d) from *7-methyl-1,4-diazepan-5-one* (356 mg, 2.75 mmol) and lithium aluminium hydride (1M in THF) (249 mg, 6.56 mL, 6.56 mmol) to afford *5-methyl-1,4-diazepane* (INTERMEDIATE XI.1) (235 mg, 2.06 mmol, 74%)

Procedure XII

INTERMEDIATE XII.1: 2-Fluoromethylpiperazine

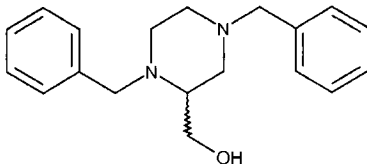


a) 1,4-Dibenzylpiperazine-2-carboxylic acid ethyl ester



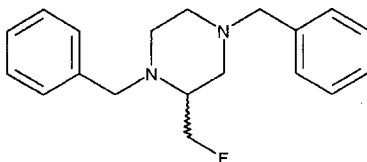
A solution of *N,N*-dibenzylethylenediamine (980 μ L, 4.10 mmol) and triethylamine (1.03 mL, 7.38 mmol) in toluene (15 mL) was added dropwise to a solution of 2-bromopropionic acid ethyl ester (601 μ L, 4.14 mmol) in toluene (15 mL). The reaction mixture was stirred at 80 °C for 72 h. The reaction mixture was filtered through a pad of celite and solvent evaporated under reduced pressure to afford *1,4-dibenzylpiperazine-2-carboxylic acid ethyl ester* (1.33g, 3.93 mmol, 96%) as a yellow oil.

Data for *1,4-dibenzylpiperazine-2-carboxylic acid ethyl ester*: MS (ESI) m/z : 339 ([M+H]⁺).

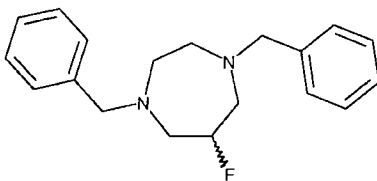
b) (1,4-Dibenzylpiperazin-2-yl)methanol

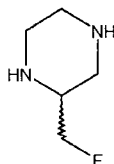
Lithium aluminium hydride (1M in THF) (4 mL, 3.93 mmol) was added to a stirred solution of 1,4-dibenzylpiperazine-2-carboxylic acid ethyl ester (1.33g, 3.93 mmol) in THF (25 mL) cooled to -78 °C under a nitrogen atmosphere. Water (145 µL), NaOH (aq.) (10 wt%, 145µL) and water (450 µL) was added at 45 min intervals. The reaction mixture was filtered through a pad of celite and solvent evaporated under reduced pressure to afford (1,4-dibenzylpiperazin-2-yl)methanol (1.16 g, 3.93 mmol, 100%) as a pale yellow oil.

Data for (1,4-dibenzylpiperazin-2-yl)methanol: MS (ESI) m/z : 298 ($[M+H]^+$).

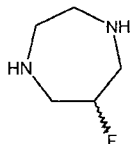
c) 1,4-Dibenzyl-2-fluoromethylpiperazine

(1,4-Dibenzylpiperazin-2-yl)methanol (15 g, 50.5 mmol) in DCM (50 mL) was added dropwise to a stirred solution of DAST (7.42 mL, 60.6 mmol) in DCM (150 mL) cooled to -78 °C. The reaction mixture was maintained below -30 °C for 24 h before warming to room temperature and stirring for an additional 20 h. The reaction was quenched by the addition of water (100 mL). The organic phase was separated, the aqueous basified with NaOH (aq.) to pH 10 and extracted with DCM (3 X 75 mL). The combined organics were washed with water (2 X 100 mL), brine (2 X 100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by chromatography on silica gel with EtOAc:heptane (1:9, v/v) as eluent to afford 1,4-dibenzyl-2-fluoromethylpiperazine (6.0 g, 20.1 mmol, 40%). A biproduct of the reaction was also isolated, 1,4-dibenzyl-6-fluoroperhydro-1,4-diazepine (1.0 g, 3.35 mmol, 7%).

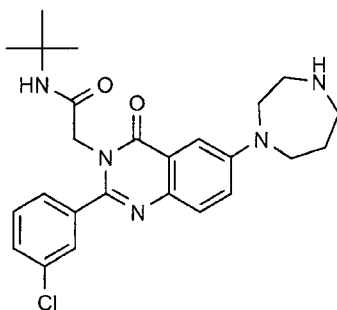


d) 2-Fluoromethylpiperazine

Palladium on charcoal (10wt%) (400 mg) as a slurry in MeOH was added to a solution of 1,4-dibenzyl-2-fluoromethylpiperazine (400 mg, 1.34 mmol) in MeOH (20 mL). This was subjected to H₂(g) at 5 bar pressure for 18 h. The reaction mixture was filtered through celite and solvent evaporated under reduced pressure. This afforded 2-fluoromethylpiperazine (*INTERMEDIATE XII.1*) (136 mg, 1.14 mmol, 86%) as a pale yellow oil.

INTERMEDIATE XII.2: 6-Fluoroperhydro-1,4-diazepine

Prepared in a similar manner from 1,4-dibenzyl-6-fluoro-perhydro-1,4-diazepine (isolated as a side product in the synthesis of *INTERMEDIATE XII.1*).

Synthesis of Examples According to the InventionEXAMPLE 1a: *N*-tert-Butyl-2-[2-(3-chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]acetamide

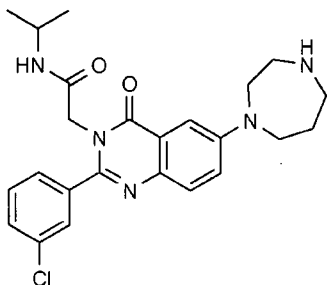
4-[3-(*tert*-Butylcarbamoylmethyl)-2-(3-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (*INTERMEDIATE VIII.1*) (38.9 mg, 0.068 mmol) was treated with TFA:DCM (1:1 (v/v), 1 mL) and the solution stirred at room temperature for 40 min. The volatiles were removed *in vacuo* and the residue

partitioned between DCM and 1 M NaOH (aq.). The organics were dried (Na_2SO_4) and concentrated *in vacuo* to yield *N*-*tert*-butyl-2-[2-(3-chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]acetamide (EXAMPLE 1a) (27 mg, 0.046 mmol, 68%) as the trifluoroacetic acid salt.

Data for *N*-*tert*-butyl-2-[2-(3-chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]acetamide (EXAMPLE 1a) trifluoroacetic acid salt: ^1H NMR (300 MHz, CDCl_3): δ 7.6-7.4 (m, 6H), 7.21 (dd, 1H), 5.65 (s, 1H), 4.44 (s, 2H), 3.7-3.6 (m, 4H), 3.09 (t, 2H), 2.85 (t, 2H), 2.47 (br s, 1H), 1.98 (m, 2H), 1.34 (s, 9H) ppm; MS (ESI) m/z : 468/470 ($[\text{M}+\text{H}]^+$).

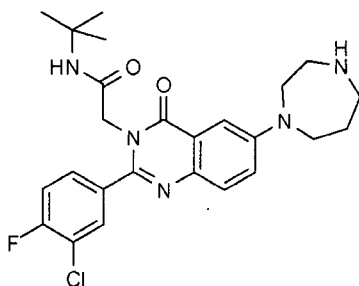
The following compounds were prepared in a similar manner from INTERMEDIATES VII or VIII:

EXAMPLE 1b: 2-[2-(3-Chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide



MS (ESI) m/z : 454/456 ($[\text{M}+\text{H}]^+$) (from INTERMEDIATE VII.2)

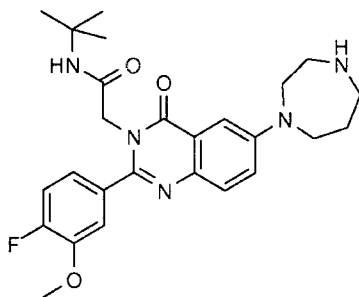
EXAMPLE 1c: *N*-*tert*-Butyl-2-(2-(3-chloro-4-fluorophenyl)-6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)acetamide



MS (ESI) m/z : 486/488 ($[\text{M}+\text{H}]^+$) (from INTERMEDIATE VII.4)

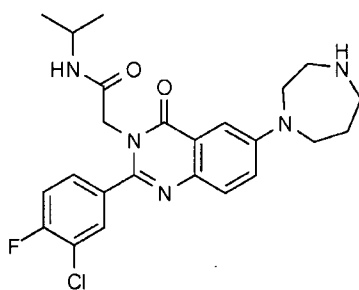
EXAMPLE 1d: 2-(6-(1,4-Diazepan-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxoquinazolin-3(4*H*)-yl)-*N*-*tert*-butylacetamide

57



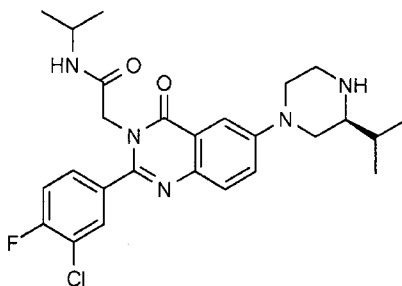
MS (ESI) m/z : 482 ($[M+H]^+$) (from INTERMEDIATE VII.5)

EXAMPLE 1e: 2-(2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl)-N-isopropylacetamide



MS (ESI) m/z : 472 ($[M+H]^+$) (from INTERMEDIATE VII.6)

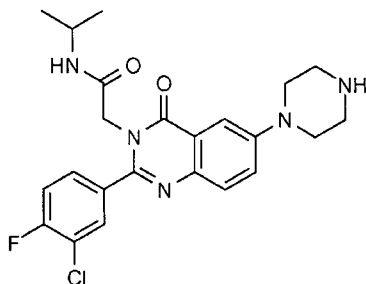
EXAMPLE 1f: (S)-2-(2-(3-Chloro-4-fluorophenyl)-6-(3-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl)-N-isopropylacetamide



MS (ESI) m/z : 500/502 ($[M+H]^+$) (from INTERMEDIATE VII.19)

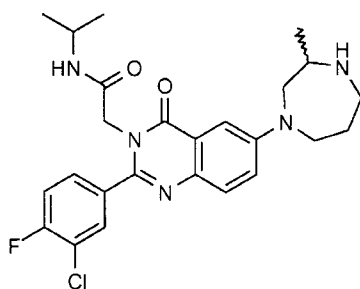
EXAMPLE 1g: 2-(2-(3-Chloro-4-fluorophenyl)-4-oxo-6-(piperazin-1-yl)quinazolin-3(4H)-yl)-N-isopropylacetamide

58



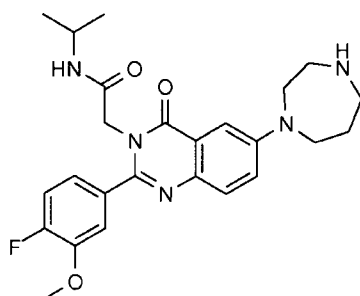
MS (ESI) m/z : 458/460 ($[M+H]^+$) (from INTERMEDIATE VII.28)

EXAMPLE 1h: 2-(2-(3-Chloro-4-fluorophenyl)-6-(3-methyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl)-N-isopropylacetamide



MS (ESI) m/z : 486 ($[M+H]^+$) (from INTERMEDIATE VII.18)

EXAMPLE 1i: 2-(6-(1,4-Diazepan-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxoquinazolin-3(4H)-yl)-N-isopropylacetamide

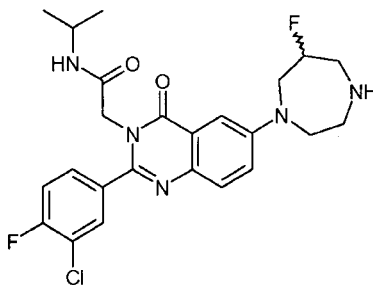


MS (ESI) m/z : 468 ($[M+H]^+$) (from INTERMEDIATE VII.7)

EXAMPLE 1j: 2-[2-(3-Chloro-4-fluorophenyl)-6-(6-fluoroperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

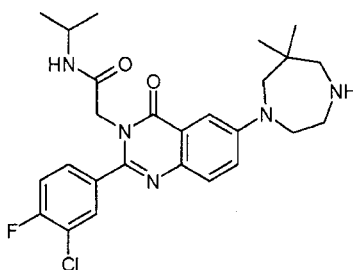
70

59



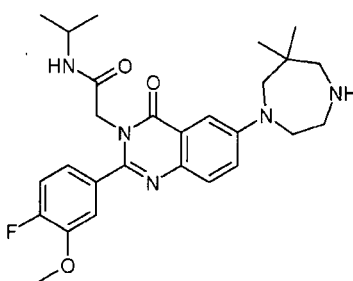
MS (ESI) m/z : 490/492 ($[M+H]^+$) (from INTERMEDIATE VII.27).

EXAMPLE 1k: 2-[2-(3-Chloro-4-fluorophenyl)-6-(dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 500/502 ($[M+H]^+$) (from INTERMEDIATE VII.11).

EXAMPLE 1l: 2-[6-(Dimethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

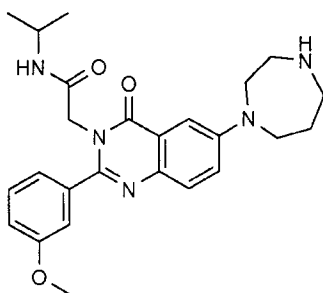


MS (ESI) m/z : 596 ($[M+H]^+$) (from INTERMEDIATE VII.10).

EXAMPLE 2a: N-Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl]-4H-quinazolin-3-yl]acetamide

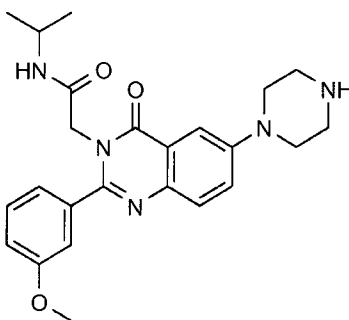
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4-[3-(Isopropylcarbamoylmethyl)-2-(3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE VII.1) (50 mg, 0.091 mmol) was treated with 4 N HCl/MeOH (10 mL) and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* to afford *N*-isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4H-quinazolin-3-yl]acetamide (EXAMPLE 2a) (40 mg, 0.091 mmol, 100%) as the hydrochloride salt. Data for *N*-isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4H-quinazolin-3-yl]acetamide (EXAMPLE 2a) (EXAMPLE 2a) hydrochloride salt: MS (ESI) *m/z*: 450 ([M+H]⁺)

The following compounds were prepared in a similar manner from INTERMEDIATES VII:
EXAMPLE 2b: *N*-Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-piperazin-1-yl-4H-quinazolin-3-yl]acetamide

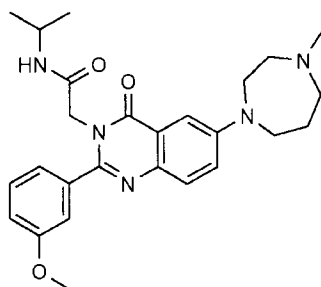


MS (ESI) *m/z*: 436 ([M+H]⁺) (from INTERMEDIATE VII.3)

EXAMPLE 3a: *N*-Isopropyl-2-[2-(3-methoxyphenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetamide

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To a solution of 2-amino-*N*-(isopropylcarbamoylmethyl)-5-(4-methylperhydro-1,4-diazepin-1-yl)benzamide (INTERMEDIATE V.1) (1.4 g, 4.1 mmol) in absolute ethanol (70 mL) was added ethyl 3-methoxybenzimidate hydrochloride (INTERMEDIATE II.2) (1.8 g, 8.3 mmol). The resultant mixture was heated to at reflux temperature for 20 h. The reaction mixture was concentrated *in vacuo*, the dark residue dissolved up in DCM (70 mL) and washed with 1 N HCl (aq.) (3 X 20 mL). The aqueous phase was washed with EtOAc (20 mL), basified to pH $\approx$ 10-11 with 4 N NaOH (aq.) and the resultant pale green precipitate was collected by suction filtration. The crude product was purified by chromatography on silica gel with a gradient of MeOH:DCM (1:19 to 3:7, v/v) as eluent to afford the product as an off-white solid (0.60 g, 1.3 mmol, 32%). Recrystallization from EtOAc:DCM afforded pure *N*-isopropyl-2-[2-(3-methoxyphenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetamide (EXAMPLE 3a) (0.35 g, 0.76 mmol, 18%) as a white solid.

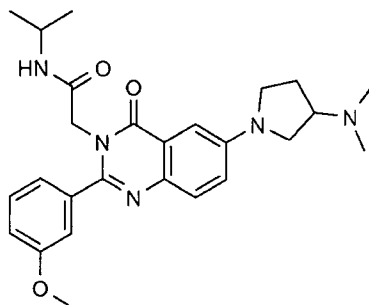
Data for *N*-isopropyl-2-[2-(3-methoxyphenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetamide (EXAMPLE 3a): ^1H NMR (300 MHz, CDCl_3): δ 7.64 (d, 1H), 7.3-7.4 (m, 2H), 7.16-7.23 (m, 3H), 7.0 (dd, 1H), 5.71 (br d, 1H, amide N-H), 4.49 (s, 2H), 4.08 (m, 1H), 3.82 (s, 3H), 3.68 (dd, 2H), 3.61 (t, 2H), 2.76 (m, 2H), 2.57 (m, 2H), 2.39 (s, 3H), 2.06 (m, 2H), 1.15 (d, 6H) ppm; MS (ESI) m/z : 46 ($[\text{M}+\text{H}]^+$), 949 ($[\text{M}+\text{Na}]^+$); M.p. 204 °C (decomp.).

The following compounds were prepared in a similar manner from INTERMEDIATES V and II:

EXAMPLE 3b: 2-[6-(3-Dimethylamino-pyrrolidin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-*N*-isopropylacetamide

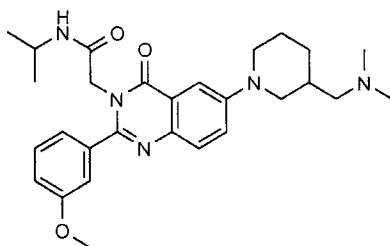
72

62



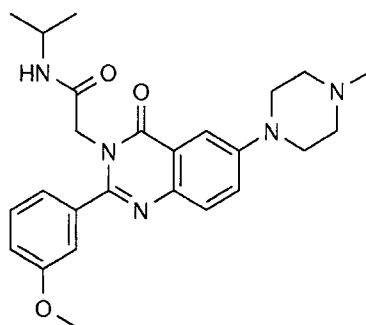
MS (ESI) m/z : 464 ($[M+H]^+$) (from INTERMEDIATE V.4 and INTERMEDIATE II.2)

EXAMPLE 3c: 2-[6-(3-Dimethylaminomethyl-piperidin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 492 ($[M+H]^+$) (from INTERMEDIATE V.5 and INTERMEDIATE II.2)

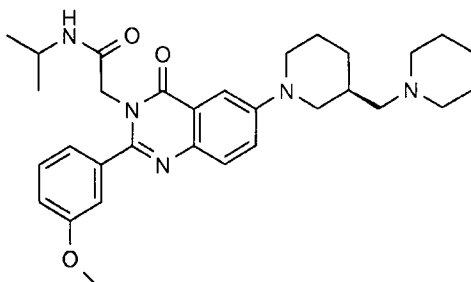
EXAMPLE 3d: N-Isopropyl-2-[2-(3-methoxyphenyl)-6-(4-methyl-piperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 450 ($[M+H]^+$) (from INTERMEDIATE V.6 and INTERMEDIATE II.2)

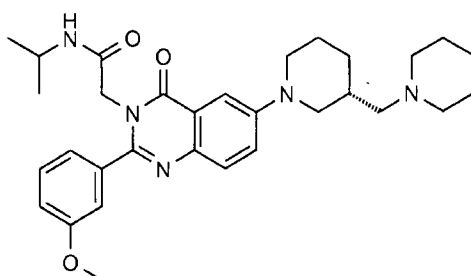
EXAMPLE 3e: N-Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-((S)-3-piperidin-1-ylmethylpiperidin-1-yl)-4H-quinazolin-3-yl]

63



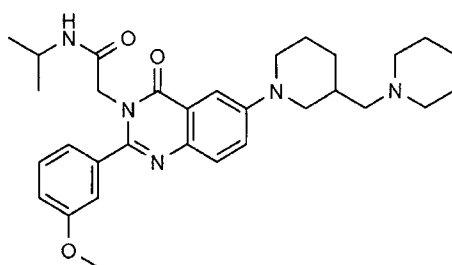
MS (ESI) m/z : 532 ($[M+H]^+$) (from INTERMEDIATE V.7 and INTERMEDIATE II.2)

EXAMPLE 3f: *N*-Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-((*R*)-3-piperidin-1-ylmethylpiperidin-1-yl)-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 532 ($[M+H]^+$) (from INTERMEDIATE V.9 and INTERMEDIATE II.2)

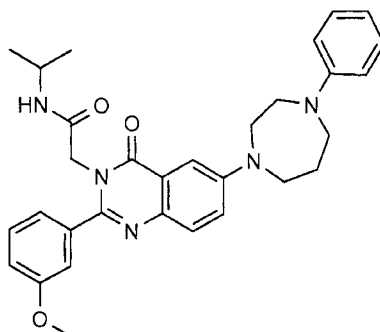
EXAMPLE 3g: *N*-Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-(3-piperidin-1-ylmethylpiperidin-1-yl)-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 532 ($[M+H]^+$) (from INTERMEDIATE V.10 and INTERMEDIATE II.2)

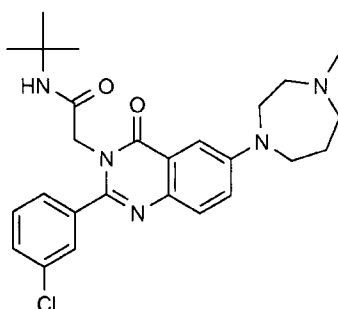
EXAMPLE 3h: *N*-Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-(4-phenylperhydro-1,4-diazepin-1-yl)-4*H*-quinazolin-3-yl]acetamide

64



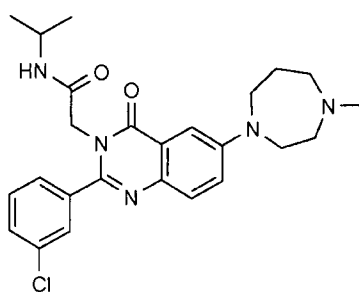
MS (ESI) m/z : 526 ($[M+H]^+$) (from INTERMEDIATE V.12 and INTERMEDIATE II.2)

EXAMPLE 3i: *N*-tert-Butyl-2-[2-(3-chlorophenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 482/484 ($[M+H]^+$) (from INTERMEDIATE V.13 and INTERMEDIATE II.1)

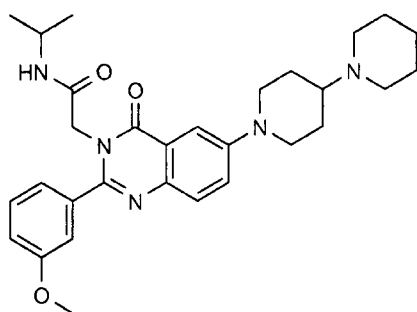
EXAMPLE 3j: 2-[2-(3-Chlorophenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide



MS (ESI) m/z : 468/470 ($[M+H]^+$) (from INTERMEDIATE V.1 and INTERMEDIATE II.1)

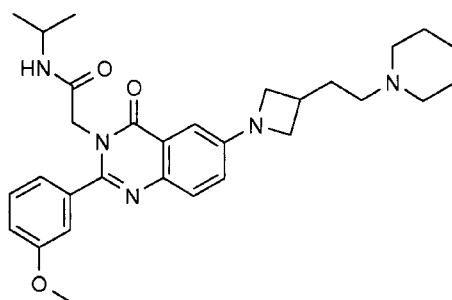
EXAMPLE 3k: 2-[6-[1,4']Bipiperidinyl-1'-yl]-2-(3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide

65



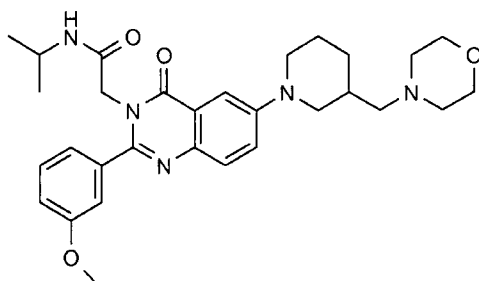
MS (ESI) m/z : 518 ($[M+H]^+$) (from INTERMEDIATE V.15 and INTERMEDIATE II.2)

EXAMPLE 3l: *N*-Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-[3-(2-piperidin-1-ylethyl)azetidin-1-yl]-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 518 ($[M+H]^+$) (from INTERMEDIATE V.16 and INTERMEDIATE II.2)

EXAMPLE 3m: *N*-Isopropyl-2-[2-(3-methoxyphenyl)-6-(3-morpholin-4-ylmethyl)piperidin-1-yl]-4-oxo-4*H*-quinazolin-3-yl]acetamide

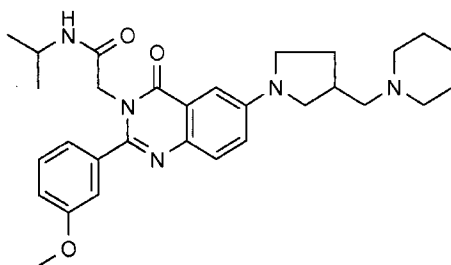


MS (ESI) m/z : 534 ($[M+H]^+$) (from INTERMEDIATE V.17 and INTERMEDIATE II.2)

EXAMPLE 3n: *N*-Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-(3-piperidin-1-ylmethylpyrrolidin-1-yl)-4*H*-quinazolin-3-yl]acetamide

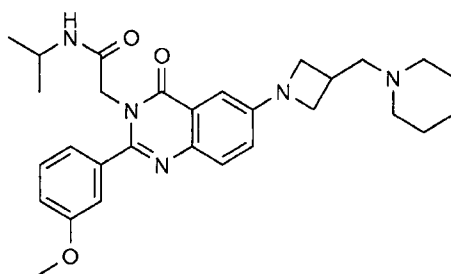
ff

66



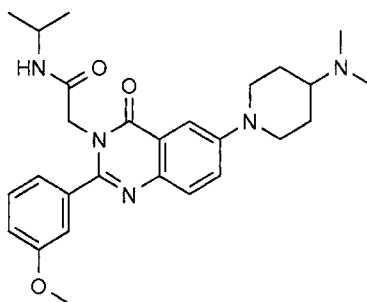
MS (ESI) m/z : 518 ($[M+H]^+$) (from INTERMEDIATE V.14 and INTERMEDIATE II.2)

EXAMPLE 3o: N-isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-(3-piperidin-1-ylmethylazetidin-1-yl)-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 504 ($[M+H]^+$) (from INTERMEDIATE V.11 and INTERMEDIATE II.2)

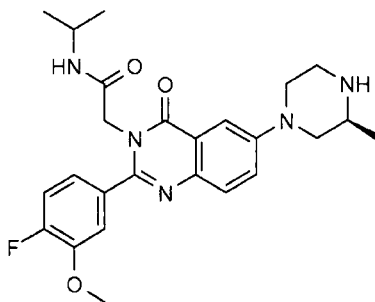
EXAMPLE 3p: 2-[6-(4-Dimethylaminopiperidin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 478 ($[M+H]^+$) (from INTERMEDIATE V.8 and INTERMEDIATE II.2)

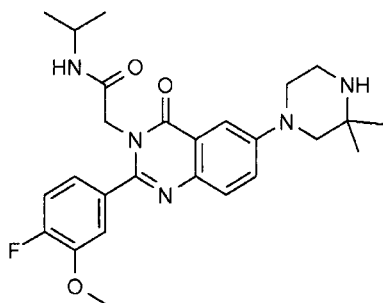
EXAMPLE 3q: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-((S)-3-methylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

67



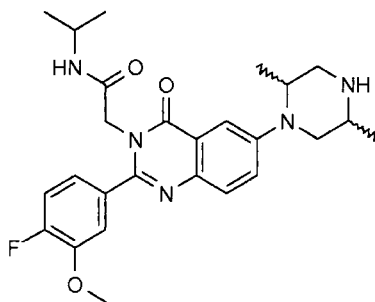
MS (ESI) m/z : 468 ($[M+H]^+$) (from INTERMEDIATE V.18 and INTERMEDIATE II.3)

EXAMPLE 3r: 2-[6-(Dimethylpiperazin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 482 ($[M+H]^+$) (from INTERMEDIATE V.19 and INTERMEDIATE II.3)

EXAMPLE 3s: 2-[6-(2,5-Dimethylpiperazin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

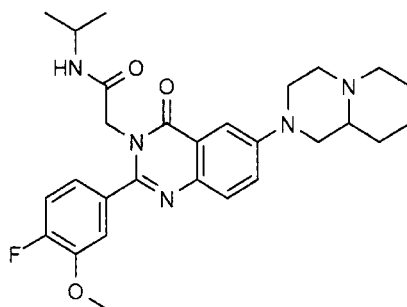


MS (ESI) m/z : 482 ($[M+H]^+$) (from INTERMEDIATE V.20 and INTERMEDIATE II.3)

EXAMPLE 3t: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-(octahydropyrido[1,2-a]pyrazin-2-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

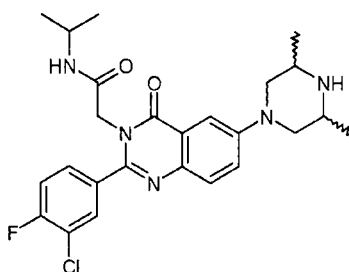
19

68



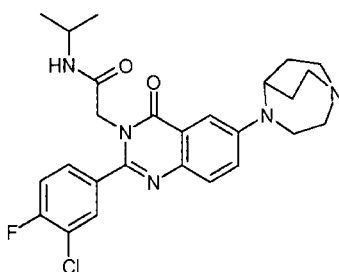
MS (ESI) m/z : 508 ($[M+H]^+$) (from INTERMEDIATE V.46 and INTERMEDIATE II.3)

EXAMPLE 3u: 2-[2-(3-Chloro-4-fluorophenyl)-6-(dimethylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 486/488 ($[M+H]^+$) (from INTERMEDIATE V.24 and INTERMEDIATE II.4).

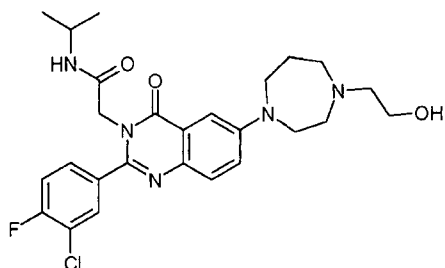
EXAMPLE 3v: 2-[2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazabicyclo[3.2.2]non-4-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 498/500 ($[M+H]^+$) (from INTERMEDIATE V.47 and INTERMEDIATE II.4).

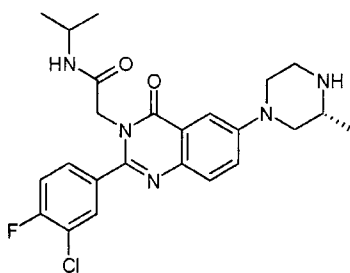
EXAMPLE 3w: 2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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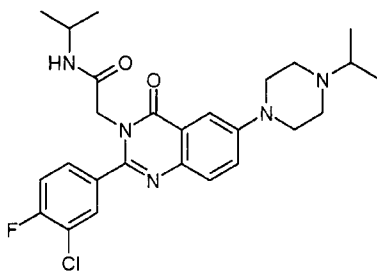
MS (ESI) m/z : 516 ($[M+H]^+$) (from INTERMEDIATE V.22 and INTERMEDIATE II.4).

EXAMPLE 3x: 2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-3-methylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 472/474 ($[M+H]^+$) (from INTERMEDIATE V.25 and INTERMEDIATE II.4)

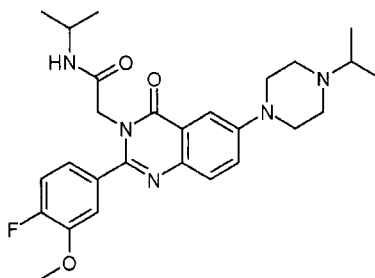
EXAMPLE 3y: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 500 ($[M+H]^+$) (from INTERMEDIATE V.23 and INTERMEDIATE II.4).

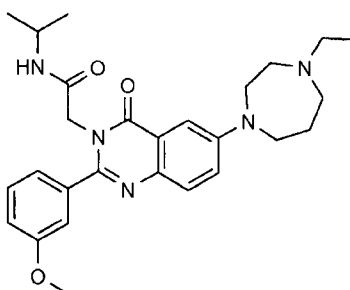
EXAMPLE 3z: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-(4-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

70



MS (ESI) m/z : 497 ($[M+H]^+$) (from INTERMEDIATE V.23 and INTERMEDIATE II.3).

EXAMPLE 4a: 2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



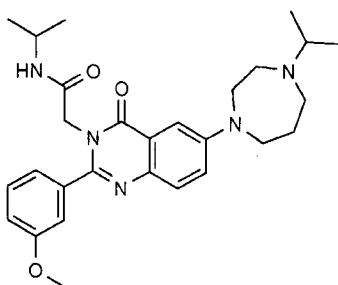
A mixture of *N*-isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4H-quinazolin-3-yl]acetamide (EXAMPLE 2a) hydrochloride salt (50 mg, 0.103 mmol), ethyl bromide (22 mg, 0.21 mmol), and K_2CO_3 (43 mg, 0.31 mmol) in acetonitrile (5 mL) was heated to reflux for 24 h. The mixture was then cooled, filtered and concentrated *in vacuo*. The crude residue was purified by preparative HPLC to afford 2-[6-(4-ethylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-*N*-isopropylacetamide (EXAMPLE 4a) (5.1 mg, 0.010 mmol, 10%) as the hydrochloride salt.

Data for 2-[6-(4-ethylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-*N*-isopropylacetamide (EXAMPLE 4a) hydrochloride salt: MS (ESI) m/z : 478 ($[M+H]^+$), 955 ($[2M+H]^+$), 977 ($[2M+Na]^+$).

The following compounds were prepared in a similar manner from EXAMPLES 1 or 2:

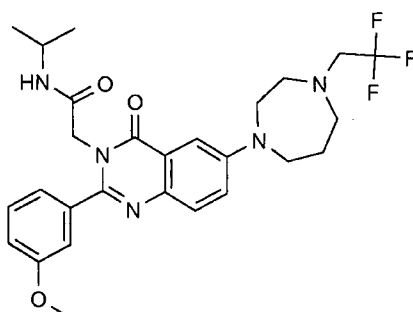
EXAMPLE 4b: *N*-Isopropyl-2-[6-(4-isopropylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide

71



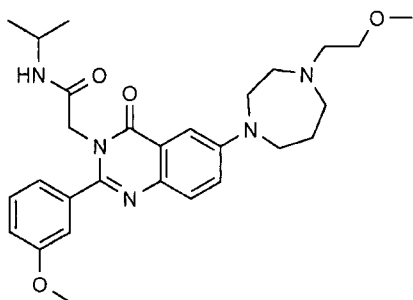
MS (ESI) m/z : 492 ($[M+H]^+$) (from EXAMPLE 2a)

EXAMPLE 4c: N-Isopropyl-2-((3-methoxyphenyl)-4-oxo-6-[4-(2,2,2-trifluoroethyl)perhydro-1,4-diazepin-1-yl]-4H-quinazolin-3-yl)acetamide



MS (ESI) m/z : 532 ($[M+H]^+$) (from EXAMPLE 2a)

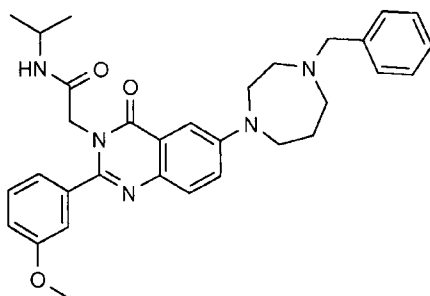
EXAMPLE 4d: N-Isopropyl-2-[[6-[4-(2-methoxyethyl)perhydro-1,4-diazepin-1-yl]-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 508 ($[M+H]^+$) (from EXAMPLE 2a)

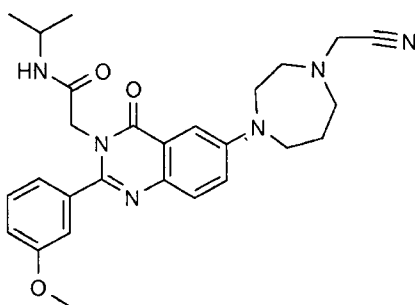
EXAMPLE 4e: 2-[[6-(4-Benzyl)perhydro-1,4-diazepin-1-yl]-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

72



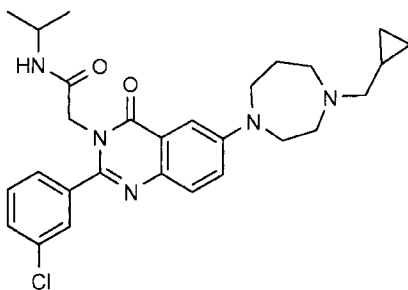
MS (ESI) m/z : 540 ($[M+H]^+$) (from EXAMPLE 2a)

EXAMPLE 4f: 2-[6-(4-Cyanomethylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 489 ($[M+H]^+$) (from EXAMPLE 2a)

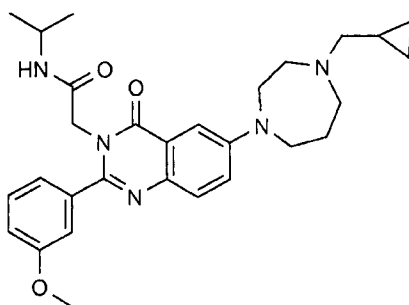
EXAMPLE 4g: 2-[2-(3-Chlorophenyl)-6-(4-cyclopropylmethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 508/5010 ($[M+H]^+$) (from EXAMPLE 1b)

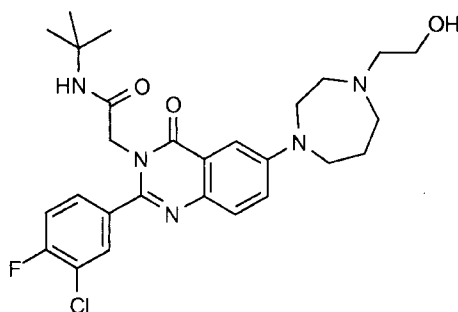
EXAMPLE 4h: 2-[6-(4-Cyclopropylmethylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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MS (ESI) m/z : 504 ($[M+H]^+$) (from EXAMPLE 2a)

EXAMPLE 4i: *N*-tert-Butyl-2-{2-(3-chloro-4-fluorophenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl}acetamide



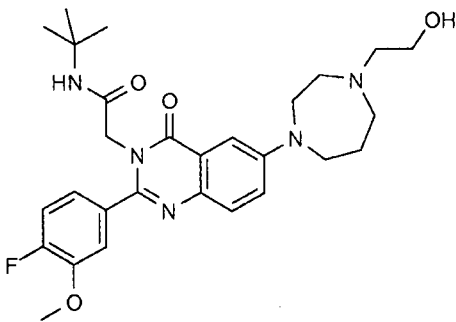
N-tert-Butyl-2-(2-(3-chloro-4-fluorophenyl)-6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)acetamide (EXAMPLE 1c) (100 mg, 0.206 mmol), 2-bromoethanol (206 mg, 0.117 ml, 1.646 mmol) and potassium carbonate (57 mg, 0.412 mmol) in DMF (1 mL) was heated in a microwave at 100 °C for 10 min. The reaction mixture was filtered and purified by SCX eluting in MeOH then 2M NH_3 /MeOH. Solvent was evaporated under reduced pressure and product further purified by HPLC. This afforded *N*-tert-butyl-2-{2-(3-chloro-4-fluorophenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl}acetamide (EXAMPLE 4i) (39 mg, 0.074 mmol, 90%) as a white solid.

Data for *N*-tert-butyl-2-{2-(3-chloro-4-fluorophenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl}acetamide (EXAMPLE 4i): MS (ESI) m/z : 530/532 ($[M+H]^+$).

EXAMPLE 4j: *N*-tert-Butyl-2-{2-(4-fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl}acetamide

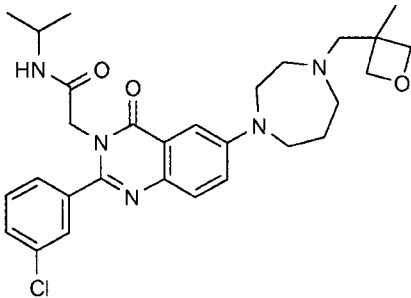
82

74



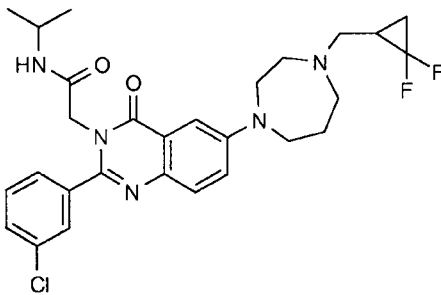
MS (ESI) m/z : 526 ($[M+H]^+$) (from EXAMPLE 1d)

EXAMPLE 4k: 2-{2-(3-Chlorophenyl)-6-[4-(3-methyloxetan-3-ylmethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide



MS (ESI) m/z : 538/540 ($[M+H]^+$) (from EXAMPLE 1b)

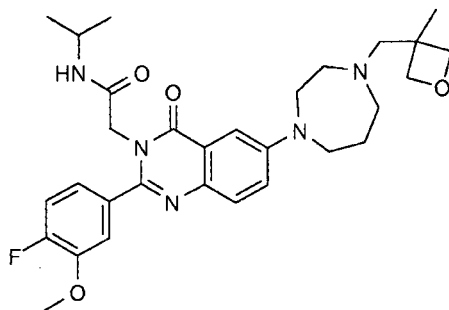
EXAMPLE 4l: 2-{2-(3-Chlorophenyl)-6-[4-(2,2-difluorocyclopropylmethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide



MS (ESI) m/z : 544/546 ($[M+H]^+$) (from EXAMPLE 1b)

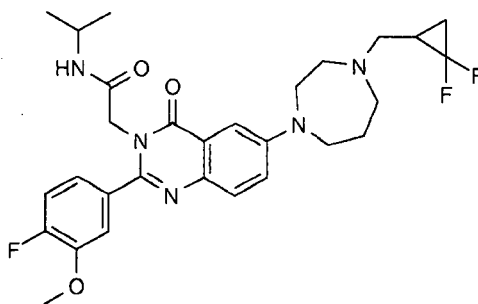
EXAMPLE 4m: 2-{2-(4-Fluoro-3-methoxyphenyl)-6-[4-(3-methyloxetan-3-ylmethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide

75



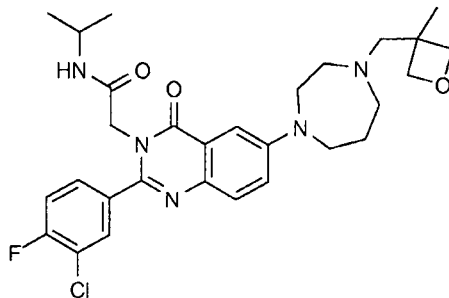
MS (ESI) m/z : 552 ($[M+H]^+$) (from EXAMPLE 1i)

EXAMPLE 4n: 2-[6-[4-(2,2-Difluorocyclopropylmethyl)perhydro-1,4-diazepin-1-yl]-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 558 ($[M+H]^+$) (from EXAMPLE 1i)

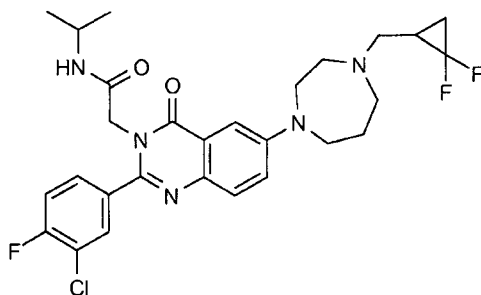
EXAMPLE 4o: 2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(3-methyloxetan-3-ylmethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 556/558 ($[M+H]^+$) (from EXAMPLE 1e)

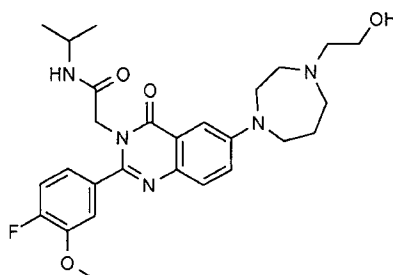
EXAMPLE 4p: 2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(2,2-difluorocyclopropylmethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

76



MS (ESI) m/z : 562/564 ($[M+H]^+$) (from EXAMPLE 1e)

EXAMPLE 4q: 2-{2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide



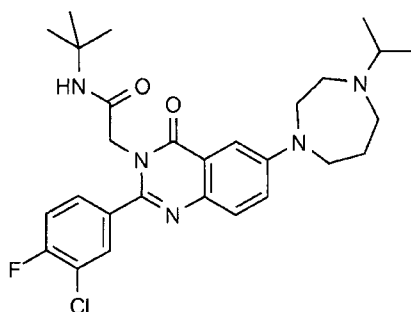
2-(6-(1,4-Diazepan-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxoquinazolin-3(4H)-yl)-N-isopropylacetamide (EXAMPLE 1i) (28 mg, 0.06 mmol), 2-bromoethanol (30 mg, 0.017 mL, 0.24 mmol), potassium carbonate (17 mg, 0.12 mmol,) and potassium iodide (1 mg, 5.99 μ mol) were combined in a microwave vial and DMF (1 mL) added. The reaction mixture was heated at 100 °C for 5 min in the microwave. LCMS indicated that the desired product was being formed. Additional 2-bromoethanol (30 mg, 0.017 mL, 0.24 mmol) was added and reaction mixture was heated at 100 °C for a further 5 min in the microwave. Product was purified by preparative LCMS to afford 2-{2-(4-fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide (EXAMPLE 4q) (4 mg, 7.82 μ mol, 13%).

2-{2-(4-fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide (EXAMPLE 4q): MS (ESI) m/z : 512 ($[M+H]^+$).

The following compounds were prepared in a similar manner from EXAMPLES 1 or 2:

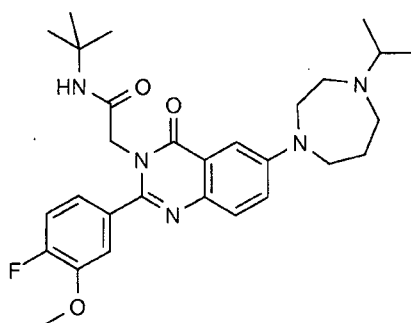
EXAMPLE 4r: N-tert-Butyl-2-[2-(3-chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetamide

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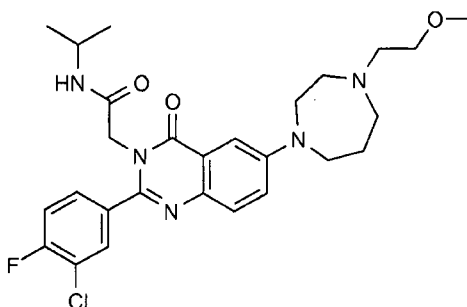
MS (ESI) m/z : 528/530 ($[M+H]^+$) (from EXAMPLE 1c)

EXAMPLE 4s: *N*-tert-Butyl-2-[2-(4-fluoro-3-methoxyphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 524 ($[M+H]^+$) (from EXAMPLE 1d)

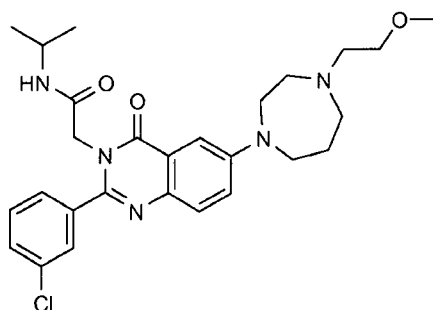
EXAMPLE 4t: 2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(2-methoxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide



MS (ESI) m/z : 530/532 ($[M+H]^+$) (from EXAMPLE 1e)

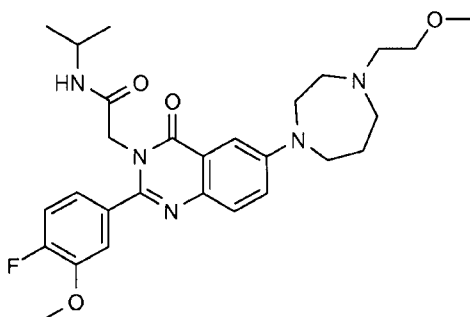
EXAMPLE 4u: 2-[2-(3-Chlorophenyl)-6-[4-(2-methoxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide

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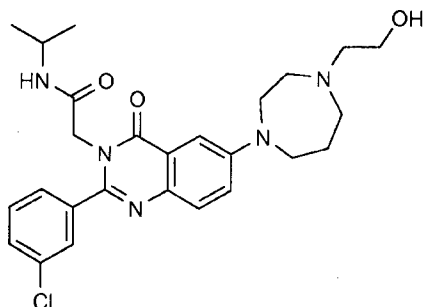
MS (ESI) m/z : 512/514 ($[M+H]^+$) (from EXAMPLE 1b)

EXAMPLE 4v: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-methoxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 526 ($[M+H]^+$) (from EXAMPLE 1i)

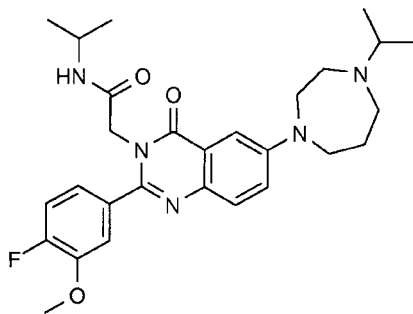
EXAMPLE 4w: 2-[2-(3-Chlorophenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 498/500($[M+H]^+$) (from EXAMPLE 1b)

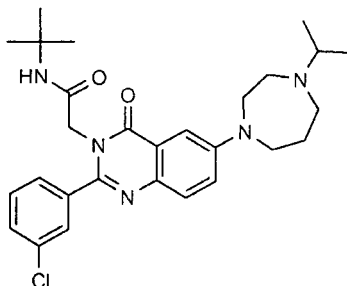
EXAMPLE 4x: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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MS (ESI) m/z : 510 ($[M+H]^+$) (from EXAMPLE 1i)

EXAMPLE 5a: *N*-tert-Butyl-2-[2-(3-chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



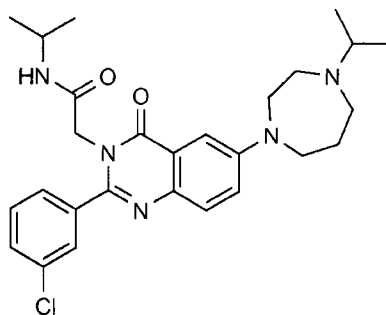
N-tert-Butyl-2-[2-(3-chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]acetamide (EXAMPLE 1a) (17 mg, 0.03 mmol), anhydrous acetone (30 μ L), sodium cyanoborohydride (3 mg, 0.03 mmol) and glacial acetic acid (12 μ L, 0.21 mmol) in anhydrous THF (0.15 mL) was heated in a microwave at 130 $^{\circ}$ C for 10 minutes. The resulting mixture was purified by preparative TLC on silica gel with DCM:MeOH: NH_4OH (40:2:1, v/v) as eluent to give *N*-tert-butyl-2-[2-(3-chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide (EXAMPLE 5a) (7.1 mg, 0.014 mmol, 47%).

Data for *N*-tert-butyl-2-[2-(3-chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide (EXAMPLE 5a): ^1H NMR (300 MHz, CDCl_3): δ 7.6 (m, 2H), 7.5-7.3 (m, 4H), 7.21 (dd, 1H), 5.63 (s, 1H), 4.44 (s, 2H), 3.64 (m, 4H), 2.94 (m, 1H), 2.81 (t, 2H), 2.57 (t, 2H), 1.96 (m, 2H), 1.34 (s, 9H), 1.00 (d, 6H) ppm; MS (ESI) m/z : 510/512 ($[M+H]^+$).

The following compounds were prepared in a similar manner from EXAMPLES 1, 2 or 3:

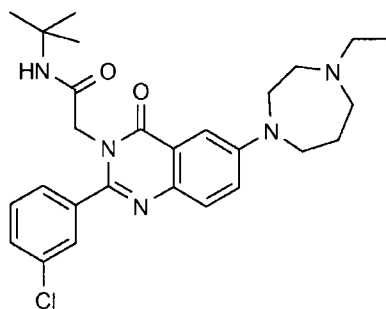
EXAMPLE 5b: 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide

80



MS (ESI) m/z : 496/498 ($[M+H]^+$) (from EXAMPLE 1b)

EXAMPLE 5c: *N-tert-Butyl-2-[2-(3-chlorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetamide*

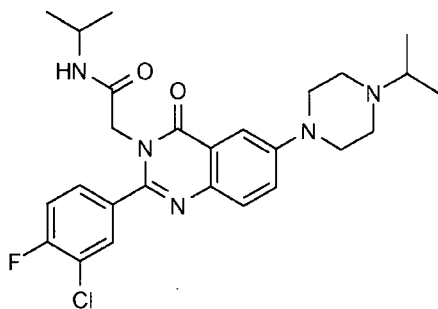


N-tert-Butyl-2-[2-(3-chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4H-quinazolin-3-yl]acetamide (EXAMPLE 1a) (50 mg, 0.107 mmol), acetaldehyde (7.1 mg, 0.160 mmol) and acetonitrile (1 mL) were placed in a microwave vial. Macroporous triethylammonium methylpolystyrene cyanoborohydride (70 mg, 0.107 mmol) and acetic acid (0.3 mL, 0.107 mmol) were added and the reaction mixture heated in a microwave at 130 °C for 1200s. Crude product was filtered and the residue dissolved in MeOH (1 mL) and purified by preparative HPLC. This afforded *N-tert-butyl-2-[2-(3-chlorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetamide* (EXAMPLE 5c) (11 mg, 0.023 mmol, 21%).

N-tert-Butyl-2-[2-(3-chlorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]acetamide (EXAMPLE 5c): MS (ESI) m/z : 496 ($[M+H]^+$).

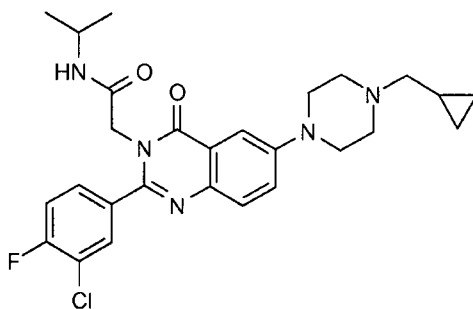
EXAMPLE 5d: *2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide*

81



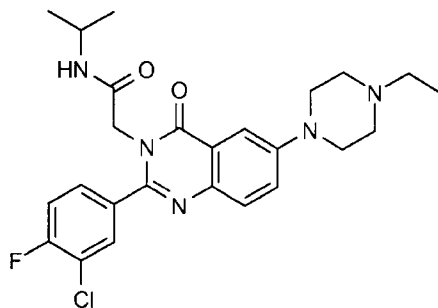
MS (ESI) m/z : 500/502 ($[M+H]^+$) (from EXAMPLE 1g)

EXAMPLE 5e: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-cyclopropylmethylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



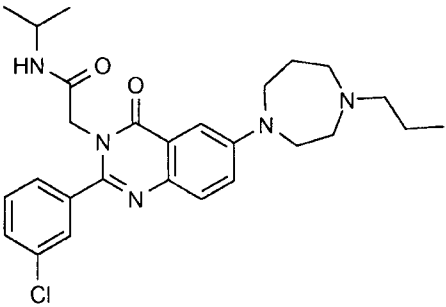
MS (ESI) m/z : 512/514 ($[M+H]^+$) (from EXAMPLE 1g)

EXAMPLE 5f: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-ethylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



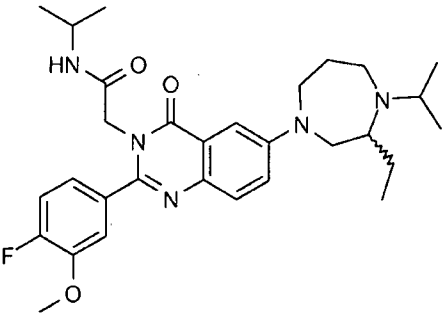
MS (ESI) m/z : 486/488 ($[M+H]^+$) (from EXAMPLE 1g)

EXAMPLE 5g: 2-[2-(3-Chlorophenyl)-4-oxo-6-(4-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide



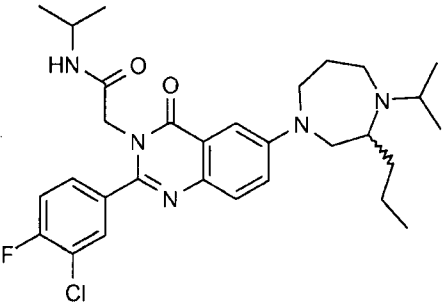
MS (ESI) *m/z*: 496/498 ([*M*+*H*]⁺) (from EXAMPLE 1b)

EXAMPLE 5h: 2-[6-(3-Ethyl-4-isopropylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide



MS (ESI) *m/z*: 538 ([*M*+*H*]⁺) (from EXAMPLE 6f)

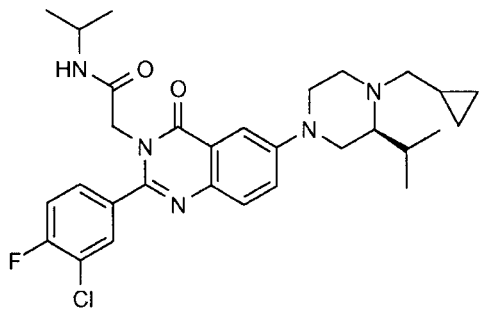
EXAMPLE 5i: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropyl-3-propylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide



MS (ESI) *m/z*: 556/558 ([*M*+*H*]⁺) (from EXAMPLE 6Av)

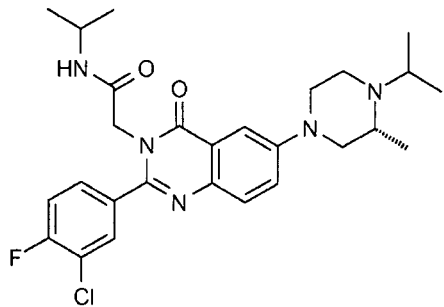
EXAMPLE 5j: 2-[2-(3-Chloro-4-fluorophenyl)-6-((*S*)-4-cyclopropylmethyl-3-isopropylpiperazin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide

83



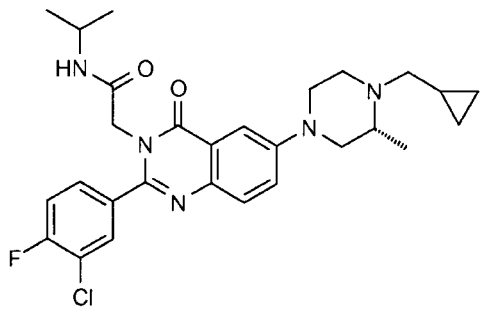
MS (ESI) *m/z*: 554/556 ([*M*+*H*]⁺) (from EXAMPLE 1f)

EXAMPLE 5k: 2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-4-isopropyl-3-methylpiperazin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide



MS (ESI) *m/z*: 514/516 ([*M*+*H*]⁺) (from EXAMPLE 3x)

EXAMPLE 5l: 2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-4-cyclopropylmethyl-3-methylpiperazin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide

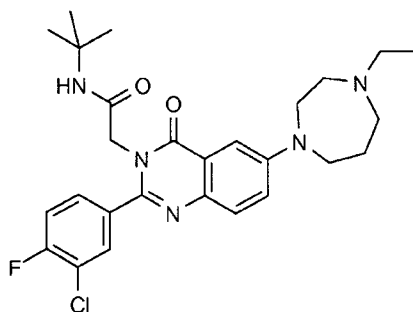


MS (ESI) *m/z*: 526/528 ([*M*+*H*]⁺) (from EXAMPLE 3x)

EXAMPLE 5m: *N*-tert-Butyl-2-[2-(3-chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide

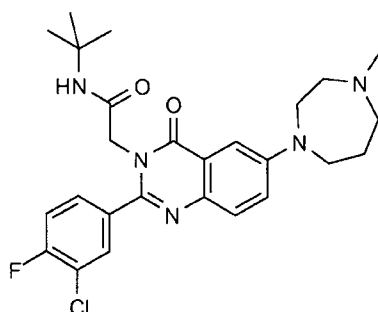
95.

84



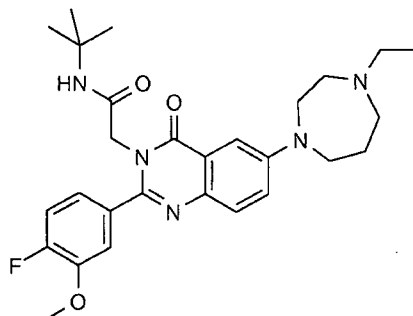
MS (ESI) m/z : 514/516 ($[M+H]^+$) (from EXAMPLE 1c)

EXAMPLE 5n: *N*-tert-Butyl-2-[2-(3-chloro-4-fluorophenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 500/502 ($[M+H]^+$) (from EXAMPLE 1c)

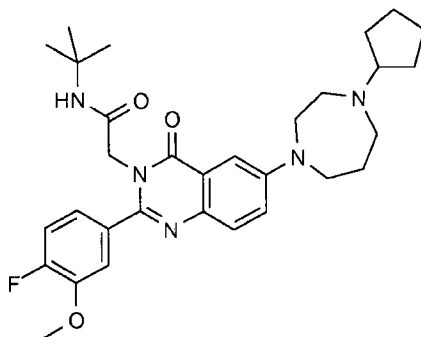
EXAMPLE 5o: *N*-tert-Butyl-2-[6-(4-ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 510 ($[M+H]^+$) (from EXAMPLE 1d)

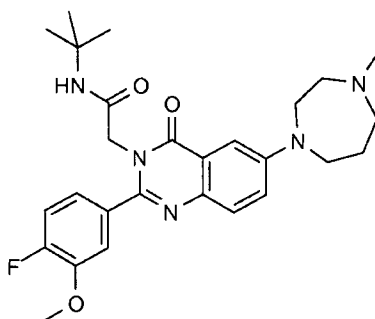
EXAMPLE 5p: *N*-tert-Butyl-2-[6-(4-cyclopentylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]acetamide

85



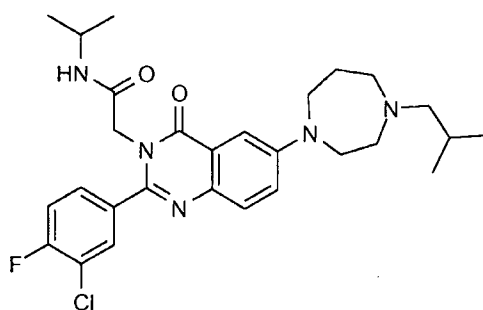
MS (ESI) m/z : 550 ($[M+H]^+$) (from EXAMPLE 1d)

EXAMPLE 5q: *N*-tert-Butyl-2-[2-(4-fluoro-3-methoxyphenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 496 ($[M+H]^+$) (from EXAMPLE 1d)

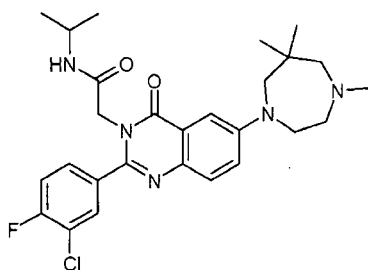
EXAMPLE 5r: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isobutylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide



MS (ESI) m/z : 528 ($[M+H]^+$) (from EXAMPLE 1e)

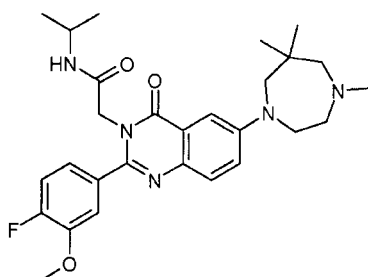
EXAMPLE 5s: 2-[2-(3-Chloro-4-fluorophenyl)-4-oxo-6-(4,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide

86



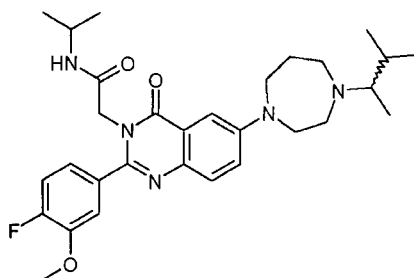
MS (ESI) m/z : 514/516 ($[M+H]^+$) (from EXAMPLE 1k).

EXAMPLE 5t: 2-[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(4,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 510 ($[M+H]^+$) (from EXAMPLE 1l).

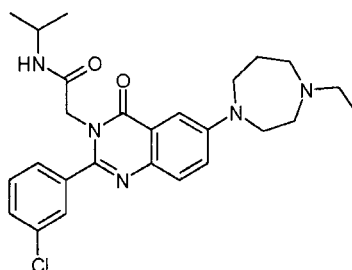
EXAMPLE 5u: 2-[6-[4-(1,2-Dimethylpropyl)perhydro-1,4-diazepin-1-yl]-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 538 ($[M+H]^+$) (from EXAMPLE 1i).

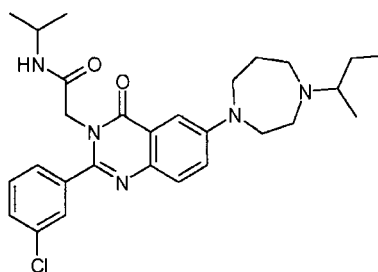
EXAMPLE 5v: 2-[2-(3-Chlorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

87



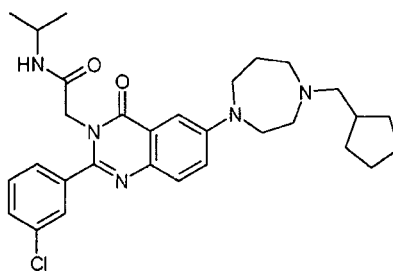
MS (ESI) m/z : 482 ($[M+H]^+$) (from EXAMPLE 1b).

EXAMPLE 5w: 2-[6-(4-sec-Butylperhydro-1,4-diazepin-1-yl)-2-(3-chlorophenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 510 ($[M+H]^+$) (from EXAMPLE 1b).

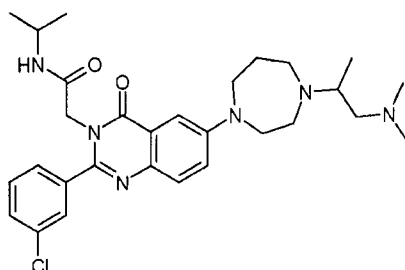
EXAMPLE 5x: 2-[2-(3-Chlorophenyl)-6-(4-cyclopentylmethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 536 ($[M+H]^+$) (from EXAMPLE 1b).

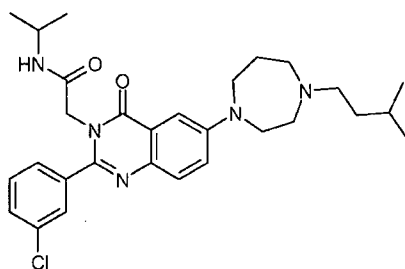
EXAMPLE 5y: 2-[2-(3-Chlorophenyl)-6-[4-(2-dimethylamino-1-methylethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

88



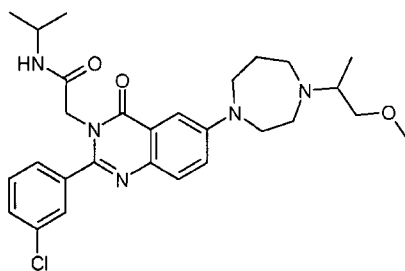
MS (ESI) m/z : 540 ($[M+H]^+$) (from EXAMPLE 1b).

EXAMPLE 5z: 2-{2-(3-Chlorophenyl)-6-[4-(3-methylbutyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide



MS (ESI) m/z : 524 ($[M+H]^+$) (from EXAMPLE 1b).

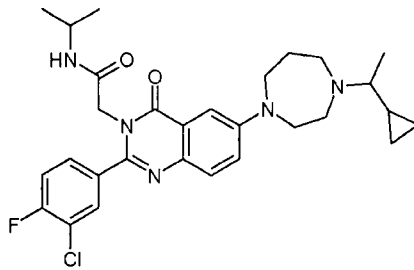
EXAMPLE 5Aa: 2-{2-(3-Chlorophenyl)-6-[4-(2-methoxy-1-methylethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide



MS (ESI) m/z : 526 ($[M+H]^+$) (from EXAMPLE 1b).

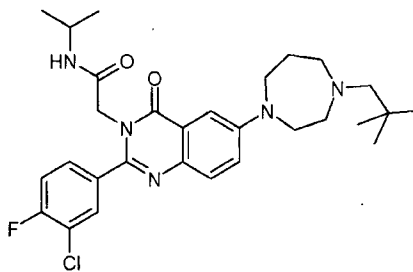
EXAMPLE 5Ab: 2-{2-(3-Chloro-4-fluorophenyl)-6-[4-(1-cyclopropylethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide

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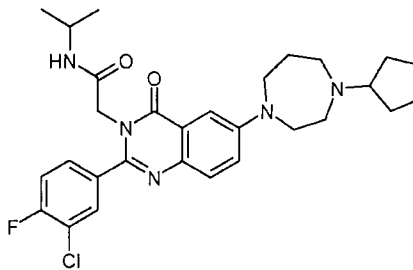
MS (ESI) m/z : 540/542 ($[M+H]^+$) (from EXAMPLE 1e).

EXAMPLE 5Ac: 2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(2,2-dimethylpropyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



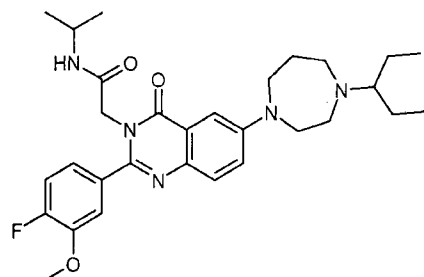
MS (ESI) m/z : 542 ($[M+H]^+$) (from EXAMPLE 1e).

