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PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 07-333794

54. **TÍTULO** QUINAZOLINAS UTILES COMO MODULADORES DE CANALES IONICOS

51. **CLASIFICACIÓN INTERNACIONAL** (Ver anexo 2) A61K 31/498

71. **SOLICITANTE** VERTEX PHARMACEUTICALS INCORPORATED

DOMICILIO 130 Waverly Street, Cambridge Ma 02139

74. **APODERADO** Alvaro Parra Gómez

22. **BOGOTÁ, D. C.,** 2 de abril de 2007

F.N. 02-04-2007

Paola Cortés

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

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FORMULARIO UNICO DE SOLICITUD DE PATENTE (71) PRESENTACION
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE:

☒ Patente de Invención ☐ Patente de Modelo de Unidad

☒ Capítulo I. ☐ Capítulo II.

(2) SOLICITANTE (71)	Nombre: VERTEX PHARMACEUTICALS INCORPORATED Dirección: 130 Waverly Street, Cambridge, Ma 02139 Nacionalidad o Domicilio: Cambridge, Ma, Estados Unidos de América. Lugar de Constitución: Teléfono: Fax: E-Mail:	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____ TP _____
(3) REPRESENTANTE O APODERADO	Nombre: ÁLVARO PARRA GÓMEZ Dirección: Carrera 9 No. 74 - 08 Oficina 504 Bogotá, D.C. Teléfono: (1) 3764200 Fax: (1) 3761707 E-Mail: Alvaro.Parra@prc-laws.com	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 79.156.180 TP 47.452
(4) INVENTOR(ES) (72)	Nombre: (Ver anexo). Dirección: Nacionalidad o Domicilio:	

(5) PCT (86)

Solicitud Internacional No. PCT/US2005/031146 Fecha 31/08/2005

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(6) Título (54) QUINAZOLINAS ÚTILES COMO MODULADORES DE CANALES IÓNICOS.

(7) Clasificación Internacional (51) (Ver anexo 2).

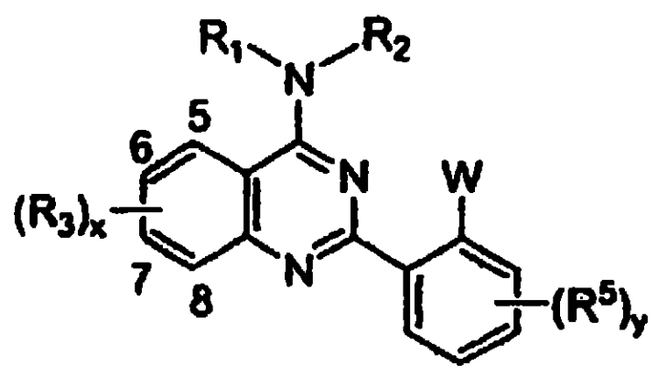
(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	(Ver anexo 3).		

(9) Comprobante de Pago No. _____ **Fecha** _____

10 **ANEXOS**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuese el caso.
- ☐ Documento de cesión del inventor al solicitante o causante.
- ☐ Declaraciones.
- ☒ Copia de solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar efectuado por IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredita la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☒ Arte final 12x12.
- ☐ De ser el caso, información sobre las solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☐ Otros.

11 **FIGURA CARACTERISTICA:**



(I)

12 **Solicito la concesión de la patente,**

NOMBRE: ÁLVARO PARRA GÓMEZ

FIRMA:

C.C. 79.156.180 de Usaquén T.P. 47.452

ANEXO 1

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ANEXO 2

Clasificación Internacional

C07D 239/94
C07D 401/04
C07D 401/12
C07D 401/14
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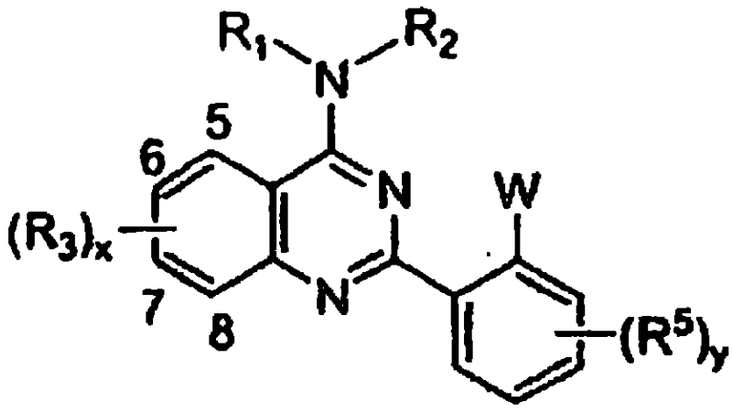
C07D 403/14
C07D 405/12
C07D 405/14
A61P 9/06
A61P 25/00
A61K 31/498

ANEXO 3

Prioridad

Datos de la prioridad	Fecha	País
60/607,150	02.09.2004	Estados Unidos
60/607,037	02.09. 2004	Estados Unidos
60/607,033	02.09. 2004	Estados Unidos
60/607,245	02.09. 2004	Estados Unidos
60/607,036	02.09. 2004	Estados Unidos

ARTES



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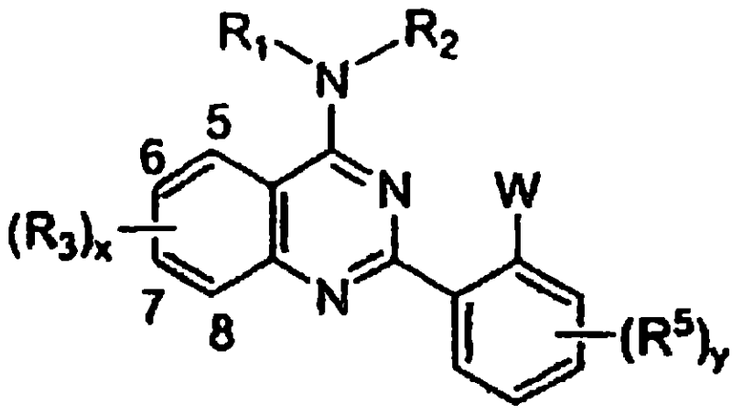

(I)

QUINAZOLINES USEFUL AS MODULATORS OF ION CHANNELS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119 to United States Provisional application serial no. 60/607,150, filed September 2, 2004, United States Provisional application serial no. 60/607,037, filed September 2, 2004, United States Provisional application serial no. 60/607,033, filed September 2, 2004, United States Provisional application serial no. 60/607,036, filed September 2, 2004, and United States Provisional application serial no. 60/607,245, filed September 2, 2004, the entire contents of each of the above application being incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to compounds useful as inhibitors of ion channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0003] Na channels are central to the generation of action potentials in all excitable cells such as neurons and myocytes. They play key roles in excitable tissue including brain, smooth muscles of the gastrointestinal tract, skeletal muscle, the peripheral nervous system, spinal cord and airway. As such they play key roles in a variety of disease states such as epilepsy (See, Moulard, B. and D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents 12(1): 85-91)), pain (See, Waxman, S. G., S. Dib-Hajj, et al. (1999) "Sodium channels and pain" Proc Natl Acad Sci U S A 96(14): 7635-9 and Waxman, S. G., T. R. Cummins, et al. (2000) "Voltage-gated sodium channels and the molecular pathogenesis of pain: a review" J Rehabil Res Dev 37(5): 517-28), myotonia (See, Meola, G. and V. Sansone (2000) "Therapy in myotonic disorders and in muscle channelopathies" Neurol Sci 21(5): S953-61 and Mankodi, A. and C. A. Thornton (2002) "Myotonic syndromes" Curr Opin Neurol 15(5): 545-52), ataxia (See,

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

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(51) International Patent Classification:

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C07D 401/14 (2006.01)	*A61P 9/06* (2006.01)
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60/607,036	2 September 2004 (02.09.2004)	US

(71) Applicant *(for all designated States except US)*: VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, Ma 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: WILSON, Dean, M. [US/US]; 9317 Pipilo Street, San Diego, CA 92129 (US). TERMIN, Andreas, P. [DE/US]; 2080 Wandering Road, Encinitas, CA 92024 (US). GONZALEZ, Jesus, E., III [US/US]; 12442 Carmel Cape, San Diego, CA 92130 (US). FANNING, Lee, T., D. [US/US]; 115 Dole Way, San Marcos, CA 92078 (US). NEUBERT, Timothy, D. [US/US]; 10721 Ballystock Court, San Diego, CA 92131 (US). KRENITSKY, Paul [US/US]; 11045 Alonda Court, San Diego, CA 92126 (US). JOSHI, Pramod [US/US]; 12767 Rifle Way, San Diego, CA 92129 (US). HURLEY, Dennis, J. [US/US]; 1513 Black Walnut Drive, San Marcos, CA 92078 (US). SHETH, Urvi [IN/US]; 8684 New Salem Street, #165, San Diego, CA 92126 (US). BOGER, Joshua, S. [US/US]; 243 Old Pickard Rd, Concord, MA 01742 (US).

(74) Agent: GOVINDASWAMY, Nandakumar; Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02139 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, 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).

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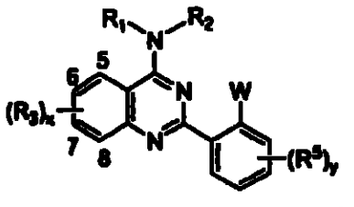
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINES USEFUL AS MODULATORS OF ION CHANNELS



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(57) Abstract: The present invention relates to compounds useful as inhibitors of voltage-gated sodium channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

WO 2006/028904 A1

Meisler, M. H., J. A. Kearney, et al. (2002) "Mutations of voltage-gated sodium channels in movement disorders and epilepsy" Novartis Found Symp 241: 72-81), multiple sclerosis (See, Black, J. A., S. Dib-Hajj, et al. (2000) "Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of mice with experimental allergic encephalomyelitis and humans with multiple sclerosis" Proc Natl Acad Sci U S A 97(21): 11598-602, and Renganathan, M., M. Gelderblom, et al. (2003) "Expression of Na(v)1.8 sodium channels perturbs the firing patterns of cerebellar purkinje cells" Brain Res 959(2): 235-42), irritable bowel (See, Su, X., R. B. Wachtel, et al. (1999) "Capsaicin sensitivity and voltage-gated sodium currents in colon sensory neurons from rat dorsal root ganglia" Am J Physiol 277(6 Pt 1): G1180-8, and Laird, J. M., V. Souslova, et al. (2002) "Deficits in visceral pain and referred hyperalgesia in Nav1.8 (SNS/PN3)- null mice" J Neurosci 22(19): 8352-6), urinary incontinence and visceral pain (See, Yoshimura, N., S. Seki, et al. (2001) "The involvement of the tetrodotoxin-resistant sodium channel Na(v)1.8 (PN3/SNS) in a rat model of visceral pain" J Neurosci 21(21): 8690-6), as well as an array of psychiatry dysfunctions such as anxiety and depression (See, Hurley, S. C. (2002) "Lamotrigine update and its use in mood disorders" Ann Pharmacother 36(5): 860-73).

[0004] Voltage gated Na channels comprise a gene family consisting of 9 different subtypes (NaV1.1-NaV1.9). These subtypes show tissue specific localization and functional differences (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol 63: 871-94). Three members of the gene family (NaV1.8, 1.9, 1.5) are resistant to block by the well-known Na channel blocker TTX, demonstrating subtype specificity within this gene family. Mutational analysis has identified glutamate 387 as a critical residue for TTX binding (See, Noda, M., H. Suzuki, et al. (1989) "A single point mutation confers tetrodotoxin and saxitoxin insensitivity on the sodium channel II" FEBS Lett 259(1): 213-6).

[0005] In general, voltage-gated sodium channels (NaVs) are responsible for initiating the rapid upstroke of action potentials in excitable tissue in nervous system, which transmit the electrical signals that compose and encode normal and aberrant pain sensations. Antagonists of NaV channels can attenuate these pain signals and are useful for treating a variety of pain conditions, including but not limited to acute, chronic, inflammatory, and neuropathic pain. Known NaV antagonists, such as TTX, lidocaine (See, Mao, J. and L. L. Chen (2000) "Systemic lidocaine for neuropathic pain relief" Pain 87(1): 7-17.) bupivacaine, phenytoin (See, Jensen, T. S. (2002) "Anticonvulsants in neuropathic pain: rationale and clinical evidence" Eur J Pain 6

(Suppl A): 61-8), lamotrigine (See, Rozen, T. D. (2001) "Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia" Headache 41 Suppl 1: S25-32 and Jensen, T. S. (2002) "Anticonvulsants in neuropathic pain: rationale and clinical evidence" Eur J Pain 6 (Suppl A): 61-8.), and carbamazepine (See, Backonja, M. M. (2002) "Use of anticonvulsants for treatment of neuropathic pain" Neurology 59(5 Suppl 2): S14-7), have been shown to be useful attenuating pain in humans and animal models.

[0006] Hyperalgesia (extreme sensitivity to something painful) that develops in the presence of tissue injury or inflammation reflects, at least in part, an increase in the excitability of high-threshold primary afferent neurons innervating the site of injury. Voltage sensitive sodium channels activation is critical for the generation and propagation of neuronal action potentials. There is a growing body of evidence indicating that modulation of NaV currents is an endogenous mechanism used to control neuronal excitability (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol 63: 871-94.). Several kinetically and pharmacologically distinct voltage-gated sodium channels are found in dorsal root ganglion (DRG) neurons. The TTX-resistant current is insensitive to micromolar concentrations of tetrodotoxin, and displays slow activation and inactivation kinetics and a more depolarized activation threshold when compared to other voltage-gated sodium channels. TTX-resistant sodium currents are primarily restricted to a subpopulation of sensory neurons likely to be involved in nociception. Specifically, TTX-resistant sodium currents are expressed almost exclusively in neurons that have a small cell-body diameter, and give rise to small-diameter slow-conducting axons and that are responsive to capsaicin. A large body of experimental evidence demonstrates that TTX-resistant sodium channels are expressed on C-fibers and are important in the transmission of nociceptive information to the spinal cord.

[0007] Intrathecal administration of antisense oligo-deoxynucleotides targeting a unique region of the TTX-resistant sodium channel (NaV1.8) resulted in a significant reduction in PGE_2-induced hyperalgesia (See, Khasar, S. G., M. S. Gold, et al. (1998) "A tetrodotoxin-resistant sodium current mediates inflammatory pain in the rat" Neurosci Lett 256(1): 17-20). More recently, a knockout mouse line was generated by Wood and colleagues, which lacks functional NaV1.8. The mutation has an analgesic effect in tests assessing the animal's response to the inflammatory agent carrageenan (See, Akopian, A. N., V. Souslova, et al. (1999) "The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways" Nat

Neurosci 2(6): 541-8.). In addition, deficit in both mechano- and thermoreception were observed in these animals. The analgesia shown by the Nav1.8 knockout mutants is consistent with observations about the role of TTX-resistant currents in nociception.

[0008] Immunohistochemical, in-situ hybridization and in-vitro electrophysiology experiments have all shown that the sodium channel NaV1.8 is selectively localized to the small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Akopian, A. N., L. Sivilotti, et al. (1996) "A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons" Nature 379(6562): 257-62.). The primary role of these neurons is the detection and transmission of nociceptive stimuli. Antisense and immunohistochemical evidence also supports a role for NaV1.8 in neuropathic pain (See, Lai, J., M. S. Gold, et al. (2002) "Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8" Pain 95(1-2): 143-52, and Lai, J., J. C. Hunter, et al. (2000) "Blockade of neuropathic pain by antisense targeting of tetrodotoxin- resistant sodium channels in sensory neurons" Methods Enzymol 314: 201-13.). NaV1.8 protein is upregulated along uninjured C-fibers adjacent to the nerve injury. Antisense treatment prevents the redistribution of NaV1.8 along the nerve and reverses neuropathic pain. Taken together the gene-knockout and antisense data support a role for NaV1.8 in the detection and transmission of inflammatory and neuropathic pain.

[0009] Several Na channel blockers are currently used or being tested in the clinic to treat epilepsy (See, Moulard, B. and D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents 12(1): 85-91.); acute (See, Wiffen, P., S. Collins, et al. (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev 3), chronic (See, Wiffen, P., S. Collins, et al. (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev 3, and Guay, D. R. (2001) "Adjunctive agents in the management of chronic pain" Pharmacotherapy 21(9): 1070-81), inflammatory (See, Gold, M. S. (1999) "Tetrodotoxin-resistant Na+ currents and inflammatory hyperalgesia." Proc Natl Acad Sci U S A 96(14): 7645-9), and neuropathic pain (See, Strichartz, G. R., Z. Zhou, et al. (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain" Novartis Found Symp 241: 189-201, and Sandner-Kiesling, A., G. Rumpold Seitlinger, et al. (2002) "Lamotrigine monotherapy for control of neuralgia after nerve section" Acta Anaesthesiol Scand 46(10): 1261-4); cardiac arrhythmias (See, An, R. H., R. Bangalore, et al.

(1996) "Lidocaine block of LQT-3 mutant human Na+ channels" Circ Res 79(1): 103-8, and Wang, D. W., K. Yazawa, et al. (1997) "Pharmacological targeting of long QT mutant sodium channels" J Clin Invest 99(7): 1714-20); neuroprotection (See, Taylor, C. P. and L. S. Narasimhan (1997) "Sodium channels and therapy of central nervous system diseases" Adv Pharmacol 39: 47-98) and as anesthetics (See, Strichartz, G. R., Z. Zhou, et al. (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain." Novartis Found Symp 241: 189-201).

[0010] Various animal models with clinical significance have been developed for the study of sodium channel modulators for numerous different pain indications. E.g., malignant chronic pain, see, Kohase, H., et al., Acta Anaesthesiol Scand. 2004; 48(3):382-3; femur cancer pain (see, Kohase, H., et al., Acta Anaesthesiol Scand. 2004; 48(3):382-3); non-malignant chronic bone pain (see, Ciocon, J. O. et al., J Am Geriatr Soc. 1994; 42(6):593-6); rheumatoid arthritis (see, Calvino, B. et al., Behav Brain Res. 1987; 24(1):11-29); osteoarthritis (see, Guzman, R. E., et al., Toxicol Pathol. 2003; 31(6):619-24); spinal stenosis (see, Takenobu, Y. et al., J Neurosci Methods. 2001; 104(2):191-8); Neuropathic low back pain (see, Hines, R., et al., Pain Med. 2002; 3(4):361-5; Massie, J. B., et al., J Neurosci Methods. 2004; 137(2):283-9; neuropathic low back pain (see, Hines, R., et al., Pain Med. 2002; 3(4):361-5; Massie, J. B., et al., J Neurosci Methods. 2004; 137(2):283-9); myofascial pain syndrome (see, Dalpiaz & Dodds, J Pain Palliat Care Pharmacother. 2002; 16(1):99-104; Sluka KA et al., Muscle Nerve. 2001; 24(1):37-46); fibromyalgia (see, Bennet & Tai, Int J Clin Pharmacol Res. 1995;15(3):115-9); temporomandibular joint pain (see, Ime H, Ren K, Brain Res Mol Brain Res. 1999; 67(1):87-97); chronic visceral pain, including, abdominal (see; Al-Chaer, E. D., et al., Gastroenterology. 2000; 119(5):1276-85); pelvic/perineal pain, (see, Wesselmann et al., Neurosci Lett. 1998; 246(2):73-6); pancreatic (see, Vera-Portocarrero, L. B., et al., Anesthesiology. 2003; 98(2):474-84); IBS pain (see, Verne, G. N., et al., Pain. 2003; 105(1-2):223-30; La JH et al., World Gastroenterol. 2003; 9(12):2791-5); chronic headache pain (see, Willimas & Stark, Cephalalgia. 2003; 23(10):963-71); migraine (see, Yamamura, H., et al., J Neurophysiol. 1999; 81(2):479-93); tension headache, including, cluster headaches (see, Costa, A., et al., Cephalalgia. 2000; 20(2):85-91); chronic neuropathic pain, including, post-herpetic neuralgia (see, Attal, N., et al., Neurology. 2004; 62(2):218-25; Kim & Chung 1992, Pain 50:355); diabetic neuropathy (see, Beidoun A et al., Clin J Pain. 2004; 20(3):174-8; Courteix, C., et al., Pain. 1993; 53(1):81-8);

HIV- associated neuropathy (see, Portegies & Rosenberg, Ned Tijdschr Geneeskd. 2001; 145(15):731-5; Joseph EK et al., Pain. 2004; 107(1-2):147-58; Oh, S. B., et al., J Neurosci. 2001; 21(14):5027-35); trigeminal neuralgia (see, Sato, J., et al., Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004; 97(1):18-22; Imamura Y et al., Exp Brain Res. 1997; 116(1):97-103); Charcot-Marie Tooth neuropathy (see, Sereda, M., et al., Neuron. 1996; 16(5):1049-60); hereditary sensory neuropathies (see, Lee, M. J., et al., Hum Mol Genet. 2003; 12(15):1917-25); peripheral nerve injury (see, Attal, N., et al., Neurology. 2004; 62(2):218-25; Kim & Chung 1992, Pain 50:355; Bennett & Xie, 1988, Pain 33:87; Decostered, I. & Woolf, C. J., 2000, Pain 87:149; Shir, Y. & Seltzer, Z. 1990; Neurosci Lett 115:62); painful neuromas (see, Nahabedian & Johnson, Ann Plast Surg. 2001; 46(1):15-22; Devor & Raber, Behav Neural Biol. 1983; 37(2):276-83); ectopic proximal and distal discharges (see, Liu, X. et al., Brain Res. 2001; 900(1):119-27); radiculopathy (see, Devers & Galer, (see, Clin J Pain. 2000; 16(3):205-8; Hayashi N et al., Spine. 1998; 23(8):877-85); chemotherapy induced neuropathic pain (see, Aley, K. O., et al., Neuroscience. 1996; 73(1):259-65); radiotherapy-induced neuropathic pain; post-mastectomy pain (see, Devers & Galer, Clin J Pain. 2000; 16(3):205-8); central pain (Cahana, A., et al., Anesth Analg. 2004; 98(6):1581-4), spinal cord injury pain (see, Hains, B. C., et al., Exp Neurol. 2000; 164(2):426-37); post-stroke pain; thalamic pain (see, LaBuda, C. J., et al., Neurosci Lett. 2000; 290(1):79-83); complex regional pain syndrome (see, Wallace, M. S., et al., Anesthesiology. 2000; 92(1):75-83; Xantos D et al., J Pain. 2004; 5(3 Suppl 2):S1); phanton pain (see, Weber, W. E., Ned Tijdschr Geneeskd. 2001; 145(17):813-7; Levitt & Heyback, Pain. 1981; 10(1):67-73); intractable pain (see, Yokoyama, M., et al., Can J Anaesth. 2002; 49(8):810-3); acute pain, acute post-operative pain (see, Koppert, W., et al., Anesth Analg. 2004; 98(4):1050-5; Brennan, T. J., et al., Pain. 1996; 64(3):493-501); acute musculoskeletal pain; joint pain (see, Gotoh, S., et al., Ann Rheum Dis. 1993; 52(11):817-22); mechanical low back pain (see, Kehl, L. J., et al., Pain. 2000; 85(3):333-43); neck pain; tendonitis; injury/exercise pain (see, Seaay, M., et al., Can J Anaesth. 2002; 49(2):137-43); acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc (see, Giambernardino, M. A., et al., Pain. 1995; 61(3):459-69); chest pain, including, cardiac Pain (see, Vergona, R. A., et al., Life Sci. 1984; 35(18):1877-84); pelvic pain, renal colic pain, acute obstetric pain, including, labor pain (see, Segal, S., et al., Anesth Analg. 1998; 87(4):864-

9); cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, including, endometriosis (see, Cason, A. M., et al.,Horm Behav. 2003; 44(2):123-31); acute herpes zoster pain; sickle cell anemia; acute pancreatitis (see, Toma, H; Gastroenterology. 2000; 119(5):1373-81); breakthrough pain; orofacial pain, including, sinusitis pain, dental pain (see, Nusstein, J., et al., J Endod. 1998; 24(7):487-91; Chidiac, J. J., et al., Eur J Pain. 2002; 6(1):55-67); multiple sclerosis (MS) pain (see, Sakurai & Kanazawa, J Neurol Sci. 1999; 162(2):162-8); pain in depression (see, Greene B, Curr Med Res Opin. 2003; 19(4):272-7); leprosy pain; behcet's disease pain; adiposis dolorosa (see, Devillers & Oranje, Clin Exp Dermatol. 1999; 24(3):240-1); phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain (see, Legroux-Crespel, E., et al., Ann Dermatol Venereol. 2003; 130(4):429-33); Fabry's disease pain (see, Germain, D. P., J Soc Biol. 2002;196(2):183-90); Bladder and urogenital disease, including, urinary incontinence (see, Berggren, T., et al., J Urol. 1993; 150(5 Pt 1):1540-3); hyperactivity bladder (see, Chuang, Y. C., et al., Urology. 2003; 61(3):664-70); painful bladder syndrome (see, Yoshimura, N., et al., J Neurosci. 2001; 21(21):8690-6); interstitial cyctitis (IC) (see, Giannakopoulos& Campilomatos, Arch Ital Urol Nefrol Androl. 1992; 64(4):337-9; Boucher, M., et al., J Urol. 2000; 164(1):203-8); and prostatitis (see, Mayersak, J. S., Int Surg. 1998; 83(4):347-9; Keith, I. M., et al., J Urol. 2001; 166(1):323-8).

[0011] Unfortunately, as described above, the efficacy of currently used sodium channel blockers and calcium channel blockers for the disease-states described above has been to a large extent limited by a number of side effects. These side effects include various CNS disturbances such as blurred vision, dizziness, nausea, and sedation as well more potentially life threatening cardiac arrhythmias and cardiac failure. Such undesirable side effects may be avoided by using a Na channel blocker that exhibit a degree of selectivity in its activity against a Na channel subtype. However, Na channel blockers currently in the market lack such selectivity. Perhaps because of this lack of molecular selectivity, drugs currently in the market exhibit use-dependent block and generally show higher affinity at depolarized potentials resulting in the preferential targeting of actively firing neurons, believed to be a key factor in the therapeutic window of existing Na channel blocking drugs. While every drug has it own unique therapeutic profile, current Na channel blockers are generally associated with central nervous system (CNS) and cardiovascular (CV) side-effects, including blood pressure changes, which are often dose-

limiting. Dizziness, sedation, nausea, ataxia, and confusion are some of the specific side-effects observed for phenytoin™, mexiletine™, and lidocaine™.

[0012] There is also a need to develop Na channel blockers that have minimal or no inhibitory activity against the hERG channel. hERG (human ether a-go-go related gene) encodes a potassium ion channel (hERG channel) that is involved in cardiac repolarization. See, e.g., Pearlstein, R., R. Vaz, et al. (2003). "Understanding the Structure-Activity Relationship of the Human Ether-a-go-go-Related Gene Cardiac K(+) Channel. A Model for Bad Behavior." J Med Chem 46(11): 2017-22. Interaction with with the hERG channel is one indicator of potential cardaic toxicity. hERG-block increases the likelihood of cardiac QT-interval prolongation and dispersion. A subset of compounds that prolong the QT interval can cause ventricular fibrillation and cardiac failure. Belardinelli, L., C. Antzelevitch and M.A. Vos (2003). "Assessing predictors of drug-induced torsade de pointes". Trends Pharmacol Sci. 24 (12): 619-25; Al-Khatib, S. M., N. M. LaPointe, et al. (2003). "What clinicians should know about the QT interval." Jama 289(16): 2120-7; http://www.fenichel.net/pages/site_map.htm.

[0013] There is also a need to develop Na channel blockers that have minimal or no inhibitory activity against the Cytochrome P450 enzyme family. Within this family, CYP 3A4 isoform is believed to be the major isoform present in the liver and small intestines. Other key isoforms include CYP 2D6, CYP 2C9, and CYP 1A2. See, e.g., United States patent 6,514,687, the disclosure whereof is incorporated herein by reference. A Na channel blocker that inhibits one or more of the isoforms can cause undesirable side effect or can cause undesirable drug-drug interactions when administered with another drug that interacts with that isoform. See, e.g, Davit, B., et al. (1999), "FDA Evaluations Using In Vitro Metabolism to Predict and Interpret In Vivo Metabolic Drug-Drug Interactions: Impact on Labeling." J. Clin. Pharmacol., 39: 899-910; "Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, Dept. of Health and Human Services, U.S.F.D.A (http://www.fda.gov/cder/guidance.htm).

[0014] There is also a need to develop Na channel blockers that exhibit selectivity against a certain sub-type of Na channel. Particularly useful are compounds that have a desirably low activity against NaV 1.2.

[0015] There is also a need to develop Na channel blockers that have a desirably low activity against L-type calcium channel 1.2. CaV1.2 calcium channels are abundantly expressed in smooth and striated muscle, especially in the heart, brain and endocrine cells. Blocking these

channels can be therapeutically useful, but it can also result in significant side effects. The most significant concerns are impairment of cardiac contractility (that is, a negative inotropic effect) and slowing of electrical conduction in the pacemaker regions of the heart. See, e.g., Kizer, J. R., et al., "Epidemiologic Review of the Calcium Channel Blocker Drugs," Arch. Intern Med. 2001; 161: 1145-1158.

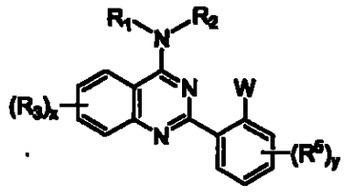
[0016] There is also a need to Na channel blockers that have a desirably low activity against potassiums channel 1.5 ("Kv1.5"; also known as KCNA5). Kv1.5 is found primarily in human atrial cells, but also in brain. See, e.g., Gutman, G. A., et al., "Compendium of Voltage-Gated Ion Channels: Potassium Channels," Pharmacol. Rev., 55: 583-585 (2003). Unwanted block of Kv1.5 could produce convulsion or ataxia.

[0017] There is also a need to develop Na channel blockers that have improved pharmacokinetic and/or pharmacodynamic properties and, therefore, are better suited for *in-vivo* administration for therapeutic purposes. Such properties include aqueous solubility, bioavailability, clearance kinetics, etc. See, e.g., Shargel, L., Yu, A., Ed's "Applied Biopharmaceutics & Pharmacokinetics", 4th Ed., McGraw-Hill, New York, 1999; Yacobi, A., Skelly, J.P., Shah, V.P., Benet, L.Z., Ed's. "Integration of Pharmacokinetics, Pharmacodynamics, and Toxicokinetics in Rational Drug Development", Plenum Press, New York, 1993; Lee, J.S., Obach, R.S., Fisher, M.B., Ed's. "Drug Metabolizing Enzymes Cytochrome P450 and Other Enzymes in Drug Discovery and Development", Marcel Dekker, New York, 2003; Birkett, D.J. "Pharmacokinetics Made Easy", McGraw-Hill Australia, Roseville, Australia, 2002; Katzung, B.G. "Basic & Clinical Pharmacology", McGraw-Hill, New York, 2001; Welling, P.G., Tse, F.L.S., Ed's. "Pharmcokinetics", Marcel Dekker, New York, 1988; Thomas, G. "Medicinal Chemistry An Introduction", Wiley & Sons, New York, 2000; and Gennaro, A. R., et al., "Remington: The Science and Practice of Pharmacy," 20th Ed., Lippincott, Williams, & Wilkins (2003).

[0018] Na channel blocker that meets one or more of the above unmet needs would be a very desirable improvement over the currently marketed Na channel blockers and would greatly benefit patients in need of a therapy therewith.

SUMMARY OF THE INVENTION

[0019] The present invention provides compounds of formula I:



I;

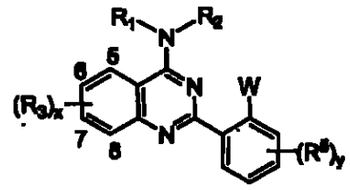
or a pharmaceutically acceptable salt or derivative thereof.

[0020] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain.

DETAILED DESCRIPTION OF THE INVENTION

[0021] *I. General Description of Compounds of the Invention:*

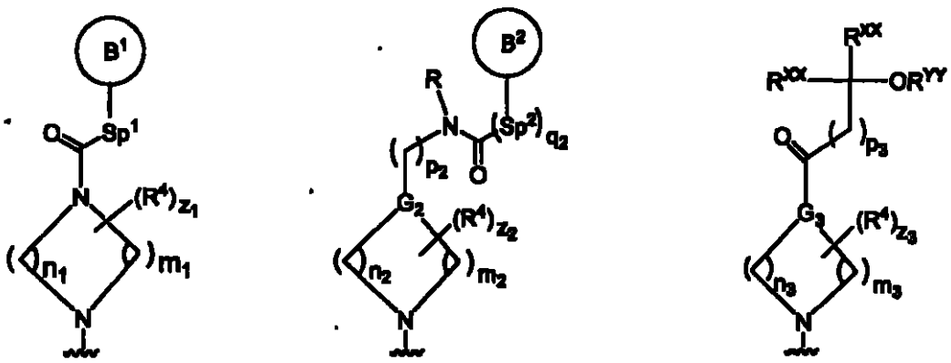
[0022] The present invention provides a compound of formula I:



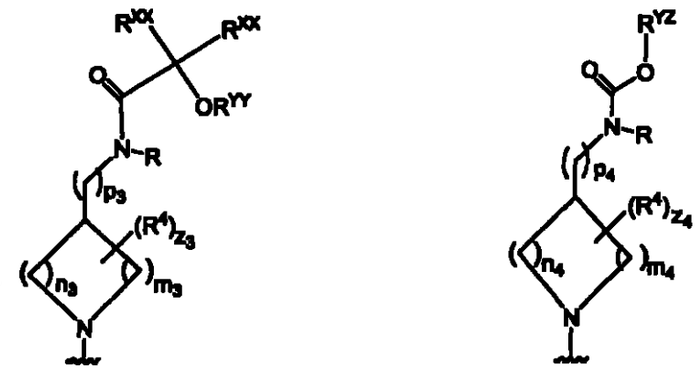
I;

or a pharmaceutically acceptable salt or derivative thereof, wherein:

R^1 and R^2, taken together with the nitrogen atom, form a substituted ring selected from:



(A) (B) (C)



(D) or (E);

wherein, in ring (A):

each of m_1 and n_1 is independently 0-3, provided that m_1+n_1 is 2-6;

z_1 is 0-4;

Sp^1 is –O-, -S-, -NR'-, or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO_2-, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, -SO_2-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-, provided that Sp^1 is attached to the carbonyl group through an atom other than carbon;

ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w_1 independent occurrences of -R^{11}, wherein w_1 is 0-4;

wherein, in ring (B):

G_2 is -N-, or CH;

each of m_2 and n_2 is independently 0-3, provided that $m_2 + n_2$ is 2-6;

p_2 is 0-2; provided that when G_2 is N, then p_2 is not 0;

q_2 is 0 or 1;

z_2 is 0-4;

Sp^2 is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, NR'SO_2-, or -NR'SO_2NR'-;

ring B^2 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4;

wherein, in ring (C) or ring (D):

G_3 is -N-, -CH-NH-, or -CH-CH_2-NH-;

each of m_3 and n_3 is independently 0-3, provided that m_3+n_3 is 2-6;

p_3 is 0-2;

z_3 is 0-4;

each R^{XX} is hydrogen, C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3;

provided that both R^{XX} are not simultaneously hydrogen;

R^{YY} is hydrogen, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', -$COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or -PO(R');

wherein, in ring (E):

each of m_4 and n_4 is independently 0-3, provided that $m_4 + n_4$ is 2-6;

p_4 is 1-2;

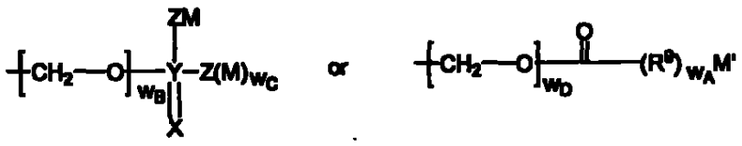
z_4 is 0-4;

R^{YZ} is C_1-C_6 aliphatic group, optionally substituted with w_4 independent occurrences of -R^{14}, wherein w_4 is 0-3;

x and y, each, is independently 0-4;

W is OR^{XY};

R^{XY} is hydrogen or a group selected from:



;

wherein:

each of w_A, w_B, w_C, and w_D is independently 0 or 1;

each M is independently selected from hydrogen, Li, Na, K, Mg, Ca, Ba, -$N(R^7)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or -R^6; wherein 1 to 4 –CH_2 radicals of the alkyl or alkenyl group, other than the –CH_2 that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, -OR^7, -R^7, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, -CO_2R^7, -$C(O)$-$N(R^7)_2$, $S(O)_2$-$N(R^7)_2$, $N(R^7)$-$C(O)$-R^7, $C(O)R^7$, -$S(O)_n$-R^7, OCF_3, -$S(O)_n$-R^6, $N(R^7)$-$S(O)_2(R^7)$, halo, $-CF_3$, or $-NO_2$;

n is 0-2;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or -R^6; wherein 1 to 4 –CH_2 radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, -OR^7, -R^7, $-N(R^7)_2$, $N(R^7)_3$, -R^7OH, -CN, -CO_2R^7, -$C(O)$-$N(R^7)_2$, -$S(O)_2$-$N(R^7)_2$, -$N(R^7)$-$C(O)$-R^7, -$C(O)R^7$, -$S(O)_n$-R^7, $-OCF_3$, -$S(O)_n$-R^6, -$N(R^7)$-$S(O)_2(R^7)$, halo, $-CF_3$, or $-NO_2$;

Z is -CH_2-, -O-, -S-, -$N(R^7)_2$-; or,

when M is absent, then Z is hydrogen, =O, or =S;

Y is P or S, wherein when Y is S, then Z is not S;

X is O or S;

each R^7 is independently selected from hydrogen, or C_1-C_4 aliphatic, optionally substituted with up to two Q_1;

each Q_1 is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatom or heteroatom group selected from O, N, NH, S, SO, or SO_2; wherein Q_1 is optionally substituted with up to three substituents selected from oxo, -OH, -O(C_1-C_4 aliphatic), -C_1-C_4 aliphatic, -NH_2, NH(C_1-C_4 aliphatic), -N(C_1-C_4 aliphatic)$_2$, -N(C_1-C_4 aliphatic)-C(O)- C_1-C_4 aliphatic, -(C_1-C_4 aliphatic)-OH, -CN, -CO_2H, -CO_2(C_1-C_4 aliphatic), -C(O)-NH_2, -C(O)-NH(C_1-C_4 aliphatic), -C(O)-N(C_1-C_4 aliphatic)$_2$, halo or -CF_3;

R^6 is a 5-6 membered saturated, partially saturated or unsatirated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, $S(O)_n$ or $N(R^7)$; and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C_1-C_4 alkyl, O-C_1-C_4 alkyl or O-C(O)-C_1-C_4 alkyl;

R^9 is $C(R^7)_2$, O or $N(R^7)$;

each occurrence of R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4, and R^5 is independently Q-R^X; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO_2-, -SO_2NR-, -NRSO_2-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO_2NR-, -SO-, -SO_2-, -PO-, -PO_2-, -OP(O)(OR)-, or -POR-; and each occurrence of R^X is independently selected from -R', halogen, =O, =NR', -NO_2, -CN, -OR', -SR', -N(R')$_2$, -NR'COR', -NR'CON(R')$_2$, -NR'CO_2R', -COR', -CO_2R', -OCOR', -CON(R')$_2$, -OCON(R')$_2$, -SOR', -SO_2R', -SO_2N(R')$_2$, -NR'SO_2R', -NR'SO_2N(R')$_2$, -COCOR', -$COCH_2$COR', -OP(O)(OR')$_2$, -P(O)(OR')$_2$, -OP(O)$_2$OR', -P(O)$_2$OR', -PO(R')$_2$, or -OPO(R')$_2$; and

each occurrence of R is independently hydrogen or C_{1-6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four

substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0023] *2. Compounds and Definitions:*

[0024] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0025] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not

substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0026] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0027] The term "heteroaliphatic", as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" groups.

[0028] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members are an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[0029] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0030] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0031] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[0032] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

[0033] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[0034] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0035] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are generally selected from halogen; -R°; -OR°; -SR°; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R°; -

CH=CH(Ph), optionally substituted with R°; $-NO_2$; -CN; $-N(R^\circ)_2$; $-NR^\circ C(O)R^\circ$; $-NR^\circ C(S)R^\circ$; $-NR^\circ C(O)N(R^\circ)_2$; $-NR^\circ C(S)N(R^\circ)_2$; $-NR^\circ CO_2R^\circ$; $-NR^\circ NR^\circ C(O)R^\circ$; $-NR^\circ NR^\circ C(O)N(R^\circ)_2$; $-NR^\circ NR^\circ CO_2R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-CO_2R^\circ$; $-C(O)R^\circ$; $-C(S)R^\circ$; $-C(O)N(R^\circ)_2$; $-C(S)N(R^\circ)_2$; $-OC(O)N(R^\circ)_2$; $-OC(O)R^\circ$; $-C(O)N(OR^\circ)\ R^\circ$; $-C(NOR^\circ)\ R^\circ$; $-S(O)_2R^\circ$; $-S(O)_3R^\circ$; $-SO_2N(R^\circ)_2$; $-S(O)R^\circ$; $-NR^\circ SO_2N(R^\circ)_2$; $-NR^\circ SO_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(=NH)-N(R^\circ)_2$; $-P(O)_2R^\circ$; $-PO(R^\circ)_2$; $-OPO(R^\circ)_2$; $-(CH_2)_{0-2}NHC(O)R^\circ$; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R°; or -CH=CH(Ph), optionally substituted with R°; wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or $-CH_2(Ph)$, or, notwithstanding the definition above, two independent occurrences of R°, on the same substituent or different substituents, taken together with the atom(s) to which each R° group is bound, to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0036] . Optional substituents on the aliphatic group of R° are selected from NH_2, $NH(C_{1-4}$aliphatic), $N(C_{1-4}$aliphatic$)_2$, halogen, C_{1-4}aliphatic, OH, $O(C_{1-4}$aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$aliphatic), O(haloC_{1-4} aliphatic), or haloC_{1-4}aliphatic, wherein each of the foregoing C_{1-4}aliphatic groups of R° is unsubstituted.

[0037] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2$(alkyl), $=NNHSO_2$(alkyl), or $=NR^*$, where each R^* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group.

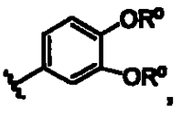
[0038] Unless otherwise defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring are generally selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^{+1})_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally

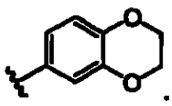
substituted phenyl, optionally substituted -O(Ph), optionally substituted -CH_2(Ph), optionally substituted -$(CH_2)_{1-2}$(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R^+, on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0039] Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from -NH_2, -NH(C_{1-4} aliphatic), -N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, -OH, -O(C_{1-4} aliphatic), -NO_2, -CN, -CO_2H, -CO_2(C_{1-4} aliphatic), -O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R^+ is unsubstituted.

[0040] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

[0041] As detailed above, in some embodiments, two independent occurrences of R° (or R^+, R, R' or any other variable similarly defined herein), are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0042] Exemplary rings that are formed when two independent occurrences of R° (or R^+, R, R' or any other variable similarly defined herein), are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R° (or R^+, R, R' or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, N(R°)$_2$, where both occurrences of R° are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R° (or R^+, R, R' or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR°  , these two occurrences of R° are taken together with

the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:  . It will be appreciated that a variety of other rings can be formed when two independent occurrences of R° (or R^+, R, R' or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0043] *3. Description of Exemplary Compounds:*

[0044] In one embodiment, R is hydrogen. Or, R is C1-C6 aliphatic. Exemplary R includes C1-C6 alkyl, e.g., methyl, ethyl, propyl, or butyl.

[0045] In one embodiment, R' is hydrogen.

[0046] In one embodiment, R' is a C1-C8 aliphatic group, optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, or $OCHF_2$, wherein up to two methylene units of said C1-C8 aliphatic is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, $-CO_2-$, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, $-SO_2$N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[0047] In one embodiment, R' is a 3-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen,

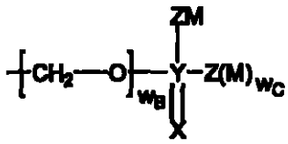
oxygen, or sulfur, wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with -CO-, -CONH(C1-C4 alkyl)-, $-CO_2-$, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, $-SO_2N$(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[0048] In one embodiment, R' is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, $-CO_2-$, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, $-SO_2N$(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[0049] In one embodiment, two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, $-CO_2-$, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, $-SO_2N$(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[0050] In another embodiment, W is *OH*.

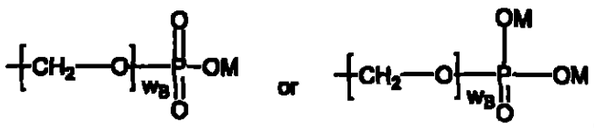
[0051] In still another embodiment, R^{XY} is:



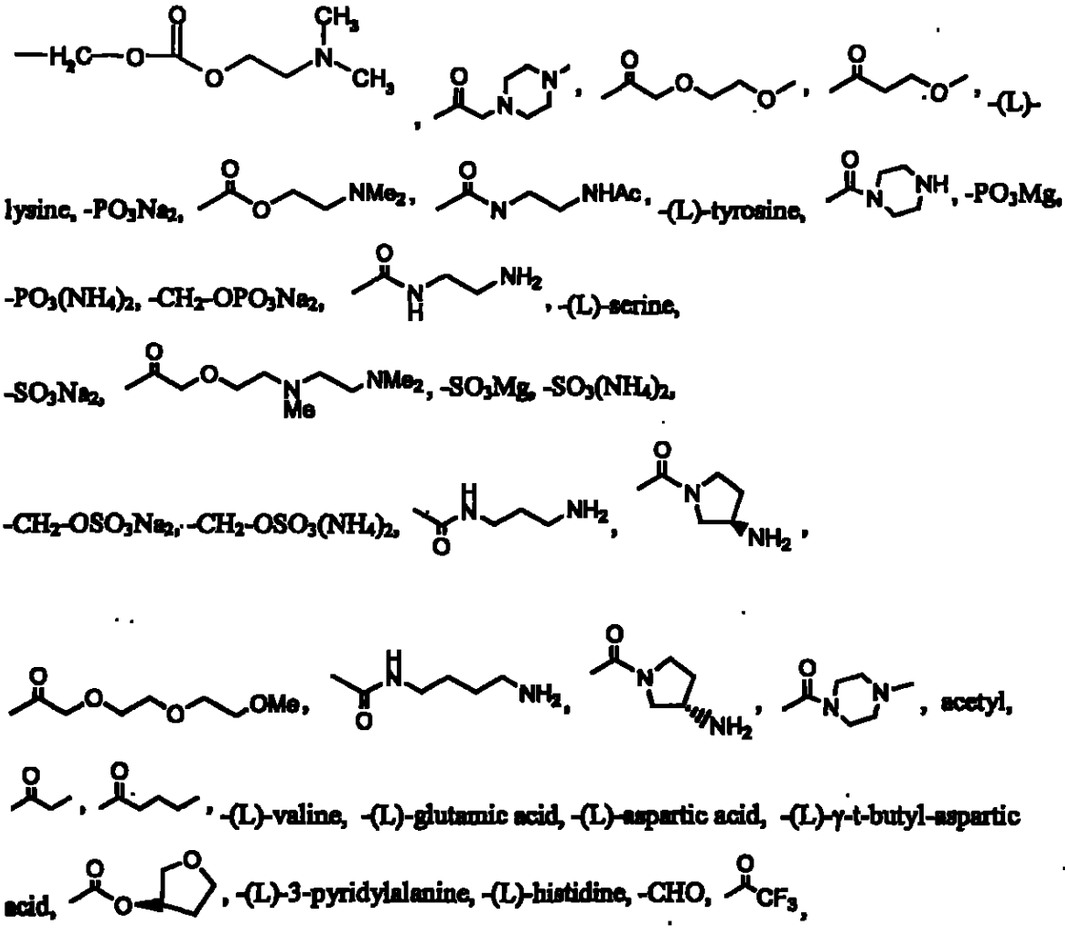
[0052] In certain embodiment, Y is P and X is O.

[0053] In another embodiment, each Z is –O-.

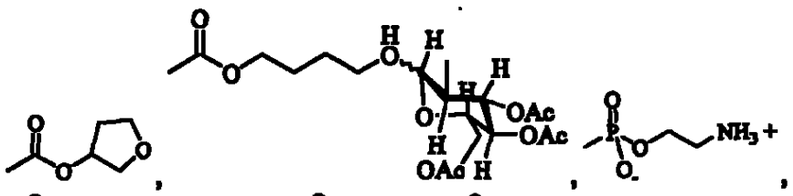
[0054] In yet another embodiment, R^{XY} is selected from:

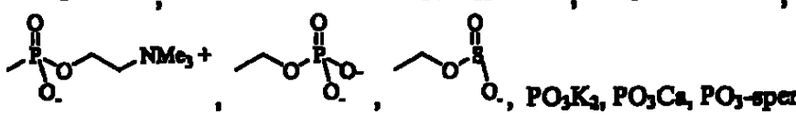


[0055] In yet another embodiment, R^{XY} is selected from:



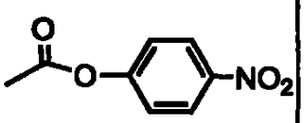
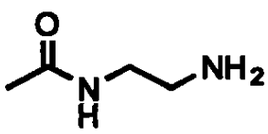
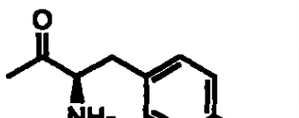
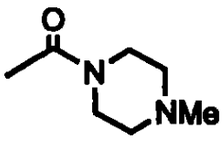
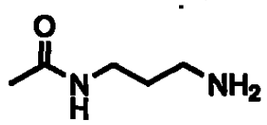
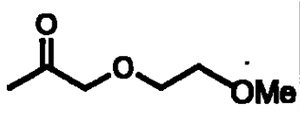
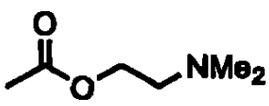
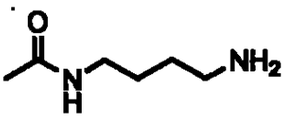
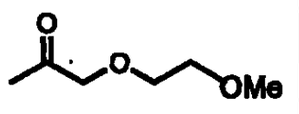
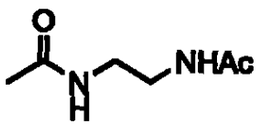
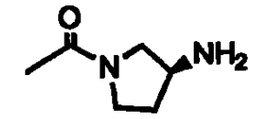
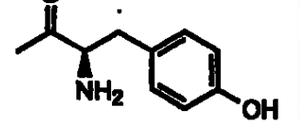
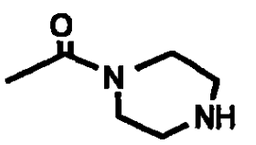
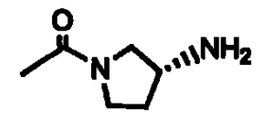
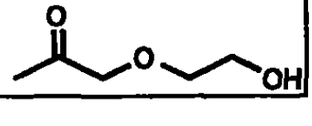
-(L)-lysine, $-PO_3Na_2$, , , -(L)-tyrosine, , $-PO_3Mg$, $-PO_3(NH_4)_2$, $-CH_2-OPO_3Na_2$, , -(L)-serine, $-SO_3Na_2$, , $-SO_3Mg$, $-SO_3(NH_4)_2$, $-CH_2-OSO_3Na_2$, $-CH_2-OSO_3(NH_4)_2$, , , , , , acetyl, , , -(L)-valine, -(L)-glutamic acid, -(L)-aspartic acid, -(L)-γ-t-butyl-aspartic acid, , -(L)-3-pyridylalanine, -(L)-histidine, -CHO, ,

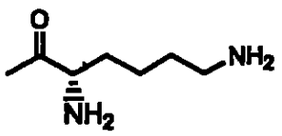
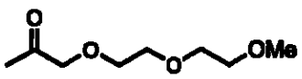
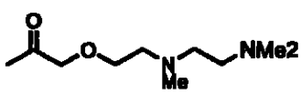
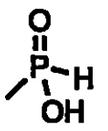
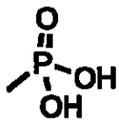
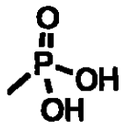
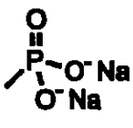


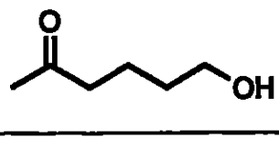
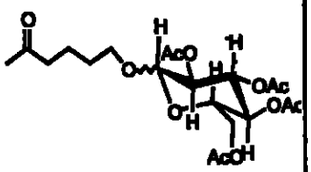
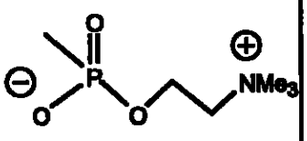
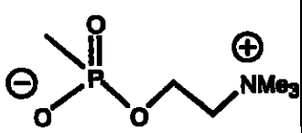
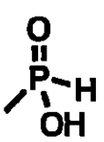
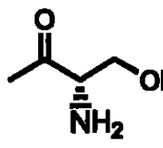


PO_3K_3, PO_3Ca, PO_3-spermine, PO_3-(spermidine)$_2$ or PO_3-(meglamine)$_2$.

[0056] In yet another embodiment, R^{XY} is selected from:

R^{XY}	R^{XY}	R^{XY}
		
		
		
		
		

R^{XY}








R^{XY}


-SO_3H
-SO_3H





R^{XY}
PO_3K_2
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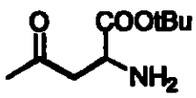
PO_3Mg


[0057] In one embodiment, x is 0-2. Or, x is 1 or 2. Or, x is 1.

[0058] In one embodiment, R^3 is present at the 6- or 7-position of the quinazoline ring.

[0059] In another embodiment, R^3 is selected from halo, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0060] In one embodiment, R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, $-COOH$, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, $-CONH$(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

[0061] In another embodiment, each R^3 group is independently halogen, CN, optionally substituted C_1-C_6alkyl, OR', $N(R')_2$, $CON(R')_2$, or NRCOR'.

[0062] In one embodiment, x is 1 or 2, and each R^3 group is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CONH$(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

[0063] In yet another embodiment, x is 1 and R^3 is at the 6-position of the quinazoline ring and is selected from -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CONH$(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or $-CN$.

[0064] In yet another embodiment, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

[0065] In one embodiment, R^3 is at the 6-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'.

[0066] In another embodiment, x is 1 and R^3 is at the 7-position of the quinazoline ring and is selected from -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, $-CONH$(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

[0067] In yet another embodiment, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$. Or, x is 1 and R^3 is at the 7-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'.

[0068] In one embodiment, y is 0-4 and R^5 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, - $-NRCOR'$, $-CON(R')_2$, $-S(O)_2N(R')_2$, $-OCOR'$, -

COR', -CO_2R', -OCON(R')$_2$, -NR'SO_2R', -OP(O)(OR')$_2$, -P(O)(OR')$_2$, -$OP(O)_2$OR', -$P(O)_2$OR', -PO(R')$_2$, -OPO(R')$_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0069] In another embodiment, R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, -NH_2, -N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -OCH_3, -OCH_2CH_3, -CH_2OH, -NHCOCH_3, -SO_2NH_2, -SO_2NHC(CH_3)$_2$, -OCOC(CH_3)$_3$, -OCOCH_2C(CH_3)$_3$, -O(CH_2)$_2$N(CH_3)$_2$, 4-CH_3-piperazin-1-yl, OCOCH(CH_3)$_2$, OCO(cyclopentyl), -$COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0070] In certain embodiments, each of z_1, z_2, z_3, or z_4 is independently 0-2. In other embodiments, each of z_1, z_2, z_3, or z_4 is 0 and the ring is unsubstituted. Preferred R^4 groups, when present, are each independently halogen, CN, NO_2, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -CON(R')$_2$, -OCON(R')$_2$, COR', -NHCOOR', -SO_2R', -SO_2N(R')$_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl. Other exemplary R^4 groups are Cl, Br, F, CF_3, CH_3, -CH_2CH_3, CN, -COOH, -N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -NHCOCH_3, -SO_2NH_2, -SO_2(CH_2)$_3$$CH_3$, -$SO_2$CH($CH_3$)$_2$, -$SO_2$N($CH_3$)$_2$, -$SO_2CH_2CH_3$, -C(O)O$CH_2$CH($CH_3$)$_2$, -C(O)NHCH$_2$CH($CH_3$)$_2$, -NHCOO$CH_3$, -C(O)C($CH_3$)$_3$, -COO($CH_2$)$_2$$CH_3$, -C(O)NHCH($CH_3$)$_2$, -C(O)$CH_2CH_3$, or an optionally substituted group selected from piperidinyl, piperizinyl, morpholino, C_{1-4}alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, -CH_2cyclohexyl, pyridyl, -CH_2pyridyl, or -CH_2thiazolyl

[0071] In certain embodiments, x is 0-2. In other embodiments, x is 1 or 2. In still other embodiments x is 1 and R^3 is substituted at the 6- or 7-position of the quinazoline ring. When the quinazoline ring is substituted (x is 1-4), R^3 groups are halogen, CN, NO_2, -N(R')$_2$, -CH_2N(R')$_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -CON(R')$_2$, -OCON(R')$_2$, COR', -NHCOOR', -SO_2R', -SO_2N(R')$_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl. In still other embodiments, each occurrence of R^3 is independently Cl, Br, F, CF_3, -OCF_3, Me, Et, CN, -COOH, -NH_2, -N(CH_3)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH_2)$_2$OCH_3, -$CONH_2$, -$COOCH_3$, -OH, -OCH_3, -OCH_2CH_3, -

CH_2OH, -$NHCOCH_3$, -$NHCOCH(CH_3)_2$, -SO_2NH_2, -CONH(cyclopropyl), -$CONHCH_3$, -$CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy. In still other embodiments, x is 1 or 2 and each R^3 group is independently halogen, CN, optionally substituted C_1-C_6alkyl, OR', $N(R')_2$, $CON(R')_2$, or NRCOR'. In yet other embodiments, x is 1 or 2, and each R^3 group is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -$CONHCH_3$, -$CONHCH_2CH_3$, -CONH(cyclopropyl), -OCH_3, -NH_2, -OCH_2CH_3, or -CN. In still other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -$CONHCH_3$, -$CONHCH_2CH_3$, -CONH(cyclopropyl), -OCH_3, -NH_2, -OCH_2CH_3, or –CN. IN yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -$CONHCH_3$, -$CONHCH_2CH_3$, -CONH(cyclopropyl), -OCH_3, -NH_2, -OCH_2CH_3, or -CN.' In other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -OCH_3, or -OCH_2CH_3. In still other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -OCH_3, or -OCH_2CH_3. In other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is –$CON(R')_2$, or NRCOR'. In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is –$CON(R')_2$, or NRCOR'.

[0072] In some embodiments, y is 0-4 and R^5 group, when present, is each independently halogen, CN, NO_2, -$N(R')_2$, -$CH_2N(R')_2$, -OR', -CH_2OR', -SR', -CH_2SR', - -NRCOR', -$CON(R')_2$, -$S(O)_2N(R')_2$, -OCOR', -COR', -CO_2R', -$OCON(R')_2$, -$NR'SO_2R'$, -$OP(O)(OR')_2$, -$P(O)(OR')_2$, -$OP(O)_2OR'$, -$P(O)_2OR'$, -$PO(R')_2$, -$OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0073] In yet other embodiments, y is 0-4 and each occurrence of R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, -NH_2, –$N(CH_3)_2$, -$N(Et)_2$, -$N(iPr)_2$, -$O(CH_2)_2OCH_3$, -$CONH_2$, -$COOCH_3$, -OH, -OCH_3, -OCH_2CH_3, -CH_2OH, -$NHCOCH_3$, -SO_2NH_2, -$SO_2NHC(CH_3)_2$, -$OCOC(CH_3)_3$, -$OCOCH_2C(CH_3)_3$, -$O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), -$COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0074] In yet another embodiment, each of z_1, z_2, z_3, or z_4 is 0-4, and R^4 groups, when present, are each independently halogen, CN, NO_2, -$N(R')_2$, -$CH_2N(R')_2$, -OR', -CH_2OR', -SR',

$-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0075] In still other embodiments, each of z_1, z_2, z_3, or z_4 is 0-4 and R^4 groups are each independently Cl, Br, F, CF_3, CH_3, $-CH_2CH_3$, CN, $-COOH$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, $-OH$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2(CH_2)_3CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)NHCH_2CH(CH_3)_2$, $-NHCOOCH_3$, $-C(O)C(CH_3)_3$, $-COO(CH_2)_2CH_3$, $-C(O)NHCH(CH_3)_2$, $-C(O)CH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, C_{1-4}alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, $-CH_2$cyclohexyl, pyridyl, $-CH_2$pyridyl, or $-CH_2$thiazolyl.

[0076] For compounds described directly above, in some embodiments, x is 0-4, and R^3 groups, when present, are each independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0077] In yet other embodiments, x is 1 or 2, and each occurrence of R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, $-COOH$, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

[0078] In still other embodiments, x is 1 or 2 and each R^3 group is independently halogen, CN, optionally substituted C_1-C_6alkyl, OR', $N(R')_2$, $CON(R')_2$, or $NRCOR'$.

[0079] In yet other embodiments, x is 1 or 2, and each R^3 group is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

[0080] In still other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

[0081] In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

[0082] In still other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

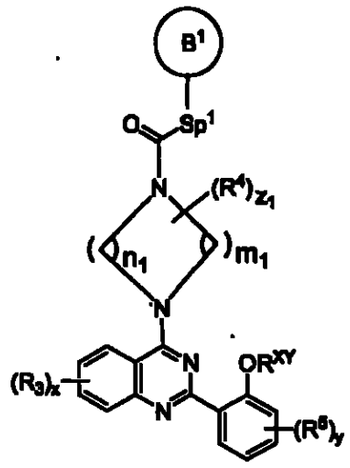
[0083] In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

[0084] In still other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'.

[0085] In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

[0086] In yet other embodiments for compounds described directly above, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN. In still other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN. In yet other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$. In still other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$. In yet other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'. In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'.

[0087] In one embodiment, the present invention provides compounds of formula I-A:



I-A;

wherein x, y, n_1, m_1, z_1, R^{XY}, R^4, R^5, Sp^1, and ring B^1 are as defined above.

[0088] In one embodiment, Sp^1 is selected from -O-, -S-, or –NR'-. Or, Sp^1 is –O-. Or, Sp^1 is –O-CH_2-. In another embodiment, Sp^1 is –NR'-. Or, Sp^1 is –NH-. Or, Sp^1 is -NH-CH_2-.

[0089] In one embodiment, each of m_1 and n_1 is 1. In another embodiment, each of m_1 and n_1 is 2.

[0090] In one embodiment, ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w independent occurrences of $-R^{11}$, wherein w_1 is 0-4.

[0091] In another embodiment, ring B^1 is a 4-8 membered, saturated, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w independent occurrences of $-R^{11}$, wherein w_1 is 0-4.

[0092] In yet another embodiment, ring B^1 is a 5-6 membered, saturated, monocyclic heterocyclic ring having having 1-2 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w independent occurrences of $-R^{11}$, wherein w_1 is 0-4.

[0093] In one embodiment, w_1 is 0.

[0094] In another embodiment, ring B^1 is tetrahydrofuranyl.

[0095] In yet another embodiment, Sp^1 is a bond, O, or –O-CH_2-; R is hydrogen; and n_1 and m_1 are both simultaneously 1 or 2.

[0096] In one embodiment, R is hydrogen. Or, R is C1-C6 alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[0097] In another embodiment, z_1 is 0.

[0098] According to another embodiment, ring B^1 is tetrahydrofuranyl, tetrahydro-[*2H*]-pyranyl, pyridyl, or phenyl.

[0099] According to yet another embodiment, Sp^1 is a bond, -O-, $-O-CH_2-$, or $-NH-CH_2$.

[00100] In one embodiment:

n_1 and m_1 each is 2;

R^{XY} is hydrogen;

y is 0 or 1 and R^5 is fluoro;

x is 1 and R^3 is Me at 7-position or fluoro at 6-position;

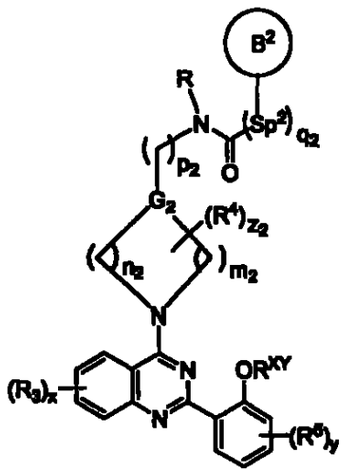
z_1 is 0;

Sp^1 is $-O-CH_2-$;

w_1 is 0; and

ring B^1 is tetrahydrofuran-3-yl, phenyl, pyridine-3-yl, pyridine-4-yl, or tetrahydro[2H]-pyran-4-yl.

[00101] According to another embodiment, the present invention provides compounds of formula I-B:



I-B;

wherein x, y, n_2, m_2, z_2, q_2, R, Sp^2, ring B^2, R^{XY}, R^3, R^4, and R^5 are as defined above.

[00102] In one embodiment, G_2 is N. Or, G_2 is CH.

[00103] In one embodiment, p_2 is 0. Or, p_2 is 1. Or, p_2 is 2.

[00104] In another embodiment, q_2 is 0. Or, q_2 is 1.

[00105] In one embodiment, p_2 is 1, and q_2 is 1.

[00106] In another embodiment, G_2 is CH, p_2 is 0, and q_2 is 1.

[00107] In one embodiment, m_2 and n_2 each is 1. Or, m_2 and n_2 each is 2. Or, n_2 is 1 and m_2 is 2. Or, n_2 is 1, and m_2 is 3.

[00108] In another embodiment, Sp^2 is selected from -O-, -S-, or $-NR'-$. In one embodiment, Sp^2 is -O-. Or, Sp^2 is $-NR'-$. Or, Sp^2 is -NH-.

[00109] In one embodiment, ring B^2 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4.

[00110] In another embodiment, ring B^2 is a 4-8 membered, saturated, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^2 is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4.

[00111] In yet another embodiment, ring B^2 is a 5-6 membered, saturated, monocyclic heterocyclic ring having having 1-2 heteroatoms selected from O, S, or N, wherein ring B^2 is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4.

[00112] In one embodiment, w_2 is 0.

[00113] According to yet another embodiment, Sp^2 is a bond, -O-, or $-O-CH_2-$.

[00114] In another embodiment, ring B^2 is tetrahydrofuranyl, tetrahydro[2*H*]pyranyl, or pyridyl.

[00115] In yet another embodiment,

i) Sp^2 is a bond, O, or $-O-CH_2-$;

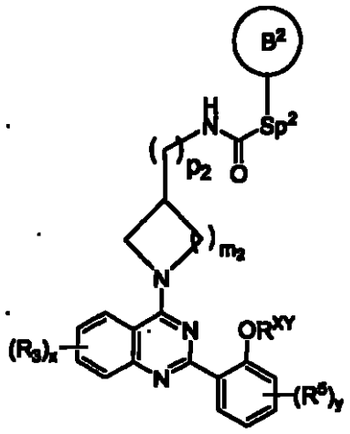
ii) p_2 is 1;

iii) R is hydrogen; and

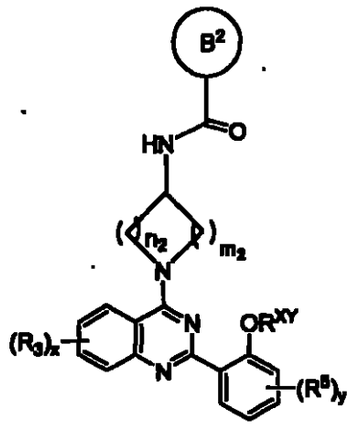
iv) n_2 is 1 and m_2 is 2 or 3.

[00116] In one embodiment, R is hydrogen. Or, R is C1-C6 alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[00117] In one embodiment, compounds of formula I-B have formula I-B-i or formula I-B-ii:



I-B-i



I-B-ii

[00118] In one embodiment of formula I-B-i:

i) p_2 is 1;

ii) m_2 is 3;

iii) Sp^2 is -O-;

iv) y is 0 or 1, and R^5 is fluoro;

v) x is 1 and R^3 is 7-Me; and

vi) ring B^2 is tetrahydrofuranyl.

[00119] In another embodiment of formula I-B-i:

i) p_2 is 0 or 1;

ii) m_2 is 1 or 2, preferably 2;

iii) Sp^2 is -O- or -O-CH_2-;

iv) y is 0;

v) x is 1 and R^3 is 7-Me; and

vi) ring B^2 is tetrahydrofuranyl, tetrahydro[2H]pyranyl, pyridyl, or phenyl.

[00120] In one embodiment of formula I-B-ii:

(i) n_2 is 1, m_2 is 1 or 2, preferably 2;

(ii) y is 0 or 1, and R^5 is fluoro;

(iii) x is 1 and R^3 is 7-Me or 6-F; and

(iv) ring B^2 is cyclopropyl optionally substituted with C1-C4 alkyl, or pyridyl.

[00121] In one embodiment of formula I-B-ii:

(i) n_2 and m_2 both are 2;

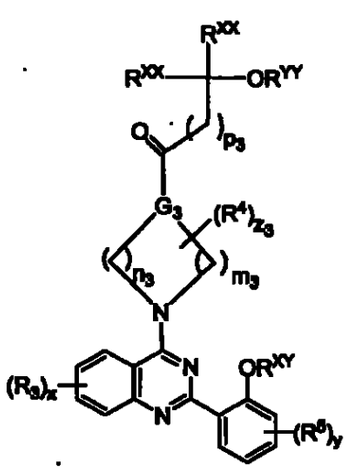
(ii) y is 0;

(iii) x is 1 and R^3 is C1-C4 alkyl at the 7-position; and

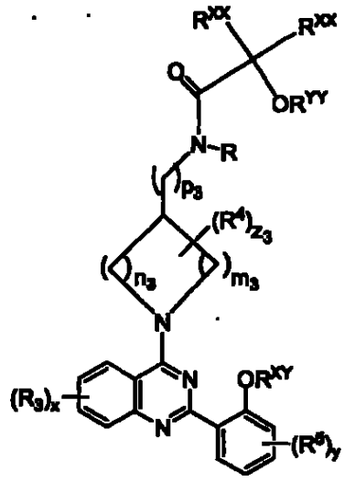
(iv) ring B^2 is an optionally substituted tetrahydrofuranyl.

[00122] In one embodiment of formula I-B-i or formula I-B-ii, R^{XY} is hydrogen.

[00123] According to one embodiment, the present invention provides compounds of formula I-C or formula I-D:



I-C



I-D;

wherein x, y, n_3, m_3, z_3, p_3, R^{XX}, R^{YY}, R^{XY}, R^3, R^4, and R^5 are as defined above.

[00124] In one embodiment of the present invention, one R^{XX} is hydrogen and the other R^{XX} is not hydrogen.

[00125] In another embodiment of the present invention, both R^{XX} are not hydrogen.

[00126] In another embodiment, one R^{XX} is hydrogen and the other R^{XX} is C1-C6 alkyl optionally substituted with halo. Or, both R^{XX} are simultaneously C1-C6 alkyl. Exemplary alkyl include methyl, ethyl, isopropyl, *n*-propyl, *n*-butyl, *sec*-butyl, or *t*-butyl.

[00127] In one embodiment of the present invention, p_3 is 0. Or, p_3 is 1. Or, p_3 is 2.

[00128] In one embodiment of the present invention, m_3 and n_3 each is 1. Or, m_3 and n_3 each is 2. Or, m_3 and n_3 each is 3.

[00129] In one embodiment of the present invention, R^{XX} is C_{1-6} aliphatic group, wherein R^{XX} is optionally substituted with w independent occurrences of $-R^{13}$, wherein w_3 is 0-3. Or, R^{XX} is

C1-C6 alkyl group optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3.

[00130] In one embodiment of the present invention, R^{XX} is C1-C6 alkyl group.

[00131] In another embodiment of the present invention, R^{XX} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3.

[00132] In another embodiment, R^{XX} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^{XX} is optionally substituted with w independent occurrences of $-R^{13}$, wherein w_3 is 0-3.

[00133] In another embodiment, R^{XX} is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3.

[00134] In another embodiment, R^{YY} is hydrogen, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or -PO(R').

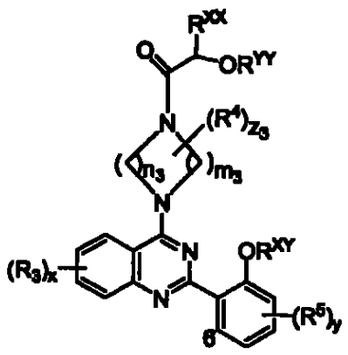
[00135] Or, R^{YY} is hydrogen.

[00136] In another embodiment, R^{YY} is -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or -PO(R').

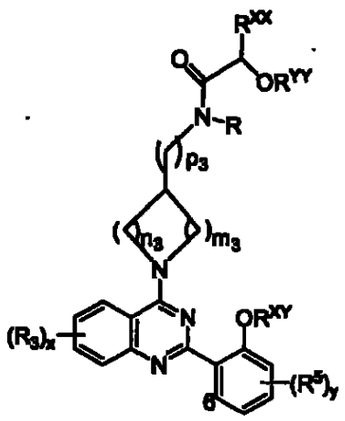
[00137] In another embodiment, R^{YY} is R^{XY}.

[00138] In one embodiment, R is hydrogen. Or, R is C1-C6 alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[00139] In one embodiment, the present invention provides a compound of formula I-C-1 or formula I-D-1:



I-C-i



I-D-i;

wherein x, y, n_3, m_3, z_3, p_3, R^{XX}, R^{YY}, R^{XY}, R^3, R^4, and R^5 are as defined above.

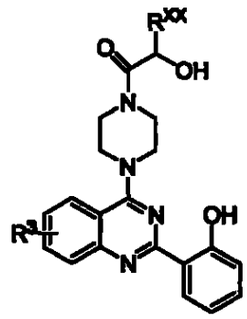
[00140] In one embodiment of I-C-i or I-D-i, R^{XX} is C1-C6 alkyl. In another embodiment, x is 1, and R^3 is C1-C4 alkyl at the 7-position. Or, x is 1 and R^3 is F, CN, or CF_3 at the 6-position.

[00141] In one embodiment, R^{XX} is methyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, or *t*-butyl.

[00142] In one embodiment, R^3 is C1-C6 alkyl. Or, R^3 is methyl, *n* -propyl, isopropyl, *n* -butyl, *sec*-butyl, or *t*-butyl.

[00143] In one embodiment of I-C-i or I-D-i, R^{XY} is hydrogen, and y is 0. Or, R^{XY} is hydrogen, y is 1 and R^5 is 6-F.

[00144] In another embodiment, the present invention provides a compound of formula I-C-ii:



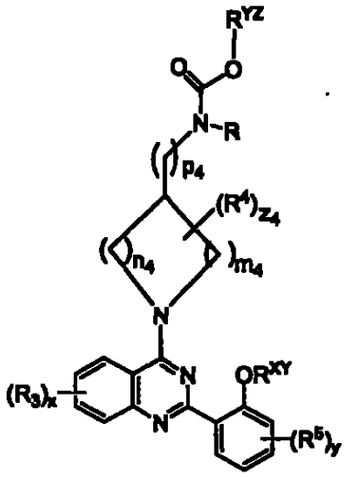
I-C-ii;

wherein R^3 and R^{XX} are as defined above.

[00145] In another embodiment, R^3 is methyl at the 6- or 7-position of the quinazoline ring.

[00146] In another embodiment of formula I-C-ii, R^{XX} is $CH_2C(O)OH$ or $CH_2C(O)NH_2$.

[00147] According to one embodiment, the present invention provides a compound of formula I-E:



I-E;

wherein x, y, n_4, m_4, z_4, p_4, R^{YZ}, R^{XY}, R^3, R^4, and R^5 are as defined above.

[00148] In one embodiment, p_4 is 1. Or, p_4 is 2.

[00149] In one embodiment, m_4 and n_4 each is 1. Or, m_4 and n_4 each is 2. Or, m_4 and n_4 each is 3. In one embodiment, n_4 is 1 and m_4 is 3. In another embodiment, n_4 is 1 and m_4 is 2.

[00150] In one embodiment, n_4 is 1, m_4 is 3, z_4 is 0, p_4 is 1, y is 0 or 1, and x is 1.

[00151] In another embodiment, n_4 is 1, m_4 is 2, z_4 is 0, p_4 is 1, y is 0 or 1, and x is 1.

[00152] In one embodiment, n_4 is 1, m_4 is 3, z_4 is 0, p_4 is 1, y is 0 or 1, x is 1, and R and R^{XY} both are hydrogen.

[00153] In another embodiment, n_4 is 1, m_4 is 2, z_4 is 0, p_4 is 1, y is 0 or 1, x is 1, and R and R^{XY} both are hydrogen.

[00154] In one embodiment, R^{YZ} is C1-C6 alkyl, optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3. In another embodiment, R^{YZ} is C1-C4 alkyl group optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3. Or, R^Y is C1-C6 alkyl group.

[00155] In one embodiment, R is hydrogen. Or, R is C1-C6 alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[00156] In another embodiment:

(i) n_4 is 1 and m_4 is 3;

(ii) p_4 is 1;

(iii) z_4 is 0;

(iv) R^{YZ} is C1-C6 alkyl, wherein up to two $-CH_2-$ groups therein is optionally replaced by -O-;

(v) y is 0 or 1, and R^5 is 6-fluoro; and

(vi) x is 1 and R^3 is C1-C4 alkyl.

[00157] In another embodiment:

(i) n_4 is 1 and m_4 is 2;

(ii) p_4 is 1;

(iii) z_4 is 0;

(iv) R^{YZ} is C1-C6 alkyl, wherein up to two $-CH_2-$ groups therein is optionally replaced by -O-;

(v) y is 0 or 1, and R^5 is 6-fluoro; and

(vi) x is 1 and R^3 is C1-C4 alkyl.

[00158] In another embodiment:

(i) n_4 is 1 and m_4 is 3;

(ii) p_4 is 1;

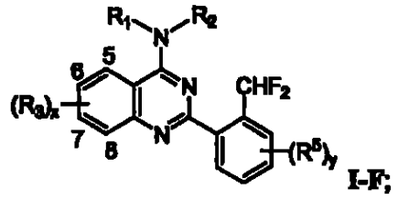
(iii) z_4 is 0;

(iv) R^{YZ} is benzyl;

(v) y is 0 or 1, and R^5 is 6-fluoro; and

(vi) x is 1 and R^3 is C1-C4 alkyl.

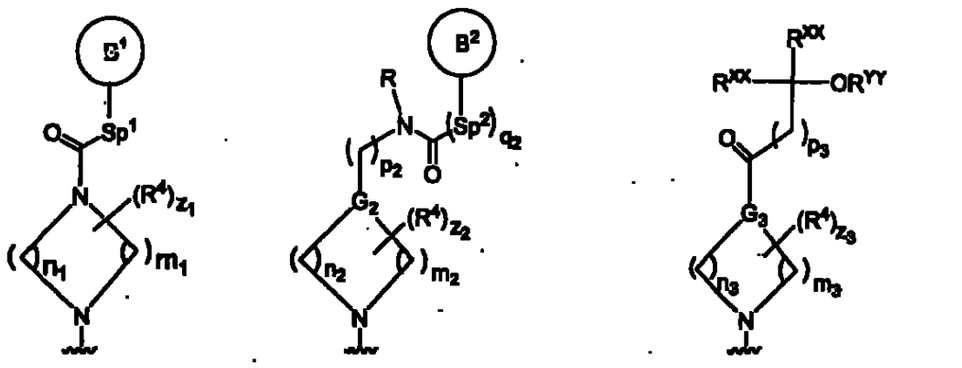
[00159] In another embodiment, the present invention provides compounds of formula I-F:



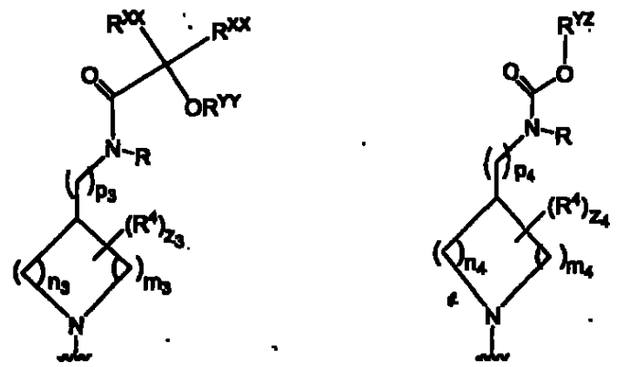
I-F;

wherein:

R^1 and R^2, taken together with the nitrogen atom, form a substituted ring selected from:



(A) (B) (C)



(D) or (E);

wherein, in ring (A):

each of m_1 and n_1 is independently 0-3, provided that m_1+n_1 is 2-6;

z_1 is 0-4;

Sp^1 is –O-, -S-, -NR'-, or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO_2-, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, -SO_2-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-, provided that Sp^1 is attached to the carbonyl group through an atom other than carbon;

ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w_1 independent occurrences of -R^{11}, wherein w_1 is 0-4;

wherein, in ring (B):

G_2 is -N-, or CH;

each of m_2 and n_2 is independently 0-3, provided that $m_2 + n_2$ is 2-6;

p_2 is 0-2; provided that when G_2 is N, then p_2 is not 0;

q_2 is 0 or 1;

z_2 is 0-4;

Sp^2 is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$;

ring B^2 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4;

wherein, in ring (C) or ring (D):

G_3 is -N-, -CH-NH-, or $-CH-CH_2-NH-$;

each of m_3 and n_3 is independently 0-3, provided that m_3+n_3 is 2-6;

p_3 is 0-2;

z_3 is 0-4;

each R^{XX} is hydrogen, C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3;

provided that both R^{XX} are not simultaneously hydrogen;

R^{YY} is hydrogen, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or -PO(R');

wherein, in ring (E):

each of m_4 and n_4 is independently 0-3, provided that $m_4 + n_4$ is 2-6;

p_4 is 1-2;

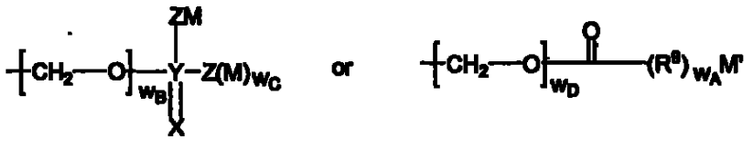
z_4 is 0-4;

R^{YZ} is C_1-C_6 aliphatic group, optionally substituted with w_4 independent occurrences of -R^{14}, wherein w_4 is 0-3;

x and y, each, is independently 0-4;

W is OR^{XY};

R^{XY} is hydrogen or a group selected from:



;

wherein:

each of w_A, w_B, w_C, and w_D is independently 0 or 1;

each M is independently selected from hydrogen, Li, Na, K, Mg, Ca, Ba, -$N(R^7)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or -R^6; wherein 1 to 4 –CH_2 radicals of the alkyl or alkenyl group, other than the –CH_2 that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, -OR^7, -R^7, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, -CO_2R^7, -C(O)-$N(R^7)_2$, $S(O)_2$-$N(R^7)_2$, $N(R^7)$-C(O)-R^7, $C(O)R^7$, -$S(O)_n$-R^7, OCF_3, -$S(O)_n$-R^6, $N(R^7)$-$S(O)_2(R^7)$, halo, -CF_3, or -NO_2;

n is 0-2;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or -R^6; wherein 1 to 4 –CH_2 radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, -OR^7, -R^7, -$N(R^7)_2$, $N(R^7)_3$, -R^7OH, -CN, -CO_2R^7, -C(O)-$N(R^7)_2$, -$S(O)_2$-$N(R^7)_2$, -$N(R^7)$-C(O)-R^7, -$C(O)R^7$, -$S(O)_n$-R^7, -OCF_3, -$S(O)_n$-R^6, -$N(R^7)$-$S(O)_2(R^7)$, halo, -CF_3, or -NO_2;

Z is -CH_2-, -O-, -S-, -$N(R^7)_2$-; or,

when M is absent, then Z is hydrogen, =O, or =S;

Y is P or S, wherein when Y is S, then Z is not S;

X is O or S;

each R^7 is independently selected from hydrogen, or C_1-C_4 aliphatic, optionally substituted with up to two Q_1;

each Q_1 is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatom or heteroatom group selected from O, N, NH, S, SO, or SO_2; wherein Q_1 is optionally substituted with up to three substituents selected from oxo, -OH, -O(C_1-C_4 aliphatic), -C_1-C_4 aliphatic, -NH_2, NH(C_1-C_4 aliphatic), -N(C_1-C_4 aliphatic)$_2$, -N(C_1-C_4 aliphatic)-C(O)- C_1-C_4 aliphatic, -(C_1-C_4 aliphatic)-OH, -CN, -CO_2H, -CO_2(C_1-C_4 aliphatic), -C(O)-NH_2, -C(O)-NH(C_1-C_4 aliphatic), -C(O)-N(C_1-C_4 aliphatic)$_2$, halo or -CF_3;

R^6 is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)$_n$ or N(R^7); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C_1-C_4 alkyl, O-C_1-C_4 alkyl or O-C(O)-C_1-C_4 alkyl;

R^9 is C(R^7)$_2$, O or N(R^7);

each occurrence of R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4, and R^5 is independently Q-R^X; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by -NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO_2-, -SO_2NR-, -NRSO_2-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO_2NR-, -SO-, -SO_2-, -PO-, -PO_2-, -OP(O)(OR)-, or -POR-; and each occurrence of R^X is independently selected from -R', halogen, =O, =NR', -NO_2, -CN, -OR', -SR', -N(R')$_2$, -NR'COR', -NR'CON(R')$_2$, -NR'CO_2R', -COR', -CO_2R', -OCOR', -CON(R')$_2$, -OCON(R')$_2$, -SOR', -SO_2R', -SO_2N(R')$_2$, -NR'SO_2R', -NR'SO_2N(R')$_2$, -COCOR', -$COCH_2$COR', -OP(O)(OR')$_2$, -P(O)(OR')$_2$, -OP(O)$_2$OR', -P(O)$_2$OR', -PO(R')$_2$, or -OPO(R')$_2$; and

each occurrence of R is independently hydrogen or C_{1-6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s)

to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00160] In compounds of formula I-F, exemplary embodiments of n_1, m_1, n_2, m_2, n_3, m_3, n_4, m_4, x, y, z_1, z_2, z_3, z_4, q_2, p_3, p_4, R^{XY}, R^{XX}, R^{YY}, R^{YZ}, R^3, R^4, R^5, R^{11}, R^{12}, R^{13}, R^{14}, R, Sp^1, Sp^2, ring B^1, ring B^2, etc., are as defined above for compounds of formula I-A through formula I-E.

[00161] In one embodiment, the present invention provides compounds shown below in Table 2.