EXAMPLE 5Ad: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-cyclopentylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



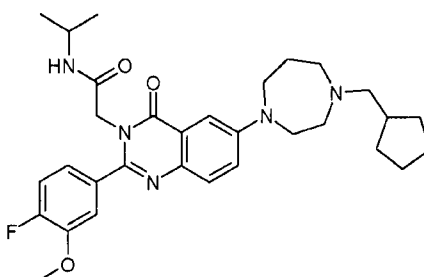
MS (ESI) m/z : 540 ($[M+H]^+$) (from EXAMPLE 1e).

EXAMPLE 5Ae: 2-[6-[4-(1-Ethylpropyl)perhydro-1,4-diazepin-1-yl]-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



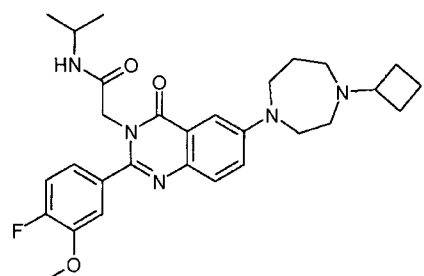
MS (ESI) m/z : 538 ($[M+H]^+$) (from EXAMPLE 1i).

EXAMPLE 5Af: 2-[6-(4-Cyclopentylmethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 550 ($[M+H]^+$) (from EXAMPLE 1i).

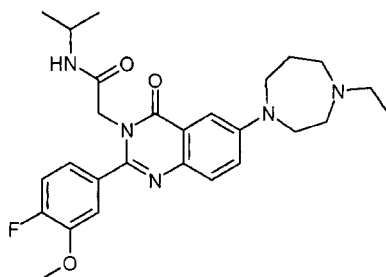
EXAMPLE 5Ag: 2-[6-(4-Cyclobutylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 522($[M+H]^+$) (from EXAMPLE 1i).

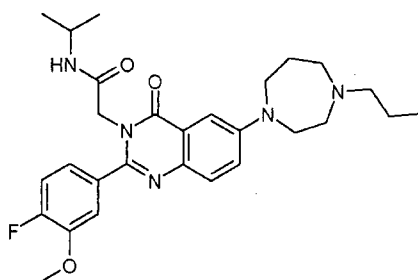
EXAMPLE 5Ah: 2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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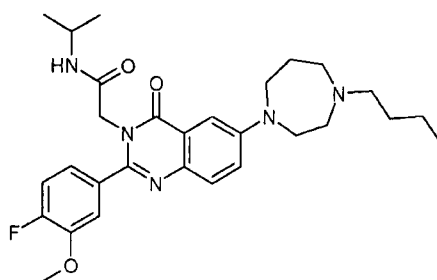
MS (ESI) m/z : 496 ($[M+H]^+$) (from EXAMPLE 1i).

EXAMPLE 5Ai: 2-[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(4-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 510 ($[M+H]^+$) (from EXAMPLE 1i).

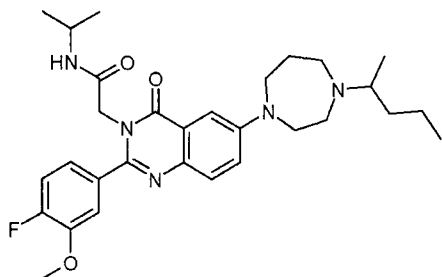
EXAMPLE 5Aj: 2-[6-(4-Butylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 525 ($[M+H]^+$) (from EXAMPLE 1i).

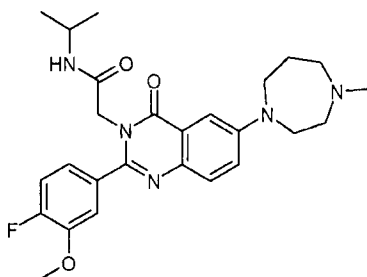
EXAMPLE 5Ak: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-[4-(1-methylbutyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

92



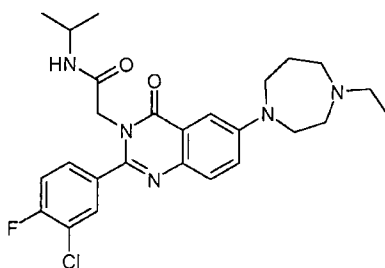
MS (ESI) m/z : 538 ($[M+H]^+$) (from EXAMPLE 1i).

EXAMPLE 5Ai: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 482 ($[M+H]^+$) (from EXAMPLE 1i).

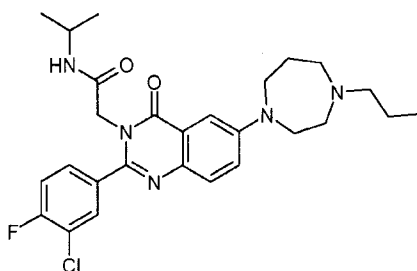
EXAMPLE 5Am: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 500 ($[M+H]^+$) (from EXAMPLE 1e).

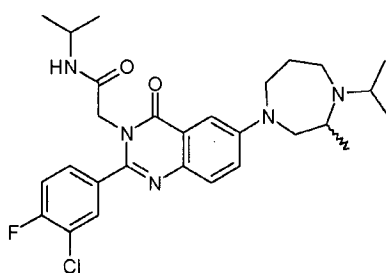
EXAMPLE 5An: 2-[2-(3-Chloro-4-fluorophenyl)-4-oxo-6-(4-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide

93



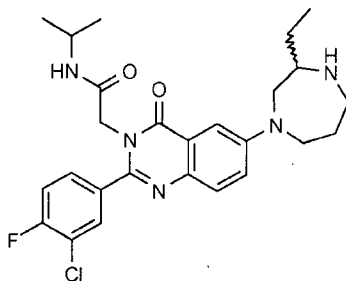
MS (ESI) m/z : 514 ($[M+H]^+$) (from EXAMPLE 1e).

EXAMPLE 5Ao: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropyl-3-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 528/530 ($[M+H]^+$) (from EXAMPLE 1h).

EXAMPLE 6a: 2-[2-(3-Chloro-4-fluorophenyl)-6-(3-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

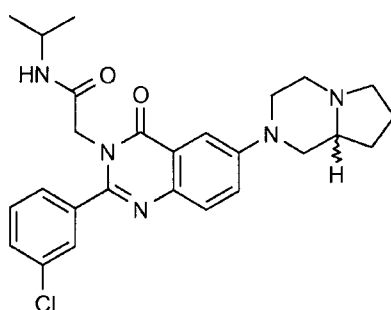


2-Amino-5-(3-ethylperhydro-1,4-diazepin-1-yl)-N-(isopropylcarbamoylmethyl)benzamide (INTERMEDIATE V.26) (100 mg, 0.277 mmol), 3-chloro-4-fluorobenzaldehyde (51 mg, 0.332 mmol) and acetic acid (4 drops, catalytic) (0.33 mmol) were dissolved in ethanol (4 mL) in a microwave vial and the vial sealed. The reaction mixture was stirred at 90 °C for 16 h. The reaction mixture was evaporated to dryness, re-dissolved in DCM and manganese dioxide (105 mg, 1.11 mmol) was added. The reaction mixture was stirred in a sealed vial at

60 °C for 3 h. Solvent was evaporated under reduced pressure and crude product purified by chromatography on silica gel with a gradient of DCM to MeOH:DCM (1:4, v/v) as eluent. This afforded 2-[2-(3-chloro-4-fluorophenyl)-6-(3-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 6a) (95 mg, 0.192 mmol, 69%).
Data for 2-[2-(3-chloro-4-fluorophenyl)-6-(3-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 6a): MS (ESI) m/z : 500/502 ($[M+H]^+$).

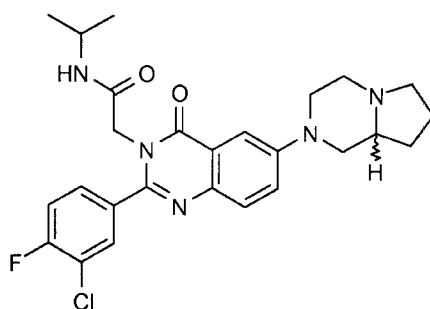
Similarly prepared from INTERMEDIATES V were:

EXAMPLE 6b: 2-[2-(3-Chlorophenyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 480/482 ($[M+H]^+$) (from INTERMEDIATE V.48)

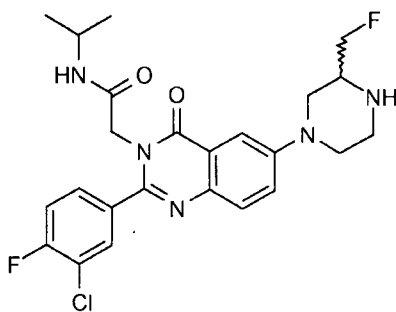
EXAMPLE 6c: 2-[2-(3-Chloro-4-fluorophenyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 498/500 ($[M+H]^+$) (from INTERMEDIATE V.48)

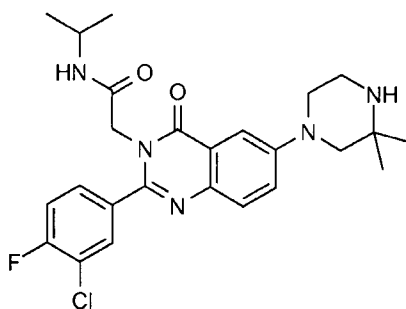
EXAMPLE 6d: 2-[2-(3-Chloro-4-fluorophenyl)-6-(3-fluoromethylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

95



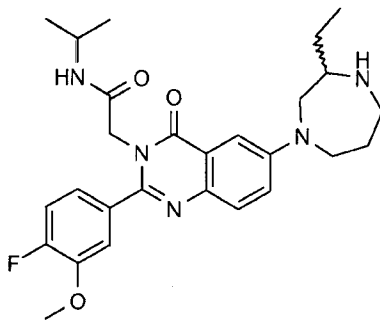
MS (ESI) m/z : 490/492 ($[M+H]^+$) (from INTERMEDIATE V.27)

EXAMPLE 6e: 2-[2-(3-Chloro-4-fluorophenyl)-6-(dimethylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 486/488 ($[M+H]^+$) (from INTERMEDIATE V.19)

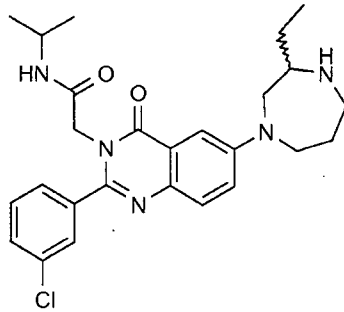
EXAMPLE 6f: 2-[6-(3-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 496 ($[M+H]^+$) (from INTERMEDIATE V.26)

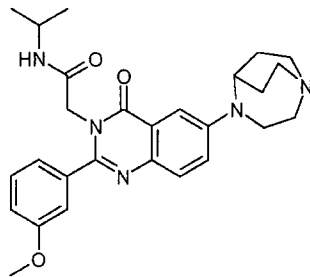
EXAMPLE 6g: 2-[2-(3-Chlorophenyl)-6-(3-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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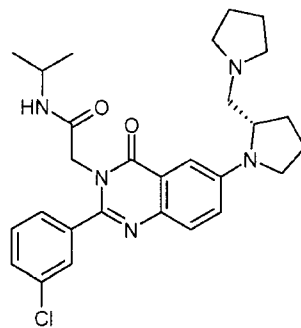
MS (ESI) m/z : 482/484 ($[M+H]^+$) (from INTERMEDIATE V.26)

EXAMPLE 6h: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



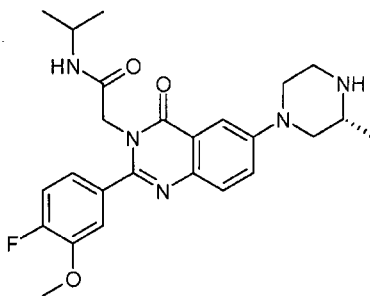
MS (ESI) m/z : 476 ($[M+H]^+$) (from INTERMEDIATE V.47)

EXAMPLE 6i: 2-[2-(3-Chlorophenyl)-4-oxo-6-((S)-2-pyrrolidin-1-ylmethylpyrrolidin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide



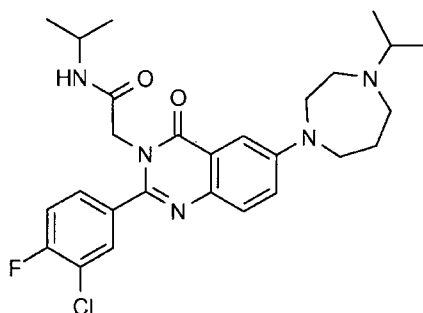
MS (ESI) m/z : 508/510 ($[M+H]^+$) (from INTERMEDIATE V.28)

EXAMPLE 6j: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-((R)-3-methylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 468 ($[M+H]^+$) (from INTERMEDIATE V.25)

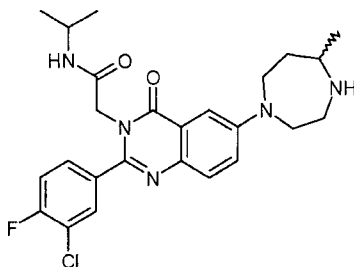
EXAMPLE 6k: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



2-Amino-5-(4-isopropyl-1,4-diazepan-1-yl)-N-(2-(isopropylamino)-2-oxoethyl)benzamide (INTERMEDIATE V.31) (400 mg, 1.07 mmol), 3-chloro-4-fluorobenzaldehyde (253 mg, 1.60 mmol) and acetic acid (0.01 mL) were dissolved in ethanol (12 mL). The reaction mixture was heated at 90 °C overnight. The reaction mixture was filtered, the residue washed with EtOAc, and the filtrate evaporated under reduced pressure. Crude product was purified by SCX eluting with 2N NH_3 /MeOH to give a purple solid.

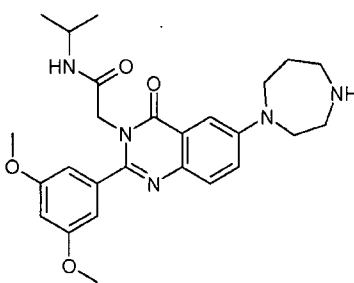
This solid was dissolved in toluene (12.00 mL) and potassium hexacyanoferrate (III) (3.51 g, 10.65 mmol) added followed by water (12 mL) and 10M KOH (aq.) (4 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with conc. HCl, diluted with MeOH (10 mL) and filtered. The residue was washed with MeOH and the filtrate purified by SCX, eluting with 2N NH_3 /MeOH. Crude product was purified by chromatography on silica gel with a gradient of DCM to DCM:MeOH: NH_3 (94:5:1, v/v) as eluent to afford 2-[2-(3-chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 6k) (155 mg, 0.302 mmol, 28%). Data for 2-[2-(3-chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 6k): MS (ESI) m/z : 515/517 ($[M+H]^+$).

EXAMPLE 6l: 2-[2-(3-Chloro-4-fluorophenyl)-6-(5-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



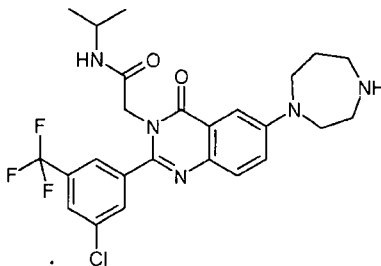
MS (ESI) m/z : 486/488 ($[M+H]^+$) (from INTERMEDIATE V.29).

EXAMPLE 6m: 2-[2-(3,5-Dimethoxyphenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl]-4H-quinazolin-3-yl]-N-isopropylacetamide



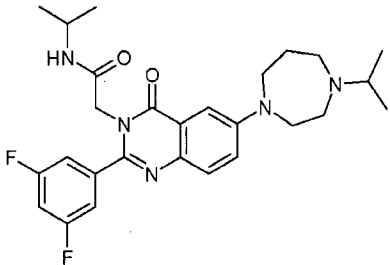
MS (ESI) m/z : 480 ($[M+H]^+$) (from INTERMEDIATE V.2)

EXAMPLE 6n: 2-[2-(3-Chloro-5-trifluoromethylphenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl]-4H-quinazolin-3-yl]-N-isopropylacetamide



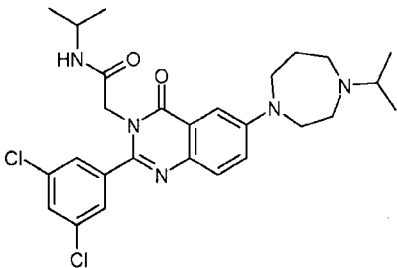
MS (ESI) m/z : 522/524 ($[M+H]^+$) (from INTERMEDIATE V.2).

EXAMPLE 6o: 2-[2-(3,5-Difluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



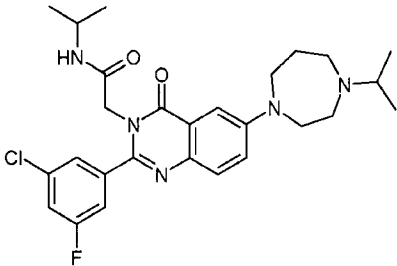
MS (ESI) *m/z*: 498 ([*M*+*H*]⁺) (from INTERMEDIATE V.31).

EXAMPLE 6p: 2-[2-(3,5-Dichlorophenyl)-6-(4-isopropyl-perhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) *m/z*: 530/532/534 ([*M*+*H*]⁺) (from INTERMEDIATE V.31).

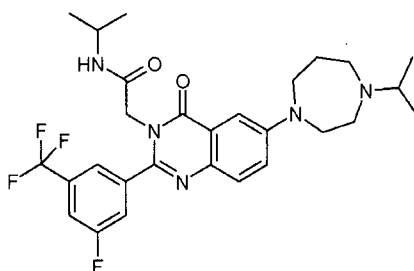
EXAMPLE 6q: 2-[2-(3-Chloro-5-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) *m/z*: 514/516 ([*M*+*H*]⁺) (from INTERMEDIATE V.31).

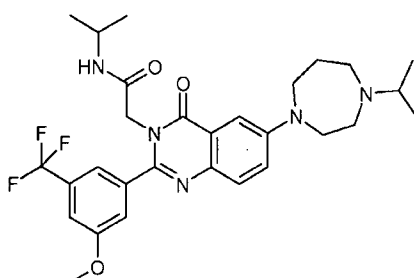
EXAMPLE 6r: 2-[2-(3-Fluoro-5-trifluoromethylphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

100



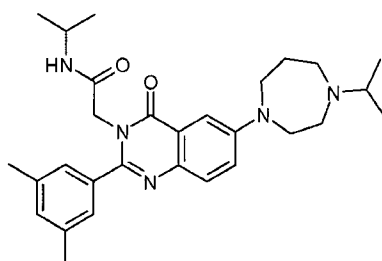
MS (ESI) m/z : 548 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 6s: N-Isopropyl-2-[6-(4-isopropylperhydro-1,4-diazepin-1-yl)-2-(3-methoxy-5-trifluoromethylphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 560 ($[M+H]^+$) (from INTERMEDIATE V.31).

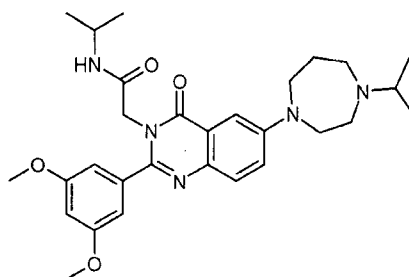
EXAMPLE 6t: 2-[2-(3,5-Dimethylphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 490 ($[M+H]^+$) (from INTERMEDIATE V.31).

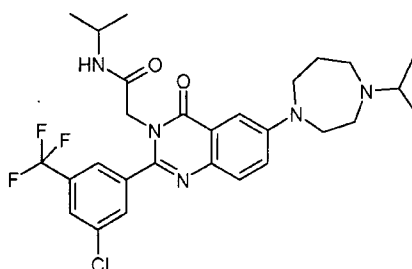
EXAMPLE 6u: 2-[2-(3,5-Dimethoxyphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

101



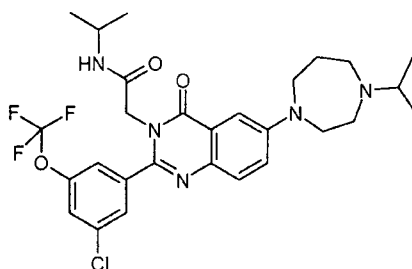
MS (ESI) m/z : 522 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 6v: 2-[2-(3-Chloro-5-trifluoromethylphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



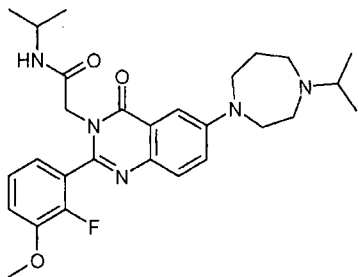
MS (ESI) m/z : 564/566 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 6w: 2-[2-(3-Chloro-5-trifluoromethoxyphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



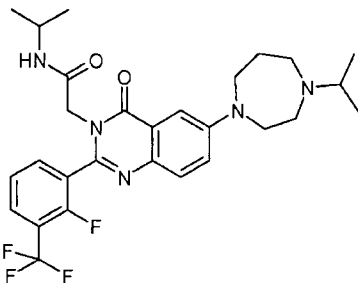
MS (ESI) m/z : 580/582 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 6x: 2-[2-(2-Fluoro-3-methoxyphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



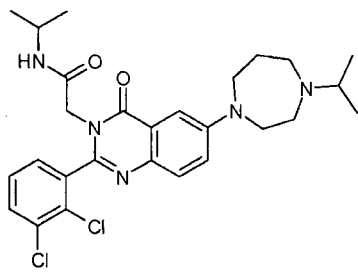
MS (ESI) m/z : 510 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 6y: 2-[2-(2-Fluoro-3-trifluoromethylphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 548 ($[M+H]^+$) (from INTERMEDIATE V.31).

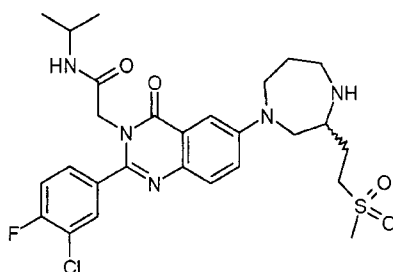
EXAMPLE 6z: 2-[2-(2,3-Dichlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 530/532 ($[M+H]^+$) (from INTERMEDIATE V.31).

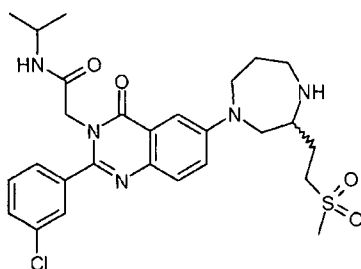
EXAMPLE 6Aa: 2-[2-(3-Chloro-4-fluorophenyl)-6-[3-(2-methanesulfonylethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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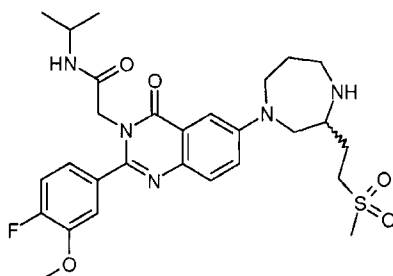
MS (ESI) m/z : 578/580 ($[M+H]^+$) (from INTERMEDIATE V.33).

EXAMPLE 6Ab: 2-[2-(3-Chlorophenyl)-6-[3-(2-methanesulfonyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 560/562 ($[M+H]^+$) (from INTERMEDIATE V.33).

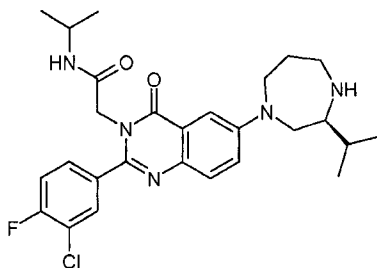
EXAMPLE 6Ac: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-[3-(2-methanesulfonyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 574 ($[M+H]^+$) (from INTERMEDIATE V.33).

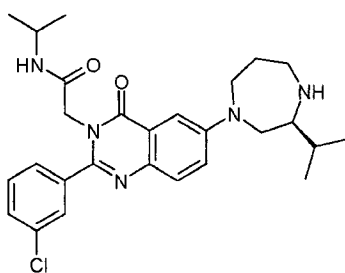
EXAMPLE 6Ad: 2-[2-(3-Chloro-4-fluorophenyl)-6-((S)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

104



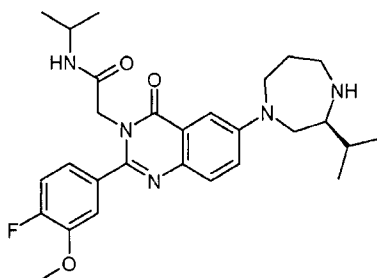
MS (ESI) m/z : 514/516 ($[M+H]^+$) (from INTERMEDIATE V.34).

EXAMPLE 6Ae: 2-[2-(3-Chlorophenyl)-6-((S)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 496/498 ($[M+H]^+$) (from INTERMEDIATE V.34).

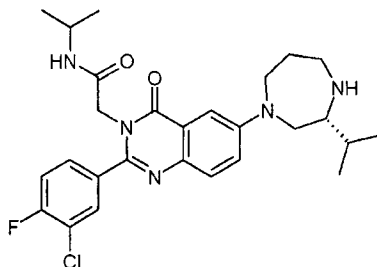
EXAMPLE 6Af: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-((S)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 510 ($[M+H]^+$) (from INTERMEDIATE V.34).

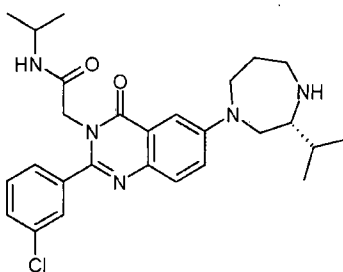
EXAMPLE 6Ag: 2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

105



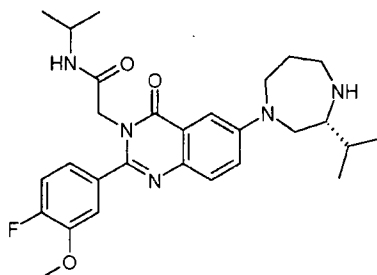
MS (ESI) m/z : 514/516 ($[M+H]^+$) (from INTERMEDIATE V.35).

EXAMPLE 6Ah: 2-[2-(3-Chlorophenyl)-6-((R)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 496/498 ($[M+H]^+$) (from INTERMEDIATE V.35).

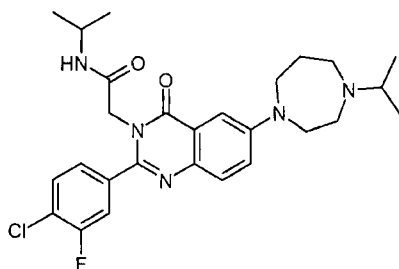
EXAMPLE 6Ai: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-((R)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 510 ($[M+H]^+$) (from INTERMEDIATE V.35).

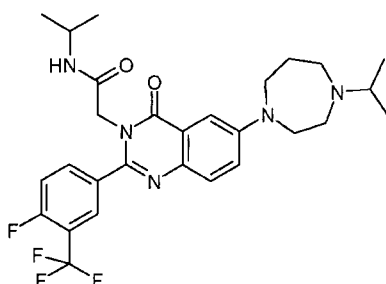
EXAMPLE 6Aj: 2-[2-(4-Chloro-3-fluorophenyl)-6-((R)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

106



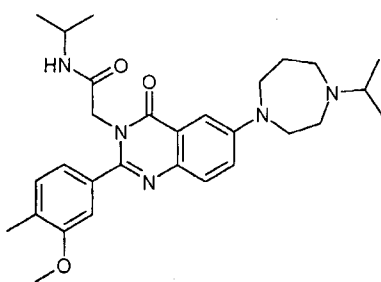
MS (ESI) m/z : 514/516 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 6Ak: 2-[2-(4-Fluoro-3-trifluoromethylphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 548 ($[M+H]^+$) (from INTERMEDIATE V.31).

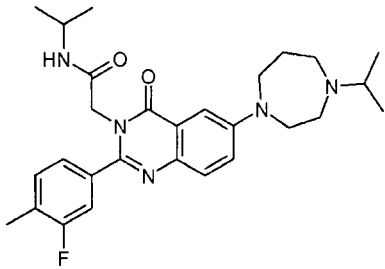
EXAMPLE 6Al: N-Isopropyl-2-[6-(4-isopropylperhydro-1,4-diazepin-1-yl)-2-(3-methoxy-4-methylphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 506 ($[M+H]^+$) (from INTERMEDIATE V.31).

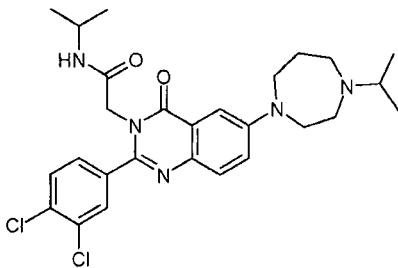
EXAMPLE 6Am: 2-[2-(3-Fluoro-4-methylphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

118



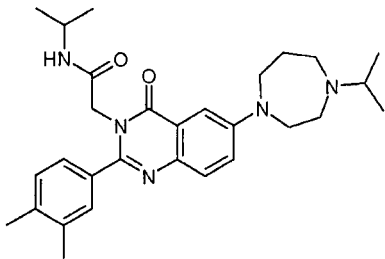
MS (ESI) *m/z*: 494 ([M+H]⁺) (from INTERMEDIATE V.31).

EXAMPLE 6An: 2-[2-(3,4-Dichlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) *m/z*: 530/532/534 ([M+H]⁺) (from INTERMEDIATE V.31).

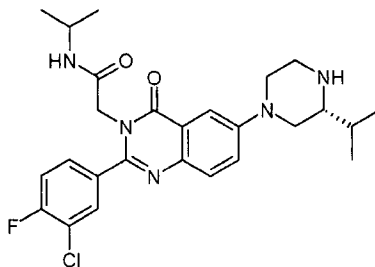
EXAMPLE 6Ao: 2-[2-(3,4-Dimethylphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) *m/z*: 490 ([M+H]⁺) (from INTERMEDIATE V.31).

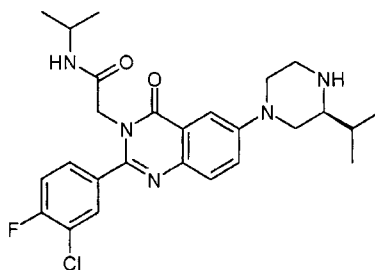
EXAMPLE 6Ap: 2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-3-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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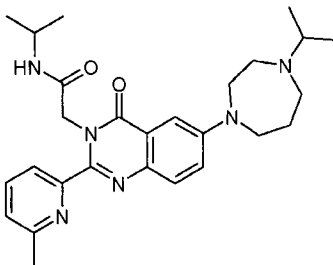
MS (ESI) m/z : 500/502 ($[M+H]^+$) (from INTERMEDIATE V.36).

EXAMPLE 6Aq: 2-[2-(3-Chloro-4-fluorophenyl)-6-((S)-3-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 500/502 ($[M+H]^+$) (from INTERMEDIATE V.37).

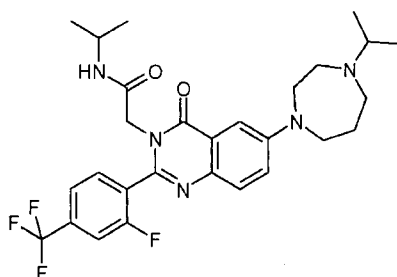
EXAMPLE 6Ar: N-Isopropyl-2-[6-(4-isopropylperhydro-1,4-diazepin-1-yl)-2-(6-methylpyridin-2-yl)-4-oxo-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 477 ($[M+H]^+$) (from INTERMEDIATE V.31).

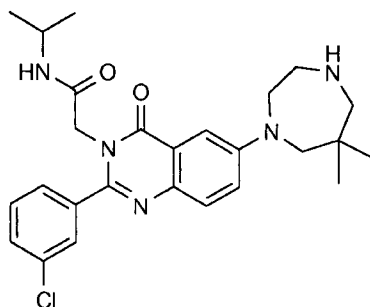
EXAMPLE 6As: 2-[2-(2-Fluoro-4-trifluoromethylphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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MS (ESI) m/z : 548 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 6At: 2-[2-(3-Chlorophenyl)-6-(6,6-dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

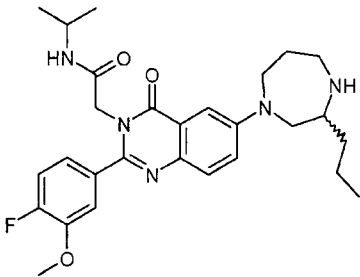


2-Amino-5-(6,6-dimethyl-1,4-diazepan-1-yl)-N-(2-(isopropylamino)-2-oxoethyl)benzamide (INTERMEDIATE V.54) (110 mg, 0.304 mmol), 3-chlorobenzaldehyde (58 mg, 0.365 mmol) and acetic acid (10 mg, 0.0003 mmol) were dissolved in ethanol (3 mL) and stirred at 90 °C for 16 h. The reaction mixture was evaporated to dryness, crude product dissolved in DCM (3 mL) and 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (138 mg, 0.609 mmol) added. The reaction mixture was stirred at room temperature for 4 h. The crude mixture was dissolved in MeOH and purified by SCX eluting with 2N NH_3 /MeOH. Solvent was evaporated under reduced pressure and the crude material purified by chromatography on silica gel with a gradient of DCM to DCM:MeOH (3:1, v/v) as eluent. This afforded 2-[2-(3-chlorophenyl)-6-(6,6-dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 6At) (17 mg, 0.034 mmol, 11%).

Data for 2-[2-(3-chlorophenyl)-6-(6,6-dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 6At): MS (ESI) m/z : 482/484 ($[M+H]^+$).

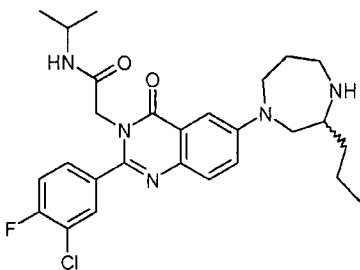
EXAMPLE 6Au: 2-[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(3-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide

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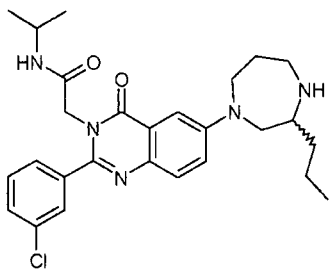
MS (ESI) m/z : 510 ($[M+H]^+$) (from INTERMEDIATE V.32).

EXAMPLE 6Av: 2-[2-(3-Chloro-4-fluorophenyl)-4-oxo-6-(3-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 514/516 ($[M+H]^+$) (from INTERMEDIATE V.32).

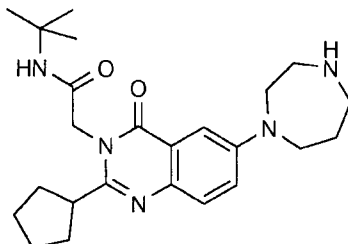
EXAMPLE 6Aw: 2-[2-(3-Chlorophenyl)-4-oxo-6-(3-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 496/498 ($[M+H]^+$) (from INTERMEDIATE V.32).

EXAMPLE 7a: N-tert-Butyl-2-(2-cyclopentyl-4-oxo-6-perhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl-acetamide

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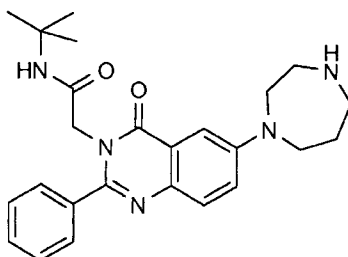


Pyridine (21 mg, 0.022 mL, 0.268 mmol) and cyclopentanecarbonyl chloride (30 mg, 0.223 mmol) were added to an ice-water cooled solution of 4-{4-amino-3-[(*tert*-butylcarbamoylmethyl)carbamoyl]phenyl}perhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (INTERMEDIATE V.38) (100 mg, 0.223 mmol) in THF (1 mL) and the reaction mixture stirred for 15 min. Solvent was removed *in vacuo* and the residue partitioned between DCM (10 mL) and water (10 mL). The organic phase was dried (Na₂SO₄) and concentrated *in vacuo*. The crude material was dissolved in 1,2-dichloroethane (5 mL) and triethylamine (1.04 g, 1.39 mL, 10.28 mmol) and trimethylsilyl chloride (364 mg, 0.428 mL, 3.35 mmol) added. The reaction mixture was heated at reflux temperature for 3 h. The reaction mixture was diluted with EtOAc (10 mL), washed with 1M HCl (aq.) and sodium bicarbonate (aq.) solution. The organic phase was dried (MgSO₄) and solvent removed *in vacuo*. Crude product was purified by chromatography on silica gel with a gradient of DCM to DCM:EtOAc (1:4, v/v) as eluent. The product was dissolved in DCM (5 mL), TFA (0.5 mL) added and the reaction stirred at room temperature for 2 h. The solution was poured directly onto an SCX cartridge and product eluted with 2N NH₃/MeOH. Solvent was removed under reduced pressure to afford *N*-*tert*-butyl-2-(2-cyclopentyl-4-oxo-6-perhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl-acetamide (EXAMPLE 7a) (35 mg, 0.082 mmol, 37%).

Data for *N*-*tert*-butyl-2-(2-cyclopentyl-4-oxo-6-perhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl-acetamide (EXAMPLE 7a): MS (ESI) *m/z*: 426 ([M+H]⁺).

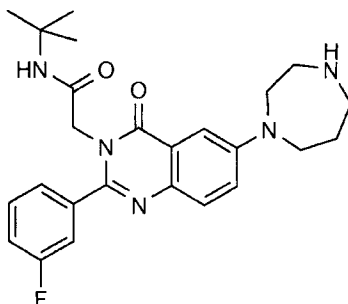
Similarly prepared from INTERMEDIATES V were:

EXAMPLE 7b: *N*-*tert*-Butyl-2-(4-oxo-6-perhydro-1,4-diazepin-1-yl)-2-phenyl-4H-quinazolin-3-yl)acetamide



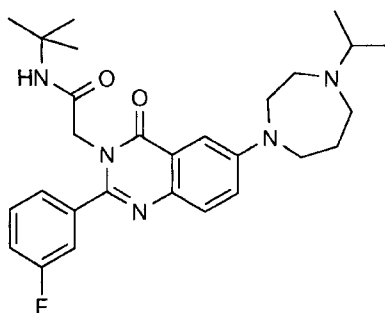
MS (ESI) m/z : 434 ($[M+H]^+$) (from INTERMEDIATE V.38).

EXAMPLE 7c: *N*-tert-Butyl-2-[2-(3-fluorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl]-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 452 ($[M+H]^+$) (from INTERMEDIATE V.38).

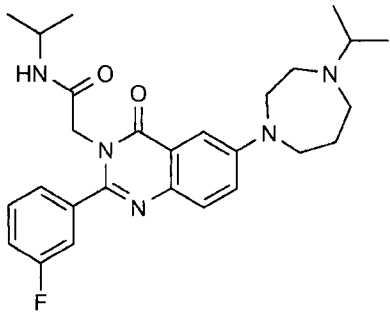
EXAMPLE 7d: *N*-tert-Butyl-2-[2-(3-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



3-Fluorobenzoyl chloride (24 mg, 0.154 mmol, 0.019 mL) was added to an ice-water cooled solution of 2-amino-*N*-(*tert*-butylcarbamoylmethyl)-5-(4-isopropylperhydro-1,4-diazepin-1-yl)benzamide (INTERMEDIATE V.49) (60 mg, 0.154 mmol) and triethylamine (716 mg, 0.96 mL, 7.09 mmol) in DCM (2 mL). Stirring was continued for 15 min. Trimethylsilyl chloride (251 mg, 0.295 mL, 2.31 mmol) was added and the reaction mixture heated in the microwave at 150°C for 7 min. The reaction mixture was diluted with DCM (10 mL) and washed with water. The organic phase was dried (MgSO₄) and concentrated *in vacuo*. Crude product was purified by chromatography on silica gel with a gradient of DCM to DCM:MeOH:NH₃ (95:4:1, v/v) as eluent. Further purification by preparative HPLC afforded *N*-*tert*-butyl-2-[2-(3-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide (EXAMPLE 7d) (5 mg, 10 μmol, 7%).

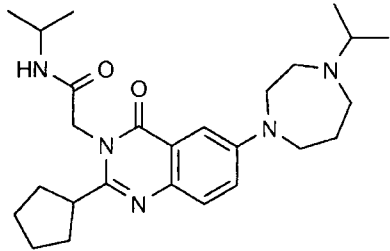
Data for *N*-*tert*-butyl-2-[2-(3-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide (EXAMPLE 7d): MS (ESI) m/z : 494 ($[M+H]^+$).

EXAMPLE 7e: 2-[2-(3-Fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



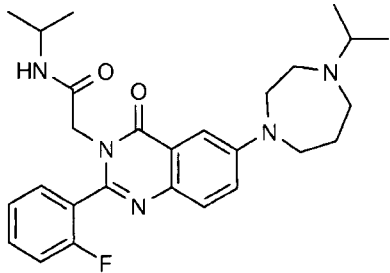
MS (ESI) *m/z*: 480 ([M+H]⁺) (from INTERMEDIATE V.31).

EXAMPLE 7f: 2-[2-Cyclopentyl-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) *m/z*: 454 ([M+H]⁺) (from INTERMEDIATE V.31).

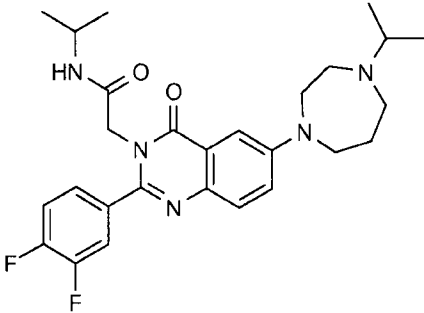
EXAMPLE 7g: 2-[2-(2-Fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) *m/z*: 480 ([M+H]⁺) (from INTERMEDIATE V.31).

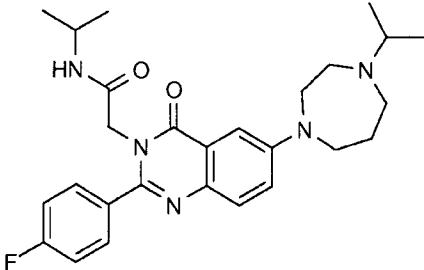
EXAMPLE 7h: 2-[2-(3,4-Difluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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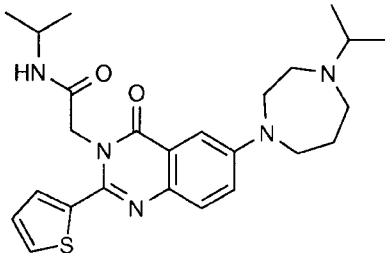
MS (ESI) m/z : 498 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 7i: 2-[2-(4-Fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



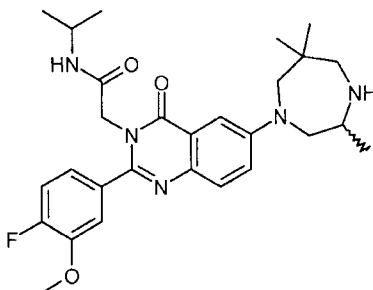
MS (ESI) m/z : 480 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 7j: N-Isopropyl-2-[6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-2-thiophen-2-yl-4H-quinazolin-3-yl]acetamide

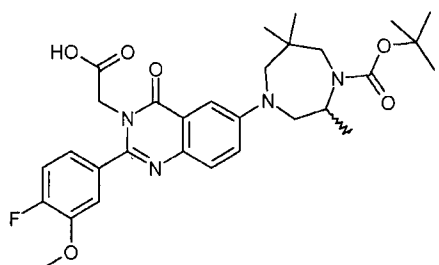


MS (ESI) m/z : 468 ($[M+H]^+$) (from INTERMEDIATE V.31).

EXAMPLE 8a: 2-[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide

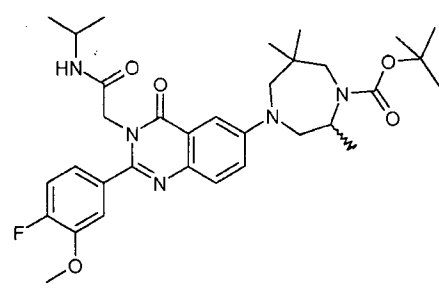


a) 4-[3-Carboxymethyl-2-(4-fluoro-3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2,6,6-trimethylperhydro-1,4-diazepine-1-carboxylic acid tert-butyl ester



[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]acetic acid (INTERMEDIATE IX.1) (160 mg, 0.341 mmol), di-*tert*-butyldicarbonate (78 mg, 0.359 mmol) and triethylamine (76 mg, 0.751 mmol) were combined and stirred at room temperature in DCM (5 mL) overnight. The crude product mixture was washed with 1N HCl (2 X 20 mL) and water (40 mL). The organic phase was dried (Na₂SO₄) and concentrated *in vacuo*. Crude product was purified by chromatography on silica gel with DCM:MeOH (3:1, v/v) as eluent to afford 4-[3-carboxymethyl-2-(4-fluoro-3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2,6,6-trimethylperhydro-1,4-diazepine-1-carboxylic acid tert-butyl ester (200 mg, 0.352 mmol, 100%).

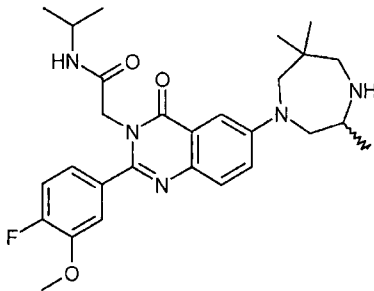
b) 4-[2-(4-Fluoro-3-methoxyphenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2,6,6-trimethylperhydro-1,4-diazepine-1-carboxylic acid tert-butyl ester



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4-[3-Carboxymethyl-2-(4-fluoro-3-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2,6,6-trimethylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.352 mmol), isopropylamine (208 mg, 299 μ L, 3.52 mmol), 1-propanephosphonic acid cyclic anyhydride (336 mg, 320 μ L, 0.528 mmol) and DIPEA (135 mg, 186 μ L, 1.06 mmol) were stirred at room temperature in DCM (15 mL) for 2 h. NaHCO_3 (aq.) (15 mL) was added, the organic layer separated, dried (Na_2SO_4) and evaporated under reduced pressure. Crude product was purified by chromatography on silica gel with a gradient of DCM to DCM:MeOH (4:1, v/v) as eluent to afford 4-[2-(4-fluoro-3-methoxyphenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2,6,6-trimethylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (120 mg, 0.197 mmol, 56%).

c) 2-[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide

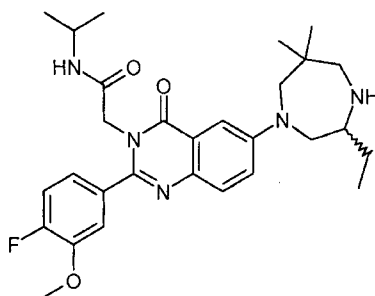


4-[2-(4-Fluoro-3-methoxyphenyl)-3-(isopropylcarbamoylmethyl)-4-oxo-3,4-dihydroquinazolin-6-yl]-2,6,6-trimethylperhydro-1,4-diazepine-1-carboxylic acid *tert*-butyl ester (120 mg, 0.197 mmol) was dissolved in DCM (6 mL) and TFA (3 mL) added. The reaction was stirred at room temperature for 4 h. Product mixture was poured directly onto an SCX cartridge and product eluted with 2N NH_3/MeOH . Solvent was evaporated under reduced pressure to afford a red solid. Product was diluted with MeOH (20 mL) and heated at reflux temperature with activated carbon. The mixture was filtered through a celite pad, solvent evaporated under reduced pressure and the resultant product recrystallised from ethanol:heptane. This afforded 2-[2-(4-fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 8a) (74 mg, 0.145 mmol, 74%).
Data for 2-[2-(4-fluoro-3-methoxyphenyl)-4-oxo-6-(3,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 8a): MS (ESI) m/z : 510 ($[\text{M}+\text{H}]^+$).

Similarly prepared were:

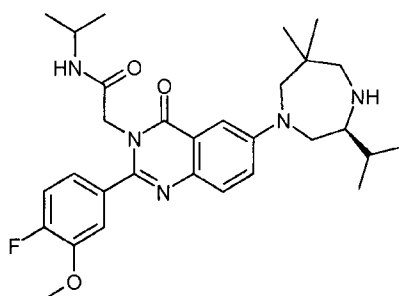
EXAMPLE 8b: 2-[6-(3-Ethyl-6,6-dimethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

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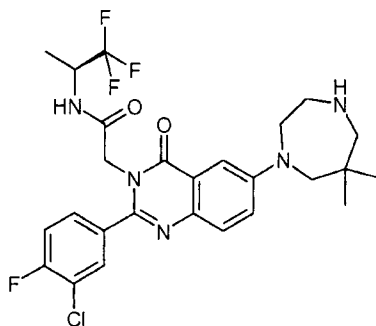
MS (ESI) m/z : 524 ($[M+H]^+$) (from INTERMEDIATE IX.3).

EXAMPLE 8c: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-((S)-3-isopropyl-6,6-dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 538 ($[M+H]^+$) (from INTERMEDIATE IX.6).

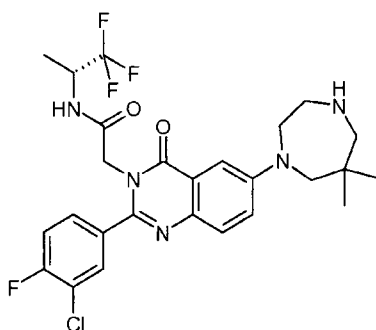
EXAMPLE 8d: 2-[2-(3-Chloro-4-fluorophenyl)-6-(dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-((S)-2,2,2-trifluoro-1-methylethyl)acetamide



MS (ESI) m/z : 554 ($[M+H]^+$) (from INTERMEDIATE IX.4).

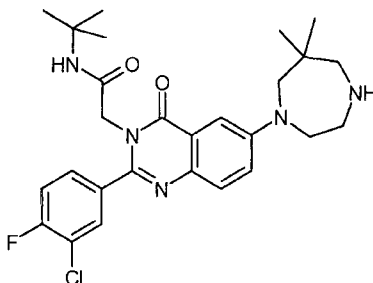
EXAMPLE 8e: 2-[2-(3-Chloro-4-fluorophenyl)-6-(dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-((R)-2,2,2-trifluoro-1-methylethyl)acetamide

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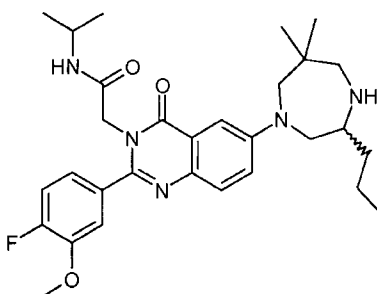
MS (ESI) m/z : 554 ($[M+H]^+$) (from INTERMEDIATE IX.4).

EXAMPLE 8f: *N*-tert-Butyl-2-[2-(3-chloro-4-fluorophenyl)-6-(dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



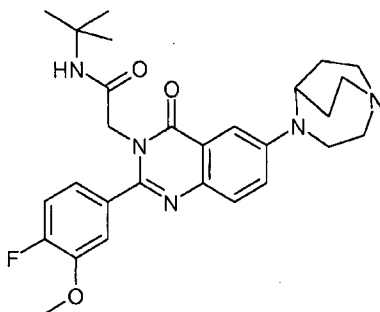
MS (ESI) m/z : 514 ($[M+H]^+$) (from INTERMEDIATE IX.4).

EXAMPLE 8g: 2-[6-(6,6-Dimethyl-3-propylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide



MS (ESI) m/z : 538 ($[M+H]^+$) (from INTERMEDIATE IX.5).

EXAMPLE 9a: *N*-tert-Butyl-2-[6-(1,4-diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]acetamide

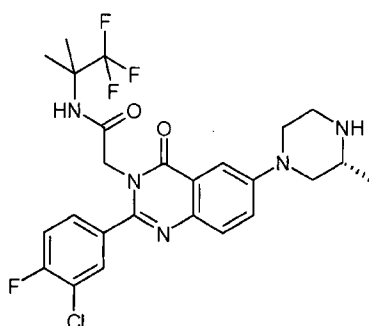


[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetic acid (INTERMEDIATE IX.7) (20 mg, 0.44 mmol) was dissolved in DCM (5 mL). *Tert*-butylamine (6.5 mg, 0.088 mmol) and *N,N*-diisopropylethylamine (7 mg, 0.053 mmol) were added followed by 1-propanephosphonic acid cyclic anhydride (21 mg, 0.02 mL, 0.066 mmol). The reaction mixture was stirred at room temperature for 12 h. Methanol (5 mL) was added and the solution poured directly onto an SCX cartridge. Elution with 2N NH_3/MeOH followed further purification by preparative HPLC afforded *N-tert-butyl-2-[6-(1,4-diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide* (EXAMPLE 9a) (7.3 mg, 0.014 mmol, 33%).

Data for *N-tert-butyl-2-[6-(1,4-diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide* (EXAMPLE 9a): MS (ESI) m/z : 508 ($[\text{M}+\text{H}]^+$).

Similarly prepared were:

EXAMPLE 9b: 2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-3-methylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-(2,2,2-trifluoro-1,1-dimethylethyl)acetamide

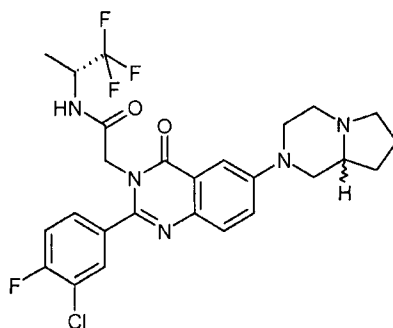


MS (ESI) m/z : 540/542 ($[\text{M}+\text{H}]^+$) (from INTERMEDIATE IX.8).

EXAMPLE 9c: 2-[2-(3-Chloro-4-fluorophenyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2-yl)-4-oxo-4H-quinazolin-3-yl]-N-((R)-2,2,2-trifluoro-1-methylethyl)acetamide

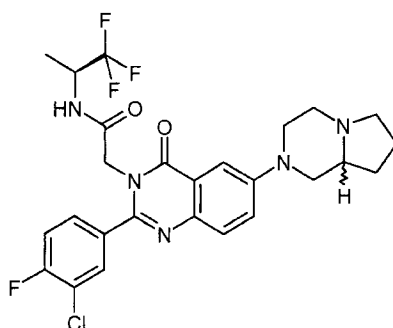
131

120



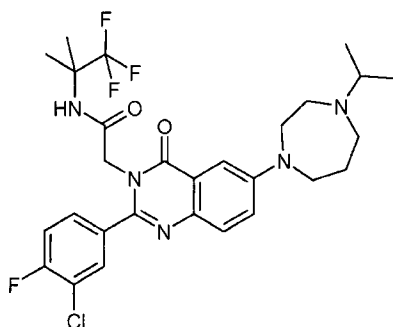
MS (ESI) m/z : 552/554 ($[M+H]^+$) (from INTERMEDIATE IX.9).

EXAMPLE 9d: 2-[2-(3-Chloro-4-fluorophenyl)-6-(hexahydropyrrolo[1,2-a]pyrazin-2-yl)-4-oxo-4H-quinazolin-3-yl]-N-((S)-2,2,2-trifluoro-1-methylethyl)acetamide



MS (ESI) m/z : 552/554 ($[M+H]^+$) (from INTERMEDIATE IX.9).

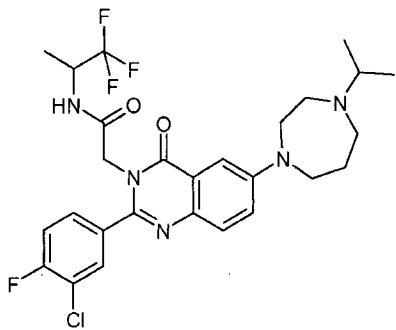
EXAMPLE 9e: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-(2,2,2-trifluoro-1,1-dimethylethyl)acetamide



MS (ESI) m/z : 582/584 ($[M+H]^+$) (from INTERMEDIATE IX.10).

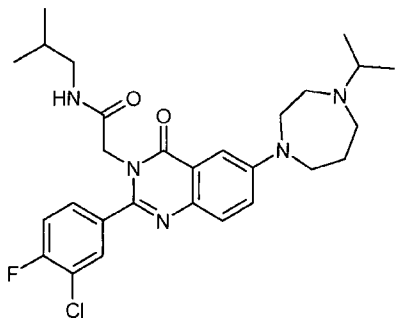
EXAMPLE 9f: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-(2,2,2-trifluoro-1-methylethyl)acetamide

121



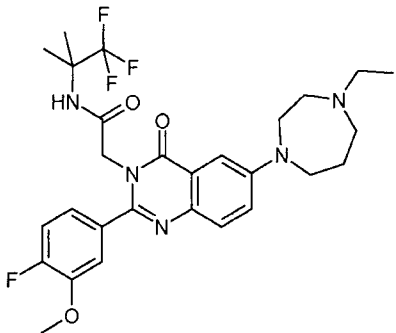
MS (ESI) m/z : 568 ($[M+H]^+$) (from INTERMEDIATE IX.10).

EXAMPLE 9g: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isobutylacetamide



MS (ESI) m/z : 528 ($[M+H]^+$) (from INTERMEDIATE IX.10).

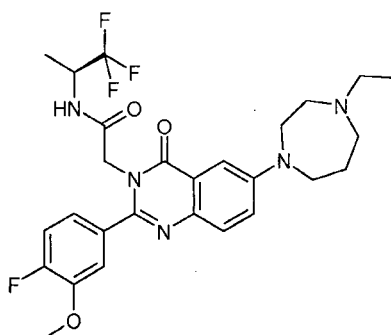
EXAMPLE 9h: 2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-(2,2,2-trifluoro-1,1-dimethylethyl)acetamide



MS (ESI) m/z : 564 ($[M+H]^+$) (from INTERMEDIATE IX.11).

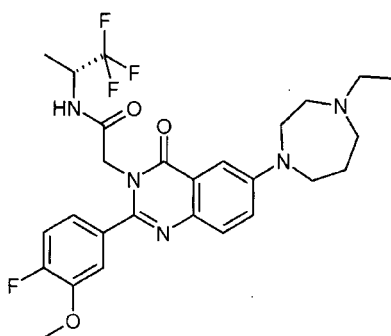
EXAMPLE 9i: 2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-((S)-2,2,2-trifluoro-1-methylethyl)acetamide

122



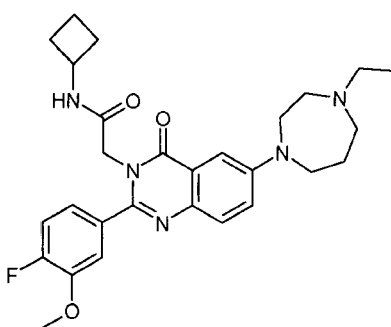
MS (ESI) m/z : 550 ($[M+H]^+$) (from INTERMEDIATE IX.11).

EXAMPLE 9j: 2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-((R)-2,2,2-trifluoro-1-methylethyl)acetamide



MS (ESI) m/z : 550 ($[M+H]^+$) (from INTERMEDIATE IX.11).

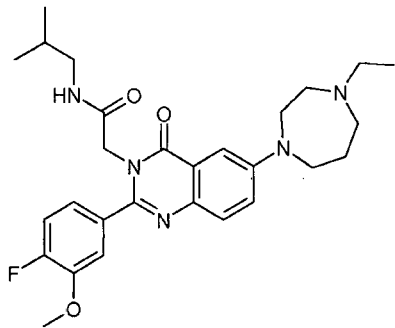
EXAMPLE 9k: N-Cyclobutyl-2-[6-(4-ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 508 ($[M+H]^+$) (from INTERMEDIATE IX.11).

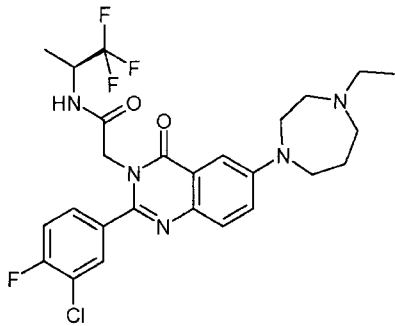
EXAMPLE 9l: 2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isobutylacetamide

123



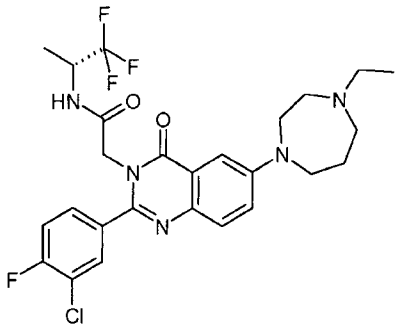
MS (ESI) m/z : 510 ($[M+H]^+$) (from INTERMEDIATE IX.11).

EXAMPLE 9m: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-((S)-2,2,2-trifluoro-1-methylethyl)acetamide



MS (ESI) m/z : 554/556 ($[M+H]^+$) (from INTERMEDIATE IX.12).

EXAMPLE 9n: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-((R)-2,2,2-trifluoro-1-methylethyl)acetamide

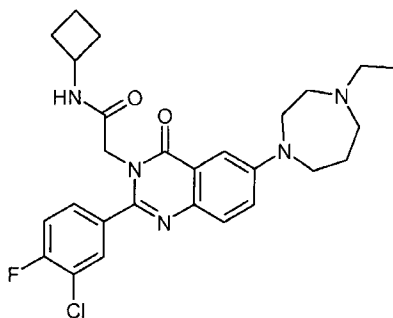


MS (ESI) m/z : 554 ($[M+H]^+$) (from INTERMEDIATE IX.12).

EXAMPLE 9o: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-ethyl-perhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-cyclobutylacetamide

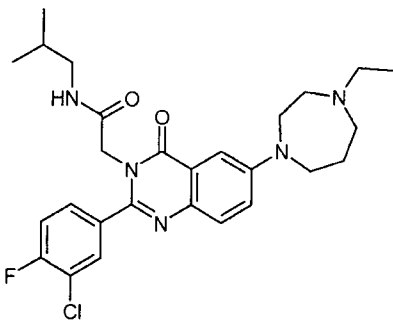
135

124



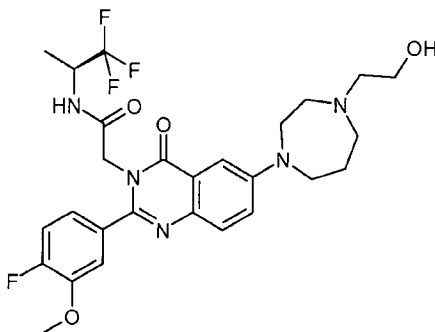
MS (ESI) m/z : 512/514 ($[M+H]^+$) (from INTERMEDIATE IX.12).

EXAMPLE 9p: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isobutylacetamide



MS (ESI) m/z : 514/516 ($[M+H]^+$) (from INTERMEDIATE IX.12).

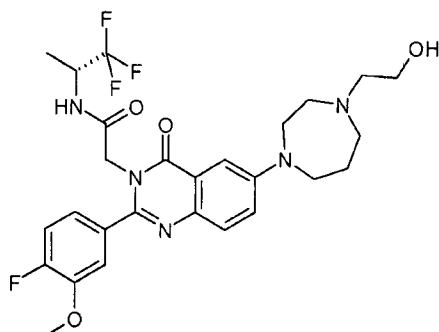
EXAMPLE 9q: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-((S)-2,2,2-trifluoro-1-methylethyl)acetamide



MS (ESI) m/z : 566 ($[M+H]^+$) (from INTERMEDIATE IX.13).

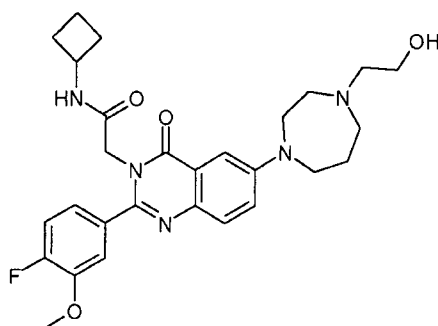
EXAMPLE 9r: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-((R)-2,2,2-trifluoro-1-methylethyl)acetamide

125



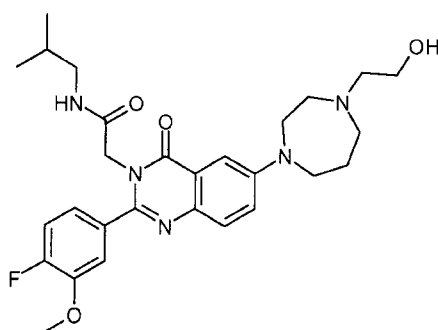
MS (ESI) m/z : 566 ($[M+H]^+$) (from INTERMEDIATE IX.13).

EXAMPLE 9s: N-Cyclobutyl-2-[2-(4-fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 524 ($[M+H]^+$) (from INTERMEDIATE IX.13).

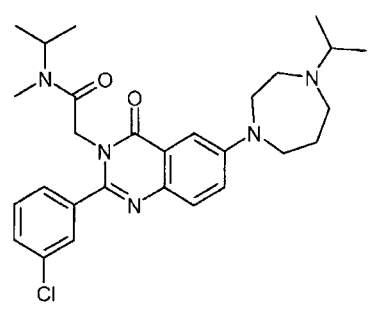
EXAMPLE 9t: 2-[2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isobutylacetamide



MS (ESI) m/z : 526 ($[M+H]^+$) (from INTERMEDIATE IX.13).

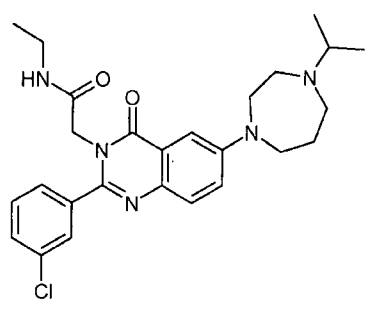
EXAMPLE 9u: 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropyl-N-methylacetamide

126



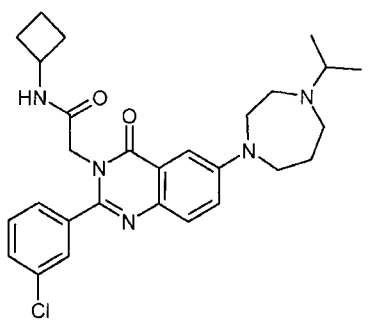
MS (ESI) m/z : 510/512 ($[M+H]^+$) (from INTERMEDIATE IX.14).

EXAMPLE 9v: 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-ethylacetamide



MS (ESI) m/z : 482/484 ($[M+H]^+$) (from INTERMEDIATE IX.14).

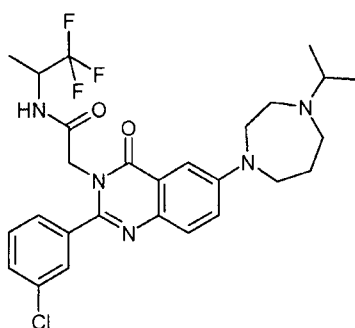
EXAMPLE 9w: 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-cyclobutylacetamide



MS (ESI) m/z : 508/510 ($[M+H]^+$) (from INTERMEDIATE IX.14).

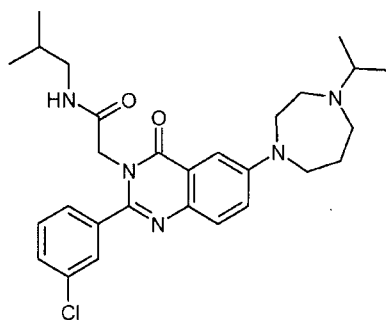
EXAMPLE 9x: 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-(2,2,2-trifluoro-1-methylethyl)acetamide

127



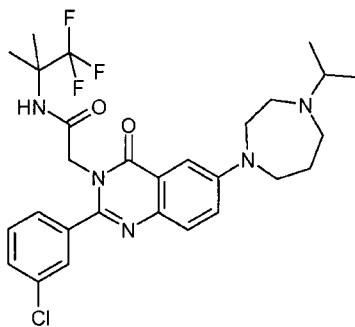
MS (ESI) m/z : 550/552 ($[M+H]^+$) (from INTERMEDIATE IX.14).

EXAMPLE 9y: 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isobutylacetamide



MS (ESI) m/z : 510/512 ($[M+H]^+$) (from INTERMEDIATE IX.14).

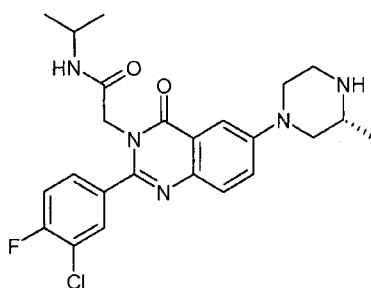
EXAMPLE 9z: 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-(2,2,2-trifluoro-1,1-dimethylethyl)acetamide



MS (ESI) m/z : 564/566 ($[M+H]^+$) (from INTERMEDIATE IX.14).

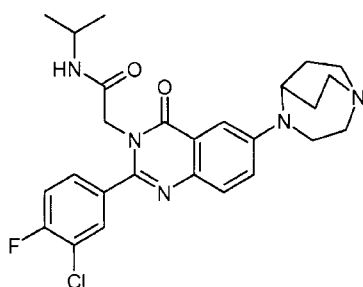
EXAMPLE 9Aa: 2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-3-methylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide

128



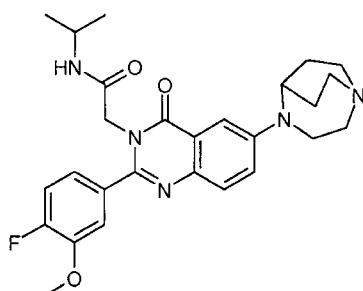
MS (ESI) m/z : 472/474 ($[M+H]^+$) (from INTERMEDIATE IX.8).