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Table 2

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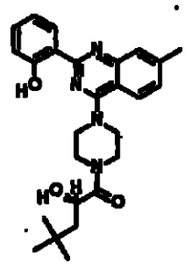	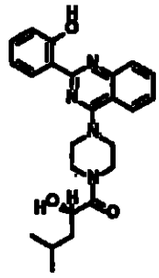	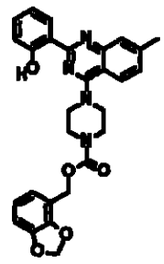
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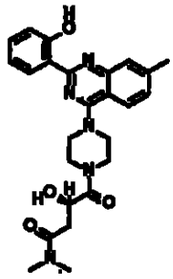	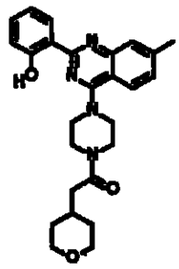	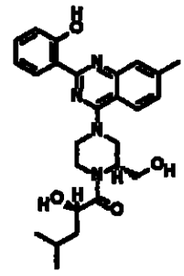
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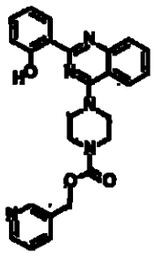	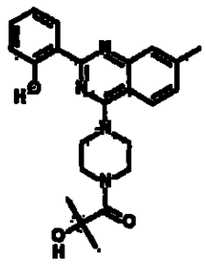	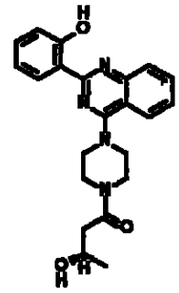
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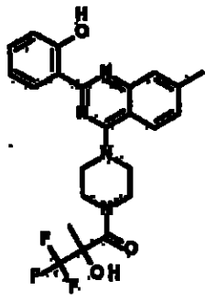	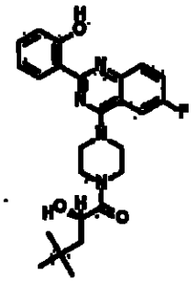	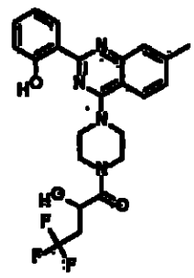

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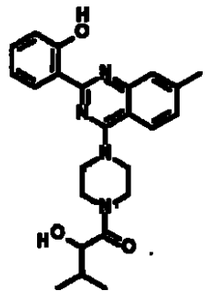	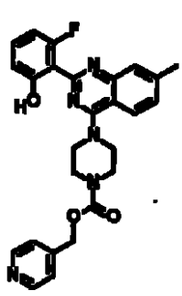	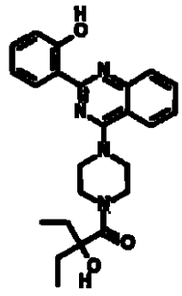
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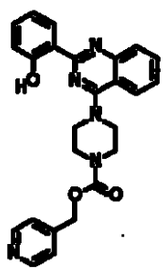	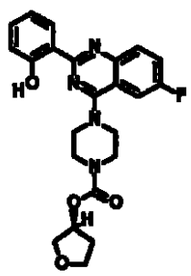	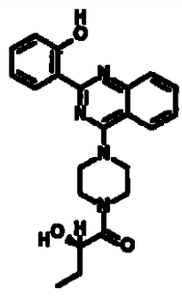
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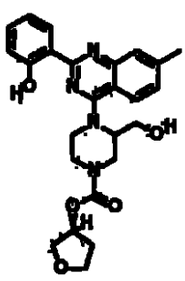	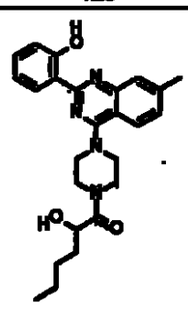	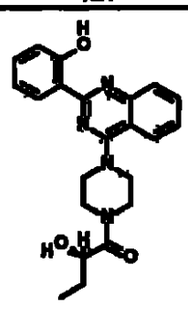
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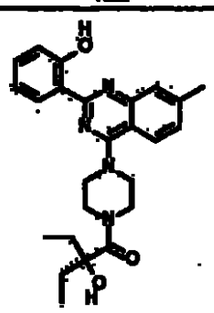	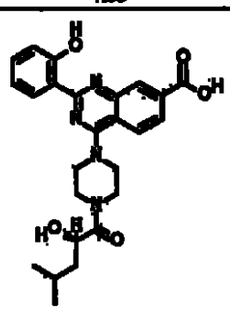	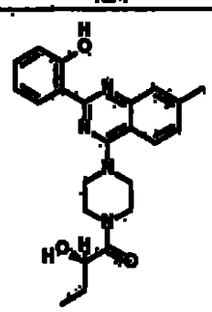

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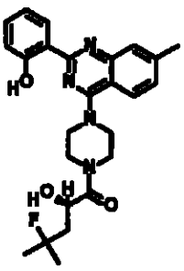	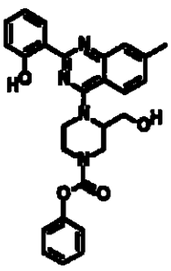	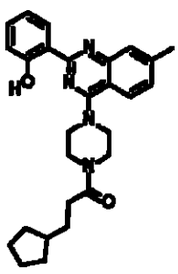
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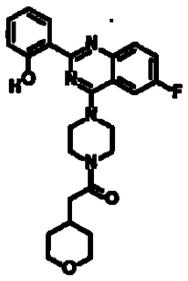	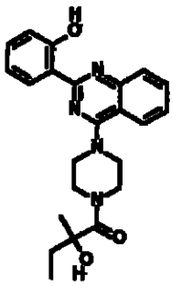	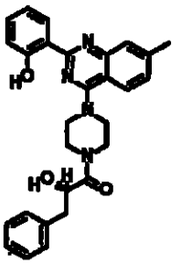
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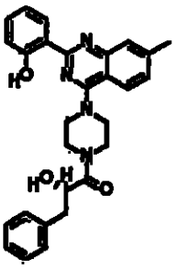	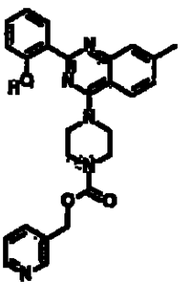	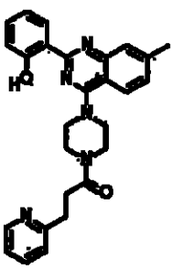
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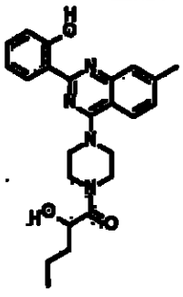	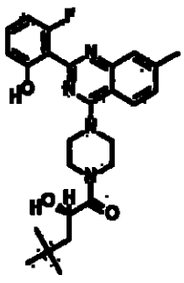	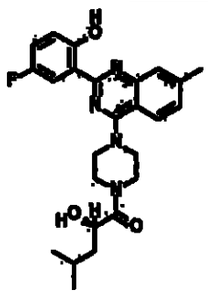

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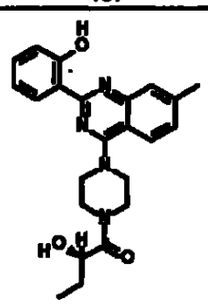	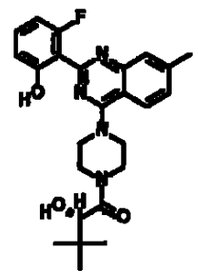	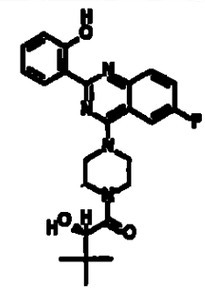
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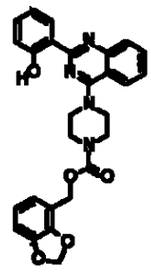	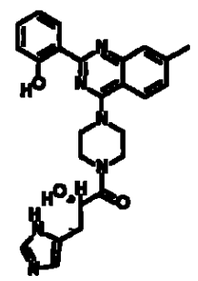	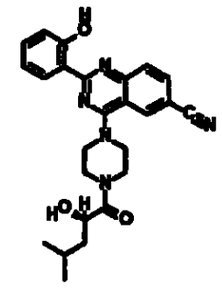
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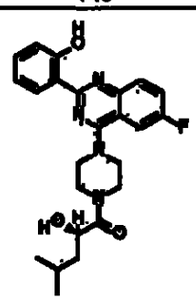	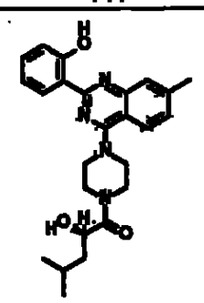	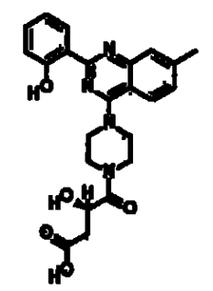
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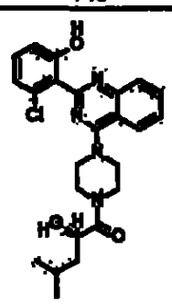	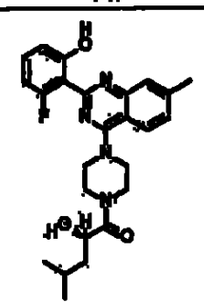	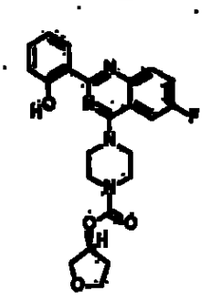

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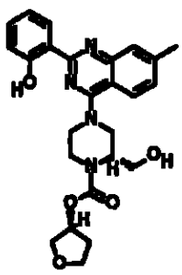	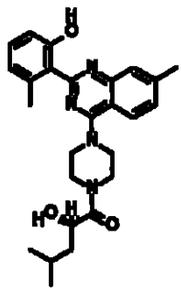	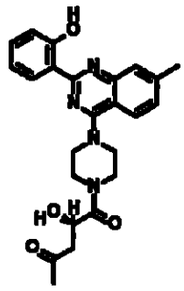
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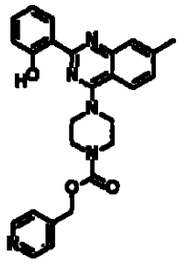	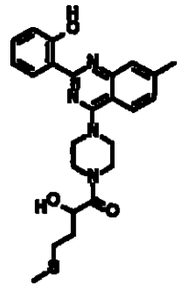	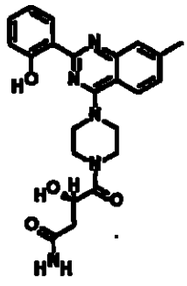
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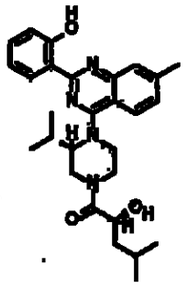	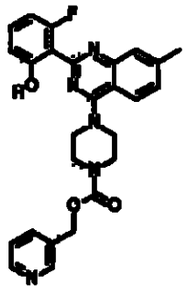	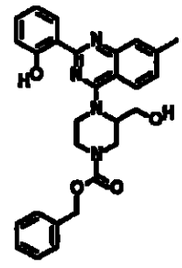
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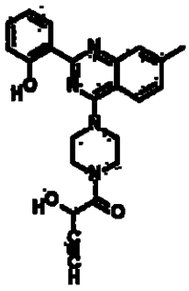	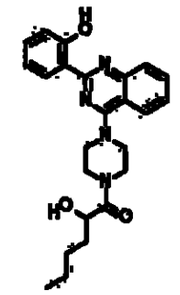	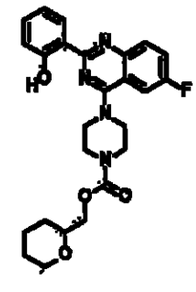

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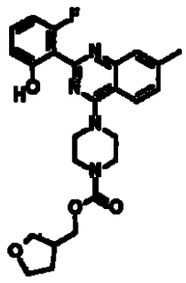	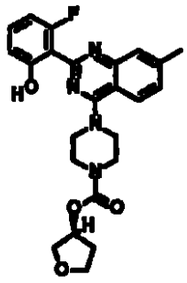	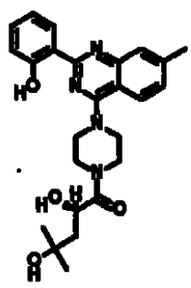
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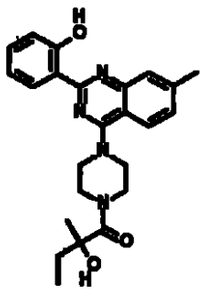	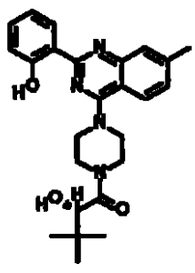	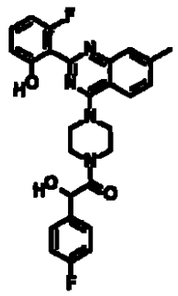
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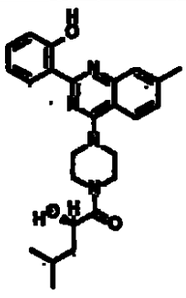	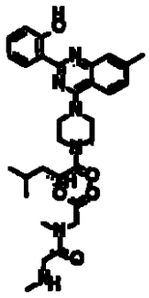	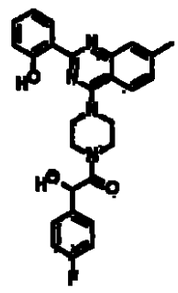
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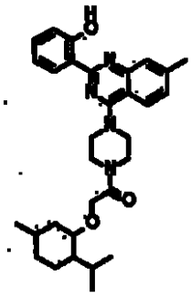	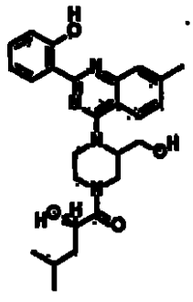	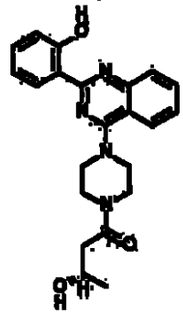

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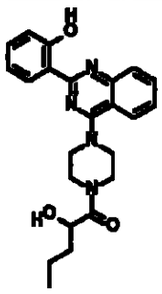	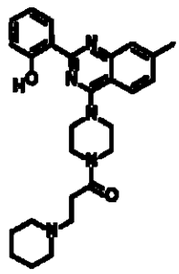	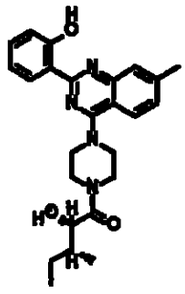
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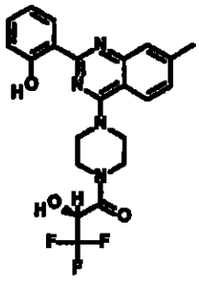	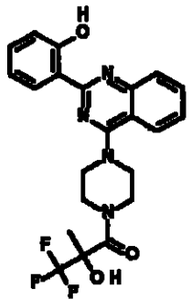	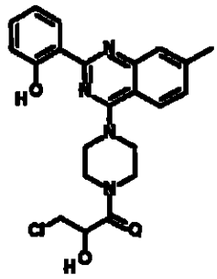
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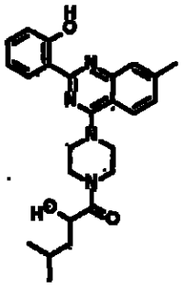	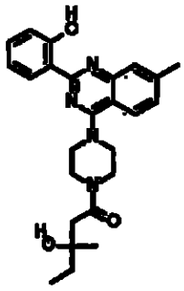	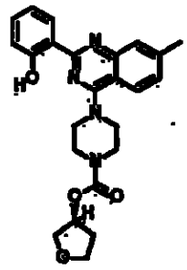
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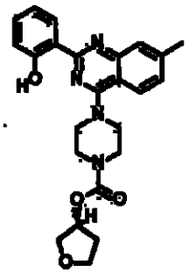	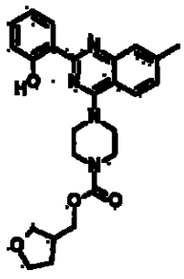	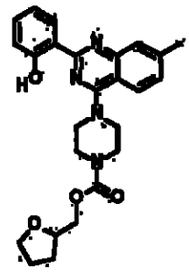

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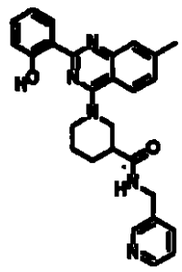	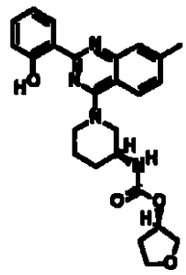	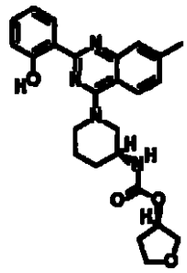
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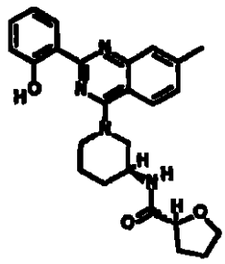	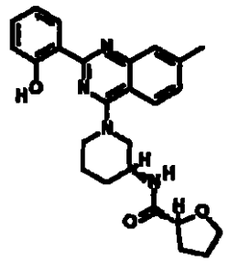	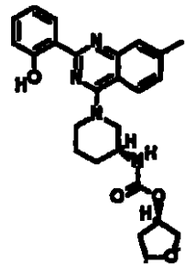
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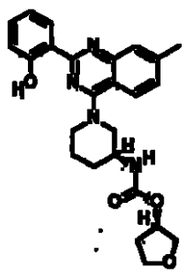	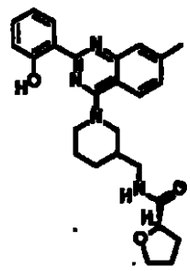	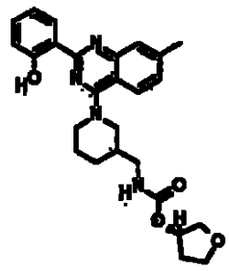
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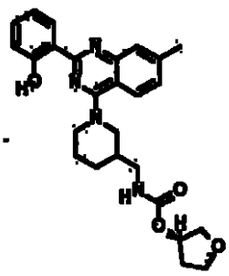	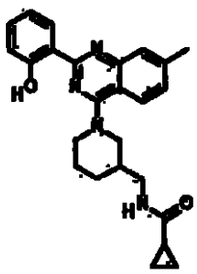	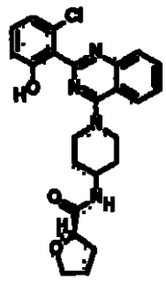

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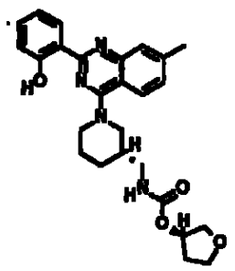
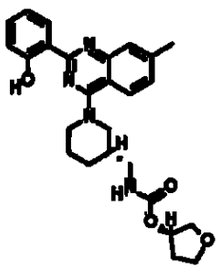
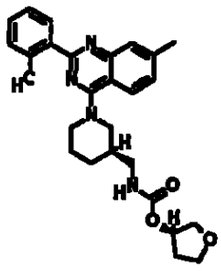
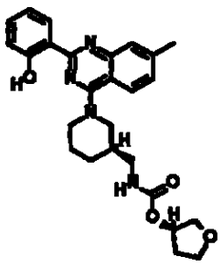
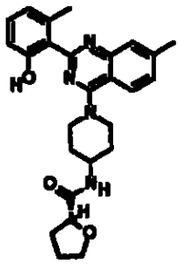
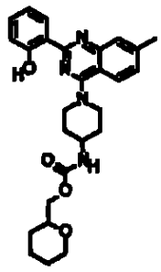
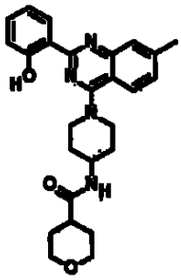
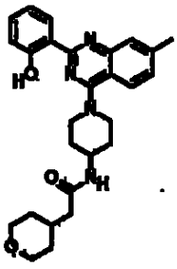
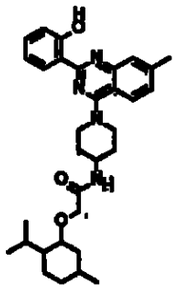
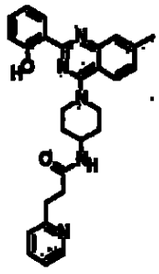
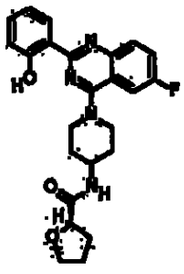
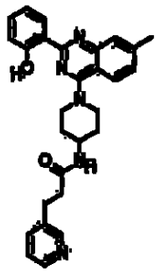
214 	215 	216 
217 	218 	219 
220 	221 	222 
223 	224 	225 

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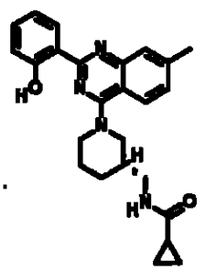	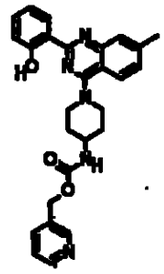	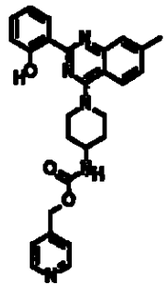
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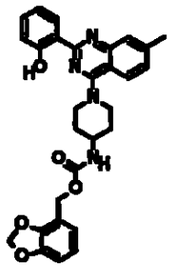	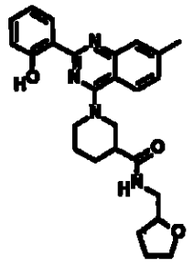	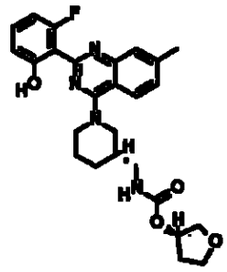
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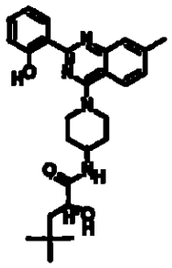	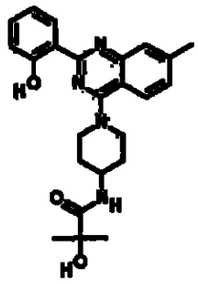	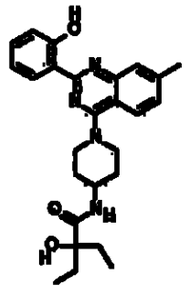
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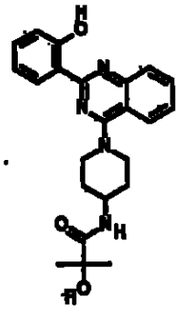	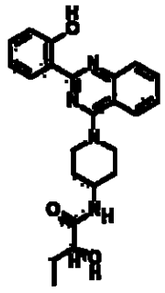	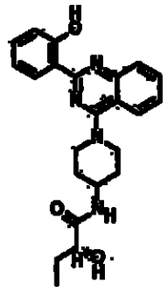

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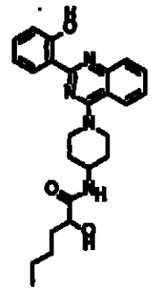	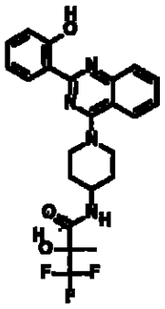	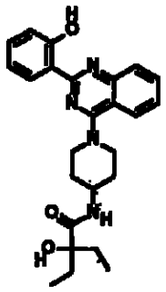
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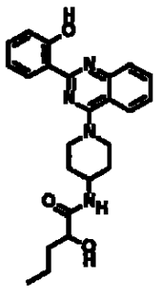	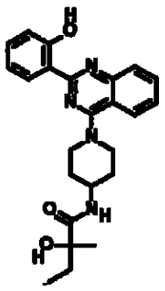	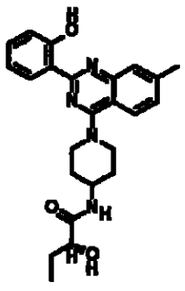
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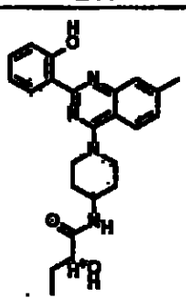	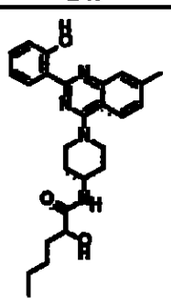	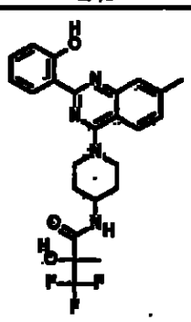
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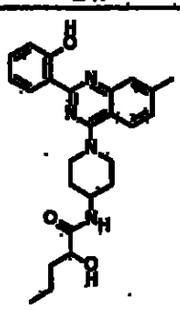	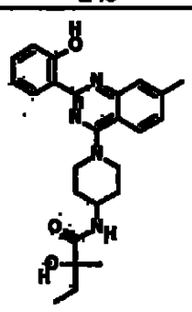	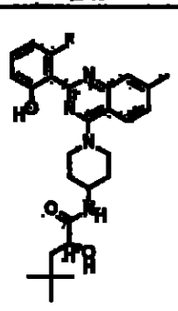

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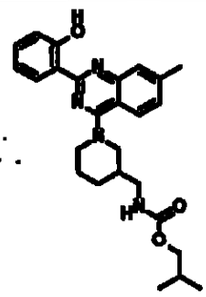	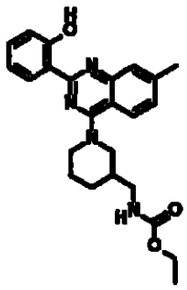	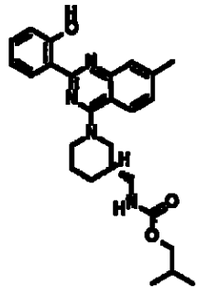
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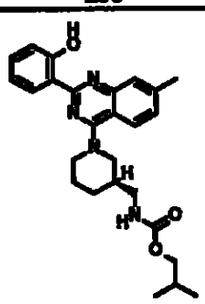	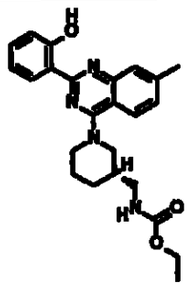	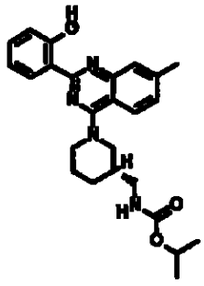
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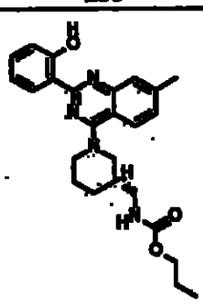	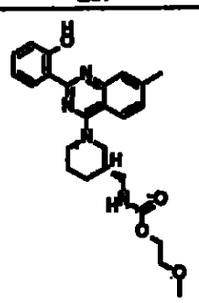	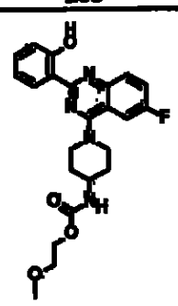
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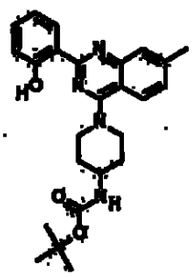	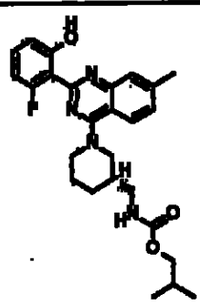	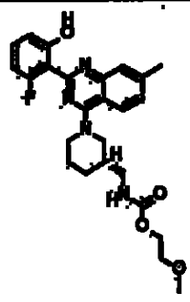

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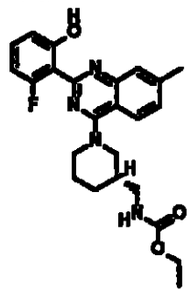	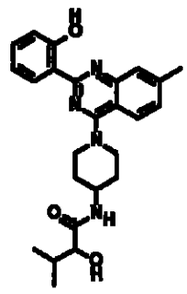	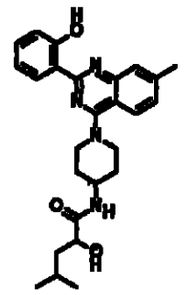
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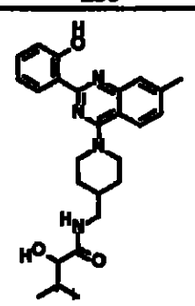	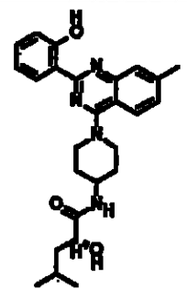	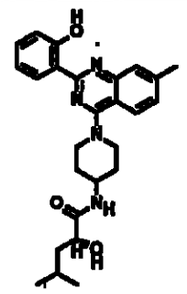
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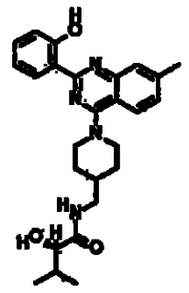	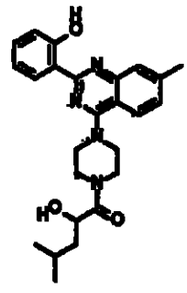	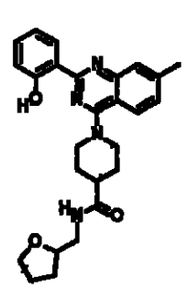
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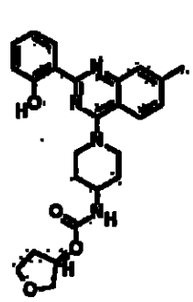	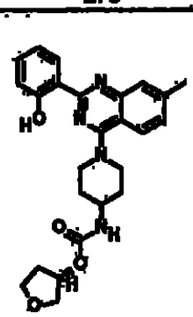	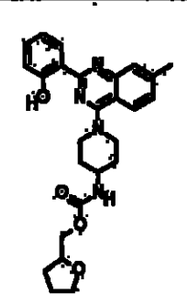

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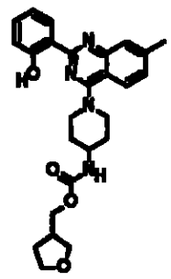	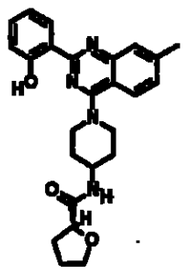	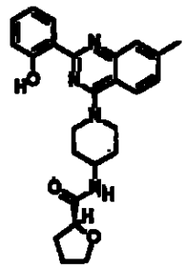
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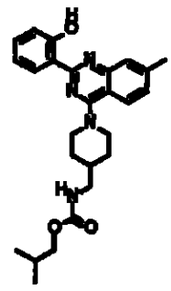	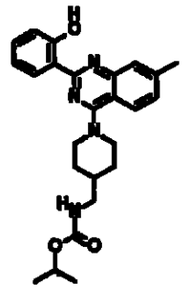	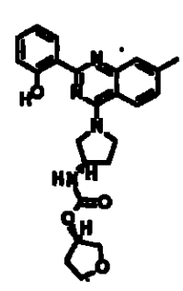
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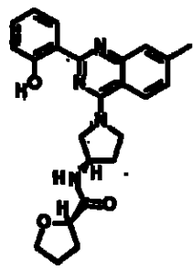	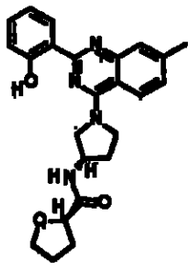	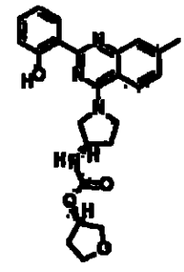
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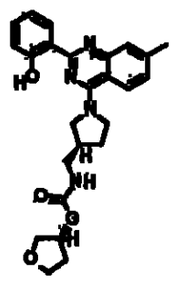	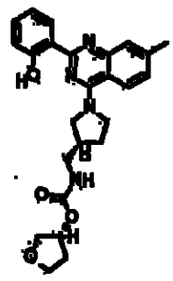	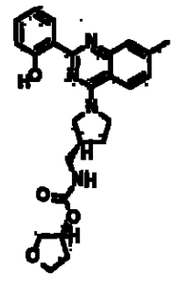

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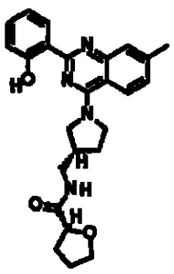	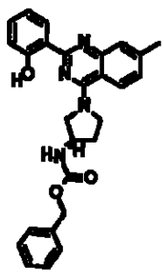	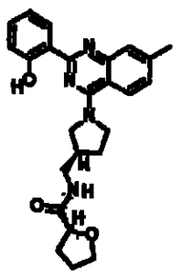
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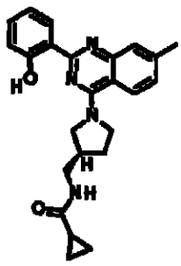	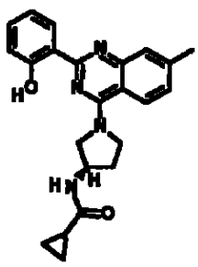	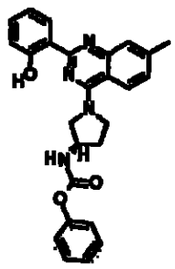
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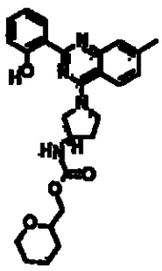	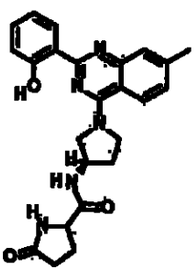	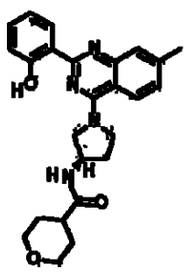
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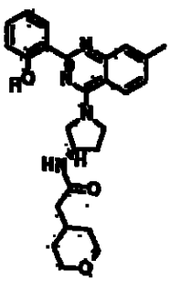	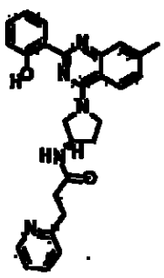	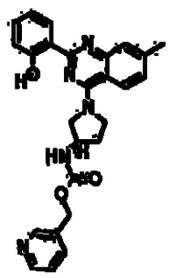

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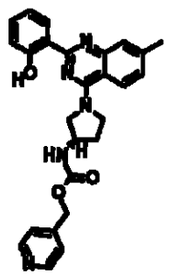	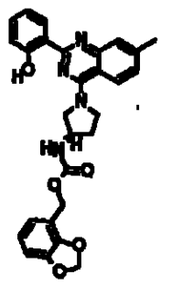	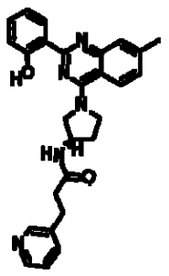
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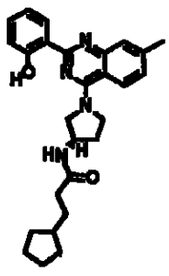	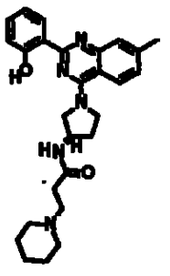	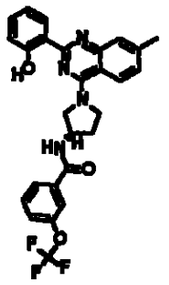
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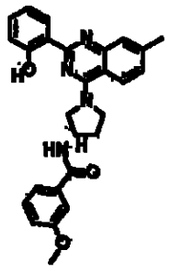	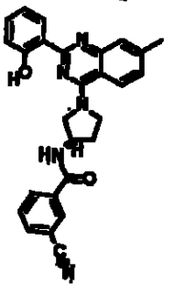	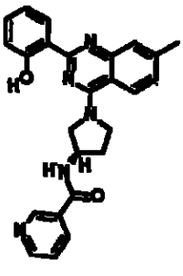
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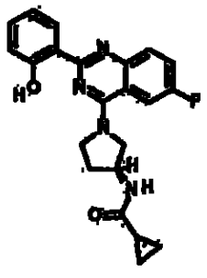
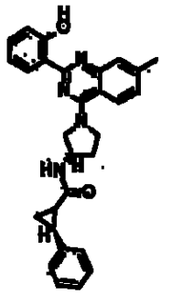
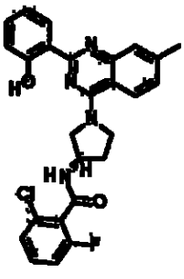
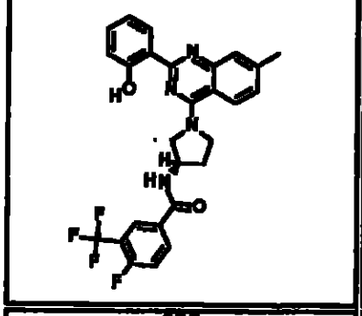
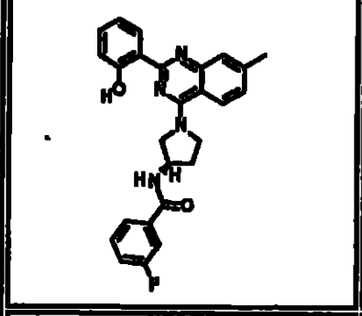
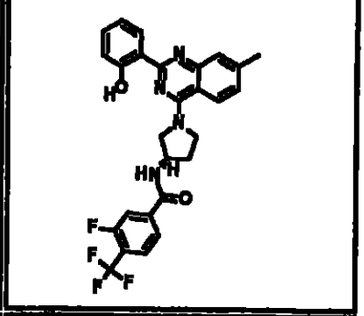
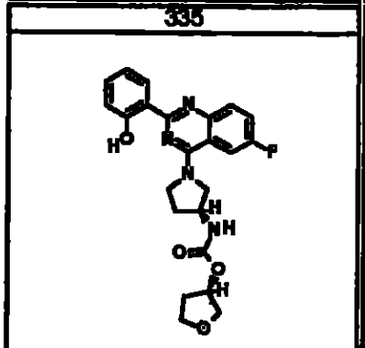
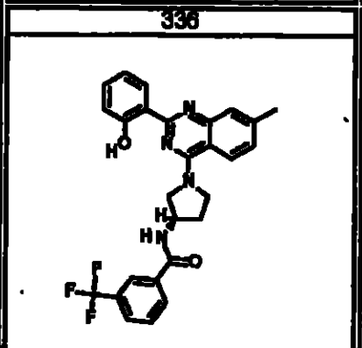
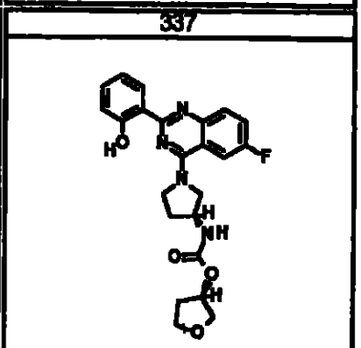
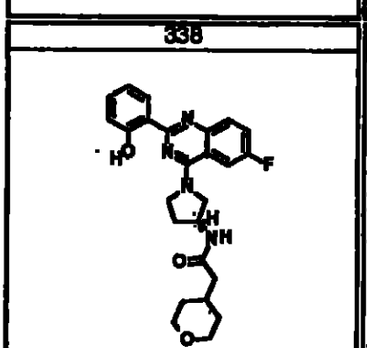
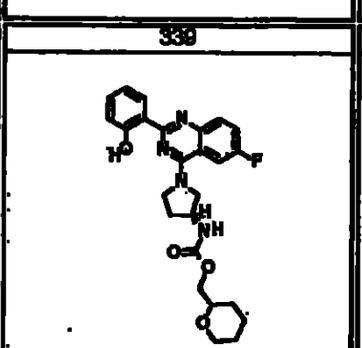
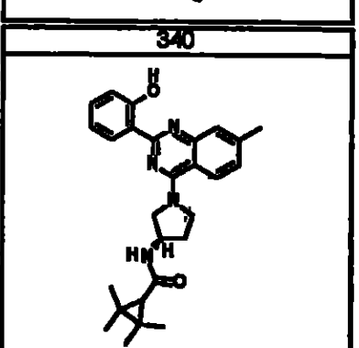
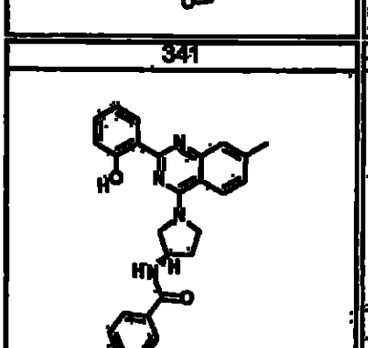
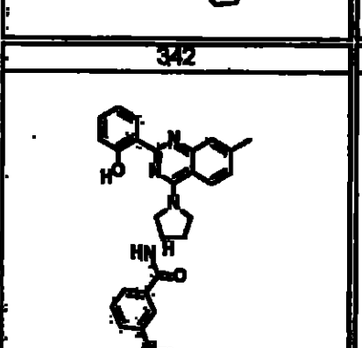
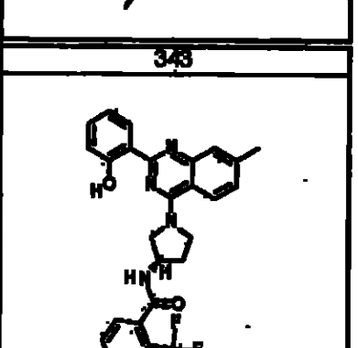
		

332 	333 	334 
335 	336 	337 
338 	339 	340 
341 	342 	343 

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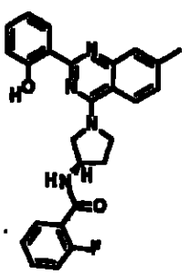	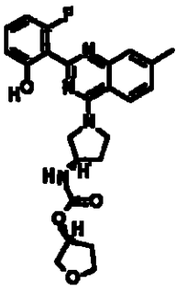	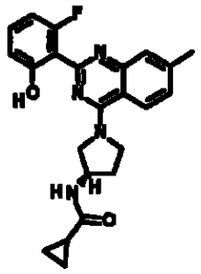
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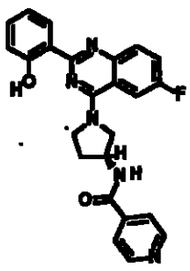	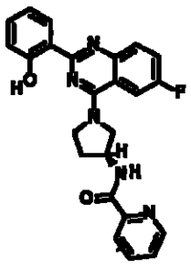	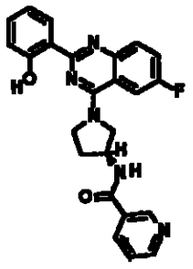
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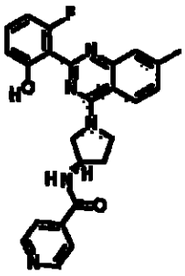	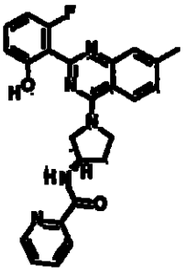	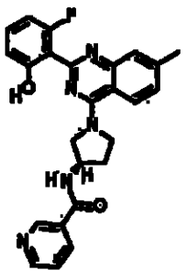
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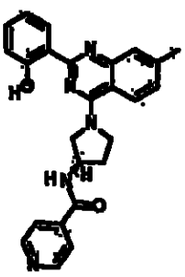	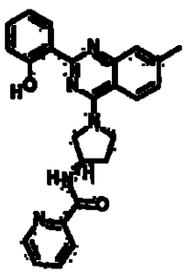	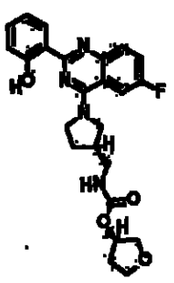

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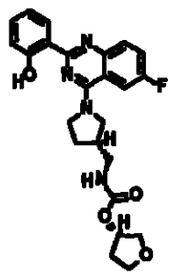	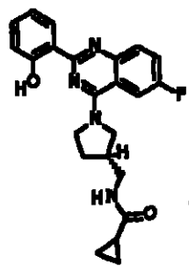	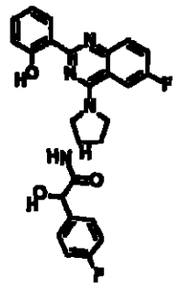
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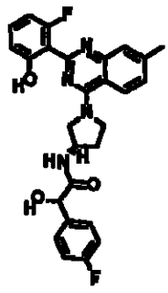	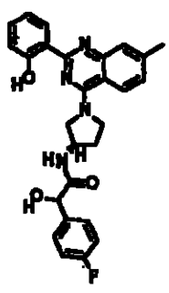	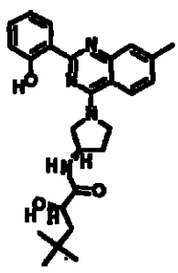
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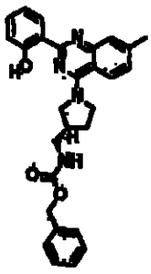	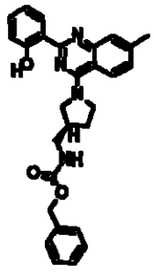	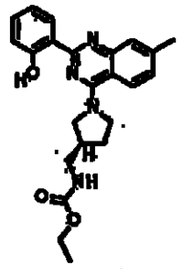
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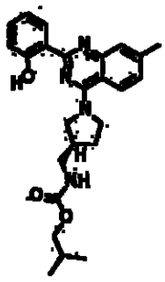	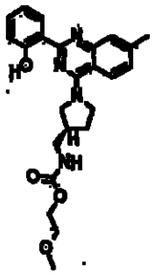	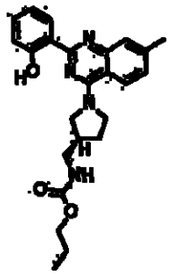

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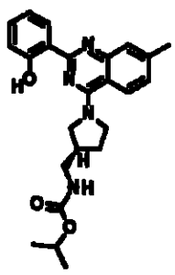	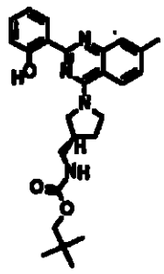	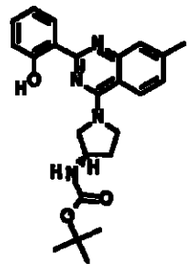
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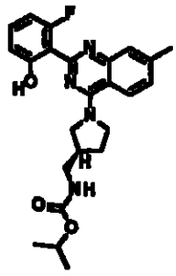	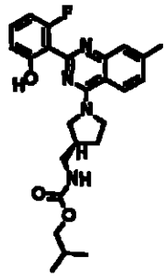	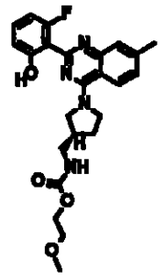
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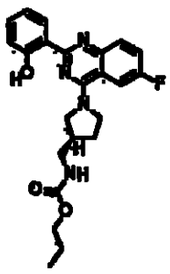	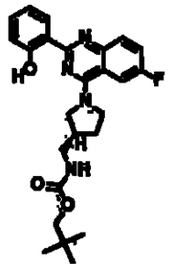	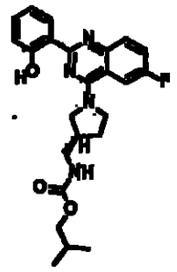
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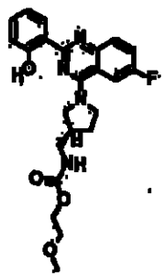	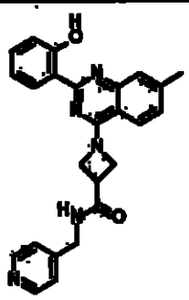	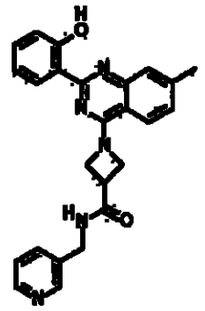

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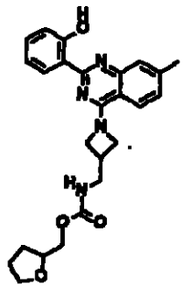	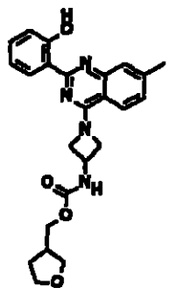	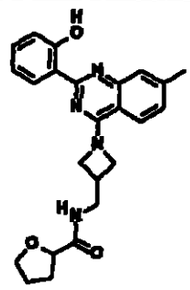
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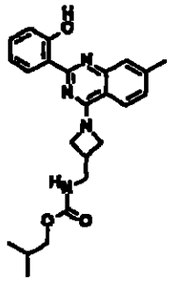	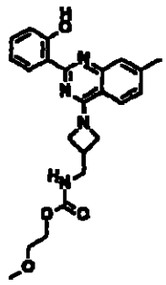	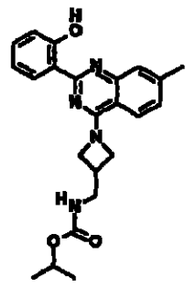

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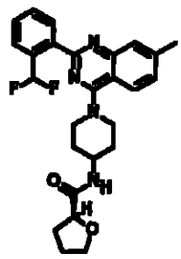	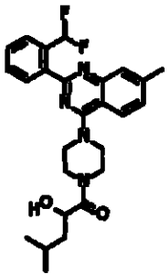	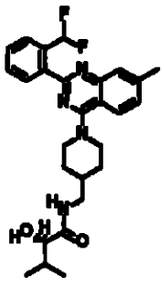
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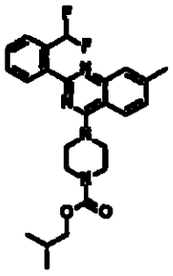	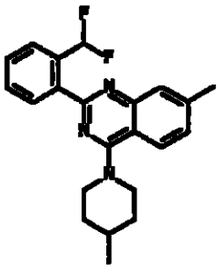	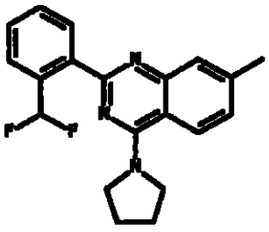
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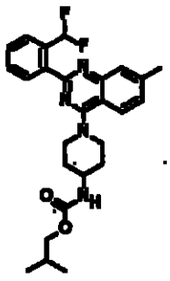
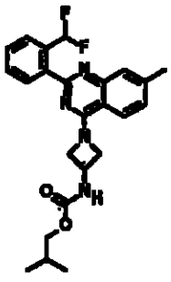
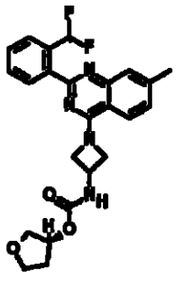
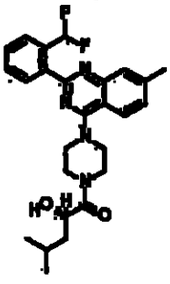
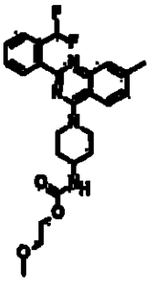
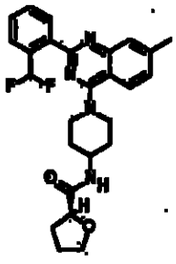
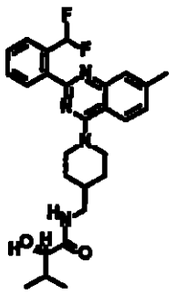
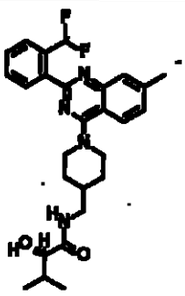
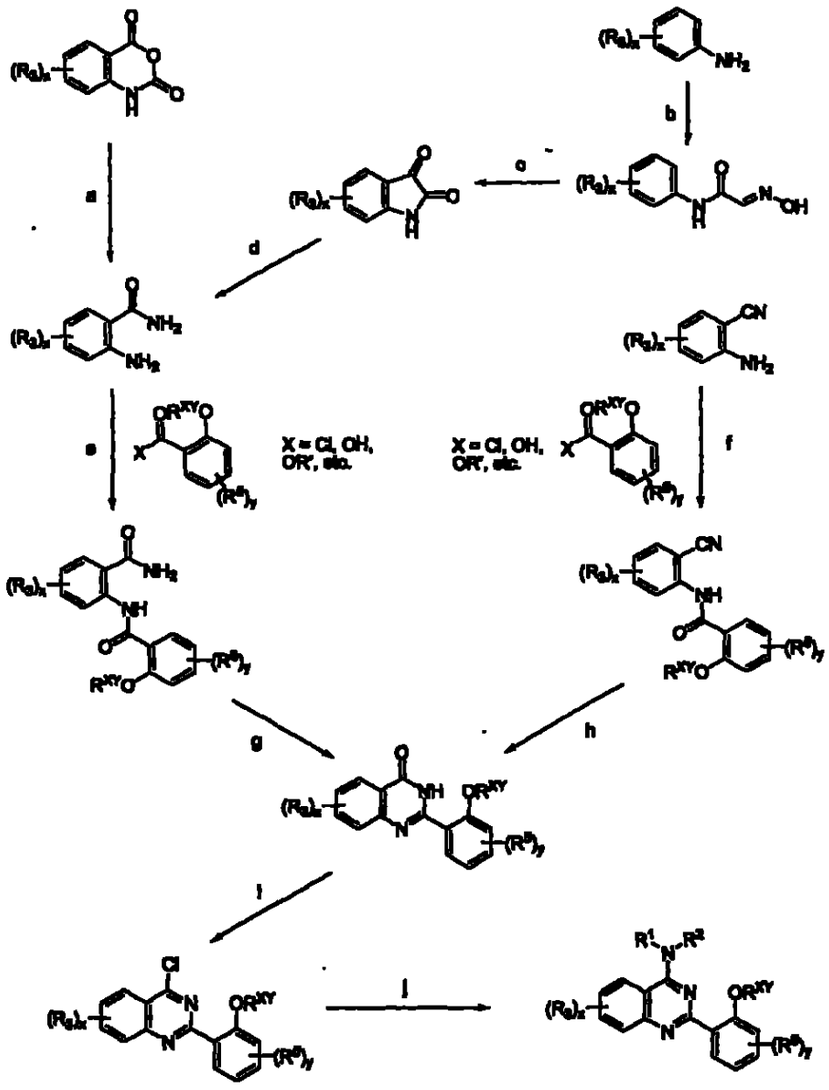
		
510	**511**	**512**
		

513	514
	

[00162] *4. General Synthetic Methodology:*

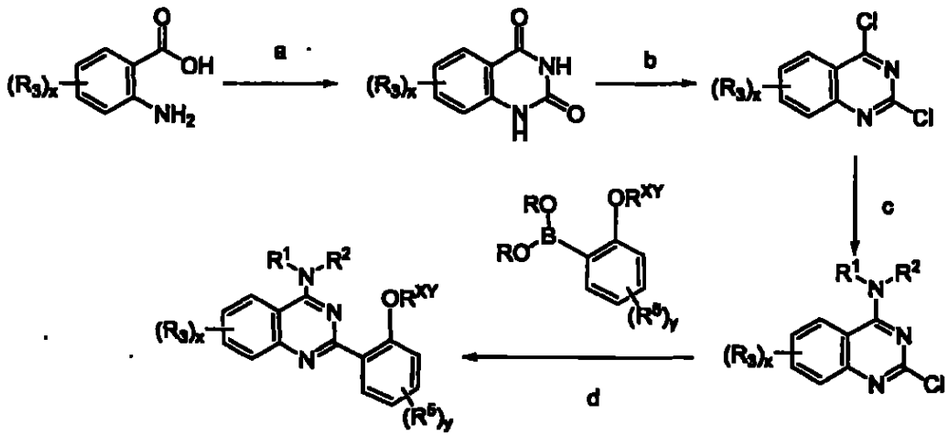
[00163] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general schemes below, and the preparative examples that follow.

[00164] Scheme A: General Preparations via 4-Chloroquinazolines



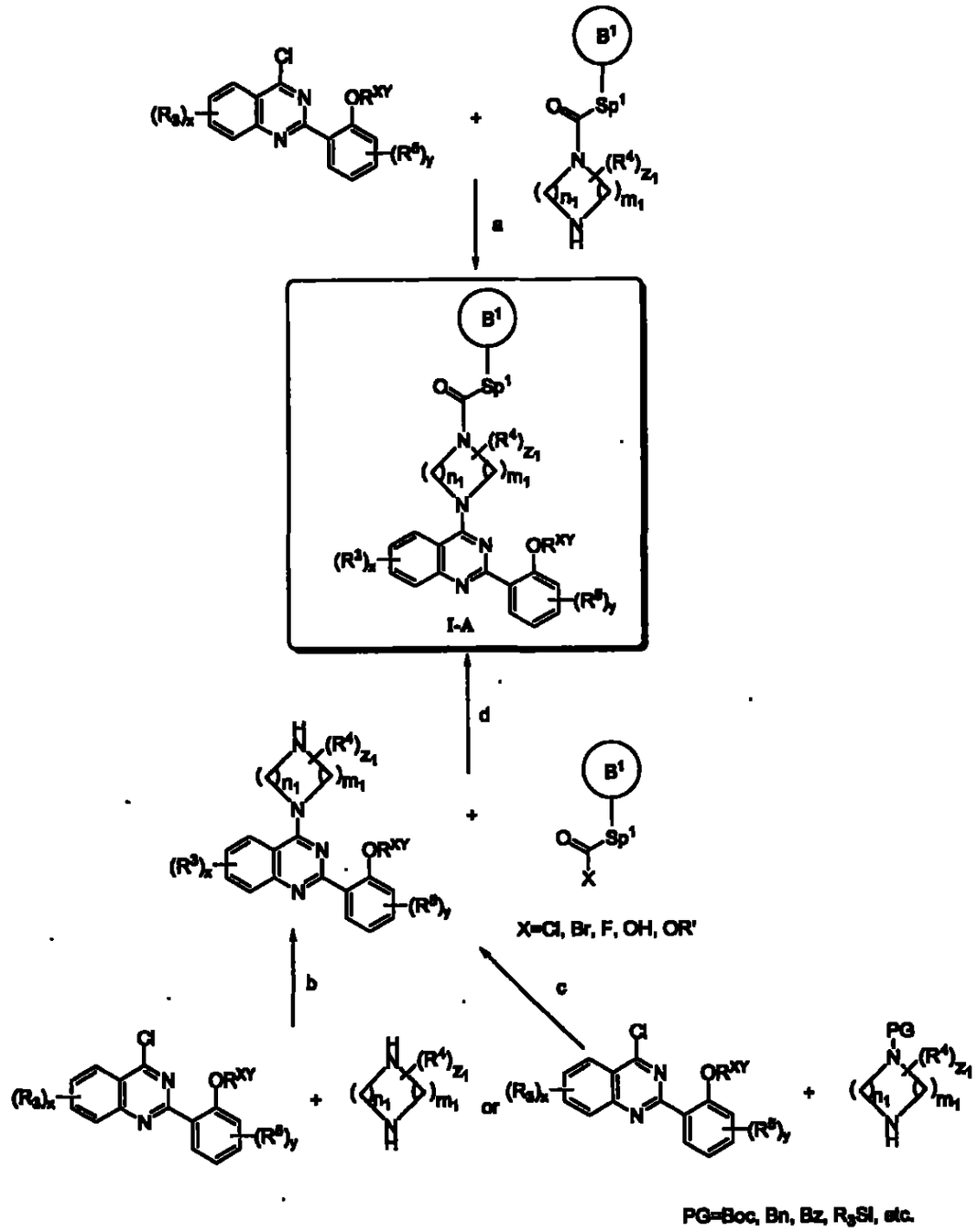
[00165] Conditions: a) aq. NH_4OH; b) chloral hydrate, HCl, Na_2SO_4, $HONH_2$*HCl c) H_2SO_4; d) acetic acid, H_2SO_4, aq. H_2O_2; e) Et_3N, THF; f) Et_3N, DMAP, CH_2Cl_2; g) aq. NaOH; h) aq. NaOH, aq. H_2O_2 i) $POCl_3$, N,N-dimethylaniline, benzene; j) R^1R^2NH, Et_3N, CH_2Cl_2

[00166] Scheme B: General Preparations via 2,4-Dichloroquinazolines



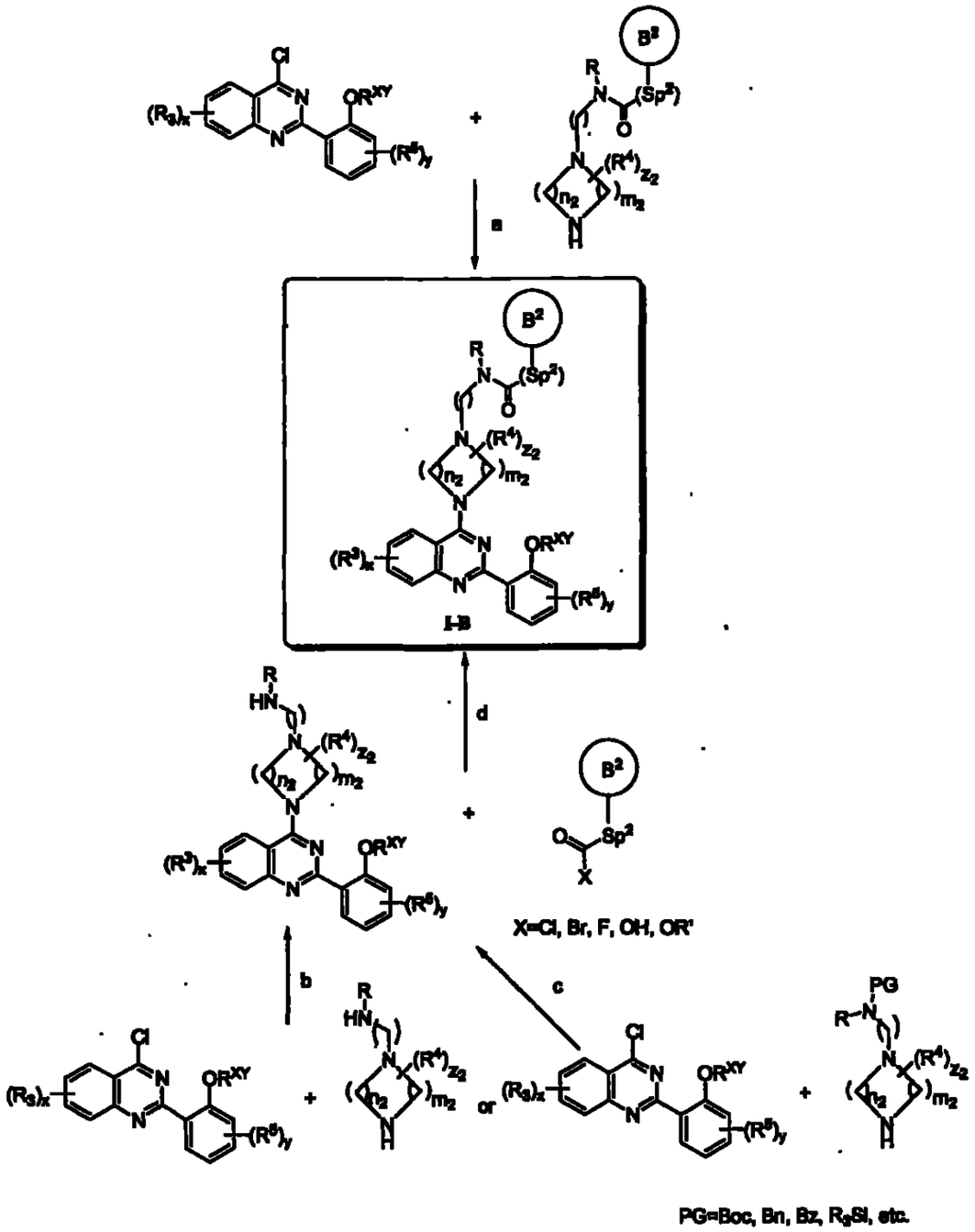
[00167] Conditions: a) AcOH, KOCN; b) $POCl_3$; c) Et_3N, DCM, R^1R^2NH; d) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, H_2O

[00168] Scheme I-A for formula I-A:


a
I-A
d
X=Cl, Br, F, OH, OR'
b
c
or
PG=Boc, Bn, Bz, R3Si, etc.

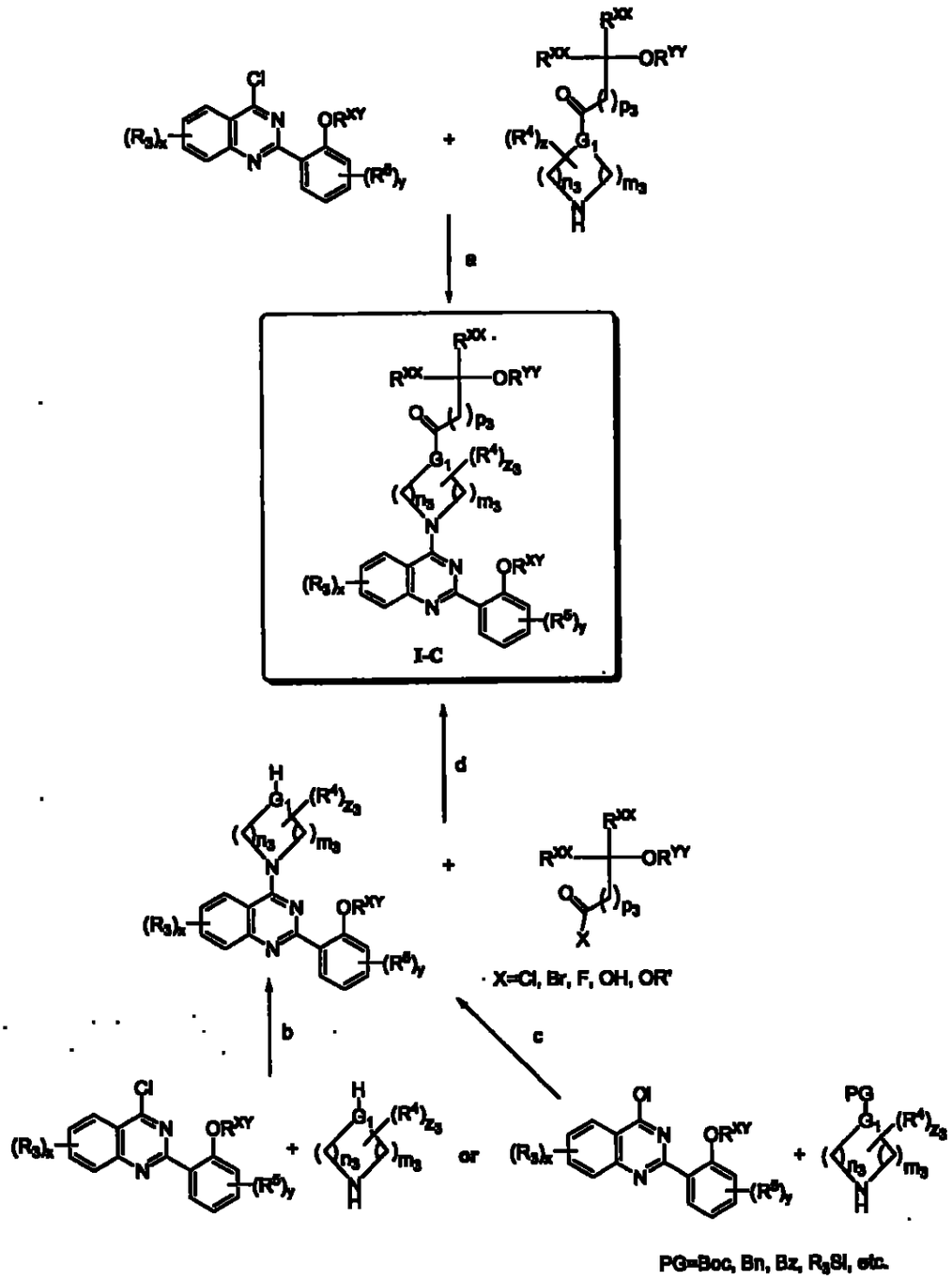
[00169] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For acid halides, DCM or THF, triethylamine; for carboxylic acids, EDC, HOBt, triethylamine, DMF; for X=OR', THF or DMF, heat.

[00170] Scheme I-B for compounds of formula I-B:



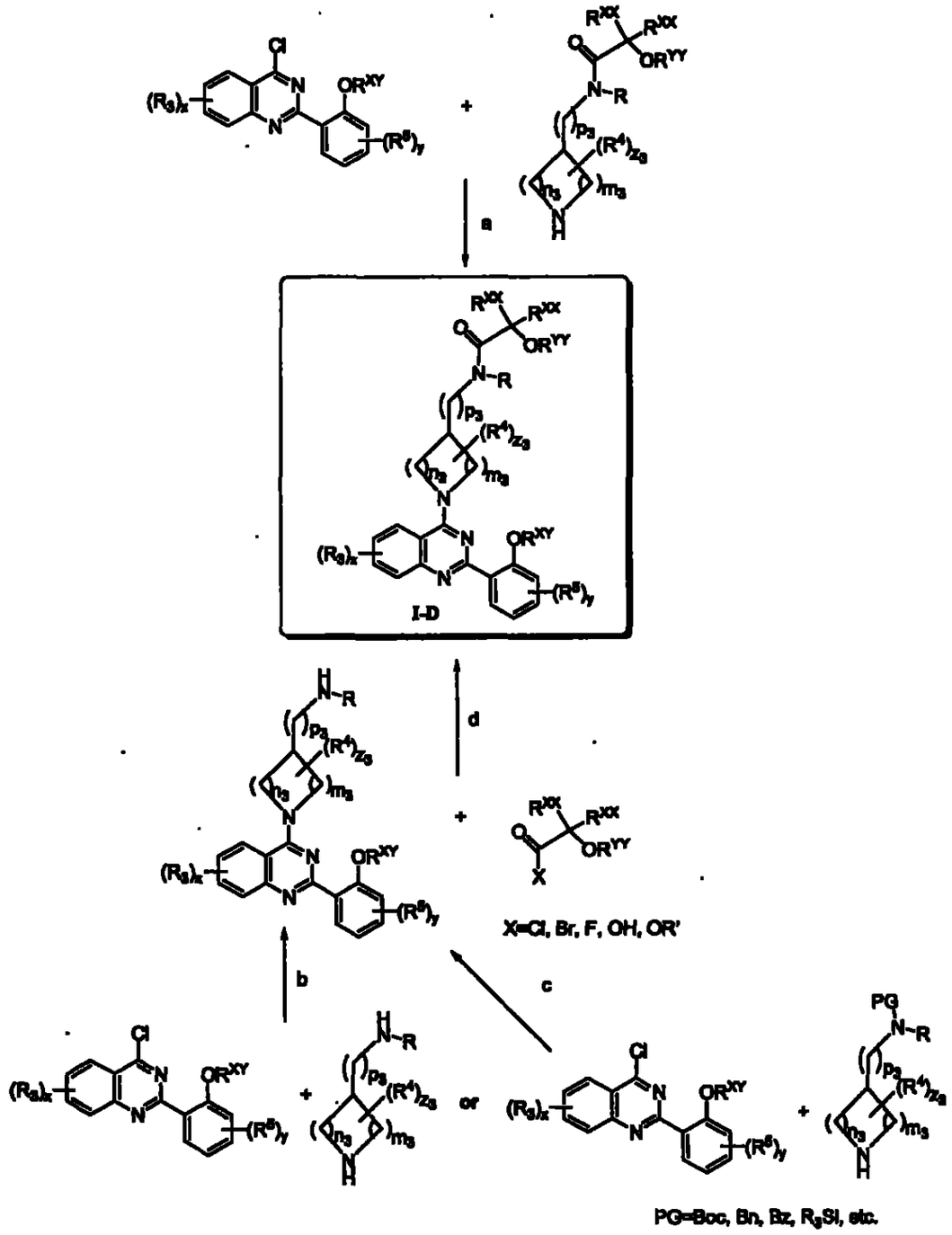
[00171] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For acid halides, DCM or THF, triethylamine; for carboxylic acids, EDC, HOBt, triethylamine, DMF; for X=OR', THF or DMF, heat.

[00172] Scheme I-C for formula I-C:



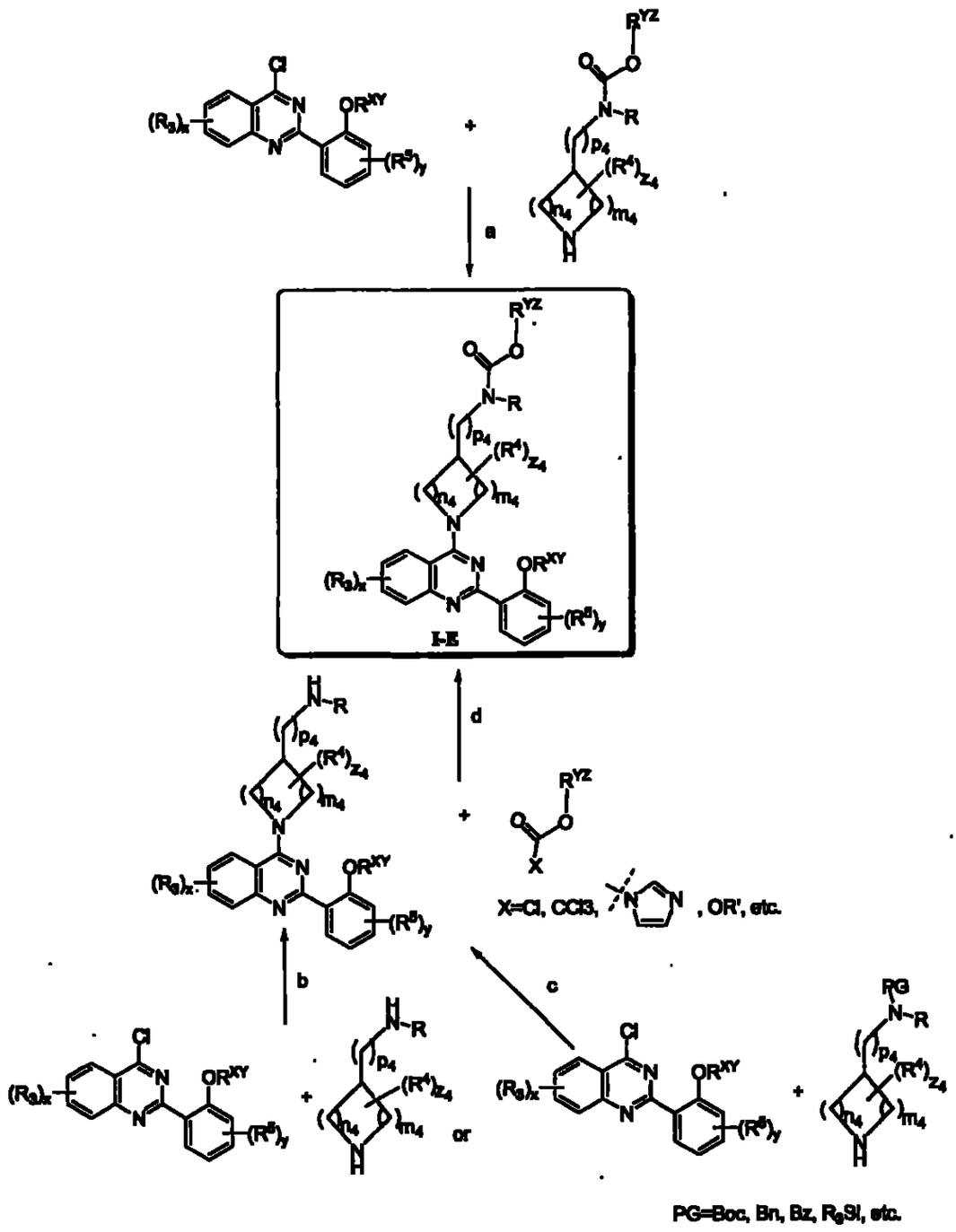
[00173] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NsOH for Bz, TBAF for R3Si, etc.; d) For acid halides, DCM or THF, triethylamine; for carboxylic acids, EDC, HOBt, triethylamine, DMF; for X=OR', THF or DMF, heat.

[00174] Scheme I-D for formula I-D:



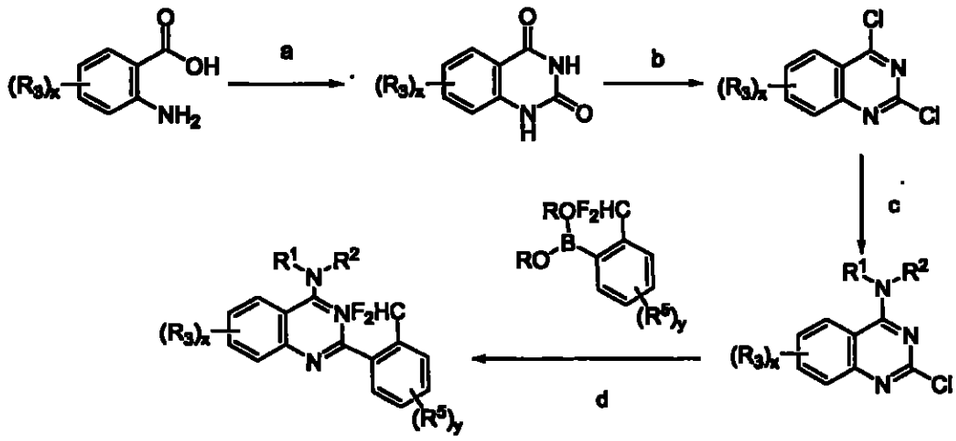
[00175] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For acid halides, DCM or THF, triethylamine; for carboxylic acids, EDC, HOBt, triethylamine, DMF; for X=OR', THF or DMF, heat.

[00176] Scheme I-E for formula I-E:



[00177] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For X=Cl, CCl_3, imidazolyl, OR', etc., DCM or THF, triethylamine, rt or heat.

[00178] Scheme I-F for preparing compounds of formula I-F:



[00179] Conditions: a) AcOH, KOCN; b) $POCl_3$; c) Et_3N, DCM, R^1R^2NH; d) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, H_2O.

[00180] *5. Uses, Formulation and Administration*

[00181] WO 2004/078733 discloses a genus of sodium channel blockers that encompasses the compounds of the present invention. However, the compounds of the present invention exhibit unexpected properties set forth below that render them therapeutically more useful.

[00182] In one embodiment, certain compounds of the present invention are useful as improved inhibitors of sodium channels.

[00183] In another embodiment, certain compounds of the present invention possess improved selectivity in inhibiting one sodium channel, e.g., NaV 1.8, over one or more of the other sodium channels. Particularly useful are compounds that have a desirably low activity against NaV 1.2 or NaV 1.5.

[00184] In another embodiment, certain compounds of the present invention are improved inhibitors of NaV 1.8.

[00185] In another embodiment, certain compounds of the present invention have improved aqueous solubility, e.g., at physiologically relevant pH.

[00186] In yet another embodiment, certain compounds of the present invention have improved pharmacokinetic and/or pharmacodynamic properties and, therefore, are better suited for *in-vivo* administration for therapeutic purposes. Such properties include oral bioavailability, clearance kinetics, efficacy, etc.

[00187] In another embodiment, certain compounds of the present invention have desirably low activity against the hERG channel.

[00188] In another embodiment, certain compounds of the present invention have desirably low activity against the key isoforms of the cytochrome P450 enzyme family, including isozymes CYP3A4, CYP2C9, CYP1A2, CYP2C19, or CYP2D6.

[00189] In another embodiment, certain compounds of the present invention have desirably low activity against the CaV 1.2 channel and/or Kv 1.5.

[00190] Thus, in one embodiment of the present invention, the compounds have one or more of the following unexpected and therapeutically beneficial features: potent inhibition of NaV 1.8 channel, selectivity for one sodium channel, e.g., NaV 1.8 over one or more of the other sodium channels, improved aqueous solubility, improved pharmacokinetic and/or pharmacodynamic properties, desirably low activity against the hERG channel, desirably low activity against the key isoforms of the cytochrome P450 enzyme family, or desirably low activity against L-type CaV 1.2 and/or Kv1.5. The presence of such features, individually or in combination, renders the compounds more suitable for administration to humans to treat various diseases as set forth below.

[00191] The phrase "desirably low activity" as used herein means a level of activity of a compound against a target/enzyme that is low enough such that said activity would be considered advantageous (e.g., mitigating a risk factor), when evaluating the suitability of said compound for administration in humans.

[00192] The present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias,

epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, and incontinence. Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00193] According to one embodiment, the compounds of the present invention are useful for treating a disease selected from femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, including, abdominal; pancreatic; IBS pain; chronic headache pain; migraine; tension headache, including, cluster headaches; chronic neuropathic pain, including, post-herpetic neuralgia; diabetic neuropathy; HIV- associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phanton pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac Pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, including, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain, including, sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); and prostatitis.

[00194] In another embodiment, the compounds of the present invention are useful in treating lower urinary tract disorders. See, e.g., International Patent Publication No. WO 2004/066990, the contents of which are incorporated herein by reference.

[00195] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00196] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of the targeted channel.

[00197] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, *66*, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate,

heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00198] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates,

waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00199] *Uses of Compounds and Pharmaceutically Acceptable Compositions*

[00200] In yet another aspect, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In certain other embodiments, a method for the treatment or lessening the severity of radicular pain, sciatica, back pain, head pain, or neck pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In still other embodiments, a method for the treatment or lessening the severity of severe or intractable pain, acute pain, postsurgical pain, back pain, or cancer pain is provided comprising administering an

effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof.

[00201] In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain.

[00202] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the

specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00203] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00204] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00205] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For

this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00206] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00207] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00208] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00209] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar–agar, calcium carbonate, potato or tapioca starch, alginic acid, certain

silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00210] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00211] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00212] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants

or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00213] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated". For example, exemplary additional therapeutic agents include, but are not limited to: nonopioid analgesics (indoles such as Etodolac, Indomethacin, Sulindac, Tolmetin; naphthylalkanones such as Nabumetone; oxicams such as Piroxicam; para-aminophenol derivatives, such as Acetaminophen; propionic acids such as Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Naproxen sodium, Oxaprozin; salicylates such as Asprin, Choline magnesium trisalicylate, Diflunisal; fenamates such as meclofenamic acid, Mefenamic acid; and pyrazoles such as Phenylbutazone); or opioid (narcotic) agonists (such as Codeine, Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Propoxyphene, Buprenorphine, Butorphanol, Dezocine, Nalbuphine, and Pentazocine). Additionally, nondrug analgesic approaches may be utilized in conjunction with administration

of one or more compounds of the invention. For example, anesthesiologic (intraspinal infusion, neural blocade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Seventeenth Edition, Ed. Mark H. Beers and Robert Berkow, Merck Research Laboratories, 1999, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[00214] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00215] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

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[00216] Another aspect of the invention relates to inhibiting NaV1.8 activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of the present invention or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00217] Inhibition of NaV1.8 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium ion channels in biological and pathological phenomena; and the comparative evaluation of new sodium ion channel inhibitors.

[00218] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

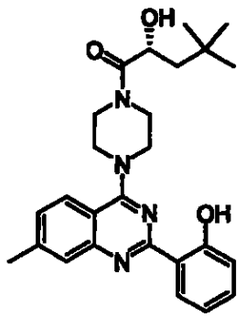
[00219] General LC/MS Methods

[00220] LC/MS data were acquired using a PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 10-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.

[00221] Example 101

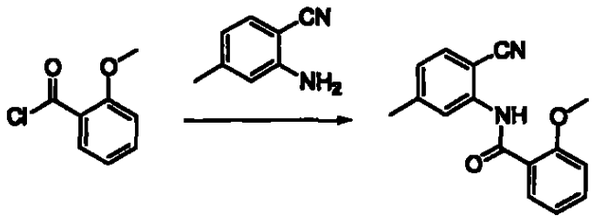
[00222] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one**

[00223]



[00224] *N*-(2-Cyano-5-methyl-phenyl)-2-methoxy-benzamide

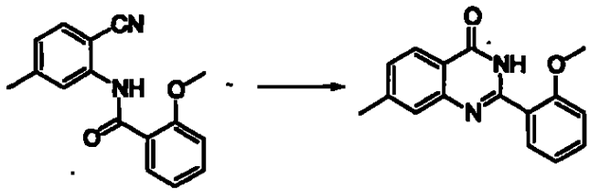
[00225]



[00226] To a stirred solution of 4-methyl-2-aminobenzonitrile (100 g, 0.75 mol) in 800 mL CH_2Cl_2 was added triethylamine (77.4 g, 0.76 mol) and dimethylaminopyridine (4.62 g, 0.037 mol). The solution was cooled to 0–5 °C, and *o*-anisoyl chloride (129 g, 0.75 mol) was added over 1 h while maintaining the reaction temperature at 0–5 °C. The reaction was then stirred at 30–40 °C for 3 h. Water (400 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (600 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to yield a solid residue, to which 800 mL hexane were added. The slurry was stirred and filtered to give *N*-(2-cyano-5-methyl-phenyl)-2-methoxy-benzamide as a yellow powder (180 g, 90%). mp 147–149 °C. ^{1}H NMR ($CDCl_3$) δ 2.429 (s, 3H), 4.2 (s, 3H), 6.8–7.2 (m, 3H), 7.4–7.6 (m, 2H), 8.2–8.4 (d, 1H), 8.6 (s, 1H), 10.8 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 22.68, 55.7, 99, 111.27, 116.7, 120.3, 121.1, 124.15, 131.7, 132.25, 133.67, 141.32, 141.1, 157.2, 163. M/z (obs., $[m+H]^+$) = 268.

[00227] 2-(2-Methoxyphenyl)-7-methyl-3*H*-quinazolin-4-one

[00228]

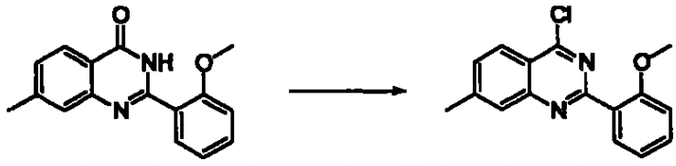


[00229] To a mechanically stirred suspension of *N*-(2-cyano-5-methylphenyl)-2-methoxybenzamide (180 g, 0.67 mol) in 1.8 L ethanol under an N_2 atmosphere was added 6 N sodium hydroxide solution (310 g in 1.25 L water). To the above mixture, 30% hydrogen peroxide (350 mL, 3.64 mol) was slowly added. The solution was then slowly heated to 80 °C

and maintained at this temperature for 4 h. The reaction mixture was concentrated under reduced pressure to remove ethanol, giving a suspension which was quenched with ice cold water (1.8 L) and acidified with acetic acid to pH 5–6 to give a solid residue. The solid was filtered and washed with water, then dissolved in 5.5 L CH_2Cl_2 and washed with water (2x18 L). The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure to give a light yellow solid (100 g, 54%). mp165–170 °C. ^{1}H NMR ($CDCl_3$) δ 2.429 (s, 3H), 4.2 (s,3), 6.8–7.2 (m, 3H), 7.4–7.6 (m, 2H), 8.2–8.4 (d, 1H), 8.6 (s, 1H), 10.8 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 21.68, 55.6, 111.3, 118.2, 119.6, 121.1, 125.7, 127.14, 127.64, 130.96, 132.56, 144.9, 149.06, 150.42, 157.25, 161.52. M/z (obs., $[m+H]^+$) = 268.

[00230] **4-Chloro-2-(2-methoxy-phenyl)-7-methyl-quinazoline**

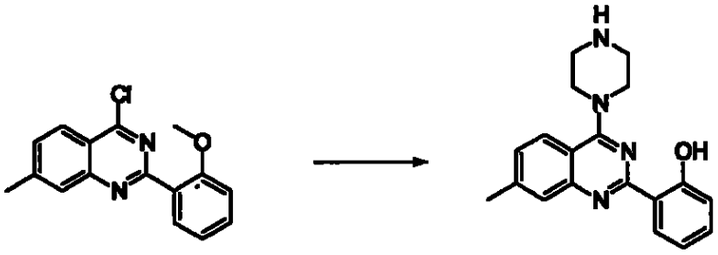
[00231]



[00232] To a mechanically stirred suspension of 2-(2-methoxyphenyl)-7-methyl-3*H*-quinazolin-4-one (100 g, 0.37 mol) in 1 L toluene was added diisopropyl ethylamine (100 mL), followed by phosphorus oxychloride (69 g, 0.45 mol). The reaction was then heated to 80 °C for 4 h. The reaction mixture was distilled under reduced pressure to remove toluene, and the resulting residue was dissolved in 2.2 L CH_2Cl_2. Ice water was added, and the pH was adjusted to 8–9 with saturated aqueous sodium bicarbonate solution while maintaining the temperature below 20 °C. The resulting organic layer was separated and the aqueous solution extracted with CH_2Cl_2, then the combined the organic layers were dried over sodium sulfate and distilled under reduced pressure. The crude product was dissolved 2:1 CH_2Cl_2/hexane, and the solution was passed through silica gel (2.5 kg, 60–120 mesh), followed by washing the silica bed with 2:1 CH_2Cl_2/hexane until the product eluted. The pure fractions were collected and combined, and the solvent was removed under reduced pressure. Hexane (500 mL) was added, and the mixture was stirred and filtered to give 4-chloro-2-(2-methoxy-phenyl)-7-methyl-quinazoline as a white to off-white solid (77 g, 72%). mp 161–164 °C. ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3H), 3.9 (s, 3H), 6.9–7.2 (m, 2H), 7.4–7.6 (m, 2H), 7.7–8 (d, 2H), 8.2 (d,1H); ^{13}C NMR ($CDCl_3$) δ 22.23, 56.06, 112.2, 120.26, 120.69, 125.34, 127.94, 130.45, 131.08, 131.08. M/z (obs., $[m+H]^+$) = 285.