EXAMPLE 9Ab: 2-[2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazabicyclo[3.2.2]non-4-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 498/500 ($[M+H]^+$) (from INTERMEDIATE IX.15).

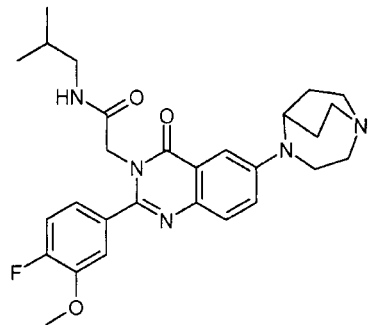
EXAMPLE 9Ac: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 494 ($[M+H]^+$) (from INTERMEDIATE IX.7).

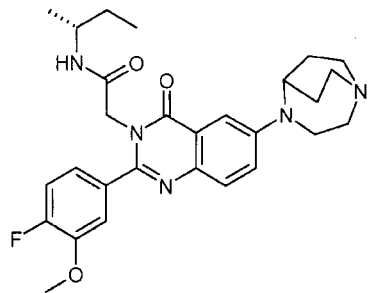
EXAMPLE 9Ad: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isobutylacetamide

129



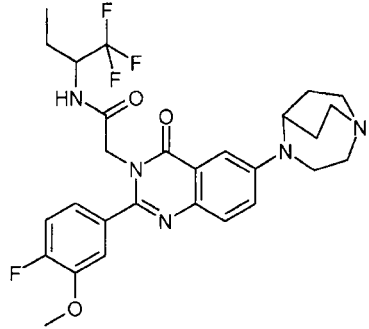
MS (ESI) m/z : 508 ($[M+H]^+$) (from INTERMEDIATE IX.7).

EXAMPLE 9Ae: *N*-((*R*)-*sec*-Butyl)-2-[6-(1,4-diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]acetamide



MS (ESI) m/z : 508 ($[M+H]^+$) (from INTERMEDIATE IX.7).

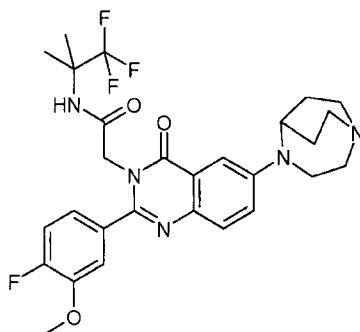
EXAMPLE 9Af: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-(1-trifluoromethylpropyl)acetamide



MS (ESI) m/z : 562 ($[M+H]^+$) (from INTERMEDIATE IX.7).

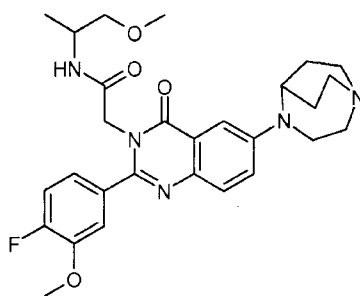
EXAMPLE 9Ag: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-(2,2,2-trifluoro-1,1-dimethylethyl)acetamide

130



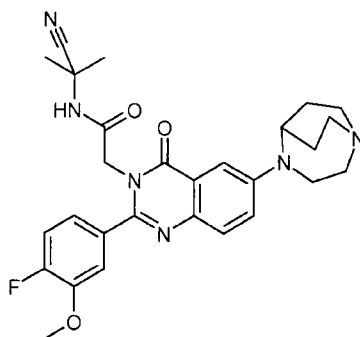
MS (ESI) m/z : 562 ($[M+H]^+$) (from INTERMEDIATE IX.7).

EXAMPLE 9Ah: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-(2-methoxy-1-methylethyl)acetamide



MS (ESI) m/z : 524 ($[M+H]^+$) (from INTERMEDIATE IX.7).

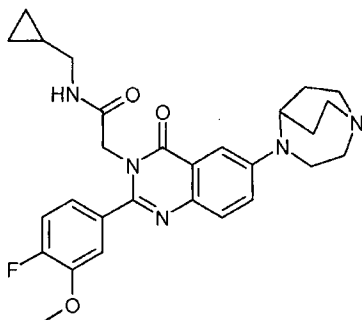
EXAMPLE 9Ai: N-(Cyanodimethyl-methyl)-2-[6-(1,4-diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide



MS (ESI) m/z : 519 ($[M+H]^+$) (from INTERMEDIATE IX.7).

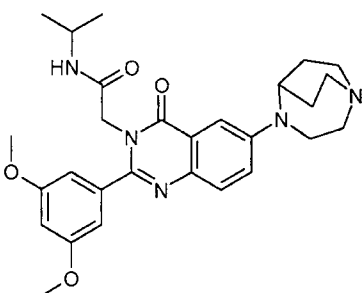
EXAMPLE 9Aj: N-Cyclopropylmethyl-2-[6-(1,4-diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide

131



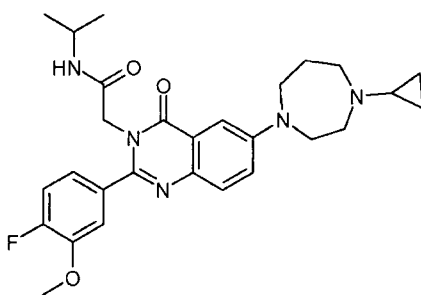
MS (ESI) m/z : 506 ($[M+H]^+$) (from INTERMEDIATE IX.7).

EXAMPLE 9Ak: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(3,5-dimethoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 506 ($[M+H]^+$) (from INTERMEDIATE IX.2).

EXAMPLE 10a: 2-[6-(4-Cyclopropylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



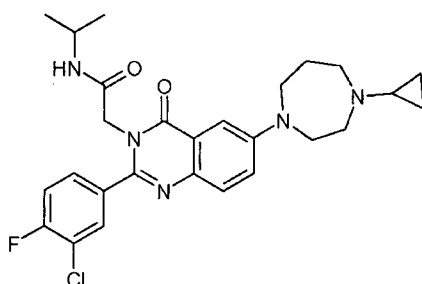
2-(6-(1,4-Diazepan-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxoquinazolin-3(4H)-yl)-N-isopropylacetamide (EXAMPLE 1i) (50 mg, 0.107 mmol), macroporous triethylammonium methylpolystyrene cyanoborohydride (70 mg, 0.107 mmol), acetonitrile (1.5 mL) and AcOH

(0.3 mL) were combined under a nitrogen atmosphere. (1-Ethoxycyclopropoxy)trimethylsilane (19 mg, 0.04 mL, 0.107 mmol) was added and the reaction mixture stirred at room temperature for 48 h. Solvent was evaporated under reduced pressure. The residue was dissolved in 2M NH_3/MeOH and purified by preparative HPLC. This afforded 2-[6-(4-cyclopropylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 10a) (3 mg, 0.0039 mmol, 6%).

Data for 2-[6-(4-cyclopropylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide (EXAMPLE 10a): MS (ESI) m/z : 508 ($[\text{M}+\text{H}]^+$).

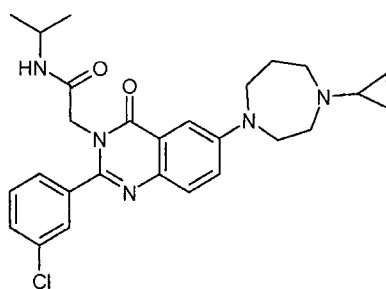
Similarly prepared were:

EXAMPLE 10b: 2-[2-(3-Chloro-4-fluorophenyl)-6-(4-cyclopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



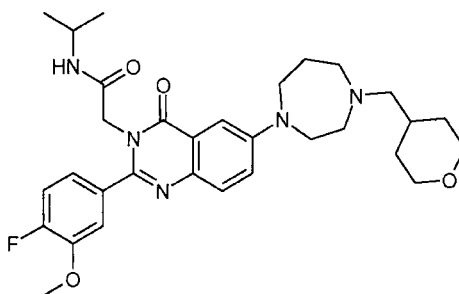
MS (ESI) m/z : 512/514 ($[\text{M}+\text{H}]^+$) (from EXAMPLE 1e).

EXAMPLE 10c: 2-[2-(3-Chlorophenyl)-6-(4-cyclopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 495/497 ($[\text{M}+\text{H}]^+$) (from EXAMPLE 1b).

EXAMPLE 11a: 2-[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-[4-(tetrahydropyran-4-ylmethyl)perhydro-1,4-diazepin-1-yl]-4H-quinazolin-3-yl]-N-isopropylacetamide

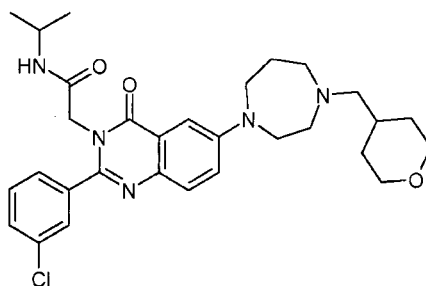


2-(6-(1,4-Diazepan-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxoquinazolin-3(4H)-yl)-N-isopropylacetamide (EXAMPLE 1i) (30 mg, 0.064 mmol), (tetrahydro-2H-pyran-4-yl)methyl 4-methylbenzenesulfonate (35 mg, 0.128 mmol) and DIPEA (17 mg, 21 μ l, 0.128 mmol) were dissolved in DMF (1 mL) and stirred at room temperature overnight. Purification by preparative HPLC afforded 2-{2-(4-fluoro-3-methoxyphenyl)-4-oxo-6-[4-(tetrahydropyran-4-ylmethyl)perhydro-1,4-diazepin-1-yl]-4H-quinazolin-3-yl}-N-isopropylacetamide (EXAMPLE 11a) (5 mg, 0.0088 mmol, 14%).

Data for 2-{2-(4-fluoro-3-methoxyphenyl)-4-oxo-6-[4-(tetrahydropyran-4-ylmethyl)perhydro-1,4-diazepin-1-yl]-4H-quinazolin-3-yl}-N-isopropylacetamide (EXAMPLE 11a): MS (ESI) m/z : 566 ($[M+H]^+$).

Similarly prepared were:

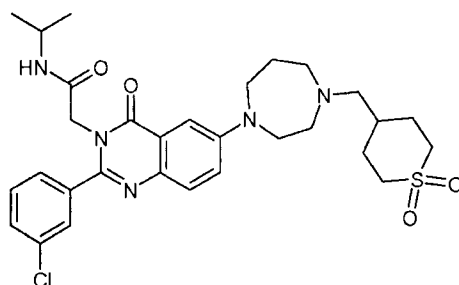
EXAMPLE 11b: 2-{2-(3-Chlorophenyl)-4-oxo-6-[4-(tetrahydropyran-4-ylmethyl)perhydro-1,4-diazepin-1-yl]-4H-quinazolin-3-yl}-N-isopropylacetamide



MS (ESI) m/z : 553/555 ($[M+H]^+$) (from EXAMPLE 1b).

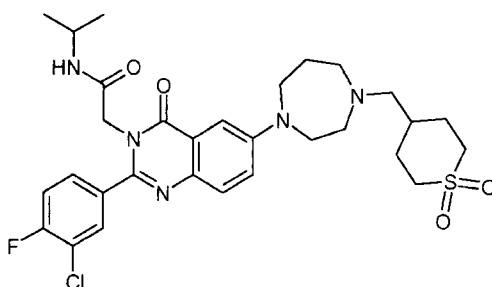
EXAMPLE 11c: 2-{2-(3-Chlorophenyl)-6-[4-(1,1-dioxohexahydro-1 λ ⁶-thiopyran-4-ylmethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl}-N-isopropylacetamide

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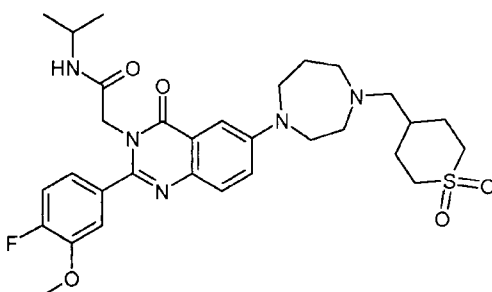
MS (ESI) m/z : 600/602 ($[M+H]^+$) (from EXAMPLE 1b).

EXAMPLE 11d: 2-(2-(3-Chloro-4-fluorophenyl)-6-[4-(1,1-dioxohexahydro-1λ⁶-thiopyran-4-ylmethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



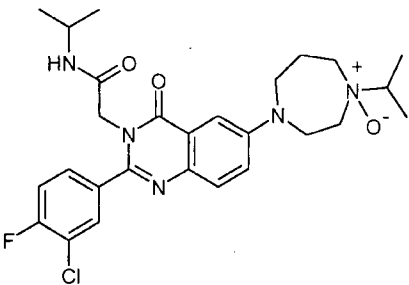
MS (ESI) m/z : 619/621 ($[M+H]^+$) (from EXAMPLE 1e).

EXAMPLE 11e: 2-(2-(4-Fluoro-3-methoxyphenyl)-6-[4-(1,1-dioxohexahydro-1λ⁶-thiopyran-4-ylmethyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide



MS (ESI) m/z : 615/617 ($[M+H]^+$) (from EXAMPLE 1i).

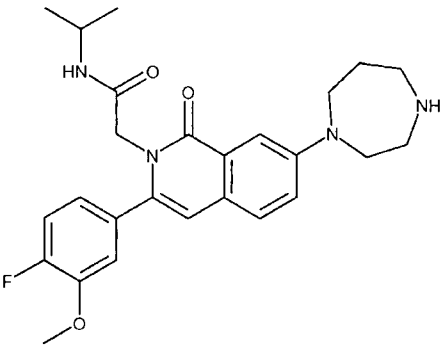
EXAMPLE 12a: 4-(2-(3-Chloro-4-fluorophenyl)-3-(2-(isopropylamino)-2-oxoethyl)-4-oxo-3,4-dihydroquinazolin-6-yl)-1-isopropyl-1,4-diazepane 1-oxide



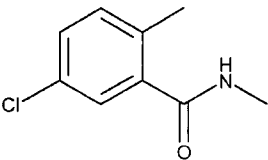
3-Chloroperoxybenzoic acid (19 mg, 0.078 mmol) was added to a stirred solution of 2-[2-(3-chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide (EXAMPLE 6k) (40 mg, 0.078 mmol) in DCM (5 mL). The reaction mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with DCM (10 mL) and washed with aqueous sodium bicarbonate solution (10 mL). The organic phase was dried (Na₂SO₄), concentrated under reduced pressure and purified by chromatography on silica gel with a gradient of DCM to DCM:MeOH (4:1, v/v) as eluent to afford 4-(2-(3-chloro-4-fluorophenyl)-3-(2-(isopropylamino)-2-oxoethyl)-4-oxo-3,4-dihydroquinazolin-6-yl)-1-isopropyl-1,4-diazepane 1-oxide (EXAMPLE 12a) (25 mg, 0.047 mmol, 61%).

Data for 2-(4-(2-(3-chloro-4-fluorophenyl)-3-(2-(isopropylamino)-2-oxoethyl)-4-oxo-3,4-dihydroquinazolin-6-yl)-1-isopropyl-1,4-diazepane 1-oxide (EXAMPLE 12a): MS (ESI) *m/z*: 530 (M⁺).

EXAMPLE 13a: 2-[3-(4-Fluoro-3-methoxyphenyl)-1-oxo-7-perhydro-1,4-diazepin-1-yl]-1*H*-isoquinolin-2-yl]-*N*-isopropylacetamide



a) 5-Chloro-2,*N*-dimethylbenzamide

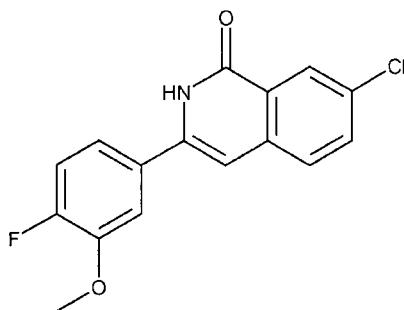


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5-Chloro-2-methylbenzoic acid (9.16 g, 53.7 mmol) and thionyl chloride (25.6 g, 15.7 ml, 215 mmol) were heated at reflux temperature for 1.5 h. Solvent was evaporated under reduced pressure and the residue dissolved in DCM (55 mL). Methylamine (aq.) (40%) (12.51 g, 13.90 mL, 161 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was extracted with EtOAc (50 mL), washed with brine (50 mL), dried (Na₂SO₄) and evaporated in *vacuo* to afford 5-chloro-2,N-dimethylbenzamide (8.79 g, 47.9mmol, 89%) as a white solid. This was used directly in the next stage without purification

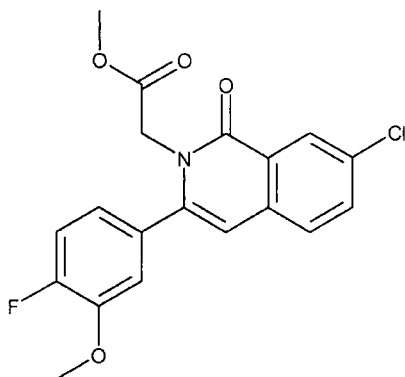
Data for 5-chloro-2,N-dimethylbenzamide: MS (ESI) *m/z*: 184 ([M+H]⁺).

b) 7-Chloro-3-(4-fluoro-3-methoxyphenyl)-2H-isoquinolin-1-one



A solution of 5-chloro-2,N-dimethylbenzamide (5.0 g, 27.2 mmol) in THF (28 mL) was cooled to -78 °C and a solution of 2M lithium diisopropylamide in THF (40.8 mL, 82 mmol) diluted with THF (68 mL) added. 4-Fluoro-3-methoxybenzonitrile (4.12 g, 27.2 mmol) in THF (28 mL) was added and the mixture stirred at -78 °C for 2.5 h. Sat. NH₄Cl (aq.) was added and the mixture extracted with EtOAc (2 X 50 mL). A precipitate formed in the aqueous which was collected by filtration to afford 7-chloro-3-(4-fluoro-3-methoxyphenyl)-2H-isoquinolin-1-one (3.74 g, 12.3 mmol, 45%).

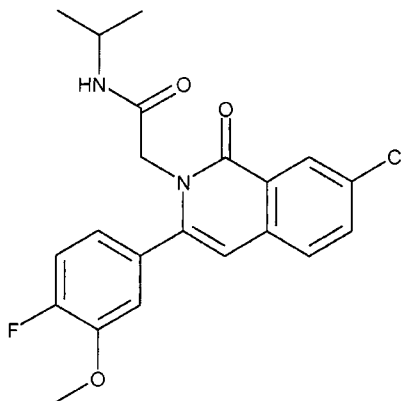
c) [7-Chloro-3-(4-fluoro-3-methoxyphenyl)-1-oxo-1H-isoquinolin-2-yl]acetic acid methyl ester



7-Chloro-3-(4-fluoro-3-methoxyphenyl)-2H-isoquinolin-1-one (500 mg, 1.646 mmol) and potassium carbonate (455 mg, 3.29 mmol) were combined and DMF (5 mL) added to give a white suspension. The reaction mixture was stirred for 30 min at room temperature. Methyl bromoacetate (756 mg, 0.456 mL, 4.94 mmol) was added and stirring continued for a further 2 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (2 x 10mL), brine (10mL) and the organic layer dried (MgSO_4) and concentrated under reduced pressure. This afforded [7-chloro-3-(4-fluoro-3-methoxyphenyl)-1-oxo-1H-isoquinolin-2-yl]acetic acid methyl ester still containing DMF (~2 mL). This solution was taken onto the next step without further purification.

Data for [7-chloro-3-(4-fluoro-3-methoxyphenyl)-1-oxo-1H-isoquinolin-2-yl]acetic acid methyl ester: MS (ESI) m/z : 376/378 ($[\text{M}+\text{H}]^+$).

d) 2-[7-Chloro-3-(4-fluoro-3-methoxyphenyl)-1-oxo-1H-isoquinolin-2-yl]-N-isopropylacetamide

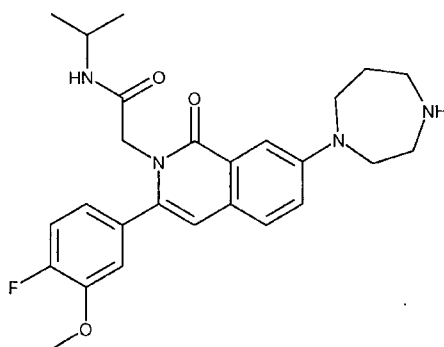


[7-Chloro-3-(4-fluoro-3-methoxyphenyl)-1-oxo-1H-isoquinolin-2-yl]acetic acid methyl ester (crude product from the previous experiment) was dissolved in NMP (4 mL). Propan-2-amine (973 mg, 1.402 mL, 16.46 mmol) was added dropwise with stirring and an exotherm

was observed. LCMS analysis indicated that the reaction had gone to about 75% completion. Further propan-2-amine (348 mg, 0.5 mL, 5.88 mmol) was added and the reaction mixture heated at reflux temperature for 5 min followed by stirring at room temperature overnight. The resultant precipitate was filtered and washed with diethyl ether (150 mL). This afforded product contaminated with isopropylamine. The solid was dissolved in DCM (50 mL) and washed with water (2 x 10 mL). The organics were dried (MgSO₄) and concentrated to afford 2-[7-chloro-3-(4-fluoro-3-methoxyphenyl)-1-oxo-1H-isoquinolin-2-yl]-N-isopropylacetamide (300 mg, 0.745 mmol).

Data for 2-[7-chloro-3-(4-fluoro-3-methoxyphenyl)-1-oxo-1H-isoquinolin-2-yl]-N-isopropylacetamide: MS (ESI) *m/z*: 404/406 ([M+H]⁺).

e) 2-[3-(4-Fluoro-3-methoxyphenyl)-1-oxo-7-perhydro-1,4-diazepin-1-yl-1H-isoquinolin-2-yl]-N-isopropylacetamide



Tert-butyl 1-homopiperazinecarboxylate (66 mg, 0.07 mL, 0.330 mmol) was added to potassium *tert*-butoxide (67 mg, 0.601 mmol), [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-IPr catalyst) (20 mg, 0.030 mmol) and 2-[7-chloro-3-(4-fluoro-3-methoxyphenyl)-1-oxo-1H-isoquinolin-2-yl]-N-isopropylacetamide (121 mg, 0.300 mmol) in toluene (3 mL). The reaction mixture was heated at 100 °C for 2 h, after which time the reaction mixture was cooled and quenched by addition of sat. NH₄Cl (aq.) (0.2 mL). Stirring was continued for 1 h at room temperature. MeOH (3 mL) was added and stirring continued for a further 30 min.

This solution was added to a pre-acidified SCX cartridge and eluted with MeOH, followed by 2M NH₃/MeOH. TLC analysis indicated that the desired product was present in the basic fractions, as well as de-boc'ed material. Solvent was evaporated under reduced pressure. The resultant greenish gum was dissolved in DCM (10 mL), cooled to 0 °C and trifluoroacetic acid (0.2 mL) added.

The reaction mixture was stirred at 0 °C for 3 h. Solvent was evaporated under reduced pressure and crude product purified on SCX eluting product with 2M NH₃/MeOH. Crude product was further purified by preparative LCMS (basic conditions) to afford 2-[3-(4-fluoro-3-methoxyphenyl)-1-oxo-7-perhydro-1,4-diazepin-1-yl-1H-isoquinolin-2-yl]-N-isopropylacetamide (2 mg, 0.004 mmol, 13%).

Data for 2-[3-(4-fluoro-3-methoxyphenyl)-1-oxo-7-perhydro-1,4-diazepin-1-yl-1H-isoquinolin-2-yl]-N-isopropylacetamide: MS (ESI) m/z: 467 ([M+H]⁺).

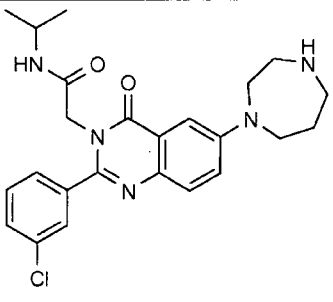
EXAMPLE 14:

Chinese Hamster Ovary (CHO) cells stably expressing the human V₃ receptor were incubated to equilibrium with the test compound (at a final assay concentration of 10⁻¹⁰ mol.L⁻¹ to 10⁻⁵ mol.L⁻¹) and [³H]AVP (at a final assay concentration of 2.5 x 10⁻⁹ mol.L⁻¹). Throughout the concentration of dimethylsulphoxide (DMSO) did not exceed 0.1% (v/v). After washing with ice-cold phosphate buffered saline (PBS), scintillation fluid was added and the plates counted on a Topcount NXT apparatus.

A sigmoidal dose response curve (non-linear regression, variable slope) was plotted as concentration of test compound (mol.L⁻¹) against percentage specific binding of [³H]AVP and a K_i value was calculated. Each determination was carried out in triplicate and repeated on at least 3 separate occasions

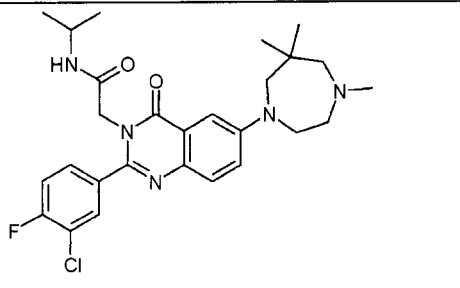
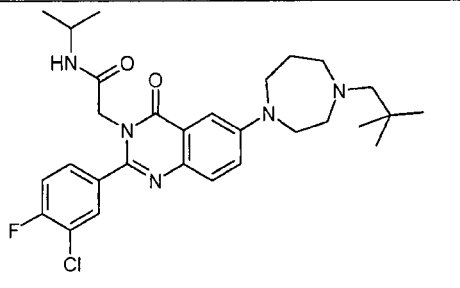
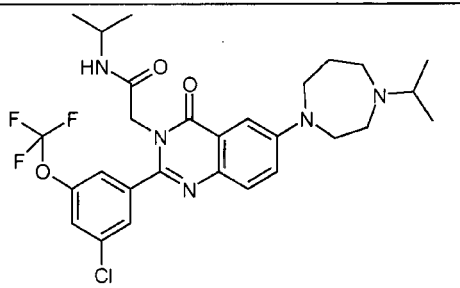
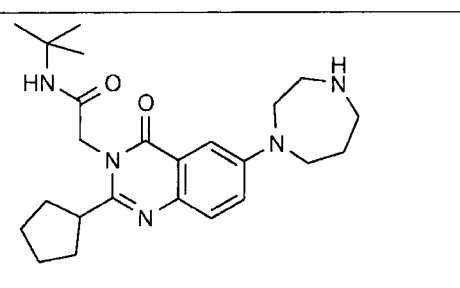
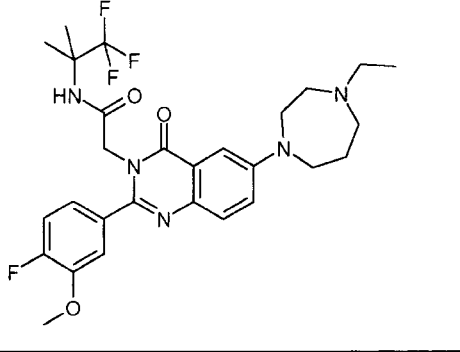
Table 1 shows the binding activity obtained for some representative compounds of the invention.

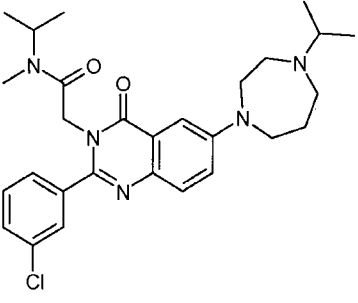
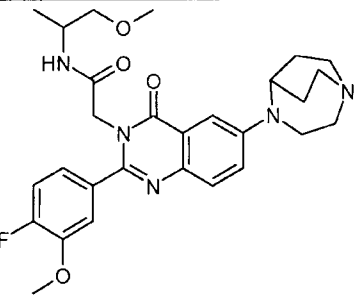
Table 1 V₃ binding activity for compounds according to the invention

EXAMPLE 1b: 2-[2-(3-Chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4H-quinazolin-3-yl]-N-isopropylacetamide		+++
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EXAMPLE 2b: <i>N</i> -Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-piperazin-1-yl]-4 <i>H</i> -quinazolin-3-yl]acetamide		++
EXAMPLE 3c: 2-[6-(3-Dimethylaminomethylpiperidin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4 <i>H</i> -quinazolin-3-yl]- <i>N</i> -isopropylacetamide		++
EXAMPLE 3f: <i>N</i> -Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-((<i>R</i>)-3-piperidin-1-ylmethylpiperidin-1-yl)-4 <i>H</i> -quinazolin-3-yl]acetamide		+++
EXAMPLE 4c: <i>N</i> -Isopropyl-2-[2-(3-methoxyphenyl)-4-oxo-6-[4-(2,2,2-trifluoroethyl)perhydro-1,4-diazepin-1-yl]-4 <i>H</i> -quinazolin-3-yl]acetamide		+
EXAMPLE 4d: <i>N</i> -Isopropyl-2-[6-[4-(2-methoxyethyl)perhydro-1,4-diazepin-1-yl]-2-(3-methoxyphenyl)-4-oxo-4 <i>H</i> -quinazolin-3-yl]acetamide		+++

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EXAMPLE 5s: 2-[2-(3-Chloro-4-fluorophenyl)-4-oxo-6-(4,6,6-trimethylperhydro-1,4-diazepin-1-yl)-4 <i>H</i> -quinazolin-3-yl]- <i>N</i> -isopropylacetamide		+++
EXAMPLE 5Ac: 2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(2,2-dimethylpropyl)perhydro-1,4-diazepin-1-yl]-4-oxo-4 <i>H</i> -quinazolin-3-yl]- <i>N</i> -isopropylacetamide		+++
EXAMPLE 6w: 2-[2-(3-Chloro-5-trifluoromethoxyphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4 <i>H</i> -quinazolin-3-yl]- <i>N</i> -isopropylacetamide		+++
EXAMPLE 7a: <i>N</i> - <i>tert</i> -Butyl-2-(2-cyclopentyl-4-oxo-6-perhydro-1,4-diazepin-1-yl)-4 <i>H</i> -quinazolin-3-yl-acetamide		++
EXAMPLE 9h: 2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4 <i>H</i> -quinazolin-3-yl]- <i>N</i> -(2,2,2-trifluoro-1,1-dimethylethyl)acetamide		+++

EXAMPLE 9u: 2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4 <i>H</i> -quinazolin-3-yl]- <i>N</i> -isopropyl- <i>N</i> -methylacetamide		++
EXAMPLE 9Ah: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4 <i>H</i> -quinazolin-3-yl]- <i>N</i> -(2-methoxy-1-methylethyl) acetamide		++

+++ 0-10nM

++ 10-100nM

+ 100nM-1uM

The ability of compounds of the invention to act as V₃ antagonists in a physiologically relevant system was determined by measuring their ability to block the release of adrenocorticotrophic hormone (ACTH) from anterior pituitary corticotrophs in response to treatment with arginine vasopressin (AVP).

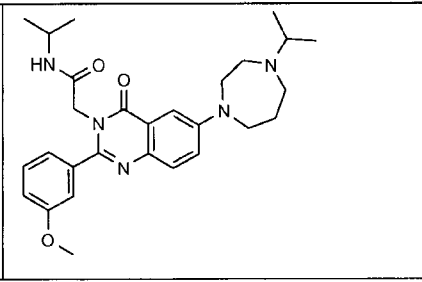
Anterior pituitary corticotrophs were prepared from adult female Sprague-Dawley rats and seeded into 48 well plates. The cells were cultured for 4 days prior to exposure to compound. Test compounds were prepared at 10⁻⁵ mol.L⁻¹ in 100% DMSO. Cells were exposed to a dose response of test compounds for 20 minutes (10⁻⁸ mol.L⁻¹ – 10⁻⁵ mol.L⁻¹). The final concentration of DMSO in the assay was kept constant at 0.3%. The cells were then exposed to 3 x 10⁻⁹ mol.L⁻¹ AVP for 120 minutes. Supernatants were harvested and stored at -20°C. ACTH levels were subsequently measured by ELISA following the manufacturer's instructions (Immunodiagnostic systems, UK (Cat No. DX-SDX018)). Each treatment was carried out in quadruplicate and a mean value obtained for the amount of ACTH released. The degree of antagonism was then calculated as a percentage of the amount of ACTH released by agonist alone after adjustment for basal levels of ACTH. A pIC₅₀ was calculated by fitting a Sigmoidal dose response (variable slope) curve with a non-

LS4

linear (fit) to the data using the software package GraphPad prism. Each determination was repeated on at least 3 separate occasions

Table 2 shows the activity obtained for some representative compounds of the invention.

Table 2 V₃ receptor antagonism in isolated rat anterior pituitary cells for compounds according to the invention

EXAMPLE 4b: <i>N</i> -Isopropyl-2-[6-(4-isopropylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4 <i>H</i> -quinazolin-3-yl]acetamide		++
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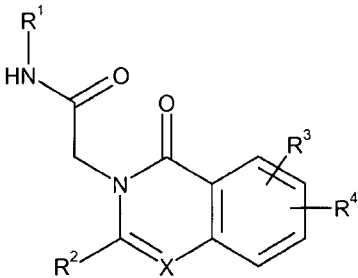
++ 10-100nM

+ 100nM-1uM

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What is claimed:

1. A quinazolinone or isoquinolinone derivative of formula I,



formula I

wherein

R¹ is C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, said C₁₋₆alkyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkylC₁₋₃alkyl being optionally substituted with hydroxy, C₁₋₆alkyloxy, cyano or one or more halogens,;

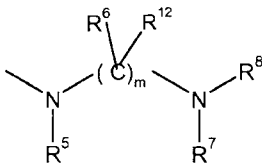
R² is C₆₋₁₀aryl optionally substituted with one to three substituents selected from halogen, hydroxy, cyano, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkyloxy and C₃₋₆cycloalkyloxy, said C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkyloxy and C₃₋₆cycloalkyloxy being optionally substituted with one or more halogens;

or R² is a 5-10 membered heteroaryl ring system comprising a heteroatom selected from N, O and S and optionally substituted with a substituent selected from methyl, C₁₋₆alkyloxy and halogen;

or R² is C₄₋₇cycloalkyl;

R³ is an optional substituent selected from C₁₋₆alkyl, C₁₋₆alkyloxy and halogen, said C₁₋₆alkyl and C₁₋₆alkyloxy being optionally substituted with one or more halogens;

R⁴ is a group located at the 6- or 7- position of the quinazolinone or isoquinolinone ring having the formula II



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formula II

wherein

R⁵ together with one of R⁶ forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR⁹, said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo or R⁵ together with one of R⁷ and R⁸ forms a 6-8 membered heterocyclic ring optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo;

Each R⁶ is independently H, halogen or C₁₋₄alkyl optionally substituted with halogen or SO₂CH₃ or one of R⁶ together with R⁵ forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR⁹, said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo;

R⁷ and R⁸ are independently H, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkylC₁₋₃alkyl, cyanoC₁₋₃alkyl, C₆₋₁₀aryl, C₆₋₁₀arylC₁₋₃alkyl, C₁₋₃alkyloxyC₁₋₃alkyl or C₁₋₆acyl said C₁₋₆alkyl, C₃₋₆cycloalkyl and C₃₋₆cycloalkylC₁₋₃alkyl being optionally substituted with hydroxy, 1 or more halogens or diC₁₋₂alkylamino;

or R⁷ and R⁸ together with the nitrogen to which they are bonded form a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR¹⁰, said heterocyclic ring being optionally substituted with one or two substituents selected from C₁₋₆alkyl, halogen, hydroxy, C₁₋₆alkyloxy, cyano and COOR¹¹;

or one of R⁷ and R⁸ is Y, CH₂Y or CH₂CH₂Y, wherein Y is a 4-6 membered saturated heterocyclic ring comprising a heterocyclic moiety selected from O, SO₂ and NR¹⁰, said ring being optionally substituted with 1-2 substituents selected from methyl or halogen;

or one of R⁷ or R⁸ together with R⁵ forms a 6-8 membered heterocyclic ring being optionally substituted with one or two substituents selected from methyl, halogen, hydroxy and oxo

or one of R⁷ and R⁸ together with R¹² forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR¹³, said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, hydroxy and oxo;

R^9 and R^{10} are independently H, C_{1-6} alkyl or C_{1-6} acyl;

R^{11} is H or C_{1-6} alkyl;

Each R^{12} is independently H or C_{1-4} alkyl or one of R^{12} together with one of R^7 or R^8 forms a 4-8 membered saturated or unsaturated heterocyclic ring optionally comprising a further heteroatomic moiety selected from O, S and NR^{13} , said heterocyclic ring being optionally substituted with one or two substituents selected from methyl, hydroxy and oxo;

R^{13} is H, C_{1-6} alkyl or C_{1-6} acyl;

m is 2-3 and

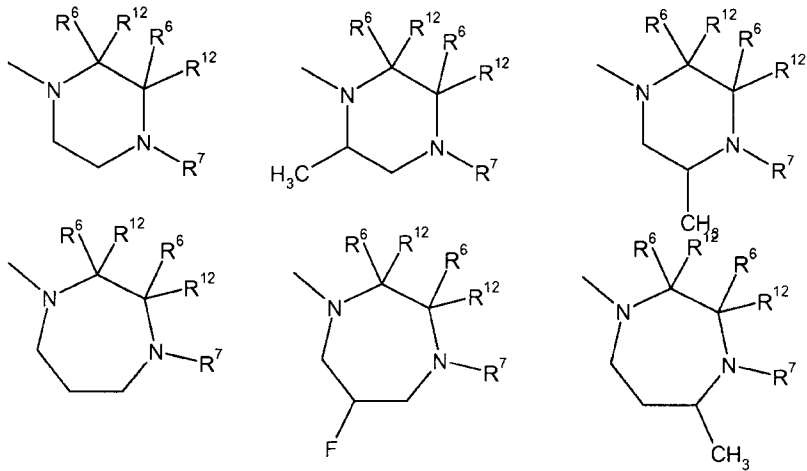
X is N or CH

or a pharmaceutically acceptable salt or solvate thereof.

2. The quinazolinone or isoquinolinone derivative according to claim 1, wherein R^1 is isopropyl, isobutyl, tertiary-butyl, cyclopropylmethyl, cyclobutyl, 2,2,2-trifluoro-1-methylethyl or 2,2,2-trifluoro-1,1-dimethylethyl.

3. The quinazolinone or isoquinolinone derivative according to claim 1 or claim 2, wherein R^2 is a substituted phenyl ring selected from 3-chlorophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-trifluoromethoxyphenyl, 3-chloro-4-fluorophenyl, 4-fluoro-3-methoxyphenyl and 3,5-dimethoxyphenyl.

4. The quinazolinone or isoquinolinone derivative according to any one of claims 1-3, wherein R^4 is a group selected from



wherein R^6 , R^7 and R^{12} have the previously defined meanings

5. The quinazolinone derivative according to any one of claims 1-4, wherein R⁴ is a substituent at the 6-position of the quinazolinone.
6. The quinazolinone derivative according to any one of claims 1-5, wherein X is N.
7. A quinazolinone derivative selected from:
- 2-[2-(3-Chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- N*-*tert*-Butyl-2-[2-(3-chlorophenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl-4*H*-quinazolin-3-yl]acetamide;
- N*-*tert*-Butyl-2-(2-(3-chloro-4-fluorophenyl)-6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)acetamide;
- 2-(2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)-*N*-isopropylacetamide;
- 2-(2-(3-Chloro-4-fluorophenyl)-6-(3-methyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl)-*N*-isopropylacetamide;
- 2-[2-(3-Chloro-4-fluorophenyl)-6-(3-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- 2-[2-(3-Chloro-4-fluorophenyl)-6-(dimethylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- 2-[6-(Dimethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- 2-[2-(3-Chloro-4-fluorophenyl)-6-((*S*)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- 2-[2-(3-Chlorophenyl)-6-((*S*)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- 2-[2-(4-Fluoro-3-methoxyphenyl)-6-((*S*)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- 2-[2-(3-Chloro-4-fluorophenyl)-6-((*R*)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- 2-[2-(3-Chlorophenyl)-6-((*R*)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;
- 2-[2-(4-Fluoro-3-methoxyphenyl)-6-((*R*)-3-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4*H*-quinazolin-3-yl]-*N*-isopropylacetamide;

2-[2-(3-Chlorophenyl)-6-(4-methylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chlorophenyl)-4-oxo-6-(4-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide;

N-tert-Butyl-2-[6-(4-ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide;

2-[2-(3-Chlorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[6-(4-Ethylperhydro-1,4-diazepin-1-yl)-2-(4-fluoro-3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(4-Fluoro-3-methoxyphenyl)-4-oxo-6-(4-propylperhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-(4-ethylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

N-Isopropyl-2-[6-(4-isopropylperhydro-1,4-diazepin-1-yl)-2-(3-methoxyphenyl)-4-oxo-4H-quinazolin-3-yl]acetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-5-trifluoromethylphenyl)-4-oxo-6-perhydro-1,4-diazepin-1-yl)-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3,5-Dimethoxyphenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(1-cyclopropylethyl)perhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(4-Fluoro-3-methoxyphenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-[4-(2-hydroxyethyl)perhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-(1,4-diazabicyclo[3.2.2]non-4-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(4-Fluoro-3-methoxyphenyl)-6-(4-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-(4-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-((S)-3-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chloro-4-fluorophenyl)-6-((R)-3-isopropylpiperazin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(3,5-dimethoxyphenyl)-4-oxo-4H-quinazolin-3-yl]-N-isopropylacetamide;

2-[2-(3-Chlorophenyl)-6-(4-isopropylperhydro-1,4-diazepin-1-yl)-4-oxo-4H-quinazolin-3-yl]-N-(2,2,2-trifluoro-1,1-dimethylethyl)acetamide;

N-Isopropyl-2-(6-(4-isopropyl-1,4-diazepan-1-yl)-2-(3-methoxyphenyl)-4-oxoquinazolin-3(4H)-yl)acetamide;

2-(2-(3-Chlorophenyl)-6-(4-cyclopropylmethyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl)-N-isopropylacetamide and

N-tert-Butyl-2-(2-(3-chlorophenyl)-6-(4-isopropyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl)acetamide

or a pharmaceutically acceptable salt or solvate thereof.

8. A quinazolinone derivative according to any one of claims 1-7 or an isoquinolinone derivative according to any one of claims 1-4 for use in therapy.

9. A pharmaceutical composition comprising a quinazolinone derivative according to any one of claims 1-7 or an isoquinolinone derivative according to any one of claims 1-4 in admixture with one or more pharmaceutically acceptable auxiliaries.

10. Use of a quinazolinone derivative according to any one of claims 1-7 or an isoquinolinone derivative according to any one of claims 1-4 for the manufacture of a medicament for the treatment or prevention of disorders or diseases influenced by modulation of the activity of the HPA axis.

11. Use according to claim 10, wherein the medicament is for the treatment or prevention of stress related disorders or depression.

DERIVADOS DE QUINAZOLINONA E ISOQUINOLINONA ACETAMIDA

MEMORIA DESCRIPTIVA

La presente invención se refiere a derivados de quinazolinona e isoquinolinona, a composiciones farmacéuticas que comprenden estos compuestos y a su uso en terapia, en particular a su uso para la fabricación de un medicamento para el tratamiento o prevención de trastornos o enfermedades influenciadas por la modulación de la actividad del eje HPA.

El eje hipotálamo-pituitario-adrenal (HPA) es el eje principal del estrés en los seres humanos y otros mamíferos. Una variedad de estímulos estresantes (y múltiples otras clases de estímulos) provocan la liberación de la hormona ACTH (hormona adrenocorticotrópica) desde la glándula pituitaria anterior. La ACTH entra a la circulación sistémica y actúa sobre la corteza adrenal para promover la síntesis y liberación de la hormona glucocorticoide (donde el glucocorticoide endógeno principal es el cortisol en humanos y la corticosterona en roedores). Los glucocorticoides ejercen un amplio espectro de efectos, cuyo propósito principal es movilizar fuentes de energía para una respuesta exitosa y una eventual adaptación al estímulo estresante.

Una actividad del eje HPA anormalmente elevada en el hombre está asociada con el desarrollo de una variedad de alteraciones siquiátricas, algunas de las cuales tienen una etiología relacionada con el estrés. Niveles elevados de cortisol, que son indicativos de hiperactividad del eje HPA y pérdida de los procesos reguladores normales de retroalimentación negativa, son un hallazgo común en trastornos afectivos y

diversas otras alteraciones siquiátricas, y son utilizados extensamente como herramienta de diagnóstico (Holsboer y colaboradores, *Biol. Psych.*, 1986, **21**, 601-611). Generalmente se considera que la desregulación del eje HPA es un reflejo de vulnerabilidad aumentada y mala adaptación al estrés crónico, y que por lo tanto, el estrés crónico tiene un papel importante en el desarrollo de enfermedades afectivas (Sperry and Carlson, "DSM-IV diagnosis to treatment", 2a. Edición, Taylor & Francis, 1996). Este concepto central es sustentado por evidencia experimental utilizando modelos animales de estrés crónico, donde la función aberrante del HPA se asemeja mucho a la que se ve en situaciones clínicas (De Goeij y colaboradores, *Neuroendocrinology*, 1991, **53**, 150-159; Plotsky y Meaney, *Mol. Brain Res.*, 1993, **18**, 195-200).

Los secretagogos principales para ACTH en humanos y ratas son CRH (hormona liberadora de corticotropina) y AVP (arginina vasopresina). Dentro del eje HPA, estas hormonas peptídicas son sintetizadas por las neuronas parvocelulares del núcleo paraventricular (PVN) del hipotálamo. Los axones de estas neuronas se proyectan hacia la zona externa de la eminencia media, desde donde los productos hormonales entran al sistema portal hipofisiario para bañar las células corticotrópicas que fabrican ACTH. CRH y AVP actúan sinérgicamente en el corticotropo para regular la secreción de ACTH tanto en ratas (Rivier y Vale, *Nature*, 1983, **305**, 325-327) como en el hombre (De Bold y colaboradores, *J. Clin. Invest.*, 1984, **73**, 533-538).

Las acciones de AVP en el corticotropo pituitario son mediadas por el receptor de vasopresina V_3 (o V_{1b}), que es conocido y ha sido clonado (receptor humano: Sugimoto y

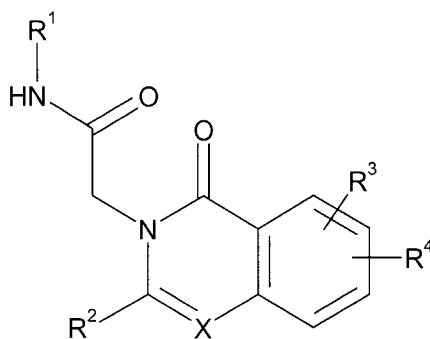
colaboradores, *J. Biol. Chem.*, 1994, **269**, 27088-27092). Un informe de estudios clínicos en pacientes deprimidos en los cuales las respuestas deficientes de ACTH a CRH pudieron ser restablecidas por la administración concomitante de desmopresina (dDAVP, un agonista de AVP con afinidad por V_3), confirma el involucramiento del receptor V_3 en la depresión (Scott y Dinan, *Life Sciences*, 1998, **62**, 1985-1988). Un estudio en roedores con antagonistas péptidos de V_3 no selectivos indica que el receptor V_3 tiene un rol funcional en el control de la liberación de ACTH por la pituitaria (Bernardini y colaboradores, *Neuroendocrinology*, 1994, **60**, 503-508). Por lo tanto, antagonistas de vasopresina se utilizan para modular y normalizar la liberación de ACTH por la pituitaria y la disfunción del eje HPA subsiguiente, en los trastornos del SNC que se caracterizan por mecanismos anormales de retroalimentación negativa del eje HPA.

Además del receptor V_3 , la vasopresina también activa los receptores periféricos, o sea el receptor V_{1a} que se encuentra predominantemente en el tejido hepático y vascular, y el receptor V_2 que se encuentra predominantemente en el tejido renal. La interacción en estos receptores media las acciones presoras y antidiuréticas de la AVP.

A pesar de que hay varios antagonistas de bajo peso molecular no péptidos conocidos que son selectivos para el receptor V_{1a} o el receptor V_2 (para una revisión reciente, véase Freidinger y Pettibone, *Medicinal Research Reviews*, 1997, **17**, 1-16), sólo hay un pequeño número de ligandos no péptidos conocidos con selectividad para el receptor V_3 (véanse por ejemplo, las patentes WO 01/55130 y WO 04/009585). Por lo tanto, existe una

necesidad de otros antagonistas no péptidos selectivos para V_3 que sean seguros y a la vez eficaces.

En un primer aspecto, la presente invención proporciona un derivado de quinazolinona o isoquinolinona de fórmula I:



fórmula I

donde

R^1 es C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{3-6} cicloalquil- C_{1-3} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, estando dichos C_{1-6} alquilo, C_{3-6} cicloalquilo y C_{3-6} cicloalquil- C_{1-3} alquilo opcionalmente sustituidos con hidroxilo, C_{1-6} alquilo, ciano o uno o más halógenos;

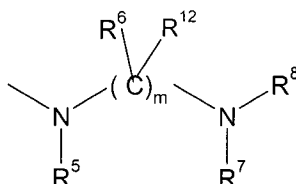
R^2 es C_{6-10} arilo opcionalmente sustituido con uno a tres sustituyentes seleccionados entre halógeno, hidroxilo, ciano, C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{1-6} alquilo y C_{3-6} cicloalquilo, estando dichos C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{1-6} alquilo y C_{3-6} cicloalquilo opcionalmente sustituidos con uno o más halógenos;

o R^2 es un sistema de anillo heteroarilo de 5-10 miembros que comprende un heteroátomo seleccionado entre N, O y S, y está opcionalmente sustituido con un sustituyente seleccionado entre metilo, C_{1-6} alquilo y halógeno;

o R^2 es C_{4-7} cicloalquilo;

R^3 es un sustituyente opcional seleccionado entre C_{1-6} alquilo, C_{1-6} alquiloxi y halógeno, estando dichos C_{1-6} alquilo y C_{1-6} alquiloxi opcionalmente sustituidos con uno o más halógenos;

R^4 es un grupo ubicado en la posición 6 ó 7 del anillo quinazolinona o isoquinolinona y tiene la fórmula II:



fórmula II

donde

R^5 junto con uno de R^6 forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^9 , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo, o R^5 junto con uno de R^7 y R^8 forman un anillo heterocíclico de 6-8 miembros opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo;

cada R^6 es independientemente H, halógeno o C_{1-4} alquilo opcionalmente sustituido con halógeno o SO_2CH_3 , o uno de R^6 junto con R^5 forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^9 , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos

sustituyentes seleccionados entre metilo, halógeno, hidroxí y oxo;

R^7 y R^8 son independientemente H, C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{3-6} cicloalquil C_{1-3} alquilo, ciano C_{1-3} alquilo, C_{6-10} arilo, C_{6-10} aril C_{1-3} alquilo, C_{1-3} alquiloxi C_{1-3} alquilo o C_{1-6} acilo, estando dichos C_{1-6} alquilo, C_{3-6} cicloalquilo y C_{3-6} cicloalquil C_{1-3} alquilo opcionalmente sustituidos con hidroxí, 1 o más halógenos o di C_{1-2} alquilamino;

o R^7 y R^8 , junto con el nitrógeno al cual están unidos, forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{10} , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre C_{1-6} alquilo, halógeno, hidroxí, C_{1-6} alquiloxi, ciano y $COOR^{11}$;

o uno de R^7 y R^8 es Y, CH_2Y ó CH_2CH_2Y , donde Y es un anillo heterocíclico saturado de 4-6 miembros que comprende una especie heterocíclica seleccionada entre O, SO_2 y NR^{10} , estando dicho anillo opcionalmente sustituido con 1-2 sustituyentes seleccionados entre metilo o halógeno;

o uno de R^7 o R^8 junto con R^5 forman un anillo heterocíclico de 6-8 miembros que está opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxí y oxo;

o uno de R^7 y R^8 junto con R^{12} forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{13} , estando dicho anillo

heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, hidroxí y oxo;

R^9 y R^{10} son independientemente H, C_{1-6} alquilo o C_{1-6} acilo;

R^{11} es H o C_{1-6} alquilo;

cada R^{12} es independientemente H o C_{1-4} alquilo, o uno de R^{12} junto con uno de R^7 o R^8 forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{13} , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, hidroxí y oxo;

R^{13} es H, C_{1-6} alquilo o C_{1-6} acilo;

m es 2-3; y

X es N ó CH;

o una sal o solvato farmacéuticamente aceptable del mismo.

El término C_{1-6} alquilo, como se usa aquí, representa un grupo alquilo ramificado o no ramificado que tiene 1-6 átomos de carbono. Ejemplos de estos grupos son metilo, etilo, isopropilo, butilo terciario, pentilo y hexilo. De manera similar el término C_{1-2} alquilo, como se usa aquí, representa un grupo alquilo que tiene 1-2 átomos de carbono.

El término C_{2-6} alquenilo, como se usa aquí, representa un grupo alquenilo ramificado o no ramificado que tiene 2-6 átomos de carbono y al menos un doble enlace. Ejemplos de estos grupos son etenilo e isopropenilo.

El término C_{2-6} alquinilo, como se usa aquí, representa un grupo alquinilo ramificado o no ramificado que tiene 2-6

átomos de carbono y al menos un triple enlace. Ejemplos de estos grupos son etinilo y 3-metil-1-butinilo.

El término C_{3-6} cicloalquilo, como se usa aquí, representa un grupo alquilo cíclico ramificado o no ramificado que tiene 3-6 átomos de carbono. Ejemplos de estos grupos son ciclopropilo, ciclopentilo y 2-metilciclopentilo. De manera similar el término C_{4-7} cicloalquilo, como se usa aquí, representa un grupo alquilo cíclico ramificado o no ramificado que tiene 4-7 átomos de carbono.

El término C_{3-6} cicloalquil C_{1-3} alquilo, como se usa aquí, representa un grupo C_{1-3} alquilo que está sustituido con un grupo C_{3-6} cicloalquilo. Ejemplos de estos grupos son ciclopropilmetilo y 2-ciclobutiletilo.

El término ciano C_{1-2} alquilo, como se usa aquí, representa un grupo C_{1-2} alquilo que está sustituido con un grupo ciano. Ejemplos de estos grupos son cianometilo y cianoetilo.

El término di C_{1-2} alquilamino, como se usa aquí, representa un grupo amino que está sustituido con dos grupos C_{1-2} alquilo. Ejemplos de estos grupos son dimetilamina y dietilamina.

El término C_{1-6} alquiloxi, como se usa aquí, representa un grupo alquiloxi ramificado o no ramificado que tiene 1-6 átomos de carbono. Ejemplos de estos grupos son metoxi, etoxi, isopropiloxi y butiloxi terciario.

El término C_{3-6} cicloalquiloxi, como se usa aquí, representa un grupo alquiloxi cíclico ramificado o no ramificado que tiene 3-6 átomos de carbono. Ejemplos de estos grupos son ciclopropiloxi, ciclopentiloxi y 2-metilciclopentiloxi.

El término C_{1-6} acilo, como se usa aquí, representa un grupo acilo derivado de un ácido carboxílico que tiene 1-6 átomos de carbono. El grupo acilo puede comprender un hidrocarburo que puede ser ramificado, no ramificado, saturado o no saturado. Ejemplos de estos grupos incluyen formilo, acetilo, propionilo, acrilóilo y pivalóilo. También están incluidos dentro de la definición de C_{1-6} acilo los grupos derivados de ácidos dicarboxílicos, tales como grupos derivados de ácido malónico.

El término C_{6-10} arilo, como se usa aquí, representa un grupo aromático que tiene 6-10 átomos de carbono. Ejemplos de estos grupos incluyen fenilo y naftilo.

El término C_{6-10} aril C_{1-2} alquilo, como se usa aquí, representa un grupo C_{1-2} alquilo que está sustituido con un grupo C_{6-10} arilo. Ejemplos de estos grupos incluyen bencilo y fenetilo.

El término halógeno, como se usa aquí, representa un flúor, cloro, bromo o yodo.

El término sistema de anillo heteroarilo de 5-10 miembros que comprende un heteroátomo seleccionado entre N, O y S, como se usa aquí, representa un sistema de anillo heteroarilo de 5-10 miembros monocíclico o bicíclico fusionado que comprende un heteroátomo seleccionado entre N, O y S. Ejemplos de estos grupos incluyen furanilo, tienilo, pirrolilo, piridinilo, indolilo, benzotienilo y quinolinilo.

Los ejemplos de anillos heterocíclicos saturados o no saturados de 4-8 miembros formados por R^5 y R^6 junto con el nitrógeno al cual están unidos, y que opcionalmente comprenden una especie heteroatómica adicional seleccionada entre O, S y NR^7 , donde R^5 - R^7 tienen los significados definidos anteriormente,

incluyen piperidina, homopiperidina, morfolina, tiomorfolina, 4-metilpiperazina y tetrahidropiridina.

Los ejemplos de anillos heterocíclicos saturados de 4-6 miembros que comprenden una especie heterocíclica seleccionada entre O, SO₂ y NR¹⁰, incluyen tetrahidropirano y piperidina.

El término solvato, como se usa aquí, se refiere a un complejo de estequiometría variable formado por un solvente y un soluto (en esta invención, un compuesto de fórmula I). Estos solventes no pueden interferir con la actividad biológica del soluto. Los ejemplos de solventes adecuados incluyen agua, metanol, etanol y ácido acético. De preferencia, el solvente usado es un solvente farmacéuticamente aceptable, tal como agua, etanol y ácido acético.

En una modalidad de la presente invención, R¹ es C₁₋₆alquilo, C₃₋₆cicloalquilo o C₃₋₆cicloalquilC₁₋₃alquilo. En otra modalidad, R¹ es C₃₋₄alquilo, C₃₋₄cicloalquilo o C₃₋₄cicloalquilC₁₋₃alquilo. En otra modalidad, R¹ es isopropilo, isobutilo, butilo terciario, ciclopropilmetilo, ciclobutilo, 2,2,2-trifluoro-1-metiletilo o 2,2,2-trifluoro-1,1-dimetiletilo.

En otra modalidad R² es C₆₋₁₀arilo, opcionalmente sustituido con uno a tres sustituyentes seleccionados entre halógeno, hidroxilo, ciano, C₁₋₆alquilo, C₃₋₆cicloalquilo, C₁₋₆alquiloxi y C₃₋₆cicloalquiloxi, estando dichos C₁₋₆alquilo, C₃₋₆cicloalquilo, C₁₋₆alquiloxi y C₃₋₆cicloalquiloxi opcionalmente sustituidos con uno o más halógenos. En otra modalidad R² es un anillo fenilo. En otra modalidad R² es un anillo fenilo 3-sustituido. En otra modalidad R² es un anillo fenilo 3-sustituido, que está sustituido con uno a tres sustituyentes seleccionados entre cloro, flúor, C₁₋₂alquilo,

trifluorometilo, C_{1-3} alquilo, C_{1-4} cicloalquilo y trifluorometoxi. En otra modalidad, R^2 es un anillo fenilo sustituido seleccionado entre 3-clorofenilo, 3-fluorofenilo, 3-metoxifenilo, 3-trifluorometoxifenilo, 3-cloro-4-fluorofenilo, 4-fluoro-3-metoxifenilo y 3,5-dimetoxifenilo.

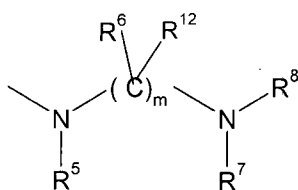
En otra modalidad, R^2 es un sistema de anillo heteroarilo de 5-10 miembros que comprende un heteroátomo seleccionado entre N, O y S, y está opcionalmente sustituido con un sustituyente seleccionado entre metilo, C_{1-6} alquilo y halógeno. En otra modalidad R^2 es un 2-tienilo, 3-tienilo o 6-indolilo opcionalmente sustituido con cloro o metilo.

En otra modalidad, R^2 es C_{4-7} cicloalquilo.

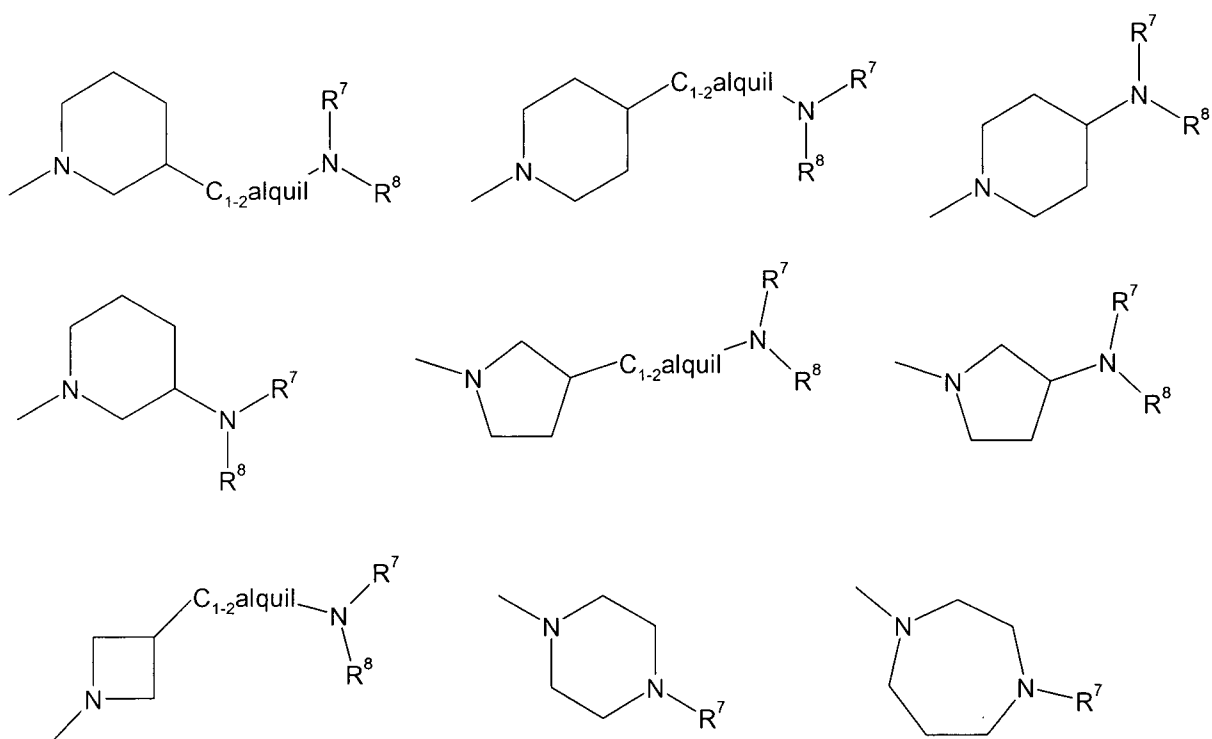
En otra modalidad, R^3 es un sustituyente seleccionado entre cloro, metilo y metoxi. En otra modalidad, R^3 es un sustituyente en la posición 7 de la quinazolinona.

En otra modalidad, R^3 es un sustituyente en la posición 6 de la isoquinolinona.

En otra modalidad, R^4 es el grupo

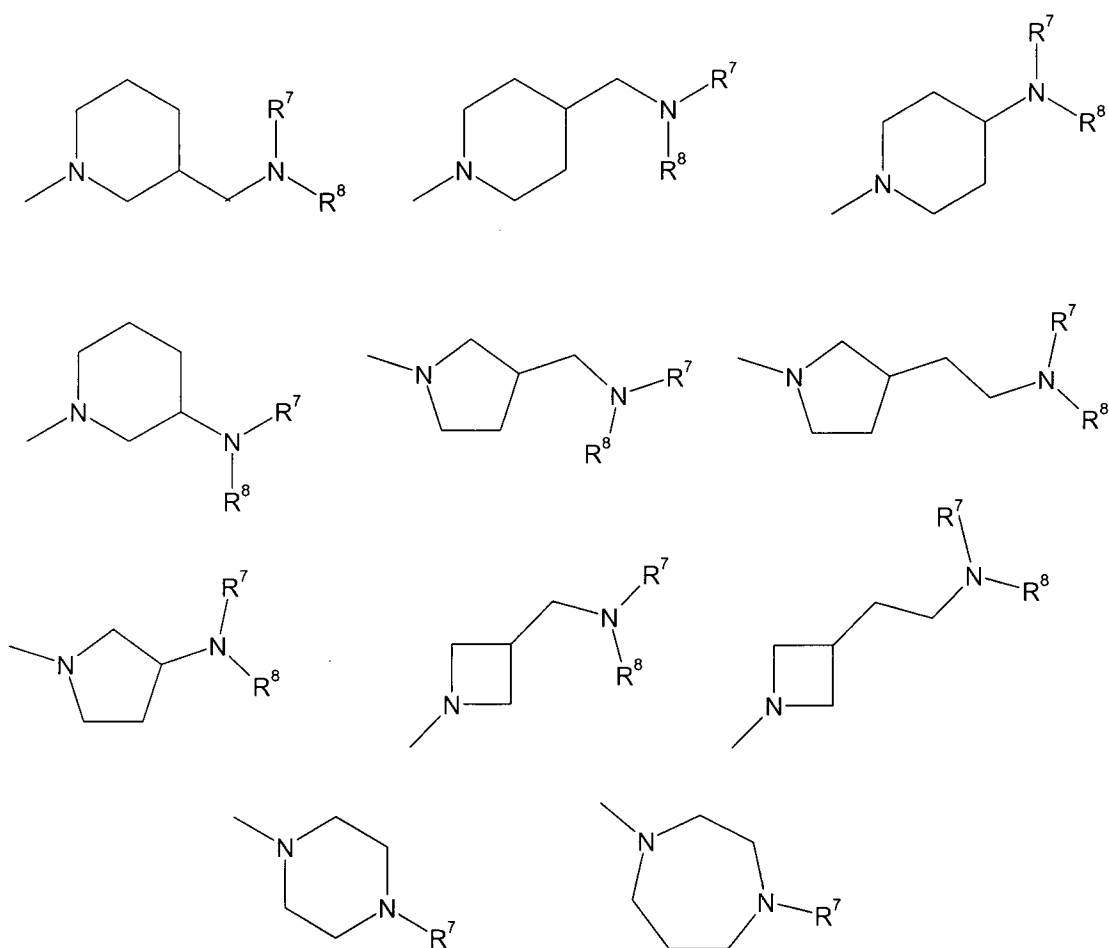


donde R^8-R^{11} tienen los significados definidos anteriormente. En otra modalidad, R^4 es un grupo seleccionado entre:



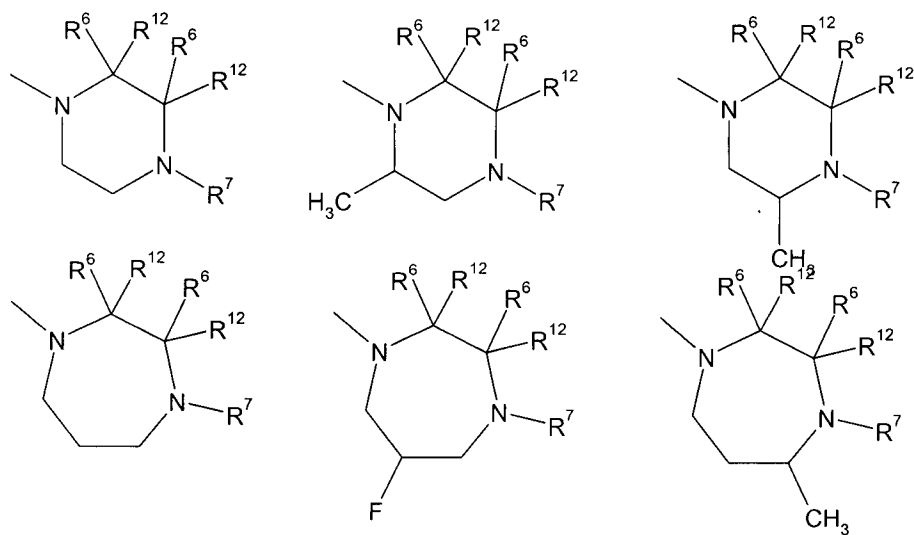
donde R^7 y R^8 tienen los significados definidos anteriormente.

En otra modalidad, R^4 es un grupo seleccionado entre:



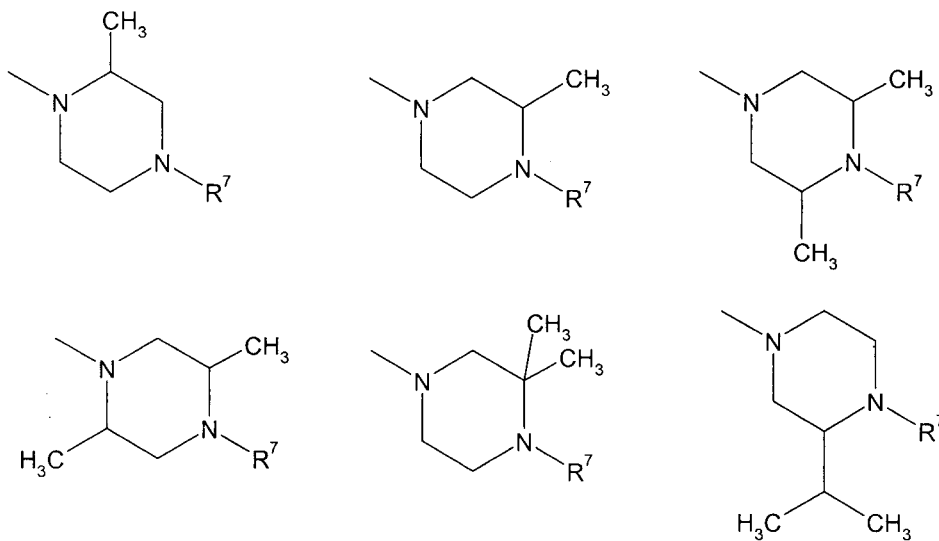
donde R⁷ y R⁸ tienen los significados definidos anteriormente.