[00233] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol

[00234]



[00235] A stirring solution of 4-chloro-2-(2-methoxyphenyl)-7-methylquinazoline (91 g, 320 mmol) and CH_2Cl_2 (2.0 L) under an N_2 atmosphere was cooled to –30 °C. Boron tribromide (957 mL, 957 mmol, 1.0 M in CH_2Cl_2) was added dropwise over a period of 30 minutes at –30 to –40 °C. The cooling bath was removed, and the mixture was allowed to warm to 25 °C. The mixture was carefully poured into a stirring solution of saturated aqueous $NaHCO_3$ (4.0 L). The organic portion was separated, dried over $MgSO_4$, and evaporated to dryness. The resulting solid was suspended in CH_2Cl_2 (400 mL) under an N_2 atmosphere, followed by the addition of triethylamine (64.8 g, 640 mmol). The solution was cooled to –10 °C. A solution of piperazine (55.0 g, 640 mmol) in CH_2Cl_2 (400 mL) was added in a single portion, and the solution was stirred at ambient temperature for 1 hour. The solution temperature rose to 23 °C upon addition of the piperazine. The solution was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried over $MgSO_4$ and evaporated to dryness. The residue was purified via silica gel chromatography using 5% MeOH in CH_2Cl_2 to obtain a tan solid. The resulting solid was triturated with 1:1 Et_2O/hexanes to obtain a yellow solid which was vacuum dried to give 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol as a light yellow solid (93.0 g, 290 mmol, 91%). LC/MS: *m/z* 321.1 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00236] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one

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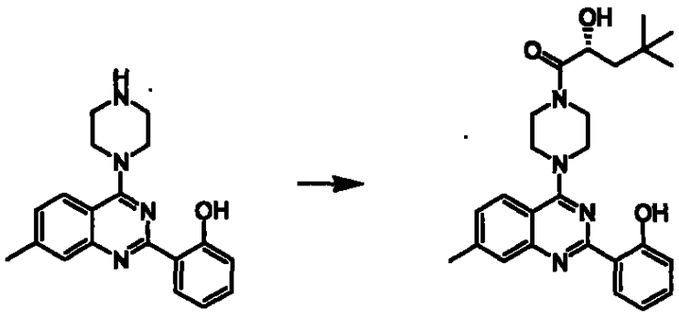


[00237] Method A

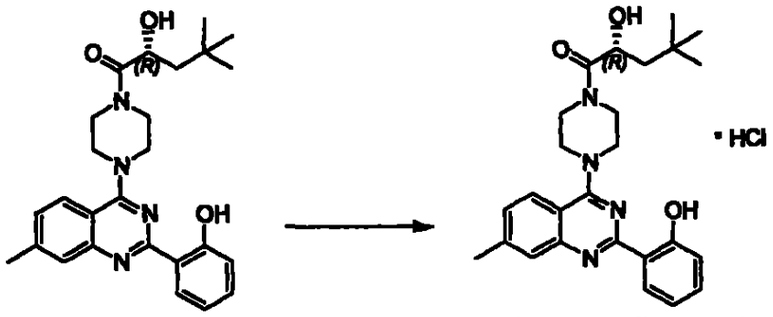
[00238] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol) was placed in a tube charged with a stir bar followed by (*R*)-2-hydroxy-4,4-dimethylpentanoic acid in 1 ml of DMF and triethylamine (31.57 mg, 0.312 mmol), and the reaction was cooled to 0 °C. HATU (71 mg, 0.187 mmol) was then added, and the reaction was allowed to stir at 0 °C for 10 minutes and then allowed to warm to room temperature. The reaction was complete after 40 minutes, filtered, and purified by reverse phase HPLC to give the TFA salt of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00239] Method B

[00240] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.74 mmol) was suspended in anhydrous DMF (5 mL) and cooled to 0 °C internal temperature. Under an N_2 atmosphere, (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (125.4 mg, 0.858 mmol) was added followed by triethylamine (0.218 mL, 1.56 mmol). To this stirring solution was added HATU (356 mg, 0.936 mmol). After the complete addition of HATU, the mixture was allowed to warm to 10 °C. After 45 min the reaction was complete, and it was quenched with an equal portion of ice water. A yellow precipitate formed which was collected by vacuum filtration and dissolved in CH_2Cl_2. This solution was desiccated with Na_2SO_4, filtered, and concentrated to give a viscous yellow-orange oil. The crude material was purified via silica gel chromatography using 88% CH_2Cl_2–hexanes (1:1) and 12% EtOAc to afford (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one as a faint yellow foam (265 mg, 76%). LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.46 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.70 (s, 1H), 7.41–7.37 (m, 2H), 6.97–6.93 (m, 2H), 4.89 (d, *J* = 7.2 Hz, 1H), 4.49–

4.44 (m, 1H), 4.06–3.67 (m,8), 2.52 (s, 3H), 1.56 (dd, J = 14.3, 3.0 Hz, 1H), 1.42 (dd, J = 14.3, 8.8 Hz, 1H), 0.97 (s, 9H)

[00241] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one hydrochloride**



[00242] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one (265 mg, 0.367 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) followed by the addition of Et_2O (6 mL) under an N_2 atmosphere. A 2.0 M HCl solution in Et_2O (0.296 mL, 0.591 mmol) was added over a 1 minute period. The reaction solution changed from a clear yellow solution to a creamy off white slurry. After complete addition of the HCl solution, the reaction was allowed to stir for an additional 10 minutes. The product was collected by vacuum filtration, washed with 3 mL of Et_2O and dried under vacuum to obtain (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one hydrochloride as a white solid (261 mg, 91%). LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.33 (d, J = 7.6 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.75 (s, 1H), 7.47–7.43 (m, 2H), 7.04–6.98 (m, 2H), 4.47–4.44 (m, 1H), 4.13–4.04 (m, 4H), 3.91–3.68 (m, 4H), 2.54 (s, 3H), 1.57 (dd, J = 14.3, 3.1 Hz, 1H), 1.42 (dd, J = 14.3, 8.8 Hz, 1H), 0.97 (s, 9H).

[00243] Example 102

[00244] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

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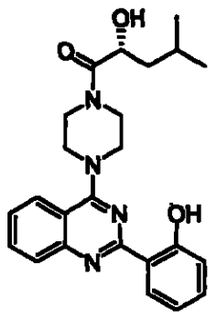
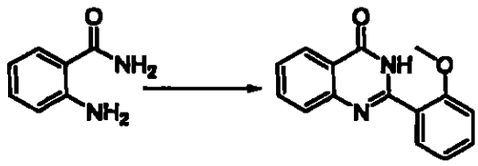
[00245]



[00246] 2-(2-Methoxyphenyl)quinazolin-4(3*H*)-one

[00247] Method A



[00248] To a cooled (0–5 °C) mixture of anthranilamide (350 g, 2.57 mol) and triethylamine (286 g, 2.83 mol) in THF (2.5 L) was added dropwise *o*-anisoyl chloride (437 g, 2.57 mol) while maintaining the temperature between 0–20 °C. The resulting suspension was stirred at room temperature overnight. The solvent was evaporated *in vacuo*, and the residue was washed several times with water. The wet residue was suspended in 2 M aq. NaOH (13 L), and the mixture was heated to reflux. After 20 minutes a clear solution was obtained. After 1 h of reflux the clear solution was cooled in an ice water bath and then acidified to pH 6 with conc. aq. HCl. The suspension was filtered, and the residue was washed thoroughly with water. The white solid was dried by azeotropic distillation with toluene. 2-(2-Methoxyphenyl)quinazolin-4(3*H*)-one (567 g) was obtained in 82%. ^{1}H-NMR (200 MHz, Me_2SO-d_6): δ 3.90 (s, 3 H), 7.20 (m, 2 H), 7.60 (t, 2 H), 7.85 (m, 3 H), 8.20 (d, 1 H), 12.20 (s, 1 H).

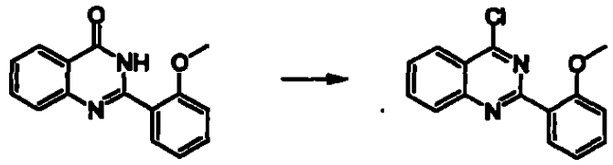
[00249] Method B

[00250] In a 2 L three-necked round-bottomed flask equipped with an overhead stirrer and reflux condenser, anthranilamide (20.0 g, 147 mmol) and potassium carbonate (28.4 g, 206 mmol) were suspended in 1 L dry ether and heated to reflux. *o*-Anisoyl chloride (32.5 g, 191 mmol) was added slowly to the refluxing mixture. After 3 hours at reflux, the reaction mixture was allowed to cool to room temperature, the ether was removed under reduced pressure, and the

resulting residue was filtered and washed with water. The resulting solid was then suspended in 600 mL of 5% aq. NaOH solution and boiled for one hour. The reaction was allowed to cool to room temperature, and it was neutralized with acetic acid, upon which 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one was precipitated. The product was collected by filtration, washed with water, and dried overnight *in vacuo* to yield 27 g (73%) of pure 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one. LC/MS: *m/z* 253.0 $(M+H)^+$ at 3.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (DMSO) δ 3.86 (s, 3H), δ 7.09 (t, 1H), δ 7.18 (d, 1H), δ 7.53 (m, 2H), δ 7.70 (m, 2H), δ 7.80 (m, 1H), δ 8.14 (d, 1H), δ 12.11 (s, 1H); ^{13}C NMR (DMSO) δ 55.75, δ 111.86, δ 120.89, δ 120.97, δ 122.74, δ 125.75, δ 126.45, δ 127.26, δ 130.41, δ 132.13, δ 134.32, δ 148.97, δ 152.48, δ 157.12, δ 161.35

[00251] **4-Chloro-3,4-dihydro-2-(2-methoxyphenyl)quinazoline**

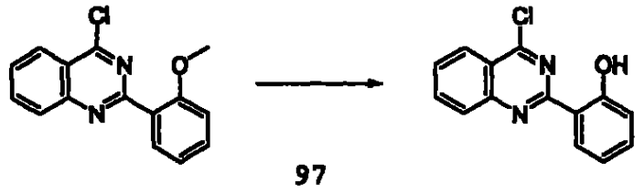
[00252]



[00253] A suspension of 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one (567 g, 2.1 mol) in phosphoryl chloride (2 L, 21 mol) and a catalytic amount of *N,N*-dimethyl aniline was brought to reflux. The reaction started immediately with the evolution of gas (HCl) upon the addition of *N,N*-dimethyl aniline. After the production of gas had ceased the mixture was cooled to room temperature. The excess $POCl_3$ was evaporated. The resulting dark solution was cooled to room temperature and slowly poured on ice and water, while maintaining the temperature below 5 °C. The cold suspension was extracted with dichloromethane. The extract was dried over sodium sulfate and filtered, and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (silica gel, CH_2Cl_2). Yield: 189 g (33%) of 4-chloro-3,4-dihydro-2-(2-methoxyphenyl)quinazoline. ^1H-NMR (300 MHz, Me_2SO-d_6): δ 3.85 (s, 3 H), 7.15 (t, 1 H), 7.25 (d, 1 H), 7.60 (t, 2 H), 7.70 (d, 1 H), 7.8 (d, 1 H), 7.9 (t, 1 H), 8.2 (d, 1 H).

[00254] **2-(4-Chloroquinazolin-2-yl)phenol**

[00255]



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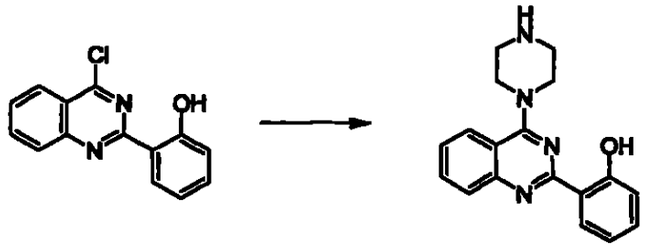
[00256] To a solution of 4-chloro-2-(2-methoxyphenyl)quinazoline (1.0 g, 3.7 mmol) in 40 mL CH_2Cl_2 at –78 °C was added 5 equivalents of 1 M BBr_3 dropwise. After complete addition the cooling bath was removed and the reaction was quenched with $NaHCO_3$ after 90 minutes. The product was extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 60:40 CH_2Cl_2: hexanes gave 2-(4-chloroquinazolin-2-yl)phenol (700 mg, 74%). LC/MS: *m/z* 257.1 $(M+H)^+$ at 3.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.44 (m, 1H), 8.24 (m, 3H), 7.89 (m, 1H), 7.49 (m, 1H), 7.05 (m, 2H).

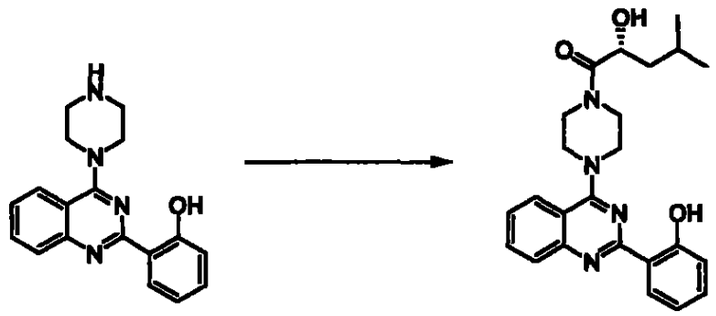
[00257] **2-(4-(Piperazin-1-yl)quinazolin-2-yl)phenol**

[00258]



[00259] To a solution of 2-(4-chloroquinazolin-2-yl)phenol (2.0 g, 7.8 mmol) in CH_2Cl_2 at 0 °C was rapidly added a solution of piperazine (2.01 g, 23.4 mmol) and triethylamine (2.17 mL, 15.6 mmol) in 10 mL CH_2Cl_2. The reaction was warmed to room temperature and stirred for 5 hours. The reaction was quenched with 25 mL of water and extracted with (3×15) mL of CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (1.98 g, 83%). LC/MS: *m/z* 307.3 $(M+H)^+$ at 1.47 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.43 (d, J = 10.1 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.85 (m, 2H), 7.53 (m, 1H), 7.38 (m, 1H), 6.95 (m, 2H), 3.85 (t, J = 4.8 Hz, 4H), 2.94 (t, J = 4.8 Hz, 4H).

[00260] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

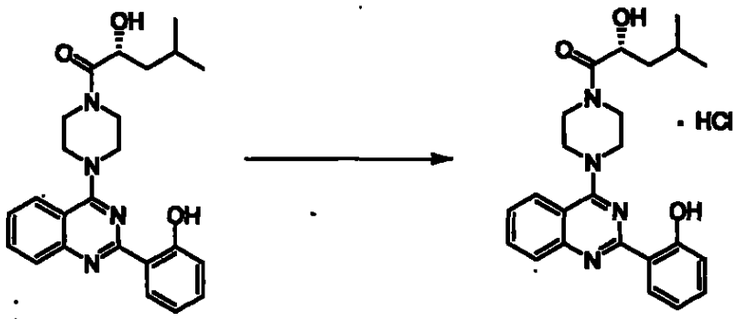


[00261]

[00262] To a solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.82 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (227 μL, 1.63 mmol) followed by the addition of (*R*)-2-hydroxy-4-methylpentanoic acid (140 mg, 1.06 mmol) and HATU (403 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (265 mg, 77%). LC/MS: *m/z* 421.30 $(M+H)^+$ at 2.57 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). H NMR (400 MHz, DMSO-d6) δ 8.47 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H) 7.88 (m, 2H), 7.57 (m, 1H), 7.40 (m, 1H), 6.96 (m, 2H), 4.92 (d, *J* = 7.2 Hz, 1H), 4.39 (m, 1H), 3.95 (m, 4H), 3.76 (m, 4H), 1.80 (m, 1H), 1.43 (m, 2H), 0.92 (q, *J* = 3.8 Hz, 6H).

[00263] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride

[00264]



[00265] To a solution of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (265 mg, 0.63 mmol) in CH_2Cl_2 (3 mL) under inert

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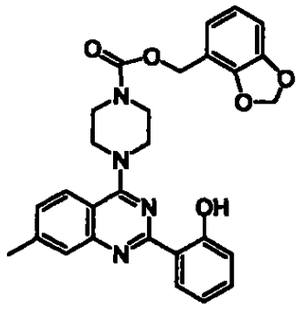
atmosphere was added 10 mL of ether followed by the dropwise addition of 2 M HCl (0.315 mL, 0.63 mmol).The reaction was stirred for 30 min before the formed precipitate was filtered to afford (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride (261 mg, 91%). *LC/MS*: *m/z* 421.3 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.28 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 3.9 Hz, 2H), 7.65 (m, 1H), 7.48 (m, 1H), 7.04 (m, 2H), 4.37 (m, 1H), 4.10 (m, 4H), 3.80 (m, 4H), 1.77 (m, 1H), 1.41 (m, 2H), 0.91 (dd, *J* = 6.6, 3.1 Hz, 6H).

[00266] Example 103

[00267] **(Benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00268]



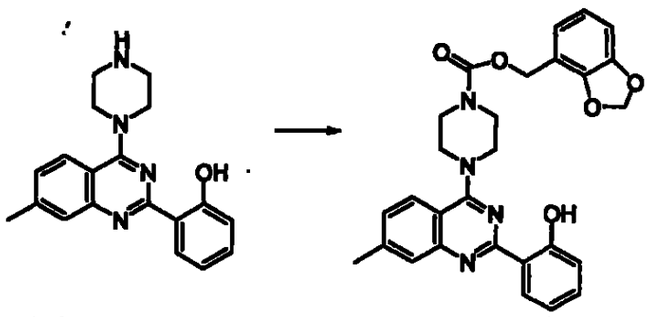
[00269] **(Benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate**

[00270]

[00271] A solution of (benzo[d][1,3]dioxol-7-yl)methanol (2 g, 13.14 mmol) and di(1*H*-imidazol-1-yl)methanone (4.26 g, 26.28 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C. The reaction was quenched with water, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (2.8 g, 86%).

[00272] **(Benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00273]

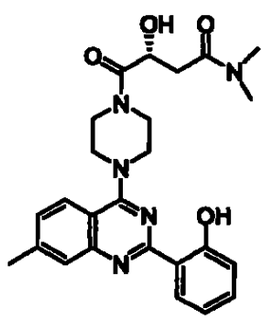


[00274] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (78 mg, 0.32 mmol) and triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 499.3 $(M+H)^+$ at 2.97 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00275] Example 104

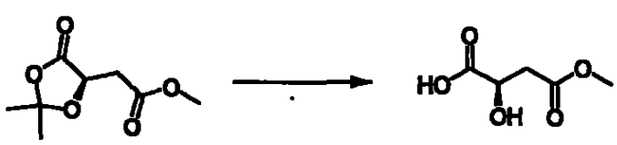
[00276] (*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-N,N-dimethyl-4-oxobutanamide

[00277]



[00278] (*R*)-3-(Methoxycarbonyl)-2-hydroxypropanoic acid

[00279]



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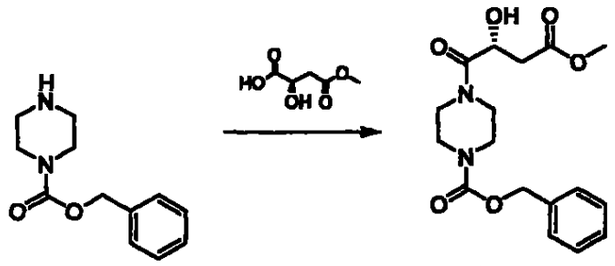
[00280] Methyl 2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate (17.1 g, 90.9 mmol) was stirred in a 1:1 mixture of THF:1 M HCl (200 mL) for 1 h at room temperature. After addition of NaCl to nearly saturate the aqueous layer, the mixture was extracted with EtOAc, and the extracts were dried over Na_2SO_4 and concentrated to obtain (*R*)-3-(methoxycarbonyl)-2-hydroxypropanoic acid as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58–4.55 (m, 1H), 3.75 (s, 3H), 2.98–2.84 (m, 2H).

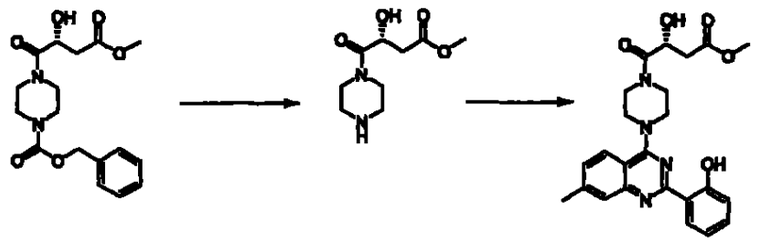
[00281] **4-((*R*)-2-Hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester**

[00282]



[00283] EDCI (3.6 g, 19 mmol) was added to a solution of (*R*)-3-(methoxycarbonyl)-2-hydroxypropanoic acid (2.8 g, 19 mmol) and HOBt (2.6 g, 19 mmol) in DMF (200 mL). After stirring this mixture for 5 min, benzyl piperazine-1-carboxylate (4.2 g, 3.6 mL, 19 mmol) and triethylamine (2.6 mL, 19 mmol) were added and stirred for 3 days at room temperature. The reaction mixture was poured into water and extracted with EtOAc. After washing the organic layers with brine and water, drying over Na_2SO_4 and concentrating, purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester as an oil (2.19 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 5.15 (s, 2H), 4.79–4.74 (m, 1H), 3.95 (d, J = 8.0 Hz, 1H), 3.79–3.74 (m, 1H), 3.74 (s, 3H), 3.71–3.44 (m, 7H), 2.62 (d, J = 5.8 Hz, 2H).

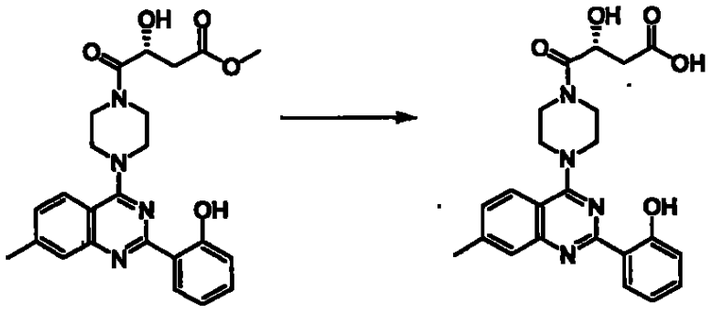
[00284] **(*R*)-Methyl 3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoate**



[00286] 4-((*R*)-2-Hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (0.52 g, 1.5 mmol) and MeOH (15 mL) were stirred with 10% Pd/C under an H_2 atmosphere at ambient pressure overnight. After filtration and evaporation of the solvent the residue was taken up in CH_2Cl_2, and 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.40 g, 1.50 mmol) plus triethylamine (0.41 mL, 3.00 mmol) were added. The reaction mixture was stirred at room temperature overnight, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/ CH_2Cl_2 provided (*R*)-methyl 3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoate (0.38 g, 57%). LC/MS: *m/z* 451.1 $(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00287] (*R*)-3-Hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid

[00288]



[00289] $LiOH \cdot H_2O$ (19.8 mg, 0.47 mmol) was added to a solution of (*R*)-3-hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid methyl ester (71 mg, 0.16 mmol) in 2 mL THF:H_2O (1:1) and stirred at room temperature for 3 h. The reaction mixture was acidified with 1 M HCl and then extracted with EtOAc. After drying the organic layer over Na_2SO_4, it was concentrated and then purified via silica gel chromatography using 0–15% MeOH/CH_2Cl_2 to provide (*R*)-3-hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid (52 mg, 75%). LC/MS: *m/z* 437.3 $(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00290] (*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-*N*,*N*-dimethyl-4-oxobutanamide

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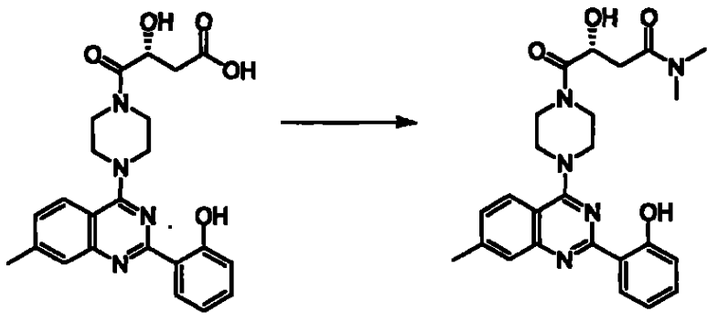
[00291]

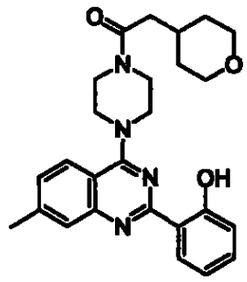


[00292] (*R*)-3-Hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid (17 mg, 0.039 mmol) and HATU (16 mg, 0.043 mmol) were stirred in DMF (0.5 mL). After adding dimethylamine (2 M in THF, 0.10 mL, 0.19 mmol), the reaction mixture was stirred at room temperature for 5 h. Purification via preparative reverse-phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-N,N-dimethyl-4-oxobutanamide as the TFA salt. LC/MS: *m/z* 436.3 $(M+H)^+$ at 1.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00293] Example 105

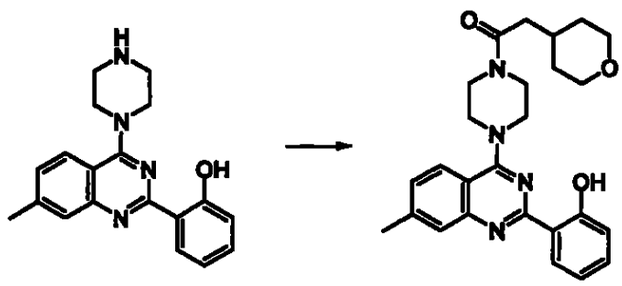
[00294] (2-(Tetrahydro-2*H*-pyran-4-yl)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone

[00295]



[00296] (2-(Tetrahydro-2*H*-pyran-4-yl)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone

[00297]

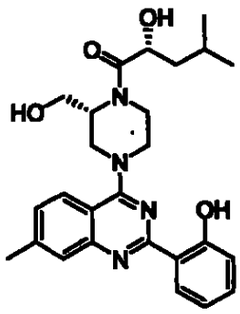


[00298] To a solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (13.5 mg, 0.09 mmol) followed by the addition of triethylamine (25 μL), then HATU (44 mg) at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2-(tetrahydro-2*H*-pyran-4-yl)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone as the TFA salt. LC/MS: *m/z* 447.10 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

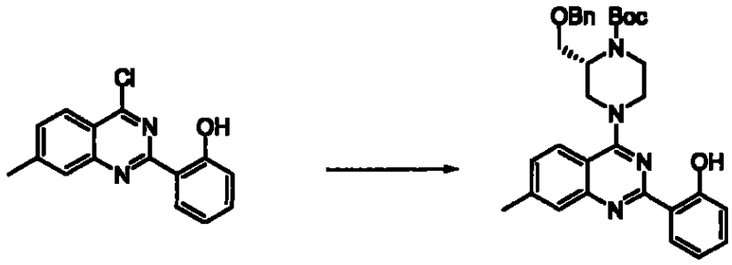
[00299] Example 106

[00300] **(*R*)-2-Hydroxy-1-((*R*)-2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

[00301]



[00302] **(*R*)-*tert*-Butyl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

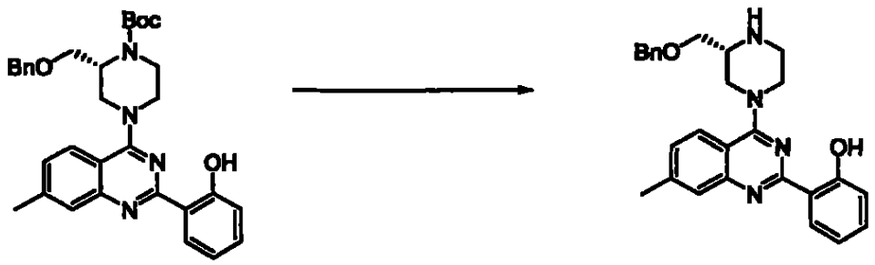


[00303]

[00304] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (450 mg, 1.66 mmol) in 10 mL DMF was added a solution of (*R*)-*tert*-butyl 2-((benzyloxy) methyl) piperazine-1-carboxylate (610 mg, 1.99 mmol) in DMF and triethylamine (0.46 mL). The reaction mixture was then refluxed at 85 °C for 30 minutes, quenched with water, extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated to give (*R*)-*tert*-butyl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate (760 mg, 85%). This material was used in the next step without further purification. LC/MS: *m/z* 541.5 $(M+H)^+$ at 3.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00305] **2-(4-((*R*)-3-((Benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol**

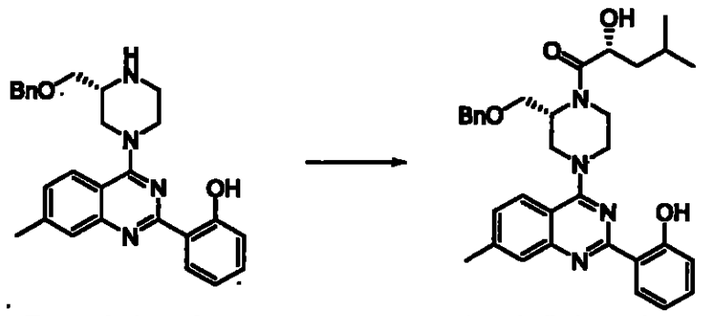
[00306]



[00307] To a solution of (*R*)-*tert*-butyl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate (760 mg, 1.72 mmol) in 15 mL CH_2Cl_2 was added 10 mL of TFA. The reaction was stirred for 1 hour. TFA was removed under vacuum and the reaction was neutralized using a 1 M NaOH solution. The aqueous layer was extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to obtain 2-(4-((*R*)-3-((benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol (570 mg, 92%). This material was used in the next step without further purification. LC/MS: *m/z* 441.5 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00308] **(*R*)-1-((*R*)-2-((Benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

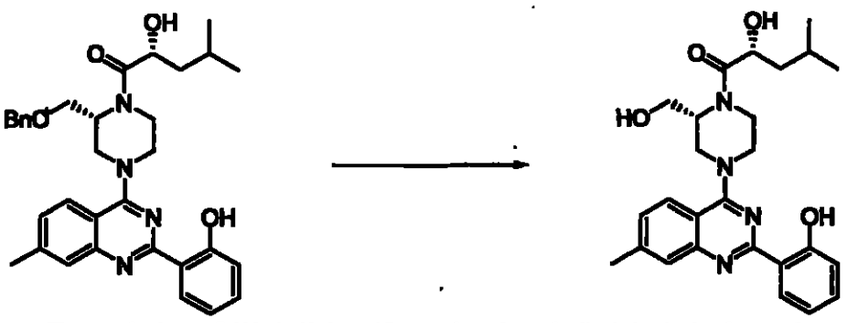
[00309]



[00310] To a solution of 2-(4-((*R*)-3-((benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol (100 mg, 0.22 mmol) in DMF (1 mL) was added (*R*)-2-hydroxy-4-methylpentanoic acid (30 mg, 0.22 mmol) followed by the addition of triethylamine (61 μL), then HATU (109 mg) at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-1-((*R*)-2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 555.7 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00311] **(*R*)-2-Hydroxy-1-((*R*)-2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

[00312]



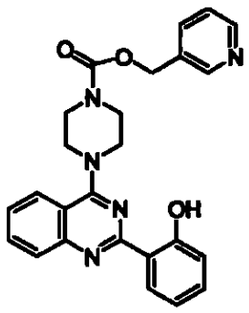
[00313] To a solution of (*R*)-1-((*R*)-2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one trifluoroacetate (29.6 mg, 0.053 mmol) in ethanol was added $Pd(OH)_2$ (188 mg), and the reaction was heated at 50 °C

under H_2 atmosphere at ambient pressure. The reaction was filtered, and purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-((*R*)-2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one as the TFA salt. *LC/MS*: *m/z* 465.50 $(M+H)^+$ at 2.47 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00314] Example 107

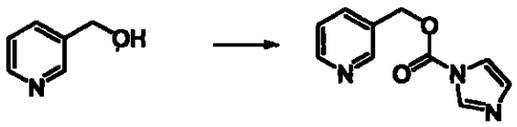
[00315] **(Pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate**

[00316]



[00317] **(Pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate**

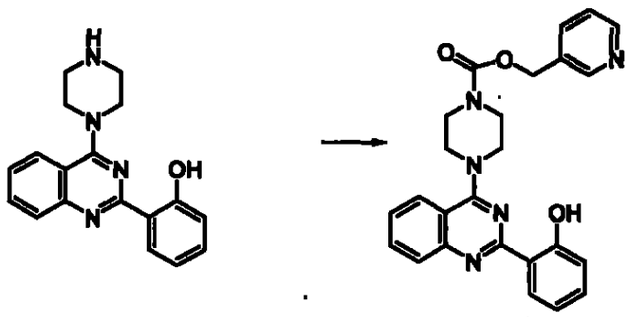
[00318]



[00319] A solution of (pyridin-3-yl)methanol (2 g, 18.32 mmol) and di(1*H*-imidazol-1-yl)methanone (5.94 g, 36.65 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C. The reaction was quenched with water, extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (3.1 g, 84%). *LC/MS*: *m/z* 204.1 $(M+H)^+$ at 0.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 1.9 Hz, 1H), 8.68 (dd, J = 4.8, 1.4 Hz, 1H), 8.16 (s, 1H), 7.81 (m, 1H), 7.44 (s, 1H), 7.38 (m, 1H), 7.09 (s, 1H), 5.46 (s, 2H).

[00320] **(Pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate**

[00321]

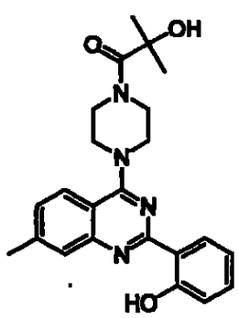


[00322] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (67 mg, 0.32 mmol) and triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 442.50 $(M+H)^+$ at 1.97 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00323] Example 108

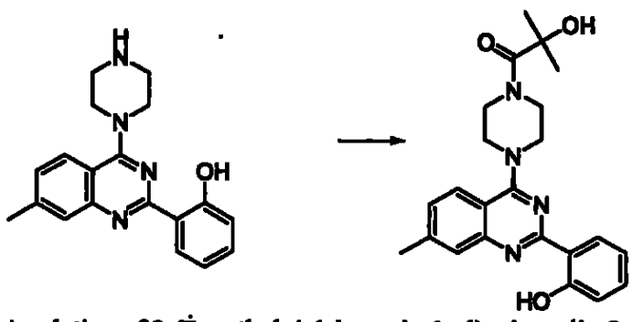
[00324] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylpropan-1-one**

[00325]



[00326] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylpropan-1-one**

[00327]

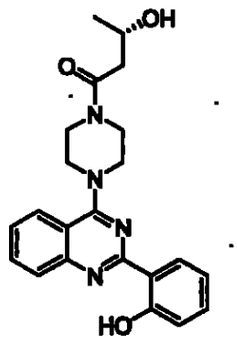


[00328] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxy-2-methylpropanoic acid (29.6 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylpropan-1-one as the TFA salt. LC/MS: *m/z* 407.50 $(M+H)^+$ at 2.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00329] Example 109

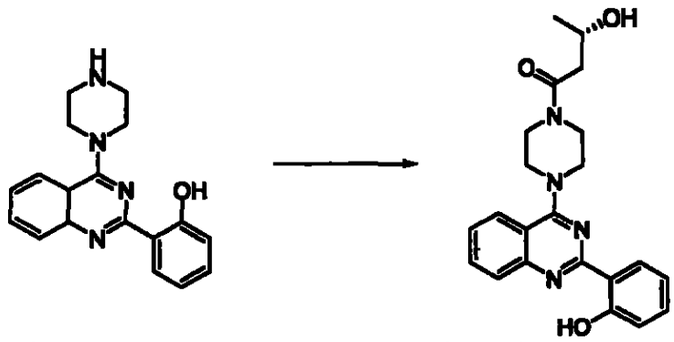
[00330] (*S*)-3-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00331]



[00332] (*S*)-3-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00333]

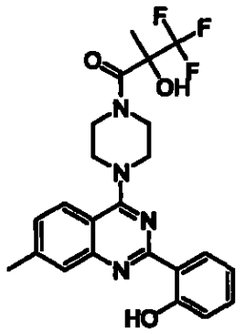


[00334] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*S*)-3-hydroxybutanoic acid (31.0 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-3-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 393.1 $(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00335] Example 110

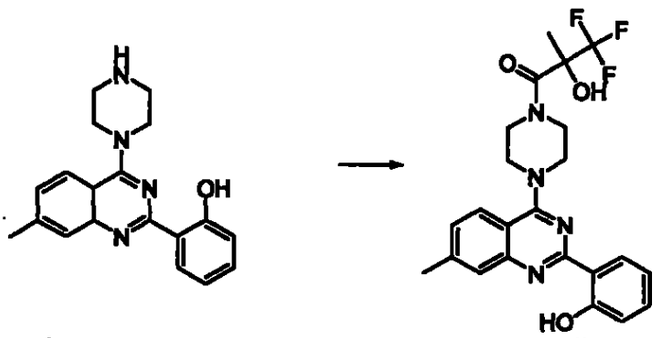
[00336] **2-(Trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one**

[00337]



[00338] **2-(Trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one**

[00339]

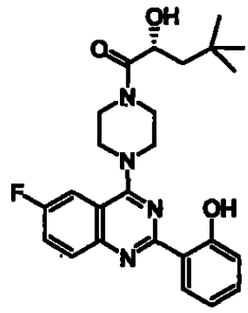


[00340] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-(trifluoromethyl)-2-hydroxypropanoic acid (45 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-(trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 461.1 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

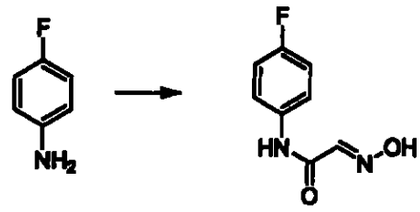
[00341] Example 111

[00342] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one**

[00343]



[00344] **(*E*)-*N*-(4-Fluorophenyl)-2-(hydroxyimino)acetamide**

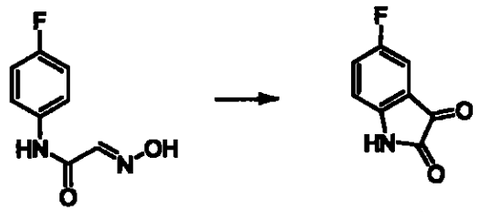


[00345]

[00346] 4-Fluoroaniline (58.2 g, 0.50 mol) was added slowly to 10% aqueous HCl solution. This suspension was added to a mixture of chloral hydrate (95 g, 0.55 mol) and sodium sulfate (0.5 kg) in 750 mL water with mechanical stirring. Hydroxylamine hydrochloride (116 g, 1.63 mol) dissolved in water (250 mL) was added, and the resulting slurry was heated at 100 °C. After this temperature was reached, the heating mantle was removed immediately, and the solution was cooled to room temperature. The formed precipitate was collected by filtration, washed with water (2x300 mL), and dried in a vacuum oven at 60 °C. Yield: 78.2 g of *N*-(4-fluorophenyl)-2-hydroxyiminoacetamide as an off-white solid.

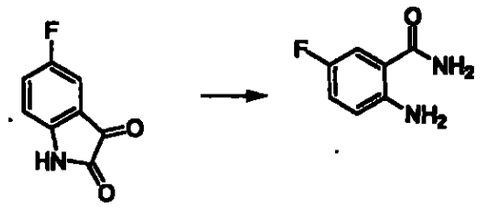
[00347] **5-Fluoroindoline-2,3-dione**

[00348]



[00349] Concentrated sulfuric acid (200 mL) was heated at 50 °C, and *N*-(4-fluorophenyl)-2-hydroxyiminoacetamide was slowly added. The black solution was carefully heated at 90 °C. At this temperature, some slight cooling was necessary to keep the temperature at 90 °C. When no more heat had developed, the reaction mixture was heated at 90 °C for an additional half hour. The dark-red solution was cooled to room temperature and poured onto 3 L ice water and 1 L ethyl acetate with vigorous stirring. The layers were separated, and the aqueous layer was extracted with ethyl acetate (1x1 L, 1x0.5 L). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated to dryness. Yield: 35.3 g (52%) of a dark red solid, 5-fluoro-1*H*-indole-2,3-dione.

[00350] **2-Amino-5-fluorobenzamide**

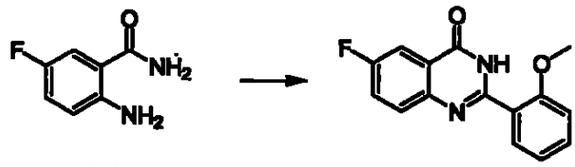


[00351]

[00352] 5-Fluoro-1*H*-indole-2,3-dione (35.3 g, 213 mmol) was heated in acetic acid (300 mL), 1 mL concentrated sulfuric acid, and 22 mL 35% aq. hydrogen peroxide at 70 °C. The solution was kept at that temperature one and a half hours during which time a solid formed in the reaction mixture. After cooling to room temperature this solid was collected by filtration and was washed three times with water. The wet solid was suspended in 150 mL water, and 40 mL of a 25% aq. ammonia solution was added. This mixture was stirred at room temperature 3 days. The formed solid was collected by filtration and was washed twice with water. The solid was dried by azeotropic distillation with toluene (3 x 100 mL) to yield 2-amino-5-fluorobenzamide (9.5 g). The combined filtrates were extracted with ethyl acetate (2x100 mL). The combined extracts were dried over sodium sulfate, filtered, and evaporated to dryness to yield 2-amino-5-fluorobenzamide (3.5 g) as an off-white solid. Both fractions were combined for use in the next reaction step.

[00353] **6-Fluoro-2-(2-methoxyphenyl)-3*H*-quinazolin-4-one**

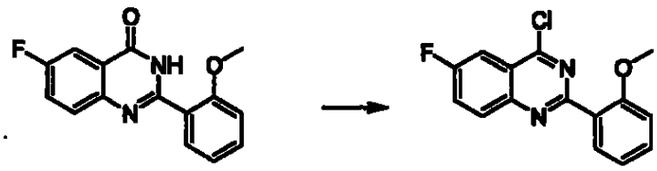
[00354]



[00355] *o*-Anisoyl chloride (15.7 g, 92 mmol) was added dropwise to a solution of aminobenzamide 2-amino-5-fluorobenzamide (13.0 g, 84 mmol) and triethylamine (16 mL, 110 mmol) in tetrahydrofuran (100 mL) cooled in an ice bath. Immediately a precipitate started forming. Stirring of the solution was continued for 5 hours at room temperature. The formed precipitate was collected by filtration and was washed twice with diethyl ether and dried at 50 °C *in vacuo*. The dried solid was suspended in 2 N aqueous sodium hydroxide solution (250 mL) and heated at reflux until a clear solution was obtained (3 hours). The reaction mixture was cooled to room temperature and filtered. The filtrate was acidified to pH<1 with concentrated aqueous HCl. The formed precipitate was collected by filtration and washed twice with water,

twice with methanol, and twice with diethyl ether. The solid was dried in an oven at 45 °C to yield 6-fluoro-2-(2-methoxyphenyl)-3*H*-quinazolin-4-one (18.2 g, 80%) as a white solid.

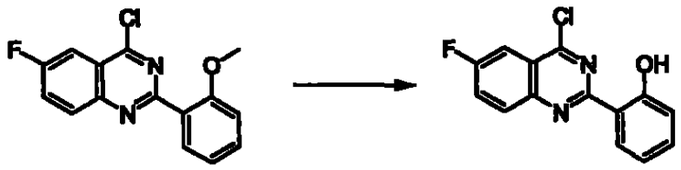
[00356] **4-Chloro-6-fluoro-2-(2-methoxyphenyl)quinazoline**



[00357] A suspension of 6-fluoro-2-(2-methoxyphenyl)-3*H*-quinazolin-4-one (14.0 g, 52 mmol), *N,N*-dimethylaniline (6.6 mL, 52 mmol), and phosphorus oxychloride (4.8 mL, 52 mmol) in benzene (100 mL) was heated at reflux until a clear, dark solution was obtained (1 hour). The reaction mixture was cooled to room temperature, and the volume was reduced under reduced pressure. The black, oily residue was poured into 300 g of ice. Dichloromethane (600 mL) was added with vigorous stirring, and the temperature was kept below 5 °C at all times. The pH was monitored, and aqueous 1 N sodium hydroxide was added until the pH was 10–11. The mixture was stirred for one hour at a temperature below 5 °C, and the pH was kept between 10–11 by addition of 1 N aqueous sodium hydroxide. The layers were separated, and the organic layer was washed with ice cold 1 N aqueous sodium hydroxide (2x200 mL). Heptanes (300 mL) were added to the organic layer. This mixture was filtered through a short plug of silica gel and eluted with dichloromethane/heptanes (2:1). All fractions containing product were combined and evaporated to dryness. The residue was triturated with heptanes to yield 4-chloro-6-fluoro-2-(2-methoxyphenyl)-quinazoline (11.5 g, 76%) as a white solid.

[00358] **2-(4-Chloro-6-fluoroquinazolin-2-yl)phenol**

[00359]

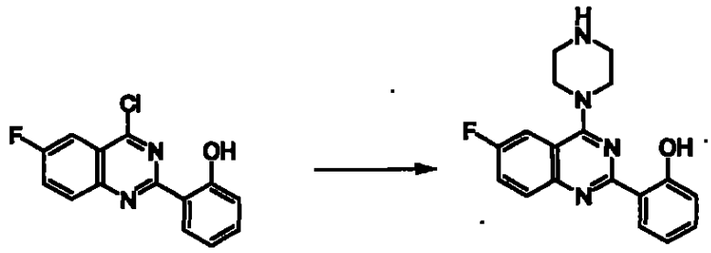


[00360] A solution of 4-chloro-6-fluoro-2-(2-methoxyphenyl)quinazoline (3.0 g, 10.3 mmol) in CH_2Cl_2 (15 mL) was cooled to –78 °C. Then, 1 M BBr_3 (51.95 mL, 59.95 mmol) was added dropwise. The reaction was warmed to room temperature and was quenched with $NaHCO_3$ and extracted twice with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered,

and concentrated. Purification via silica gel chromatography using 5–20% CH_2Cl_2 in hexanes gave 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (1.61 g, 57%). LC/MS: *m/z* 275.1 $(M+H)^+$ at 3.8 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

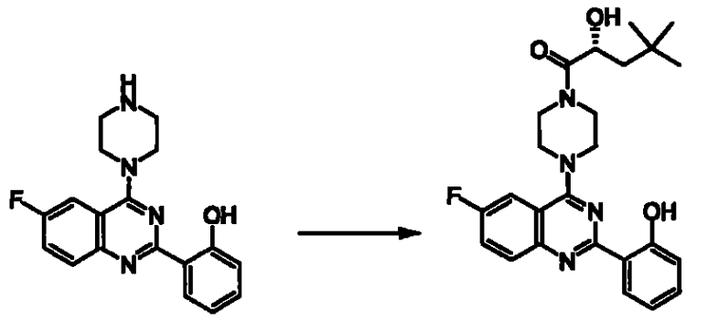
[00361] **2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol**

[00362]



[00363] To a stirring solution of 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (500 mg, 1.82 mmol) in CH_2Cl_2 (20 mL) at 0 °C, under an N_2 atmosphere was rapidly added a solution of piperazine (0.263 g, 7.28 mmol) and triethylamine (0.35 mL, 2.55 mmol) in CH_2Cl_2. The mixture was stirred for 1 h and then quenched with H_2O, extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–5% MeOH in CH_2Cl_2 gave 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (400 mg, 68%). LC/MS: *m/z* 325.5 $(M+H)^+$ at 2.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.42 (m, 1H), 7.97 (m, 1H), 7.78 (m, 2H), 7.39 (m, 1H), 6.95 (m, 2H), 3.83 (t, J = 4.9 Hz, 4H), 2.92 (t, J = 4.9 Hz, 4H).

[00364] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one**



[00365]

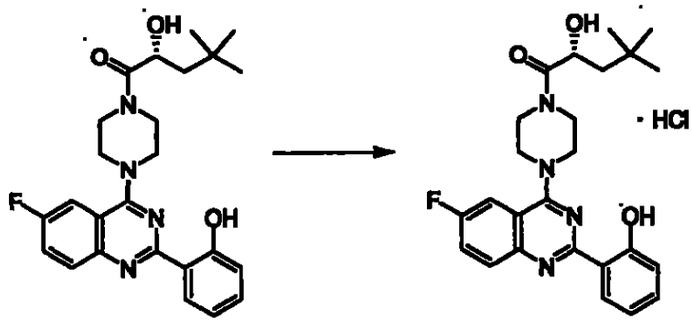
[00366] <u>Method A</u>

[00367] To a solution of 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol) in DMF (1 mL) was added (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (20.28 mg, 0.14 mmol) followed by the addition of triethylamine (25 μL), then HATU (44 mg) at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))–H_2O) gave (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one as the TFA salt. LC/MS: *m/z* 453.52 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00368] Method B

[00369] To a solution of 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (200 mg, 0.61 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (170 μL, 1.22 mmol) followed by the addition of (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (116 mg, 0.79 mmol), then HATU (301 mg, 0.79 mmol). An additional 3 mL of CH_2Cl_2 were added, and the reaction was stirred for 3 h. After quenching with water, the mixture was extracted twice with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes yielded (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one (240 mg, 86%). *m/z*: M+1 *obs* = 453.5; t_R = 3.19 minutes ^1H NMR (400 MHz, DMSO-d6) δ 8.46 (m, 1H), 8.01 (m, 1H), 7.84 (m, 2H), 7.40 (m, 1H), 6.96 (m, 2H), 4.89 (d, *J* = 7.1 Hz, 1H), 4.45 (m, 1H), 3.97 (m, 4H), 3.76 (m, 4H), 1.56 (m, 1H), 1.42 (m, 1H), 0.97 (s, 9H).

[00370] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride**



[00371]

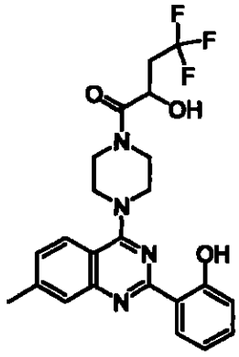
[00372] To a solution of (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2- hydroxy-4,4-dimethylpentan-1-one (230 mg, 0.51 mmol) in CH_2Cl_2 (3 mL)

under an inert atmosphere was added dropwise a 2 M HCl solution in ether (2.55 mL, 0.51 mmol). To it was then added ether (15 mL) which resulted in formation of a precipitate that was allowed to stir for an hour. The product was collected by vacuum filtration and dried to afford (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride (230 mg, 92%). LCMS: *m/z* 453.5 $(M+H)^+$ at 3.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.40 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.04 (m, 1H), 7.88 (m, 2H), 7.43 (m, 1H), 6.99 (m, 2H), 4.45 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.02 (m, 4H), 3.79 (m, 4H), 1.56 (m, 1H), 1.42 (m, 1H), 0.97 (s, 9H).

[00373] Example 112

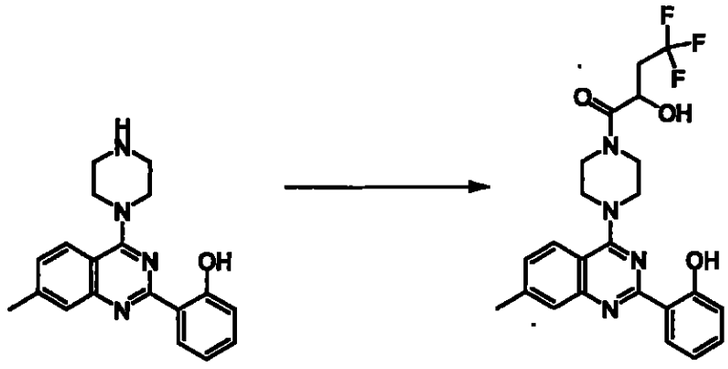
[00374] **4,4,4-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one**

[00375]



[00376] **4,4,4-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one**

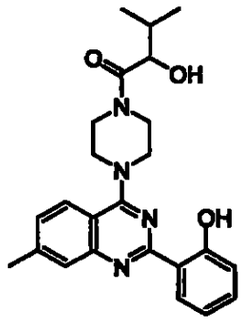
[00377]



[00378] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (87 mg, 0.27 mmol), 4,4,4-trifluoro-2-hydroxybutanoic acid (43 mg, 0.27 mmol), HATU (0.12 g, 0.33 mmol) and triethylamine (45 μL, 0.33 mmol) were stirred in DMF (3 mL) at room temperature overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and water, dried over Na_2SO_4 and concentrated. Purification via silica gel chromatography using 0–20% EtOAc in 1:1 CH_2Cl_2: hexanes gave 4,4,4-trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one as an off-white solid (86 mg, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, J = 8.0, 1.7 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.41–7.37 (m, 1H), 7.31 (dd, J = 8.5, 1.5 Hz, 1H), 7.05–7.03 (m, 1H), 6.97–6.93 (m, 1H), 4.80–4.75 (m, 1H), 4.07–3.68 (m, 9H), 2.56 (s, 3H), 2.50–2.39 (m, 2H); LC/MS: *m/z* 461.3 $(M+H)^+$ at 2.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

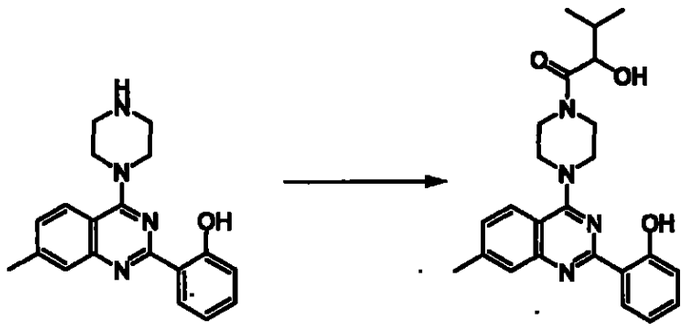
[00379] Example 113

[00380] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one



[00381]

[00382] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one



[00383]

[00384] Method A

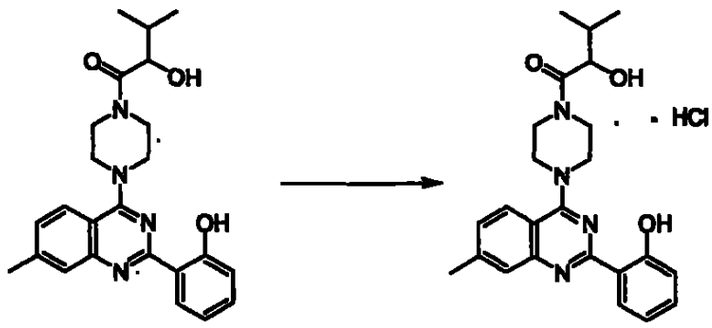
[00385] Under an N_2 atmosphere, a mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol), 2-hydroxy-3-methylbutanoic acid (9 mg, 0.08 mmol), BOP (35 mg, 0.08 mmol), triethylamine (22 μL, 0.16 mmol) and DMF (0.2 mL) was stirred at room temperature for 1 hour. The reaction mixture was then purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 421.10 $(M+H)^+$ at 2.76 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00386] Method B

[00387] To a solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.78 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (217 μL, 1.56 mmol) followed by the addition of 2-hydroxy-3-methylbutanoic acid (120 mg, 1.0 mmol) and HATU (380 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one (230 mg, 70%). LC/MS: *m/z* 421.3 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.45 (m, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.39 (m, 2H), 6.95 (m, 2H), 4.79 (d, J = 7.2 Hz, 1H), 4.11 (dd, J = 7.0, 5.9 Hz, 1H), 3.87 (m, 8H), 2.52 (s, 3H), 1.91 (m, 1H), 0.88 (dd, J = 22.8, 6.7 Hz, 6H).

[00388] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one hydrochloride

[00389]

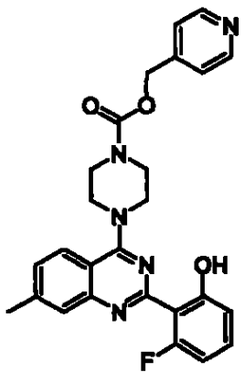


[00390] To a solution of 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one (230 mg, 0.54 mmol) in CH_2Cl_2 (3 mL) under an inert atmosphere was added ether (12 mL) followed by the dropwise addition of 2 M HCl solution in ether (0.27 mL, 0.54 mmol) which resulted in the formation of a precipitate which was stirred for an hour and then collected by vacuum filtration and dried to afford 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one hydrochloride (205 mg, 83%). *LC/MS*: *m/z* 421.3 $(M+H)^+$ at 2.48 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.25 (d, J = 7.9 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.48 (t, J = 6.6 Hz, 2H), 7.04 (m, 2H), 4.10 (m, 5H), 3.79 (m, 4H), 2.53 (s, 3H), 1.90 (m, 1H), 0.87 (dd, J = 16.3, 6.7 Hz, 6H)

[00391] Example 114

[00392] (Pyridin-4-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

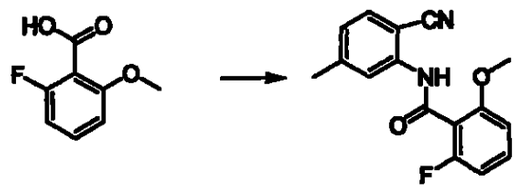
[00393]



[00394]

[00395] *N*-(2-Cyano-5-methyl-phenyl)-2-fluoro-6-methoxy-benzamide

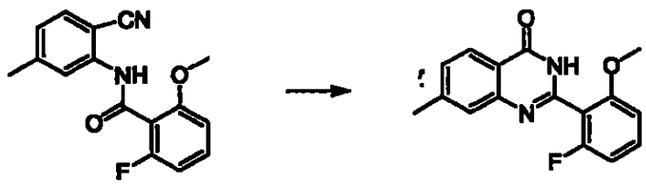
[00396]



[00397] 6-Fluoro-2-anisoic acid (110 g, 0.70 mol) was added in portions over 15 minutes to a mixture of thionyl chloride (230 ml, 3.2 mol), toluene (200 mL), and DMF (1 mL). The resulting mixture was stirred overnight at room temperature. The solution was evaporated to dryness and added dropwise to an ice-bath cooled solution of anthranilonitrile (92.5 g, 0.70 mol) in pyridine (200 mL). The dropping funnel was rinsed with a minimal amount of acetonitrile. The resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere and was subsequently poured into 2 L ice water. The resulting slurry was stirred vigorously for 1 hour. The formed solid was collected by filtration and was washed twice with water. The filter cake was dissolved in 2 L dichloromethane, and this solution was washed with 1 N aq. HCl (400 mL) and with saturated aq. NaCl (400 mL), dried over sodium sulfate, filtered, and evaporated to dryness to give *N*-(2-cyano-5-methylphenyl)-2-fluoro-6-methoxybenzamide (186 g, 93%) as a brownish solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 9.09 (s, 1H), 8.58 (s, 1H), 7.59–7.42 (m, 2H), 7.09–7.02 (m, 1H), 6.94–6.83 (m, 2H), 4.11 (s, 3H), 2.57 (s, 3H) ppm.

[00398] **2-(2-Fluoro-6-methoxy-phenyl)-7-methyl-3*H*-quinazolin-4-one**

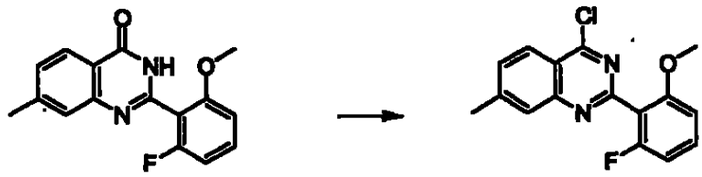
[00399]



[00400] To a suspension of *N*-(2-cyano-5-methylphenyl)-2-fluoro-6-methoxybenzamide (31.5 g, 111 mmol) in ethanol (626 mL) was added 6 M aqueous NaOH solution (205 mL). After 10 minutes, 30% aqueous H_2O_2 (60 mL) was added, forming a slurry. The reaction was heated to reflux for 18 h and cooled to room temperature. NaOH (22.2 g, 0.56 mol) and 30% aqueous H_2O_2 (26 mL) were added, and the reaction was heated to reflux for six hours. The reaction cooled to room temperature, 30% aqueous H_2O_2 (45 mL) was added, and the reaction was heated to reflux for 18 h. The reaction was cooled to room temperature, NaOH (10 g, 0.25 mol) and 30% aqueous H_2O_2 (70 mL) were added, and the reaction was heated to reflux for six hours. The reaction was cooled to room temperature and poured over ice (800 mL). The pH was adjusted to 3–4 by addition of conc. HCl solution, and the precipitated off-white solid was filtered and washed with water (3 x 40 mL). The solid was dried under vacuum to provide 2-(2-fluoro-6-methoxy-phenyl)-7-methyl-3*H*-quinazolin-4-one (28 g, 89%).

[00401] 4-Chloro-2-(2-fluoro-6-methoxyphenyl)-7-methylquinazoline

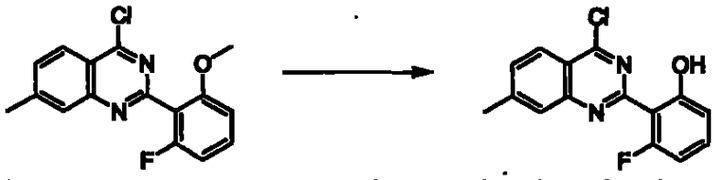
[00402]



[00403] Under an N_2 atmosphere, 2-(2-fluoro-6-methoxyphenyl)-7-methylquinazolin-4(3*H*)-one (20 g, 70.35 mmol) was suspended in benzene (300 mL), followed by the addition of *N,N*-dimethylaniline (26.8 mL, 211.05 mmol), then $POCl_3$ (13.11 mL, 140.7 mmol). The reaction was heated at reflux, and completion of product formation was observed after 1.5 h. After cooling to room temperature, the mixture was slowly poured over 1 liter of ice. The solution was then diluted with CH_2Cl_2, and the pH was adjusted to 7 using a saturated aqueous $NaHCO_3$ solution. The layers were partitioned, separated and extracted with CH_2Cl_2. All organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to a dark oil. The crude material was purified by silica gel chromatography using 75% CH_2Cl_2/ 25% hexanes to obtain 4-chloro-2-(2-fluoro-6-methoxyphenyl)-7-methylquinazoline as a yellow solid (18.82 g, 88%). *LC/MS*: *m/z* 302.9 $(M+H)^+$ at 3.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.5 Hz, 1H), 7.95 (s, 1H), 7.60 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.42–7.40 (m, 1H), 6.86–6.84 (m, 2H), 3.81 (s, 3H), 2.64 (s, 3H)

[00404] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol

[00405]

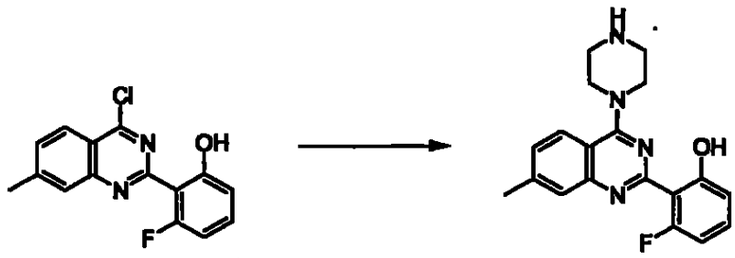


[00406] Under an N_2 atmosphere, 4-chloro-2-(2-fluoro-6-methoxyphenyl)-7-methylquinazolin (7.0 g, 23.12 mmol) was dissolved in CH_2Cl_2 (110 mL) and cooled to ~50 °C internal temperature using a dry ice/acetone bath. A 1.0 M solution of BBr_3 in CH_2Cl_2 (115.6 mL, 115.6 mmol) was added dropwise via an addition funnel while maintaining the internal temperature at –50 °C. The reaction mixture was allowed to warm to 0 °C, and the reaction was complete after 1.5 h. It was then slowly quenched with saturated aqueous $NaHCO_3$ solution to

pH 7. After partitioning between CH_2Cl_2 and H_2O, the mixture was separated and the aqueous layer was twice extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to a brown solid. Purification via silica gel chromatography using 75% CH_2Cl_2/ 25% hexanes gave 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol as a yellow solid (4.37 g, 66%). *LC/MS*: *m/z* 289.1 $(M+H)^+$ at 3.71 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 7.60 (dd, J = 8.6, 1.5 Hz, 1H), 7.42–7.36 (m, 1H), 6.86–6.82 (m, 2H), 3.81 (s, 3H), 2.64 (s, 3H)

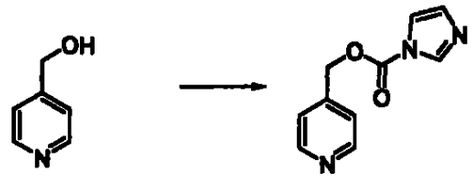
[00407] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol

[00408]



[00409] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (4.37 g, 15.14 mmol) was suspended in CH_2Cl_2 (65 mL) under an N_2 atmosphere and placed into an ice water bath. To this solution was added a solution of piperazine (4.00 g, 45.42 mmol) and triethylamine (4.2 mL, 30.28 mmol) in CH_2Cl_2 (15 mL) in one portion. After stirring the reaction for 30 minutes, it was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted twice more with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated to a bright yellow solid which was purified via silica gel chromatography using a 95%/5% mixture of CH_2Cl_2/MeOH to afford 3-fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (4.32 g, 85%) as a bright yellow solid. *LC/MS*: *m/z* 339.3 $(M+H)^+$ at 1.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 7.92 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.39–7.30 (m, 2H), 6.78 (d, J = 8.3 Hz, 1H), 6.74–6.69 (m, 1H), 3.83 (t, J = 4.8 Hz, 4H), 2.88 (t, J = 4.9 Hz, 4H).

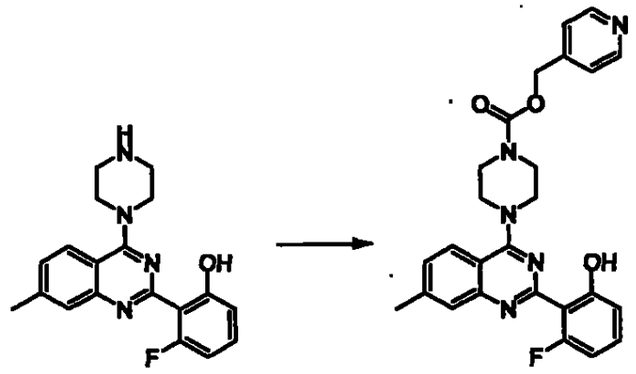
[00410] (Pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate



[00411]

[00412] A solution of (pyridin-4-yl)methanol (2.0 g, 18.3 mmol) and di(1*H*-imidazol-1-yl)methanone (5.94 g, 36.6 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was quenched with water, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (3 g, 81%). LC/MS: *m/z* 204.3 $(M+H)^+$ at 0.38 min (v). ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 4.4, 1.6 Hz, 2H), 8.20 (t, *J* = 0.9 Hz, 1H), 7.47 (t, *J* = 1.5 Hz, 1H), 7.34 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.11 (dd, *J* = 1.6, 0.8 Hz, 1H), 5.45 (s, 2H).

[00413] **(Pyridin-4-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**



[00414]

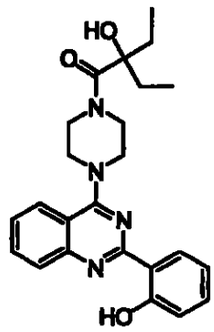
[00415] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.15 mmol), (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (53 mg, 0.26 mmol) and triethylamine (30.4 mg, 0.3 mmol) were added into a tube, followed by the addition of DMSO (1 mL). The mixture was stirred at room temperature for 18 h and then filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) giving (pyridin-4-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate. LC/MS: *m/z* 474.30 (M+H)+ at 1.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00416] Example 115

72

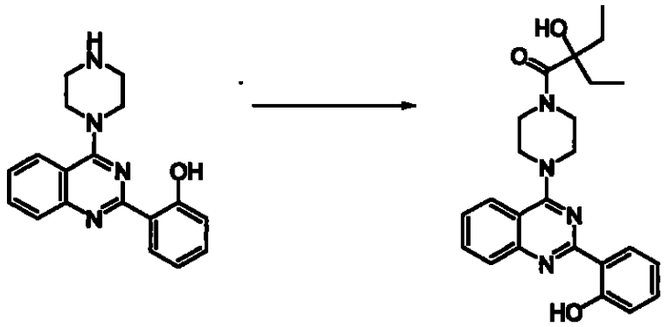
[00417] 2-Ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00418]



[00419] 2-Ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00420]

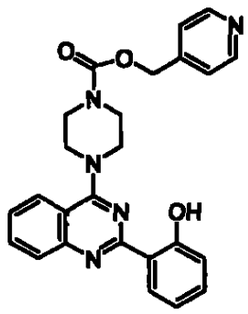


[00421] To a solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added 2-ethyl-2-hydroxybutanoic acid (39.30 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 421.3 $(M+H)^+$ at 2.51 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00422] Example 116

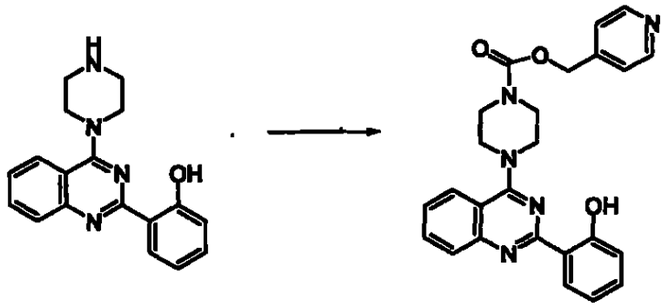
[00423] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00424]



[00425] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00426]

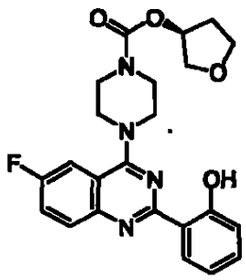


[00427] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (67 mg, 0.32 mmol) and triethylamine (45 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 442.50 $(M+H)^+$ at 1.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00428] Example 117

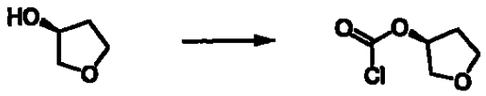
[00429] (*S*)-Tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl) quinazolin-4-yl)piperazine-1-carboxylate

[00430]



[00431] **(*S*)-Tetrahydrofuran-3-yl chloroformate**

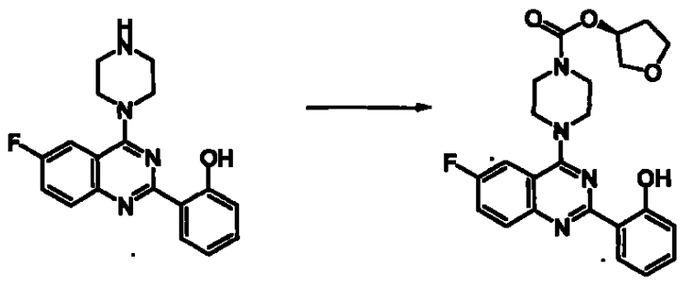
[00432]



[00433] A stirred solution of (*S*)-tetrahydrofuran-3-ol (7.9 g, 90 mmol) in anhydrous CH_2Cl_2 (50 mL) under an N_2 atmosphere was cooled in an ice bath, and a 20% solution of phosgene in toluene (134 mL, 270 mmol) was slowly added. The reaction was allowed to warm to room temperature overnight, and the solvent was removed under vacuum to afford (*S*)-tetrahydrofuran-3-yl chloroformate (12.1 g, 85%) as a clear liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 5.42–5.39 (m, 1H), 4.01–3.84 (m, 4H), 2.31–2.13 (m, 2H).

[00434] **(*S*)-Tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl) quinazolin-4-yl)piperazine-1-carboxylate**

[00435]



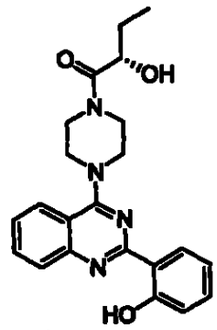
[00436] To a solution of 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol) in DMF (1 mL) was added triethylamine (22 μL, 0.16 mmol) followed by the dropwise addition of (*S*)-tetrahydrofuran-3-yl chloroformate (12 mg, 0.08 mmol) at 0 °C. The reaction was complete immediately after the addition of the chloroformate. Purification using

reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00437] Example 118

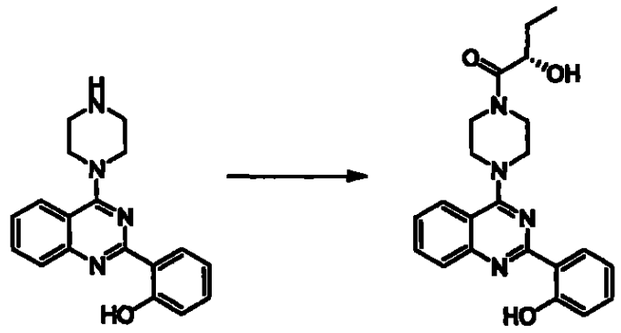
[00438] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00439]



[00440] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00441]



[00442] Method A

[00443] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*R*)-2-hydroxybutanoic acid (31 mg, 0.297 mmol), followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-(4-(2-(2-

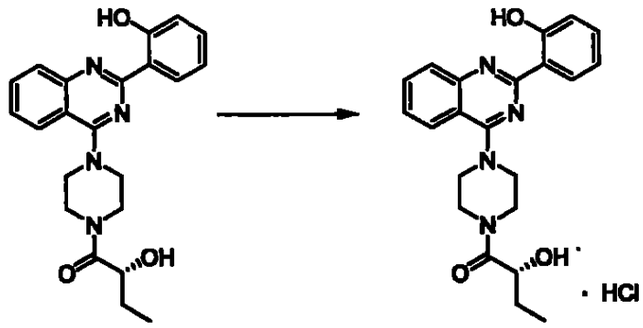
hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 421.30 $(M+H)^+$ at 2.51 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00444] Method B

[00445] To a solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.82 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (227 μL, 1.63 mmol) followed by the addition of (*R*)-2-hydroxybutanoic acid (110 mg, 1.06 mmol) and HATU (380 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one (280 mg, 88%). *LC/MS*: *m/z* 393.3 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.47 (m, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.89 (m, 2H), 7.57 (m, 1H), 7.40 (m, 1H), 6.96 (m, 2H), 4.92 (d, *J* = 7.1 Hz, 1H), 3.88 (m, 8H), 1.67 (m, 1H), 1.51 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

[00446] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride**

[00447]



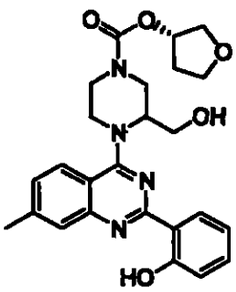
[00448] To a solution of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one (280 mg, 0.71 mmol) in CH_2Cl_2 under an N_2 atmosphere was added a 2 M HCl solution in ether (0.355 mL, 0.71 mmol), followed by the addition of ether which resulted in the formation of precipitate which was stirred for an hour and then filtered and dried to afford (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride (272 mg, 90%). LC/MS: *m/z* 393.1 $(M+H)^+$ at 2.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.27 (dd, *J* = 7.9, 1.6 Hz,

1H), 8.19 (d, J = 8.4 Hz, 1H), 7.96 (m, 2H), 7.65 (m, 1H), 7.48 (m, 1H), 7.04 (m, 2H), 4.26 (dd, J = 7.7, 4.8 Hz, 1H), , 4.03 (m, 4H), 3.79 (m, 5H), 1.65 (m, 1H), 1.50 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H).

[00449] Example 119

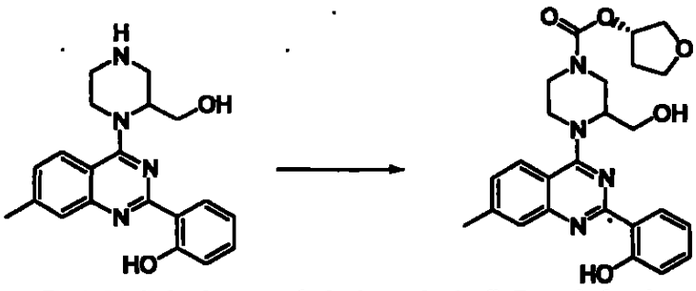
[00450] (*S*)-3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid tetrahydro-furan-3-yl ester

[00451]



[00452] (*S*)-3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid tetrahydro-furan-3-yl ester

[00453]

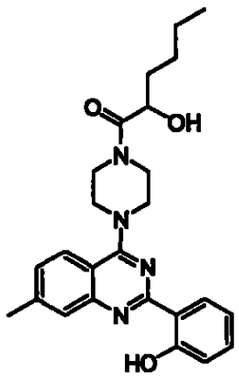


[00454] To 2-[4-(2-hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (69.2 mg, 0.19 mmol) in 650 μL of CH_2Cl_2 at 0 °C was added (*S*)-tetrahydro-furan-3-ol-chloroformate (26.8 mg, 0.17 mmol), followed by triethylamine (30 μL, 0.22 mmol). The reaction mixture was stirred for an hour and then diluted with 5 mL of CH_2Cl_2 and 5 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to purification using 30–100% EtOAc–hexanes to give the desired product. LC/MS: *m/z* 465.2 $(M+H)^+$ at 2.5 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00455] Example 120

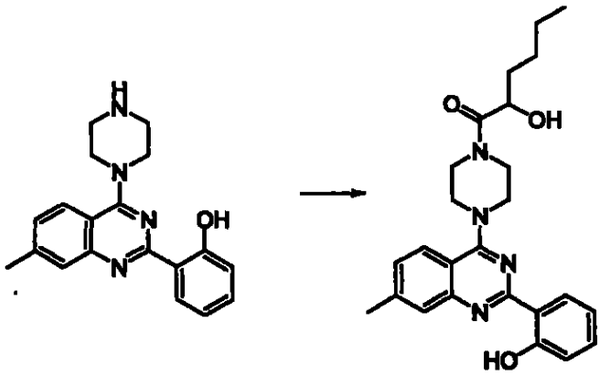
[00456] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00457]



[00458] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00459]

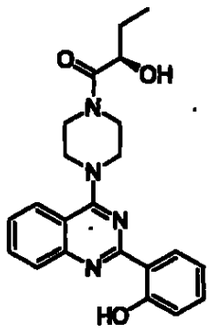


[00460] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxyhexanoic acid (37.5 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one as the TFA salt. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.65 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00461] Example 121

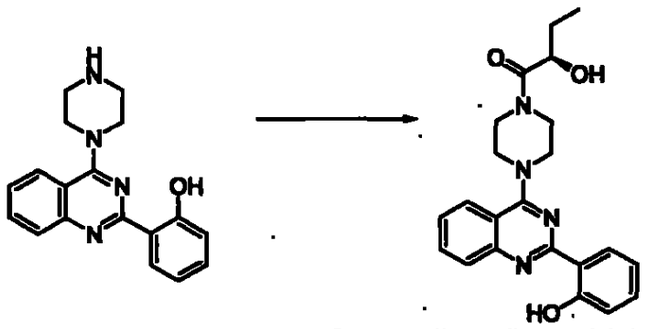
[00462] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00463]



[00464] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00465]

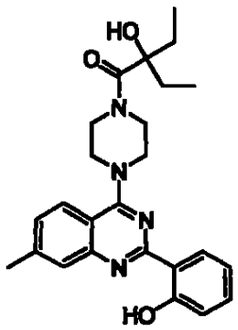


[00466] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*R*)-2-hydroxybutanoic acid (31 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00467] Example 122

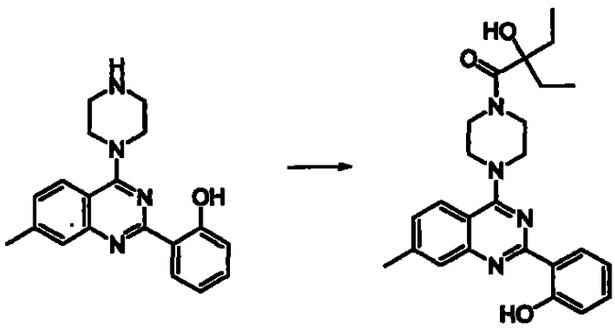
[00468] 2-Ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00469]



[00470] 2-Ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00471]

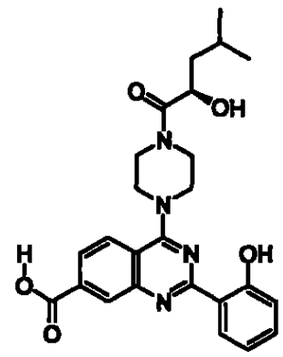


[00472] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-ethyl-2-hydroxybutanoic acid (37.5 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00473] Example 123

[00474] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-7-carboxylic acid

[00475]



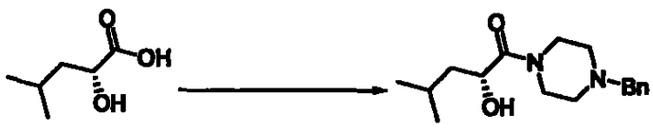
[00476] (*R*)-α-hydroxyisocaproic acid

[00477]

[00478] To a cooled solution (0–5 °C) of D-leucine (200 g, 1.5 mol) in sulfuric acid (3 L, 1 M) was added dropwise a solution of sodium nitrite (240 g, 3.5 mol) in water (1 L) while maintaining the temperature between 0–5 °C. The reaction mixture was stirred at room temperature overnight. The solution was saturated with sodium chloride and extracted with *tert*-butyl methyl ether (3x). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. (*R*)-α-hydroxyisocaproic acid was isolated as a white solid in a yield of 67% (132 g).

[00479] 1-(4-Benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one

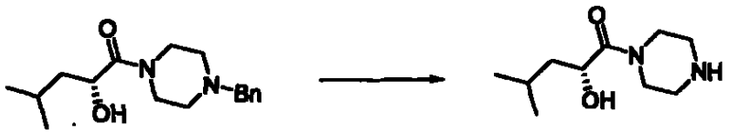
[00480]



[00481] To a cooled solution (0–5 °C) of (*R*)-α-hydroxyisocaproic acid (64.5 g, 0.5 mol), 1-benzylpiperazine (88 g, 0.5 mol) and triethylamine (71 ml, 0.5 mol) in CH_2Cl_2 (850 ml) was added in portions HOBt (68 g, 0.5 mol) and EDCI·HCl (96 g, 0.5 mol). The reaction mixture was stirred at room temperature overnight. The organic layer was washed with water (3x) and once with brine, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. Crude

1-(4-benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one (132 g, 91%) was used in the next step without further purification

[00481] **2-Hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one**



[00482] To a solution of 1-(4-benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one (132 g) in methanol (1 L) was added Pd/C (20 g,10% weight Pd on carbon). The reaction mixture was stirred at room temperature overnight under an atmosphere of hydrogen. The reaction mixture was filtered through Celite, and the solvent was removed *in vacuo*. 2-Hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one was obtained as an oil (68 g, 74%).

[00483] **1,2,3,4-Tetrahydro-2,4-dioxoquinazoline-7-carboxylic acid**

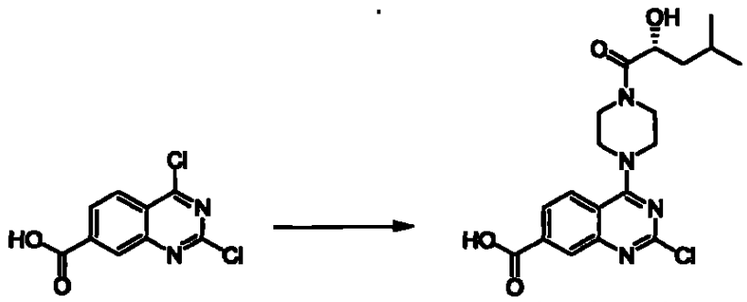
[00484] To a stirring mixture of dimethyl 2-aminobenzene-1,4-dioate (10.5 g, 50 mmol) and AcOH (3.4 mL, 60 mmol) in H_2O (200 mL) was added KOCN (8.1 g, 100 mmol). The reaction mixture was heated at 100 °C for 3 h. After cooling in an ice bath, NaOH (24 g, 600 mmol) was slowly added to the mixture and stirred for another 3 h at room temperature. Acidification with concentrated HCl resulted in formation of a yellow solid which was filtered, washed with water and dried under vacuum (8.3 g). NMR data showed that the solid consisted of a 3:1 mixture of the desired 1,2,3,4-tetrahydro-2,4-dioxoquinazoline-7-carboxylic acid and a side product. This mixture was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.98 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.67 (dd, J = 8.2, 1.4 Hz, 1H).

[00485] **2,4-Dichloroquinazoline-7-carboxylic acid**

[00490] A mixture of 1,2,3,4-tetrahydro-2,4-dioxoquinazoline-7-carboxylic acid (1.0 g, 4.9 mmol), $POCl_3$ (10 mL) and dimethylaniline (0.5 mL, 3.94 mmol) was heated at 90 °C for 3 h. After cooling and pouring the reaction mixture over ice, it was extracted with EtOAc. The combined extracts were washed with water, dried over Na_2SO_4 and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 provided 2,4-dichloroquinazoline-7-carboxylic acid as a yellow solid (0.45 g, 38%). ^1H NMR (400 MHz, DMSO-d6) δ 8.46 (d, J = 1.4 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.30 (dd, J = 8.6, 1.5 Hz, 1H); LC/MS: m/z 243.1 $(M+H)^+$ at 2.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00491] **2-Chloro-4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-quinazoline-7-carboxylic acid**

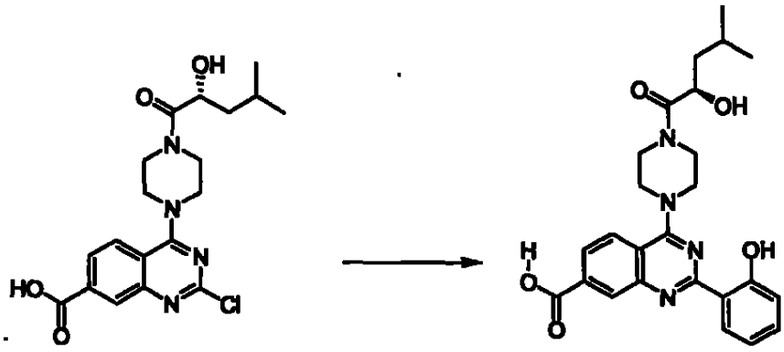
[00492]



[00493] To a solution of 2,4-dichloroquinazoline-7-carboxylic acid (0.45 g, 1.9 mmol) in CH_2Cl_2 (20 mL) was added (*R*)-2-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one (0.37 g, 1.9 mmol) and triethylamine (0.52 mL, 3.7 mmol). The reaction mixture was stirred overnight at room temperature and then purified via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 to obtain 2-chloro-4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-quinazoline-7-carboxylic acid (0.58 g, 77%). LC/MS: m/z 407.3 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00494] **4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-7-carboxylic acid**

[00495]

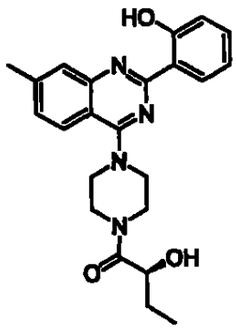


[00496] A mixture of 2-chloro-4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-quinazoline-7-carboxylic acid (114 mg, 0.28 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 μL, 0.42 mmol) *Pd*(dppf)Cl_2 (14 mg, 0.017 mmol) and K_2CO_3 (155 mg, 1.1 mmol) in DMF (4 mL) and H_2O (1 mL) was heated in a sealed microwave vial at 170 °C for 6 minutes. After filtration and evaporation of the solvents, the mixture was purified using preparative HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-7-carboxylic acid as the TFA salt. LC/MS: *m/z* 465.3 $(M+H)^+$ at 2.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00497] Example 124

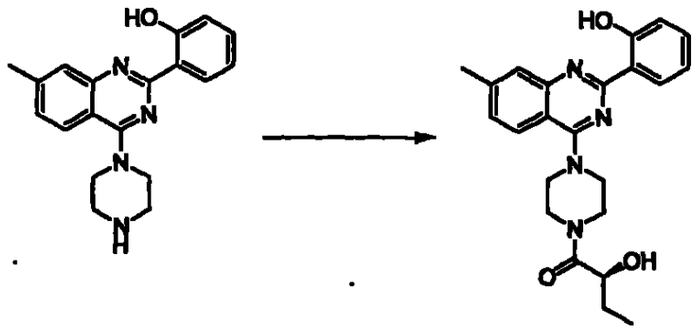
[00498] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00499]



[00500] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00501]

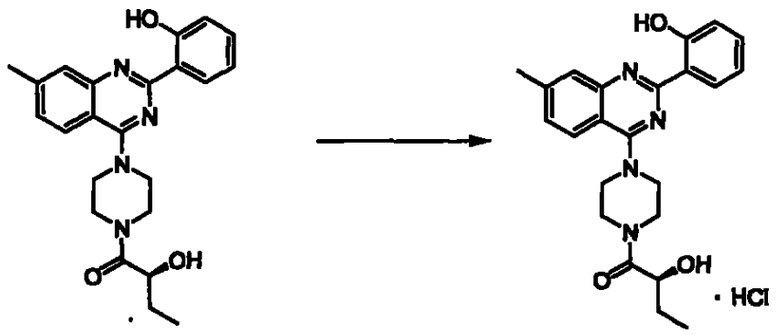


[00502] Method A: A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to (*S*)-2-hydroxybutanoic acid (31 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00503] Method B: To a solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.78 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (217 μL, 1.56 mmol) followed by the addition of (*S*)-2-hydroxybutanoic acid (105 mg, 1.0 mmol) and HATU (380 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one (300 mg, 95%). LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.45 (m, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.39 (m, 2H), 6.95 (m, 2H), 4.92 (d, J = 7.0 Hz, 1H), 4.28 (q, J = 6.5 Hz, 1H), 3.89 (m, 8H), 2.52 (s, 3H), 1.67 (m, 1H), 1.51 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H)

[00504] **(*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride**

[00505]

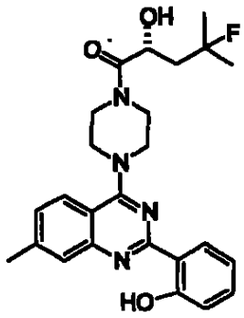


[00506] To a solution of (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one (300 mg, 0.73 mmol) in CH_2Cl_2 was added a 2 M HCl solution in ether (0.365 mL, 0.73 mmol), followed by the addition of ether until the salt precipitated out, which was stirred for an hour, collected by vacuum filtration and dried to afford (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride (270 mg, 84%). LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.26 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.73 (s, 1H), 7.47 (m, 2H), 7.03 (m, 2H), 4.26 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.08 (m, 4H), 3.79 (m, 4H), 2.53 (s, 3H), 1.65 (m, 1H), 1.50 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H).