En otra modalidad, R⁴ es un grupo seleccionado entre:



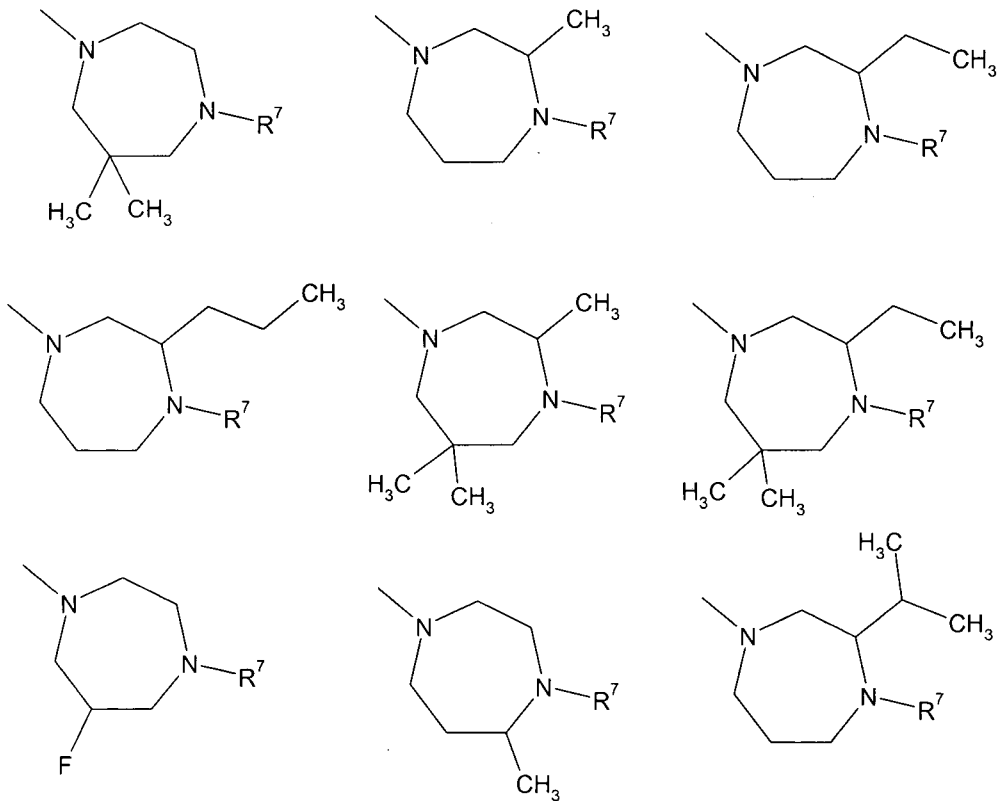
donde R^6 , R^7 y R^{12} tienen los significados definidos anteriormente.

En otra modalidad, R^4 es un grupo seleccionado entre:



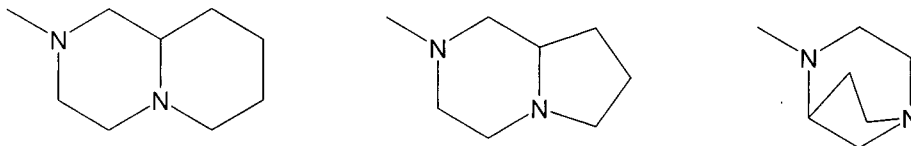
donde R^7 tiene el significado definido anteriormente.

En otra modalidad, R^4 es un grupo seleccionado entre:



donde R^7 tiene el significado definido anteriormente.

En otra modalidad, R^4 es un grupo seleccionado entre:



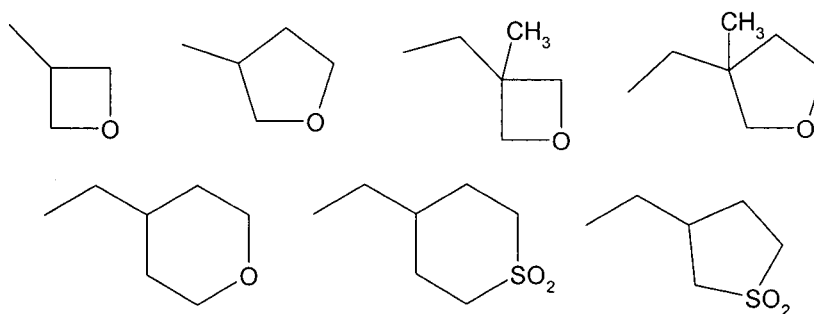
donde R^7 tiene el significado definido anteriormente.

En otra modalidad, R^4 es un sustituyente en la posición 6 de la quinazolinona. En otra modalidad, R^4 es un sustituyente en la posición 7 de la isoquinolinona.

En otra modalidad, R^7 y R^8 son independientemente H, C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{3-6} cicloalquil C_{1-3} alquilo, C_{6-10} arilo o C_{6-10} aril C_{1-3} alquilo. En otra modalidad, R^7 y R^8 son independientemente H o C_{1-4} alquilo.

En otra modalidad, R^7 y R^8 son independientemente H, metilo, etilo, propilo, butilo, isopropilo, hidroxietilo, metoxietilo, ciclopropilmetilo, 1-ciclopropiletilo, ciclopentilo o ciclobutilo.

En otra modalidad, R^7 y R^8 son independientemente seleccionados entre: H, metilo y



En otra modalidad, R^7 y R^8 , junto con el nitrógeno al cual están unidos, forman un anillo heterocíclico de 4 a 6 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S ó NR^{10} , estando dicho anillo heterocíclico opcionalmente sustituido con un sustituyente hidroxilo, donde R^{10} tiene el significado definido anteriormente. En otra modalidad, R^7 y R^8 , junto con el nitrógeno al cual están unidos, forman un anillo heterocíclico seleccionado entre pirrolidina, piperidina, 3-hidroxipiperidina y morfolina.

En otra modalidad, m es 2. En otra modalidad, m es 3.

En otra modalidad, X es N. En otra modalidad, X es CH.

Otra modalidad es una quinazolinona seleccionada entre:

2-[2-(3-Clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]-N-isopropilacetamida;

N-ter-Butil-2-[2-(3-clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]acetamida;

N-ter-Butil-2-(2-(3-cloro-4-fluorofenil)-6-(1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)acetamida;

2-(2-(3-Cloro-4-fluorofenil)-6-(1,4-diazepan-1-il)-4-oxo-quinazolin-3(4H)-il)-N-isopropilacetamida;

2-(2-(3-Cloro-4-fluorofenil)-6-(3-metil-1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(3-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[6-(Dimetilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(4-Fluoro-3-metoxifenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(4-Fluoro-3-metoxifenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-4-oxo-6-(4-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida;

N-ter-Butil-2-[6-(4-etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acetamida;

2-[2-(3-Clorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(4-Fluoro-3-metoxifenil)-4-oxo-6-(4-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

N-Isopropil-2-[6-(4-isopropilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-5-trifluorometilfenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3,5-Dimetoxifenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-{2-(3-Cloro-4-fluorofenil)-6-[4-(1-ciclopropiletil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida;

2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida;

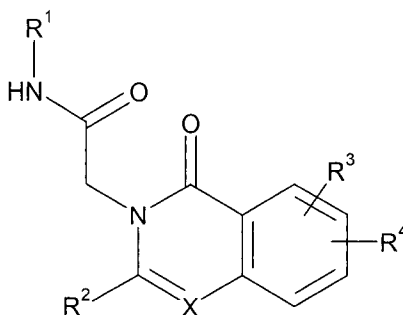
2-{2-(3-Cloro-4-fluorofenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(1,4-diazabicciclo[3.2.2]non-4-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(4-Fluoro-3-metoxifenil)-6-(4-isopropilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;
2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;
2-[2-(3-Cloro-4-fluorofenil)-6-((S)-3-isopropilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;
2-[2-(3-Cloro-4-fluorofenil)-6-((R)-3-isopropilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;
2-[6-(1,4-Diazabicciclo[3.2.2]non-4-il)-2-(3,5-dimetoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;
2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-(2,2,2-trifluoro-1,1-dimetiletil)-acetamida;
N-Isopropil-2-(6-(4-isopropil-1,4-diazepan-1-il)-2-(3-metoxifenil)-4-oxoquinazolin-3(4H)-il)acetamida;
2-(2-(3-Clorofenil)-6-(4-ciclopropilmetil-1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida y
N-ter-Butil-2-(2-(3-clorofenil)-6-(4-isopropil-1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)acetamida
o una sal o solvato farmacéuticamente aceptable de la misma.

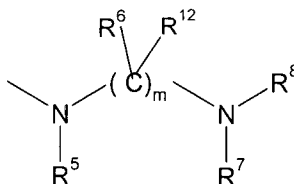
Los derivados de quinazolinona e isoquinolinona de la presente invención se preparan por métodos bien conocidos en el arte de la química orgánica. Véase por ejemplo, J. March, "Advanced Organic Chemistry" 4a. Edición, John Wiley and Sons. Durante las secuencias sintéticas, puede ser necesario y/o deseable proteger los grupos sensibles o reactivos en cualquiera de las moléculas involucradas. Esto se logra por medio de grupos protectores convencionales, tales como los descritos en T.W.

Greene y P.G.M. Wuts, "Protective Groups in Organic Synthesis" 2a. Edición, John Wiley and Sons, 1991. Los grupos protectores son removidos opcionalmente en una etapa posterior conveniente, usando métodos bien conocidos en el arte.



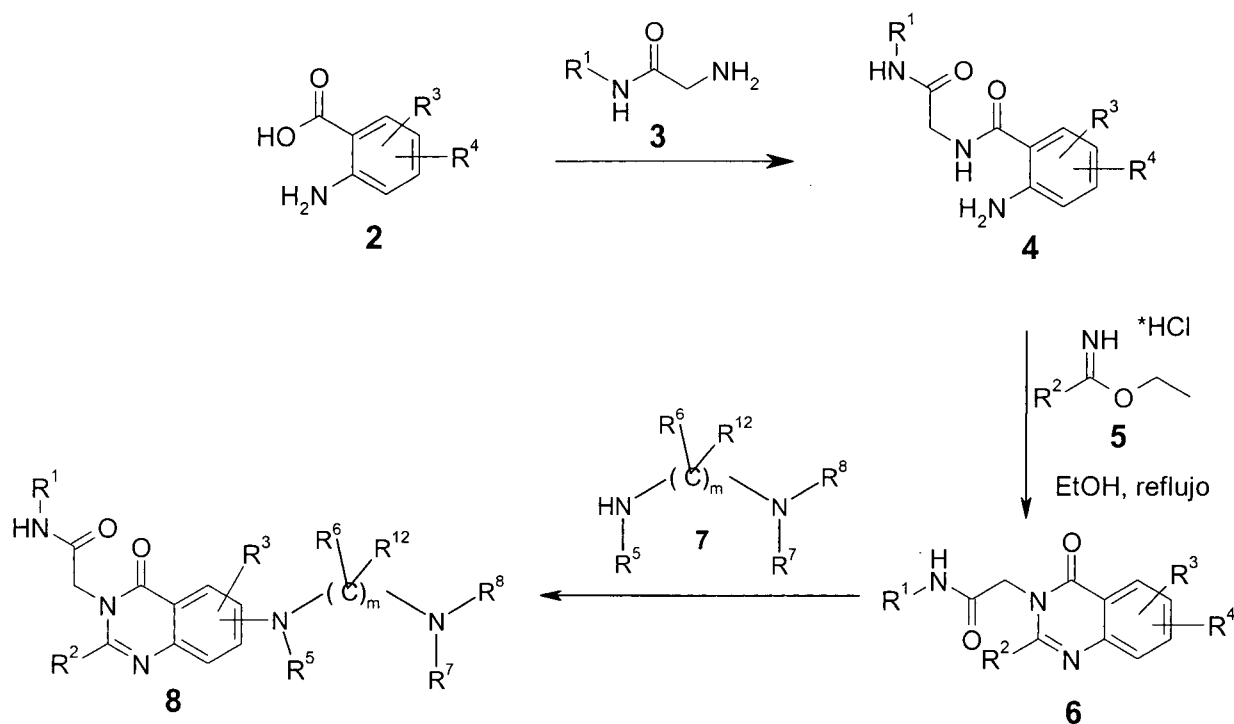
fórmula I

Los derivados de quinazolinona e isoquinolinona de fórmula I donde R⁴ es el grupo



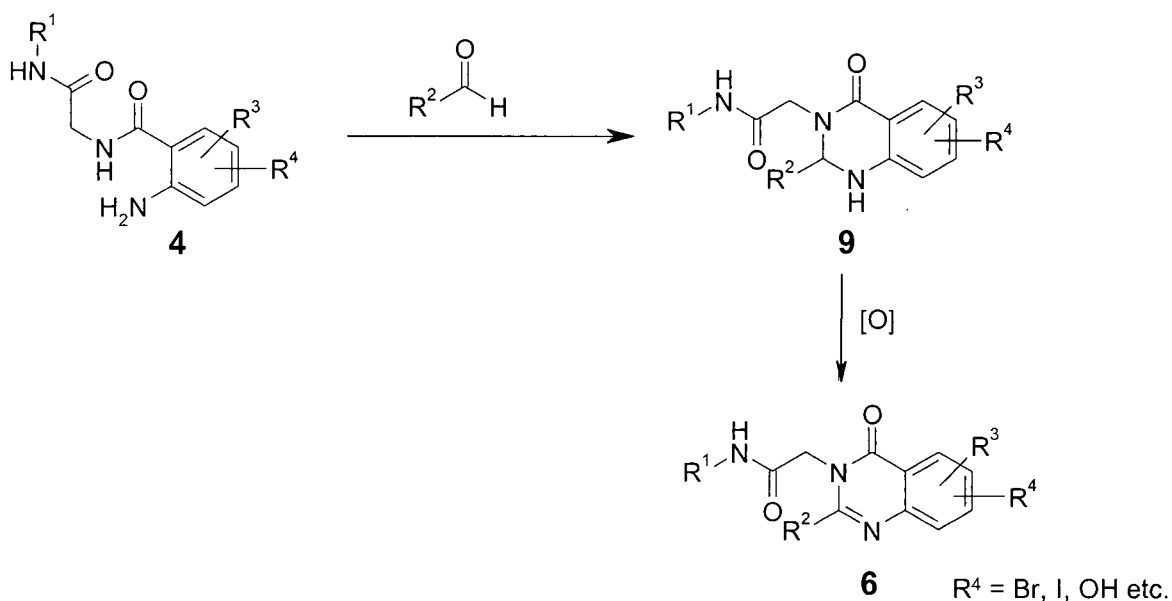
y X es N (mostrado como 8 más adelante), pueden prepararse por la secuencia sintética general en tres etapas mostrada en el **Esquema 1**. En primer lugar, un ácido antranílico de fórmula 2 donde R⁴ es OH o un grupo adecuadamente reactivo tal como halógeno (por ejemplo bromo o yodo) etc., se hace reaccionar con una glicina amida de fórmula 3 en presencia de un reactivo de acoplamiento de enlace amida adecuado, para dar el producto acoplado 4. Un ejemplo de este reactivo de acoplamiento sería EDCI. El reactivo de acoplamiento se agrega solo o bien en presencia de un aditivo tal como HOBT, y en un solvente inerte adecuado tal como

diclorometano o DMF. Los ácidos antranílicos **2** y glicina amidas **3** necesarios están disponibles en el comercio, o bien pueden prepararse fácilmente mediante procedimientos bien conocidos en el arte. Las quinazolinonas intermediarias de fórmula general **6** pueden prepararse por condensación de la sal imidato **5** en un solvente adecuado tal como etanol, y a temperaturas elevadas tal como a reflujo. Los intermediarios **6** donde R^4 es un grupo reactivo tal como triflato, pueden prepararse fácilmente a partir del intermediario **6** correspondiente donde R^4 es OH, usando procedimientos bien conocidos en el arte, por ejemplo el triflato puede prepararse por tratamiento de los alcoholes **6** con anhídrido trifluorometanosulfónico y piridina. Enseguida, las quinazolinonas intermediarias **6** donde R^4 es un grupo adecuadamente reactivo tal como halógeno (por ejemplo bromo o yodo), triflato, etc., pueden ser funcionalizadas con diaminas de fórmula **7** en presencia de un sistema catalizador adecuado, tal como $Pd_2(dba)_3$ y BINAP, bajo condiciones bien conocidas en el arte para proporcionar el producto deseado **8**. Las diaminas de fórmula **7** están disponibles en el comercio o pueden prepararse fácilmente mediante procedimientos bien conocidos en el arte.

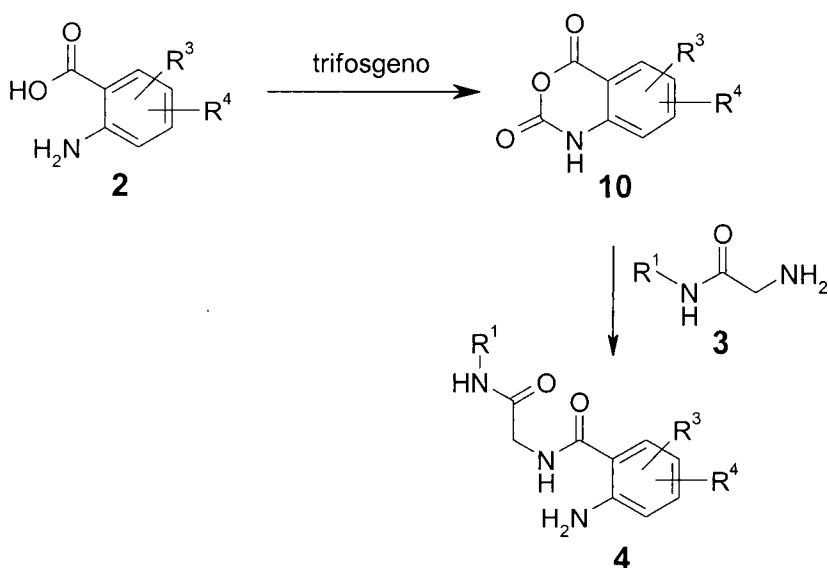


Esquema 1

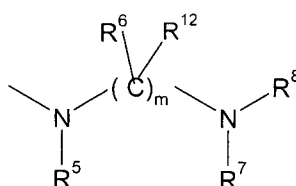
Alternativamente, las quinazolinonas intermediarias 6 pueden formarse por condensación del intermediario 4 con un aldehído adecuado, R^2CHO , seguido por la oxidación subsiguiente de la dihidroquinazolinona intermediaria resultante 9 con un oxidante adecuado tal como MnO_2 , DDQ o $CuCl_2$ (Esquema 2). Los aldehídos R^2CHO están disponibles en el comercio o pueden prepararse fácilmente mediante procedimientos bien conocidos en el arte.



La amida intermediaria **4** puede prepararse alternativamente por reacción de un anhídrido isatoico de fórmula general **10** con una glicina amida de fórmula **3**, en un solvente aprótico polar tal como acetonitrilo. Los anhídridos isatoicos **10** están disponibles en el comercio, o pueden prepararse fácilmente por reacción de un ácido antranílico de fórmula **2** adecuado con un reactivo de carbonilación tal como fosgeno o trifosgeno (**Esquema 3**).

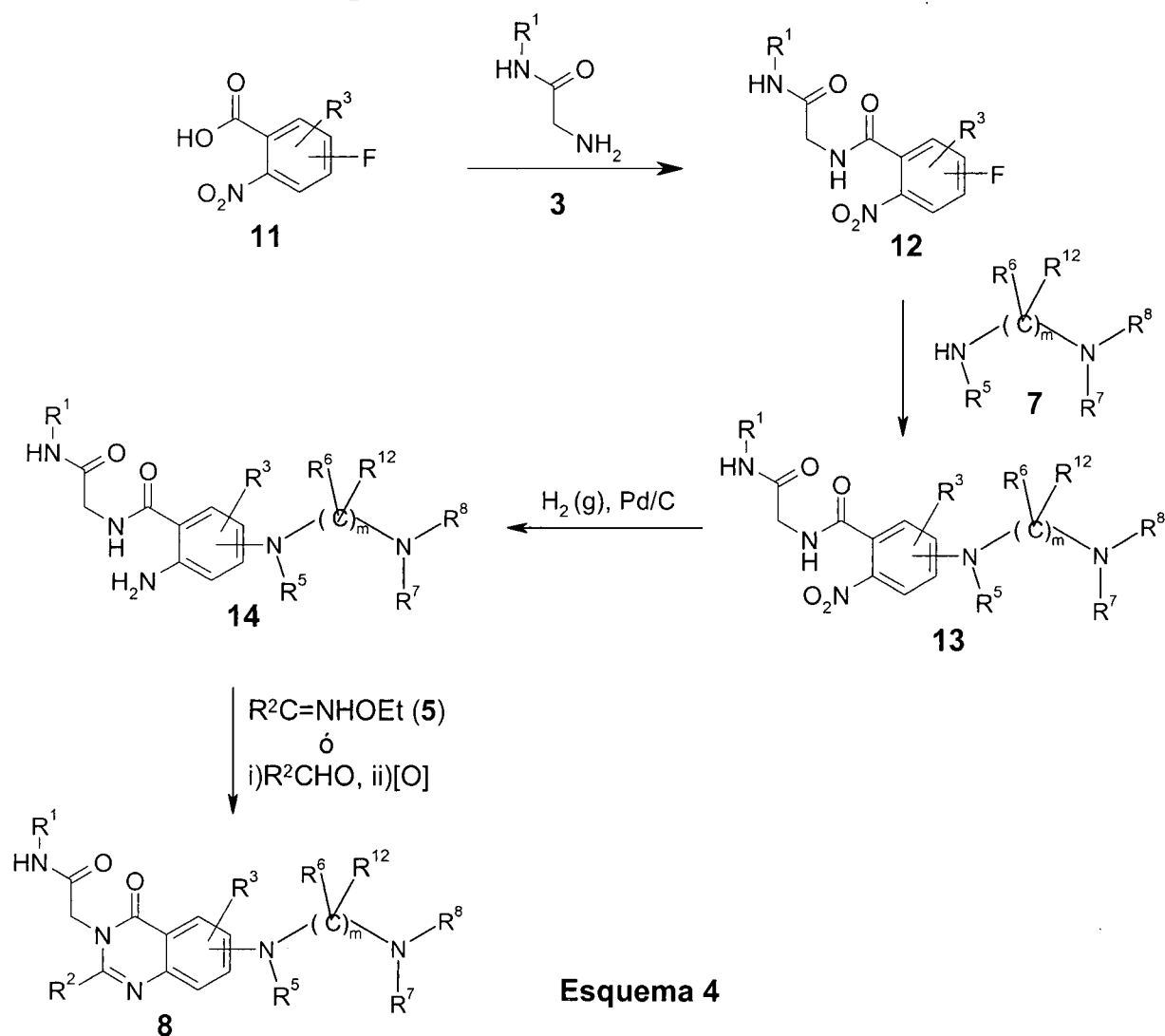


Los compuestos de fórmula I donde R^4 es el grupo

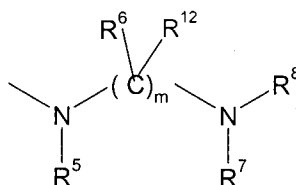


y X es N también pueden prepararse en cuatro etapas a partir del ácido fluoro-2-nitrobenzoico requerido **11**, como se ve en el **Esquema 4**. Los derivados del ácido fluoro-2-nitrobenzoico están disponibles en el comercio o pueden prepararse usando procedimientos bien conocidos en el arte de la química orgánica. El ácido **11** puede ser acoplado con una glicina amida de fórmula **3** usando procedimientos análogos a los indicados anteriormente (véase **Esquema 1**), para proporcionar la amida **12**. Ésta a su vez puede ser tratada después con la amina **7** en un solvente aprótico polar inerte tal como DMF, DMSO o DMP, a temperaturas elevadas y en presencia de una base adecuada (por ejemplo, carbonato de potasio o de cesio), para proporcionar el aducto **13**. Las aminas

7 están disponibles en el comercio o pueden prepararse fácilmente mediante procedimientos bien conocidos en el arte. Enseguida, el grupo nitro es reducido para dar la anilina **14** usando métodos bien conocidos en el arte, por ejemplo reducción bajo una atmósfera de hidrógeno y en presencia de un catalizador adecuado tal como paladio en carbón. Finalmente, las quinazolinonas deseadas **8** pueden prepararse por reacción del compuesto **14** con un imidato*, sal de HCl de fórmula **5** (como se describió anteriormente - **Esquema 1**), o por reacción del compuesto **14** con un aldehído R^2CHO seguido por oxidación (como se describió anteriormente - **Esquema 2**).

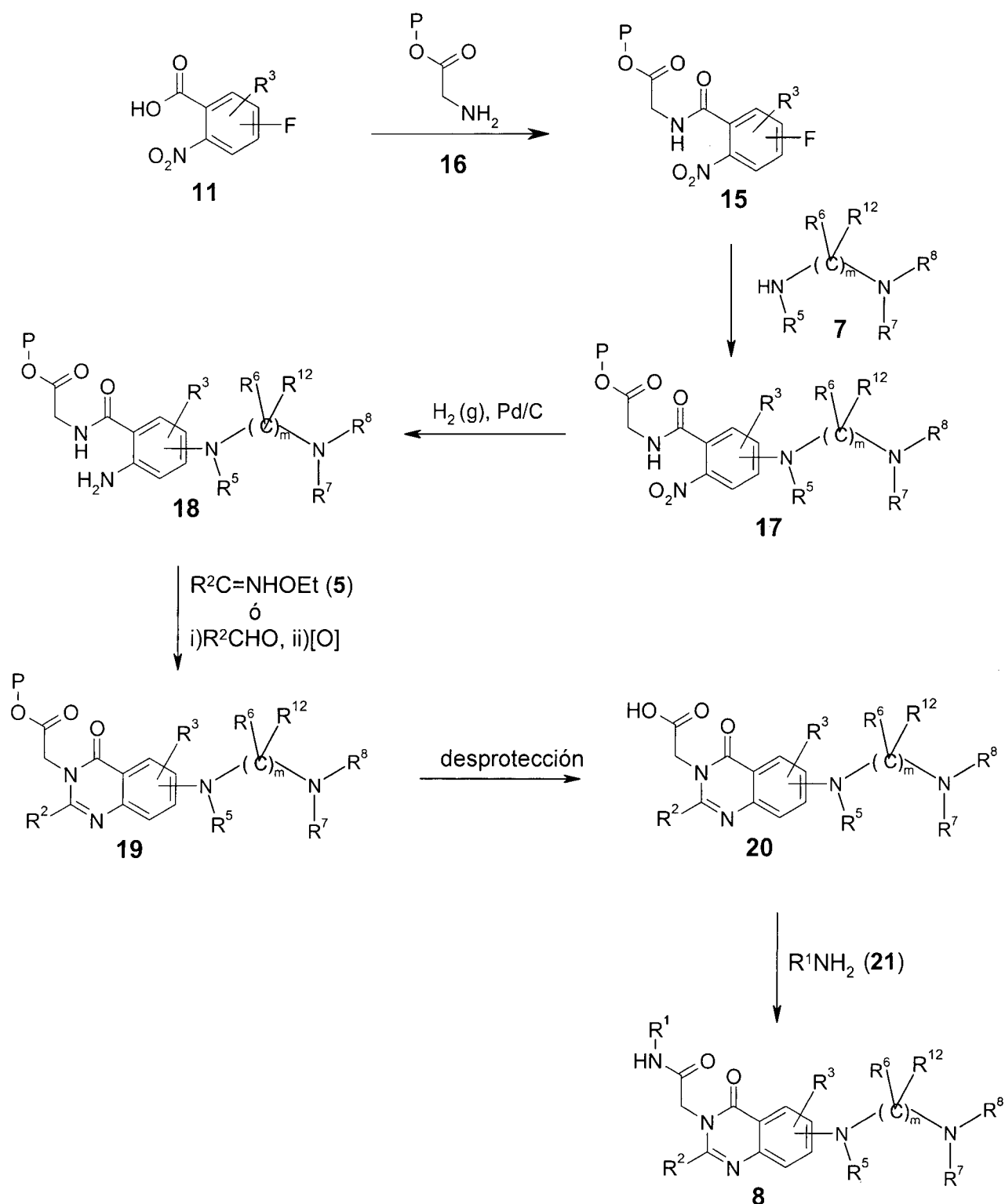


Los compuestos de fórmula **I** donde R^4 es el grupo



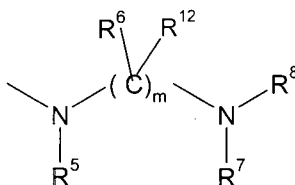
y X es N también pueden prepararse en 6 etapas a partir del ácido fluoro-2-nitrobenzoico requerido **15**, como se ve en el **Esquema 5**. Los derivados del ácido fluoro-2-nitrobenzoico **11** están disponibles en el comercio o pueden prepararse usando procedimientos bien conocidos en el arte de la química orgánica. El ácido **11** puede ser acoplado con una glicina adecuadamente protegida de fórmula **16**, por ejemplo ter-butil éster de glicina o metil éster de glicina, usando procedimientos análogos a los indicados anteriormente (véase **Esquema 1**) para proporcionar la amida **15**. La glicina adecuadamente protegida de fórmula **16** está disponible en el comercio o puede prepararse usando procedimientos bien conocidos en el arte de la química orgánica. A su vez, la amida **15** puede ser tratada con la amina **7** en un solvente aprótico polar inerte tal como DMF, DMSO o DMP, a temperaturas elevadas y en presencia de una base adecuada (por ejemplo, carbonato de potasio o de cesio), para proporcionar el aducto **17**. Las aminas **7** están disponibles en el comercio o pueden prepararse fácilmente mediante procedimientos bien conocidos en el arte de la química orgánica. Enseguida, el grupo nitro puede ser reducido para dar la anilina **18** usando métodos bien conocidos en el arte, por ejemplo reducción bajo una atmósfera de hidrógeno y en presencia de un catalizador adecuado

tal como paladio en carbón. Las quinazolinonas **19** se preparan por reacción del compuesto **18** con un imidato*, sal de HCl de fórmula **5** (como se describió anteriormente - **Esquema 1**), o por reacción del compuesto **18** con un aldehído R^2CHO seguido por oxidación (como se describió anteriormente - **Esquema 2**). La remoción del grupo protector del ácido carboxílico puede efectuarse fácilmente usando procedimientos bien conocidos en el arte de la química orgánica, por ejemplo el ter-butil éster puede ser removido bajo condiciones ácidas, por ejemplo ácido trifluoroacético en un solvente aprótico tal como DMF o DCM, para dar los ácidos carboxílicos **20**. Finalmente, las quinazolinonas deseadas **8** pueden prepararse por reacción del ácido carboxílico **20** con la amina **21** usando procedimientos bien conocidos en el arte, por ejemplo un reactivo de acoplamiento de amida adecuado. Un ejemplo de este reactivo de acoplamiento sería EDCI. El agente de acoplamiento se agrega solo o bien en presencia de un aditivo tal como HOBT, y en un solvente inerte adecuado tal como DMF o DCM.



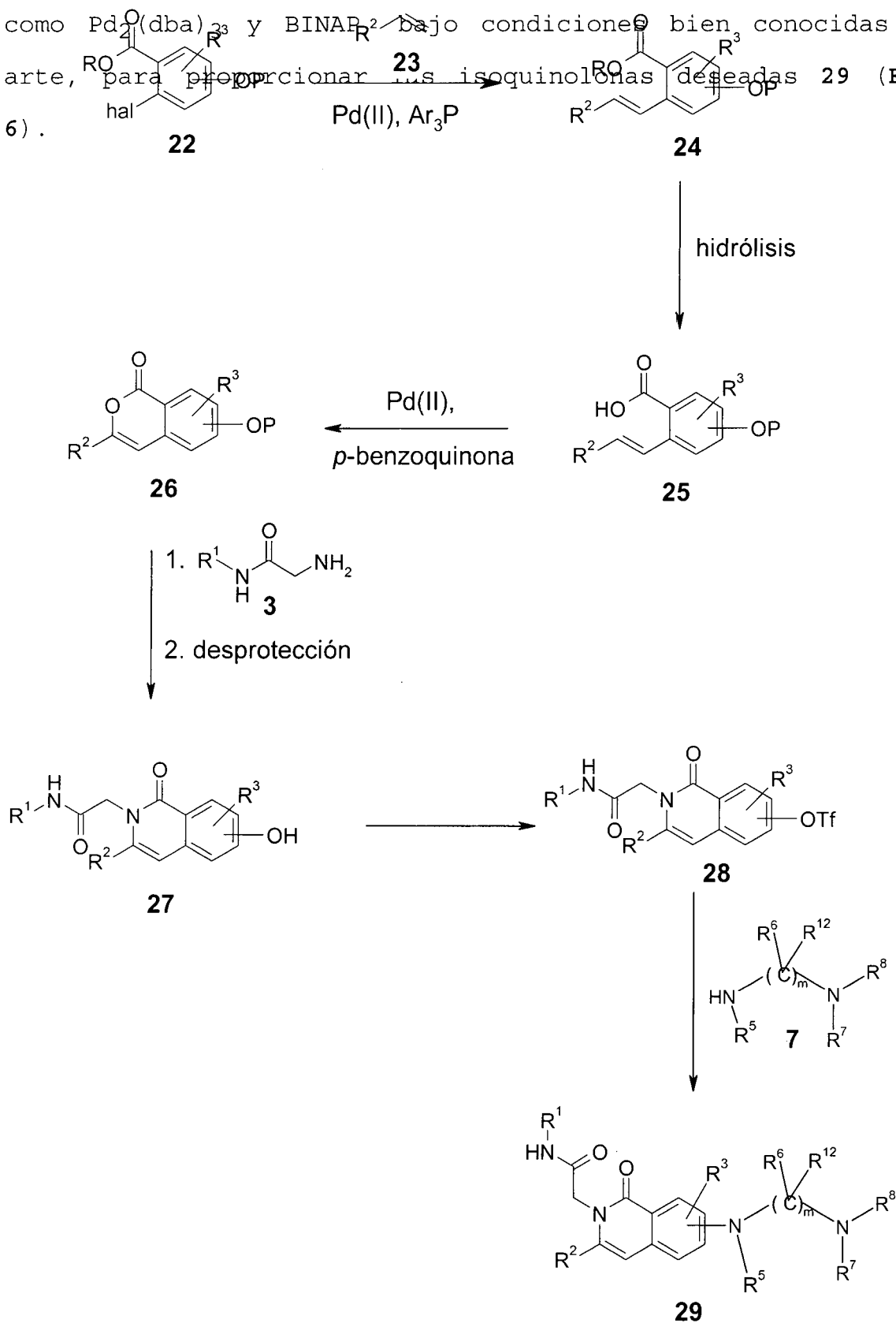
Esquema 5

Los compuestos de fórmula **I** donde R^4 es el grupo



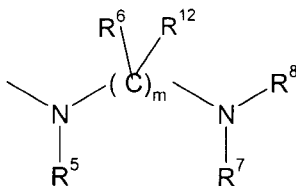
y X es CH (mostrado como **29** más abajo) pueden prepararse por la secuencia sintética general en seis etapas mostrada en el **Esquema 6**. En primer lugar, un éster de ácido 2-halobenzoico adecuadamente funcionalizado de fórmula **22**, puede hacerse reaccionar con un estireno adecuadamente funcionalizado de fórmula **23**, en presencia de un catalizador de Pd(II) adecuado (por ejemplo diacetato de paladio), un ligando de triarilfosfina (por ejemplo tri(o-tolil)fosfina) y una base amina terciaria (por ejemplo trietilamina) en un solvente aprótico polar (por ejemplo acetonitrilo), para dar el producto acoplado **24**. P representa un grupo protector adecuado, por ejemplo metilo. Los ácidos 2-halobenzoicos **22** y los estirenos **23** están disponibles en el comercio, o pueden prepararse fácilmente mediante procedimientos bien conocidos en el arte. Enseguida, el éster de ácido carboxílico **24** puede ser hidrolizado al ácido carboxílico **25**, usando ya sea ácido o base en un solvente adecuado tal como etanol. El ácido carboxílico intermediario **25** puede ser posteriormente ciclado a la isocumarina **26** usando un catalizador de paladio(II), por ejemplo bis(acetonitrilo)dicloropaladio(II), y un oxidante por ejemplo *p*-benzoquinona, en un solvente inerte por ejemplo tetrahidrofurano. La isocumarina **26** así obtenida puede ser calentada junto con una glicina amida **3** para proporcionar la isoquinolinona, que posteriormente puede ser desprotegida para dar la isoquinolinona **27**. El alcohol libre **27** así obtenido puede ser convertido en el triflato correspondiente

usando procedimientos bien conocidos en el arte, por ejemplo por tratamiento del alcohol **27** con anhídrido trifluorometanosulfónico y piridina. El triflato **28** puede hacerse reaccionar con diaminas de fórmula **7**, en presencia de un sistema catalizador adecuado tal como $\text{Pd}(\text{dba})_3$ y BINAP , bajo condiciones bien conocidas en el arte, para proporcionar las isoquinolonas deseadas **29** (Esquema 6).



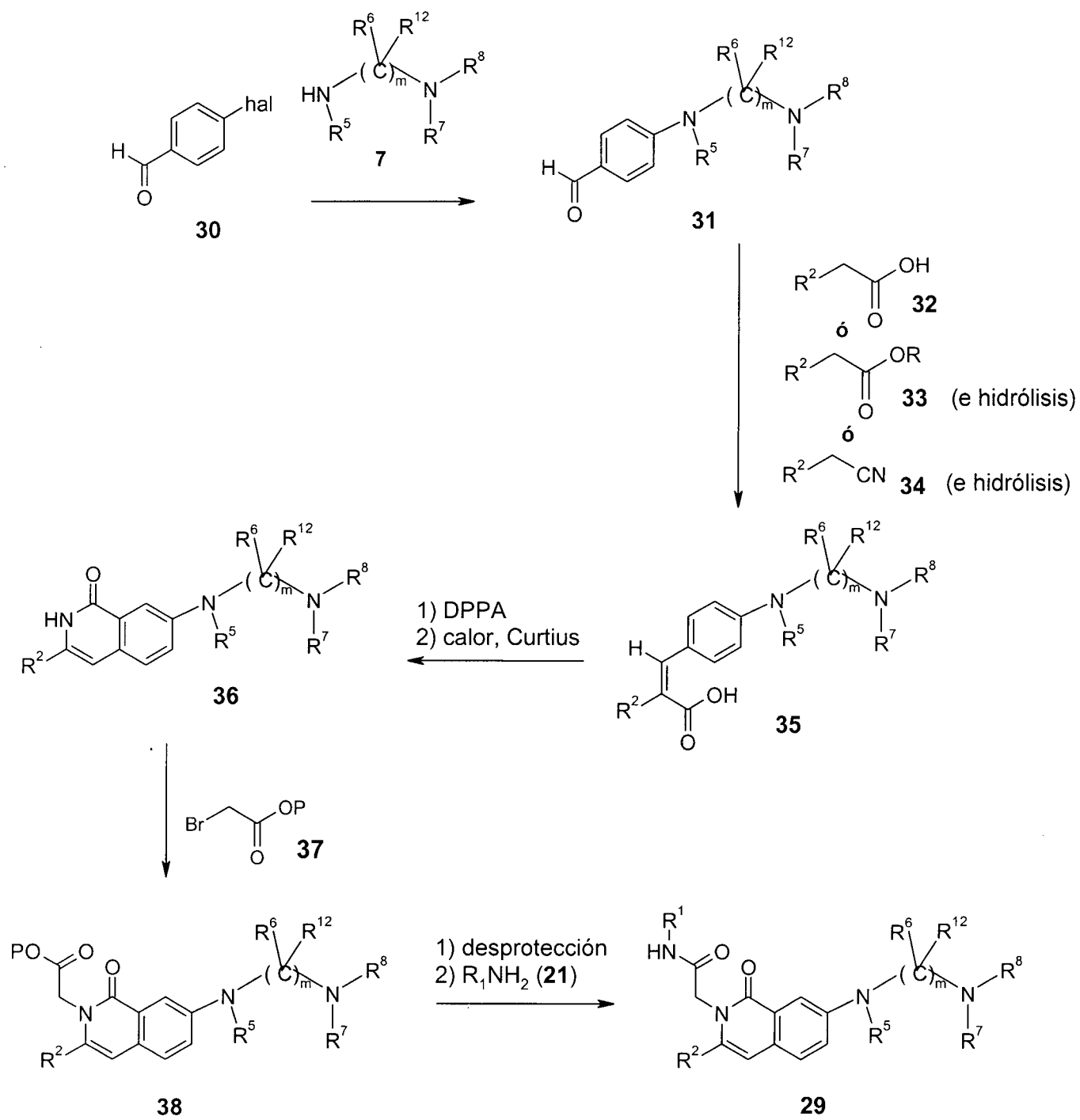
Esquema 6

Los compuestos de fórmula I donde R^4 es el grupo



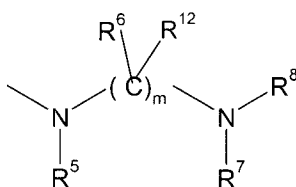
y X es CH (mostrado como 29 más abajo) pueden prepararse alternativamente por la secuencia sintética general en cinco etapas mostrada en el **Esquema 7**. En primer lugar, un 4-halo-benzaldehído de fórmula 30, halo puede ser por ejemplo fluoro, puede hacerse reaccionar con una amina 7 en un solvente aprótico polar inerte tal como DMF, DMSO o DMP, a temperaturas elevadas y en presencia de una base adecuada (por ejemplo, carbonato de potasio o de cesio), para proporcionar el aldehído 31. El aldehído 31 puede hacerse reaccionar con un ácido carboxílico adecuadamente funcionalizado 32, un éster de ácido carboxílico 33 o un nitrilo 34, para proporcionar el ácido carboxílico 35. El ácido carboxílico 35 puede formarse directamente cuando se usa un ácido carboxílico adecuadamente funcionalizado 32, o después de la hidrólisis subsiguiente del éster de ácido carboxílico o nitrilo cuando se usa un éster de ácido carboxílico 33 o un nitrilo 34, respectivamente. La hidrólisis puede efectuarse usando procedimientos bien conocidos en el arte de la química orgánica. El tratamiento subsiguiente del aducto 35, por ejemplo con DPPA a temperaturas elevadas, puede proporcionar la isoquinolona 36 a través de una reacción de Curtius. La alquilación de la isoquinolona 36 con un derivado de ácido

bromoacético adecuadamente protegido **37** (P representa un grupo protector adecuado, por ejemplo metilo) puede proporcionar el éster **38**. La hidrólisis del éster **38** usando procedimientos bien conocidos en el arte de la química orgánica, y la reacción subsiguiente con la amina **21** usando procedimientos bien conocidos en el arte (como se describió anteriormente - **Esquema 7**), pueden proporcionar las isoquinolonas deseadas **29**.



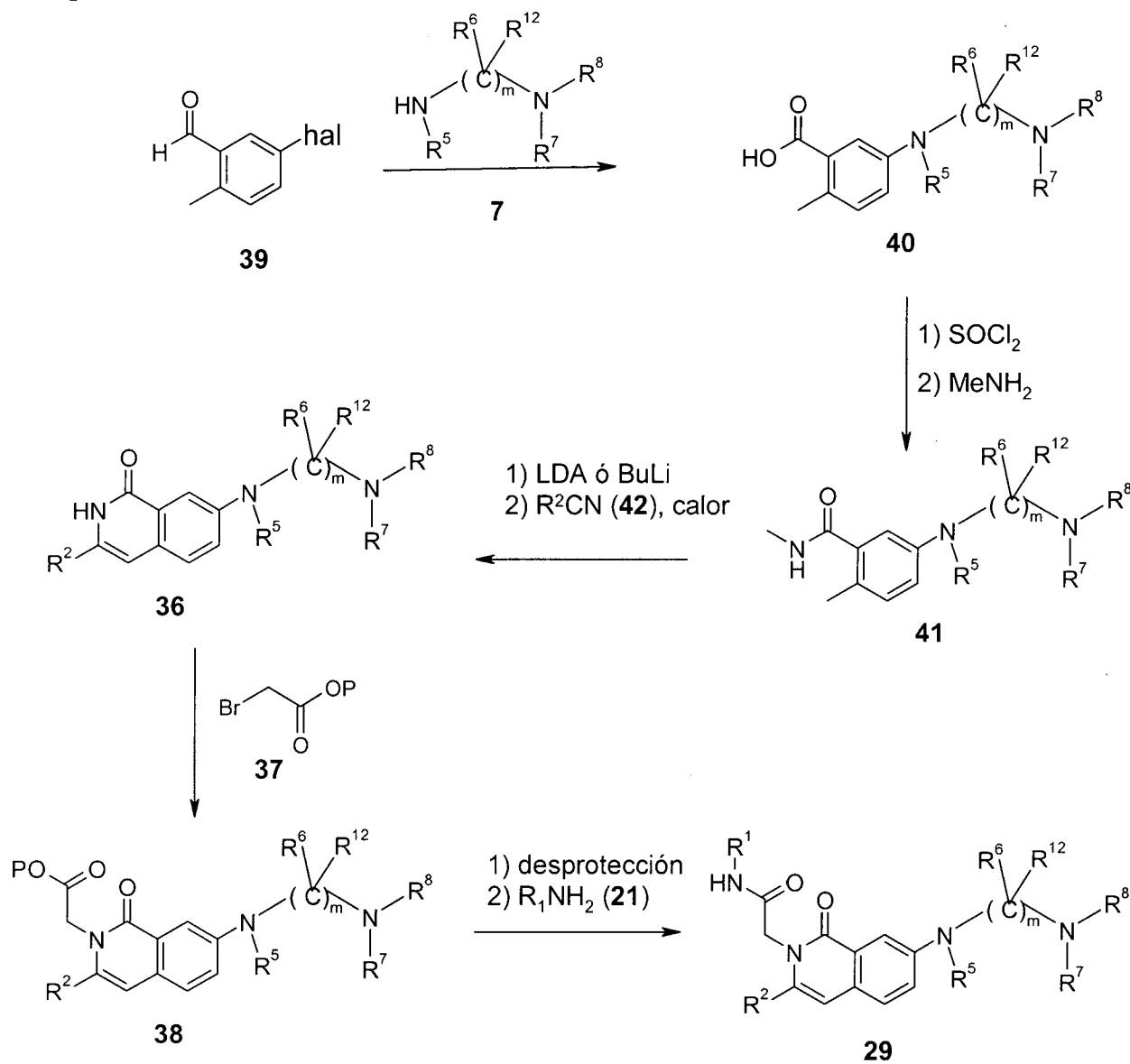
Esquema 7

Los compuestos de fórmula I donde R^4 es el grupo



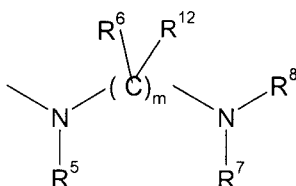
y X es CH (mostrado como **29** más abajo), pueden prepararse alternativamente por la secuencia sintética general en cinco etapas mostrada en el **Esquema 8**. Un ácido 3-halo-6-metilbenzoico de fórmula **39**, halo puede ser por ejemplo fluoro, puede hacerse reaccionar con diaminas de fórmula **7** en un solvente aprótico polar inerte tal como DMF, DMSO o DMP, a temperaturas elevadas y en presencia de una base tal como carbonato de potasio, para proporcionar el ácido carboxílico **40**. El ácido carboxílico **40** puede ser convertido en la amida **41** por reacción con metilamina usando procedimientos bien conocidos en el arte de la química orgánica, por ejemplo por conversión en el cloruro de ácido con cloruro de tionilo o cloruro de oxalilo y reacción subsiguiente con metilamina. La amida **41** puede ser tratada con una base adecuada, por ejemplo LDA o BuLi, y posteriormente se hace reaccionar con un nitrilo apropiadamente sustituido **42** en un solvente adecuado, para proporcionar la isoquinolona **36**. Las isoquinolonas **38** pueden prepararse por reacción del compuesto **36** con un derivado de ácido bromoacético adecuadamente protegido **37** en un solvente aprótico polar inerte tal como DMF, y en presencia de una base adecuada tal como carbonato de potasio. P representa un grupo protector, por ejemplo metilo. Enseguida, el éster de ácido carboxílico puede ser hidrolizado al ácido carboxílico, usando ya sea ácido o base en un solvente adecuado, y posteriormente se hace reaccionar con la amina **21** (como se

describió anteriormente - **Esquema 7)** para proporcionar las isoquinolonas **29**.



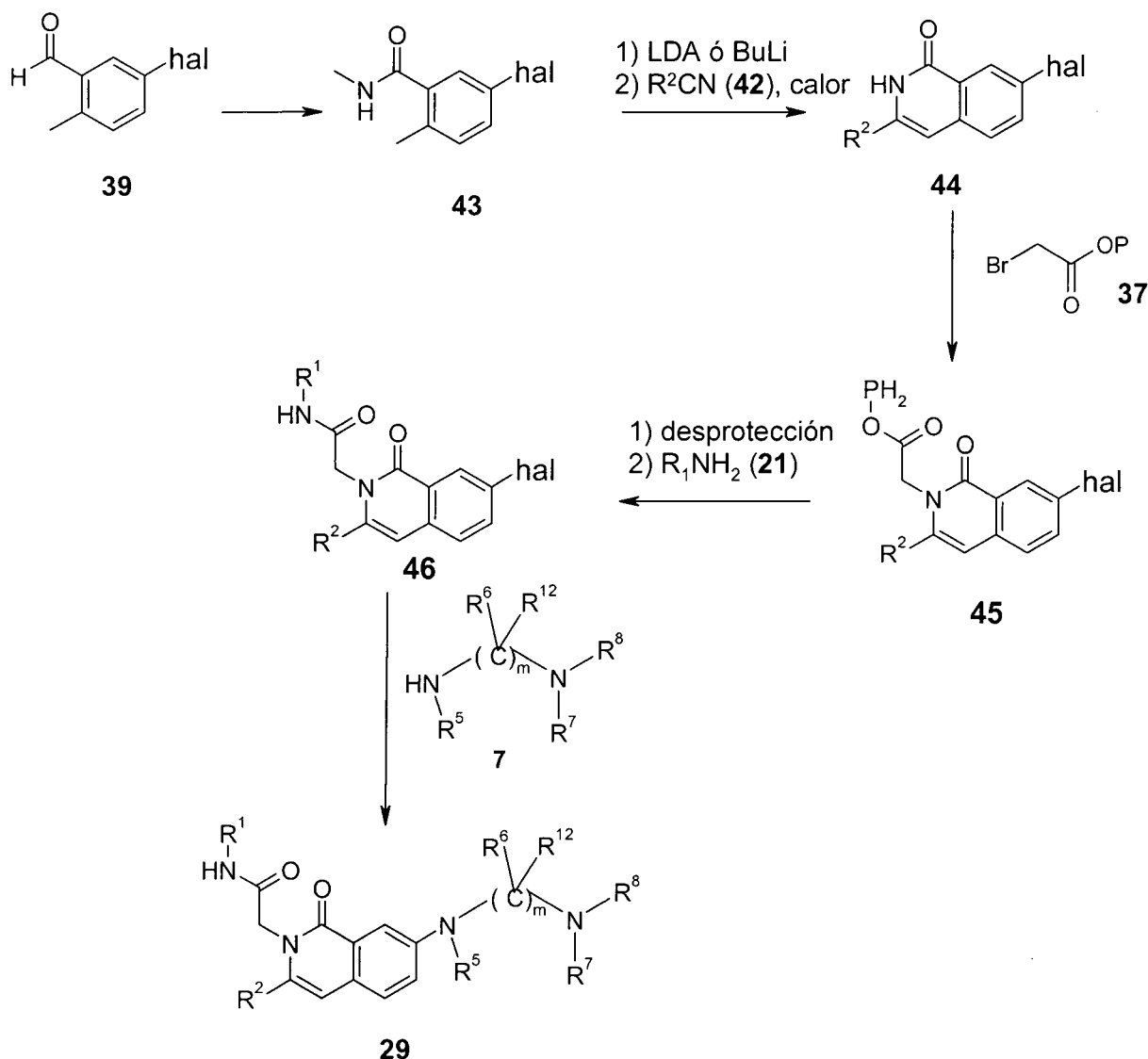
Esquema 8

Los compuestos de fórmula I donde R^4 es el grupo



y X es CH (mostrado como **29** más abajo) pueden prepararse alternativamente por la secuencia sintética general en cinco etapas mostrada en el **Esquema 9**. Un ácido 3-halo-6-metilbenzoico de fórmula **39**, donde halo puede ser por ejemplo cloro o bromo, puede hacerse reaccionar con metilamina usando procedimientos bien conocidos en el arte de la química orgánica, para proporcionar la amida **43**. Por ejemplo, el ácido **39** puede ser convertido en el cloruro de ácido por reacción, por ejemplo, con cloruro de tionilo o cloruro de oxalilo a temperatura elevada. Enseguida, el cloruro de ácido puede ser tratado con metilamina. La amida **43** puede hacerse reaccionar con una base adecuada por ejemplo LDA o BuLi, en un solvente adecuado tal como THF, y posteriormente se trata con un nitrilo apropiadamente sustituido de fórmula **42**, para proporcionar la isoquinolona **44**. La isoquinolona **45** puede prepararse por alquilación de la isoquinolona **44** con un derivado éster del ácido bromoacético **37**, en un solvente aprótico polar tal como DMF y en presencia de una base adecuada tal como carbonato de potasio. P es un grupo protector, por ejemplo metilo. La desprotección usando procedimientos bien conocidos en el arte de la química orgánica, seguida por la reacción con la amina **21**, puede proporcionar las isoquinolonas de fórmula **46**. Las isoquinolonas de fórmula **29** pueden prepararse haciendo reaccionar las isoquinolonas **46** con diaminas de fórmula **7** a temperaturas elevadas, en un solvente adecuado y en presencia de un sistema catalizador adecuado, tal

como dicloruro de [1,3-bis(2,6-diisopropilfenil)imidazol-2-ilideno] (3-cloropiridil)paladio(II).



Esquema 9

Un experto en el arte podrá apreciar fácilmente que las quinazolinonas e isoquinolinonas de fórmula general I pueden prepararse usando los procedimientos generales y/o secuencias de reacción descritas más arriba en cualquier orden adecuado. Por ejemplo, a pesar de que los procesos detallados más arriba describen la introducción de los grupos R^4 más tarde en las

síntesis, utilizando quinazolinonas e isoquinolinonas intermediarias preformadas, se podrá reconocer que en algunos casos, los grupos R^4 pueden ser introducidos antes de la formación del sistema de anillo quinazolinona e isoquinolinona.

La presente invención también incluye dentro de su alcance todas las formas estereoisoméricas de los derivados de quinazolinona e isoquinolinona que resultan, por ejemplo, por isomería configuracional o geométrica. Estas formas estereoisoméricas son enantiómeros, diastereoisómeros, isómeros cis y trans, etc. Por ejemplo, en el caso en que R^1 es 2-metilciclopropilamina, el compuesto existe como un par de enantiómeros. En el caso en que R^4 comprende un fragmento alqueno, ambas formas estereoisoméricas (Z) y (E) del compuesto son posibles. En el caso de los enantiómeros individuales de los derivados de quinazolinona e isoquinolinona de fórmula I o sus sales o solvatos, la presente invención incluye los estereoisómeros mencionados más arriba sustancialmente libres, o sea asociados con menos de 5%, de preferencia menos de 2%, y en particular menos de 1% del otro enantiómero. Mezclas de estereoisómeros en todas proporciones, por ejemplo una mezcla racémica que comprende cantidades sustancialmente iguales de dos enantiómeros, también están incluidas dentro del alcance de la presente invención.

Para los compuestos quirales, los métodos para la síntesis asimétrica por la cual se obtienen los estereoisómeros puros son bien conocidos en el arte, por ejemplo síntesis con inducción quiral, síntesis partiendo de intermediarios quirales, conversiones enzimáticas enantioselectivas, separación de estereoisómeros usando cromatografía en medios quirales. Estos

métodos se describen en "Chirality in Industry" (editado por A.N. Collins, G.N. Sheldrake y J. Crosby, 1992; John Wiley). De manera similar, los métodos para la síntesis de isómeros geométricos también son bien conocidos en el arte.

La presente invención también incluye dentro de su alcance todas las formas marcadas isotópicamente de los compuestos de la invención. Por ejemplo, compuestos marcados isotópicamente con ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{131}I , ^{125}I , ^{123}I y ^{18}F . Los compuestos marcados son útiles como herramientas de diagnóstico, radiotrazadores o agentes de monitoreo en diversos métodos de diagnóstico, y para la formación de imágenes de receptores in vivo.

Los derivados de quinazolinona e isoquinolinona de la presente invención, en la forma de una base libre, son aislados de las mezclas de reacción como sales farmacéuticamente aceptables. Estas sales también se obtienen por tratamiento de dicha base libre con un ácido orgánico o inorgánico, por ejemplo cloruro de hidrógeno, bromuro de hidrógeno, yoduro de hidrógeno, ácido sulfúrico, ácido fosfórico, ácido acético, ácido trifluoroacético, ácido propiónico, ácido glicólico, ácido maleico, ácido malónico, ácido metanosulfónico, ácido fumárico, ácido succínico, ácido tartárico, ácido cítrico, ácido benzoico y ácido ascórbico.

Los derivados de quinazolinona e isoquinolinona de la presente invención también existen como formas amorfas. Múltiples formas cristalinas también son posibles. Todas estas formas físicas están incluidas dentro del alcance de la presente invención.

En otro aspecto, los derivados de quinazolinona e isoquinolinona de la presente invención y sus sales y solvatos farmacéuticamente aceptables, son útiles en terapia. Así, los derivados de quinazolinona e isoquinolinona de la presente invención son útiles para la fabricación de un medicamento para el tratamiento o prevención de enfermedades influenciadas por la modulación de la actividad del eje HPA. En particular, los derivados de quinazolinona e isoquinolinona son útiles para la fabricación de un medicamento para el tratamiento de esquizofrenia, ansiedad, accesos repentinos de calor (bochornos) adicción, anorexia nerviosa, trastornos relacionados con el estrés y demencia de Alzheimer.

En otro aspecto, los derivados de quinazolinona e isoquinolinona de la presente invención son útiles para la fabricación de un medicamento para el tratamiento o prevención de la depresión. Los estados de depresión en cuyo tratamiento los compuestos de la presente invención y sus sales y solvatos farmacéuticamente aceptables son particularmente útiles, son aquéllos clasificados como trastornos del ánimo en el "*Diagnostic and Statistical Manual of Mental Disorders*", Cuarta Edición - Texto revisado, American Psychiatric Association, Washington D.C. (2000), incluyendo episodios de alteración del estado de ánimo, trastornos depresivos, trastornos bipolares y otros trastornos del ánimo.

La presente invención incluye además un método para el tratamiento de un mamífero, incluyendo un ser humano, que sufre o está expuesto a sufrir de depresión o cualquiera de los trastornos mencionados más arriba, que comprende administrar una cantidad eficaz de un derivado de quinazolinona o isoquinolinona

de la presente invención, o una sal o solvato farmacéuticamente aceptable del mismo.

La cantidad de un derivado de quinazolinona o isoquinolinona de la presente invención o una sal o solvato farmacéuticamente aceptable del mismo, también denominado aquí el ingrediente activo, que se requiere para lograr un efecto terapéutico, por supuesto variará con el compuesto particular, la vía de administración, la edad y condición del sujeto receptor, y el trastorno o enfermedad particular que se está tratando.

Una dosis diaria adecuada para cualquiera de los trastornos mencionados más arriba estará en el rango de 0,001 a 50 mg por kilogramo de peso corporal del sujeto receptor (por ejemplo, un ser humano) por día, de preferencia en el rango de 0,01 a 20 mg por kilogramo de peso corporal por día. La dosis deseada puede ser presentada como subdosis múltiples administradas a intervalos apropiados durante el día.

A pesar de que es posible que el ingrediente activo sea administrado solo, es preferible presentarlo como una formulación farmacéutica. Por lo tanto, la presente invención también proporciona una composición farmacéutica que comprende un derivado de quinazolinona e isoquinolinona de acuerdo con la presente invención, mezclado con uno o más excipientes farmacéuticamente aceptables tales como los descritos en Gennaro y colaboradores, Remington: *"The Science and Practice of Pharmacy"*, 20a. Edición, Lippincott, Williams and Wilkins, 2000; véase especialmente Parte 5: Pharmaceutical Manufacturing. El término "aceptable" significa que es compatible con los otros ingredientes de la composición y no es perjudicial para los sujetos receptores de la misma. Los excipientes adecuados se

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describen *por ejemplo*, en el "Handbook of Pharmaceutical Excipients", 2a. Edición; Editores A. Wade y P.J. Weller, American Pharmaceutical Association, Washington, The Pharmaceutical Press, Londres, 1994. Las composiciones incluyen aquéllas adecuadas para administración oral, nasal, tópica (incluyendo bucal, sublingual y transdérmica), parenteral (incluyendo subcutánea, intravenosa e intramuscular) o rectal.

Las mezclas de un derivado de quinazolinona e isoquinolinona de acuerdo con la presente invención con uno o más excipientes farmacéuticamente aceptables pueden ser comprimidas a unidades de dosificación sólidas, tales como tabletas, o pueden ser procesadas a cápsulas o supositorios. Por medio de líquidos farmacéuticamente adecuados, los compuestos también pueden ser aplicados como una preparación inyectable en la forma de una solución, suspensión, emulsión, o como un spray, por ejemplo un spray nasal o bucal. Para fabricar unidades de dosificación, por ejemplo tabletas, se contempla el uso de aditivos convencionales tales como rellenos, colorantes, aglutinantes poliméricos y similares. En general, puede usarse cualquier aditivo farmacéuticamente aceptable. Los compuestos de la invención también son adecuados para el uso en un implante, un parche, un gel o cualquier otra preparación para liberación inmediata y/o sostenida.

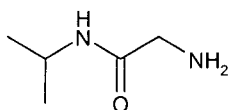
Los rellenos adecuados con los cuales las composiciones farmacéuticas pueden ser preparadas y administradas incluyen lactosa, almidón, celulosa y sus derivados y similares, o mezclas de los mismos, usados en cantidades adecuadas.

Los siguientes Ejemplos ilustran mejor los compuestos de la presente invención y los métodos para su síntesis. En la

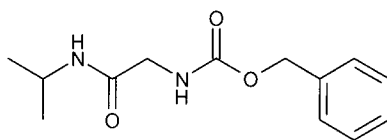
sección siguiente, se describe la síntesis de precursores e intermediarios comunes para los compuestos de la presente invención.

Procedimiento I

INTERMEDIARIO I.1: 2-Amino-N-isopropilacetamida



a) Bencil éster del ácido (isopropilcarbamoilmetil)carbámico

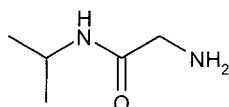


A una solución de *N*-Cbz-glicina (20,9 g, 100 mmoles) en THF (400 ml) a 0°C, se agregó *N*-metilmorfolina (NMM) (12,1 ml, 110 mmoles) y cloroformiato de *i*-butilo (13 ml, 100 mmoles). La mezcla resultante fue agitada a 0°C por 2 minutos y después se agregó *i*-propilamina (9,4 ml, 110 mmoles). La mezcla de reacción fue entibiada hasta temperatura ambiente y agitada a esta temperatura por 16 horas. La mezcla fue filtrada a través de una almohadilla de Celite® y concentrada al vacío. El residuo crudo fue disuelto en acetato de etilo (500 ml) y lavado con HCl 1N (acuoso) (1 x 100 ml), NaHCO₃ saturado (acuoso) (1 x 100 ml) y solución salina (1 x 100 ml). La capa orgánica fue secada (MgSO₄), filtrada y concentrada al vacío, para proporcionar bencil éster del ácido (isopropilcarbamoilmetil)carbámico como un

sólido blanco (24,5 g, 98 mmoles, 98%) que fue usado sin mayor purificación.

Datos: ^1H NMR (300 MHz, CDCl_3): δ 7,37 (m, 5H), 5,78 (br s, 1H), 5,41 (br s, 1H), 5,15 (s, 2H), 4,07 (septeto, 1H), 3,82 (d, 2H), 1,15 (d, 6H) ppm.

b) 2-Amino-N-isopropilacetamida



Pd al 10%/C (425 mg) fue agregado a una solución de bencil éster del ácido (isopropilcarbamoilmetil)carbámico (10 g, 40 mmoles) en etanol (200 ml), y se agitó en un agitador Parr bajo una atmósfera de hidrógeno (50 p.s.i. [344,35 kPa]) por 16 horas. La mezcla de reacción fue filtrada a través de una almohadilla de Celite® y el solvente fue removido al vacío. Esto proporcionó 2-amino-N-isopropilacetamida (INTERMEDIARIO I.1) como un aceite incoloro claro (5,1 g, 40 mmoles, 100%).

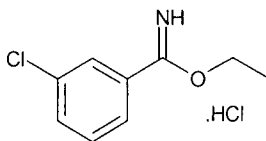
Datos para 2-amino-N-isopropilacetamida (INTERMEDIARIO I.1): ^1H NMR (300 MHz, CDCl_3): δ 7,05 (br s, 1H), 4,11 (septeto, 1H), 3,33 (s, 2H), 1,48 (br s, 2H, amina NH_2), 1,15 (d, 6H) ppm.

De manera similar se preparó:

INTERMEDIARIO I.2: 2-Amino-N-ter-butilacetamida

Procedimiento II

INTERMEDIARIO II.1: 3-Clorobencimidato de etilo clorhidrato



En una solución de 3-clorobenzonitrilo (50 g, 363 mmoles) en etanol anhidro (500 ml), enfriada a 0°C en un baño de hielo, se hizo burbujear HCl (g) a través de tubo de dispersión de gas por aproximadamente 20 minutos hasta que la solución se saturó. La mezcla de reacción resultante fue agitada a temperatura ambiente por 16 horas. Los materiales volátiles fueron removidos al vacío y el residuo fue triturado con éter anhidro (≈200 ml). El sólido blanco fue recolectado por filtración y secado al vacío durante la noche para proporcionar 3-clorobencimidato de etilo clorhidrato (INTERMEDIARIO II.1) (80 g, 363 mmoles, 100%), que fue usado directamente sin mayor purificación.

Datos para 3-clorobencimidato de etilo clorhidrato (INTERMEDIARIO II.1): ^1H NMR (300 MHz, DMSO): δ 12,0-11,8 (br s, 1H), 8,22-8,17 (t, 1H), 8,10-8,04 (dt, 1H), 7,90-7,85 (dt, 1H), 7,71-7,64 (t, 1H), 4,66-4,50 (q, 2H), 1,55-1,40 (t, 3H) ppm.

De manera similar fueron preparados:

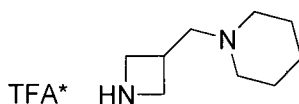
INTERMEDIARIO II.2: 3-Metoxibencimidato de etilo clorhidrato

INTERMEDIARIO II.3: 4-Fluoro-3-metoxibencimidato de etilo clorhidrato

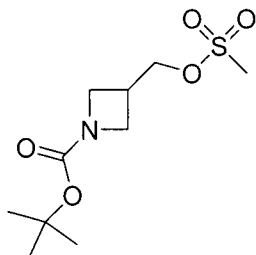
INTERMEDIARIO II.4: 3-Cloro-4-fluorobencimidato de etilo clorhidrato

Procedimiento III

INTERMEDIARIO III.1: 1-Azetidin-3-ilmetilpiperidina



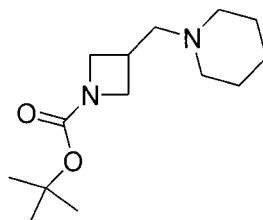
a) ter-Butil éster del ácido 3-metanosulfoniloximetilazetidina-1-carboxílico



A una solución de ter-butil éster del ácido 3-hidroximetilazetidina-1-carboxílico (para la preparación véase: Askew, B. y colaboradores, patente US 20033225106) (0,3 g, 1,60 mmol) en DCM (3 ml), se agregó Et₃N (1 ml, 7,17 mmoles) seguido por cloruro de metanosulfonilo (0,5 ml, 6,46 mmoles), y la mezcla de reacción fue agitada a temperatura ambiente por una hora. La mezcla de reacción fue concentrada al vacío, el residuo fue disuelto en DCM y la fase orgánica fue lavada con bicarbonato de sodio saturado (acuoso). La capa orgánica fue secada (MgSO₄) y concentrada al vacío para dar ter-butil éster del ácido 3-metanosulfoniloximetilazetidina-1-carboxílico (0,36 g, 1,40 mmol, 85%) como un aceite, que fue usado en la etapa siguiente sin mayor purificación.

Datos para ter-butil éster del ácido 3-metanosulfoniloximetilazetidina-1-carboxílico: ¹H NMR (300 MHz, CDCl₃): δ 4,36 (d, 2H), 4,05 (app t, 2H), 3,72 (dd, 2H), 3,05 (s, 3H), 2,92 (m, 1H), 1,42 (s, 9H) ppm.

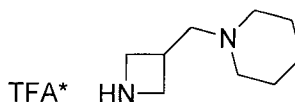
b) ter-Butil éster del ácido 3-piperidin-1-ilmetilazetidina-1-carboxílico



A una suspensión de ter-butil éster del ácido 3-metanosulfoniloximetilazetidina-1-carboxílico (0,36 g, 1,40 mmol) en tolueno (2 ml), se agregó piperidina (0,7 ml, 7,00 mmoles) y la mezcla resultante fue calentada a 110°C en un tubo sellado por 18 horas. La solución fue concentrada al vacío, y el residuo crudo fue disuelto en DCM y lavado con KOH 0,5 N (acuoso) (1 X) y solución salina (1 X). La capa orgánica fue secada (Na₂SO₄), filtrada y concentrada al vacío. El aceite resultante fue purificado por cromatografía en sílica gel con MeOH:DCM (1:19, v/v) como eluyente, para proporcionar ter-butil éster del ácido 3-piperidin-1-ilmetilazetidina-1-carboxílico (180 mg, 0,70 mmol, 50%) como un aceite.

Datos para ter-butil éster del ácido 3-piperidin-1-ilmetilazetidina-1-carboxílico: ¹H NMR (300 MHz, CDCl₃): δ 4,04 (app t, 2H), 3,60 (dd, 2H), 2,91 (br m, 1H), 2,72 (br m, 2 H), 2,48 (br m, 4 H), 1,71 (br m, 4 H), 1,49 (br m, 2H), 1,41 (s, 9H) ppm.

c) 1-Azetidin-3-ilmetilpiperidina



ter-Butil éster del ácido 3-piperidin-1-ilmetil-azetidina-1-carboxílico (180 mg, 0,70 mmol) fue tratado con una solución de TFA:DCM (1:1 v/v, 5 ml), y la solución resultante fue agitada a temperatura ambiente por una hora. La solución fue concentrada al vacío para proporcionar 1-azetidin-3-ilmetilpiperidina (INTERMEDIARIO III.1) (190 mg, 0,70 mmol, 100%) como la sal de ácido trifluoroacético, que fue usada sin mayor purificación.

Datos para 1-azetidin-3-ilmetilpiperidina (INTERMEDIARIO III.1), sal de ácido trifluoroacético: MS (ESI) m/z : 155 ($[M+H]^+$).

De manera similar fueron preparados:

INTERMEDIARIO III.2: 1-Pirrolidin-3-ilmetilpiperidina (a partir del 3-(hidroximetil)pirrolidina-1-carboxilato de ter-butilo disponible en el comercio, Pharmacore)

INTERMEDIARIO III.3: 1-Piperidin-3-ilmetilpiperidina (a partir del 3-(hidroximetil)piperidina-1-carboxilato de ter-butilo disponible en el comercio, Pharmacore)

INTERMEDIARIO III.4: (R)-1-Piperidin-3-ilmetilpiperidina (a partir del (R)-3-(hidroximetil)piperidina-1-carboxilato de ter-butilo disponible en el comercio, Astatech)

INTERMEDIARIO III.5: (S)-1-Piperidin-3-ilmetilpiperidina (a partir del (S)-3-(hidroximetil)piperidina-1-carboxilato de ter-butilo disponible en el comercio, Astatech)

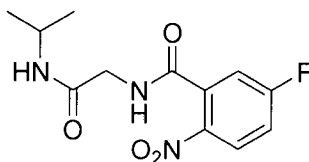
INTERMEDIARIO III.6: 4-Piperidin-3-ilmetilmorfolina (a partir del 3-(hidroximetil)piperidina-1-carboxilato de ter-butilo disponible en el comercio, Pharmacore)

INTERMEDIARIO III.7: *N,N*-Dimetilpiperidin-3-ilmetanamina (a partir del 3-(hidroximetil)piperidina-1-carboxilato de ter-butilo disponible en el comercio, Pharmacore)

INTERMEDIARIO III.8: 1-(2-Azetidin-3-iletíl)piperidina (a partir del 3-(2-hidroxietil)azetidina-1-carboxilato de ter-butilo (preparado de acuerdo con Duggan, M. E., y colaboradores, patente US 5.281.585))

Procedimiento IV

INTERMEDIARIO IV.1: 5-Fluoro-*N*-(isopropilcarbamoilmetil)-2-nitrobenzamida



A una solución de ácido 5-fluoro-2-nitrobenzoico (370 mg, 2,0 mmoles) en DMF anhidra (5 ml), se agregó 1-hidroxibenzotriazol hidrato (330 mg, 2,4 mmoles), 1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato (460 mg, 2,4 mmoles) y 2-amino-*N*-isopropilacetamida (INTERMEDIARIO I.1) (230 mg, 2,0 mmoles). La mezcla resultante fue agitada a temperatura ambiente por 18 horas. La mezcla de reacción fue concentrada al vacío, el residuo crudo de color amarillo fue disuelto en EtOAc (20 ml) y lavado con HCl diluido (acuoso) (3 X 5 ml), NaHCO₃ saturado (acuoso) (3 X 5 ml) y solución salina (1 X 5 ml). La capa orgánica fue secada (Na₂SO₄), concentrada al vacío y purificada por cromatografía en sílica gel con MeOH:DCM (1:19, v/v) como eluyente, para proporcionar 5-fluoro-*N*-(isopropil-

carbamoilmetil)-2-nitrobenzamida (INTERMEDIARIO IV.1) (400 mg, 1,4 mmol, 70%) como un sólido de color amarillo.

Datos para 5-fluoro-N-(isopropilcarbamoilmetil)-2-nitrobenzamida (INTERMEDIARIO IV.1): ^1H NMR (300 MHz, CDCl_3): δ 8,15 (dd, 1H), 7,2-7,3 (m, 2H), 6,94 (br s, 1H), 6,18 (br d, 1H), 4,07 (s, 2H), 4,06 (septeto, 1H), 1,19 (d, 6H) ppm; MS (ESI) m/z : 283 ($[\text{M}+\text{H}]^+$).

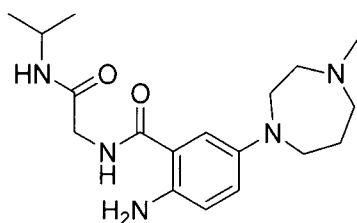
De manera similar fueron preparados:

INTERMEDIARIO IV.2: N-(ter-Butilcarbamoilmetil)-5-fluoro-2-nitrobenzamida (a partir del INTERMEDIARIO I.2)

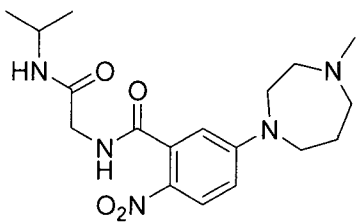
INTERMEDIARIO IV.3: ter-Butil éster del ácido (5-fluoro-2-nitrobenzoilamino)acético (a partir de ter-butil éster de glicina)

Procedimiento V

INTERMEDIARIO V.1: 2-Amino-N-(isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)benzamida



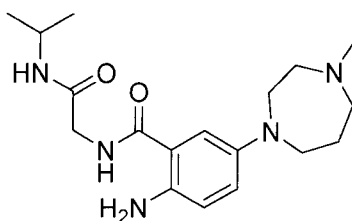
a) N-(Isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)-2-nitrobenzamida



Una mezcla de 5-fluoro-*N*-(isopropilcarbamoilmetil)-2-nitrobenzamida (INTERMEDIARIO IV.1) (400 mg, 1,4 mmol), 1-metilhomopiperazina (0,20 ml, 1,6 mmol) y carbonato de potasio (1 g) en acetonitrilo (20 ml), fue calentada a temperatura de reflujo bajo una atmósfera de argón por 16 horas. La mezcla fue enfriada y filtrada, el residuo fue lavado con DCM (2 X 1 ml) y los materiales volátiles fueron evaporados bajo presión reducida. El residuo de color rojo fue disuelto en DCM (15 ml), lavado con NaOH 1N (acuoso) (2 X 5 ml) y solución salina (1 X 5 ml), secado (Na_2SO_4) y concentrado bajo presión reducida, para proporcionar *N*-(isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)-2-nitrobenzamida (510 mg, 1,4 mmol, 100%) como un sólido de color rojo anaranjado. Éste fue usado en la etapa siguiente sin mayor purificación.

Datos para *N*-(isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)-2-nitrobenzamida: MS (ESI) m/z : 378 ($[\text{M}+\text{H}]^+$).

b) 2-Amino-*N*-(isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)benzamida



Una mezcla de *N*-(isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)-2-nitrobenzamida (510 mg, 1,4 mmol) y Pd al 10%/C (60 mg) en MeOH (30 ml) fue agitada bajo 50 psi [344,35 kPa] de H_2 (g) en un agitador Parr por 5 horas. La mezcla fue filtrada a través de una almohadilla de Celite, y el

solvente fue removido al vacío para proporcionar 2-amino-N-(isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)-benzamida (INTERMEDIARIO V.1) (470 mg, 1,4 mmol, 100%) como un vidrio de color verde parduzco.

Datos para 2-amino-N-(isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)benzamida (INTERMEDIARIO V.1): ^1H NMR (300 MHz, CDCl_3): δ 7,38 (br s, 1H), 6,6-6,8 (m, 3H), 6,22 (br d, 1H), 4,36 (br s, 2H, NH_2), 4,0-4,2 (m, 3H), 3,47-3,51 (m, 2H), 3,39 (t, 2H), 2,72 (dd, 2H), 2,60 (dd, 2H), 2,38 (s, 3H), 2,00 (m, 2H), 1,16 (d, 6H) ppm; MS (ESI) m/z : 348 ($[\text{M}+\text{H}]^+$).

De manera similar fueron preparados:

INTERMEDIARIO V.2: ter-Butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}perhidro-1,4-diazepina-1-carboxílico (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.3: ter-Butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}piperazina-1-carboxílico (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.4: 2-Amino-5-(3-dimetilaminopirrolidin-1-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.5: 2-Amino-5-(3-dimetilaminometilpiperidin-1-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO III.7)

INTERMEDIARIO V.6: 2-Amino-N-(isopropilcarbamoilmetil)-5-(4-metilpiperazin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.7: 2-Amino-N-(isopropilcarbamoilmetil)-5-((S)-3-piperidin-1-ilmetilpiperidin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO III.5)

INTERMEDIARIO V.8: 2-Amino-5-(4-dimetilaminopiperidin-1-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.9: 2-Amino-N-(isopropilcarbamoilmetil)-5-((R)-3-piperidin-1-ilmetilpiperidin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO III.4)

INTERMEDIARIO V.10: 2-Amino-N-(isopropilcarbamoilmetil)-5-(3-piperidin-1-ilmetilpiperidin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO III.3)

INTERMEDIARIO V.11: 2-Amino-N-(isopropilcarbamoilmetil)-5-(3-piperidin-1-ilmetilazetidin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO III.1)

INTERMEDIARIO V.12: 2-Amino-N-(isopropilcarbamoilmetil)-5-(4-fenilperhidro-1,4-diazepin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.13: 2-Amino-N-(ter-butilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)benzamida (a partir del INTERMEDIARIO IV.2)

INTERMEDIARIO V.14: 2-Amino-N-(isopropilcarbamoilmetil)-5-(3-piperidin-1-ilmetilpirrolidin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO III.2)

INTERMEDIARIO V.15: 2-Amino-5-[1,4']bipiperidinil-1'-il-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.16: 2-Amino-N-(isopropilcarbamoilmetil)-5-[3-(2-piperidin-1-iletal)azetidin-1-il]benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO III.8)

INTERMEDIARIO V.17: 2-Amino-N-(isopropilcarbamoilmetil)-5-(3-morfolin-4-ilmetilpiperidin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO III.6)

INTERMEDIARIO V.18: 2-Amino-N-(isopropilcarbamoilmetil)-5-((S)-3-metilpiperazin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.19: 2-Amino-5-(3,3-dimetilpiperazin-1-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.20: 2-Amino-5-(2,5-dimetilpiperazin-1-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.21: ter-Butil éster del ácido [2-amino-5-(hexahidropirrolo[1,2-a]pirazin-2-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3)

INTERMEDIARIO V.22: 2-Amino-5-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.23: 2-Amino-N-(isopropilcarbamoilmetil)-5-(4-isopropilpiperazin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.24: 2-Amino-5-(3,5-dimetilpiperazin-1-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.25: 2-Amino-N-(isopropilcarbamoilmetil)-5-((R)-3-metilpiperazin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.26: 2-Amino-5-(3-etilperhidro-1,4-diazepin-1-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO X.1)

INTERMEDIARIO V.27: 2-Amino-5-(3-fluorometilpiperazin-1-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO XII.1)

INTERMEDIARIO V.28: 2-Amino-N-(isopropilcarbamoilmetil)-5-((S)-2-pirrolidin-1-ilmetilpirrolidin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.29: 2-Amino-N-(isopropilcarbamoilmetil)-5-(5-metilperhidro-1,4-diazepin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO XI.1)

INTERMEDIARIO V.30: ter-Butil éster del ácido [2-amino-5-(4-etilperhidro-1,4-diazepin-1-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3)

INTERMEDIARIO V.31: 2-Amino-N-(isopropilcarbamoilmetil)-5-(4-isopropilperhidro-1,4-diazepin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.32: 2-Amino-N-(isopropilcarbamoilmetil)-5-(3-propilperhidro-1,4-diazepin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO X.3)

INTERMEDIARIO V.33: 2-Amino-N-(isopropilcarbamoilmetil)-5-[3-(2-metanosulfoniletil)perhidro-1,4-diazepin-1-il]benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO X.4)

INTERMEDIARIO V.34: 2-Amino-N-(isopropilcarbamoilmetil)-5-((S)-3-isopropilperhidro-1,4-diazepin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO X.5)

INTERMEDIARIO V.35: 2-Amino-N-(isopropilcarbamoilmetil)-5-((R)-3-isopropilperhidro-1,4-diazepin-1-il)benzamida (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO X.6)

INTERMEDIARIO V.36: 2-Amino-*N*-(isopropilcarbamoilmetil)-5-((*R*)-3-isopropilpiperazin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.37: 2-Amino-*N*-(isopropilcarbamoilmetil)-5-((*S*)-3-isopropilpiperazin-1-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.38: *ter*-Butil éster del ácido 4-{4-amino-3-[(*ter*-butilcarbamoilmetil)carbamoil]fenil}perhidro-1,4-diazepina-1-carboxílico (a partir del INTERMEDIARIO IV.2)

INTERMEDIARIO V.39: *ter*-Butil éster del ácido [2-amino-5-(6,6-dimetil-3-propilperhidro-1,4-diazepin-1-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3 y el INTERMEDIARIO X.9)

INTERMEDIARIO V.40: *ter*-Butil éster del ácido [2-amino-5-((*S*)-3-isopropilperhidro-1,4-diazepin-1-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3 y el INTERMEDIARIO X.11)

INTERMEDIARIO V.41: *ter*-Butil éster del ácido {2-amino-5-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]benzoilamino}acético (a partir del INTERMEDIARIO IV.3)

INTERMEDIARIO V.42: *ter*-Butil éster del ácido (*S*)-4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}-2-isopropilpiperazina-1-carboxílico (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.43: *ter*-Butil éster del ácido [2-amino-5-(6,6-dimetilperhidro-1,4-diazepin-1-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3 y el INTERMEDIARIO X.10)

INTERMEDIARIO V.44: *ter*-Butil éster del ácido [2-amino-5-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3 y el INTERMEDIARIO X.7)

INTERMEDIARIO V.45: ter-Butil éster del ácido [2-amino-5-(3-etil-6,6-dimetilperhidro-1,4-diazepin-1-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3 y el INTERMEDIARIO X.8)

INTERMEDIARIO V.46: 2-Amino-N-(isopropilcarbamoilmetil)-5-(octahidropirido[1,2-a]pirazin-2-il)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.47: 2-Amino-5-(1,4-diazabicyclo[3.2.2]non-4-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

INTERMEDIARIO V.48: 2-Amino-5-(hexahidropirrollo[1,2-a]pirazin-2-il)-N-(isopropilcarbamoilmetil)benzamida (a partir del INTERMEDIARIO IV.1)

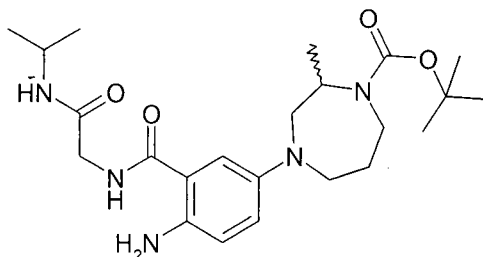
INTERMEDIARIO V.49: 2-Amino-N-(ter-butilcarbamoilmetil)-5-(4-isopropilperhidro-1,4-diazepin-1-il)benzamida (a partir del INTERMEDIARIO IV.2)

INTERMEDIARIO V.50: ter-Butil éster del ácido [2-amino-5-((R)-3-metilpiperazin-1-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3)

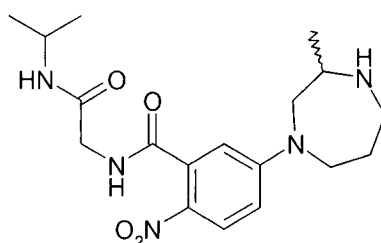
INTERMEDIARIO V.51: ter-Butil éster del ácido [2-amino-5-(1,4-diazabicyclo[3.2.2]non-4-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3)

INTERMEDIARIO V.52: ter-Butil éster del ácido [2-amino-5-(4-isopropilperhidro-1,4-diazepin-1-il)benzoilamino]acético (a partir del INTERMEDIARIO IV.3)

INTERMEDIARIO V.53: ter-Butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}-2-metilperhidro-1,4-diazepina-1-carboxílico



a) N-(Isopropilcarbamoilmetil)-5-(3-metilperhidro-1,4-diazepin-1-il)-2-nitrobenzamida

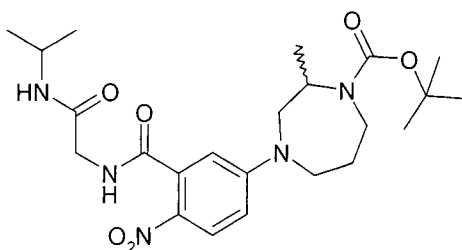


5-Fluoro-N-(isopropilcarbamoilmetil)-2-nitrobenzamida

(INTERMEDIARIO IV.1) (150 mg, 0,530 mmol), 2-metilperhidro-1,4-diazepina (INTERMEDIARIO X.2) (61 mg, 0,530 mmol) y carbonato de potasio (220 mg, 1,589 mmol) en acetonitrilo (3 ml) fueron agitados a temperatura ambiente por 48 horas, seguido por calentamiento a 50-60°C por 2 horas. La mezcla de reacción fue filtrada a través de un tapón de sílice, el solvente fue evaporado bajo presión reducida y el producto crudo fue purificado por cromatografía en sílica gel, con una gradiente de DCM a DCM:MeOH (4:1, v/v) como eluyente. Esto proporcionó N-(isopropilcarbamoilmetil)-5-(3-metilperhidro-1,4-diazepin-1-il)-2-nitrobenzamida (72 mg, 0,191 mmol, 36%).

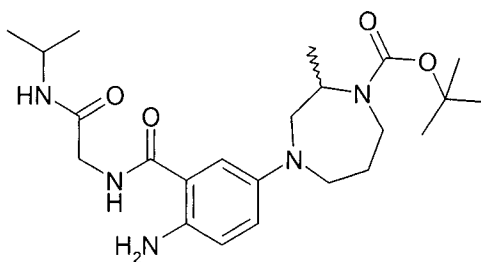
Datos para N-(isopropilcarbamoilmetil)-5-(3-metilperhidro-1,4-diazepin-1-il)-2-nitrobenzamida: MS (ESI) m/z : 379 ($[M+H]^+$).

b) ter-Butil éster del ácido 4-{3-[(isopropilcarbamoilmetil)carbamoil]-4-nitrofenil}-2-metilperhidro-1,4-diazepina-1-carboxílico



N-(Isopropilcarbamoilmetil)-5-(3-metilperhidro-1,4-diazepin-1-il)-2-nitrobenzamida (72 mg, 0,191 mmol) y dicarbonato de di-ter-butilo (42 mg, 0,191 mmol) en DCM (5 ml) fueron agitados a temperatura ambiente durante la noche. El solvente fue evaporado bajo presión reducida para proporcionar ter-butil éster del ácido 4-{3-[(isopropilcarbamoilmetil)carbamoil]-4-nitrofenil}-2-metilperhidro-1,4-diazepina-1-carboxílico crudo (100 mg, 0,209 mmol, 100%), que fue usado directamente en la etapa siguiente.

c) ter-Butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}-2-metilperhidro-1,4-diazepina-1-carboxílico



ter-Butil éster del ácido 4-{3-[(isopropilcarbamoilmetil)carbamoil]-4-nitrofenil}-2-metilperhidro-1,4-diazepina-1-carboxílico (100 mg, 0,209 mmol) y Pd al 10%/C. (10 mg, 0,209 mmol) en MeOH (5 ml), fueron agitados bajo 4 bar [400 kPa] de H₂ (g) a temperatura ambiente durante la noche. La mezcla fue filtrada a través de una almohadilla de Celite, y el solvente fue

removido al vacío para proporcionar ter-butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}-2-metil-perhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO V.53) (94 mg, 0,210 mmol, 100%). Éste fue usado directamente sin purificación.

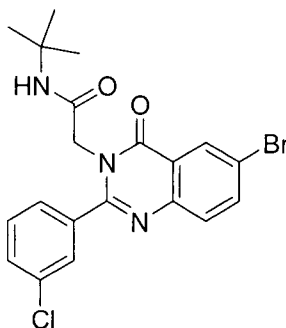
De manera similar fueron preparados:

INTERMEDIARIO V.54: ter-Butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}-6,6-dimetilperhidro-1,4-diazepina-1-carboxílico (a partir del INTERMEDIARIO IV.1 y el INTERMEDIARIO X.10)

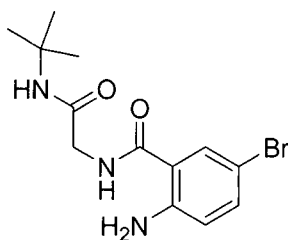
INTERMEDIARIO V.55: ter-Butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}-6-fluoroperhidro-1,4-diazepina-1-carboxílico (a partir de los INTERMEDIARIOS IV.1 y XII.2)

Procedimiento VI

INTERMEDIARIO VI.1: 2-[6-Bromo-2-(3-clorofenil)-4-oxo-4H-quinazolin-3-il]-N-ter-butilacetamida



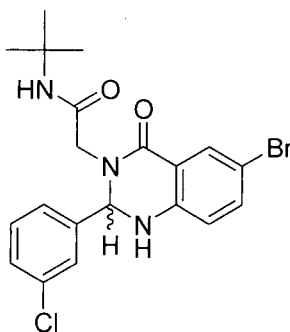
a) 2-Amino-5-bromo-N-(ter-butilcarbamoilmetil)benzamida



Una suspensión de anhídrido 5-bromoisatoico (1,2 g, 5,0 mmoles) y 2-amino-*N*-*ter*-butilacetamida (INTERMEDIARIO I.2) (0,78 g, 6,0 mmoles) en acetonitrilo (8 ml) fue agitada a temperatura ambiente por 20 horas. La suspensión blanca fue filtrada, y el precipitado blanco fue lavado con EtOH frío para dar 2-amino-5-bromo-*N*-(*ter*-butilcarbamoilmetil)benzamida (1,06 g, 3,22 mmoles, 65%).

Datos para 2-amino-5-bromo-*N*-(*ter*-butilcarbamoilmetil)benzamida: ^1H NMR (300 MHz, d^6 -DMSO): δ 8,44 (t, 1H), 7,68 (d, 1H), 7,49 (s, 1H), 7,27 (dd, 1H), 6,67 (d, 1H), 6,56 (br s, 1H), 3,73 (d, 1H), 3,33 (br s, 2H), 1,26 (s, 9H) ppm; MS (ESI) m/z : 328/330 ($[\text{M}+\text{H}]^+$).

b) 2-[6-Bromo-2-(3-clorofenil)-4-oxo-1,4-dihidro-2*H*-quinazolin-3-il]-*N*-*ter*-butilacetamida

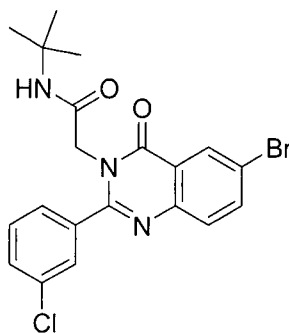


En un frasco de centelleo de 20 ml tapado, una solución de 2-amino-5-bromo-*N*-(*ter*-butilcarbamoilmetil)benzamida (0,65 g, 2,0 mmoles), 3-clorobenzaldehído (0,27 ml, 2,4 mmoles) y ácido acético glacial catalítico (2 gotas) en etanol anhidro (10 ml),

fue calentada con agitación a 85°C por 16 horas. La suspensión blanca resultante fue enfriada hasta temperatura ambiente, y el sólido blanco fue recolectado por filtración con succión y lavado con EtOH frío, para dar 2-[6-bromo-2-(3-clorofenil)-4-oxo-1,4-dihidro-2H-quinazolin-3-il]-N-ter-butilacetamida (0,53 g, 1,21 mmol, 58%).

Datos para 2-[6-bromo-2-(3-clorofenil)-4-oxo-1,4-dihidro-2H-quinazolin-3-il]-N-ter-butilacetamida: MS (ESI) m/z: 450/452 ([M+H]⁺).

c) 2-(6-Bromo-2-(3-clorofenil)-4-oxoquinazolin-3(4H)-il)-N-ter-butilacetamida

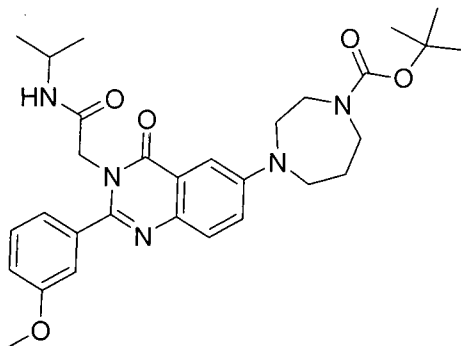


En un frasco de centelleo de 20 ml tapado, una mezcla de 2-[6-bromo-2-(3-clorofenil)-4-oxo-1,4-dihidro-2H-quinazolin-3-il]-N-ter-butilacetamida (0,51 g, 1,13 mmol) y dióxido de manganeso(IV) (0,44 g, 5,10 mmoles) en cloroformo (10 ml) fue calentada a 70°C por 3 horas. La suspensión negra fue enfriada hasta temperatura ambiente, filtrada a través de una almohadilla de Celite y concentrada al vacío, para proporcionar 2-[6-bromo-2-(3-clorofenil)-4-oxo-4H-quinazolin-3-il]-N-ter-butilacetamida (INTERMEDIARIO VI.1) (0,51 g, 1,13 mmol, 100%) como un sólido blanco.

Datos para 2-[6-bromo-2-(3-clorofenil)-4-oxo-4H-quinazolin-3-il]-N-ter-butilacetamida (INTERMEDIARIO VI.1): ^1H NMR (300 MHz, CDCl_3): δ 9,44 (d, 1H), 7,86 (dd, 1H), 7,65-7,54 (m, 2H), 7,53-7,4 (m, 3H), 5,47 (s, 1H), 4,46 (s, 2H), 1,34 (s, 9H) ppm; MS (ESI) m/z : 448/450 ($[\text{M}+\text{H}]^+$).

Procedimiento VII

INTERMEDIARIO VII.1: ter-Butil éster del ácido 4-[3-(isopropilcarbamoilmetil)-2-(3-metoxifenil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico



Una mezcla de ter-butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}perhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO V.2) (300 mg, 0,69 mmol) y 3-metoxibencimidato de etilo clorhidrato (INTERMEDIARIO II.2) (298 mg, 1,38 mmol) en EtOH (6 ml), fue calentada a temperatura de reflujo por 16 horas. La mezcla de reacción fue enfriada y filtrada, y el filtrado fue concentrado al vacío. El residuo crudo fue purificado por HPLC preparatoria para dar ter-butil éster del ácido 4-[3-(isopropilcarbamoilmetil)-2-(3-metoxifenil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO VII.1) (50 mg, 0,09 mmol, 13%).

De manera similar fueron preparados:

INTERMEDIARIO VII.2: ter-Butil éster del ácido 4-[2-(3-clorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico (a partir de los INTERMEDIARIOS V.2 y II.1)

INTERMEDIARIO VII.3: ter-Butil éster del ácido 4-[2-(3-clorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]piperazina-1-carboxílico (a partir de los INTERMEDIARIOS V.3 y II.1)

INTERMEDIARIO VII.4: ter-Butil éster del ácido 4-[3-(ter-butilcarbamoilmetil)-2-(3-cloro-4-fluorofenil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico (a partir de los INTERMEDIARIOS V.38 y II.4)

INTERMEDIARIO VII.5: ter-Butil éster del ácido 4-[3-(ter-butilcarbamoilmetil)-2-(4-fluoro-3-metoxifenil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico (a partir de los INTERMEDIARIOS V.38 y II.3)

INTERMEDIARIO VII.6: ter-Butil éster del ácido 4-[2-(3-cloro-4-fluorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico (a partir de los INTERMEDIARIOS V.2 y II.4)

INTERMEDIARIO VII.7: ter-Butil éster del ácido 4-[2-(4-fluoro-3-metoxifenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico (a partir de los INTERMEDIARIOS V.2 y II.3)

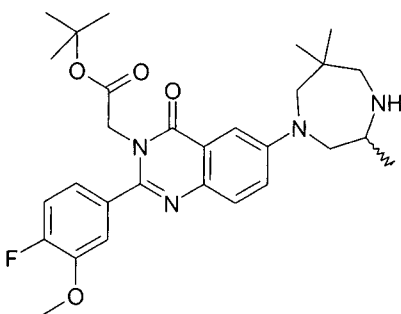
INTERMEDIARIO VII.8: ter-Butil éster del ácido [2-(3-cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir de los INTERMEDIARIOS V.30 y II.4)

INTERMEDIARIO VII.9: ter-Butil éster del ácido {2-(4-fluoro-3-metoxifenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4*H*-quinazolin-3-il}acético (a partir de los INTERMEDIARIOS V.41 y II.3)

INTERMEDIARIO VII.10: ter-Butil éster del ácido 4-[2-(4-fluoro-3-metoxifenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]-6,6-dimetilperhidro-1,4-diazepina-1-carboxílico (a partir de los INTERMEDIARIOS V.54 y II.3)

INTERMEDIARIO VII.11: ter-Butil éster del ácido 4-[2-(3-cloro-4-fluorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]-6,6-dimetilperhidro-1,4-diazepina-1-carboxílico (a partir de los INTERMEDIARIOS V.54 y II.2)

INTERMEDIARIO VII.12: ter-Butil éster del ácido [2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4*H*-quinazolin-3-il]acético



ter-Butil éster del ácido [2-amino-5-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)benzoilamino]acético (INTERMEDIARIO V.44) (1,00 g, 2,56 mmoles), 4-fluoro-3-metoxibenzaldehído (414 mg, 2,69 mmoles), etanol (20 ml) y ácido acético (3 gotas) fueron agitados durante la noche a temperatura de reflujo. El solvente fue evaporado bajo presión reducida. La mezcla de reacción cruda fue purificada por SCX y el producto fue

eluido con NH_3 2N/MeOH. El solvente fue evaporado bajo presión reducida y el producto fue disuelto en tolueno (10 ml) y agua (10 ml). Se agregó hexacianoferrato(III) de potasio (8,43 g, 25,6 mmoles) y la mezcla de reacción fue agitada vigorosamente durante la noche. Enseguida, la reacción fue extinguida por adición de metanol (300 ml), la mezcla fue filtrada a través de una almohadilla de Celite, y la torta fue lavada con más cantidad de metanol (200 ml). El filtrado fue evaporado a sequedad y purificado por cromatografía en sílica gel, con una gradiente de DCM a DCM:MeOH (3:1, v/v) como eluyente, para proporcionar *ter*-butil éster del ácido [2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]acético (INTERMEDIARIO VII.12) (160 mg, 0,305 mmol, 12%).

INTERMEDIARIO VII.13: *ter*-Butil éster del ácido [2-(3-cloro-4-fluorofenil)-6-(1,4-diazabicyclo[3.2.2]non-4-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.51)

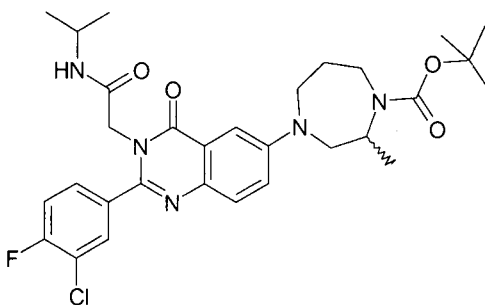
INTERMEDIARIO VII.14: *ter*-Butil éster del ácido [6-(1,4-diazabicyclo[3.2.2]non-4-il)-2-(3,5-dimetoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.51)

INTERMEDIARIO VII.15: *ter*-Butil éster del ácido [6-(1,4-diazabicyclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.51)

INTERMEDIARIO VII.16: *ter*-Butil éster del ácido [6-(3-etil-6,6-dimetilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.45)

INTERMEDIARIO VII.17: ter-Butil éster del ácido [2-(3-cloro-4-fluorofenil)-6-((R)-3-metilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.50)

INTERMEDIARIO VII.18: ter-Butil éster del ácido 4-[2-(3-cloro-4-fluorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidro-quinazolin-6-il]-2-metilperhidro-1,4-diazepina-1-carboxílico



ter-Butil éster del ácido 4-{4-amino-3-[(isopropilcarbamoilmetil)carbamoil]fenil}-2-metilperhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO V.53) (94 mg, 0,201 mmol), 3-cloro-4-fluorobenzaldehído (40 mg, 0,252 mmol) y ácido acético (3 μ l, catalítico) fueron disueltos en etanol (3 ml) en un frasco para microondas y el frasco fue sellado. La mezcla de reacción fue agitada a 90°C por 16 horas. La mezcla de reacción fue evaporada a sequedad, el material crudo fue disuelto en DCM (3 ml) y se agregó dióxido de manganeso (80 mg, 0,840 mmol). La mezcla de reacción fue agitada en un frasco sellado a 60°C por 3 horas. La TLC mostró una reacción incompleta, de manera que se agregó más cantidad de dióxido de manganeso (80 mg, 0,840 mmol), y la mezcla de reacción fue calentada a 60°C por 2 horas más. El solvente fue evaporado bajo presión reducida y el producto crudo fue purificado por cromatografía en sílica gel con DCM:MeOH (9:1, v/v) como eluyente. Esto proporcionó ter-butil éster del ácido

4-[2-(3-cloro-4-fluorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]-2-metilperhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO VII.18) (65 mg, 0,111 mmol, 53%).

Datos para ter-butil éster del ácido 4-[2-(3-cloro-4-fluorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]-2-metilperhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO VII.18): MS (ESI) m/z : 586/588 ($[M+H]^+$).

INTERMEDIARIO VII.19: ter-Butil éster del ácido (S)-4-[2-(3-cloro-4-fluorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]-2-isopropilpiperazina-1-carboxílico (a partir del INTERMEDIARIO V.42)

INTERMEDIARIO VII.20: ter-Butil éster del ácido [2-(3-cloro-4-fluorofenil)-6-(hexahidropirrolo[1,2-a]pirazin-2-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.21)

INTERMEDIARIO VII.21: ter-Butil éster del ácido [2-(3-cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.52)

INTERMEDIARIO VII.22: ter-Butil éster del ácido [2-(3-cloro-4-fluorofenil)-6-(dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.43)

INTERMEDIARIO VII.23: ter-Butil éster del ácido [2-(3-clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.52)

INTERMEDIARIO VII.24: ter-Butil éster del ácido [6-(4-etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.30)

INTERMEDIARIO VII.25: ter-Butil éster del ácido [6-(6,6-dimetil-3-propilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-

metoxifenil)-4-oxo-4*H*-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.39)

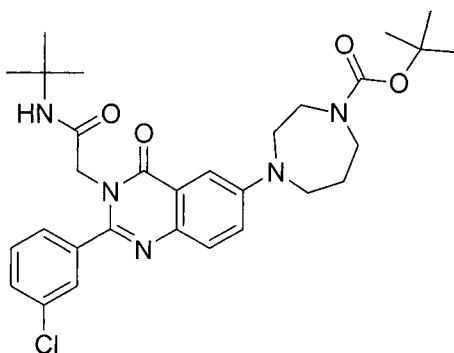
INTERMEDIARIO VII.26: ter-Butil éster del ácido [2-(4-fluoro-3-metoxifenil)-6-((*S*)-3-isopropil-6,6-dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acético (a partir del INTERMEDIARIO V.40)

INTERMEDIARIO VII.27: ter-Butil éster del ácido 4-[2-(3-cloro-4-fluorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidro-quinazolin-6-il]-6-fluoroperhidro-1,4-diazepina-1-carboxílico (a partir del INTERMEDIARIO V.55)

INTERMEDIARIO VII.28: ter-Butil éster del ácido 4-[2-(3-cloro-4-fluorofenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidro-quinazolin-6-il]piperazina-1-carboxílico (a partir del INTERMEDIARIO V.3)

Procedimiento VIII

INTERMEDIARIO VIII.1: ter-Butil éster del ácido 4-[3-(ter-butilcarbamoilmetil)-2-(3-clorofenil)-4-oxo-3,4-dihidro-quinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico



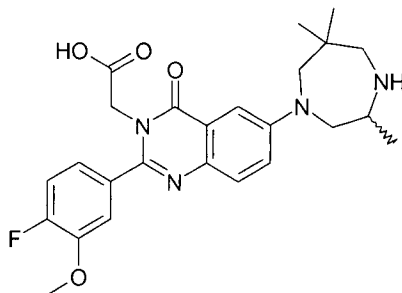
2,2'-Bis(difenilfosfino)-1,1'-binaftilo racémico (5 mg, 0,009 mmol) y tolueno anhidro (0,5 ml) fueron calentados en un frasco para microondas con agitación a 80°C bajo una atmósfera de

argón, hasta que se obtuvo una solución lechosa homogénea (≈5 minutos). Esta solución fue enfriada hasta temperatura ambiente y se agregó acetato de paladio(II) (2 mg, 0,006 mmol). Después de agitar a temperatura ambiente por 2 minutos, 2-[6-bromo-2-(3-clorofenil)-4-oxo-4*H*-quinazolin-3-il]-*N*-ter-butilacetamida (INTERMEDIARIO VI.1) (67 mg, 0,15 mmol), 1-homopiperazinacarboxilato de ter-butilo (35 μ l, 0,18 mmol) y carbonato de cesio recién molido (68 mg, 0,21 mmol) fueron agregados a la solución de color rojo. Se agregó dioxano anhidro (0,2 ml) para enjuagar hacia abajo el sólido que quedaba en el lado del frasco. El frasco fue tapado y calentado en un horno de microondas a 120°C por 40 minutos. La mezcla de reacción fue diluida con DCM (3 ml) y filtrada, y el filtrado fue concentrado al vacío. Este producto crudo fue purificado por TLC preparatoria en sílica gel, con hexano:EtOAc:CH₂Cl₂ (1:1:1, v/v) como eluyente, para dar ter-butil éster del ácido 4-[3-(ter-butilcarbamoilmetil)-2-(3-clorofenil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO VIII.1) (38,9 mg, 0,07 mmol, 46%) como un sólido de color amarillo.

Datos para ter-butil éster del ácido 4-[3-(ter-butilcarbamoilmetil)-2-(3-clorofenil)-4-oxo-3,4-dihidroquinazolin-6-il]perhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO VIII.1):
¹H NMR (300 MHz, CDCl₃): δ 7,7-7,4 (m, 6H), 7,3-7,2 (m, 1H), 5,70 (s, 1H), 4,43 (s, 2H), 3,7-3,6 (m, 6H), 3,3-3,2 (m, 2H), 2,02 (m, 2H), 1,33 (s, 18H) ppm; MS (ESI) *m/z*: 568/570 ([M+H]⁺).

Procedimiento IX

INTERMEDIARIO IX.1: Ácido [2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-acético



ter-Butil éster del ácido [2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]acético (INTERMEDIARIO VII.12) (160 mg, 0,305 mmol) fue disuelto en DCM (10 ml) y se agregó TFA (3 ml). La mezcla de reacción fue agitada a temperatura ambiente durante la noche. La mezcla de reacción cruda fue vertida directamente sobre un cartucho de SCX, el cartucho fue lavado con MeOH y el producto fue eluido con NH_3 2N/MeOH. El solvente fue removido bajo presión reducida para proporcionar ácido [2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]acético (INTERMEDIARIO IX.1), que fue usado sin mayor purificación.

Datos para ácido [2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]acético (INTERMEDIARIO IX.1): MS (ESI) m/z : 469 ($[\text{M}+\text{H}]^+$).

De manera similar fueron preparados:

INTERMEDIARIO IX.2: Ácido [6-(1,4-diazabicyclo[3.2.2]non-4-il)-2-(3,5-dimetoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.14)

INTERMEDIARIO IX.3: Ácido [6-(3-etil-6,6-dimetilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.16)

INTERMEDIARIO IX.4: Ácido [2-(3-cloro-4-fluorofenil)-6-(dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.22)

INTERMEDIARIO IX.5: Ácido [6-(6,6-dimetil-3-propilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.25)

INTERMEDIARIO IX.6: Ácido [2-(4-fluoro-3-metoxifenil)-6-((S)-3-isopropil-6,6-dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.26)

INTERMEDIARIO IX.7: Ácido [6-(1,4-diazabicyclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.15)

INTERMEDIARIO IX.8: Ácido [2-(3-cloro-4-fluorofenil)-6-((R)-3-metilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.17)

INTERMEDIARIO IX.9: Ácido [2-(3-cloro-4-fluorofenil)-6-(hexahidropirrólo[1,2-a]pirazin-2-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.20)

INTERMEDIARIO IX.10: Ácido [2-(3-cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.21)

INTERMEDIARIO IX.11: Ácido [6-(4-etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.24)

INTERMEDIARIO IX.12: Ácido [2-(3-cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.8)

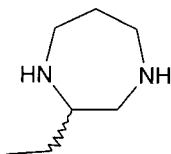
INTERMEDIARIO IX.13: Ácido {2-(4-fluoro-3-metoxifenil)-6-[4-(2-hidroxietilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]}acético (a partir del INTERMEDIARIO VII.9)

INTERMEDIARIO IX.14: Ácido [2-(3-clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.23)

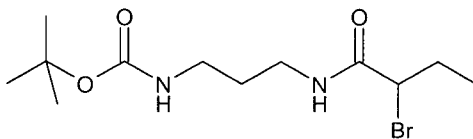
INTERMEDIARIO IX.15: Ácido [2-(3-cloro-4-fluorofenil)-6-(1,4-diazabicyclo[3.2.2]non-4-il)-4-oxo-4*H*-quinazolin-3-il]acético (a partir del INTERMEDIARIO VII.13)

Procedimiento X

INTERMEDIARIO X.1: 2-Etilperhidro-1,4-diazepina



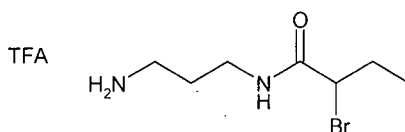
a) ter-Butil éster del ácido [3-(2-bromobutirilamino)-propil]carbámico



Anhídrido cíclico del ácido 1-propanofosfónico (4,11 g, 3,84 ml, 6,46 mmoles) fue agregado a una solución enfriada de 3-aminopropilcarbamato de ter-butilo (750 mg, 4,30 mmoles), ácido 2-bromobutanoico (791 mg, 0,51 ml, 4,73 mmoles) y trietilamina (1,31 g, 1,82 ml, 12,91 mmoles) en DCM (5 ml). La mezcla de

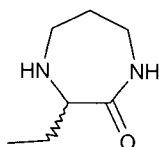
reacción fue agitada a temperatura ambiente por 2 horas, seguido por la adición de Na_2CO_3 (acuoso). Esto fue agitado por 30 minutos y después la capa orgánica fue separada. El solvente fue evaporado bajo presión reducida y el producto crudo fue purificado por cromatografía en sílica gel, con $\text{DCM}:\text{MeOH}$ (9:1, v/v) como eluyente. Esto proporcionó ter-butil éster del ácido [3-(2-bromobutirilamino)propil]carbámico (1,41 g, 4,36 mmoles, 100%).

b) N-(3-Aminopropil)-2-bromobutiramida, sal de ácido tri-fluoroacético



ter-Butil éster del ácido [3-(2-bromobutirilamino)-propil]carbámico (1,41 g, 4,36 mmoles) fue tratado con $\text{TFA}:\text{DCM}$ (1:1 (v/v), 20 ml), y la solución fue agitada a temperatura ambiente por 3 horas. Los materiales volátiles fueron removidos al vacío y el producto crudo, aislado como la sal de ácido trifluoroacético, fue usado directamente en la etapa siguiente.

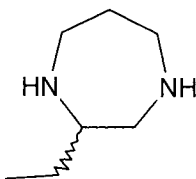
c) 3-Etilperhidro-1,4-diazepin-2-ona



N-(3-Aminopropil)-2-bromobutiramida, sal de ácido trifluoroacético (1,8 g, 5,33 mmoles), K_2CO_3 (2,94 g, 21,33 mmoles) y acetonitrilo (30 ml) fueron combinados y agitados a

140°C en un horno de microondas por 3.500 segundos. El análisis mostró la presencia de una cantidad considerable de material de partida, de manera que la mezcla de reacción fue sometida a 2.000 segundos más a 140°C. La mezcla de reacción fue diluida con DCM (50 ml) y filtrada a través de Celite. El solvente fue evaporado bajo presión reducida y purificado por cromatografía en sílica gel, con una gradiente de DCM a DCM:MeOH (3:1, v/v) como eluyente. Esto proporcionó 3-etilperhidro-1,4-diazepin-2-ona (540 mg, 3,80 mmoles, 71%).

d) 2-Etilperhidro-1,4-diazepina



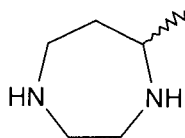
Hidruro de litio y aluminio (475 mg, 12,49 mmoles) fue agregado en porciones a una solución con agitación de 3-etilperhidro-1,4-diazepin-2-ona (740 mg, 5,20 mmoles) en THF (10 ml). Después de que la efervescencia resultante había disminuido, la mezcla de reacción fue calentada a 50-60°C por 3 horas. La mezcla de reacción fue enfriada y extinguida por adición lenta de agua y NaOH al 10% (acuoso). La mezcla de reacción fue diluida con éter dietílico (20 ml) y filtrada a través de Celite. La torta de filtrado fue lavada acabadamente con THF (50 ml), éter dietílico (50 ml), THF (50 ml) y éter dietílico (50 ml). La evaporación bajo presión reducida proporcionó 2-etilperhidro-1,4-diazepina (INTERMEDIARIO X.1) (615 mg, 5,20 mmoles), 92%).

De manera similar, fueron preparados:

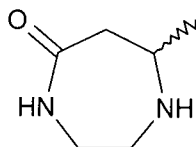
INTERMEDIARIO X.2: 2-Metilperhidro-1,4-diazepina
INTERMEDIARIO X.3: 2-Propilperhidro-1,4-diazepina
INTERMEDIARIO X.4: 2-(2-Metanosulfoniletil)perhidro-1,4-diazepina
INTERMEDIARIO X.5: (S)-2-Isopropilperhidro-1,4-diazepina
INTERMEDIARIO X.6: (R)-2-Isopropilperhidro-1,4-diazepina
INTERMEDIARIO X.7: 2,6,6-Trimetilperhidro-1,4-diazepina
INTERMEDIARIO X.8: 2-Etil-6,6-dimetilperhidro-1,4-diazepina
INTERMEDIARIO X.9: 6,6-Dimetil-2-propilperhidro-1,4-diazepina
INTERMEDIARIO X.10: 6,6-Dimetilperhidro-1,4-diazepina
INTERMEDIARIO X.11: 6,6-Dimetil-(S)-2-isopropilperhidro-1,4-diazepina

Procedimiento XI

INTERMEDIARIO XI.1: 5-Metil-1,4-diazepano



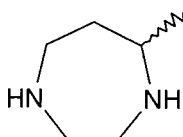
a) 7-Metil-1,4-diazepan-5-ona



Etano-1,2-diamina (1,35 g, 22,44 mmoles) y (E)-but-2-enoato de etilo (2,56 g, 22,44 mmoles) en MeOH (22 ml) fueron agitados a temperatura ambiente durante la noche. El solvente fue evaporado bajo presión reducida y el producto crudo fue purificado por cromatografía en sílica gel, con una gradiente de DCM a DCM:NH₃ 2M/MeOH (4:1, v/v) como eluyente. Esto proporcionó una mezcla del producto deseado y material no ciclado. La mezcla

fue diluida con MeOH (4 ml) y calentada en el horno de microondas a 150°C por 10 minutos, seguido por 160°C por 10 minutos. Se agregó bicarbonato de sodio (100 mg) y la mezcla de reacción fue agitada a temperatura ambiente por 48 horas. La mezcla de reacción fue filtrada, el solvente fue evaporado bajo presión reducida, y el producto crudo fue purificado por cromatografía en sílica gel con una gradiente de DCM a DCM:NH₃ 2M/MeOH (4:1, v/v) como eluyente, para proporcionar 7-metil-1,4-diazepan-5-ona (310 mg, 2,42 mmoles, 11%).

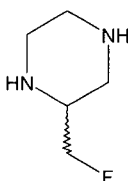
b) 5-Metil-1,4-diazepano



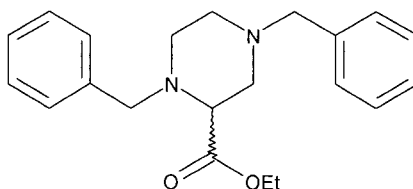
Procedimiento similar al INTERMEDIARIO X.1 paso d), a partir de 7-metil-1,4-diazepan-5-ona (356 mg, 2,75 mmoles) e hidruro de litio y aluminio (1M en THF) (249 mg, 6,56 ml, 6,56 mmoles), para proporcionar 5-metil-1,4-diazepano (INTERMEDIARIO XI.1) (235 mg, 2,06 mmoles, 74%).

Procedimiento XII

INTERMEDIARIO XII.1: 2-Fluorometilpiperazina

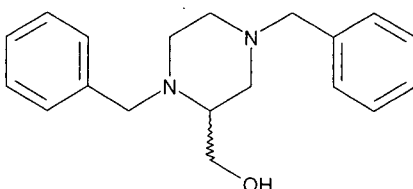


a) Etil éster del ácido 1,4-dibencilpiperazina-2-carboxílico



Una solución de *N,N*-dibenciletilendiamina (980 μ l, 4,10 mmoles) y trietilamina (1,03 ml, 7,38 mmoles) en tolueno (15 ml) fue agregada gota a gota a una solución de etil éster del ácido 2-bromopropiónico (601 μ l, 4,14 mmoles) en tolueno (15 ml). La mezcla de reacción fue agitada a 80°C por 72 horas. La mezcla de reacción fue filtrada a través de una almohadilla de Celite y el solvente fue evaporado bajo presión reducida, para proporcionar etil éster del ácido 1,4-dibencilpiperazina-2-carboxílico (1,33 g, 3,93 mmoles, 96%) como un aceite de color amarillo. Datos para etil éster del ácido 1,4-dibencilpiperazina-2-carboxílico: MS (ESI) m/z : 339 ($[M+H]^+$).

b) (1,4-Dibencilpiperazin-2-il)metanol

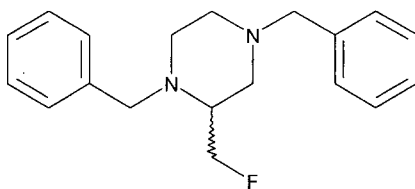


Hidruro de litio y aluminio (1M en THF) (4 ml, 3,93 mmoles) fue agregado a una solución con agitación de etil éster del ácido 1,4-dibencilpiperazina-2-carboxílico (1,33 g, 3,93 mmoles) en THF (25 ml) enfriada a -78°C bajo una atmósfera de nitrógeno. Se agregó agua (145 μ l), NaOH (acuoso) (al 10% en peso, 145 μ l) y agua (450 μ l), a intervalos de 45 minutos. La mezcla de reacción fue filtrada a través de una almohadilla de Celite y el solvente fue evaporado bajo presión reducida, para

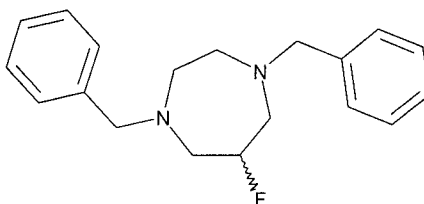
proporcionar (1,4-dibencilpiperazin-2-il)metanol (1,16 g, 3,93 mmoles, 100%) como un aceite de color amarillo pálido.

Datos para (1,4-dibencilpiperazin-2-il)metanol: MS (ESI) m/z : 298 ($[M+H]^+$).

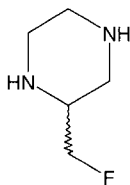
c) 1,4-Dibencil-2-fluorometilpiperazina



(1,4-Dibencilpiperazin-2-il)metanol (15 g, 50,5 mmoles) en DCM (50 ml) fue agregado gota a gota a una solución con agitación de DAST (7,42 ml, 60,6 mmoles) en DCM (150 ml) enfriada a -78°C . La mezcla de reacción fue mantenida a menos de -30°C por 24 horas, antes de entibiar hasta temperatura ambiente y agitar por 20 horas más. La reacción fue extinguida por adición de agua (100 ml). La fase orgánica fue separada, y la fase acuosa fue basificada con NaOH (acuoso) hasta pH 10 y extraída con DCM (3 X 75 ml). Los orgánicos combinados fueron lavados con agua (2 X 100 ml) y solución salina (2 X 100 ml), secados (Na_2SO_4) y concentrados bajo presión reducida. El aceite resultante fue purificado por cromatografía en sílica gel con EtOAc:heptano (1:9, v/v) como eluyente, para proporcionar 1,4-dibencil-2-fluorometilpiperazina (6,0 g, 20,1 mmoles, 40%). También se aisló un subproducto de la reacción, 1,4-dibencil-6-fluoroperhidro-1,4-diazepina (1,0 g, 3,35 mmoles, 7%).

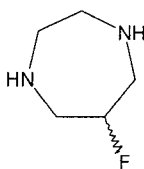


d) 2-Fluorometilpiperazina



Paladio en carbón de leña (al 10% en peso) (400 mg) como una lechada en MeOH fue agregado a una solución de 1,4-dibencil-2-fluorometilpiperazina (400 mg, 1,34 mmol) en MeOH (20 ml). Esto fue sometido a H₂ (g) a una presión de 5 bar [500 kPa] por 18 horas. La mezcla de reacción fue filtrada a través de Celite y el solvente fue evaporado bajo presión reducida. Esto proporcionó 2-fluorometilpiperazina (INTERMEDIARIO XII.1) (136 mg, 1,14 mmol, 86%) como un aceite de color amarillo pálido.

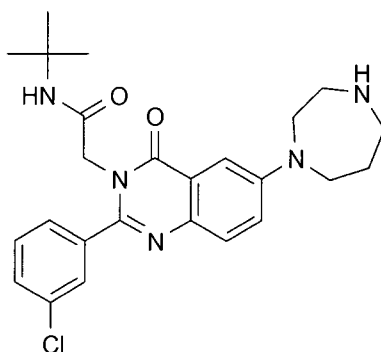
INTERMEDIARIO XII.2: 6-Fluoroperhidro-1,4-diazepina



Preparado de una manera similar a partir de 1,4-dibencil-6-fluoroperhidro-1,4-diazepina (aislada como un producto secundario en la síntesis del INTERMEDIARIO XII.1).

Síntesis de los Ejemplos de acuerdo con la invención

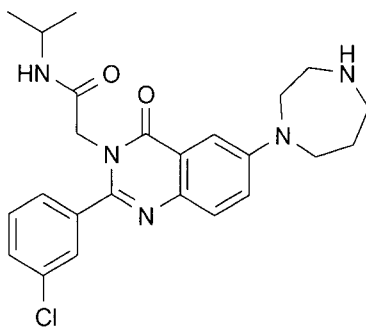
EJEMPLO 1a: N-ter-Butil-2-[2-(3-clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]acetamida



ter-Butil éster del ácido 4-[3-(ter-butilcarbamoil-metil)-2-(3-clorofenil)-4-oxo-3,4-dihidroquinazolin-6-il]-perhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO VIII.1) (38,9 mg, 0,068 mmol) fue tratado con TFA:DCM (1:1 (v/v), 1 ml), y la solución fue agitada a temperatura ambiente por 40 minutos. Los materiales volátiles fueron removidos al vacío y el residuo fue sometido a partición entre DCM y NaOH 1M (acuoso). Los orgánicos fueron secados (Na₂SO₄) y concentrados al vacío, para proporcionar N-ter-butil-2-[2-(3-clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]acetamida (EJEMPLO 1a) (27 mg, 0,046 mmol, 68%) como la sal de ácido trifluoroacético. Datos para N-ter-butil-2-[2-(3-clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]acetamida (EJEMPLO 1a)), sal de ácido trifluoroacético: ¹H NMR (300 MHz, CDCl₃): δ 7,6-7,4 (m, 6H), 7,21 (dd, 1H), 5,65 (s, 1H), 4,44 (s, 2H), 3,7-3,6 (m, 4H), 3,09 (t, 2H), 2,85 (t, 2H), 2,47 (br s, 1H), 1,98 (m, 2H), 1,34 (s, 9H) ppm; MS (ESI) m/z: 468/470 ([M+H]⁺).

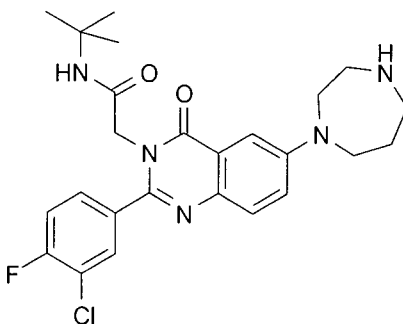
Los siguientes compuestos fueron preparados de una manera similar a partir de INTERMEDIARIOS VII u VIII:

EJEMPLO 1b: 2-[2-(3-Clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]-N-isopropilacetamida



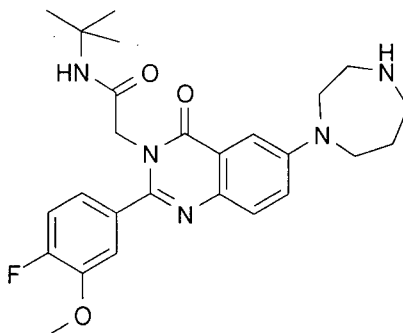
MS (ESI) m/z : 454/456 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.2).

EJEMPLO 1c: N-ter-Butil-2-(2-(3-cloro-4-fluorofenil)-6-(1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)acetamida



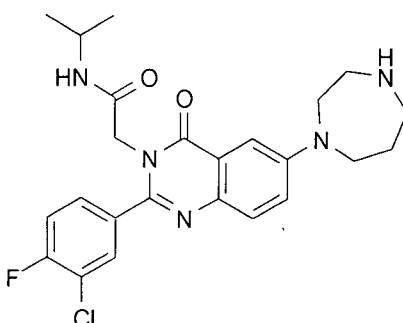
MS (ESI) m/z : 486/488 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.4).

EJEMPLO 1d: 2-(6-(1,4-Diazepan-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxoquinazolin-3(4H)-il)-N-ter-butilacetamida



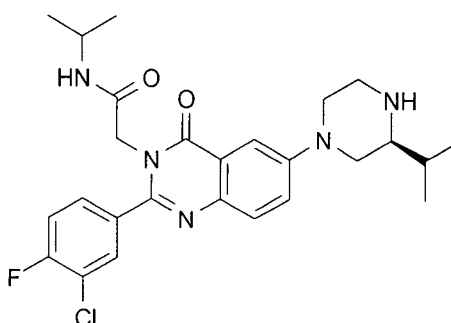
MS (ESI) m/z : 482 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.5).

EJEMPLO 1e: 2-(2-(3-Cloro-4-fluorofenil)-6-(1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida



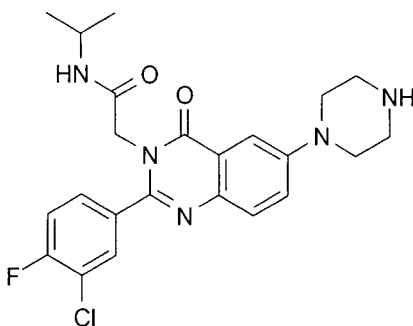
MS (ESI) m/z : 472 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.6).

EJEMPLO 1f: (S)-2-(2-(3-Cloro-4-fluorofenil)-6-(3-isopropilpiperazin-1-il)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida



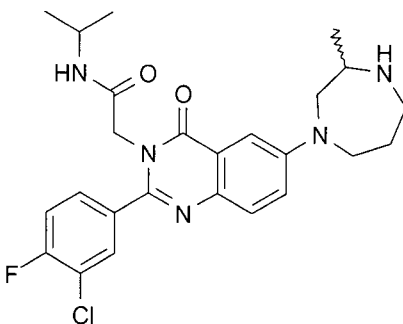
MS (ESI) m/z : 500/502 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.19).

EJEMPLO 1g: 2-(2-(3-Cloro-4-fluorofenil)-4-oxo-6-(piperazin-1-il)quinazolin-3(4H)-il)-N-isopropilacetamida



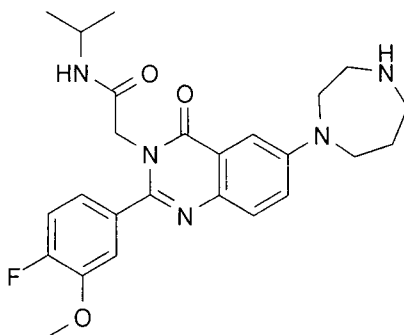
MS (ESI) m/z : 458/460 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.28).

EJEMPLO 1h: 2-(2-(3-Cloro-4-fluorofenil)-6-(3-metil-1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida



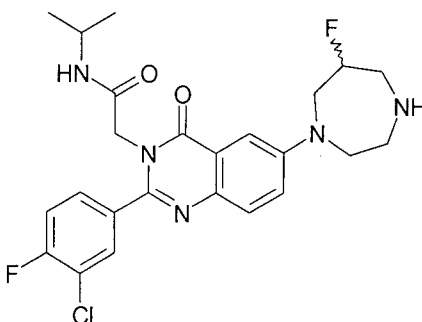
MS (ESI) m/z : 486 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.18).

EJEMPLO 1i: 2-(6-(1,4-Diazepan-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida



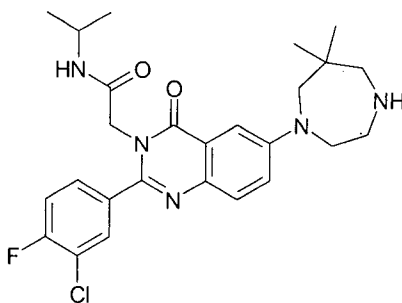
MS (ESI) m/z : 468 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.7).

EJEMPLO 1j: 2-[2-(3-Cloro-4-fluorofenil)-6-(6-fluoroperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



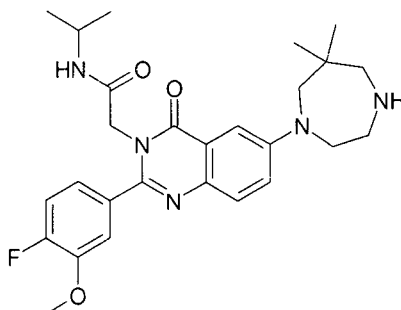
MS (ESI) m/z : 490/492 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.27).

EJEMPLO 1k: 2-[2-(3-Cloro-4-fluorofenil)-6-(dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



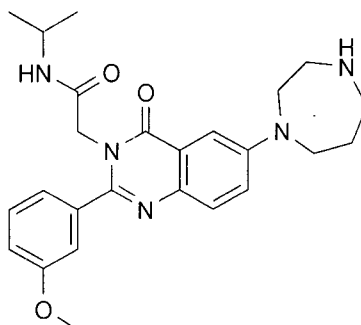
MS (ESI) m/z : 500/502 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.11).

EJEMPLO 11: 2-[6-(Dimetilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 596 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.10).

EJEMPLO 2a: N-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]acetamida

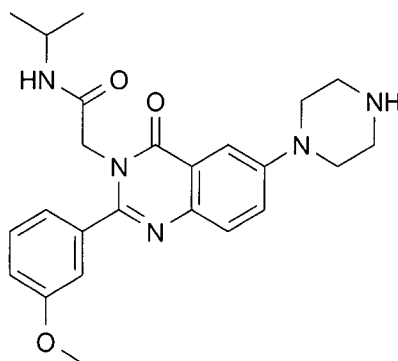


ter-Butil éster del ácido 4-[3-(isopropilcarbamoilmetil)-2-(3-metoxifenil)-4-oxo-3,4-dihidroquinazolin-6-il]-perhidro-1,4-diazepina-1-carboxílico (INTERMEDIARIO VII.1) (50 mg, 0,091 mmol) fue tratado con HCl 4N/MeOH (10 ml), y la solución resultante fue agitada a temperatura ambiente por 2 horas. La mezcla de reacción fue concentrada al vacío para proporcionar N-isopropil-2-[2-(3-metoxifenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]acetamida (EJEMPLO 2a) (40 mg, 0,091 mmol, 100%) como la sal clorhidrato.

Datos para *N*-isopropil-2-[2-(3-metoxifenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4*H*-quinazolin-3-il]acetamida (EJEMPLO 2a), sal clorhidrato: MS (ESI) m/z : 450 ($[M+H]^+$).

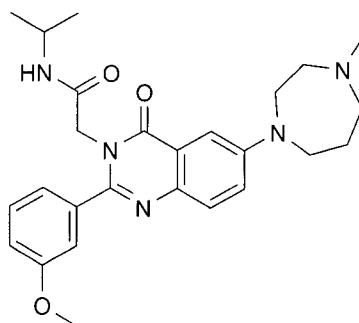
Los siguientes compuestos fueron preparados de una manera similar a partir de INTERMEDIARIOS VII:

EJEMPLO 2b: *N*-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-piperazin-1-il-4*H*-quinazolin-3-il]acetamida



MS (ESI) m/z : 436 ($[M+H]^+$) (a partir del INTERMEDIARIO VII.3).

EJEMPLO 3a: *N*-Isopropil-2-[2-(3-metoxifenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acetamida



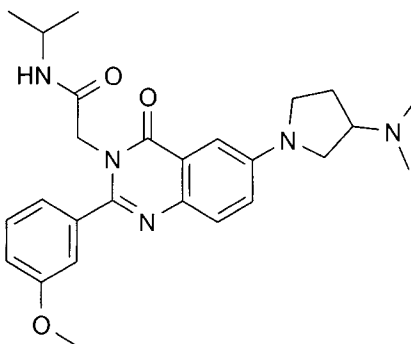
A una solución de 2-amino-*N*-(isopropilcarbamoilmetil)-5-(4-metilperhidro-1,4-diazepin-1-il)benzamida (INTERMEDIARIO V.1) (1,4 g, 4,1 mmoles) en etanol absoluto (70 ml), se agregó 3-

metoxibencimidato de etilo clorhidrato (INTERMEDIARIO II.2) (1,8 g, 8,3 mmoles). La mezcla resultante fue calentada a temperatura de reflujo por 20 horas. La mezcla de reacción fue concentrada al vacío, y el residuo de color oscuro fue disuelto en DCM (70 ml) y lavado con HCl 1N (acuoso) (3 X 20 ml). La fase acuosa fue lavada con EtOAc (20 ml) y basificada hasta pH $\approx$ 10-11 con NaOH 4N (acuoso), y el precipitado de color verde pálido resultante fue recolectado por filtración con succión. El producto crudo fue purificado por cromatografía en sílica gel con una gradiente de MeOH:DCM (1:19 a 3:7, v/v) como eluyente, para proporcionar el producto como un sólido blanquecino (0,60 g, 1,3 mmol, 32%). La recristalización en EtOAc:DCM proporcionó *N-isopropil-2-[2-(3-metoxifenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acetamida pura* (EJEMPLO 3a) (0,35 g, 0,76 mmol, 18%) como un sólido blanco.

Datos para *N-isopropil-2-[2-(3-metoxifenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acetamida* (EJEMPLO 3a): ^1H NMR (300 MHz, CDCl_3): δ 7,64 (d, 1H), 7,3-7,4 (m, 2H), 7,16-7,23 (m, 3H), 7,0 (dd, 1H), 5,71 (br d, 1H, amida N-H), 4,49 (s, 2H), 4,08 (m, 1H), 3,82 (s, 3H), 3,68 (dd, 2H), 3,61 (t, 2H), 2,76 (m, 2H), 2,57 (m, 2H), 2,39 (s, 3H), 2,06 (m, 2H), 1,15 (d, 6H) ppm; MS (ESI) m/z : 46 ($[\text{M}+\text{H}]^+$), 949 ($[\text{M}+\text{Na}]^+$); P.f. 204°C (descomp.).

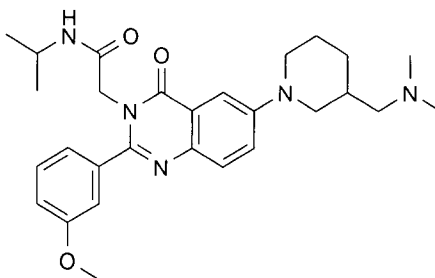
Los siguientes compuestos fueron preparados de una manera similar a partir de INTERMEDIARIOS V y II:

EJEMPLO 3b: 2-[6-(3-Dimetilaminopirrolidin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



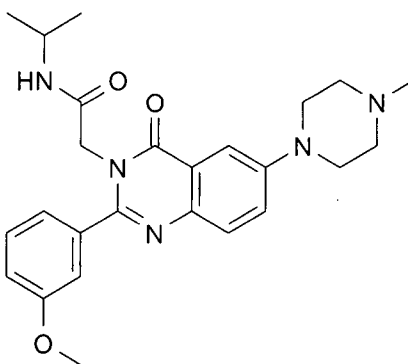
MS (ESI) m/z : 464 ($[M+H]^+$) (a partir del INTERMEDIARIO V.4 y el INTERMEDIARIO II.2).

EJEMPLO 3c: 2-[6-(3-Dimetilaminometilpiperidin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



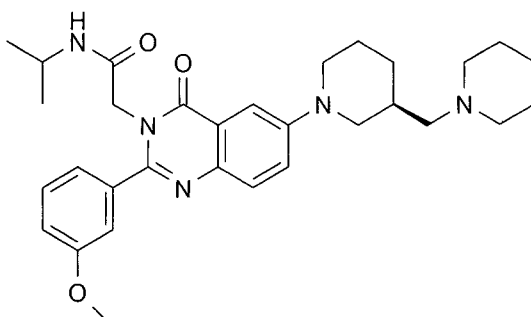
MS (ESI) m/z : 492 ($[M+H]^+$) (a partir del INTERMEDIARIO V.5 y el INTERMEDIARIO II.2).