[00507] Example 125

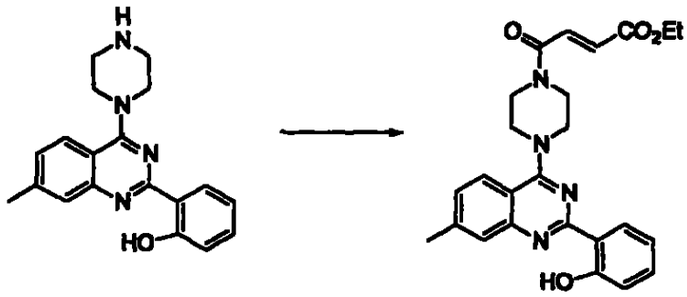
[00508] **(*R*)-4-Fluoro-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one**

[00509]



[00510] 4-{4-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-but-2-enoic acid ethyl ester

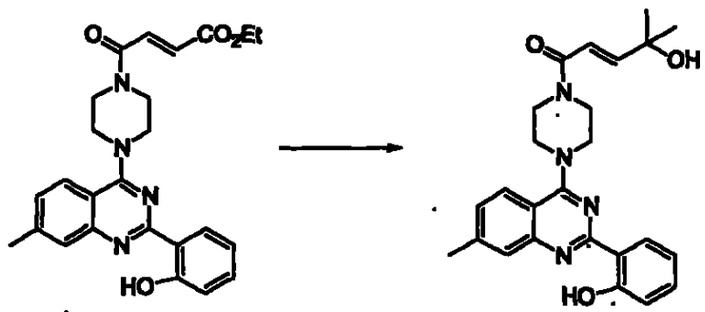
[00511]



[00512] To 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (787 mg, 2.46 mmol) in 8 mL of CH_2Cl_2 at room temperature was added sequentially but-2-enedioic acid monoethyl ester (531 mg, 3.69 mmol), triethylamine(686 μL, 4.92 mmol), BOP (1.63 g, 3.69 mmol). The reaction mixture was stirred for 20 min and diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was subjected to purification by normal phase LC using 10–100% EtOAc–hexanes to give 4-{4-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-but-2-enoic acid ethyl ester (1.00 g, 91% yield). LC/MS: *m/z* 447.3 $(M+H)^+$ at 2.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00513] 4-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1- one

[00514]

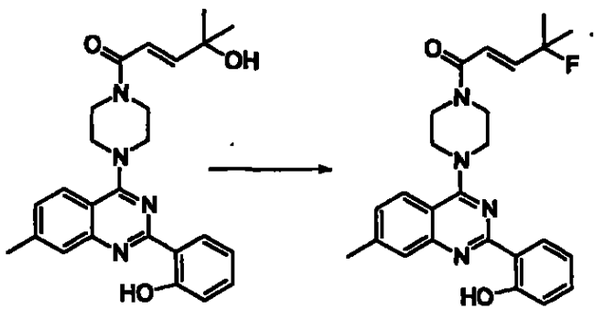


[00515] To 4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-but-2-enoic acid ethyl ester (655 mg, 1.47 mmol) in 2 mL of diethyl ether at –20 °C was added methyl magnesium bromide (8.4 mL, 11.7 mmol, 1.4 M THF/Toluene), and the reaction mixture

was allowed to warm to 0 °C over 15 minutes The mixture was diluted with 10 mL of water and 15 mL of CH_2Cl_2. The resulting emulsion was filtered, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the alcohol. LC/MS: *m/z* 433.5 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

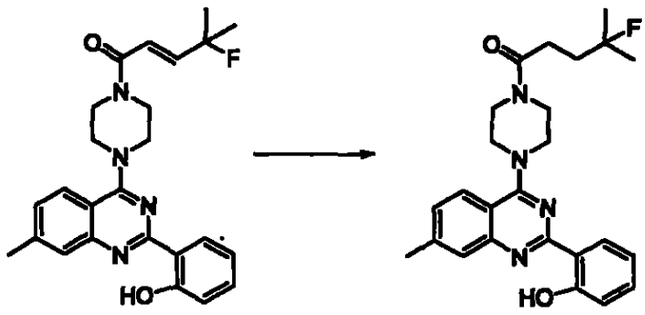
[00516] **4-Fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1-one**

[00517]



[00518] To 4-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1- one (330 mg, 0.76 mmol) at –78 °C in 3 mL of CH_2Cl_2 was added (diethylamino)sulfur trifluoride (185 mg, 1.15 mmol). The reaction mixture was stirred –78 °C for 2.5 h. The reaction mixture was diluted with 10 mL of water and 10 mL of CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was subjected to purification by normal phase LC using 10–100% EtOAc–hexanes to give 4-fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1-one (133 mg, 40% yield). LC/MS: *m/z* 435.4.3 $(M+H)^+$ at 2.92 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00519] **4-Fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one**

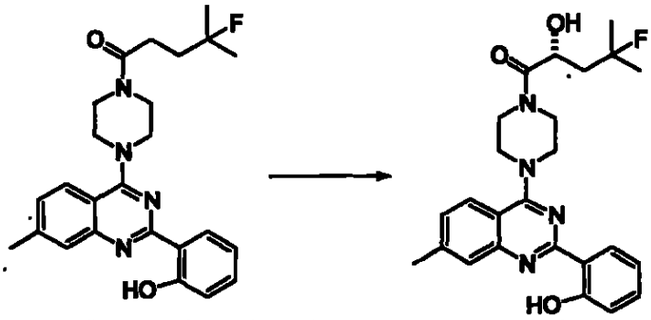


[00520]

[00521] To 4-fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1-one (228 mg) in 1.5 mL of methanol was added Pd/C (34 mg, 10% weight Pd on carbon), and the reaction mixture was hydrogenated with a hydrogen balloon for 1 h. The resulting mixture was filtered through Celite, and the solvent was removed to give 4-fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one. LC/MS: *m/z* 437.4 $(M+H)^+$ at 2.86 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00522] **(*R*)-4-Fluoro-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one**

[00523]



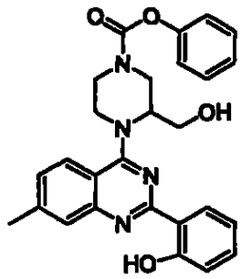
[00524] To 4-fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one (225 mg, 0.53 mmol) in 500 μL of THF was added a 2.7 M LDA solution (0.8 mL, 2.1 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 25 min, and then (1*R*)-(-)-(10-camphorsulfonyl)oxaziridine (361 mg, 1.6 mmol) in 1.5 mL of THF was added slowly. The reaction mixture was allowed to warm to –45 °C over 30 min, and then diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by preparative reverse

phase HPLC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-4-fluoro-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one as the TFA salt. LC/MS: *m/z* 453.4 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00525] Example 126

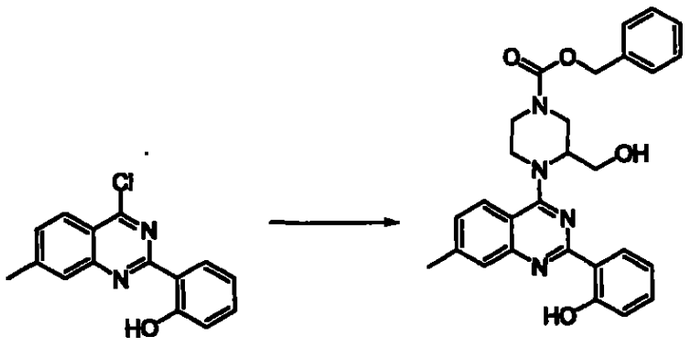
[00526] **3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid phenyl ester**

[00527]



[00528] **3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester**

[00529]

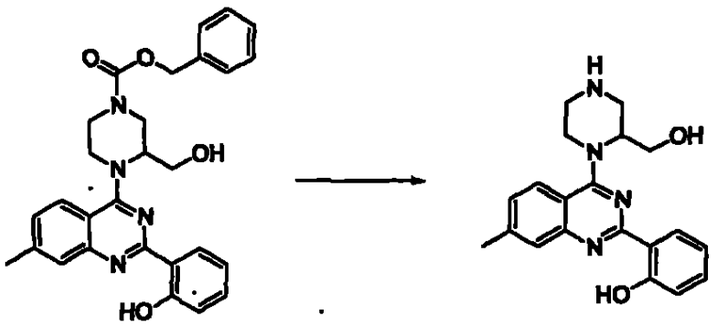


[00530] To 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol (245 mg, 0.91 mmol) in 3.0 mL of CH_2Cl_2 was added 3-hydroxymethyl-piperazine-1-carboxylic acid benzyl ester (226 mg, 0.58 mmol) and triethylamine (190 μL, 1.37 mmol). The reaction mixture was stirred for 12 hours at room temperature, and additional 3-hydroxymethyl-piperazine-1-carboxylic acid benzyl ester (100 mg, 0.4 mmol) and triethylamine (200 μL, 1.4 mmol) was added, and the reaction mixture was heated at 40 °C for 6 h. The reaction mixture was cooled, and diluted with 5 mL of CH_2Cl_2

and 5 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography eluting with 20–85% EtOAc/hexanes to give 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester(216 mg, 65 %). LCMS: *m/z* 485 $(M+H)^+$ at 3.03 min (10%-99% CH_3CN/H_2O)

[00531] **2-[4-(2-Hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol**

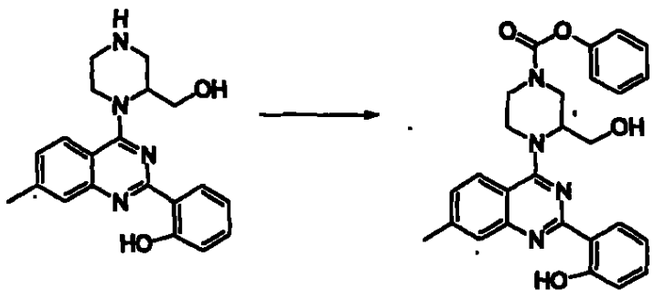
[00532]



[00533] To 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester (200 mg, 0.41 mmol) in 1.7 mL of methanol was added 39 mg of Pd/C (10% wt Pd on carbon). The reaction mixture was stirred under a hydrogen atmosphere for 3 h. The mixture was filtered through Celite, and the solvent was removed to give 2-[4-(2-hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol. LCMS: *m/z* 351.2 $(M+H)^+$ at 2.11 min (10%-99% CH_3CN/H_2O).

[00534] **3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid phenyl ester**

[00535]

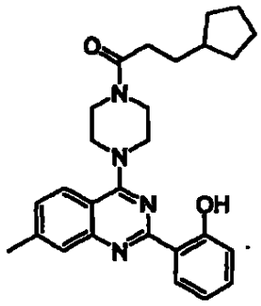


[00536] To 2-[4-(2-hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (31.9 mg, 0.091 mmol) in 300 µL of CH_2Cl_2 was added at 0 °C sequentially triethylamine (13.9 µL) and phenyl chloroformate (14.3 mg, 0.091 mmol). The reaction mixture was stirred for 30 min and was warmed to room temperature and stirred for an additional 40 minutes At the end of this period, the solvent was removed, and the residue was dissolved in DMSO and purified by preparative reverse phase HPLC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) as eluent to give 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid phenyl ester as the TFA salt. LC/MS: *m/z* 471.2 (M+H)+ at 2.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00537] Example 127

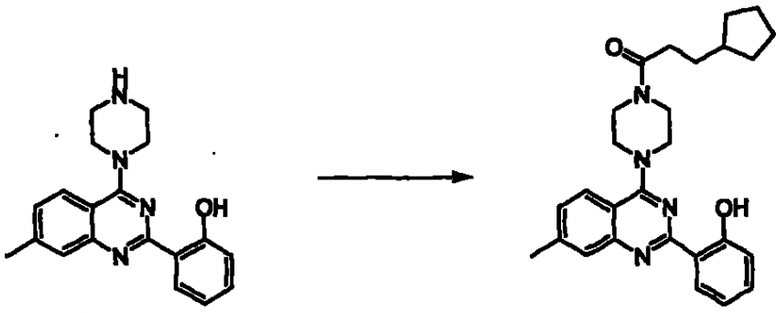
[00538] 3-Cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[00539]



[00540] 3-Cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[00541]



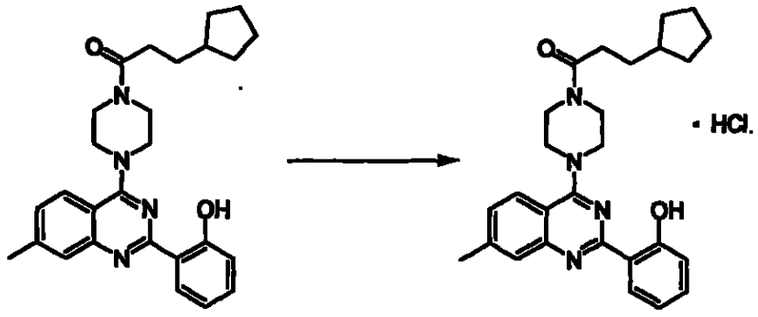
[00542] Method A

[00543] To 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (53 mg, 0.17 mmol) was added sequentially 3-cyclopentylpropanoyl chloride (29 mg, 0.19 mmol) in 550 μL of CH_2Cl_2 and triethylamine (28 μL, 0.2 mmol). The mixture was stirred at 0 °C for 20 minutes After adding H_2O and CH_2Cl_2, the phases were separated, and the organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification using preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 445.5 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00544] Method B

[00545] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (200 mg, 0.62 mmol) in CH_2Cl_2 (6.0 mL) was stirred under an N_2 atmosphere. Then triethylamine (170 μL, 1.24 mmol) was added, and the reaction was cooled to –10 to –20 °C. After adding 3-cyclopentylpropanoyl chloride (96 μL in 600 μL THF, 0.62 mmol), the reaction mixture was stirred for 30 minutes. CH_2Cl_2 was added, and the organic phase was washed 2x with H_2O, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2: hexanes gave 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one (240 mg, 86%). LC/MS: *m/z* 445.50 $(M+H)^+$ at 3.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.45 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.39 (m, 2H), 6.95 (m, 2H), 3.95 (dd, *J* = 19.9, 5.6 Hz, 4H), 3.74 (m, 4H), 2.52 (s, 3H), 2.38 (t, *J* = 7.8 Hz, 2H), 1.76 (m, 3H), 1.55 (m, 6H), 1.16 (m, 2H).

[00546] **3-Cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one hydrochloride**

[00547] 

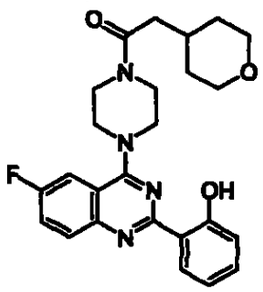
Under an N_2 atmosphere, a 1 M HCl solution in diethyl ether (0.54 mL, 0.54 mmol) was added dropwise to a stirring solution of 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one (240 mg, 0.54 mmol) in CH_2Cl_2 (20 mL). After 10 min, ether was added until a precipitate formed. The solid was collected by filtration and dried under vacuum to give 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one hydrochloride (230 mg, 88%). *LC/MS*: *m/z* 445.30 $(M+H)^+$ at 3.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.26 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.78 (s, 1H), 7.50–7.46 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.04–7.00 (m, 1H), 4.15–4.11 (m, 4H), 3.79–3.74 (m, 4H), 2.54 (s, 3H), 2.37 (t, *J* = 7.7 Hz, 2H), 1.82–1.74 (m, 3H), 1.60–1.45 (m, 6H), 1.12–1.08 (m, 2H)

[00548]

[00549] Example 128

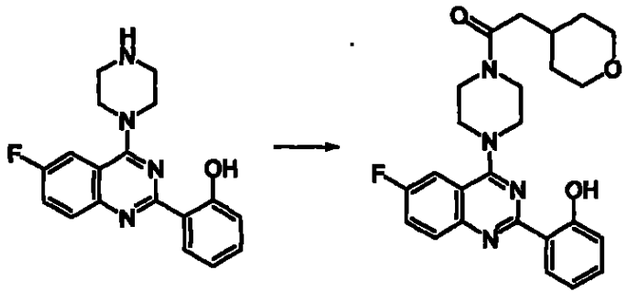
[00550] 1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanone

[00551]



[00552] 1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanone

[00553]

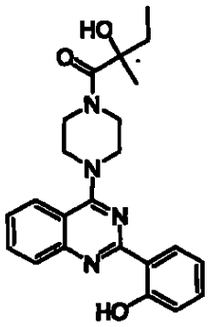


[00554] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.077 mmol), 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (14.3 mg, 0.10 mmol), triethylamine (22μL, 0.154 mmol), and HATU (38 mg, 0.10 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanone. LC/MS: *m/z* 451.5 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00555] Example 129

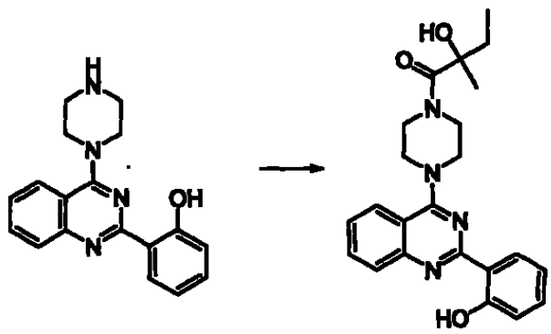
[00556] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one

[00557]

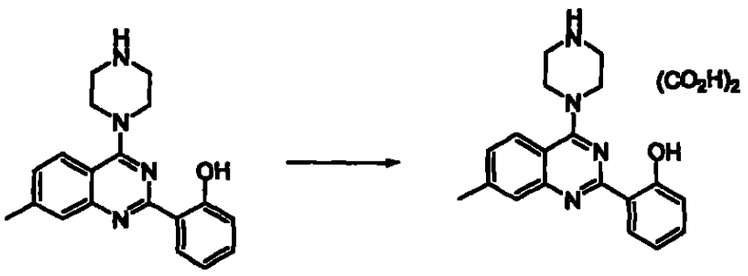


[00558] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one

[00559]



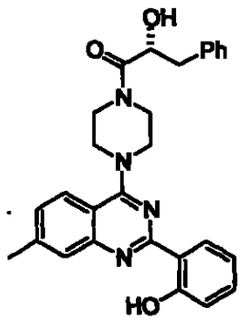
[00560] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-hydroxy-2-methylbutanoic acid (39.3 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL) and a solution of HATU (113 mg) in 0.5 mL



[00557] DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00558] Example 130

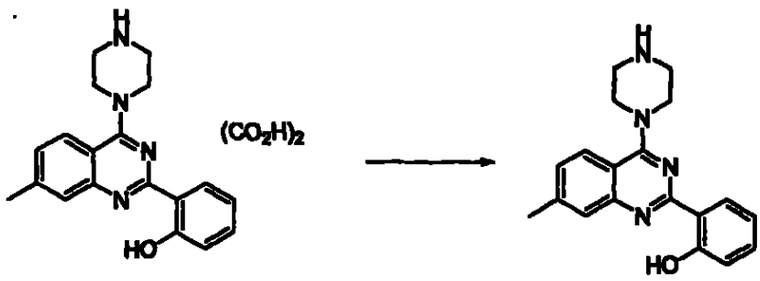
[00559] (*R*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone



[00560] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol, oxalate salt

[00561] To 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (30.6 g, 95.4 mmol) in 900 mL CH_2Cl_2 was added oxalic acid (9.45 g, 105 mmol, 1.1 eq.) dissolved in 36 mL of methanol. The resulting cloudy solution was stirred for 3h and the resulting solid was filtered, washed with hexanes, and dried to give 29.3 g (75 %) the oxalate salt of 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol. LC/MS: *m/z* 321.2 $(M+H)^+$ at 2.36 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00562] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol

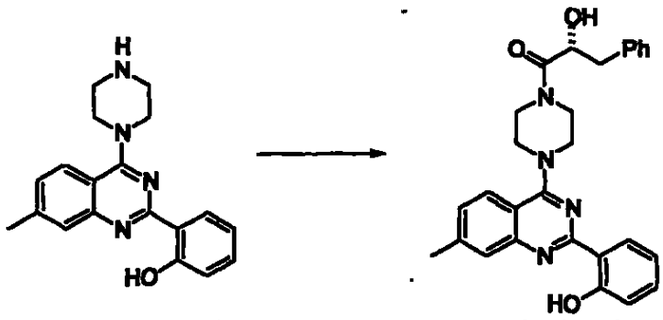


[00568]

[00569] To the oxalate salt of 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (1.32 g, 3.2 mmol) in 10 mL of CH_2Cl_2 was added triethylamine (2.2 mL, 16.0 mmol) at room temperature. The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with 10 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol as an oil which was used without further purification.

[00570] **(*R*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone**

[00571]



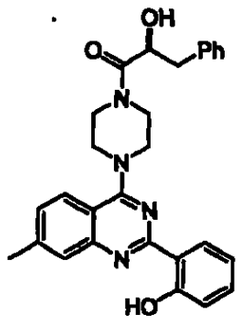
[00572] To 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (64 mg, 0.19 mmol) in 600 μL of CH_2Cl_2 was added sequentially 3-(*R*)-phenyl lactic acid (35 mg, 0.21 mmol), BOP (93 mg, 0.21 mmol), and triethylamine (27.7 μL, 0.2 mmol) at room temperature. The reaction mixture was stirred for 1.5 h, diluted with 10 mL of methylene chloride, and washed with water (2 x 10 mL). The solvent was removed under reduced pressure to give an oil which was purified by normal phase LC (35%–100% EtOAc/ hexanes) to give (*R*)-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone. LC/MS: *m/z* 469.3 $(M+H)^+$ at 2.87 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00573] Example 131

85

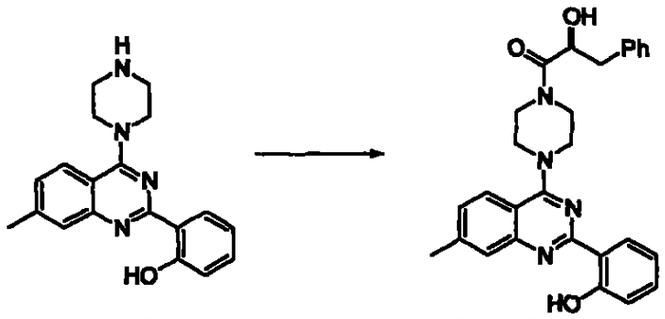
[00574] (*S*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone

[00575]



[00576] (*S*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone

[00577]

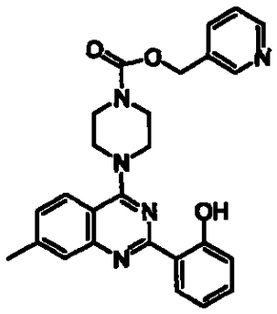


[00578] To 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (79.9 mg, 0.25 mmol) in 800 μL of CH_2Cl_2 was added sequentially 3-(*R*)-phenyl lactic acid(41.4 mg, 0.25 mmol), BOP(110 mg, 0.25 mmol), triethylamine (34.7 μL, 0.25 mmol) at room temperature. The reaction mixture was stirred for 1.5 h, diluted with 10 mL of methylene chloride, and washed with water (2 x 10 mL). The solvent was removed under reduced pressure to give an oil which was purified by normal phase LC (35%-100% EtOAc/hexanes) to give (*S*)-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone. LC/MS: *m/z* 469.4 $(M+H)^+$ at 2.88 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00579] Example 132

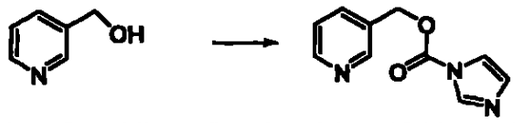
[00580] (Pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00581]



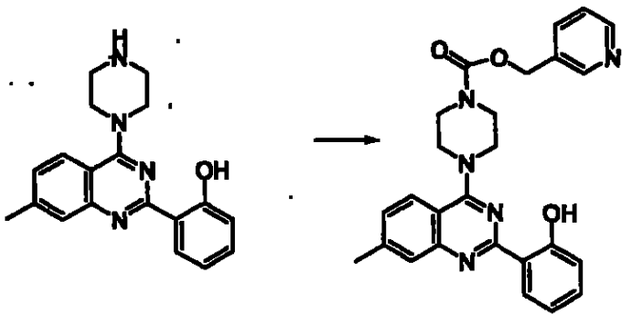
[00582] (Pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate

[00583]



[00584] A solution of (pyridin-3-yl)methanol (2 g, 18.32 mmol) and di(1*H*-imidazol-1-yl)methanone (5.94 g, 36.65 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was washed with water, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (3 g, 81%). LC/MS: *m/z* 204.1 $(M+H)^+$ at 0.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 1.9 Hz, 1H), 8.68 (dd, J = 4.8, 1.4 Hz, 1H), 8.16 (s, 1H), 7.81 (m, 1H), 7.44 (s, 1H), 7.38 (m, 1H), 7.09 (s, 1H), 5.46 (s, 2H).

[00585] (Pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate



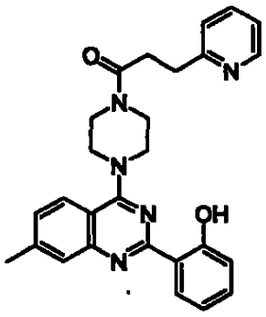
[00586]

[00587] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (67 mg, 0.32 mmol), and triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. *LC/MS*: *m/z* 456.5 $(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00588] Example 133

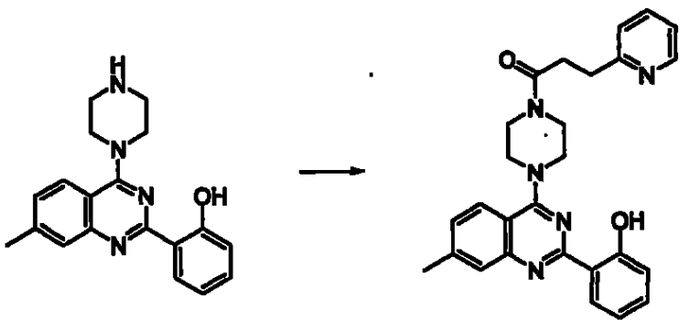
[00589] **1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(pyridin-2-yl)propan-1-one**

[00590]



[00591] **1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(pyridin-2-yl)propan-1-one**

[00592]

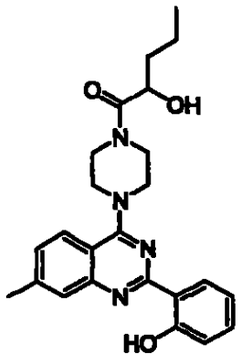


[00593] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (0.5 mL) was added to 3-(pyridin-2-yl)propanoic acid (21.23 mg, 0.14 mmol). Triethylamine (25 μL) was added, followed by a solution of HATU (45 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(pyridin-2-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 454.3 $(M+H)^+$ at 1.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00594] Example 134

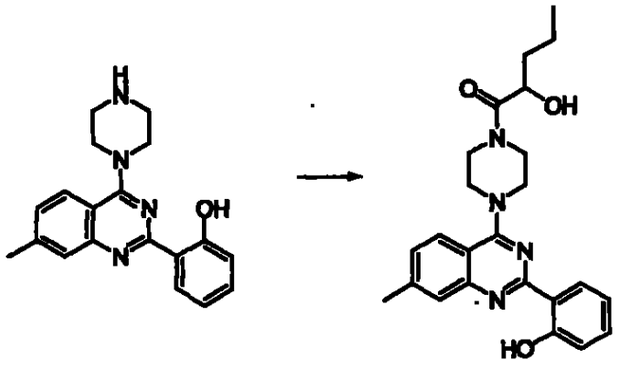
[00595] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentan-1-one

[00596]



[00597] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentan-1-one

[00598]

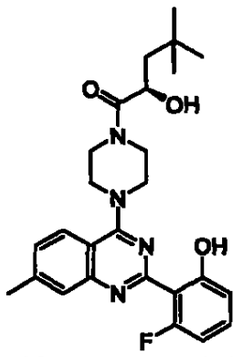


[00599] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxypentanoic acid (33.6 mg, 0.28 mmol). It was followed by the addition of triethylamine (61 μL), and a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentan-1-one as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00600] Example 135

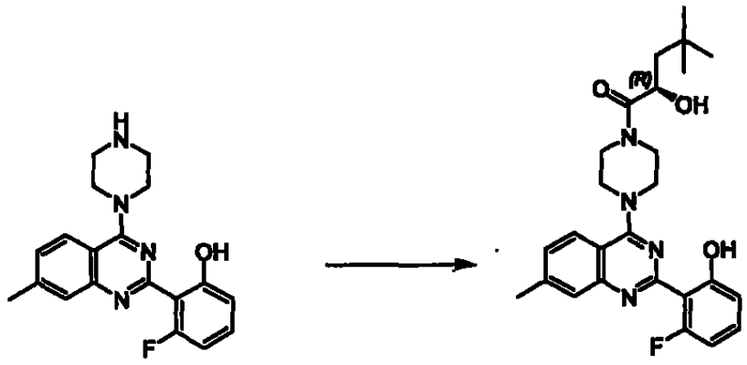
[00601] **(*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one**

[00602]



[00603] **(*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one**

[00604]



[00605] Method A

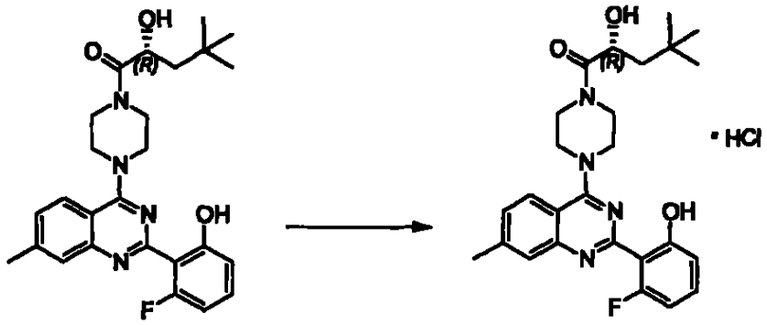
[00606] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.15 mmol) was placed in a tube charged with a stir bar, (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (26 mg, 0.18 mmol) in1 ml of DMF, and triethylamine (30 mg, 41 μL, 0.29 mmol), and the tube was cooled to 0 °C. HATU (68 mg, 0.18 mmol) was added, and the reaction was stirred at 0 °C for 10 minutes and then allowed to warm to room temperature. After 40 minutes, the reaction was filtered, and purified by reverse phase HPLC to give the TFA salt of (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one. LC/MS: *m/z* 467.1 $(M+H)^+$ at 2.59 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00607] Method B

[00608] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.74 mmol) was suspended in anhydrous DMF (5 mL) and cooled to 0 °C (internal temperature). Under an N_2 atmosphere, (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (118.4 mg, 0.81 mmol) was added followed by triethylamine (0.207 mL, 1.48 mmol). To this stirring solution was added HATU (337 mg, 0.888 mmol). After the complete addition of HATU, the mixture was allowed to warm to 10 °C. After 45 min the reaction was complete, and it was quenched with an equal portion of ice water. A yellow precipitate formed which was collected by vacuum filtration, dissolved in CH_2Cl_2, and the CH_2Cl_2 solution was desiccated with Na_2SO_4, filtered, and concentrated to a viscous yellow-orange oil. The crude material was purified via silica gel chromatography using 70% CH_2Cl_2/hexanes (1:1) and 30% EtOAc to afford (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one as a yellow solid (171 mg, 50%). LC/MS: *m/z* 467.1 $(M+H)^+$ at 2.63 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.02 (d, J = 8.6 Hz, 1H), 7.69 (s, 1H), 7.43 (dd, J = 8.6, 1.5 Hz, 1H), 7.37–7.32 (m, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.76–6.71 (m, 1H), 4.87 (d, J = 7.2 Hz, 1H), 4.47–4.43 (m, 1H), 4.01–3.75 (m, 8H), 2.52 (s, 3H), 1.55 (dd, J = 14.3, 3.0 Hz, 1H), 1.40 (dd, J = 14.3, 8.8 Hz, 1H), 0.96 (s, 9H)

[00609] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride

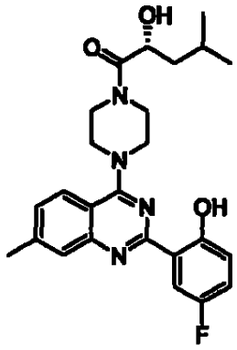
[00610]



[00611] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one (171 mg, 0.367 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) followed by the addition of Et_2O (6 ml) under an N_2 atmosphere. A 2.0 M HCl solution in Et_2O (0.184 mL, 0.367 mmol) was added over a 1 minute period. The reaction solution changed from a clear yellow solution to a milky white slurry. After complete addition of the HCl solution, the reaction was allowed to stir for an additional 10 minutes. The product was collected by vacuum filtration and dried under vacuum to obtain (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride as a light yellow solid (170 mg, 92%). LC/MS: *m/z* 467.3 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.66 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.48–7.43 (m, 1H), 6.92–6.83 (m, 2H), 4.44–4.41 (m, 1H), 3.87–3.68 (m, 8H), 2.56 (s, 3H), 1.55 (dd, *J* = 14.3, 3.0 Hz, 1H), 1.41 (dd, *J* = 14.3, 8.8 Hz, 1H), 0.96 (s, 9H).

[00612] Example 136

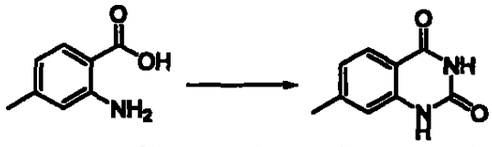
[00613] (*R*)-1-(4-(2-(5-Fluoro-2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one



[00614]

[00615] 7-Methylquinazoline-2,4(1*H*,3*H*)-dione

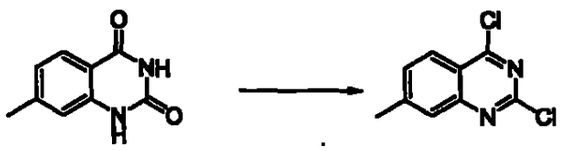
[00616]



[00617] To a suspension of 2-amino-4-methylbenzoic acid (58.9 g, 390 mmol) in water (1.5 L) and glacial acetic acid (50 ml) was added dropwise a solution of potassium cyanate (80.5 g, 993 mmol) in water (300 ml). After completion of the addition and stirring at room temperature for half an hour, sodium hydroxide pellets (500 g) were added at such a rate that the temperature was kept below 50 °C (with ice cooling). During the addition the mixture became a clear solution for a short period, and upon continuation of the sodium hydroxide addition a cream precipitate started forming. The suspension was cooled to 0–5 °C and the precipitate was collected by filtration and washed twice with water (150 ml). The solid was poured in water (1 L) and was acidified with concentrated aqueous HCl (30%, 150 ml). The solid was collected by filtration and washed with water (150 ml) to yield 7-methylquinazoline-2,4(1*H*,3*H*)-dione (57.0 g, 83%) after drying at 45°C under vacuum.

[00618] 2,4-Dichloro-7-methyl-quinazoline

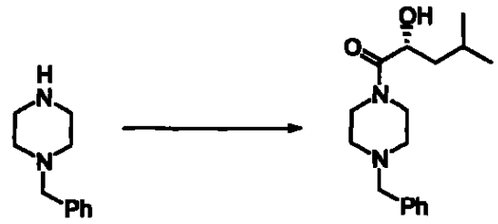
[00619]



[00620] 7-Methylquinazoline-2,4(1*H*,3*H*)-dione (57.0 g, 324 mmol) was refluxed overnight in phosphorus oxychloride (250 ml) in a flask equipped with a calcium chloride guard tube. The clear, dark solution was cooled in an ice bath and poured slowly into 2 L of ice water. The chocolate brown solid was collected by filtration and washed with cold water (150 ml). The solid was dissolved in dichloromethane (500 ml) and filtered. The filtrate was washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and evaporated to dryness yielding 43.0 g of crude 2,4-dichloro-7-methyl-quinazoline. This material was dissolved in hot heptanes (0.5 L),and filtered while hot, and after cooling to room temperature, the precipitated solid was collected by filtration and washed with pentane (100 ml). The solid was purified by chromatography on silica gel with dichloromethane as the eluent to yield 2,4-dichloro-7-methyl-quinazoline (28.5 g, 41%) as an off-white solid.

[00621] 1-(4-benzyl-piperazin-1-yl)-2-(*R*)-hydroxy-4-methyl-pentan-1-one

[00622]



[00623] (R)-α-hydroxyisocaproic acid (52.1 g, 0.394 mol) was added to a solution of 1-benzylpiperazine (69.46 g, 0.394 mol) in CH_2Cl_2 (500 mL). The mixture was cooled in ice and Et_3N (57 mL, 0.5 mol) was added, followed by HOBt (53.25 g, 0.394 mol) and EDCI·HCl (76.0 g, 0.396 mol). The reaction mixture was allowed to warm to room temperature overnight. The organic layer was washed with water (3x200 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were washed with water (3x20 mL), dried over Na_2SO_4 and concentrated to give 1-(4-benzyl-piperazin-1-yl)-2-(*R*)-hydroxy-4-methyl-pentan-1-one as a brown oil (109 g, 0.375 mol, 95%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.24 (m, 5H); 4.35 (dd, *J*= 10 Hz, 2 Hz, 1H); 3.77-3.55 (m, 4H); 3.52 (s, 2H); 3.36 (m, 2H); 4.45 (m, 4H); 1.97 (m, 1H); 1.47-1.38 (m, 1H); 1.29-1.21 (m, 1H); 0.96 (d, *J*= 6 Hz, 3H); 0.94 (d, *J*= 6 Hz, 3H).

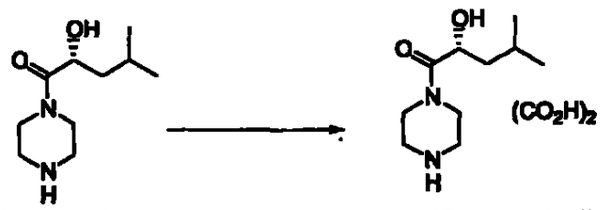
[00624] 2-(R)-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one

[00625]

[00626] 1-(4-benzyl-piperazin-1-yl)-2-(*R*)-hydroxy-4-methyl-pentan-1-one (109 g, 0.375 mol) was dissolved in MeOH (0.5 L). Crystals formed upon addition of 10% Pd/C (16 grams). The mixture was hydrogenated under 1-4 bar hydrogen pressure for two days. The catalyst was filtered off, the filtrate was concentrated to give 2-(R)-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one as a brownish oil (72.7 g, 0.363 mol, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (dd, *J*= 10 Hz, 2 Hz, 1H); 3.76-3.66 (m, 1H); 3.62-3.52 (m, 1H); 3.37 (m, 2H); 2.99 (br. s, 2H); 2.89 (br. m, 4H); 1.96 (m, 1H); 1.48-1.38 (m, 1H); 1.29-1.21 (m, 1H); 0.96 (d, *J*= 9 Hz, 3H); 0.94 (d, *J*= 9 Hz, 3H).

[00627] **2-(R)-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one oxalate**

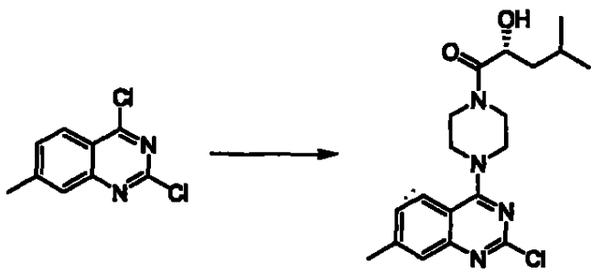
[00628]



[00629] The above product was dissolved in ethanol (250 mL). Oxalic acid dihydrate (45.76 g, 0.363 mol) was added. The thick slurry was diluted with ethanol (250 mL) and stirred at room temperature for 3 hours. The salt was filtered off, washed with ethanol (2x100 mL) and dried *in vacuo* over drying pearls. Yield: 89.0 grams (0.307 mol, 84%) of 2-(R)-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one oxalate as a white solid. ^{1}H NMR (300 MHz, D_2O): δ 4.68 (dd, *J*=3.3, 9.9 Hz, 1H); 3.95 (m, 4H); 3.35 (m, 4H); 1.80 (m, 1H); 1.59 (m, 1H); 1.41 (m, 1H); 0.96 (d, *J*= 6.5 Hz, 3H); 0.95 (d, *J*= 6.5 Hz, 3H).