EJEMPLO 3d: N-Isopropil-2-[2-(3-metoxifenil)-6-(4-metilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]acetamida



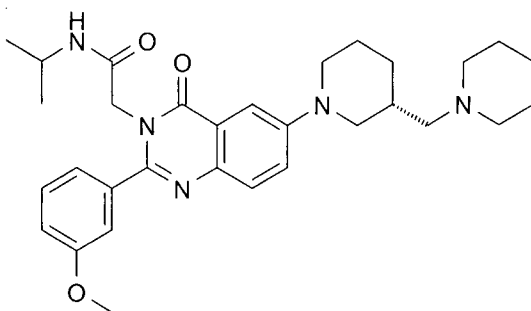
MS (ESI) m/z : 450 ($[M+H]^+$) (a partir del INTERMEDIARIO V.6 y el INTERMEDIARIO II.2).

EJEMPLO 3e: *N*-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-((*S*)-3-piperidin-1-ilmetilpiperidin-1-il)-4*H*-quinazolin-3-il]acetamida



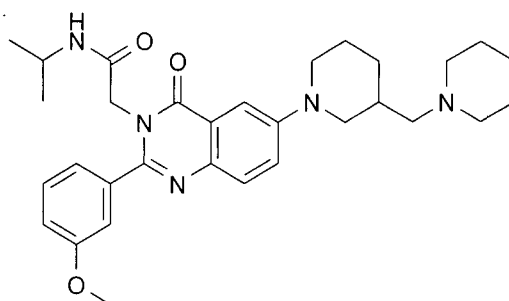
MS (ESI) m/z : 532 ($[M+H]^+$) (a partir del INTERMEDIARIO V.7 y el INTERMEDIARIO II.2).

EJEMPLO 3f: *N*-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-((*R*)-3-piperidin-1-ilmetilpiperidin-1-il)-4*H*-quinazolin-3-il]acetamida



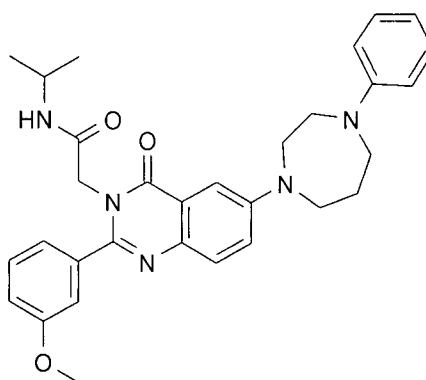
MS (ESI) m/z : 532 ($[M+H]^+$) (a partir del INTERMEDIARIO V.9 y el INTERMEDIARIO II.2).

EJEMPLO 3g: *N*-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-(3-piperidin-1-ilmetilpiperidin-1-il)-4*H*-quinazolin-3-il]acetamida



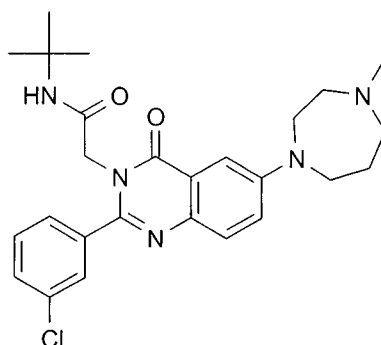
MS (ESI) m/z : 532 ($[M+H]^+$) (a partir del INTERMEDIARIO V.10 y el INTERMEDIARIO II.2).

EJEMPLO 3h: N-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-(4-fenil-perhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]acetamida



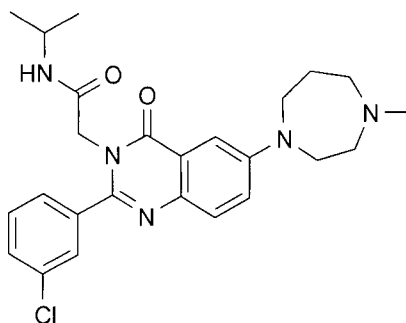
MS (ESI) m/z : 526 ($[M+H]^+$) (a partir del INTERMEDIARIO V.12 y el INTERMEDIARIO II.2).

EJEMPLO 3i: N-ter-Butil-2-[2-(3-clorofenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acetamida



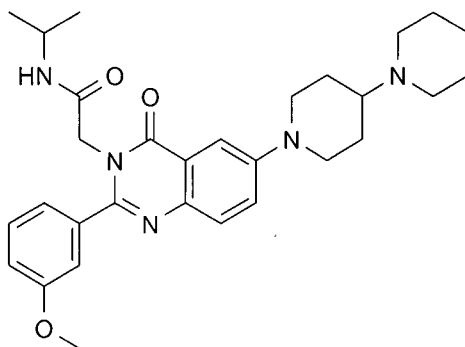
MS (ESI) m/z : 482/484 ($[M+H]^+$) (a partir del INTERMEDIARIO V.13 y el INTERMEDIARIO II.1).

EJEMPLO 3j: 2-[2-(3-Clorofenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



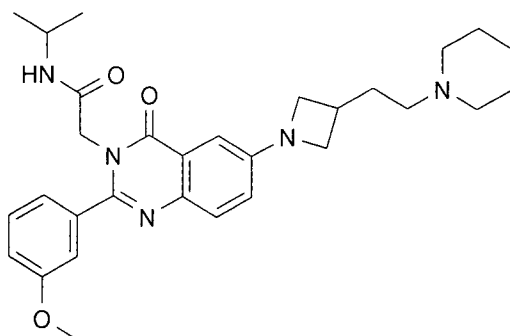
MS (ESI) m/z : 468/470 ($[M+H]^+$) (a partir del INTERMEDIARIO V.1 y el INTERMEDIARIO II.1).

EJEMPLO 3k: 2-[6-[1,4']Bipiperidinil-1'-il-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



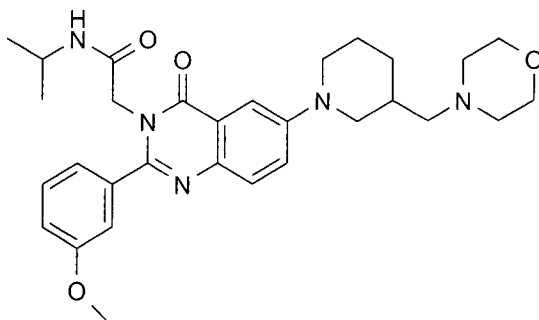
MS (ESI) m/z : 518 ($[M+H]^+$) (a partir del INTERMEDIARIO V.15 y el INTERMEDIARIO II.2).

EJEMPLO 3l: N-Isopropil-2-{2-(3-metoxifenil)-4-oxo-6-[3-(2-piperidin-1-iletíl)azetidin-1-il]-4H-quinazolin-3-il}acetamida



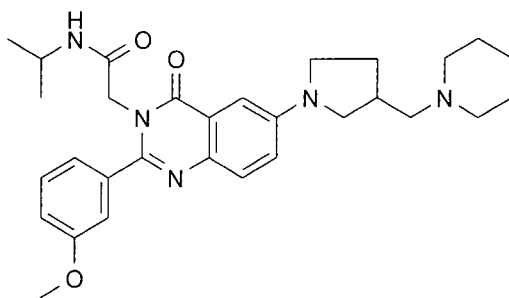
MS (ESI) m/z : 518 ($[M+H]^+$) (a partir del INTERMEDIARIO V.16 y el INTERMEDIARIO II.2).

EJEMPLO 3m: *N*-Isopropil-2-[2-(3-metoxifenil)-6-(3-morfolin-4-ilmetilpiperidin-1-il)-4-oxo-4*H*-quinazolin-3-il]acetamida



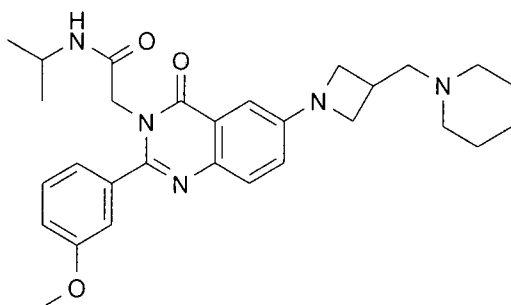
MS (ESI) m/z : 534 ($[M+H]^+$) (a partir del INTERMEDIARIO V.17 y el INTERMEDIARIO II.2).

EJEMPLO 3n: *N*-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-(3-piperidin-1-ilmetilpirrolidin-1-il)-4*H*-quinazolin-3-il]acetamida



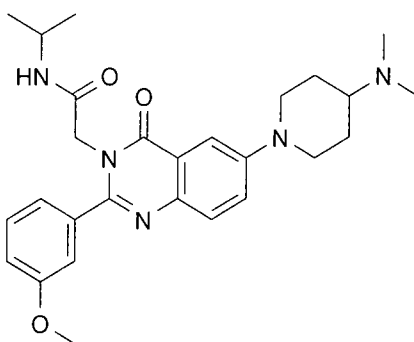
MS (ESI) m/z : 518 ($[M+H]^+$) (a partir del INTERMEDIARIO V.14 y el INTERMEDIARIO II.2).

EJEMPLO 3o: N-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-(3-piperidin-1-ilmetilazetidín-1-il)-4H-quinazolin-3-il]acetamida



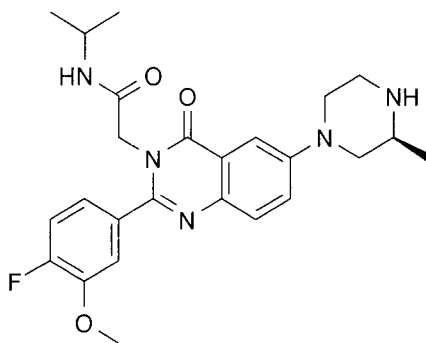
MS (ESI) m/z : 504 ($[M+H]^+$) (a partir del INTERMEDIARIO V.11 y el INTERMEDIARIO II.2).

EJEMPLO 3p: 2-[6-(4-Dimetilaminopiperidin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



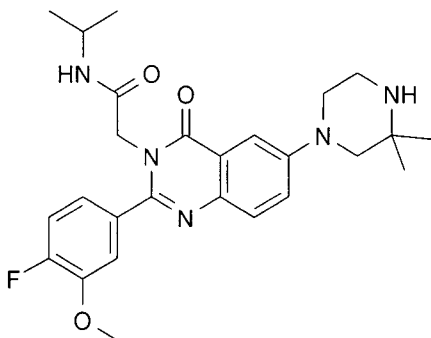
MS (ESI) m/z : 478 ($[M+H]^+$) (a partir del INTERMEDIARIO V.8 y el INTERMEDIARIO II.2).

EJEMPLO 3q: 2-[2-(4-Fluoro-3-metoxifenil)-6-((S)-3-metilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



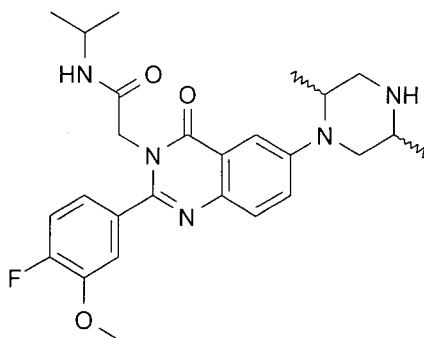
MS (ESI) m/z : 468 ($[M+H]^+$) (a partir del INTERMEDIARIO V.18 y el INTERMEDIARIO II.3).

EJEMPLO 3r: 2-[6-(Dimetilpiperazin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



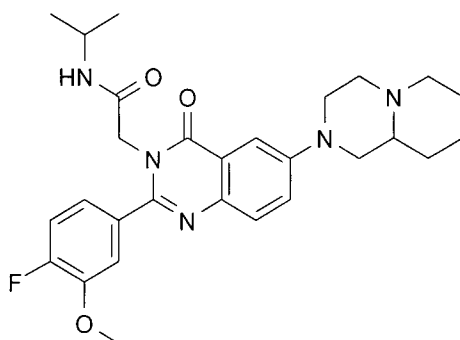
MS (ESI) m/z : 482 ($[M+H]^+$) (a partir del INTERMEDIARIO V.19 y el INTERMEDIARIO II.3).

EJEMPLO 3s: 2-(6-(2,5-Dimetilpiperazin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il)-N-isopropilacetamida



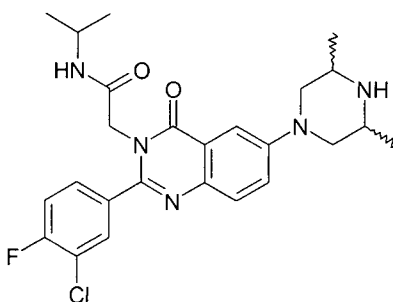
MS (ESI) m/z : 482 ($[M+H]^+$) (a partir del INTERMEDIARIO V.20 y el INTERMEDIARIO II.3).

EJEMPLO 3t: 2-[2-(4-Fluoro-3-metoxifenil)-6-(octahidropirido-[1,2-a]pirazin-2-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



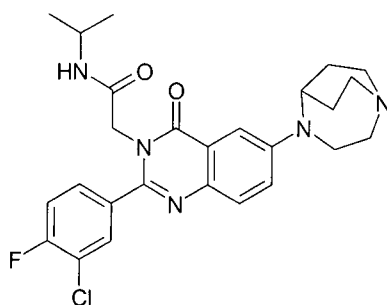
MS (ESI) m/z : 508 ($[M+H]^+$) (a partir del INTERMEDIARIO V.46 y el INTERMEDIARIO II.3).

EJEMPLO 3u: 2-[2-(3-Cloro-4-fluorofenil)-6-(dimetilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



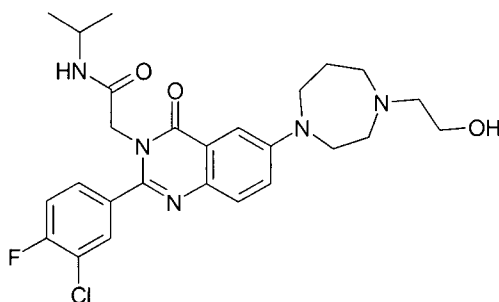
MS (ESI) m/z : 486/488 ($[M+H]^+$) (a partir del INTERMEDIARIO V.24 y el INTERMEDIARIO II.4).

EJEMPLO 3v: 2-[2-(3-Cloro-4-fluorofenil)-6-(1,4-diazabicciclo-[3.2.2]non-4-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



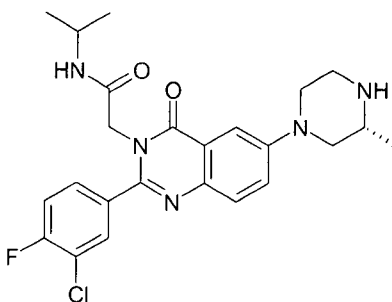
MS (ESI) m/z : 498/500 ($[M+H]^+$) (a partir del INTERMEDIARIO V.47 y el INTERMEDIARIO II.4).

EJEMPLO 3w: 2-{2-(3-Cloro-4-fluorofenil)-6-[4-(2-hidroxietil)-perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



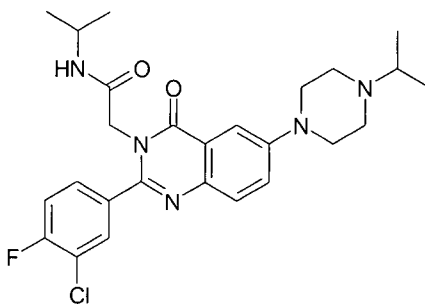
MS (ESI) m/z : 516 ($[M+H]^+$) (a partir del INTERMEDIARIO V.22 y el INTERMEDIARIO II.4).

EJEMPLO 3x: 2-[2-(3-Cloro-4-fluorofenil)-6-((R)-3-metil-piperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



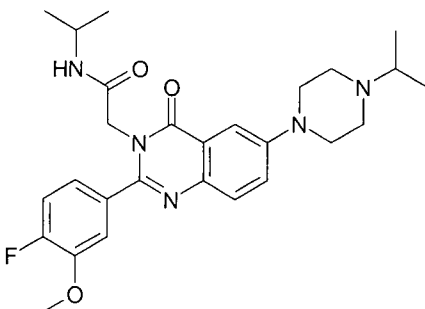
MS (ESI) m/z : 472/474 ($[M+H]^+$) (a partir del INTERMEDIARIO V.25 y el INTERMEDIARIO II.4).

EJEMPLO 3y: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropil-piperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



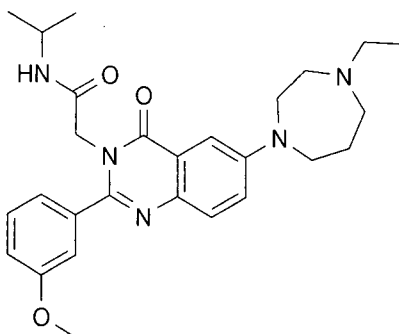
MS (ESI) m/z : 500 ($[M+H]^+$) (a partir del INTERMEDIARIO V.23 y el INTERMEDIARIO II.4).

EJEMPLO 3z: 2-[2-(4-Fluoro-3-metoxifenil)-6-(4-isopropil-piperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 497 ($[M+H]^+$) (a partir del INTERMEDIARIO V.23 y el INTERMEDIARIO II.3).

EJEMPLO 4a: 2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

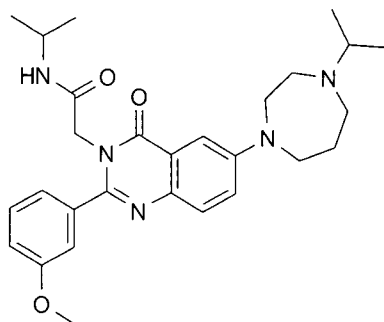


Una mezcla de *N*-isopropil-2-[2-(3-metoxifenil)-4-oxo-6-perhidro-1,4-diazepin-1-il]-4*H*-quinazolin-3-il]acetamida (EJEMPLO 2a), sal clorhidrato (50 mg, 0,103 mmol), bromuro de etilo (22 mg, 0,21 mmol) y K_2CO_3 (43 mg, 0,31 mmol) en acetonitrilo (5 ml) fue calentada a reflujo por 24 horas. Enseguida, la mezcla fue enfriada, filtrada y concentrada al vacío. El residuo crudo fue purificado por HPLC preparatoria para dar 2-[6-(4-etilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida (EJEMPLO 4a) (5,1 mg, 0,010 mmol, 10%) como la sal clorhidrato.

Datos para 2-[6-(4-etilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida (EJEMPLO 4a), sal clorhidrato: MS (ESI) m/z : 478 ($[M+H]^+$), 955 ($[2M+H]^+$), 977 ($[2M+Na]^+$).

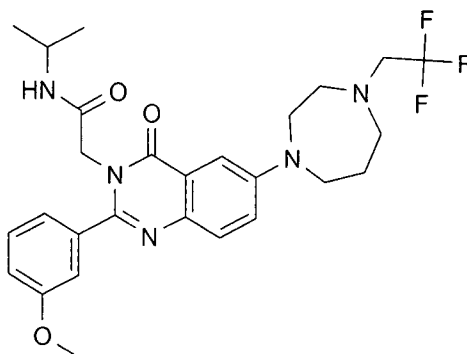
Los siguientes compuestos fueron preparados de una manera similar a partir de los EJEMPLOS 1 ó 2:

EJEMPLO 4b: *N*-Isopropil-2-[6-(4-isopropilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]acetamida



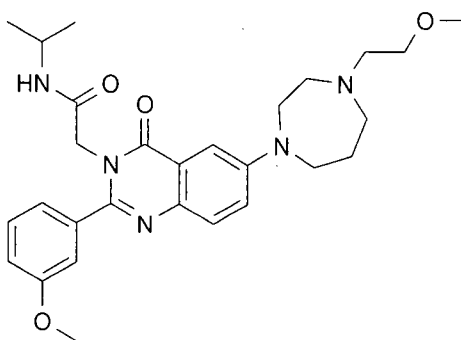
MS (ESI) m/z : 492 ($[M+H]^+$) (a partir del EJEMPLO 2a).

EJEMPLO 4c: *N*-Isopropil-2-{2-(3-metoxifenil)-4-oxo-6-[4-(2,2,2-trifluoroetil)perhidro-1,4-diazepin-1-il]-4*H*-quinazolin-3-il}-acetamida



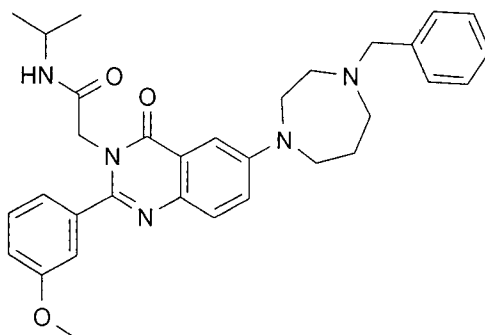
MS (ESI) m/z : 532 ($[M+H]^+$) (a partir del EJEMPLO 2a).

EJEMPLO 4d: *N*-Isopropil-2-[6-[4-(2-metoxietil)perhidro-1,4-diazepin-1-il]-2-(3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]-acetamida



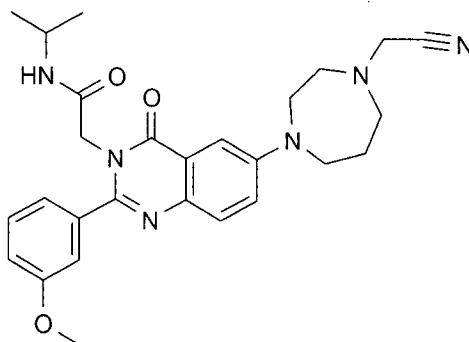
MS (ESI) m/z : 508 ($[M+H]^+$) (a partir del EJEMPLO 2a).

EJEMPLO 4e: 2-[6-(4-Bencilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



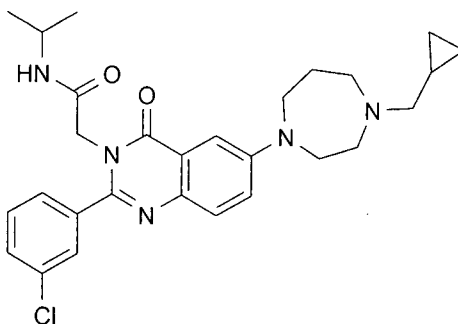
MS (ESI) m/z : 540 ($[M+H]^+$) (a partir del EJEMPLO 2a).

EJEMPLO 4f: 2-[6-(4-Cianometilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



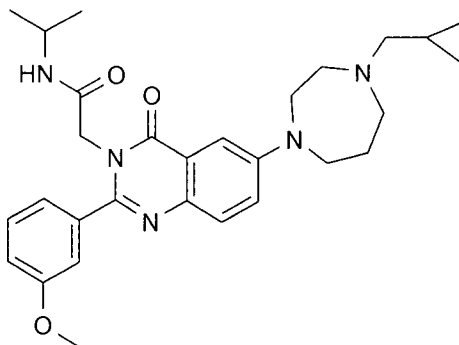
MS (ESI) m/z : 489 ($[M+H]^+$) (a partir del EJEMPLO 2a).

EJEMPLO 4g: 2-[2-(3-Clorofenil)-6-(4-ciclopropilmetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



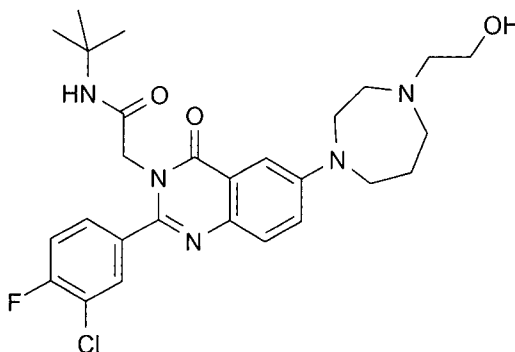
MS (ESI) m/z : 508/510 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 4h: 2-[6-(4-Ciclopropilmetilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 504 ($[M+H]^+$) (a partir del EJEMPLO 2a).

EJEMPLO 4i: N-ter-Butil-2-{2-(3-cloro-4-fluorofenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}acetamida

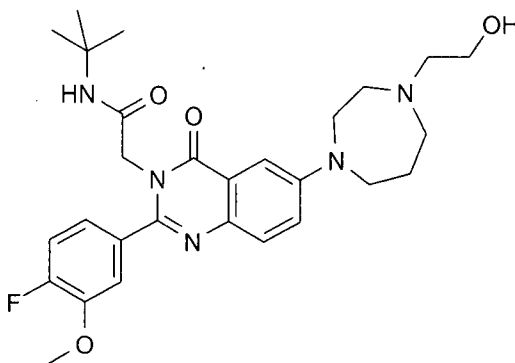


N-ter-Butil-2-(2-(3-cloro-4-fluorofenil)-6-(1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)acetamida (EJEMPLO 1c) (100 mg, 0,206 mmol), 2-bromoetanol (206 mg, 0,117 ml, 1,646 mmol) y carbonato de potasio (57 mg, 0,412 mmol) en DMF (1 ml), fueron calentados en un horno de microondas a 100°C por 10 minutos. La mezcla de reacción fue filtrada y purificada por SCX, eluyendo con MeOH y después NH_3 2M/MeOH. El solvente fue

evaporado bajo presión reducida y el producto fue purificado adicionalmente por HPLC. Esto proporcionó *N*-ter-butil-2-{2-(3-cloro-4-fluorofenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4*H*-quinazolin-3-il}acetamida (EJEMPLO 4i) (39 mg, 0,074 mmol, 90%) como un sólido blanco.

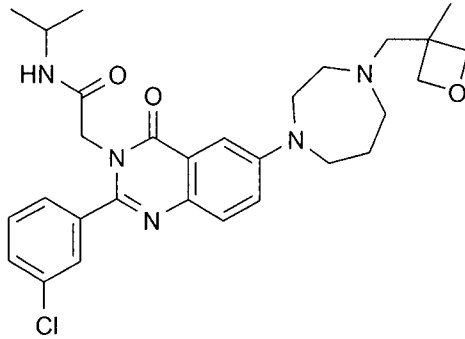
Datos para *N*-ter-butil-2-{2-(3-cloro-4-fluorofenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4*H*-quinazolin-3-il}acetamida (EJEMPLO 4i): MS (ESI) m/z : 530/532 ($[M+H]^+$).

EJEMPLO 4j: *N*-ter-Butil-2-{2-(4-fluoro-3-metoxifenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4*H*-quinazolin-3-il}acetamida



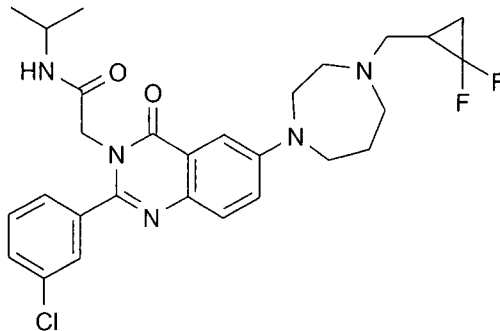
MS (ESI) m/z : 526 ($[M+H]^+$) (a partir del EJEMPLO 1d).

EJEMPLO 4k: 2-{2-(3-Clorofenil)-6-[4-(3-metiloxetan-3-il-metil)perhidro-1,4-diazepin-1-il]-4-oxo-4*H*-quinazolin-3-il}-*N*-isopropilacetamida



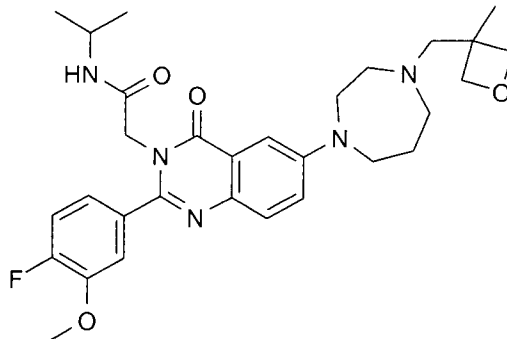
MS (ESI) m/z : 538/540 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 4l: 2-{2-(3-Clorofenil)-6-[4-(2,2-difluorociclopropil-metil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



MS (ESI) m/z : 544/546 ($[M+H]^+$) (a partir del EJEMPLO 1b).

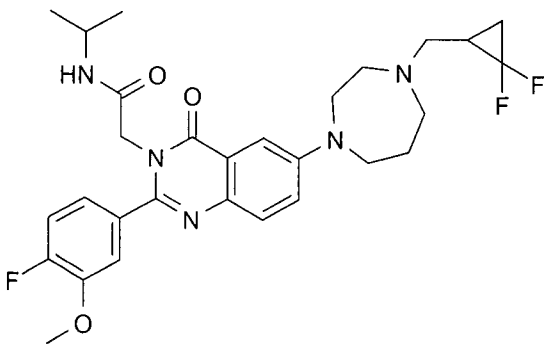
EJEMPLO 4m: 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(3-metiloxetan-3-ilmetil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



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265

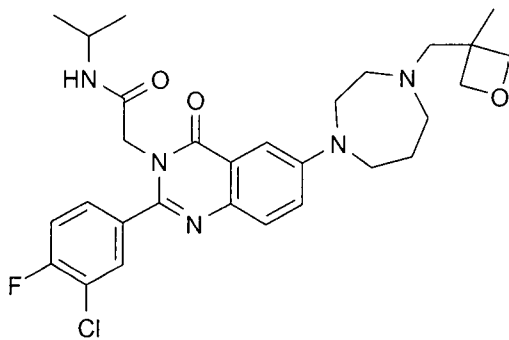
MS (ESI) m/z : 552 ($[M+H]^+$) (a partir del EJEMPLO 1i).

EJEMPLO 4n: 2-[6-[4-(2,2-Difluorociclopropilmetil)perhidro-1,4-diazepin-1-il]-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



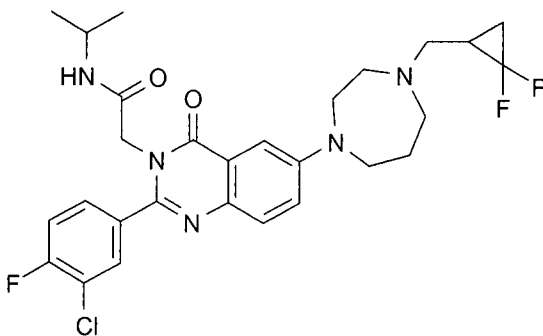
MS (ESI) m/z : 558 ($[M+H]^+$) (a partir del EJEMPLO 1i).

EJEMPLO 4o: 2-{2-(3-Cloro-4-fluorofenil)-6-[4-(3-metiloxetan-3-ilmetil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



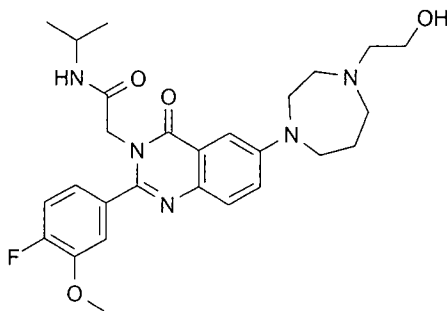
MS (ESI) m/z : 556/558 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 4p: 2-{2-(3-Cloro-4-fluorofenil)-6-[4-(2,2-difluorociclopropilmetil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida

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MS (ESI) m/z : 562/564 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 4q: 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(2-hidroxi-etil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



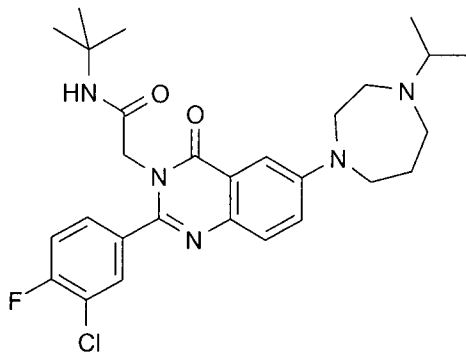
2-(6-(1,4-Diazepan-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida (EJEMPLO 1i) (28 mg, 0,06 mmol), 2-bromoetanol (30 mg, 0,017 ml, 0,24 mmol), carbonato de potasio (17 mg, 0,12 mmol) y yoduro de potasio (1 mg, 5,99 μ moles) fueron combinados en un frasco para microondas y se agregó DMF (1 ml). La mezcla de reacción fue calentada a 100°C por 5 minutos en el horno de microondas. La LCMS indicó que el producto deseado se estaba formando. Se agregó más cantidad de 2-bromo-etanol (30 mg, 0,017 ml, 0,24 mmol) y la mezcla de reacción fue calentada a 100°C por 5 minutos más en el horno de microondas. El producto fue purificado por LCMS preparatoria para dar 2-{2-(4-fluoro-3-metoxifenil)-6-[4-(2-hidroxi-etil)-

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perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida (EJEMPLO 4q) (4 mg, 7,82 μ moles, 13%).
 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(2-hidroxietyl)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida (EJEMPLO 4q): MS (ESI) m/z : 512 ($[M+H]^+$).

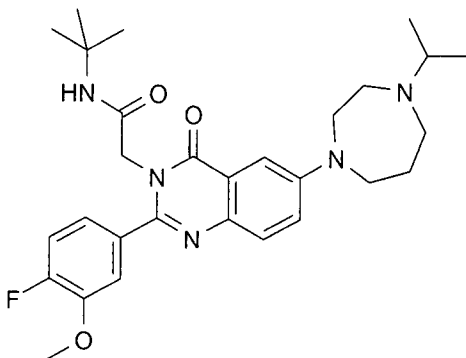
Los siguientes compuestos fueron preparados de una manera similar a partir de los EJEMPLOS 1 ó 2:

EJEMPLO 4r: N-ter-Butil-2-[2-(3-cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-acetamida



MS (ESI) m/z : 528/530 ($[M+H]^+$) (a partir del EJEMPLO 1c).

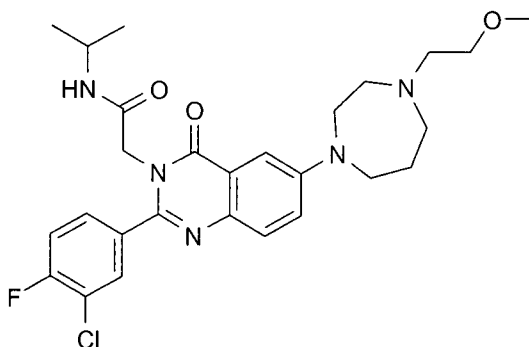
EJEMPLO 4s: N-ter-Butil-2-[2-(4-fluoro-3-metoxifenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-acetamida



MS (ESI) m/z : 524 ($[M+H]^+$) (a partir del EJEMPLO 1d).

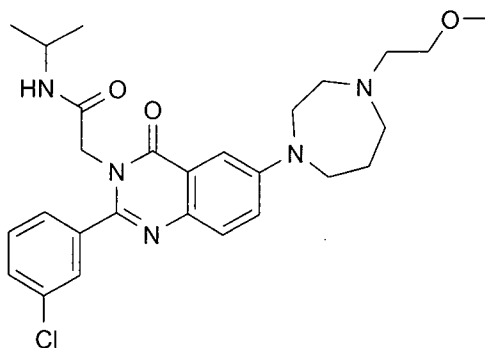
268

EJEMPLO 4t: 2-{2-(3-Cloro-4-fluorofenil)-6-[4-(2-metoxietil)-perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



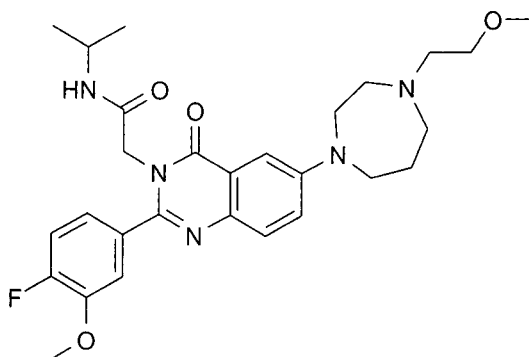
MS (ESI) m/z : 530/532 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 4u: 2-{2-(3-Clorofenil)-6-[4-(2-metoxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



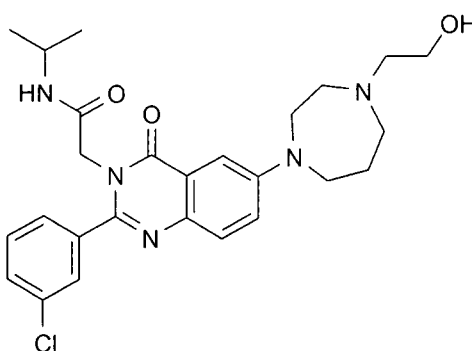
MS (ESI) m/z : 512/514 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 4v: 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(2-metoxietil)-perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida

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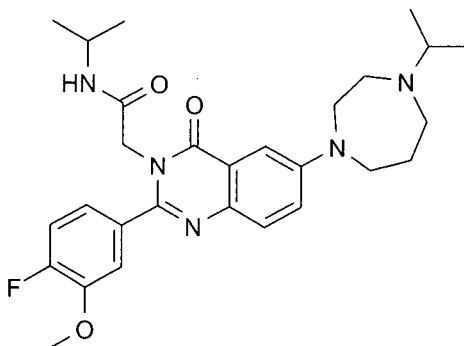
MS (ESI) m/z : 526 ($[M+H]^+$) (a partir del EJEMPLO 1i).

EJEMPLO 4w: 2-{2-(3-Clorofenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



MS (ESI) m/z : 498/500 ($[M+H]^+$) (a partir del EJEMPLO 1b).

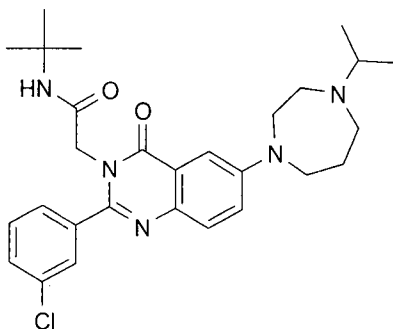
EJEMPLO 4x: 2-[2-(4-Fluoro-3-metoxifenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del EJEMPLO 1i).

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EJEMPLO 5a: *N*-ter-Butil-2-[2-(3-clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acetamida



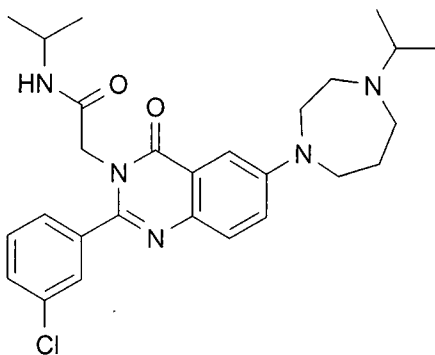
N-ter-Butil-2-[2-(3-clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4*H*-quinazolin-3-il]acetamida (EJEMPLO 1a) (17 mg, 0,03 mmol), acetona anhidra (30 μ l), cianoborohidruro de sodio (3 mg, 0,03 mmol) y ácido acético glacial (12 μ l, 0,21 mmol) en THF anhidro (0,15 ml), fueron calentados en un horno de microondas a 130°C por 10 minutos. La mezcla resultante fue purificada por TLC preparatoria en sílica gel con DCM:MeOH:NH₄OH (40:2:1, v/v) como eluyente, para dar *N*-ter-butyl-2-[2-(3-clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]-acetamida (EJEMPLO 5a) (7,1 mg, 0,014 mmol, 47%).

Datos para *N*-ter-butyl-2-[2-(3-clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acetamida (EJEMPLO 5a): ¹H NMR (300 MHz, CDCl₃): δ 7,6 (m, 2H), 7,5-7,3 (m, 4H), 7,21 (dd, 1H), 5,63 (s, 1H), 4,44 (s, 2H), 3,64 (m, 4H), 2,94 (m, 1H), 2,81 (t, 2H), 2,57 (t, 2H), 1,96 (m, 2H), 1,34 (s, 9H), 1,00 (d, 6H) ppm; MS (ESI) *m/z*: 510/512 ([M+H]⁺).

Los siguientes compuestos fueron preparados de una manera similar a partir de los EJEMPLOS 1, 2 ó 3:

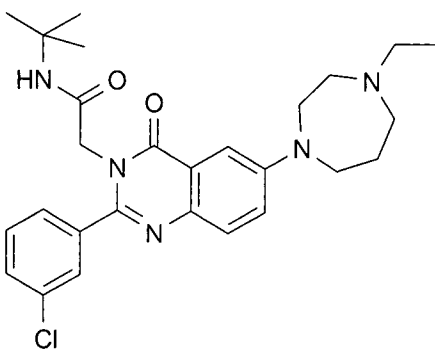
341
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EJEMPLO 5b: 2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 496/498 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 5c: N-ter-Butil-2-[2-(3-clorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acetamida



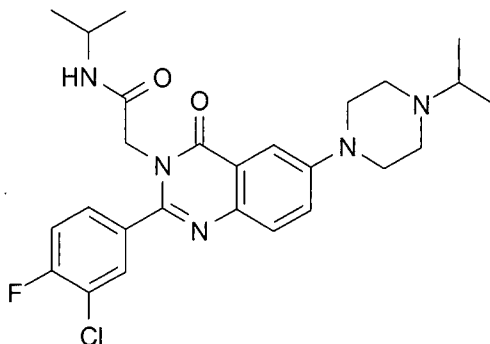
N-ter-Butil-2-[2-(3-clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]acetamida (EJEMPLO 1a) (50 mg, 0,107 mmol), acetaldehído (7,1 mg, 0,160 mmol) y acetonitrilo (1 ml), fueron colocados en un frasco para microondas. Se agregó cianoborohidruro de metilpoliestireno trietilamonio macroporoso (70 mg, 0,107 mmol) y ácido acético (0,3 ml, 0,107 mmol) y la mezcla de reacción fue calentada en un horno de microondas a 130°C por 1.200 s. El producto crudo fue filtrado y el residuo fue disuelto en MeOH (1 ml) y purificado por HPLC preparatoria.

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Esto proporcionó *N*-ter-butil-2-[2-(3-clorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acetamida (EJEMPLO 5c) (11 mg, 0,023 mmol, 21%).

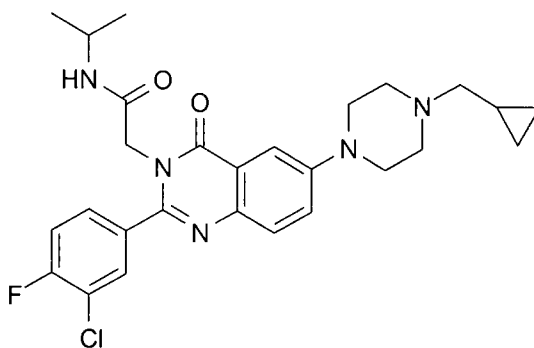
N-ter-Butil-2-[2-(3-clorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acetamida (EJEMPLO 5c): MS (ESI) m/z : 496 ($[M+H]^+$).

EJEMPLO 5d: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilpiperazin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida



MS (ESI) m/z : 500/502 ($[M+H]^+$) (a partir del EJEMPLO 1g).

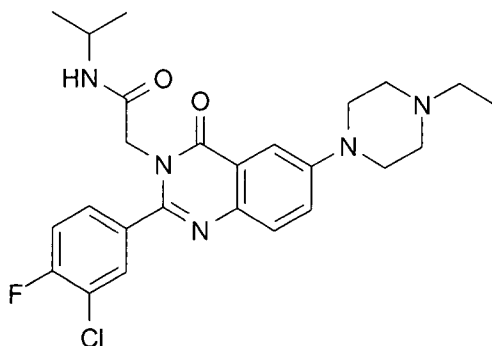
EJEMPLO 5e: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-ciclopropilmetilpiperazin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida



MS (ESI) m/z : 512/514 ($[M+H]^+$) (a partir del EJEMPLO 1g).

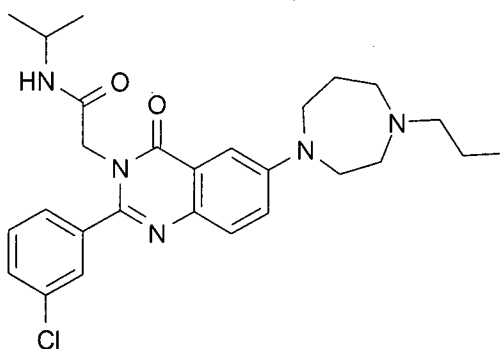
375
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EJEMPLO 5f: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-etilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



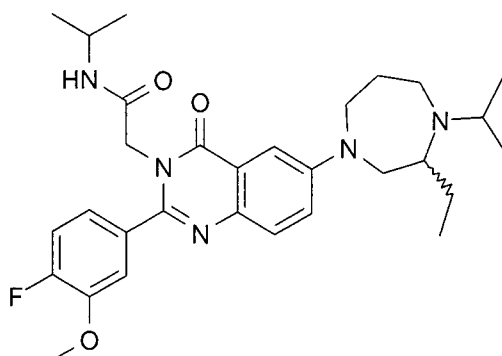
MS (ESI) m/z : 486/488 ($[M+H]^+$) (a partir del EJEMPLO 1g).

EJEMPLO 5g: 2-[2-(3-Clorofenil)-4-oxo-6-(4-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida



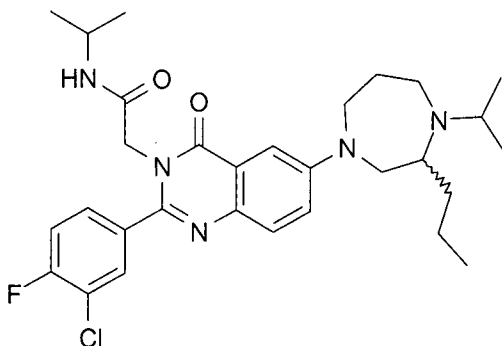
MS (ESI) m/z : 496/498 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 5h: 2-[6-(3-Etil-4-isopropilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

374
274

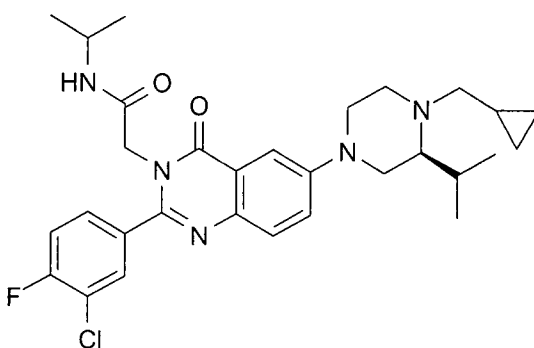
MS (ESI) m/z : 538 ($[M+H]^+$) (a partir del EJEMPLO 6f).

EJEMPLO 5i: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropil-3-propilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 556/558 ($[M+H]^+$) (a partir del EJEMPLO 6Av).

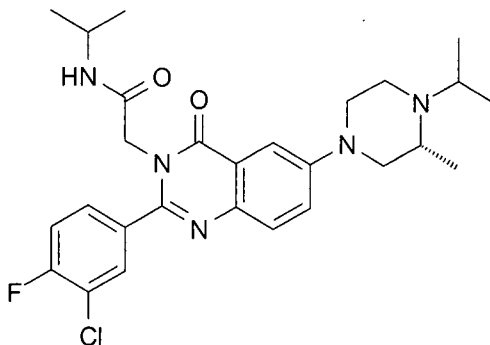
EJEMPLO 5j: 2-[2-(3-Cloro-4-fluorofenil)-6-((S)-4-ciclopropil-metil-3-isopropilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



375.
275

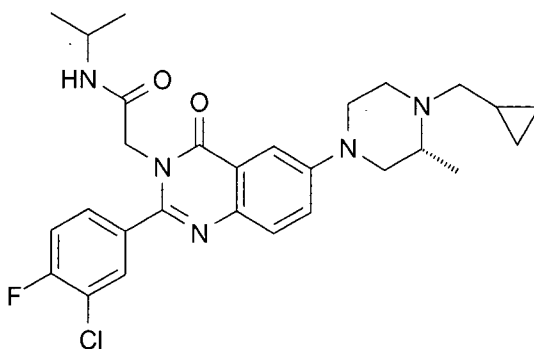
MS (ESI) m/z : 554/556 ($[M+H]^+$) (a partir del EJEMPLO 1f).

EJEMPLO 5k: 2-[2-(3-Cloro-4-fluorofenil)-6-((R)-4-isopropil-3-metilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del EJEMPLO 3x).

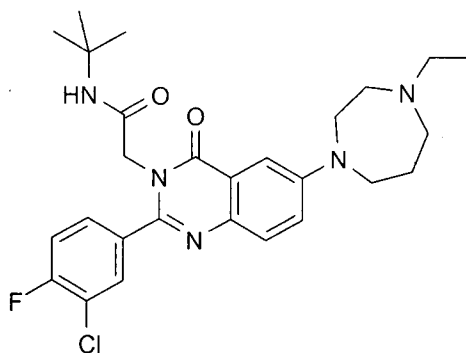
EJEMPLO 5l: 2-[2-(3-Cloro-4-fluorofenil)-6-((R)-4-ciclopropil-metil-3-metilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 526/528 ($[M+H]^+$) (a partir del EJEMPLO 3x).

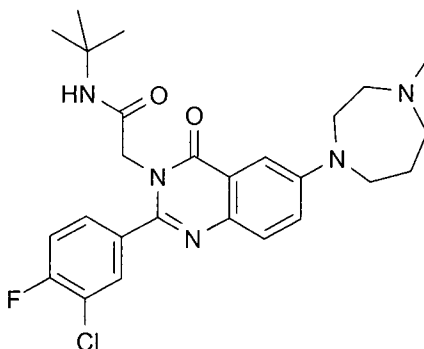
EJEMPLO 5m: N-ter-Butil-2-[2-(3-cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-acetamida

376
276



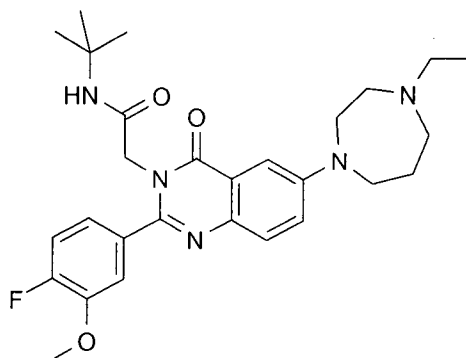
MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del EJEMPLO 1c).

EJEMPLO 5n: N-ter-Butil-2-[2-(3-cloro-4-fluorofenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-acetamida



MS (ESI) m/z : 500/502 ($[M+H]^+$) (a partir del EJEMPLO 1c).

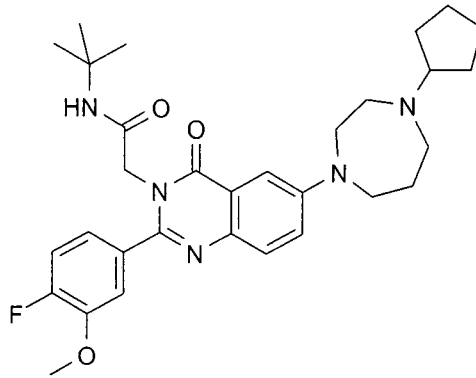
EJEMPLO 5o: N-ter-Butil-2-[6-(4-etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acetamida



MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del EJEMPLO 1d).

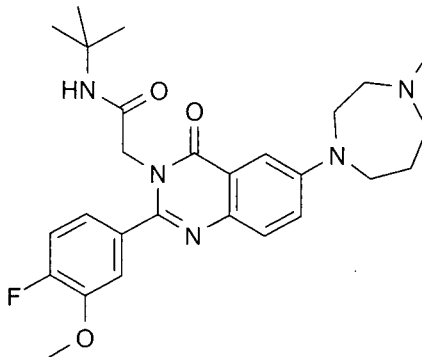
3#
27x

EJEMPLO 5p: N-ter-Butil-2-[6-(4-ciclopentilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-acetamida



MS (ESI) m/z : 550 ($[M+H]^+$) (a partir del EJEMPLO 1d).

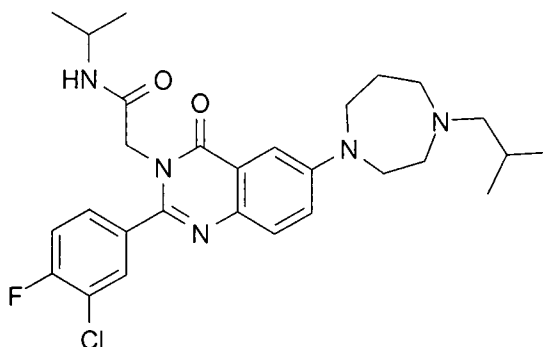
EJEMPLO 5q: N-ter-Butil-2-[2-(4-fluoro-3-metoxifenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-acetamida



MS (ESI) m/z : 496 ($[M+H]^+$) (a partir del EJEMPLO 1d).

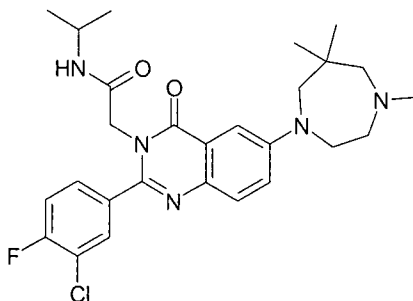
EJEMPLO 5r: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isobutilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

378
278



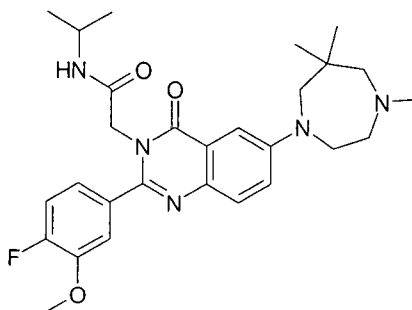
MS (ESI) m/z : 528 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 5s: 2-[2-(3-Cloro-4-fluorofenil)-4-oxo-6-(4,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del EJEMPLO 1k).

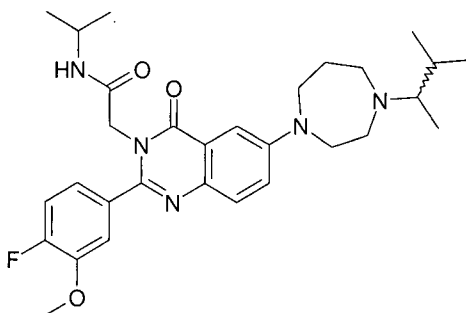
EJEMPLO 5t: 2-[2-(4-Fluoro-3-metoxifenil)-4-oxo-6-(4,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del EJEMPLO 1l).

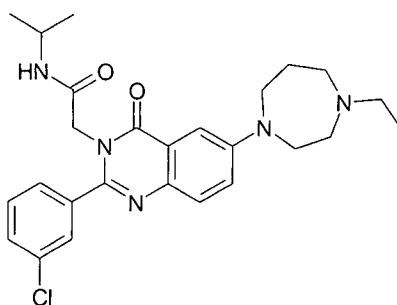
379
279

EJEMPLO 5u: 2-[6-[4-(1,2-Dimetilpropil)perhidro-1,4-diazepin-1-il]-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 538 ($[M+H]^+$) (a partir del EJEMPLO 1i).

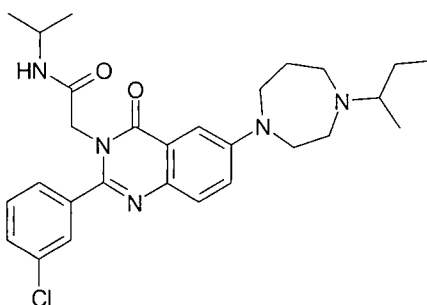
EJEMPLO 5v: 2-[2-(3-Clorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 482 ($[M+H]^+$) (a partir del EJEMPLO 1b).

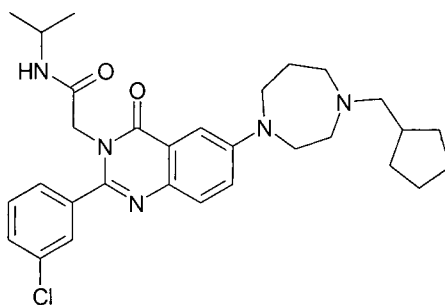
EJEMPLO 5w: 2-[6-(4-sec-Butilperhidro-1,4-diazepin-1-il)-2-(3-clorofenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

~~280~~
280



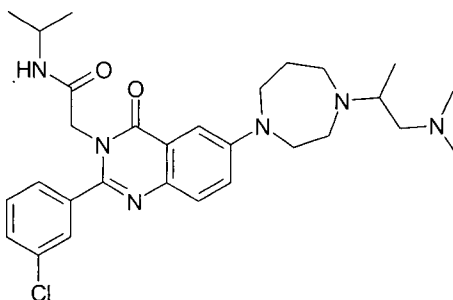
MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 5x: 2-[2-(3-Clorofenil)-6-(4-ciclopentilmetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



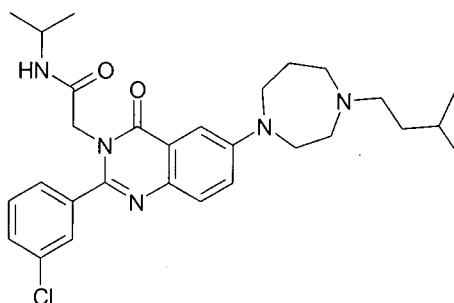
MS (ESI) m/z : 536 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 5y: 2-{2-(3-Clorofenil)-6-[4-(2-dimetilamino-1-metil-etil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



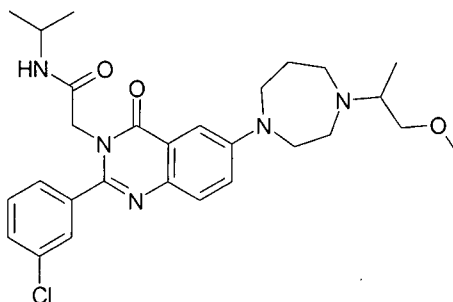
MS (ESI) m/z : 540 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 5z: 2-{2-(3-Clorofenil)-6-[4-(3-metilbutil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida

281
281

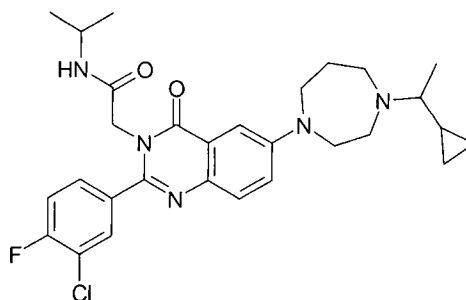
MS (ESI) m/z : 524 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 5Aa: 2-{2-(3-Clorofenil)-6-[4-(2-metoxi-1-metiletil)-perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



MS (ESI) m/z : 526 ($[M+H]^+$) (a partir del EJEMPLO 1b).

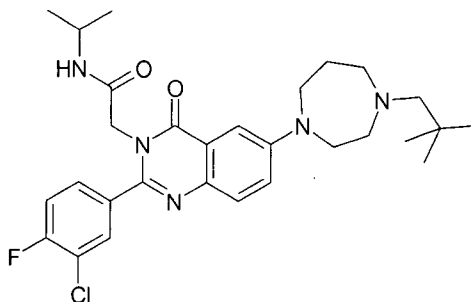
EJEMPLO 5Ab: 2-{2-(3-Cloro-4-fluorofenil)-6-[4-(1-ciclopropil-etil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



MS (ESI) m/z : 540/542 ($[M+H]^+$) (a partir del EJEMPLO 1e).

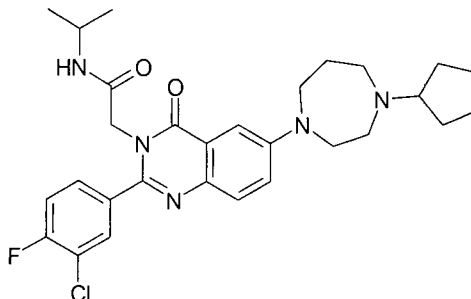
382
282

EJEMPLO 5Ac: 2-{2-(3-Cloro-4-fluorofenil)-6-[4-(2,2-dimetil-propil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



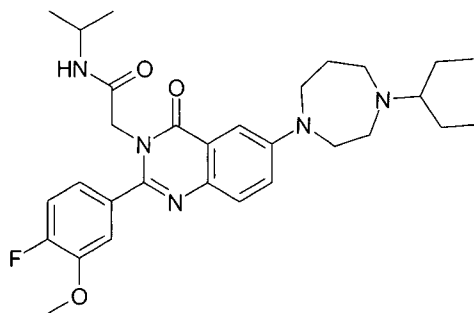
MS (ESI) m/z : 542 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 5Ad: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-ciclopentil-perhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



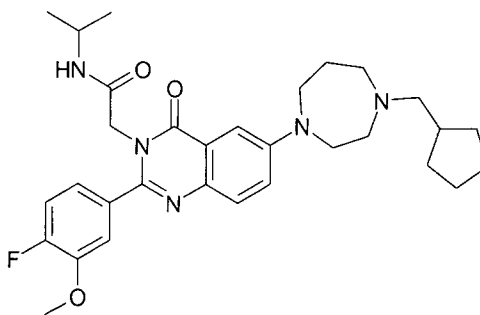
MS (ESI) m/z : 540 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 5Ae: 2-[6-[4-(1-Etilpropil)perhidro-1,4-diazepin-1-il]-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

~~283~~
283

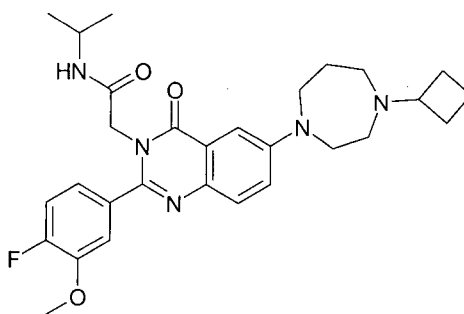
MS (ESI) m/z : 538 ($[M+H]^+$) (a partir del EJEMPLO 1i).

EJEMPLO 5Af: 2-[6-(4-Ciclopentilmetilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 550 ($[M+H]^+$) (a partir del EJEMPLO 1i).

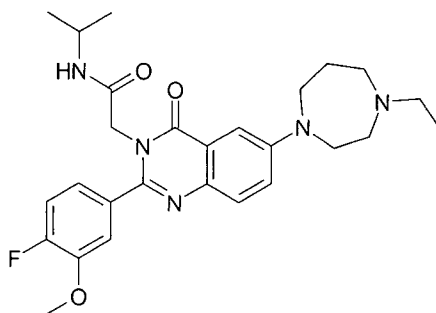
EJEMPLO 5Ag: 2-[6-(4-Ciclobutilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 522 ($[M+H]^+$) (a partir del EJEMPLO 1i).

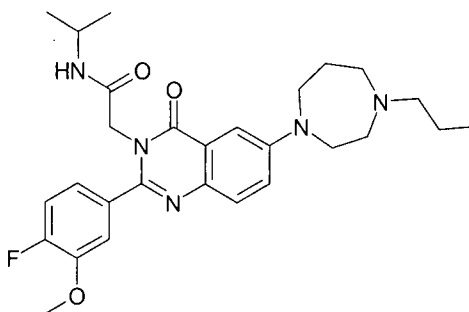
284
284

EJEMPLO 5Ah: 2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropil-acetamida



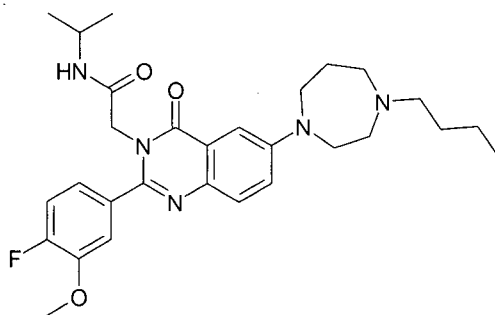
MS (ESI) m/z : 496 ($[M+H]^+$) (a partir del EJEMPLO 1i).

EJEMPLO 5Ai: 2-[2-(4-Fluoro-3-metoxifenil)-4-oxo-6-(4-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropil-acetamida



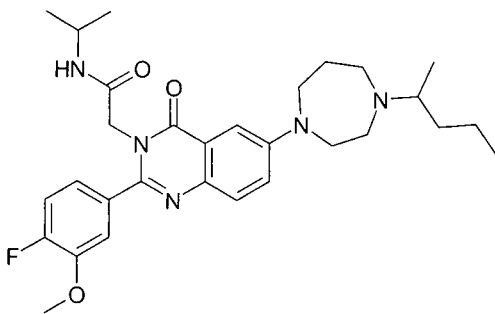
MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del EJEMPLO 1i).

EJEMPLO 5Aj: 2-[6-(4-Butilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropil-acetamida

305
285

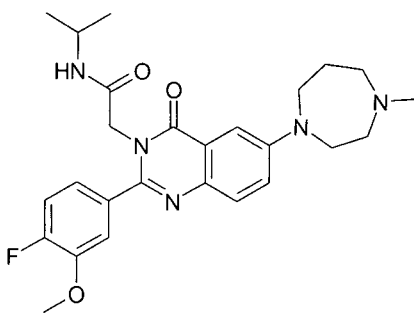
MS (ESI) m/z : 525 ($[M+H]^+$) (a partir del EJEMPLO 1i).

EJEMPLO 5Ak: 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(1-metilbutil)-perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



MS (ESI) m/z : 538 ($[M+H]^+$) (a partir del EJEMPLO 1i).

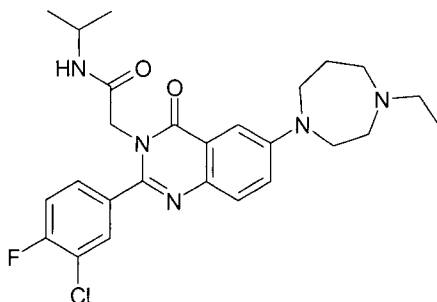
EJEMPLO 5Al: 2-[2-(4-Fluoro-3-metoxifenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 482 ($[M+H]^+$) (a partir del EJEMPLO 1i).

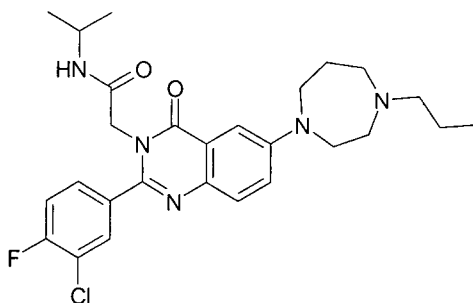
386
286

EJEMPLO 5Am: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



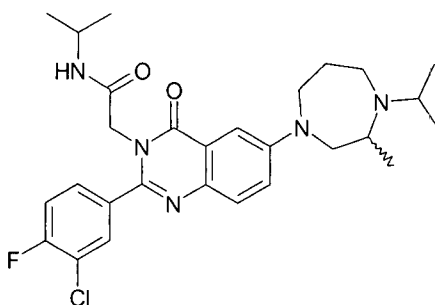
MS (ESI) m/z : 500 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 5An: 2-[2-(3-Cloro-4-fluorofenil)-4-oxo-6-(4-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida



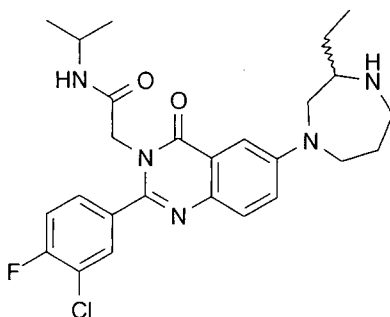
MS (ESI) m/z : 514 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 5Ao: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropil-3-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

307
287

MS (ESI) m/z : 528/530 ($[M+H]^+$) (a partir del EJEMPLO 1h).

EJEMPLO 6a: 2-[2-(3-Cloro-4-fluorofenil)-6-(3-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



2-Amino-5-(3-etilperhidro-1,4-diazepin-1-il)-N-(isopropilcarbamoyl)benzamida (INTERMEDIARIO V.26) (100 mg, 0,277 mmol), 3-cloro-4-fluorobenzaldehído (51 mg, 0,332 mmol) y ácido acético (4 gotas, catalítico) (0,33 mmol) fueron disueltos en etanol (4 ml) en un frasco para microondas, y el frasco fue sellado. La mezcla de reacción fue agitada a 90°C por 16 horas. La mezcla de reacción fue evaporada a sequedad y re-disuelta en DCM, y se agregó dióxido de manganeso (105 mg, 1,11 mmol). La mezcla de reacción fue agitada en un frasco sellado a 60°C por 3 horas. El solvente fue evaporado bajo presión reducida y el producto crudo fue purificado por cromatografía en sílica gel, con una gradiente de DCM a MeOH:DCM (1:4, v/v) como eluyente. Esto proporcionó 2-[2-(3-cloro-4-fluorofenil)-6-(3-etilperhidro-

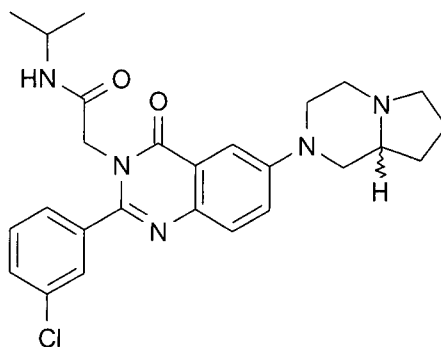
288
288

1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida
(EJEMPLO 6a) (95 mg, 0,192 mmol, 69%).

Datos para 2-[2-(3-cloro-4-fluorofenil)-6-(3-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida
(EJEMPLO 6a): MS (ESI) m/z : 500/502 ($[M+H]^+$).

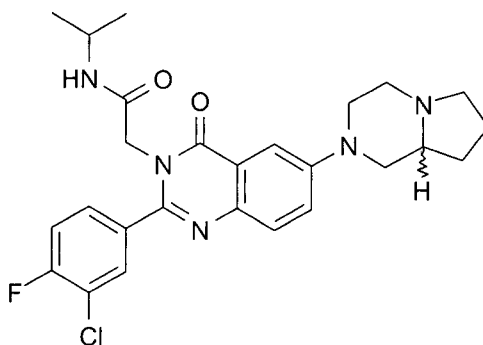
De manera similar, fueron preparados a partir de
INTERMEDIARIOS V:

EJEMPLO 6b: 2-[2-(3-Clorofenil)-6-(hexahidropirrolo[1,2-a]pirazin-2-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 480/482 ($[M+H]^+$) (a partir del INTERMEDIARIO V.48).

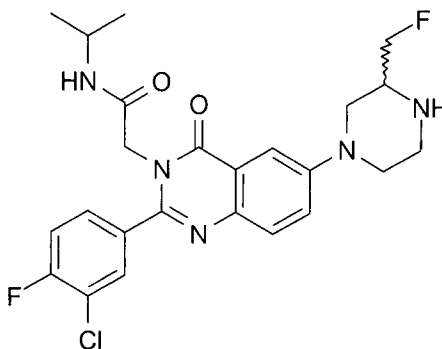
EJEMPLO 6c: 2-[2-(3-Cloro-4-fluorofenil)-6-(hexahidropirrolo[1,2-a]pirazin-2-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 498/500 ($[M+H]^+$) (a partir del INTERMEDIARIO V.48).

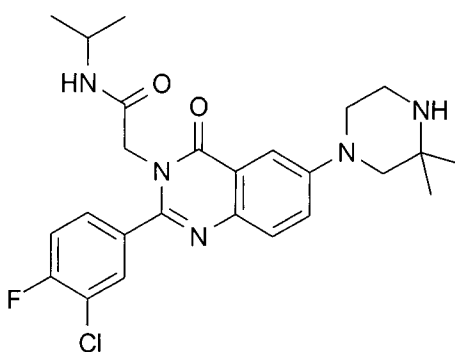
384
289

EJEMPLO 6d: 2-[2-(3-Cloro-4-fluorofenil)-6-(3-fluorometil-piperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



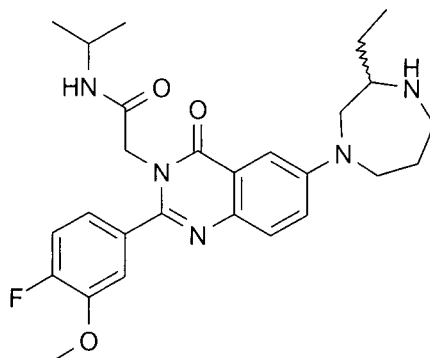
MS (ESI) m/z : 490/492 ($[M+H]^+$) (a partir del INTERMEDIARIO V.27).

EJEMPLO 6e: 2-[2-(3-Cloro-4-fluorofenil)-6-(dimetilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



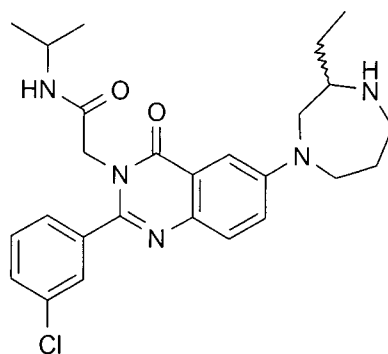
MS (ESI) m/z : 486/488 ($[M+H]^+$) (a partir del INTERMEDIARIO V.19).

EJEMPLO 6f: 2-[6-(3-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

390
290

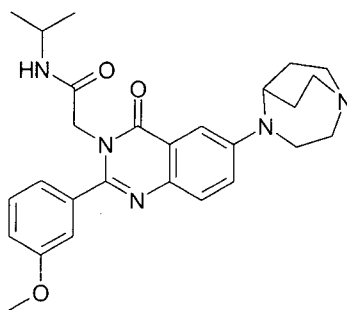
MS (ESI) m/z : 496 ($[M+H]^+$) (a partir del INTERMEDIARIO V.26).

EJEMPLO 6g: 2-[2-(3-Clorofenil)-6-(3-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



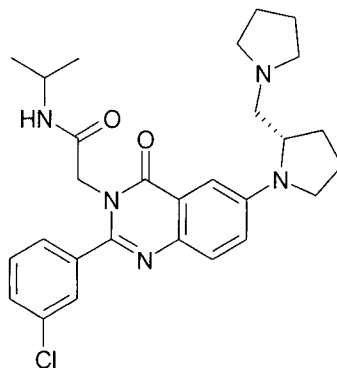
MS (ESI) m/z : 482/484 ($[M+H]^+$) (a partir del INTERMEDIARIO V.26).

EJEMPLO 6h: 2-[6-(1,4-Diazabicciclo[3.2.2]non-4-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



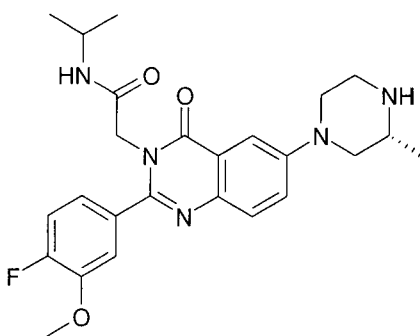
MS (ESI) m/z : 476 ($[M+H]^+$) (a partir del INTERMEDIARIO V.47).

EJEMPLO 6i: 2-[2-(3-Clorofenil)-4-oxo-6-((S)-2-pirrolidin-1-ilmetilpirrolidin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida



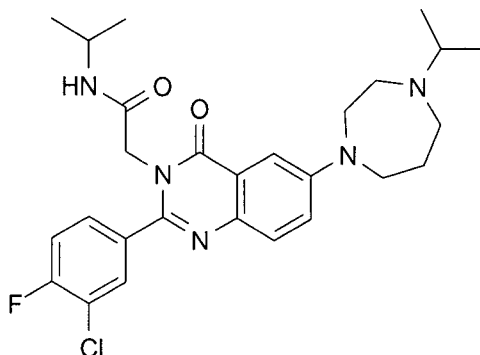
MS (ESI) m/z : 508/510 ($[M+H]^+$) (a partir del INTERMEDIARIO V.28).

EJEMPLO 6j: 2-[2-(4-Fluoro-3-metoxifenil)-6-((R)-3-metil-piperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 468 ($[M+H]^+$) (a partir del INTERMEDIARIO V.25).

EJEMPLO 6k: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

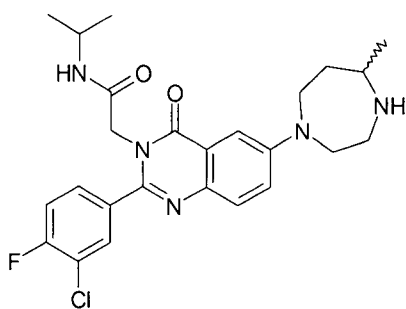


2-Amino-5-(4-isopropil-1,4-diazepan-1-il)-N-(2-(isopropilamino)-2-oxoetil)benzamida (INTERMEDIARIO V.31) (400 mg, 1,07 mmol), 3-cloro-4-fluorobenzaldehído (253 mg, 1,60 mmol) y ácido acético (0,01 ml) fueron disueltos en etanol (12 ml). La mezcla de reacción fue calentada a 90°C durante la noche. La mezcla de reacción fue filtrada, el residuo fue lavado con EtOAc, y el filtrado fue evaporado bajo presión reducida. El producto crudo fue purificado por SCX, eluyendo con NH₃ 2N/MeOH para dar un sólido de color morado.

Este sólido fue disuelto en tolueno (12,00 ml) y se agregó hexacianoferrato(III) de potasio (3,51 g, 10,65 mmoles) seguido por agua (12 ml) y KOH 10M (acuoso) (4 ml). La mezcla de reacción fue agitada a temperatura ambiente durante la noche. La mezcla de reacción fue acidificada con HCl concentrado, diluida con MeOH (10 ml) y filtrada. El residuo fue lavado con MeOH y el filtrado fue purificado por SCX, eluyendo con NH₃ 2N/MeOH. El producto crudo fue purificado por cromatografía en sílica gel, con una gradiente de DCM a DCM:MeOH:NH₃ (94:5:1, v/v) como eluyente, para proporcionar 2-[2-(3-cloro-4-fluorofenil)-6-(4-isopropil-perhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida (EJEMPLO 6k) (155 mg, 0,302 mmol, 28%).

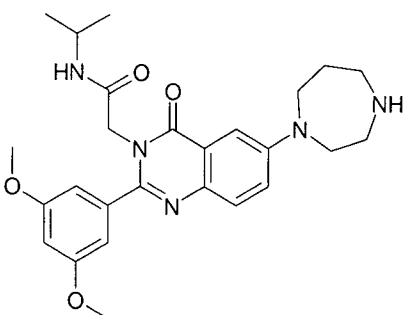
Datos para 2-[2-(3-cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida (EJEMPLO 6k): MS (ESI) m/z : 515/517 ($[M+H]^+$).

EJEMPLO 6l: 2-[2-(3-Cloro-4-fluorofenil)-6-(5-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



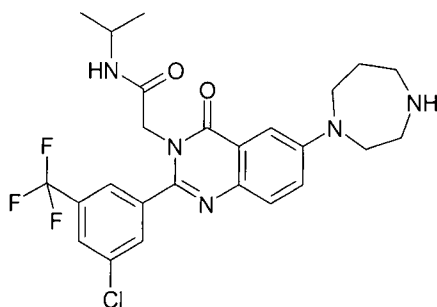
MS (ESI) m/z : 486/488 ($[M+H]^+$) (a partir del INTERMEDIARIO V.29).

EJEMPLO 6m: 2-[2-(3,5-Dimetoxifenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]-N-isopropilacetamida



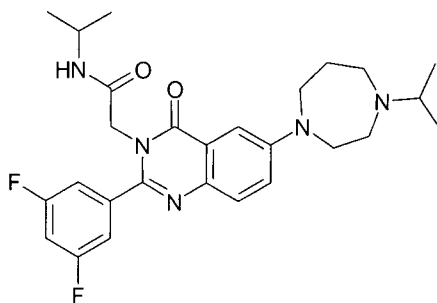
MS (ESI) m/z : 480 ($[M+H]^+$) (a partir del INTERMEDIARIO V.2).

EJEMPLO 6n: 2-[2-(3-Cloro-5-trifluorometilfenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]-N-isopropilacetamida



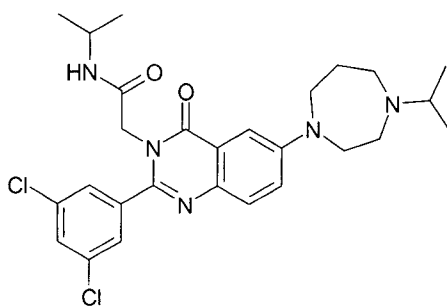
MS (ESI) m/z : 522/524 ($[M+H]^+$) (a partir del INTERMEDIARIO V.2).

EJEMPLO 6o: 2-[2-(3,5-Difluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



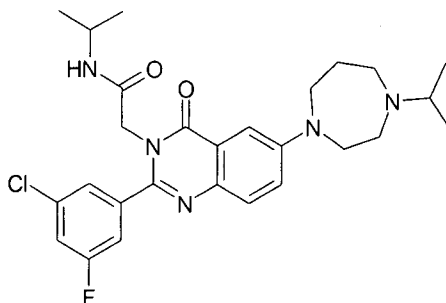
MS (ESI) m/z : 498 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6p: 2-[2-(3,5-Diclorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



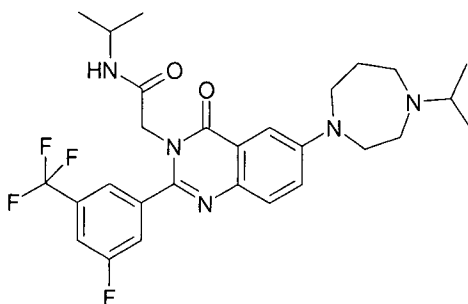
MS (ESI) m/z : 530/532/534 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6q: 2-[2-(3-Cloro-5-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



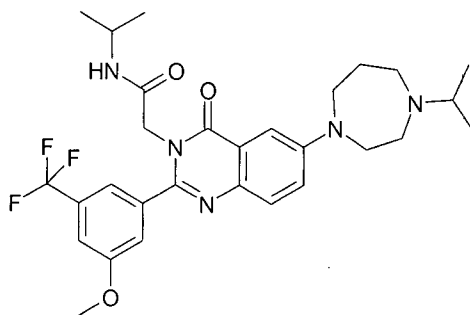
MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6r: 2-[2-(3-Fluoro-5-trifluorometilfenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



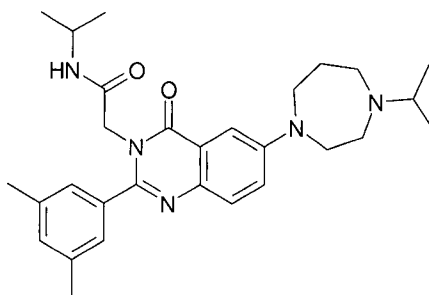
MS (ESI) m/z : 548 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6s: N-Isopropil-2-[6-(4-isopropilperhidro-1,4-diazepin-1-il)-2-(3-metoxi-5-trifluorometilfenil)-4-oxo-4H-quinazolin-3-il]-acetamida



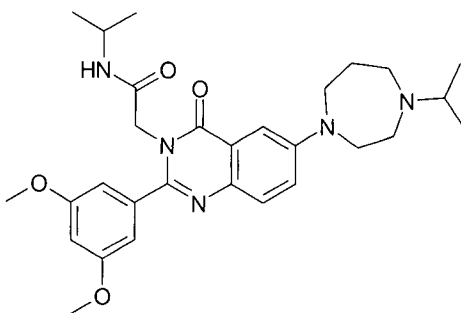
MS (ESI) m/z : 560 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6t: 2-[2-(3,5-Dimetilfenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



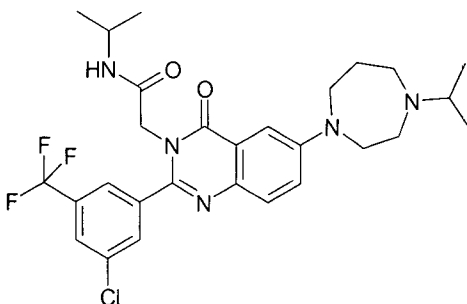
MS (ESI) m/z : 490 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6u: 2-[2-(3,5-Dimetoxifenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



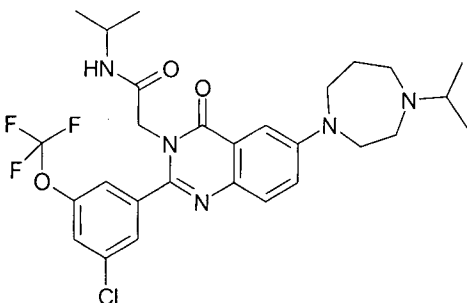
MS (ESI) m/z : 522 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6v: 2-[2-(3-Cloro-5-trifluorometilfenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



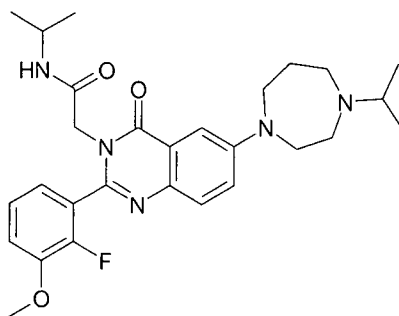
MS (ESI) m/z : 564/566 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6w: 2-[2-(3-Cloro-5-trifluorometoxifenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



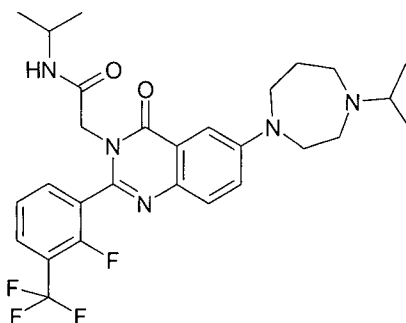
MS (ESI) m/z : 580/582 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6x: 2-[2-(2-Fluoro-3-metoxifenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



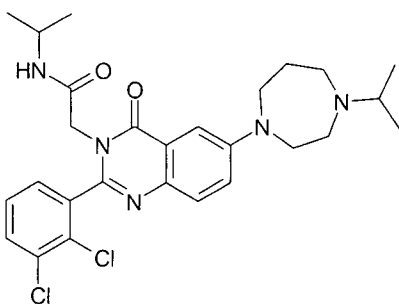
MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6y: 2-[2-(2-Fluoro-3-trifluorometilfenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



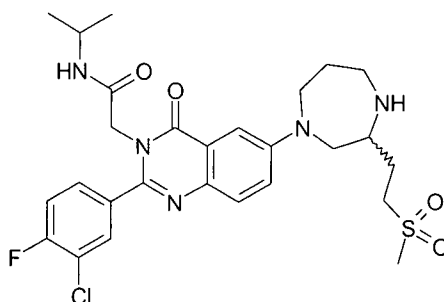
MS (ESI) m/z : 548 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6z: 2-[2-(2,3-Diclorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



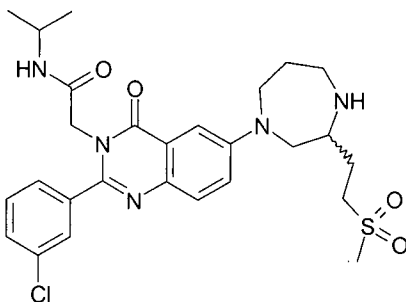
MS (ESI) m/z : 530/532 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6Aa: 2-{2-(3-Cloro-4-fluorofenil)-6-[3-(2-metano-sulfoniletil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



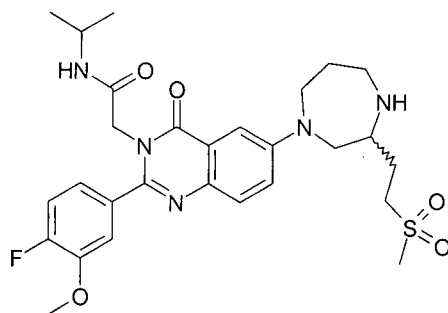
MS (ESI) m/z : 578/580 ($[M+H]^+$) (a partir del INTERMEDIARIO V.33).

EJEMPLO 6Ab: 2-{2-(3-Clorofenil)-6-[3-(2-metanosulfoniletil)-perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



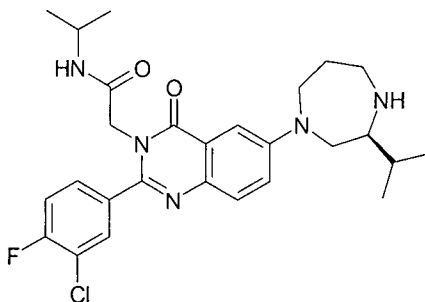
MS (ESI) m/z : 560/562 ($[M+H]^+$) (a partir del INTERMEDIARIO V.33).

EJEMPLO 6Ac: 2-{2-(4-Fluoro-3-metoxifenil)-6-[3-(2-metano-sulfoniletil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



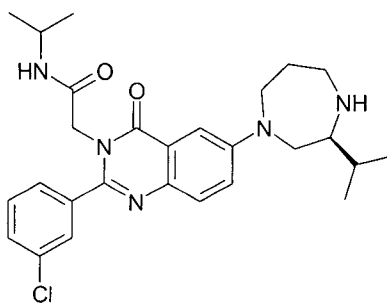
MS (ESI) m/z : 574 ($[M+H]^+$) (a partir del INTERMEDIARIO V.33).

EJEMPLO 6Ad: 2-[2-(3-Cloro-4-fluorofenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



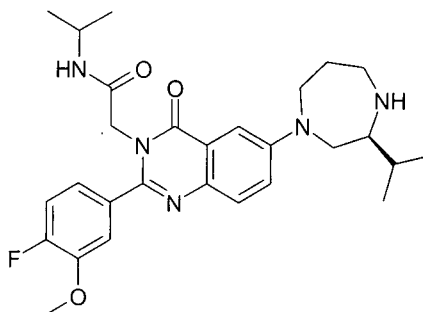
MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del INTERMEDIARIO V.34).

EJEMPLO 6Ae: 2-[2-(3-Clorofenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



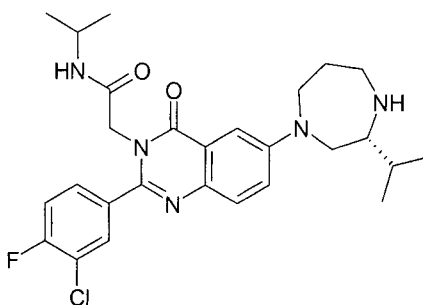
MS (ESI) m/z : 496/498 ($[M+H]^+$) (a partir del INTERMEDIARIO V.34).

EJEMPLO 6Af: 2-[2-(4-Fluoro-3-metoxifenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



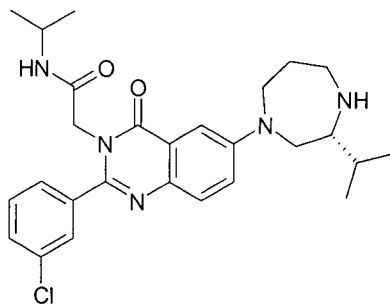
MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del INTERMEDIARIO V.34).

EJEMPLO 6Ag: 2-[2-(3-Cloro-4-fluorofenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



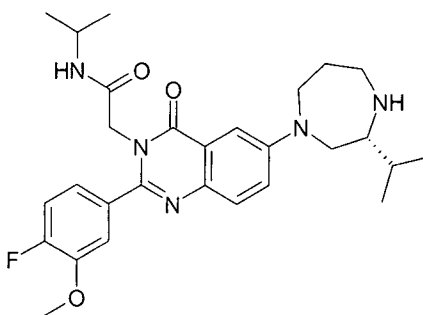
MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del INTERMEDIARIO V.35).

EJEMPLO 6Ah: 2-[2-(3-Clorofenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



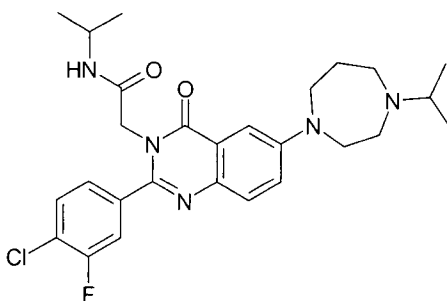
MS (ESI) m/z : 496/498 ($[M+H]^+$) (a partir del INTERMEDIARIO V.35).

EJEMPLO 6Ai: 2-[2-(4-Fluoro-3-metoxifenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



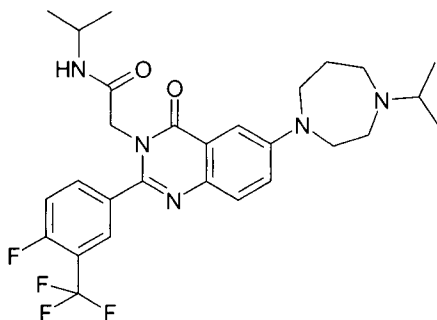
MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del INTERMEDIARIO V.35).

EJEMPLO 6Aj: 2-[2-(4-Cloro-3-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



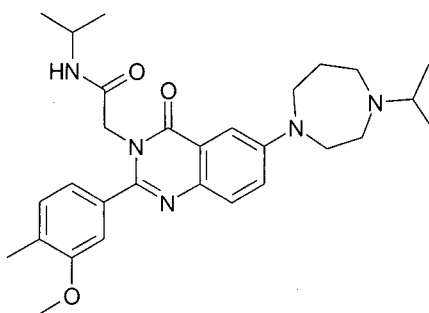
MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6Ak: 2-[2-(4-Fluoro-3-trifluorometilfenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



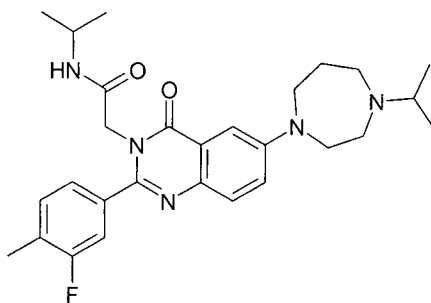
MS (ESI) m/z : 548 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6Al: N-Isopropil-2-[6-(4-isopropilperhidro-1,4-diazepin-1-il)-2-(3-metoxi-4-metilfenil)-4-oxo-4H-quinazolin-3-il]-acetamida



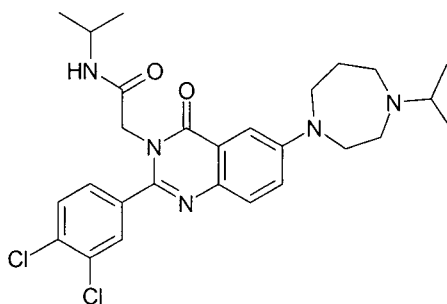
MS (ESI) m/z : 506 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6Am: 2-[2-(3-Fluoro-4-metilfenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



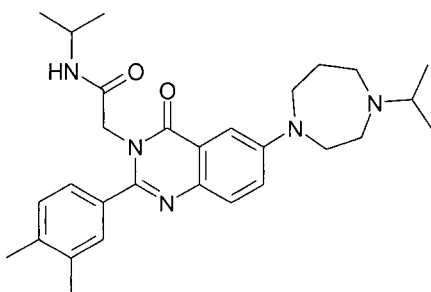
MS (ESI) m/z : 494 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6An: 2-[2-(3,4-Diclorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 530/532/534 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

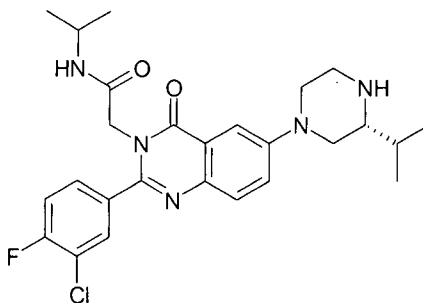
EJEMPLO 6Ao: 2-[2-(3,4-Dimetilfenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 490 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

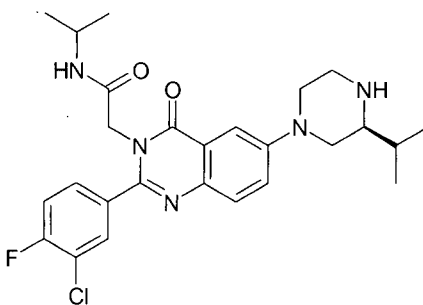
305

EJEMPLO 6Ap: 2-[2-(3-Cloro-4-fluorofenil)-6-((R)-3-isopropil-piperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



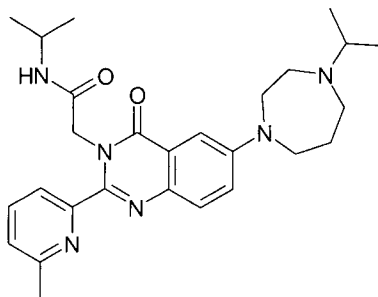
MS (ESI) m/z : 500/502 ($[M+H]^+$) (a partir del INTERMEDIARIO V.36).

EJEMPLO 6Aq: 2-[2-(3-Cloro-4-fluorofenil)-6-((S)-3-isopropil-piperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



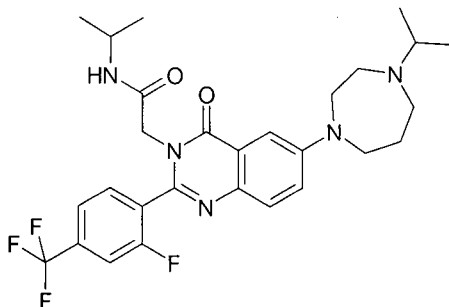
MS (ESI) m/z : 500/502 ($[M+H]^+$) (a partir del INTERMEDIARIO V.37).

EJEMPLO 6Ar: N-Isopropil-2-[6-(4-isopropilperhidro-1,4-diazepin-1-il)-2-(6-metilpiridin-2-il)-4-oxo-4H-quinazolin-3-il]acetamida



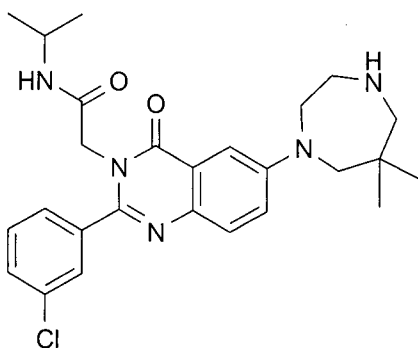
MS (ESI) m/z : 477 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6As: 2-[2-(2-Fluoro-4-trifluorometilfenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 548 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 6At: 2-[2-(3-Clorofenil)-6-(6,6-dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida

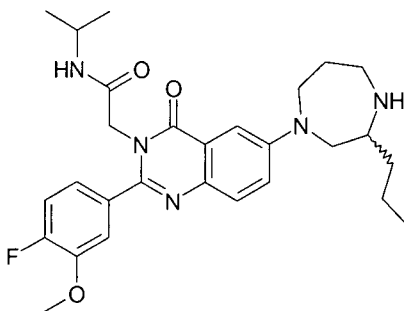


2-Amino-5-(6,6-dimetil-1,4-diazepan-1-il)-N-(2-(isopropilamino)-2-oxoetil)benzamida (INTERMEDIARIO V.54) (110 mg, 0,304 mmol), 3-clorobenzaldehído (58 mg, 0,365 mmol) y ácido acético (10 mg, 0,0003 mmol) fueron disueltos en etanol (3 ml), y se agitó a 90°C por 16 horas. La mezcla de reacción fue evaporada a sequedad, el producto crudo fue disuelto en DCM (3 ml) y se agregó 4,5-dicloro-3,6-dioxociclohexa-1,4-dieno-1,2-dicarbonitrilo (138 mg, 0,609 mmol). La mezcla de reacción fue agitada a temperatura ambiente por 4 horas. La mezcla cruda fue disuelta

en MeOH y purificada por SCX eluyendo con NH_3 2N/MeOH. El solvente fue evaporado bajo presión reducida y el material crudo fue purificado por cromatografía en sílica gel, con una gradiente de DCM a DCM:MeOH (3:1, v/v) como eluyente. Esto proporcionó 2-[2-(3-clorofenil)-6-(6,6-dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida (Ejemplo 6At) (17 mg, 0,034 mmol, 11%).

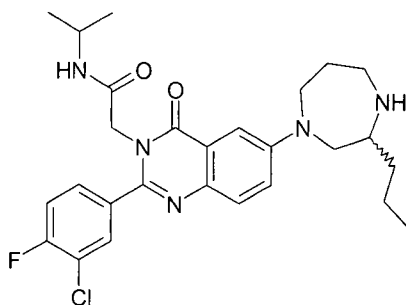
Datos para 2-[2-(3-clorofenil)-6-(6,6-dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida (EJEMPLO 6At): MS (ESI) m/z : 482/484 ($[\text{M}+\text{H}]^+$).

EJEMPLO 6Au: 2-[2-(4-Fluoro-3-metoxifenil)-4-oxo-6-(3-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida



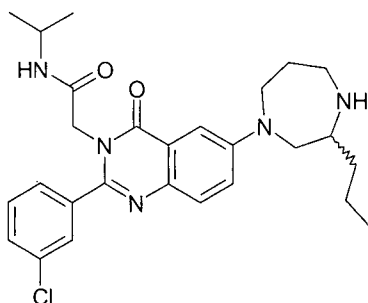
MS (ESI) m/z : 510 ($[\text{M}+\text{H}]^+$) (a partir del INTERMEDIARIO V.32).

EJEMPLO 6Av: 2-[2-(3-Cloro-4-fluorofenil)-4-oxo-6-(3-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida



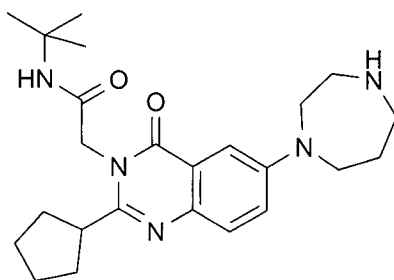
MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del INTERMEDIARIO V.32).

EJEMPLO 6Aw: 2-[2-(3-Clorofenil)-4-oxo-6-(3-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 496/498 ($[M+H]^+$) (a partir del INTERMEDIARIO V.32).

EJEMPLO 7a: N-ter-Butil-2-(2-ciclopentil-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il)-acetamida



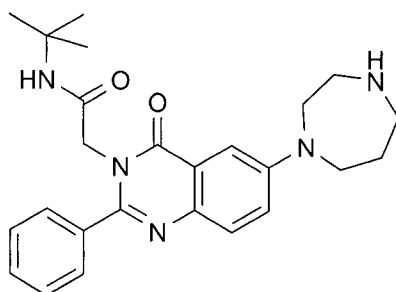
Piridina (21 mg, 0,022 ml, 0,268 mmol) y cloruro de ciclopentanocarbonilo (30 mg, 0,223 mmol) fueron agregados a una solución enfriada con hielo-agua de ter-butyl éster del ácido 4-{4-amino-3-[(ter-butylcarbamoilmetil)carbamoil]fenil}perhidro-

1,4-diazepina-1-carboxílico (INTERMEDIARIO V.38) (100 mg, 0,223 mmol) en THF (1 ml), y la mezcla de reacción fue agitada por 15 minutos. El solvente fue removido al vacío y el residuo fue sometido a partición entre DCM (10 ml) y agua (10 ml). La fase orgánica fue secada (Na_2SO_4) y concentrada al vacío. El material crudo fue disuelto en 1,2-dicloroetano (5 ml) y se agregó trietilamina (1,04 g, 1,39 ml, 10,28 mmoles) y cloruro de trimetilsililo (364 mg, 0,428 ml, 3,35 mmoles). La mezcla de reacción fue calentada a temperatura de reflujo por 3 horas. La mezcla de reacción fue diluida con EtOAc (10 ml) y lavada con HCl 1M (acuoso) y solución (acuosa) de bicarbonato de sodio. La fase orgánica fue secada (MgSO_4) y el solvente fue removido al vacío. El producto crudo fue purificado por cromatografía en sílica gel, con un gradiente de DCM a DCM:EtOAc (1:4, v/v) como eluyente. El producto fue disuelto en DCM (5 ml), se agregó TFA (0,5 ml) y la reacción fue agitada a temperatura ambiente por 2 horas. La solución fue vertida directamente sobre un cartucho de SCX y el producto fue eluido con NH_3 2N/MeOH. El solvente fue removido bajo presión reducida para proporcionar *N*-ter-butil-2-(2-ciclopentil-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il)-acetamida (Ejemplo 7a) (35 mg, 0,082 mmol, 37%).

Datos para *N*-ter-butil-2-(2-ciclopentil-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il)-acetamida (Ejemplo 7a): MS (ESI) m/z : 426 ($[\text{M}+\text{H}]^+$).

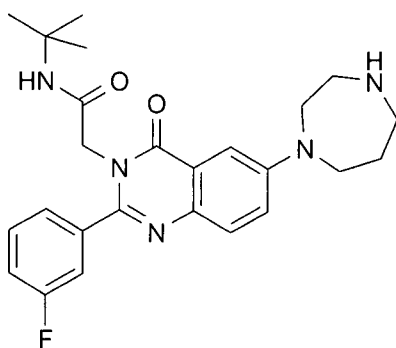
De manera similar, fueron preparados a partir de INTERMEDIARIOS V:

EJEMPLO 7b: *N*-ter-Butil-2-(4-oxo-6-perhidro-1,4-diazepin-1-il-2-fenil-4H-quinazolin-3-il)acetamida



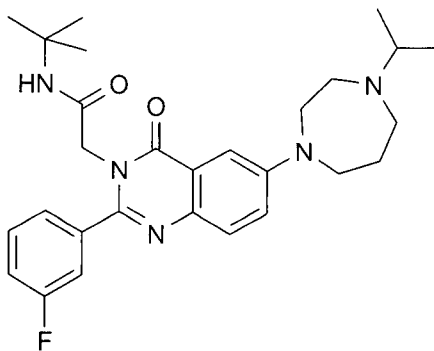
MS (ESI) m/z : 434 ($[M+H]^+$) (a partir del INTERMEDIARIO V.38).

EJEMPLO 7c: *N*-ter-Butil-2-[2-(3-fluorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il]-4H-quinazolin-3-il]acetamida



MS (ESI) m/z : 452 ($[M+H]^+$) (a partir del INTERMEDIARIO V.38).

EJEMPLO 7d: *N*-ter-Butil-2-[2-(3-fluorofenil)-6-(4-isopropil-perhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]acetamida



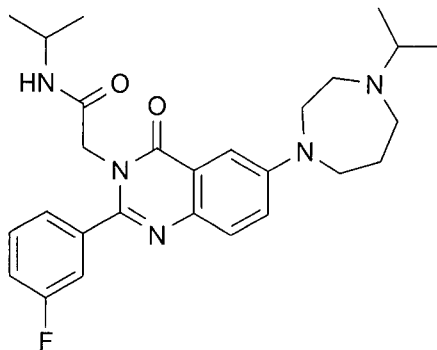
Cloruro de 3-fluorobenzoílo (24 mg, 0,154 mmol, 0,019 ml) fue agregado a una solución enfriada con hielo-agua de 2-

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amino-*N*-(*ter*-butilcarbamoilmetil)-5-(4-isopropilperhidro-1,4-diazepin-1-il)benzamida (INTERMEDIARIO V.49) (60 mg, 0,154 mmol) y trietilamina (716 mg, 0,96 ml, 7,09 mmoles) en DCM (2 ml). La agitación se continuó por 15 minutos. Se agregó cloruro de trimetilsililo (251 mg, 0,295 ml, 2,31 mmoles) y la mezcla de reacción fue calentada en el horno de microondas a 150°C por 7 minutos. La mezcla de reacción fue diluida con DCM (10 ml) y lavada con agua. La fase orgánica fue secada (MgSO₄) y concentrada al vacío. El producto crudo fue purificado por cromatografía en sílica gel, con una gradiente de DCM a DCM:MeOH:NH₃ (95:4:1, v/v) como eluyente. La purificación adicional por HPLC preparatoria proporcionó *N*-*ter*-butil-2-[2-(3-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acetamida (Ejemplo 7d) (5 mg, 10 μmoles, 7%).

Datos para *N*-*ter*-butil-2-[2-(3-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]acetamida (Ejemplo 7d): MS (ESI) *m/z*: 494 ([M+H]⁺).

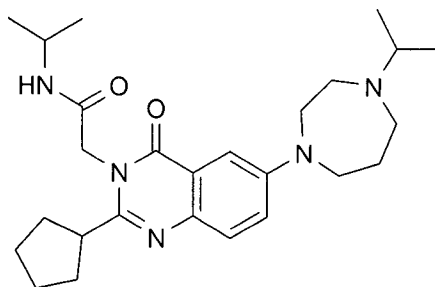
EJEMPLO 7e: 2-[2-(3-Fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida



MS (ESI) *m/z*: 480 ([M+H]⁺) (a partir del INTERMEDIARIO V.31).

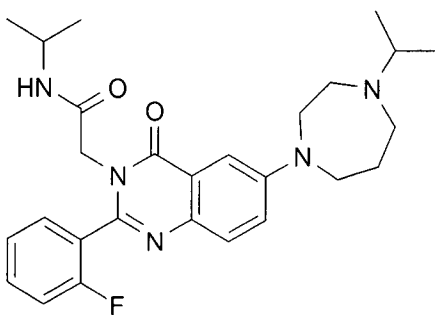
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EJEMPLO 7f: 2-[2-Ciclopentil-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



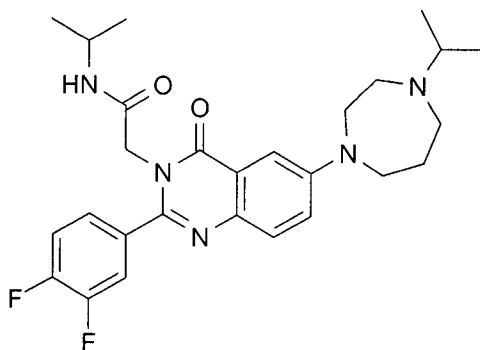
MS (ESI) m/z : 454 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 7g: 2-[2-(2-Fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



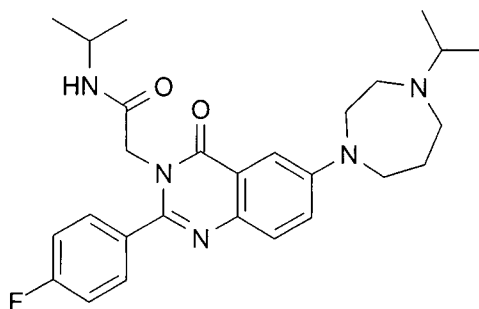
MS (ESI) m/z : 480 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 7h: 2-[2-(3,4-Difluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



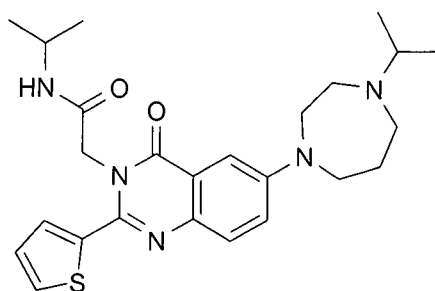
MS (ESI) m/z : 498 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 7i: 2-[2-(4-Fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



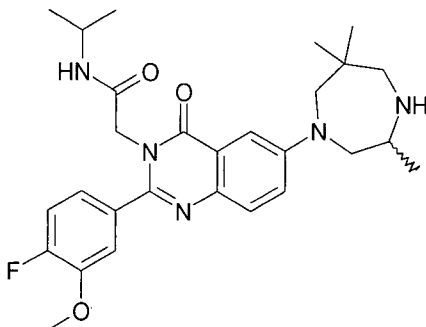
MS (ESI) m/z : 480 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

EJEMPLO 7j: N-Isopropil-2-[6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-2-tiofen-2-il-4H-quinazolin-3-il]acetamida

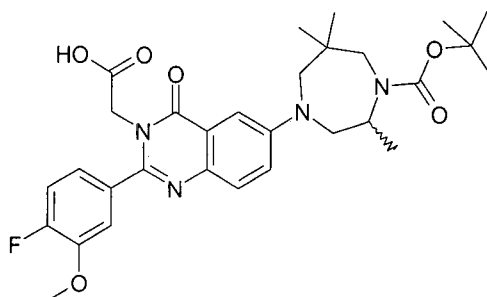


MS (ESI) m/z : 468 ($[M+H]^+$) (a partir del INTERMEDIARIO V.31).

Ejemplo 8a: 2-[2-(4-Fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida

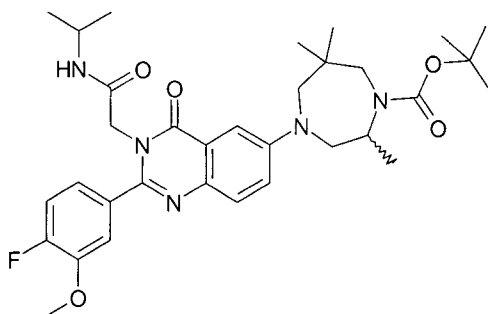


a) ter-Butil éster del ácido 4-[3-carboximetil-2-(4-fluoro-3-metoxifenil)-4-oxo-3,4-dihidroquinazolin-6-il]-2,6,6-trimetilperhidro-1,4-diazepina-1-carboxílico



Ácido [2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]acético (INTERMEDIARIO IX.1) (160 mg, 0,341 mmol), dicarbonato de di-ter-butilo (78 mg, 0,359 mmol) y trietilamina (76 mg, 0,751 mmol), fueron combinados y agitados a temperatura ambiente en DCM (5 ml) durante la noche. La mezcla de producto crudo fue lavada con HCl 1N (2 X 20 ml) y agua (40 ml). La fase orgánica fue secada (Na_2SO_4) y concentrada al vacío. El producto crudo fue purificado por cromatografía en sílica gel con DCM:MeOH (3:1, v/v) como eluyente, para proporcionar ter-butil éster del ácido 4-[3-carboximetil-2-(4-fluoro-3-metoxifenil)-4-oxo-3,4-dihidroquinazolin-6-il]-2,6,6-trimetilperhidro-1,4-diazepina-1-carboxílico (200 mg, 0,352 mmol, 100%).

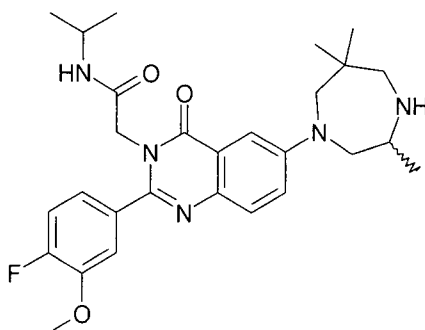
b) ter-Butil éster del ácido 4-[2-(4-fluoro-3-metoxifenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]-2,6,6-trimetilperhidro-1,4-diazepina-1-carboxílico



ter-Butil éster del ácido 4-[3-carboximetil-2-(4-fluoro-3-metoxifenil)-4-oxo-3,4-dihidroquinazolin-6-il]-2,6,6-trimetilperhidro-1,4-diazepina-1-carboxílico (200 mg, 0,352 mmol), isopropilamina (208 mg, 299 μ l, 3,52 mmoles), anhídrido cíclico del ácido 1-propanofosfónico (336 mg, 320 μ l, 0,528 mmol) y DIPEA (135 mg, 186 μ l, 1,06 mmol), fueron agitados a temperatura ambiente en DCM (15 ml) por 2 horas. Se agregó NaHCO_3 (acuoso) (15 ml), y la capa orgánica fue separada, secada (Na_2SO_4) y evaporada bajo presión reducida. El producto crudo fue purificado por cromatografía en sílica gel con una gradiente de DCM a DCM:MeOH (4:1, v/v) como eluyente, para proporcionar ter-butil éster del ácido 4-[2-(4-fluoro-3-metoxifenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidroquinazolin-6-il]-2,6,6-trimetilperhidro-1,4-diazepina-1-carboxílico (120 mg, 0,197 mmol, 56%).

c) 2-[2-(4-Fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida

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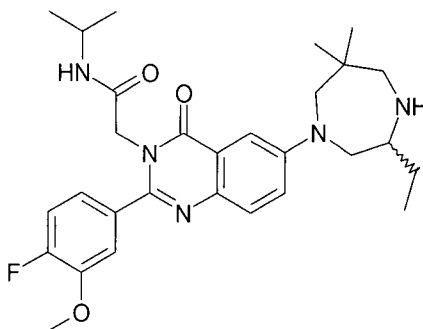
ter-Butil éster del ácido 4-[2-(4-fluoro-3-metoxifenil)-3-(isopropilcarbamoilmetil)-4-oxo-3,4-dihidro-quinazolin-6-il]-2,6,6-trimetilperhidro-1,4-diazepina-1-carboxílico (120 mg, 0,197 mmol) fue disuelto en DCM (6 ml) y se agregó TFA (3 ml). La reacción fue agitada a temperatura ambiente por 4 horas. La mezcla de producto fue vertida directamente sobre un cartucho de SCX y el producto fue eluido con NH_3 2N/MeOH. El solvente fue evaporado bajo presión reducida para proporcionar un sólido de color rojo. El producto fue diluido con MeOH (20 ml) y se calentó a temperatura de reflujo con carbón activado. La mezcla fue filtrada a través de una almohadilla de Celite, el solvente fue evaporado bajo presión reducida y el producto resultante fue recrystalizado en etanol:heptano. Esto proporcionó 2-[2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida (Ejemplo 8a) (74 mg, 0,145 mmol, 74%).

Datos para 2-[2-(4-fluoro-3-metoxifenil)-4-oxo-6-(3,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida (Ejemplo 8a): MS (ESI) m/z : 510 ($[\text{M}+\text{H}]^+$).

De manera similar fueron preparados:

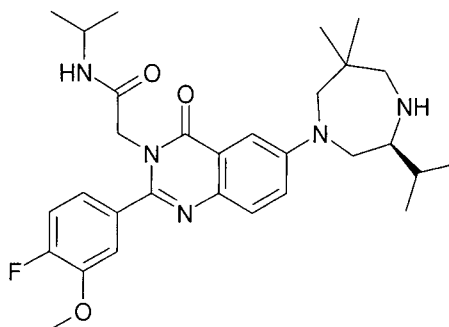
317

EJEMPLO 8b: 2-[6-(3-Etil-6,6-dimetilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



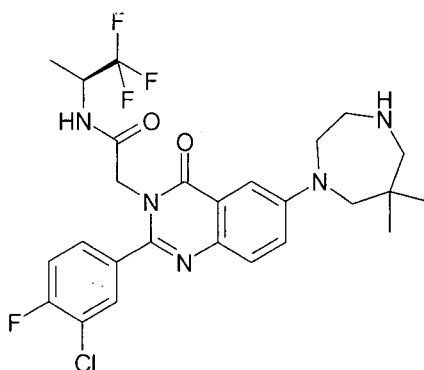
MS (ESI) m/z : 524 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.3).

EJEMPLO 8c: 2-[2-(4-Fluoro-3-metoxifenil)-6-((S)-3-isopropil-6,6-dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



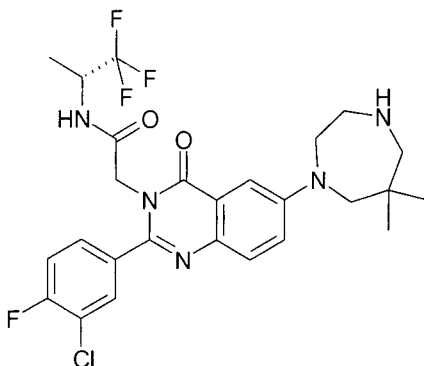
MS (ESI) m/z : 538 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.6).

EJEMPLO 8d: 2-[2-(3-Cloro-4-fluorofenil)-6-(dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-((S)-2,2,2-trifluoro-1-metiletil)acetamida



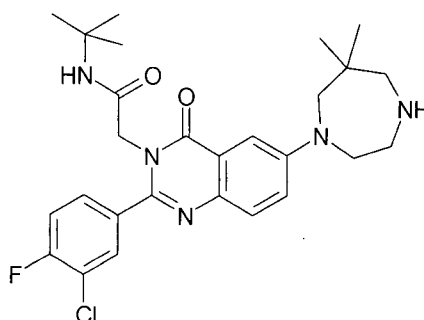
MS (ESI) m/z : 554 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.4).

EJEMPLO 8e: 2-[2-(3-Cloro-4-fluorofenil)-6-(dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-((R)-2,2,2-trifluoro-1-metiletil)acetamida



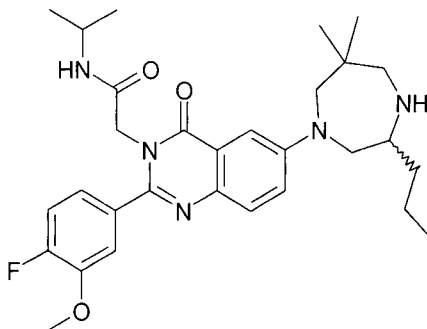
MS (ESI) m/z : 554 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.4).

EJEMPLO 8f: N-ter-Butil-2-[2-(3-cloro-4-fluorofenil)-6-(dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-acetamida



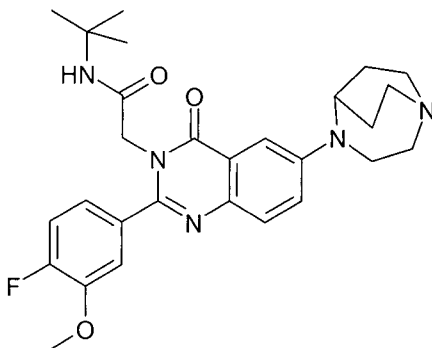
MS (ESI) m/z : 514 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.4).

EJEMPLO 8g: 2-[6-(6,6-Dimetil-3-propilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 538 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.5).

EJEMPLO 9a: N-ter-Butil-2-[6-(1,4-diazabicciclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acetamida



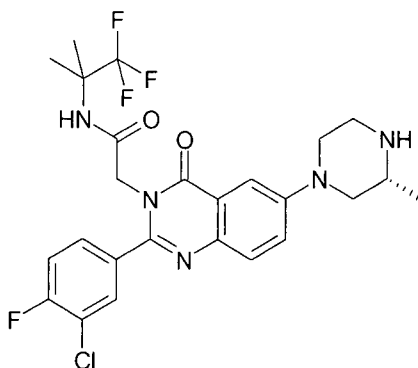
Ácido [6-(1,4-diazabicciclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acético (INTERMEDIARIO IX.7) (20 mg, 0,44 mmol) fue disuelto en DCM (5 ml). ter-Butilamina (6,5 mg, 0,088 mmol) y N,N-diisopropiletilamina (7 mg, 0,053 mmol) fueron agregadas, seguidas por anhídrido cíclico del ácido 1-propanofosfónico (21 mg, 0,02 ml, 0,066 mmol). La mezcla

de reacción fue agitada a temperatura ambiente por 12 horas. Se agregó metanol (5 ml) y la solución fue vertida directamente sobre un cartucho de SCX. La elución con NH_3 2N/MeOH, seguida por la purificación adicional por HPLC preparatoria, proporcionó *N*-*ter*-butil-2-[6-(1,4-diazabicyclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]acetamida (Ejemplo 9a) (7,3 mg, 0,014 mmol, 33%).

Datos para *N*-*ter*-butil-2-[6-(1,4-diazabicyclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]acetamida (Ejemplo 9a): MS (ESI) m/z : 508 ($[\text{M}+\text{H}]^+$).

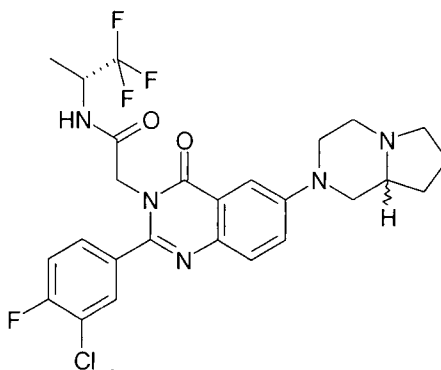
De manera similar fueron preparados:

EJEMPLO 9b: 2-[2-(3-Cloro-4-fluorofenil)-6-((*R*)-3-metilpiperazin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-(2,2,2-trifluoro-1,1-dimetiletil)acetamida



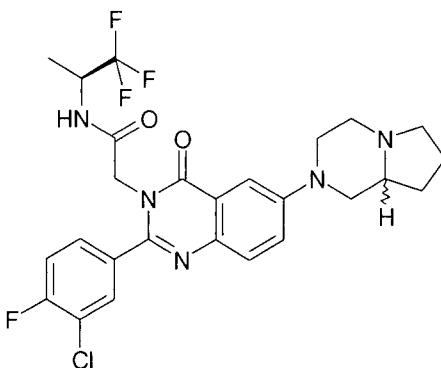
MS (ESI) m/z : 540/542 ($[\text{M}+\text{H}]^+$) (a partir del INTERMEDIARIO IX.8).

EJEMPLO 9c: 2-[2-(3-Cloro-4-fluorofenil)-6-(hexahidropirrolo[1,2-a]pirazin-2-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-((*R*)-2,2,2-trifluoro-1-metiletil)acetamida



MS (ESI) m/z : 552/554 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.9).

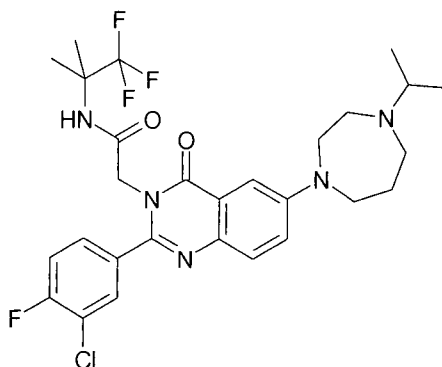
EJEMPLO 9d: 2-[2-(3-Cloro-4-fluorofenil)-6-(hexahidropirrolo[1,2-a]pirazin-2-il)-4-oxo-4H-quinazolin-3-il]-N-((S)-2,2,2-trifluoro-1-metiletil)acetamida



MS (ESI) m/z : 552/554 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.9).

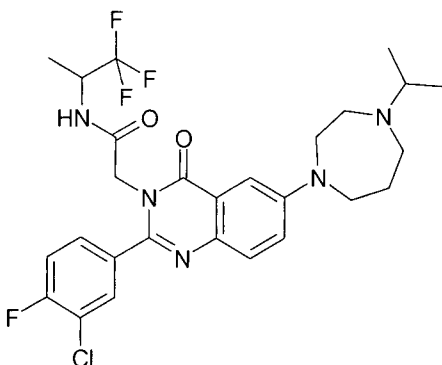
EJEMPLO 9e: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-(2,2,2-trifluoro-1,1-dimetiletil)acetamida

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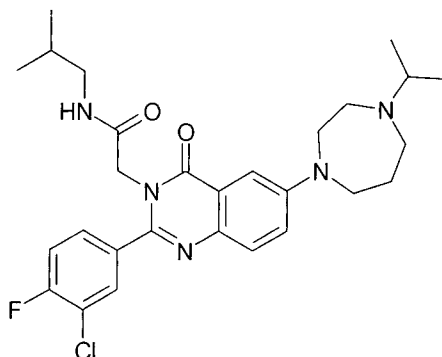
MS (ESI) m/z : 582/584 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.10).

EJEMPLO 9f: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-(2,2,2-trifluoro-1-metiletil)acetamida



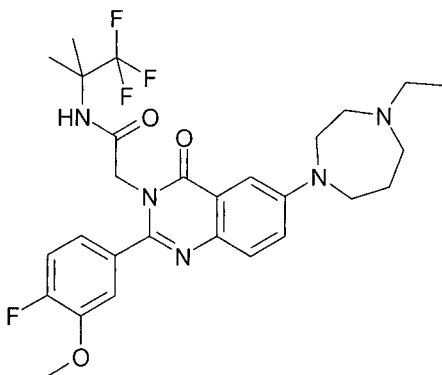
MS (ESI) m/z : 568 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.10).

EJEMPLO 9g: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isobutilacetamida



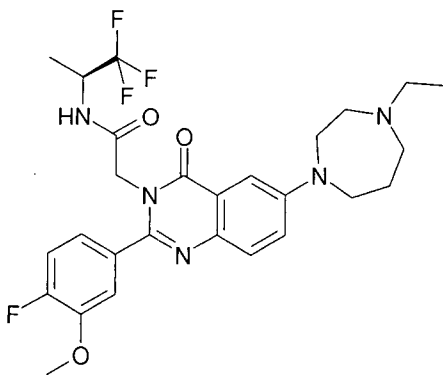
MS (ESI) m/z : 528 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.10).

EJEMPLO 9h: 2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-(2,2,2-trifluoro-1,1-dimetiletil)acetamida



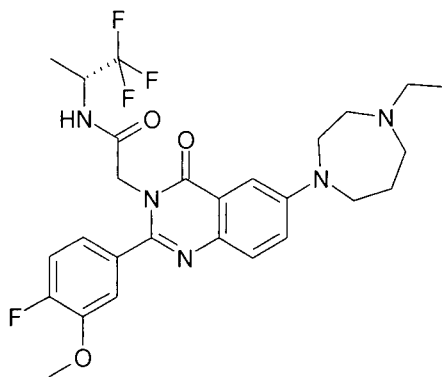
MS (ESI) m/z : 564 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.11).

EJEMPLO 9i: 2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-((S)-2,2,2-trifluoro-1-metiletil)acetamida



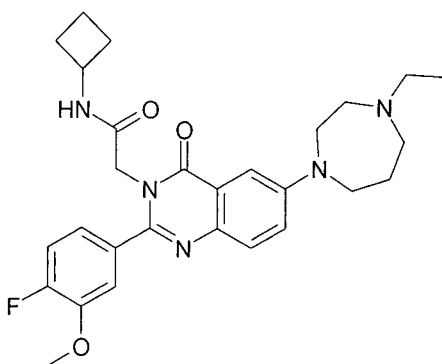
MS (ESI) m/z : 550 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.11).

EJEMPLO 9j: 2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-((R)-2,2,2-trifluoro-1-metiletil)acetamida



MS (ESI) m/z : 550 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.11).

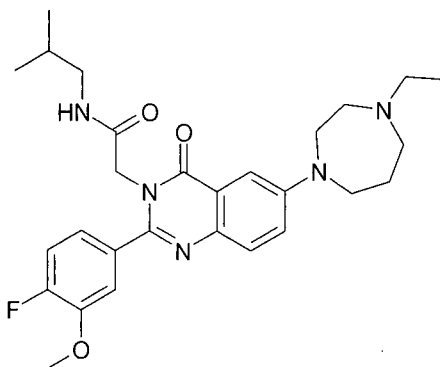
EJEMPLO 9k: N-Ciclobutil-2-[6-(4-etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acetamida



MS (ESI) m/z : 508 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.11).

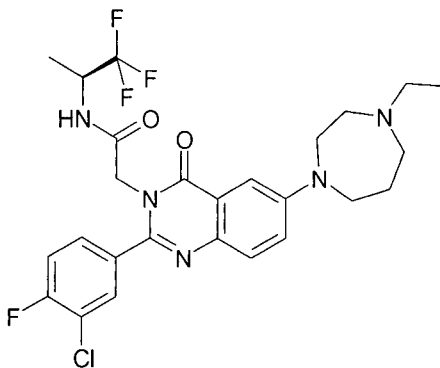
EJEMPLO 9l: 2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isobutilacetamida

325



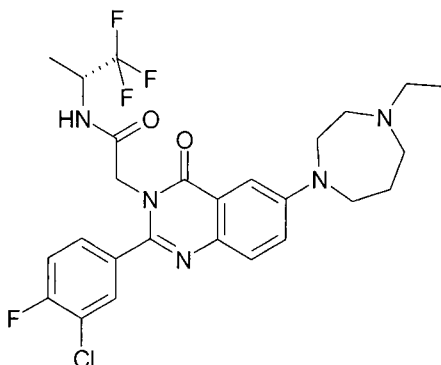
MS (ESI) m/z : 510 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.11).

EJEMPLO 9m: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-((S)-2,2,2-trifluoro-1-metiletil)acetamida



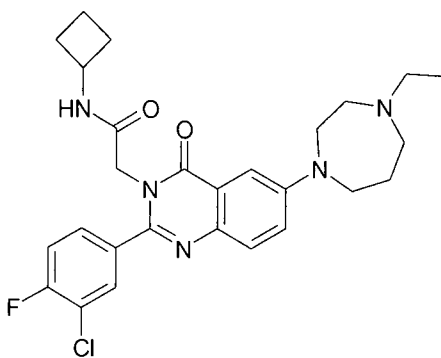
MS (ESI) m/z : 554/556 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.12).

EJEMPLO 9n: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-((R)-2,2,2-trifluoro-1-metiletil)acetamida



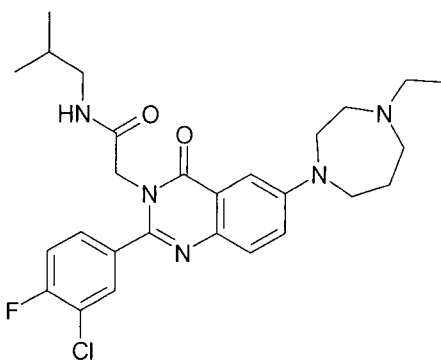
MS (ESI) m/z : 554 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.12).

EJEMPLO 9o: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-ciclobutilacetamida



MS (ESI) m/z : 512/514 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.12).

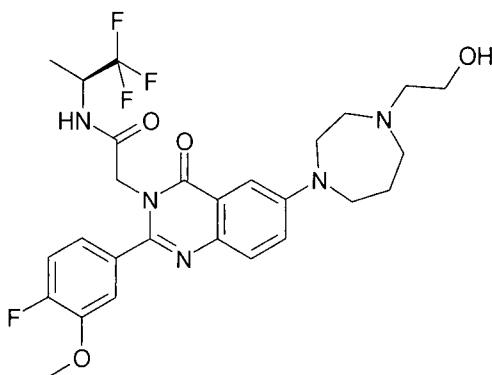
EJEMPLO 9p: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isobutilacetamida



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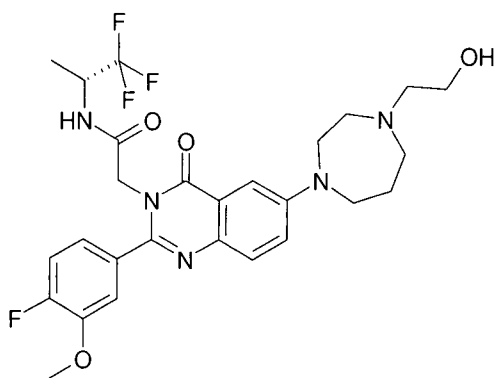
MS (ESI) m/z : 514/516 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.12).

EJEMPLO 9q: 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(2-hidroxi-etil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-((S)-2,2,2-trifluoro-1-metiletil)acetamida



MS (ESI) m/z : 566 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.13).

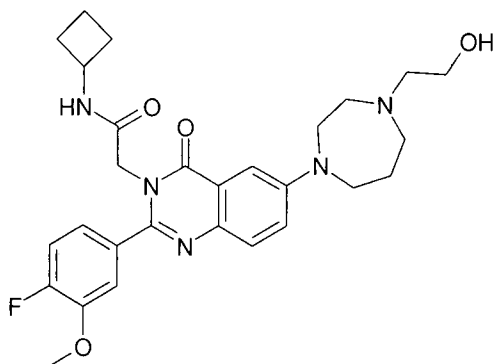
EJEMPLO 9r: 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(2-hidroxi-etil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-((R)-2,2,2-trifluoro-1-metiletil)acetamida



MS (ESI) m/z : 566 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.13).

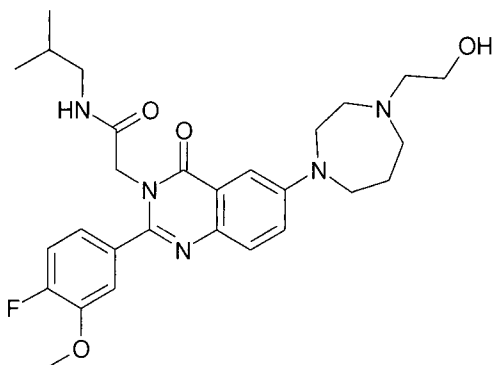
30

EJEMPLO 9s: N-Ciclobutil-2-{2-(4-fluoro-3-metoxifenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}acetamida



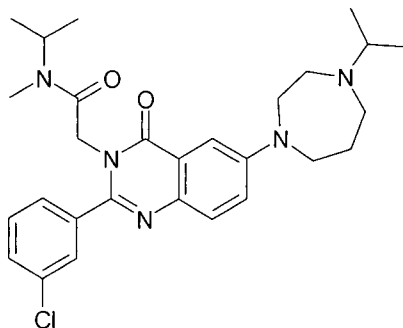
MS (ESI) m/z : 524 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.13).

EJEMPLO 9t: 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isobutilacetamida



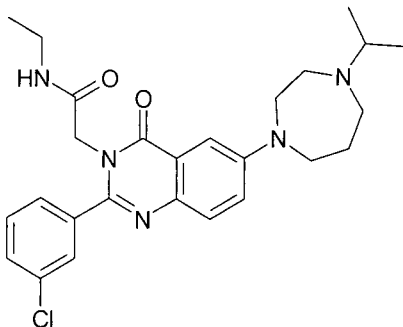
MS (ESI) m/z : 526 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.13).

EJEMPLO 9u: 2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropil-N-metilacetamida



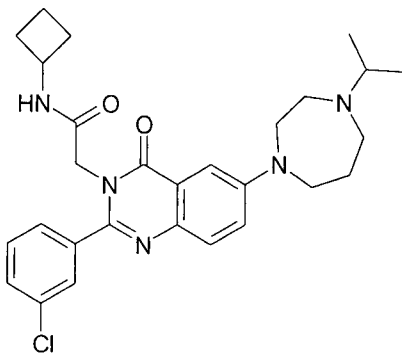
MS (ESI) m/z : 510/512 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.14).

EJEMPLO 9v: 2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-etilacetamida



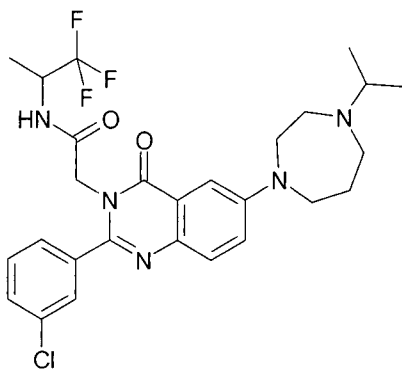
MS (ESI) m/z : 482/484 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.14).

EJEMPLO 9w: 2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-ciclobutilacetamida



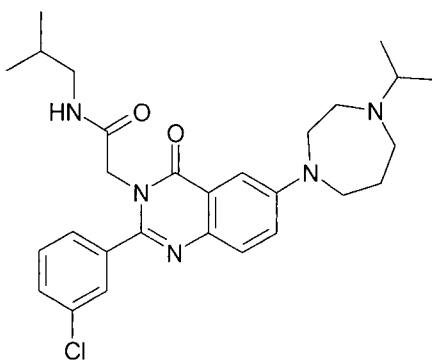
MS (ESI) m/z : 508/510 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.14).

EJEMPLO 9x: 2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-(2,2,2-trifluoro-1-metiletil)acetamida



MS (ESI) m/z : 550/552 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.14).

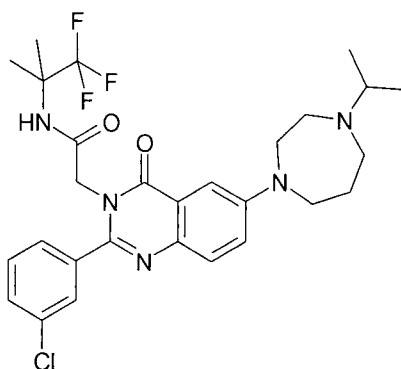
EJEMPLO 9y: 2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isobutilacetamida



MS (ESI) m/z : 510/512 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.14).

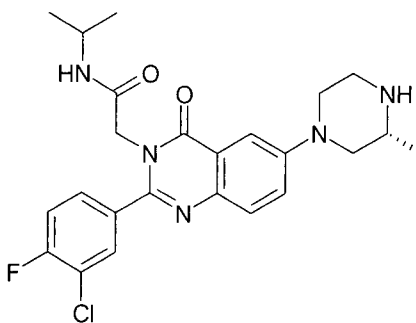
331

EJEMPLO 9z: 2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-(2,2,2-trifluoro-1,1-dimetiletil)acetamida



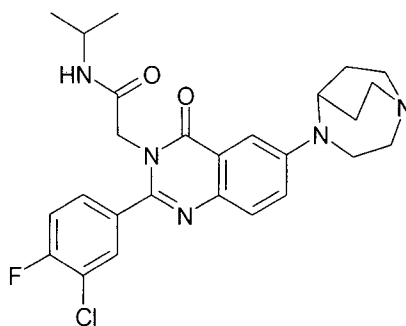
MS (ESI) m/z : 564/566 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.14).

EJEMPLO 9Aa: 2-[2-(3-Cloro-4-fluorofenil)-6-((R)-3-metil-piperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



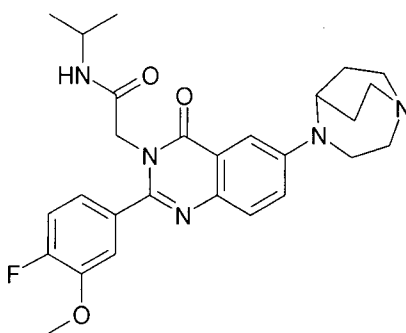
MS (ESI) m/z : 472/474 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.8).

EJEMPLO 9Ab: 2-[2-(3-Cloro-4-fluorofenil)-6-(1,4-diazabicciclo-[3.2.2]non-4-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



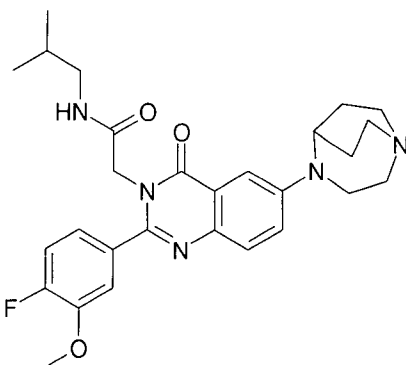
MS (ESI) m/z : 498/500 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.15).

EJEMPLO 9Ac: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-yl]-N-isopropilacetamida



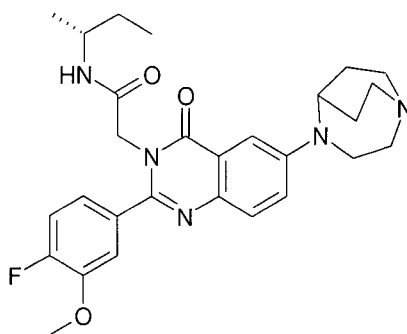
MS (ESI) m/z : 494 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.7).

EJEMPLO 9Ad: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-yl]-N-isobutilacetamida



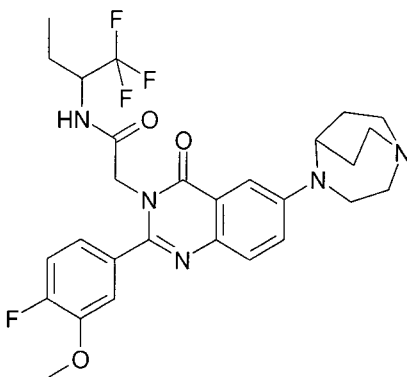
MS (ESI) m/z : 508 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.7).

EJEMPLO 9Ae: N-((R)-sec-Butil)-2-[6-(1,4-diazabicciclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-acetamida



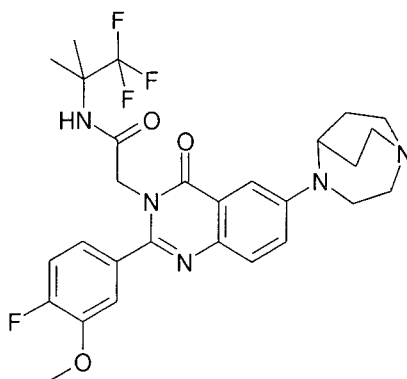
MS (ESI) m/z : 508 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.7).

EJEMPLO 9Af: 2-[6-(1,4-Diazabicciclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-(1-trifluorometil-propil)acetamida



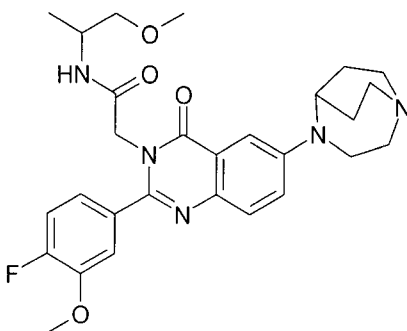
MS (ESI) m/z : 562 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.7).

EJEMPLO 9Ag: 2-[6-(1,4-Diazabicciclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-(2,2,2-trifluoro-1,1-dimetiletil)acetamida



MS (ESI) m/z : 562 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.7).

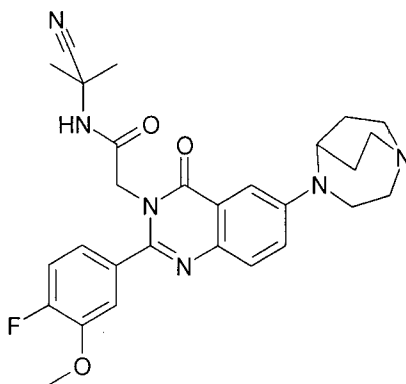
EJEMPLO 9Ah: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-(2-metoxi-1-metiletil)acetamida



MS (ESI) m/z : 524 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.7).

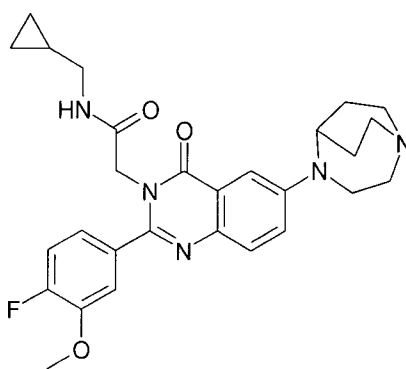
EJEMPLO 9Ai: N-(Cianodimetil-metil)-2-[6-(1,4-diazabicyclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acetamida

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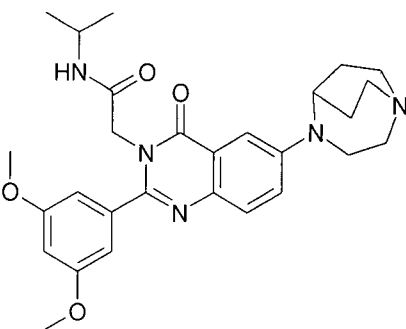
MS (ESI) m/z : 519 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.7).

EJEMPLO 9Aj: N-Ciclopropilmetil-2-[6-(1,4-diazabicyclo[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-acetamida



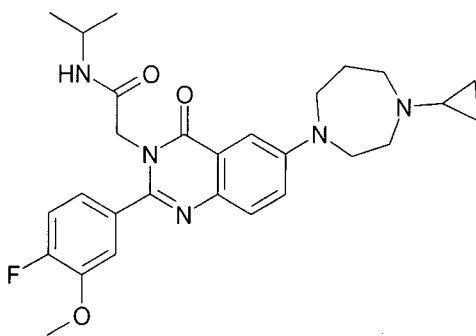
MS (ESI) m/z : 506 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.7).

EJEMPLO 9Ak: 2-[6-(1,4-Diazabicyclo[3.2.2]non-4-il)-2-(3,5-dimetoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 506 ($[M+H]^+$) (a partir del INTERMEDIARIO IX.2).

EJEMPLO 10a: 2-[6-(4-Ciclopropilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropil-acetamida

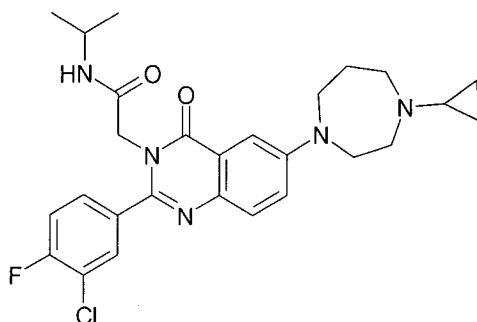


2-(6-(1,4-Diazepan-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida (EJEMPLO 1i) (50 mg, 0,107 mmol), cianoborohidruro de metilpoliestireno trietilamonio macroporoso (70 mg, 0,107 mmol), acetonitrilo (1,5 ml) y AcOH (0,3 ml) fueron combinados bajo una atmósfera de nitrógeno. Se agregó (1-etoxiciclopropoxi)trimetilsilano (19 mg, 0,04 ml, 0,107 mmol) y la mezcla de reacción fue agitada a temperatura ambiente por 48 horas. El solvente fue evaporado bajo presión reducida. El residuo fue disuelto en NH₃ 2M/MeOH y purificado por HPLC preparatoria. Esto proporcionó 2-[6-(4-ciclopropilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida (Ejemplo 10a) (3 mg, 0,0039 mmol, 6%). Datos para 2-[6-(4-ciclopropilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida (Ejemplo 10a): MS (ESI) m/z: 508 ([M+H]⁺).

De manera similar fueron preparados:

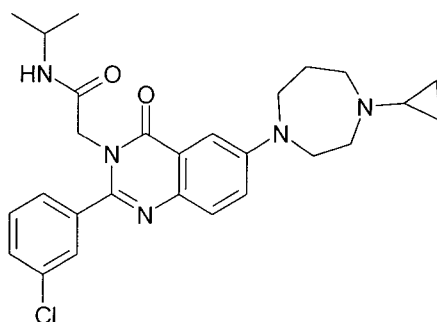
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EJEMPLO 10b: 2-[2-(3-Cloro-4-fluorofenil)-6-(4-ciclopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 512/514 ($[M+H]^+$) (a partir del EJEMPLO 1e).

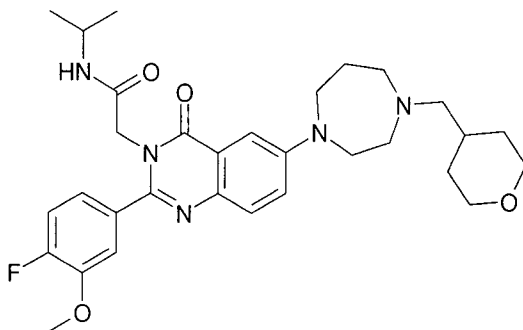
EJEMPLO 10c: 2-[2-(3-Clorofenil)-6-(4-ciclopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida



MS (ESI) m/z : 495/497 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 11a: 2-{2-(4-Fluoro-3-metoxifenil)-4-oxo-6-[4-(tetrahidropiran-4-ilmetil)perhidro-1,4-diazepin-1-il]-4H-quinazolin-3-il}-N-isopropilacetamida

338

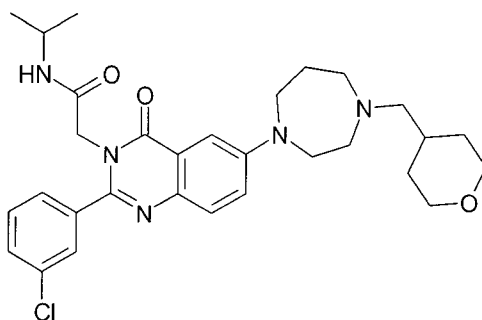


2-(6-(1,4-Diazepan-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida (EJEMPLO 1i) (30 mg, 0,064 mmol), 4-metilbencenosulfonato de (tetrahidro-2H-piran-4-il)metilo (35 mg, 0,128 mmol) y DIPEA (17 mg, 21 μ l, 0,128 mmol) fueron disueltos en DMF (1 ml), y se agitó a temperatura ambiente durante la noche. La purificación por HPLC preparatoria dio 2-{2-(4-fluoro-3-metoxifenil)-4-oxo-6-[4-(tetrahidro-piran-4-ilmetil)-perhidro-1,4-diazepin-1-il]-4H-quinazolin-3-il}-N-isopropilacetamida (EJEMPLO 11a) (5 mg, 0,0088 mmol, 14%).

Datos para 2-{2-(4-fluoro-3-metoxifenil)-4-oxo-6-[4-(tetrahidro-piran-4-ilmetil)perhidro-1,4-diazepin-1-il]-4H-quinazolin-3-il}-N-isopropilacetamida (EJEMPLO 11a): MS (ESI) m/z : 566 ($[M+H]^+$).

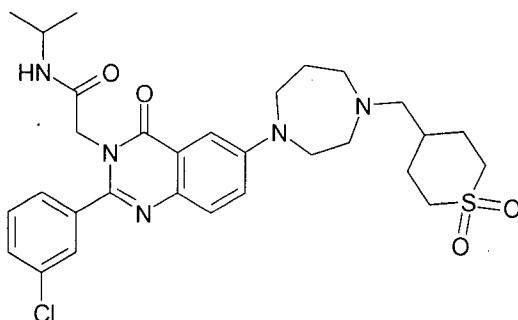
De manera similar fueron preparados:

EJEMPLO 11b: 2-{2-(3-Clorofenil)-4-oxo-6-[4-(tetrahidropiran-4-ilmetil)perhidro-1,4-diazepin-1-il]-4H-quinazolin-3-il}-N-isopropilacetamida



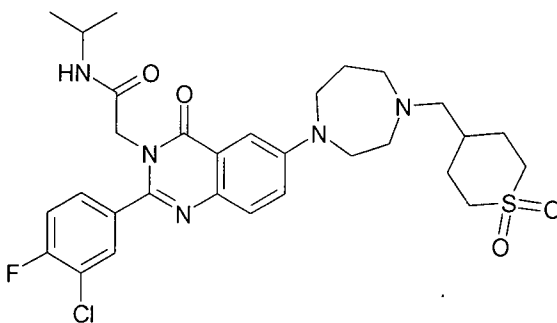
MS (ESI) m/z : 553/555 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 11c: 2-{2-(3-Clorofenil)-6-[4-(1,1-dioxohexahidro-1 λ^6 -tiopiran-4-ilmetil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



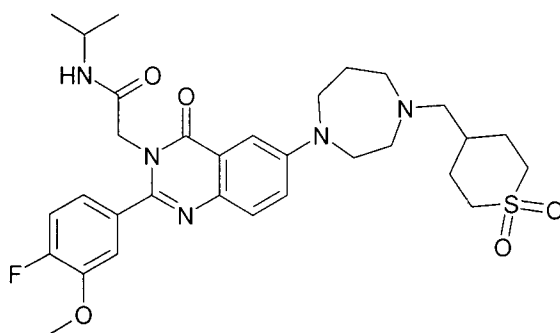
MS (ESI) m/z : 600/602 ($[M+H]^+$) (a partir del EJEMPLO 1b).

EJEMPLO 11d: 2-{2-(3-Cloro-4-fluorofenil)-6-[4-(1,1-dioxohexahidro-1 λ^6 -tiopiran-4-ilmetil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



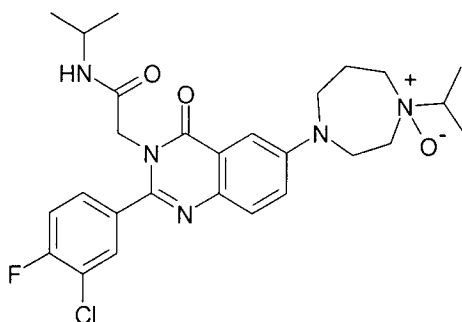
MS (ESI) m/z : 619/621 ($[M+H]^+$) (a partir del EJEMPLO 1e).

EJEMPLO 11e: 2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(1,1-dioxohexahidro-1 λ^6 -tiopiran-4-ilmetil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida



MS (ESI) m/z : 615/617 ($[M+H]^+$) (a partir del EJEMPLO 1i).

EJEMPLO 12a: 4-(2-(3-Cloro-4-fluorofenil)-3-(2-(isopropil-amino)-2-oxoetil)-4-oxo-3,4-dihidroquinazolin-6-il)-1-isopropil-1,4-diazepano 1-óxido



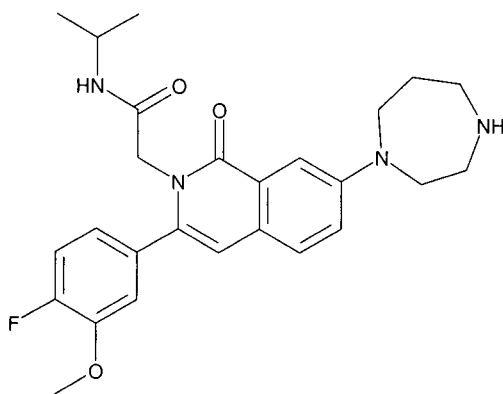
Ácido 3-cloroperoxibenzoico (19 mg, 0,078 mmol) fue agregado a una solución con agitación de 2-[2-(3-cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida (EJEMPLO 6k) (40 mg, 0,078 mmol) en DCM (5 ml). La mezcla de reacción fue agitada por 10 minutos a temperatura ambiente. La mezcla de reacción fue diluida con DCM (10 ml) y lavada con solución acuosa de bicarbonato de sodio (10 ml). La fase orgánica fue secada (Na_2SO_4), concentrada bajo presión reducida y purificada por cromatografía en sílica gel, con una gradiente de DCM a DCM:MeOH (4:1, v/v) como eluyente para proporcionar 4-(2-(3-cloro-4-fluorofenil)-3-(2-(isopropil-

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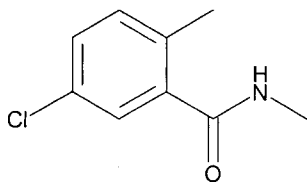
amino)-2-oxoetil)-4-oxo-3,4-dihidroquinazolin-6-il)-1-isopropil-1,4-diazepano 1-óxido (EJEMPLO 12a) (25 mg, 0,047 mmol, 61%).

Datos para 4-(2-(3-cloro-4-fluorofenil)-3-(2-(isopropilamino)-2-oxoetil)-4-oxo-3,4-dihidroquinazolin-6-il)-1-isopropil-1,4-diazepano 1-óxido (EJEMPLO 12a): MS (ESI) m/z : 530 (M^+).

EJEMPLO 13a: 2-[3-(4-Fluoro-3-metoxifenil)-1-oxo-7-perhidro-1,4-diazepin-1-il-1H-isoquinolin-2-il]-N-isopropilacetamida



a) 5-Cloro-2,N-dimetilbenzamida

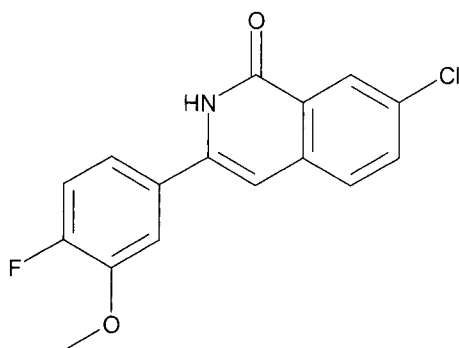


Ácido 5-cloro-2-metilbenzoico (9,16 g, 53,7 mmoles) y cloruro de tionilo (25,6 g, 15,7 ml, 215 mmoles) fueron calentados a temperatura de reflujo por 1,5 hora. El solvente fue evaporado bajo presión reducida y el residuo fue disuelto en DCM (55 ml). Se agregó gota a gota metilamina (acuosa) (al 40%) (12,51 g, 13,90 ml, 161 mmoles) a 0°C. La mezcla de reacción se dejó entibiar hasta temperatura ambiente durante la noche. La

mezcla de reacción fue extraída con EtOAc (50 ml), lavada con solución salina (50 ml), secada (Na_2SO_4) y evaporada al vacío, para proporcionar 5-cloro-2,N-dimetilbenzamida (8,79 g, 47,9 mmoles, 89%) como un sólido blanco. Éste fue usado directamente en la etapa siguiente sin purificación

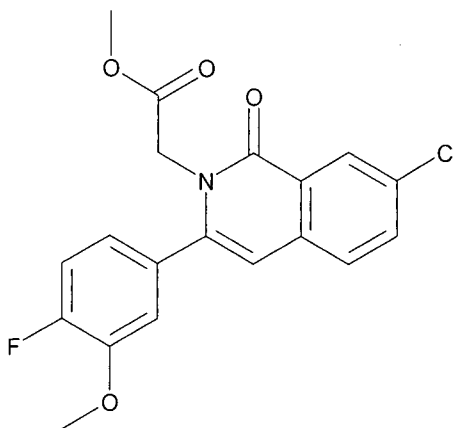
Datos para 5-cloro-2,N-dimetilbenzamida: MS (ESI) m/z : 184 ($[\text{M}+\text{H}]^+$).

b) 7-Cloro-3-(4-fluoro-3-metoxifenil)-2H-isoquinolin-1-ona



Una solución de 5-cloro-2,N-dimetilbenzamida (5,0 g, 27,2 mmoles) en THF (28 ml) fue enfriada a -78°C , y se agregó una solución de diisopropilamida de litio 2M en THF (40,8 ml, 82 mmoles) diluida con THF (68 ml). Se agregó 4-fluoro-3-metoxibenzonitrilo (4,12 g, 27,2 mmoles) en THF (28 ml) y la mezcla fue agitada a -78°C por 2,5 horas. Se agregó NH_4Cl (acuoso) saturado y la mezcla fue extraída con EtOAc (2 X 50 ml). Un precipitado se formó en el acuoso, que fue recolectado por filtración para proporcionar 7-cloro-3-(4-fluoro-3-metoxifenil)-2H-isoquinolin-1-ona (3,74 g, 12,3 mmoles, 45%).

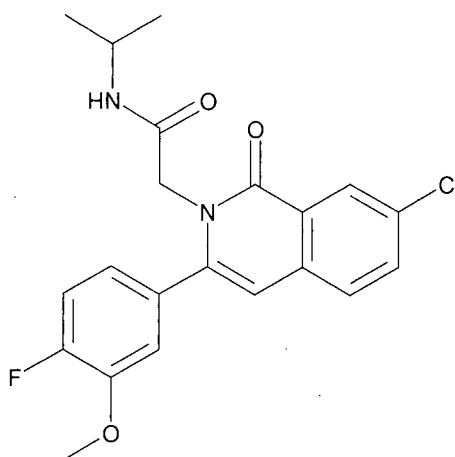
c) Metil éster del ácido [7-cloro-3-(4-fluoro-3-metoxifenil)-1-oxo-1H-isoquinolin-2-il]acético



7-Cloro-3-(4-fluoro-3-metoxifenil)-2H-isoquinolin-1-ona (500 mg, 1,646 mmol) y carbonato de potasio (455 mg, 3,29 mmoles) fueron combinados y se agregó DMF (5 ml) para dar una suspensión blanca. La mezcla de reacción fue agitada por 30 minutos a temperatura ambiente. Se agregó bromoacetato de metilo (756 mg, 0,456 ml, 4,94 mmoles) y la agitación se continuó por 2 horas más. La mezcla de reacción fue diluida con EtOAc (50 ml) y lavada con agua (2 x 10 ml) y solución salina (10 ml), y la capa orgánica fue secada (MgSO₄) y concentrada bajo presión reducida. Esto proporcionó metil éster del ácido [7-cloro-3-(4-fluoro-3-metoxifenil)-1-oxo-1H-isoquinolin-2-il]acético que todavía contenía DMF (≈2 ml). Esta solución fue llevada a la etapa siguiente sin mayor purificación.

Datos para metil éster del ácido [7-cloro-3-(4-fluoro-3-metoxifenil)-1-oxo-1H-isoquinolin-2-il]acético: MS (ESI) m/z: 376/378 ([M+H]⁺).

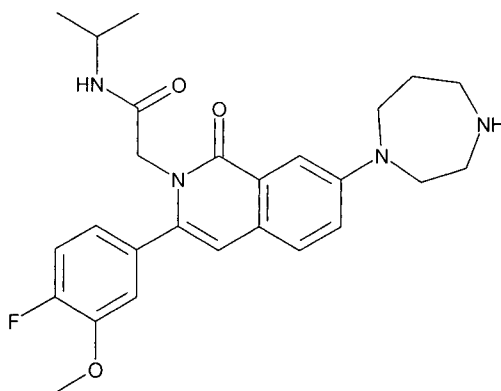
d) 2-[7-Cloro-3-(4-fluoro-3-metoxifenil)-1-oxo-1H-isoquinolin-2-il]-N-isopropilacetamida



Metil éster del ácido [7-cloro-3-(4-fluoro-3-metoxifenil)-1-oxo-1H-isoquinolin-2-il]acético (el producto crudo del experimento anterior) fue disuelto en NMP (4 ml). Se agregó gota a gota propan-2-amina (973 mg, 1,402 ml, 16,46 mmoles) con agitación y se observó una exoterma. El análisis por LCMS indicó que la reacción se había completado en alrededor de un 75%. Se agregó más cantidad de propan-2-amina (348 mg, 0,5 ml, 5,88 mmoles) y la mezcla de reacción fue calentada a temperatura de reflujo por 5 minutos, seguido por agitación a temperatura ambiente durante la noche. El precipitado resultante fue filtrado y lavado con éter dietílico (150 ml). Esto proporcionó el producto contaminado con isopropilamina. El sólido fue disuelto en DCM (50 ml) y lavado con agua (2 x 10 ml). Los orgánicos fueron secados (MgSO₄) y concentrados para proporcionar 2-[7-cloro-3-(4-fluoro-3-metoxifenil)-1-oxo-1H-isoquinolin-2-il]-N-isopropilacetamida (300 mg, 0,745 mmol).

Datos para 2-[7-cloro-3-(4-fluoro-3-metoxifenil)-1-oxo-1H-isoquinolin-2-il]-N-isopropilacetamida: MS (ESI) m/z: 404/406 ([M+H]⁺).

e) 2-[3-(4-Fluoro-3-metoxifenil)-1-oxo-7-perhidro-1,4-diazepin-1-il-1H-isoquinolin-2-il]-N-isopropilacetamida



1-Homopiperazinacarboxilato de ter-butilo (66 mg, 0,07 ml, 0,330 mmol) fue agregado a ter-butóxido de potasio (67 mg, 0,601 mmol), dicloruro de [1,3-bis(2,6-diisopropilfenil)imidazol-2-ilideno](3-cloropiridil)paladio(II) (catalizador PEPPSI-IPr) (20 mg, 0,030 mmol) y 2-[7-cloro-3-(4-fluoro-3-metoxifenil)-1-oxo-1H-isoquinolin-2-il]-N-isopropilacetamida (121 mg, 0,300 mmol) en tolueno (3 ml). La mezcla de reacción fue calentada a 100°C por 2 horas y después de este tiempo, la misma fue enfriada y extinguida por adición de NH₄Cl (acuoso) saturado (0,2 ml). La agitación se continuó por 1 hora a temperatura ambiente. Se agregó MeOH (3 ml) y la agitación se continuó por 30 minutos más.

Esta solución fue agregada a un cartucho de SCX pre-acidificado y se eluyó con MeOH seguido por NH₃ 2M/MeOH. El análisis por TLC indicó que el producto deseado estaba presente en las fracciones básicas, al igual que el material sin BOC. El solvente fue evaporado bajo presión reducida. La goma verdosa resultante fue disuelta en DCM (10 ml) y enfriada a 0°C, y se agregó ácido trifluoroacético (0,2 ml).

La mezcla de reacción fue agitada a 0°C por 3 horas. El solvente fue evaporado bajo presión reducida y el producto crudo fue purificado en SCX, eluyendo el producto con NH₃ 2M/MeOH. El producto crudo fue purificado adicionalmente por LCMS preparatoria (condiciones básicas) para proporcionar 2-[3-(4-fluoro-3-metoxifenil)-1-oxo-7-perhidro-1,4-diazepin-1-il-1H-isoquinolin-2-il]-N-isopropilacetamida (2 mg, 0,004 mmol, 13%). Datos para 2-[3-(4-fluoro-3-metoxifenil)-1-oxo-7-perhidro-1,4-diazepin-1-il-1H-isoquinolin-2-il]-N-isopropilacetamida: MS (ESI) m/z: 467 ([M+H]⁺).

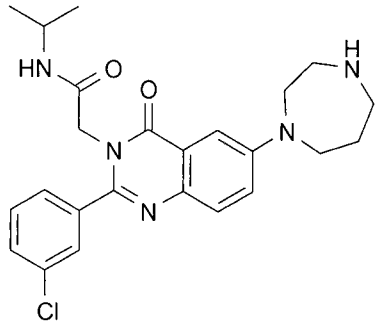
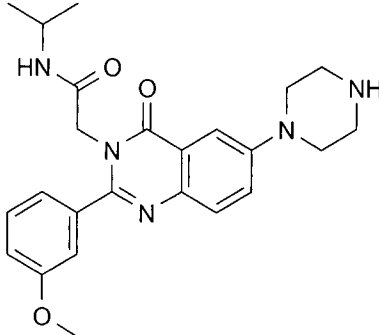
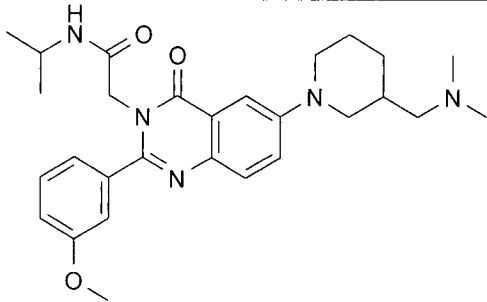
EJEMPLO 14:

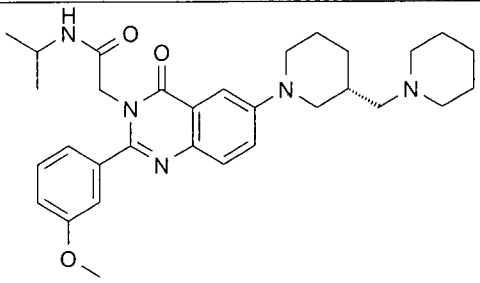
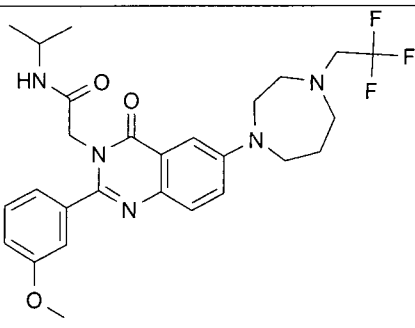
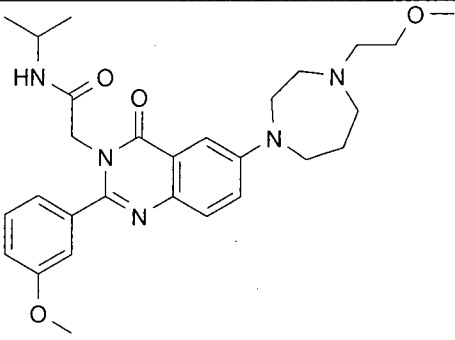
Células de ovario de hámster chino (CHO) que expresaban en forma estable el receptor V₃ humano fueron incubadas hasta equilibrio con el compuesto de prueba (a una concentración final en el ensayo de 10⁻¹⁰ mol.l⁻¹ a 10⁻⁵ mol.l⁻¹) y [³H]AVP (a una concentración final en el ensayo de 2,5 x 10⁻⁹ mol.l⁻¹). Durante el ensayo, la concentración de dimetilsulfóxido (DMSO) no excedió 0,1% (v/v). Después de lavar con suero fisiológico tamponado con fosfato (PBS) helado, se agregó fluido de centelleo y las placas fueron sometidas a conteo en un aparato Topcount NXT.

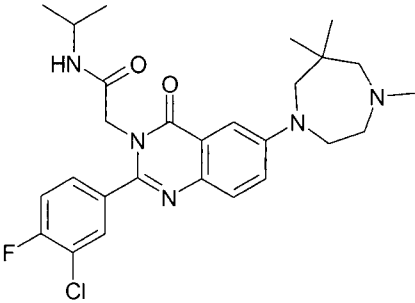
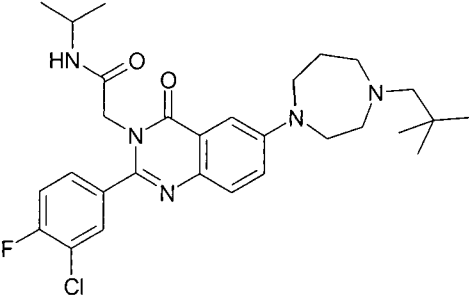
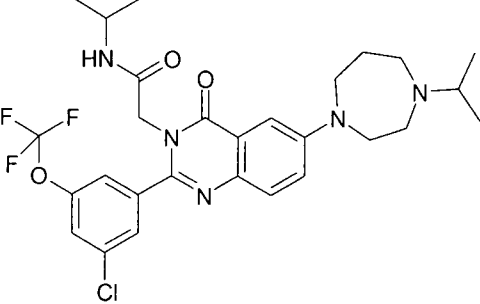
Una curva de dosis respuesta sigmoide (regresión no lineal, pendiente variable) fue graficada como concentración del compuesto de prueba (mol.l⁻¹) contra porcentaje de unión específica de [³H]AVP, y se calculó un valor de K_i. Cada determinación fue efectuada en triplicado y repetida en al menos 3 ocasiones separadas.

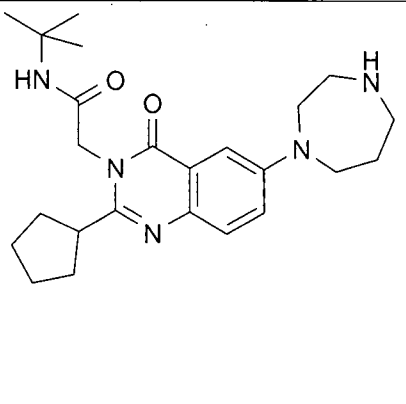
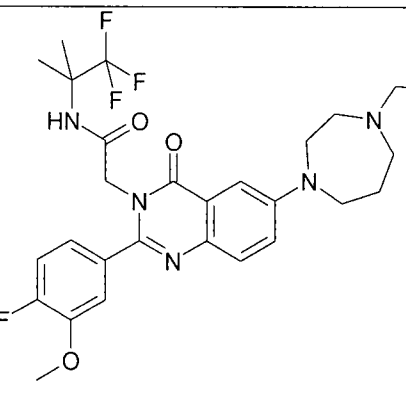
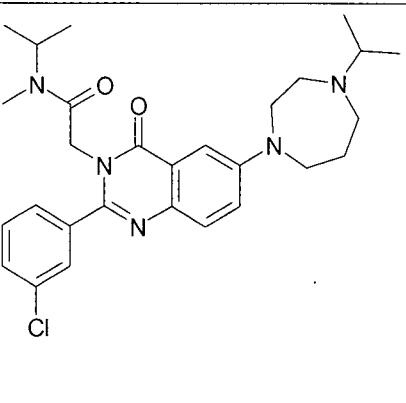
La Tabla 1 muestra la actividad de unión obtenida para algunos compuestos representativos de la invención.

Tabla 1. Actividad de unión a V₃ para compuestos de acuerdo con la invención.

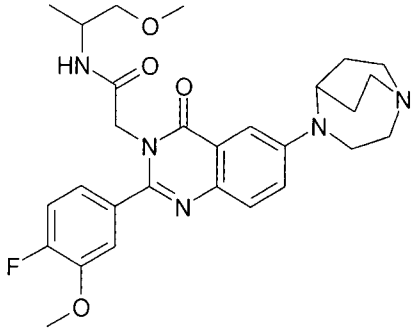
EJEMPLO 1b: 2-[2-(3-Clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]-N-isopropilacetamida		+++
EJEMPLO 2b: N-Isopropil-2-[2-(3-metoxifenil)-4-oxo-6-piperazin-1-il-4H-quinazolin-3-il]-acetamida		++
EJEMPLO 3c: 2-[6-(3-Dimetilaminometil-piperidin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida		++

EJEMPLO 3f: N-Isopropil-2-[2-(3-metoxi-fenil)-4-oxo-6-((R)-3-piperidin-1-ilmetil-piperidin-1-il)-4H-quinazolin-3-il]acetamida		+++
EJEMPLO 4c: N-Isopropil-2-{2-(3-metoxi-fenil)-4-oxo-6-[4-(2,2,2-trifluoroetil)perhidro-1,4-diazepin-1-il]-4H-quinazolin-3-il}acetamida		+
EJEMPLO 4d: N-Isopropil-2-[6-[4-(2-metoxietil)-perhidro-1,4-diazepin-1-il]-2-(3-metoxi-fenil)-4-oxo-4H-quinazolin-3-il]acetamida		+++

EJEMPLO 5s: 2-[2-(3-Cloro-4-fluoro-fenil)-4-oxo-6-(4,6,6-trimetilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida		+++
EJEMPLO 5Ac: 2-{2-(3-Cloro-4-fluoro-fenil)-6-[4-(2,2-dimetil-propil)perhidro-1,4-diazepin-1-il]-4-oxo-4H-quinazolin-3-il}-N-isopropilacetamida		+++
EJEMPLO 6w: 2-[2-(3-Cloro-5-trifluorometoxifenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida		+++

EJEMPLO 7a: <i>N</i>-ter-Butil-2-(2-ciclopentil-4-oxo-6-perhidro-1,4-diazepin-1-il)-4<i>H</i>-quinazolin-3-il)-acetamida		++
EJEMPLO 9h: 2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4<i>H</i>-quinazolin-3-il]-<i>N</i>-(2,2,2-trifluoro-1,1-dimetiletil)-acetamida		+++
EJEMPLO 9u: 2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4<i>H</i>-quinazolin-3-il]-<i>N</i>-isopropil-<i>N</i>-metilacetamida		++

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EJEMPLO 9Ah: 2-[6-(1,4-Diazabicciclo-[3.2.2]non-4-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-(2-metoxi-1-metiletil)-acetamida		++
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- +++ 0-10 nM
- ++ 10-100 nM
- + 100 nM-1 µM

La capacidad de los compuestos de la invención para actuar como antagonistas de V₃ en un sistema fisiológicamente relevante, se determinó midiendo su capacidad para bloquear la liberación de hormona adrenocorticotrópica (ACTH) desde los corticotropos de la pituitaria anterior en respuesta al tratamiento con arginina vasopresina (AVP).

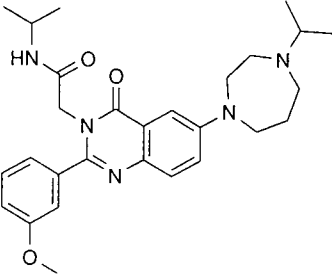
Se prepararon corticotropos de pituitaria anterior de ratas Sprague-Dawley hembras adultas, y se sembraron en placas de 48 pocillos. Las células fueron cultivadas por 4 días antes de la exposición al compuesto. Los compuestos de prueba fueron preparados a 10⁻⁵ mol.l⁻¹ en DMSO al 100%. Las células fueron expuestas a un ensayo de dosis respuesta con compuestos de prueba por 20 minutos (10⁻⁸ mol.l⁻¹ - 10⁻⁵ mol.l⁻¹). La concentración final de DMSO en el ensayo se mantuvo constante en 0,3%. Enseguida, las células fueron expuestas a 3 x 10⁻⁹ mol.l⁻¹ de AVP por 120 minutos. Los sobrenadantes fueron cosechados y

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almacenados a -20°C. Posteriormente, los niveles de ACTH fueron medidos por ELISA siguiendo las instrucciones del fabricante (Immunodiagnostic Systems, UK (N° de Cat. DX-SDX018)). Cada tratamiento se efectuó en cuadruplicado y se obtuvo un valor medio para la cantidad de ACTH liberada. Enseguida se calculó el grado de antagonismo como un porcentaje de la cantidad de ACTH liberada por el agonista solo, después de ajustar para los niveles basales de ACTH. Se calculó un pIC₅₀ ajustando una curva de dosis respuesta sigmoide (pendiente variable) con un ajuste no lineal a los datos, usando el paquete de software GraphPad Prism. Cada determinación fue repetida en al menos 3 ocasiones separadas.

La Tabla 2 muestra la actividad obtenida para algunos compuestos representativos de la invención.

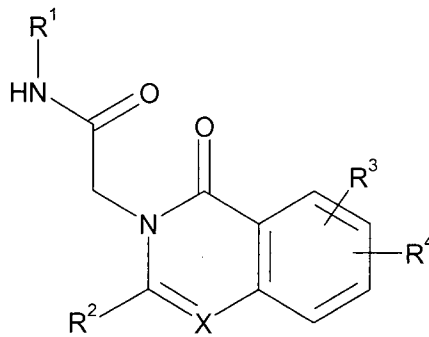
Tabla 2. Antagonismo del receptor V₃ en células aisladas de pituitaria anterior de rata para compuestos de acuerdo con la invención.

EJEMPLO 4b: N-Isopropil-2-[6-(4-isopropilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]acetamida		++
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++ 10-100 nM
+ 100 nM-1 µM

REIVINDICACIONES

1. Un derivado de quinazolinona o isoquinolinona CARACTERIZADO porque tiene la fórmula I:



fórmula I

donde

R¹ es C₁₋₆alquilo, C₃₋₆cicloalquilo, C₃₋₆cicloalquil-C₁₋₃alquilo, C₂₋₆alquenilo, C₂₋₆alquinilo, estando dichos C₁₋₆alquilo, C₃₋₆cicloalquilo y C₃₋₆cicloalquilC₁₋₃alquilo opcionalmente sustituidos con hidroxilo, C₁₋₆alquilo, ciano o uno o más halógenos;

R² es C₆₋₁₀arilo opcionalmente sustituido con uno a tres sustituyentes seleccionados entre halógeno, hidroxilo, ciano, C₁₋₆alquilo, C₃₋₆cicloalquilo, C₁₋₆alquilo y C₃₋₆cicloalquilo, estando dichos C₁₋₆alquilo, C₃₋₆cicloalquilo, C₁₋₆alquilo y C₃₋₆cicloalquilo opcionalmente sustituidos con uno o más halógenos;

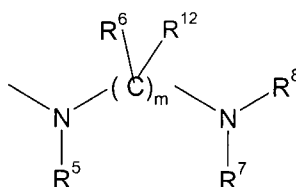
o R² es un sistema de anillo heteroarilo de 5-10 miembros que comprende un heteroátomo seleccionado entre N, O y

S, y está opcionalmente sustituido con un sustituyente seleccionado entre metilo, C₁₋₆alquiloxi y halógeno;

o R² es C₄₋₇cicloalquilo;

R³ es un sustituyente opcional seleccionado entre C₁₋₆alquilo, C₁₋₆alquiloxi y halógeno, estando dichos C₁₋₆alquilo y C₁₋₆alquiloxi opcionalmente sustituidos con uno o más halógenos;

R⁴ es un grupo ubicado en la posición 6 ó 7 del anillo quinazolinona o isoquinolinona y tiene la fórmula **II**:



fórmula **II**

donde

R⁵ junto con uno de R⁶ forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR⁹, estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo, o R⁵ junto con uno de R⁷ y R⁸ forman un anillo heterocíclico de 6-8 miembros opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo;

cada R⁶ es independientemente H, halógeno o C₁₋₄alquilo opcionalmente sustituido con halógeno o SO₂CH₃, o uno de R⁶ junto con R⁵ forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR⁹, estando

dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo;

R^7 y R^8 son independientemente H, C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{3-6} cicloalquil C_{1-3} alquilo, ciano C_{1-3} alquilo, C_{6-10} arilo, C_{6-10} aril C_{1-3} alquilo, C_{1-3} alquiloxi C_{1-3} alquilo o C_{1-6} acilo, estando dichos C_{1-6} alquilo, C_{3-6} cicloalquilo y C_{3-6} cicloalquil C_{1-3} alquilo opcionalmente sustituidos con hidroxilo, 1 o más halógenos o di C_{1-2} alquilamino;

o R^7 y R^8 , junto con el nitrógeno al cual están unidos, forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{10} , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre C_{1-6} alquilo, halógeno, hidroxilo, C_{1-6} alquiloxi, ciano y $COOR^{11}$;

o uno de R^7 y R^8 es Y, CH_2Y ó CH_2CH_2Y , donde Y es un anillo heterocíclico saturado de 4-6 miembros que comprende una especie heterocíclica seleccionada entre O, SO_2 y NR^{10} , estando dicho anillo opcionalmente sustituido con 1-2 sustituyentes seleccionados entre metilo o halógeno;

o uno de R^7 o R^8 junto con R^5 forman un anillo heterocíclico de 6-8 miembros que está opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo;

o uno de R^7 y R^8 junto con R^{12} forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{13} , estando dicho anillo

heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, hidroxilo y oxo;

R^9 y R^{10} son independientemente H, C_{1-6} alquilo o C_{1-6} acilo;

R^{11} es H o C_{1-6} alquilo;

cada R^{12} es independientemente H o C_{1-4} alquilo, o uno de R^{12} junto con uno de R^7 o R^8 forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{13} , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, hidroxilo y oxo;

R^{13} es H, C_{1-6} alquilo o C_{1-6} acilo;

m es 2-3; y

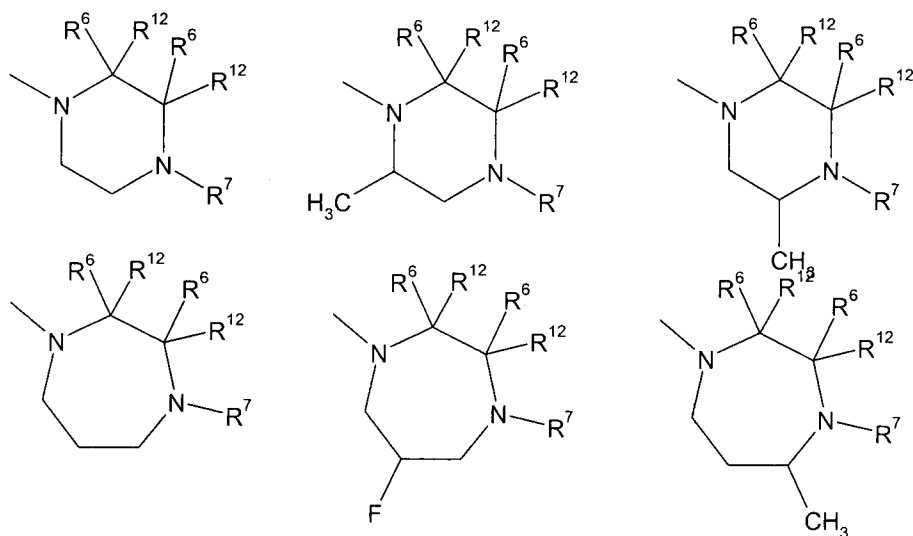
X es N ó CH;

o una sal o solvato farmacéuticamente aceptable del mismo.

2. El derivado de quinazolinona o isoquinolinona de acuerdo con la reivindicación 1, CARACTERIZADO porque R^1 es isopropilo, isobutilo, butilo terciario, ciclopropilmetilo, ciclobutilo, 2,2,2-trifluoro-1-metiletilo o 2,2,2-trifluoro-1,1-dimetiletilo.

3. El derivado de quinazolinona o isoquinolinona de acuerdo con la reivindicación 1 o la reivindicación 2, CARACTERIZADO porque R^2 es un anillo fenilo sustituido seleccionado entre 3-clorofenilo, 3-fluorofenilo, 3-metoxifenilo, 3-trifluorometoxifenilo, 3-cloro-4-fluorofenilo, 4-fluoro-3-metoxifenilo y 3,5-dimetoxifenilo.

4. El derivado de quinazolinona o isoquinolinona de acuerdo con cualquiera de las reivindicaciones 1-3, CARACTERIZADO porque R^4 es un grupo seleccionado entre:



donde R^6 , R^7 y R^{12} tienen los significados definidos anteriormente.

5. El derivado de quinazolinona de acuerdo con cualquiera de las reivindicaciones 1-4, CARACTERIZADO porque R^4 es un sustituyente en la posición 6 de la quinazolinona.

6. El derivado de quinazolinona de acuerdo con cualquiera de las reivindicaciones 1-5, CARACTERIZADO porque X es N.

7. Un derivado de quinazolinona CARACTERIZADO porque es seleccionado entre:

2-[2-(3-Clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]-N-isopropilacetamida;

N-ter-Butil-2-[2-(3-clorofenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4H-quinazolin-3-il]acetamida;

N-ter-Butil-2-(2-(3-cloro-4-fluorofenil)-6-(1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)acetamida;

2-(2-(3-Cloro-4-fluorofenil)-6-(1,4-diazepan-1-il)-4-oxo-quinazolin-3(4H)-il)-N-isopropilacetamida;

2-(2-(3-Cloro-4-fluorofenil)-6-(3-metil-1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(3-etilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(dimetilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[6-(Dimetilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(4-Fluoro-3-metoxifenil)-6-((S)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(4-Fluoro-3-metoxifenil)-6-((R)-3-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-6-(4-metilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-4-oxo-6-(4-propilperhidro-1,4-diazepin-1-il)-4H-quinazolin-3-il]-N-isopropilacetamida;

N-ter-Butil-2-[6-(4-etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]acetamida;

2-[2-(3-Clorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

2-[6-(4-Etilperhidro-1,4-diazepin-1-il)-2-(4-fluoro-3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

2-[2-(4-Fluoro-3-metoxifenil)-4-oxo-6-(4-propilperhidro-1,4-diazepin-1-il)-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(4-etilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

N-Isopropil-2-[6-(4-isopropilperhidro-1,4-diazepin-1-il)-2-(3-metoxifenil)-4-oxo-4*H*-quinazolin-3-il]acetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

2-[2-(3-Cloro-5-trifluorometilfenil)-4-oxo-6-perhidro-1,4-diazepin-1-il-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

2-[2-(3,5-Dimetoxifenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

2-{2-(3-Cloro-4-fluorofenil)-6-[4-(1-ciclopropiletil)perhidro-1,4-diazepin-1-il]-4-oxo-4*H*-quinazolin-3-il}-*N*-isopropilacetamida;

2-{2-(4-Fluoro-3-metoxifenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4*H*-quinazolin-3-il}-*N*-isopropilacetamida;

2-{2-(3-Cloro-4-fluorofenil)-6-[4-(2-hidroxietil)perhidro-1,4-diazepin-1-il]-4-oxo-4*H*-quinazolin-3-il}-*N*-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(1,4-diazabicciclo[3.2.2]non-4-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

2-[2-(4-Fluoro-3-metoxifenil)-6-(4-isopropilpiperazin-1-il)-4-oxo-4*H*-quinazolin-3-il]-*N*-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-(4-isopropilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-((S)-3-isopropilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Cloro-4-fluorofenil)-6-((R)-3-isopropilpiperazin-1-il)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[6-(1,4-Diazabicciclo[3.2.2]non-4-il)-2-(3,5-dimetoxifenil)-4-oxo-4H-quinazolin-3-il]-N-isopropilacetamida;

2-[2-(3-Clorofenil)-6-(4-isopropilperhidro-1,4-diazepin-1-il)-4-oxo-4H-quinazolin-3-il]-N-(2,2,2-trifluoro-1,1-dimetiletil)-acetamida;

N-Isopropil-2-(6-(4-isopropil-1,4-diazepan-1-il)-2-(3-metoxifenil)-4-oxoquinazolin-3(4H)-il)acetamida;

2-(2-(3-Clorofenil)-6-(4-ciclopropilmetil-1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)-N-isopropilacetamida y

N-ter-Butil-2-(2-(3-clorofenil)-6-(4-isopropil-1,4-diazepan-1-il)-4-oxoquinazolin-3(4H)-il)acetamida

o una sal o solvato farmacéuticamente aceptable del mismo.

8. Un derivado de quinazolinona de acuerdo con cualquiera de las reivindicaciones 1-7, o un derivado de isoquinolinona de acuerdo con cualquiera de las reivindicaciones 1-4, CARACTERIZADO porque se usa en terapia.

9. Una composición farmacéutica CARACTERIZADA porque comprende un derivado de quinazolinona de acuerdo con cualquiera de las reivindicaciones 1-7 o un derivado de isoquinolinona de acuerdo con cualquiera de las reivindicaciones 1-4, mezclado con uno o más auxiliares farmacéuticamente aceptables.

10. Uso de un derivado de quinazolinona de acuerdo con cualquiera de las reivindicaciones 1-7 o de un derivado de

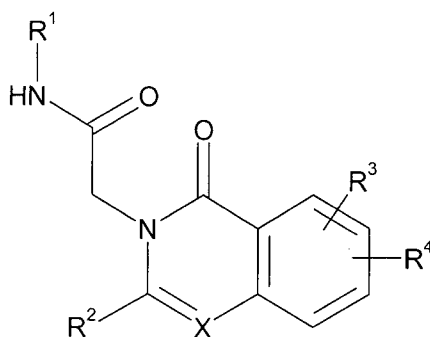
isoquinolinona de acuerdo con cualquiera de las reivindicaciones 1-4, CARACTERIZADO porque sirve para la preparación de un medicamento para el tratamiento o prevención de trastornos o enfermedades influenciadas por la modulación de la actividad del eje HPA.

11. Uso de acuerdo con la reivindicación 10, CARACTERIZADO porque el medicamento sirve para el tratamiento o prevención de trastornos relacionados con el estrés o depresión.

808.108

RESUMEN

La presente invención se refiere a un derivado de quinazolinona o isoquinolinona de fórmula I:



fórmula I

donde

R^1 es C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{3-6} cicloalquil- C_{1-3} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, estando dichos C_{1-6} alquilo, C_{3-6} cicloalquilo y C_{3-6} cicloalquil- C_{1-3} alquilo opcionalmente sustituidos con hidroxilo, C_{1-6} alquilo, ciano o uno o más halógenos;

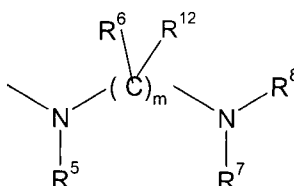
R^2 es C_{6-10} arilo opcionalmente sustituido con uno a tres sustituyentes seleccionados entre halógeno, hidroxilo, ciano, C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{1-6} alquilo y C_{3-6} cicloalquilo, estando dichos C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{1-6} alquilo y C_{3-6} cicloalquilo opcionalmente sustituidos con uno o más halógenos;

o R^2 es un sistema de anillo heteroarilo de 5-10 miembros que comprende un heteroátomo seleccionado entre N, O y S, y está opcionalmente sustituido con un sustituyente seleccionado entre metilo, C_{1-6} alquilo y halógeno;

o R^2 es C_{4-7} cicloalquilo;

R^3 es un sustituyente opcional seleccionado entre C_{1-6} alquilo, C_{1-6} alquiloxi y halógeno, estando dichos C_{1-6} alquilo y C_{1-6} alquiloxi opcionalmente sustituidos con uno o más halógenos;

R^4 es un grupo ubicado en la posición 6 ó 7 del anillo quinazolinona o isoquinolinona y tiene la fórmula **II**:



fórmula **II**

donde

R^5 junto con uno de R^6 forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^9 , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo, o R^5 junto con uno de R^7 y R^8 forman un anillo heterocíclico de 6-8 miembros opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo;

cada R^6 es independientemente H, halógeno o C_{1-4} alquilo opcionalmente sustituido con halógeno o SO_2CH_3 , o uno de R^6 junto con R^5 forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^9 , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos

sustituyentes seleccionados entre metilo, halógeno, hidroxil y oxo;

R^7 y R^8 son independientemente H, C_{1-6} alquilo, C_{3-6} cicloalquilo, C_{3-6} cicloalquil C_{1-3} alquilo, ciano C_{1-3} alquilo, C_{6-10} arilo, C_{6-10} aril C_{1-3} alquilo, C_{1-3} alquiloxi C_{1-3} alquilo o C_{1-6} acilo, estando dichos C_{1-6} alquilo, C_{3-6} cicloalquilo y C_{3-6} cicloalquil C_{1-3} alquilo opcionalmente sustituidos con hidroxil, 1 o más halógenos, o di C_{1-2} alquilamino;

o R^7 y R^8 , junto con el nitrógeno al cual están unidos, forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{10} , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre C_{1-6} alquilo, halógeno, hidroxil, C_{1-6} alquiloxi, ciano y $COOR^{11}$;

o uno de R^7 y R^8 es Y, CH_2Y ó CH_2CH_2Y , donde Y es un anillo heterocíclico saturado de 4-6 miembros que comprende una especie heterocíclica seleccionada entre O, SO_2 y NR^{10} , estando dicho anillo opcionalmente sustituido con 1-2 sustituyentes seleccionados entre metilo o halógeno;

o uno de R^7 o R^8 junto con R^5 forman un anillo heterocíclico de 6-8 miembros que está opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxil y oxo;

o uno de R^7 y R^8 junto con R^{12} forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{13} , estando dicho anillo

heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, hidroxí y oxo;

R^9 y R^{10} son independientemente H, C_{1-6} alquilo o C_{1-6} acilo;

R^{11} es H o C_{1-6} alquilo;

cada R^{12} es independientemente H o C_{1-4} alquilo, o uno de R^{12} junto con uno de R^7 o R^8 forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR^{13} , estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, hidroxí y oxo;

R^{13} es H, C_{1-6} alquilo o C_{1-6} acilo;

m es 2-3; y

X es N ó CH;

o una sal o solvato farmacéuticamente aceptable del mismo. La presente invención se refiere además a una composición farmacéutica que comprende una quinazolinona o isoquinolinona de acuerdo con la presente invención, y a su uso en terapia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/78022

A. CLASSIFICATION OF SUBJECT MATTER IPC: C07D 239/70(2006.01),243/08(2006.01),217/24(2006.01);A61K 31/519(2006.01),31/5513(2006.01),31/472(2006.01),31/4725(2006.01),31/496(2006.01);A61P 25/24(2006.01) USPC: 544/287,141;540/575;514/266.22,309,252.16,211.08 According to International Patent Classification (IPC) or to both national classification and IPC												
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 544/287,141; 540/575; 514/266.22,309,252.16,211.08 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS online structure database												
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A, P</td> <td>WO 2006/095014 A1 (LETOURNEAU et al) 14 September 2006 (14.09.2006), entire document.</td> <td>1-3 and 7</td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A, P	WO 2006/095014 A1 (LETOURNEAU et al) 14 September 2006 (14.09.2006), entire document.	1-3 and 7				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
A, P	WO 2006/095014 A1 (LETOURNEAU et al) 14 September 2006 (14.09.2006), entire document.	1-3 and 7										
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.												
* Special categories of cited documents: <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"I" 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)</td> <td>"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</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"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	"E" earlier application or patent published on or after the international filing date	"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	"I" 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)	"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	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
"A" document defining the general state of the art which is not considered to be of particular relevance	"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											
"E" earlier application or patent published on or after the international filing date	"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											
"I" 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)	"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											
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family											
"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search 27 August 2008 (27.08.2008)		Date of mailing of the international search report 03 OCT 2008										
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201		Authorized officer James Wilson Telephone No. (571) 272-9046										

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/78022

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)	
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
1.	☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2.	☐ Claims Nos.: 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.: 4-6 and 8-11 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)	
This International Searching Authority found multiple inventions in this international application, as follows:	
1.	☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.	☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3.	☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.	☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest	☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
	☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
	☐ No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 2006.957WO	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2007/078022	International filing date (<i>day/month/year</i>) 10 September 2007 (10.09.2007)	Priority date (<i>day/month/year</i>) 11 September 2006 (11.09.2006)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant N.V. ORGANON			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

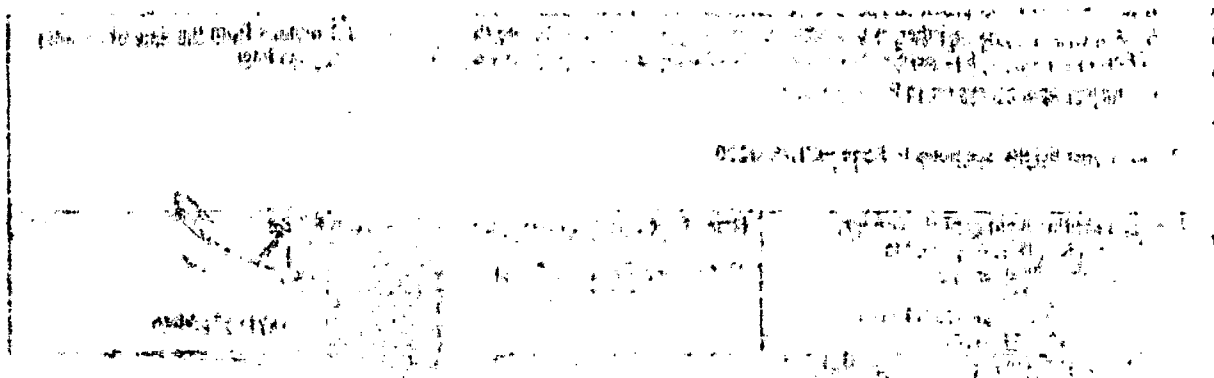
In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | 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 Article 35(2) 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 |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

	Date of issuance of this report 17 March 2009 (17.03.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Beate Giffo-Schmitt
Facsimile No. +41 22 338 82 70	e-mail: pt03.pct@wipo.int



PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITYTo:
SUSAN HESS
ORGANON INTERNATIONAL INC.
56 LIVINGSTON AVENUE
ROSELAND, NJ 07068

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 2006.957WO		Date of mailing (day/month/year) 03 OCT 2008
International application No. PCT/US07/78022		International filing date (day/month/year) 10 September 2007 (10.09.2007)
Priority date (day/month/year) 11 September 2006 (11.09.2006)		
International Patent Classification (IPC) or both national classification and IPC IPC: Please See Continuation Sheet USPC: 544/287,141;540/575;514/266.22,309,252.16,211.08		
Applicant N.V. ORGANON		

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 be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(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 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 2 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 27 August 2008 (27.08.2008)	Authorized Officer James Wilson Telephone No. (571) 272-3046
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Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US07/78022

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
- ☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
- ☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
- ☐ filed together with the international application in electronic form.
- ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US07/78022

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. 4-6 and 8-11

because:

- ☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 4-6 and 8-11 are so unclear that no meaningful opinion could be formed (*specify*):
Claims 4-6 and 8-11 are improper multiple dependent claims.
- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☐ no international search report has been established for said claims Nos. _____
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/78022

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>1-3 and 7</u>	YES
	Claims <u>NONE</u>	NO
Inventive step (IS)	Claims <u>1-3 and 7</u>	YES
	Claims <u>NONE</u>	NO
Industrial applicability (IA)	Claims <u>1-3 and 7</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-3 and 7 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest compounds of formula (I) the appropriate substitution at R⁴, as noted in claim 1.

Claims 1-3 and 7 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US07/78022

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
Claim 1 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: the term "Each" should not be capitalized on page 145, line 9.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US07/78022

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-3 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 1-3 are indefinite for the following reason(s): the term "derivative" is indefinite. The term derivative is defined as a substance or compound obtained from, or regarded as derived from, another substance or compound. The metes and bounds of the term "derivative" are not known, thus, the term lacks clarity.

Claims 1-3 and 7 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims 1-3 and 7 are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: the term "solvates" are not enabled by the disclosure. The Specification does not support solvates.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/78022

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of IPC:

C07D 239/70(2006.01),243/08(2006.01),217/24(2006.01);A61K 31/519(2006.01),31/5513(2006.01),31/472(2006.01),31/4725(2006.01),31/496(2006.01);A61P 25/24(2006.01)

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

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

To:

HESS, Susan
Organon International Inc.
56 Livingston Avenue
Roseland, NJ 07068
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 19 January 2009 (19.01.2009)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2006.957WO	
International application No. PCT/US2007/078022	International filing date (day/month/year) 10 September 2007 (10.09.2007)

1. The following indications appeared on record concerning:

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

Name and Address NAPIER, Elizabeth c/o Organon Laboratories Ltd. New Edinburgh Road Newhouse, Lanarkshire ML1 5SH United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	E-mail address	

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

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

Name and Address NAPIER, Susan, Elizabeth c/o Organon Laboratories Ltd. New Edinburgh Road Newhouse, Lanarkshire ML1 5SH United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

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

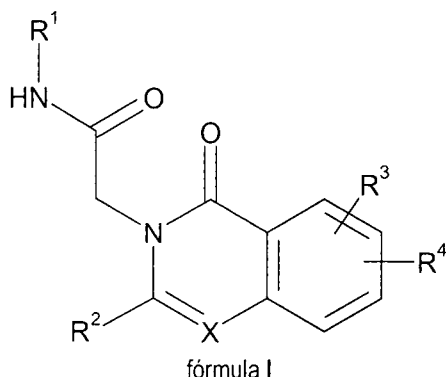
☒ the receiving Office	☒ the designated Offices concerned
☐ the International Searching Authority	☐ the elected Offices concerned
☐ the International Preliminary Examining Authority	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Thorax Bernard e-mail pt03.pct@wipo.int Telephone No. +41 22 338 74 03
---	--

(21) N° de solicitud: 22) Fecha de solicitud: (30) Prioridad (31) Prioridad (32) Fecha (33) País 60/843,718 11/09/2006 US	(51) Int Cl: C07D 239/070 (71) Solicitante(s) N. V. ORGANON Y PHARMACOEPIA, LLC. (72) Inventor(es) JEFFREY LETOURNEAU Y OTROS (74) Apoderado: EMILIO FERRERO
(85) Fecha limite inicio fase nacional: 11/04/2009 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 10/09/2007 No. de solicitud PCT/US2007/078022	(87) Publicación internacional Fecha: 20/03/2008 N° publicación: WO 2008/033764 A3
(54) Título: DERIVADOS DE QUINAZOLINONA E ISOQUINOLINONA ACETAMIDA	

Reivindicación(es):

1. Un derivado de quinazolinona o isoquinolinona **CARACTERIZADO** porque tiene la fórmula I:



donde

R¹ es C₁₋₆alquilo, C₃₋₆cicloalquilo, C₃₋₆cicloalquil-C₁₋₃alquilo, C₂₋₆alquenilo, C₂₋₆alquinilo, estando dichos C₁₋₆alquilo, C₃₋₆cicloalquilo y C₃₋₆cicloalquilC₁₋₃alquilo opcionalmente sustituidos con hidroxí, C₁₋₆alquiloí, ciano o uno o más halógenos;

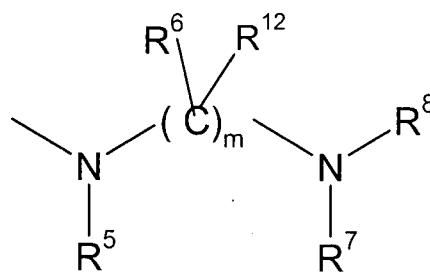
R² es C₆₋₁₀arilo opcionalmente sustituido con uno a tres sustituyentes seleccionados entre halógeno, hidroxilo, ciano, C₁₋₆alquilo, C₃₋₆cicloalquilo, C₁₋₆alquiloxi y C₃₋₆cicloalquiloxi, estando dichos C₁₋₆alquilo, C₃₋₆cicloalquilo, C₁₋₆alquiloxi y C₃₋₆cicloalquiloxi opcionalmente sustituidos con uno o más halógenos;

o R² es un sistema de anillo heteroarilo de 5-10 miembros que comprende un heteroátomo seleccionado entre N, O y S, y está opcionalmente sustituido con un sustituyente seleccionado entre metilo, C₁₋₆alquiloxi y halógeno;

o R² es C₄₋₇cicloalquilo;

R³ es un sustituyente opcional seleccionado entre C₁₋₆alquilo, C₁₋₆alquiloxi y halógeno, estando dichos C₁₋₆alquilo y C₁₋₆alquiloxi opcionalmente sustituidos con uno o más halógenos;

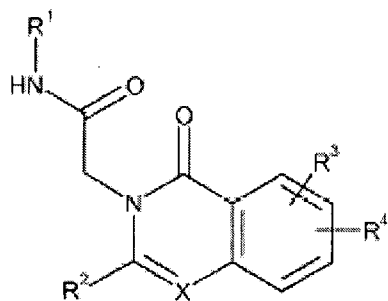
R⁴ es un grupo ubicado en la posición 6 ó 7 del anillo quinazolinona o isoquinolinona y tiene la fórmula II:



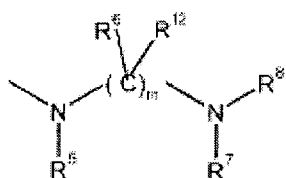
fórmula II

donde

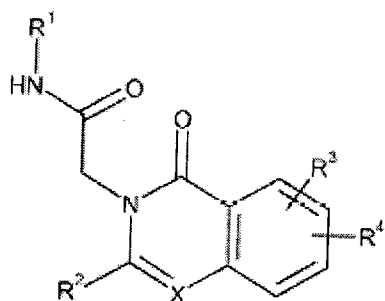
R⁵ junto con uno de R⁶ forman un anillo heterocíclico saturado o no saturado de 4-8 miembros que opcionalmente comprende una especie heteroatómica adicional seleccionada entre O, S y NR⁹, estando dicho anillo heterocíclico opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo, o R⁵ junto con uno de R⁷ y R⁸ forman un anillo heterocíclico de 6-8 miembros opcionalmente sustituido con uno o dos sustituyentes seleccionados entre metilo, halógeno, hidroxilo y oxo;



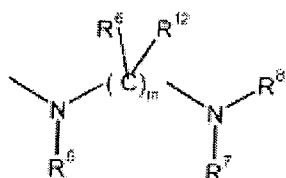
I



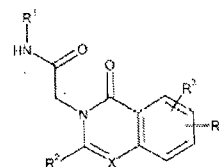
II



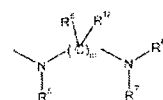
I



II



I



II

379

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-036257 - 00000-0000

Fecha: 2009-04-08 13:31:50 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 379

RECIBO OFICIAL DE CAJA : 09 - 24,790
FECHA : MARZO 30 DE 2009

***** CONSIGNACION *****

DEP. ANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	19774650	30/03/2009	45,049,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL :	\$ 540,000.00

SUN: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

COLO: 16962-841-001-2.



No. 09-036257- -00000-0000

Fecha: 2009-04-08 13:31:50 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 379

SUPERINTENDENCIA

**REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT**

PATENTE DE INVENCION []

MODELO DE UTILIDAD []

- ◇ Indicación de que se solicita la concesión de una patente []
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◇ Descripción de la invención []
- ◇ Dibujos de ser estos pertinentes []
- ◇ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◇ Indicación de que se solicita el registro de Diseño Industrial []
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◇ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◇ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

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 08-04-09

Carrera 13 No. 27-00 Piso 5,7y10'
Conmutador: 3 82 0840
Fax: 3505220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá D.C. - Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO

REFERENCIA	Radicación No.	09 36257
	Solicitud internacional	PCT/US2007/078022
	Fecha inicio fase nacional	11/04/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	-5135

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene el poder debidamente otorgado por la sociedad PHARMACOPEIA, LLC., con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

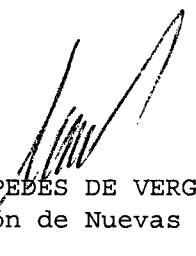
En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.

Continúa en la página siguiente...

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación No.: 9 36257



ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha _____
adpall . **28 MAYO 2009**