[00630] **(*R*)-1-(4-(2-Chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

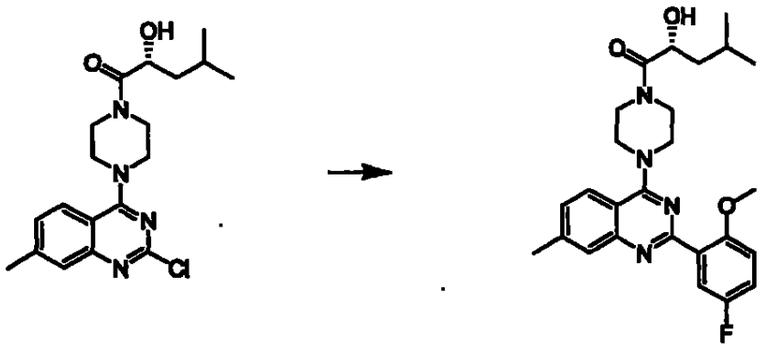
[00631]



[00632] To a solution of 2,4-dichloro-7-methylquinazoline (2.09 g, 9.83 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (2.74 mL, 19.66 mmol), followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (1.97 g, 9.83 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The mixture was then quenched with water and extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to obtain (*R*)-1-(4-(2-chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (6.78 g, 95%). LC/MS: *m/z* 377.5 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00633] **(*R*)-1-(4-(2-(5-Fluoro-2-methoxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00634]

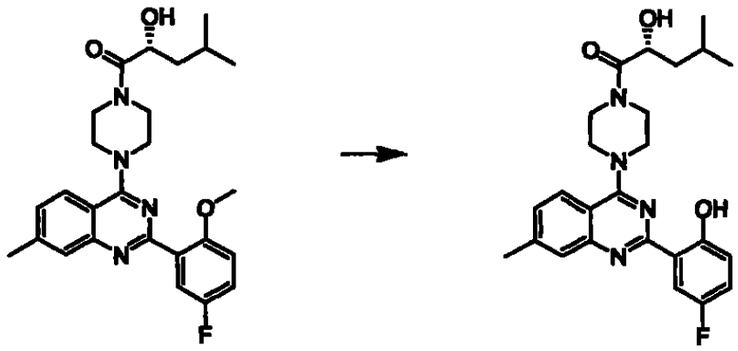


[00635] (*R*)-1-(4-(2-Chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (50 mg, 0.13 mmol), 5-fluoro-2-methoxyphenylboronic acid (27 mg, 0.16 mmol), $Pd(Ph_3P)_4$ (9.2 mg, 0.008 mmol), and K_2CO_3 (37 mg, 0.27 mmol) were placed into a microwave tube charged with a stir bar. Acetonitrile (2 mL) and H_2O (400 μL) were added, and the vessel was capped and heated at 160 °C for 12 minutes in the microwave reactor. The

reaction was partitioned between EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted once more with EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to an orange gel. The reaction was purified by silica gel chromatography using 10%–30% EtOAc in CH_2Cl_2/hexanes (2:1) to afford (*R*)-1-(4-(2-(5-fluoro-2-methoxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as a white foam (70%). *LC/MS*: *m/z* 467.30 $(M+H)^+$ at 2.38 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00636] **(*R*)-1-(4-(2-(5-Fluoro-2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00637]

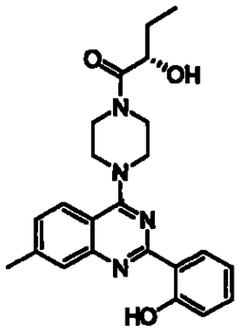


[00638] (*R*)-1-(4-(2-(5-Fluoro-2-methoxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (30 mg, 0.064 mmol) was dissolved in 1.5 mL anhydrous CH_2Cl_2. The flask was sealed with a septum, placed under an N_2 atmosphere and cooled to –78 °C, and 0.32 mL of a 1 M solution of BBr_3 in CH_2Cl_2 was added over 2 minutes. The reaction was allowed to warm to room temperature. After 5 hours, the reaction was quenched with saturated aqueous $NaHCO_3$, and partitioned between CH_2Cl_2 and water, and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated to a red oil. The reaction was purified by reverse phase HPLC to give (*R*)-1-(4-(2-(5-fluoro-2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 453.30 $(M+H)^+$ at 3.02 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00639] Example 137

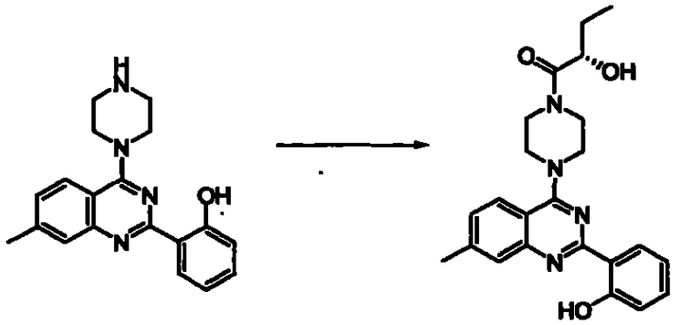
[00640] **(*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one**

[00641]



[00642] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00643]

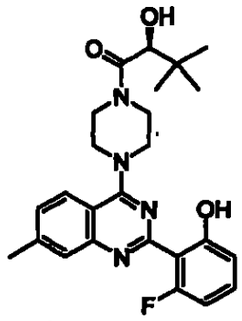


[00644] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to (*S*)-2-hydroxybutanoic acid (29.6 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL) and a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)H_2O (0.05% TFA)) gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 407.3 $(M+H)^+$ at 2.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00645] Example 138

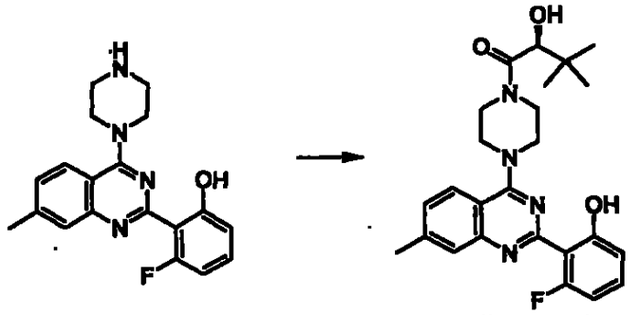
[00646] (*S*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one

[00647]



[00648] (*S*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one

[00649]

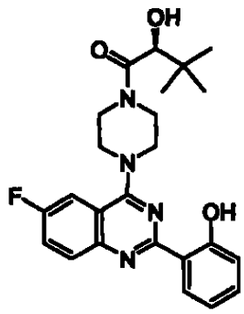


[00650] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol), (*S*)-2-hydroxy-3,3-dimethylbutanoic acid (15.24 mg, 0.12 mmol), triethylamine (25μL, 0.18 mmol), and HATU (45.6 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one as the TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00651] Example 139

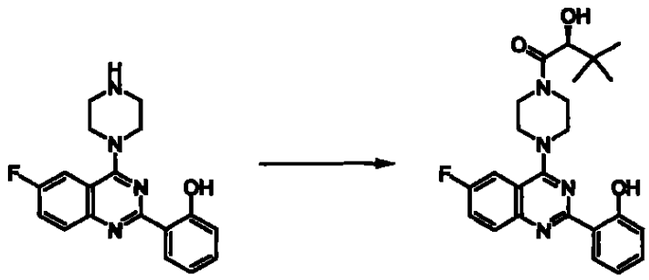
[00652] (*S*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one

[00653]



[00654] (*S*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one

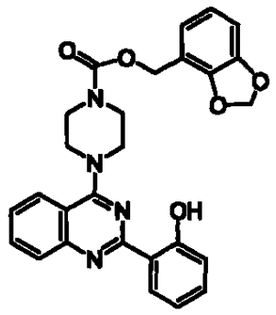
[00655]



[00656] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol), (*S*)-2-hydroxy-3,3-dimethylbutanoic acid (16 mg, 0.12 mmol), triethylamine (25 mL, 0.18 mmol), and HATU (45.6 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00657] Example 140

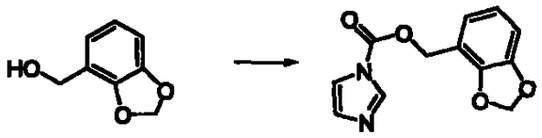
(Benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate



[00658]

[00659] **(Benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate**

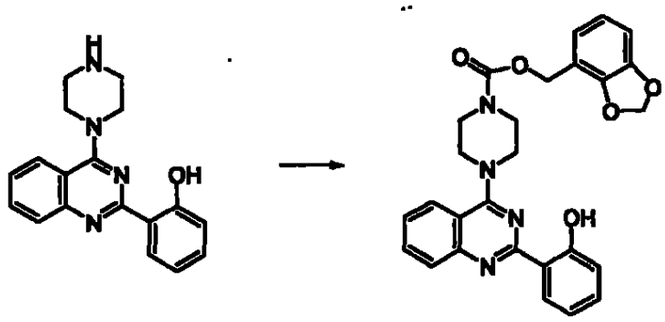
[00660]



[00661] A solution of (benzo[d][1,3]dioxol-7-yl)methanol (2.0 g, 13.1 mmol) and di(1*H*-imidazol-1-yl)methanone (4.26 g, 26.2 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was quenched with water and extracted with CH_2Cl_2, and the combined layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (2.8 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, J = 0.9 Hz, 1H), 7.44 (t, J = 1.4 Hz, 1H), 7.07 (dd, J = 1.6, 0.8 Hz, 1H), 6.95 (m, 2H), 6.84 (m, 1H), 6.01 (s, 2H), 5.33 (s, 2H).

[00662] **(Benzo[d][1,3]dioxol-7-yl)methyl 4-(4a,8a-dihydro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate**

[00663]



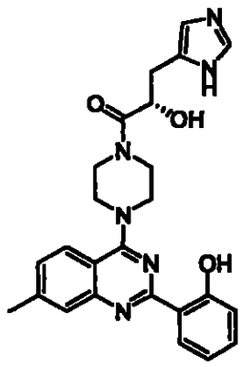
[00664] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (78 mg, 0.32 mmol), and

triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. *LC/MS*: *m/z* 485.5 $(M+H)^+$ at 2.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00665] Example 141

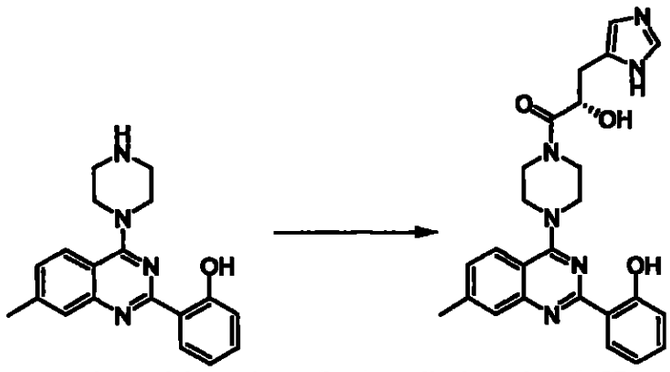
[00666] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(1*H*-imidazol-5-yl)propan-1-one

[00667]



[00668] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(1*H*-imidazol-5-yl)propan-1-one

[00669]



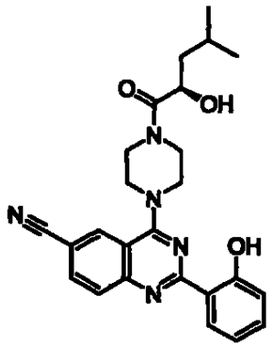
[00670] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (87 mg, 0.27 mmol), (*S*)-2-hydroxy-3-(1*H*-imidazol-5-yl)propanoic acid (64 mg, 0.41 mmol), triethylamine (76 μL, 0.54 mmol), and BOP (180 mg, 0.41 mmol) in 1 mL of CH_2Cl_2 were stirred at room temperature for

1.5 h. The reaction mixture was diluted with H_2O and CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Purification using 1–15% MeOH in CH_2Cl_2 gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(1*H*-imidazol-5-yl)propan-1-one. LC/MS: *m/z* 459.3 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00671] Example 142

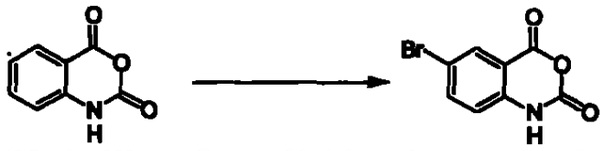
[00672] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile

[00673]



[00674] 6-Bromo-1*H*-benzo[d][1,3]oxazine-2,4-dione

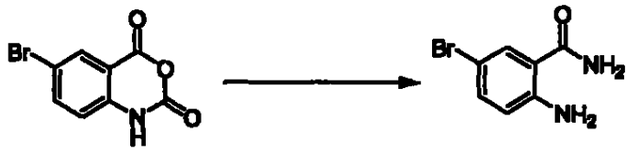
[00675]



[00676] Bromine (35 mL, 660 mmol) was added dropwise to a suspension of isatoic anhydride (100 g, 610 mmol) in 1.6 L water at 50 °C. This temperature was maintained for an additional 2 hours. After cooling the solution to room temperature, the solid was filtered and washed twice with water and twice with acetone, yielding 125.6 g (85%) 6-bromo-1*H*-benzo[d][1,3]oxazine-2,4-dione as a pink solid.

[00677] 2-Amino-5-bromo-benzamide

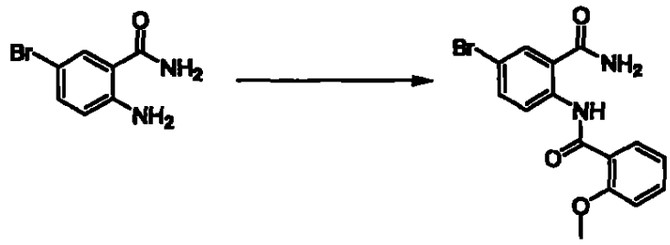
[00678]



[00679] 6-Bromo-1*H*-benzo[d][1,3]oxazine-2,4-dione (56.0 g, 230 mmol) was suspended in 1 N aq. NH_4OH (600 mL, 2.6 equivalents), and the suspension was stirred 3 d at room temperature. After filtration, the collected solid was washed with water and subsequently dissolved in tetrahydrofuran. This solution was filtered, evaporated to dryness, and dried by repeated azeotropic distillation with toluene. The solid was suspended in CH_2Cl_2, filtered, and washed once CH_2Cl_2 with yielding 35.4 g (71.2%) 2-amino-5-bromo-benzamide.

[00680] **2-(*o*-Anisoyl)-amino-5-bromo-benzamide**

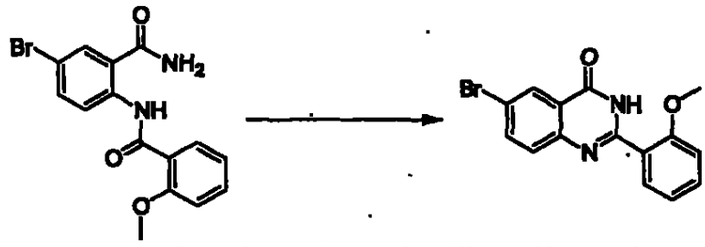
[00681]



[00682] To a solution of 2-amino-5-bromo-benzamide (29.2 g, 136 mmol) and triethylamine (25.0 mL, 173 mmol) in THF (500 mL) was added dropwise *o*-anisoyl chloride (24.0 g, 140 mmol). Stirring at room temperature was continued for 3 h, after which the formed precipitate was filtered and washed once with THF and twice with dichloromethane yielding 2-(*o*-anisoyl)-amino-5-bromo-benzamide (51.4 g, 84%) with 1 equivalent of triethylamine hydrochloride.

[00683] ***6-Bromo-2-(2-methoxy-phenyl)-3H-quinazolin-4-one***

[00684]



[00685] 2-(*o*-Anisoyl)-amino-5-bromo-benzamide (50.8 g, 105 mmol) was suspended in 2 N aq. NaOH (500 mL) and heated to reflux until a clear solution was obtained (1.5 h). The solution was cooled to room temperature and filtered. The filtrate was acidified with conc. aq. HCl, and the precipitate formed was filtered and washed twice with 1 N aq. HCl and twice with

water. The solid was dried by repeated azeotropic distillation with toluene yielding 6-bromo-2-(2-methoxy-phenyl)-3*H*-quinazolin-4-one (31.3 g, 91%).

[00686] **6-Bromo-4-chloro-2-(2-methoxyphenyl)quinazoline**

[00687]

[00688] Method A

[00689] 6-Bromo-2-(2-methoxyphenyl)quinazolin-4(3*H*)-one (674 mg, 2.0 mmol), $POCl_3$ (624 mg, 4 mmol), and *N*, *N*-dimethylaniline (740 mg, 6.1 mmol) were dissolved in benzene (12 mL) and refluxed for 3 h. The reaction mixture was diluted with EtOAc, and the organic phase was washed with aqueous saturated $NaHCO_3$ (1x) and H_2O (2x), dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–5% EtOAc in CH_2Cl_2/hexanes (1:1) gave 6-bromo-4-chloro-2-(2-methoxyphenyl)quinazoline. LC/MS: *m/z* 348.9 $(M+H)^+$ at 3.66 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00690] Method B

[00691] 6-Bromo-2-(2-methoxyphenyl)quinazolin-4(3*H*)-one (0.31 g, 0.94 mmol), $POCl_3$ (86 μL, 0.94 mmol), and *N*, *N*-dimethylaniline (180 μL, 1.4 mmol) were refluxed in dry toluene for 3 h. Additional $POCl_3$ (0.94 mmol) was added, and the reaction was refluxed for one additional hour. The reaction mixture was diluted with EtOAc and water. The aqueous layer was made basic with $NaHCO_3$, and the layers were separated. After the organic phase was washed with water, dried over Na_2SO_4 and concentrated, purification via silica gel chromatography using 0–50% EtOAc in 1:1 hexanes:CH_2Cl_2 gave 6-bromo-4-chloro-2-(2-methoxyphenyl)quinazoline as a yellow solid (144 mg, 44%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.45–8.45 (m, 1H), 8.04–7.99 (m, 2H), 7.82 (dd, J = 7.6, 1.7 Hz, 1H), 7.49–7.45 (m, 1H), 7.12–7.08 (m, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H); LC/MS: *m/z* 350.9 $(M+H)^+$ at 3.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00692] **2-(6-Bromo-4-chloroquinazolin-2-yl)phenol**

[00693]

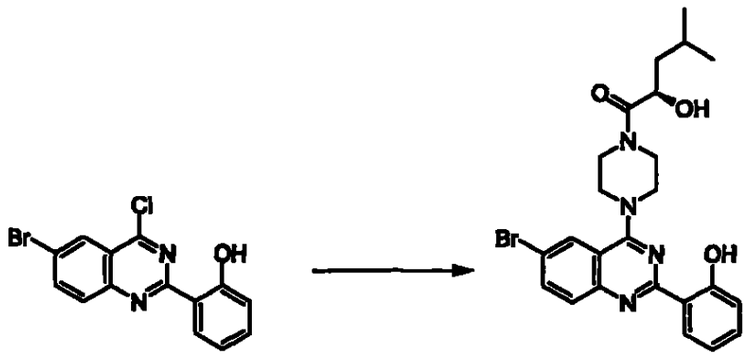
[00694] Method A

[00695] 6-Bromo-4-chloro-2-(2-methoxyphenyl)quinazoline (393 mg, 1.12 mmol) was dissolved in CH_2Cl_2 (3 mL), and the flask was flushed with N_2. After cooling the reaction mixture to –78 °C, 1 M BBr_3 in CH_2Cl_2 (3.37 mL, 3.37 mmol) was added dropwise, then the reaction was slowly warmed to room temperature and stirred for 2 h. After quenching the mixture with saturated aqueous $NaHCO_3$ (1x), it was transferred into a separatory funnel with CH_2Cl_2. The organic layer was washed with H_2O (2x), dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–5% EtOAc and CH_2Cl_2:hexanes (1:1) gave 2-(6-bromo-4-chloroquinazolin-2-yl)phenol (229 mg, 61%). LC/MS: *m/z* 335.30 $(M+H)^+$ at 4.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00696] Method B

[00697] A solution of 6-bromo-4-chloro-2-(2-methoxyphenyl)quinazoline (0.14 g, 0.4 mmol) in CH_2Cl_2 (mL) was cooled in a dry ice/acetone bath. A solution of 1.0 M BBr_3 in CH_2Cl_2 (1.2 mL, 1.2 mmol) was slowly added. The cooling bath was removed, and the reaction was stirred at room temperature for 2 h. The reaction was diluted with CH_2Cl_2 and made basic with a saturated $NaHCO_3$ solution. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to give 6-bromo-4-chloro-2-(2-hydroxyphenyl)quinazoline (0.15 g).

[00698] **(*R*)-1-(4-(6-Bromo-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**



[00699]

[00700] Method A

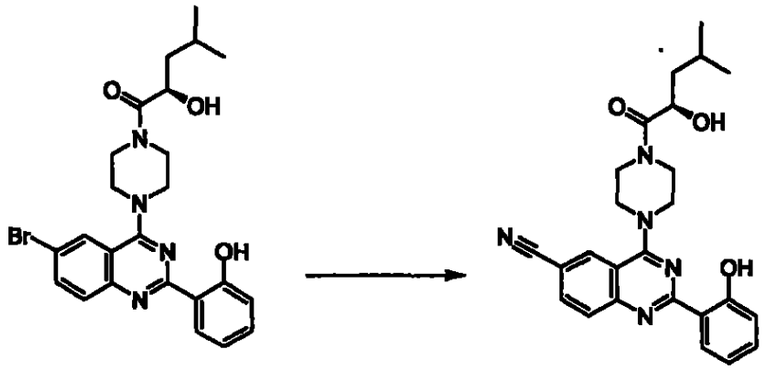
[00701] To a solution of 2-(6-bromo-4-chloroquinazolin-2-yl)phenol (228 mg, 0.68 mmol), triethylamine (129 μL, 0.92 mmol), and CH_2Cl_2 (6 mL) was added (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (185 mg, 0.92 mmol) dissolved in CH_2Cl_2 (3 mL). The flask was flushed with N_2 and stirred for 3 hours. The reaction mixture was then transferred into a separatory funnel with CH_2Cl_2, and the organic phase was washed with H_2O (2x), dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0 to 20% EtOAc and CH_2Cl_2:hexanes (1:1) gave (*R*)-1-(4-(6-bromo-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (285 mg, 84%). *LC/MS*: *m/z* 500.30 $(M+H)^+$ at 3.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00702] Method B

[00703] A solution of 6-bromo-4-chloro-2-(2-hydroxyphenyl)quinazoline (75 mg, 0.22 mmol), (*R*)-2-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one (60 mg, 0.3 mmol), triethylamine (42 μL, 0.3 mmol), and CH_2Cl_2 (2 mL) was stirred at room temperature overnight. After diluting with CH_2Cl_2, the reaction mixture was washed with H_2O, dried over Na_2SO_4, and concentrated. The crude material was purified by silica gel chromatography using 0–10% MeOH/CH_2Cl_2 to give (*R*)-1-{4-[6-bromo-2-(2-methoxy-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-2-hydroxy-4-methyl-pentan-1-one (40 mg, 36%). LC/MS: *m/z* 449.3 $(M+H)^+$ at 3.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00704] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile

[00705]



[00706] Method A

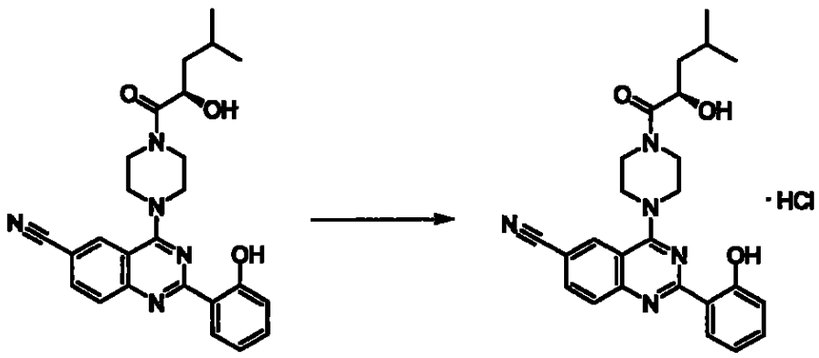
[00707] A mixture of (*R*)-1-{4-[6-bromo-2-(2-methoxy-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-2-hydroxy-4-methyl-pentan-1-one (20 mg, 0.04 mmol), $Zn(CN)_2$ (4.7 mg, 0.04 mmol), and $Pd(PPh_3)_4$ (1.4 mg, 1.4 μmol) in DMF (0.5 mL) was heated in a microwave synthesizer at 200 °C for 15 minutes Purification via preparative HPLC gave 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile as the TFA salt. LC/MS: *m/z* 446.3 $(M+H)^+$ at 3.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00708] Method B

[00709] (*R*)-1-(4-(6-Bromo-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (188 mg, 0.38 mmol), $Zn(CN)_2$ (44 mg, 0.38 mmol), and $Pd(Ph_3)_4$ (6.5 mg, 0.0112 mmol) were dissolved in DMF (4 mL) and the reaction mixture was heated in a microwave synthesizer at 200 °C for 15 minutes EtOAc (50 mL) was added and the mixture was washed twice with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in CH_2Cl_2:hexanes (1:1) gave 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile (127 mg, 75%). LC/MS: *m/z* 446 $(M+H)^+$ at 3.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.60 (d, J = 1.5 Hz, 1H), 8.46 (dd, J = 8.4, 1.8 Hz, 1H), 8.15 (dd, J = 8.7, 1.7 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.45–7.41 (m, 1H), 6.99–6.95 (m, 2H), 4.94 (d, J = 7.0 Hz, 1H), 4.39–4.36 (m, 1H), 4.14–4.04 (m, 4H), 3.89–3.67 (m, 4H), 1.82–1.76 (m, 1H), 1.47–1.37 (m, 2H), 0.93–0.91 (m, 6H).

[00710] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile hydrochloride

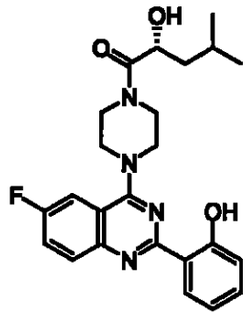
[00711]



[00712] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile (137 mg, 0.31 mmol) was dissolved in the minimum amount of CH_2Cl_2. After stirring the solution under an N_2 atmosphere for 30 minutes, 1 M HCl in ether (0.31 mL, 0.31 mmol) was added dropwise to the solution and stirred for 10 minutes. Ether was added to precipitate the hydrochloride salt of 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile, which was filtered and dried to obtain 136 mg of solid (91%). LC/MS: *m/z* 446 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.62 (s, 1H), 8.43–8.41 (m, 1H), 8.17 (dd, J = 8.7, 1.5 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.47–7.43 (m, 1H), 7.00–6.96 (m, 2H), 4.39–4.36 (m, 1H), 4.18–4.00 (m, 4H), 3.91–3.68 (m, 4H), 1.85–1.75 (m, 1H), 1.51–1.35 (m, 2H), 0.94–0.91 (m, 6H); ^{13}C NMR (100 MHz, DMSO–d6) δ 172.5, 161.7, 160.6, 135.1, 133.6, 132.4, 129.7, 126.9, 118.8, 118.4, 118.2, 117.4, 113.3, 107.3, 66.9, 48.7, 48.1, 43.5, 42.8, 41.1, 24.0, 23.4, 21.6.

[00713] Example 143

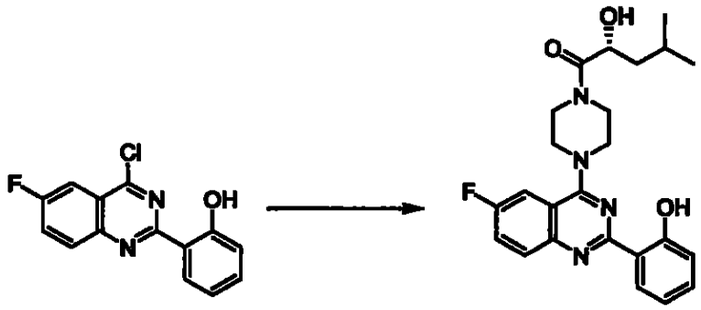
[00714] (*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one



[00715]

[00716] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00717]



[00718] Method A

[00719] To a solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (25 mg, 0.09 mmol) in DMF (1 mL) was added triethylamine (25 μL, 0.18 mmol) followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one oxalate (52 mg, 0.18 mmol) at 0 °C. The reaction was stirred for 2 hours, and purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.99 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

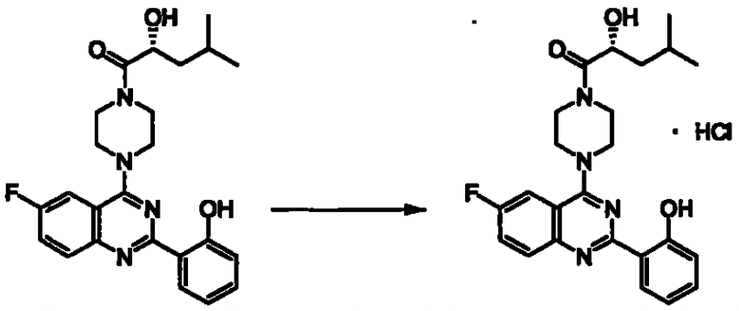
[00720] Method B

[00721] To a mixture of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (200 mg, 0.72 mmol) and CH_2Cl_2 (7 mL) was added (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one oxalate (275 mg, 0.95 mmol). The reaction was complete after two hours. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 mixture of CH_2Cl_2:hexanes gave (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

(289 mg, 91%). *LC/MS*: *m/z* 439.30 $(M+H)^+$ at 3.00 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.46 (m, 1H), 8.02 (m, 1H), 7.84 (m, 2H), 7.40 (m, 1H), 6.97 (m, 2H), 4.92 (d, *J* = 7.2 Hz, 1H), 4.38 (m, 1H), 3.98 (m, 4H), 3.76 (m, 4H), 1.80 (m, 1H), 1.42 (m, 2H), 0.92 (q, *J* = 3.8 Hz, 6H).

[00722] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one hydrochloride**

[00723]

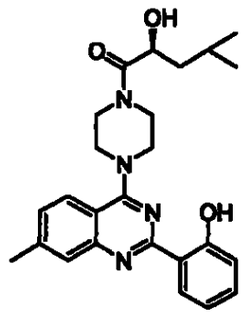


[00724] To a solution of (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (285 mg, 0.65 mmol) in CH_2Cl_2 (2 mL) under an N_2 atmosphere was added ether (10 mL), followed by the dropwise addition of a 2 M HCl solution in ether (0.325 mL, 0.65 mmol). A precipitate was formed which was stirred for 30 min, collected by vacuum filtration, and dried to afford (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one hydrochloride (284 mg, 92%). *LC/MS*: *m/z* 439.30 $(M+H)^+$ at 3.00 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)): ^1H NMR (400 MHz, DMSO-d6) δ 8.32 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.02 (m, 1H), 7.92 (dd, *J* = 9.7, 2.7 Hz, 1H), 7.85 (m, 1H), 7.45 (m, 1H), 7.01 (m, 2H), 4.37 (dd, *J* = 9.2, 4.1 Hz, 1H), 4.04 (m, 4H), 3.83 (m, 4H), 1.76 (m, 1H), 1.41 (m, 2H), 0.90 (dd, *J* = 6.6, 3.7 Hz, 6H).

[00725] Example 144

[00726] **(*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

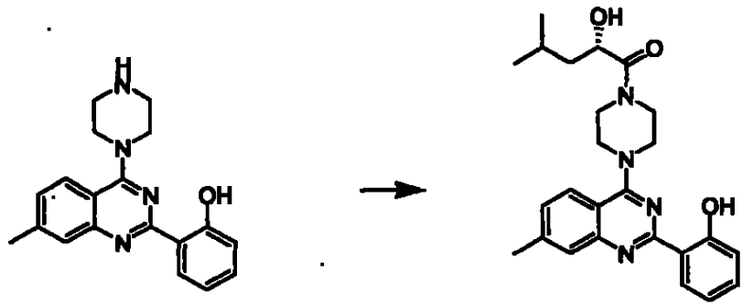
98
98



[00727]

[00728] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

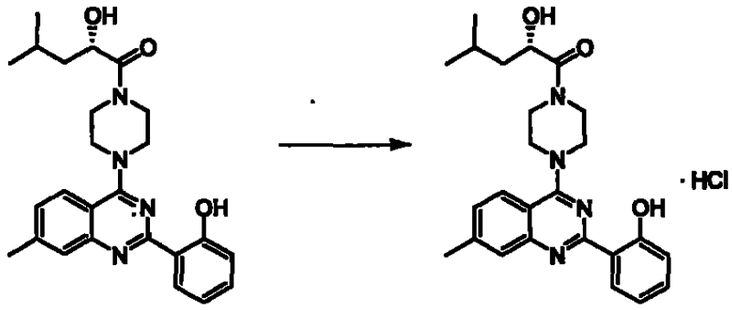
[00729]



[00730] Under an N_2 atmosphere, BOP (137 mg, 0.31 mmol) was added in a single portion to a stirring solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (100 mg, 0.31 mmol), (*S*)-2-hydroxy-4-methylpentanoic acid (41 mg, 0.31 mmol), and triethylamine (43 μL, 0.31 mmol) in DMF (0.5 ml). After stirring the mixture for 1 h at room temperature, it was partitioned between H_2O and ether. The organic phase was washed with H_2O (3x 20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 1:1 ethyl acetate / hexane gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one as a white solid. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.62 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.44 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.67 (s, 1H), 7.40–7.36 (m, 2H), 6.96-6.93 (m, 2H), 4.92 (d, *J* = 7.2 Hz, 1H) 4.41–4.36 (m, 1H), 4.06–3.67 (m, 8H), 2.51 (s, 3H), 1.85–1.73 (m, 1H), 1.49–1.35 (m, 2H), 0.93–0.91 (m, 6H).

[00731] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride

[00732]

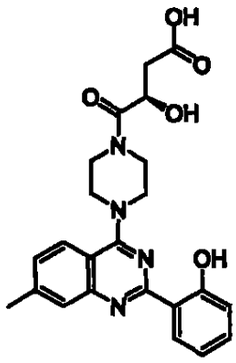


[00733] (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (90 mg, 0.20 mmol) was dissolved in 1 mL CH_2Cl_2 and treated with 1 equivalent of 2.0 M HCl in ether (100 μL, 0.20 mmol). The formed precipitate was filtered and vacuum dried to obtain (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride. LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.62 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.27 (d, *J* = 6.8 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.50–7.45 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.03–6.99 (m, 1H), 4.39–4.35 (m, 1H), 4.16–3.68 (m, 8H), 2.54 (s, 3H), 1.84–1.72 (m, 1H), 1.49–1.35 (m, 2H), 0.93 (d, *J* = 2.8 Hz, 6H).

[00734] Example 145

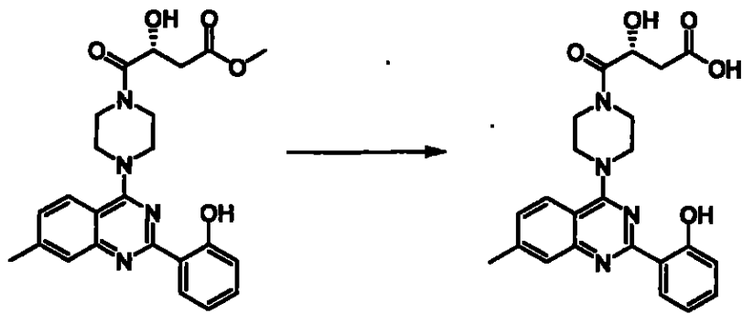
[00735] (*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoic acid

[00736]



[00737] **(*R*)-3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoic acid**

[00738]

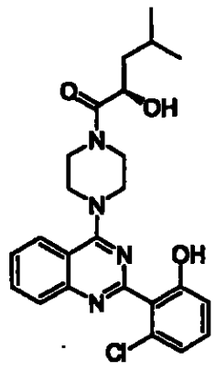


[00739] (*R*)-Methyl 3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoate (88 mg, 0.20 mmol) and $LiOH \cdot H_2O$ (33 mg, 0.78 mmol) were stirred in THF:H_2O 1:1 at room temperature for 3 h. After acidification with 1 M HCl and extraction with EtOAc, the organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The crude material was then purified via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 to obtain (*R*)-3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoic acid (75 mg, 88%). *LC/MS*: *m/z* 437.3 $(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00740] Example 146

[00741] **(*R*)-1-(4-(2-(2-Chloro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00742]



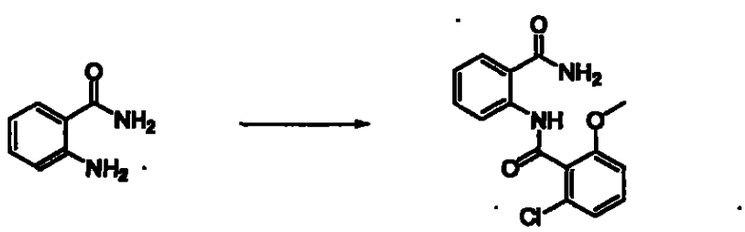
[00743] **2-Amino-benzamide**

[00744]

[00745] Isatoic anhydride (40 g, 245 mmol) was suspended in 650 mL 1 N NH_4OH (2.5 equiv) and stirred at room temperature for 3 days. The precipitate was filtered and washed with water. The product was then dissolved in THF, filtered, and concentrated to dryness. The product was dried by azeotropic distillation with toluene and washed with CH_2Cl_2 to yield 10.9 g (32.7%) of 2-amino-benzamide.

[00746] **2-Chloro-*N*-(2-carboxylic acid amide phenyl)-2-methoxy-benzamide**

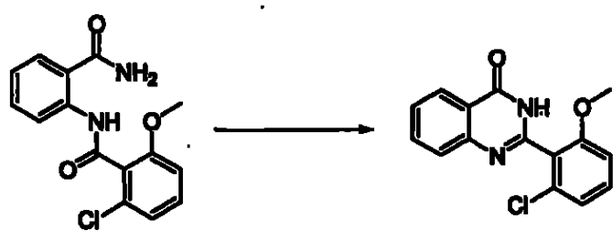
[00747]



[00748] 2-Amino-benzamide (6.9 g, 50.8 mmol) was dissolved in 50 mL of pyridine and cooled to 0 °C. 2-Chloro-6-methoxy-benzoyl chloride was added dropwise to the solution. After complete addition, the reaction was left to stir at room temperature for three days, which resulted in formation of a brown, cloudy solution. The reaction mixture was then poured into 150 mL of ice water. The precipitate was filtered and washed twice with water, twice with THF and finally twice with CH_2Cl_2 to obtain 2-chloro-*N*-(2-carboxylic acid amide phenyl)-2-methoxy-benzamide (13.3 g, 43.7 mmol, 86%).

[00749] **2-(2-Chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one**

[00750]



[00751] 2-Chloro-*N*-(2-carboxylic acid amide phenyl)-2-methoxy-benzamide (13 g, 42.7 mmol) was suspended in 100 mL of a 2 N NaOH solution and heated to reflux. After refluxing for 3 hours, another 25 mL of a 2 N NaOH solution was added, and the reaction was refluxed for another hour. The mixture was cooled to room temperature and acidified with acetic acid to pH 5. The formed precipitate was collected by filtration. The product was purified over alumina using EtOAc as an eluent giving 1.7 g (5.9 mmol, 14%) of 2-(2-chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one.

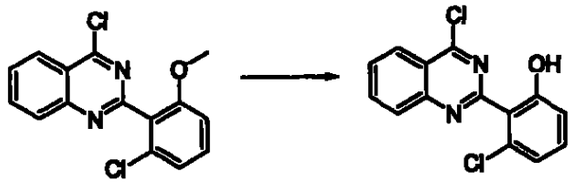
[00752] **4-Chloro-2-(2-chloro-6-methoxy-phenyl)-quinazoline**

[00753]

[00754] 2-(2-Chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one (1.7 g, 5.9 mmol) was dissolved in 25 mL benzene. Then, *N,N*-dimethylaniline (1.15 mL, 9 mmol)and $POCl_3$ (1.65 mL, 17.7 mmol) were added. The reaction mixture was refluxed for 3 hours during which the yellow suspension changed to a dark red color. The mixture was cooled and diluted with 50 mL toluene. The solution was poured onto ice. Saturated aq. $NaHCO_3$ was added while stirring and cooling the mixture until the pH remained constant at 7. The layers were separated, and the aqueous layer was extracted with 100 mL toluene. The toluene layers were combined and washed with 100 mL saturated aqueous NaCl solution, 150 mL 0.5 N HCl, 150 mL 5% aq. $NaHCO_3$ and saturated aqueous NaCl solution. The toluene layer was dried over Na_2SO_4, filtered, and concentrated to dryness to yield 1.87 g impure product. The product was purified over silica gel with heptane/CH_2Cl_2 (2:1) as an eluent to yield 4-chloro-2-(2-chloro-6-methoxy-phenyl)-quinazoline (1.22 g, 64%).

[00755] **3-Chloro-2-(4-chloroquinazolin-2-yl)phenol**

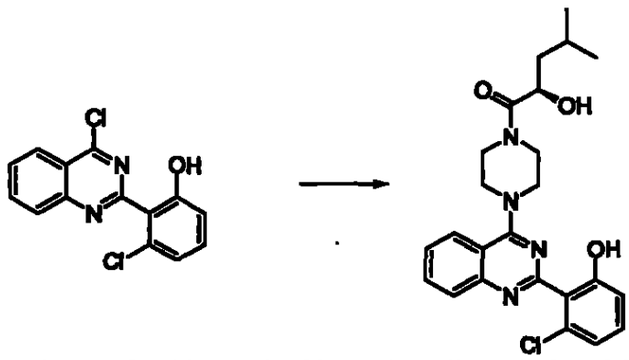
[00756]



[00757] To a solution of 4-chloro-2-(2-chloro-6-methoxyphenyl)quinazoline (300 mg, 0.98 mmol) in 10 mL CH_2Cl_2 was added dropwise 5 equivalents of a 1 M BBr_3 solution in CH_2Cl_2 at –78 °C. The reaction was warmed to room temperature and was complete in 30 minutes. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution to pH 7. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4, filtered, and concentrated to obtain 3-chloro-2-(4-chloroquinazolin-2-yl)phenol. LC/MS: *m/z* 291.3 $(M+H)^+$ at 3.16 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00758] **(*R*)-1-(4-(2-(2-Chloro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00759]

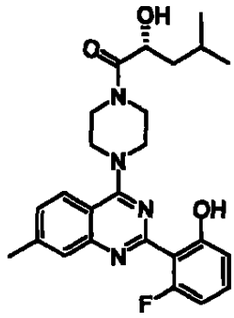


[00760] To a solution of 3-chloro-2-(4-chloroquinazolin-2-yl)phenol (42 mg, 0.14 mmol) in 2 mL CH_2Cl_2 was added triethylamine (40 μL) followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (37.5 mg, 0.187 mmol). The reaction was complete after 1 hour. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-1-(4-(2-(2-chloro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 455.5 $(M+H)^+$ at 2.45 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00761] Example 147

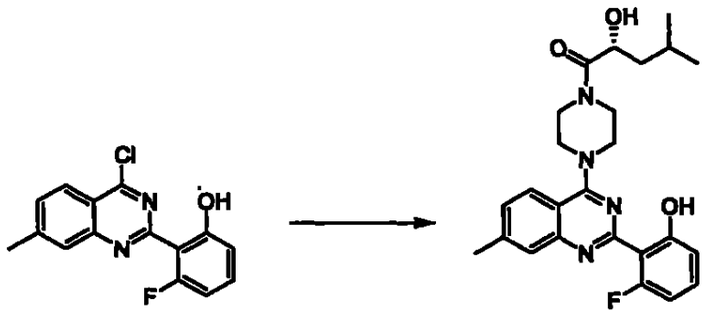
[00762] **(*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00763]



[00764] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[00765]



[00766] Method A

[00767] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (50 mg, 0.174 mmol) in 1 mL DMF was added triethylamine (35.2 mg, 0.348 mmol), followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (42.1 mg, 0.21 mmol). After stirring the reaction for 1 hour, it was filtered, and purified via preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 453.3 (M+H)+ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

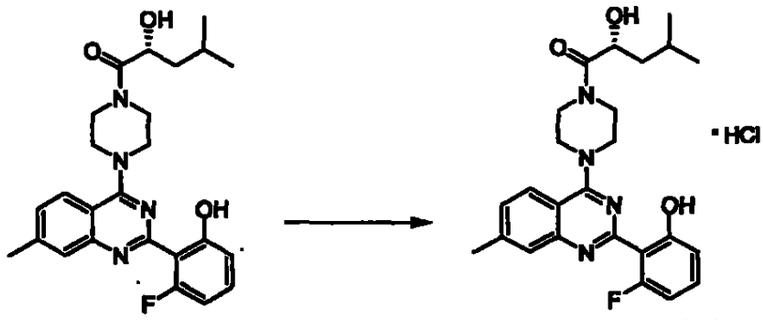
[00768] Method B

[00769] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (300 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) was cooled using an ice water batch. To this stirring solution was added (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (312 mg, 1.56 mmol), followed by

triethylamine (210 mg, 291 μL, 2.08 mmol). After letting the reaction warm to room temperature, it was stirred overnight. The mixture was partitioned between water and CH_2Cl_2 and separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to a viscous yellow oil. Purification via silica gel chromatography using 0–30% EtOAc in CH_2Cl_2/hexanes (2:1) gave (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as a bright yellow foam/solid. (413 mg, 88%). LC/MS: *m/z* 453.1 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.01 (d, *J* = 8.5 Hz, 1H), 7.68 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.37–7.32 (m, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.76–6.71 (m, 1H), 4.91 (d, *J* = 7.2 Hz, 1H), 4.40–4.35 (m, 1H), 4.02–3.65 (m, 8H), 2.52 (s, 3H), 1.82–1.73 (m, 1H), 1.47–1.34 (m, 2H), 0.91 (dd, *J* = 6.5, 4.1 Hz, 6H).

[00770] **(*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one hydrochloride**

[00771]



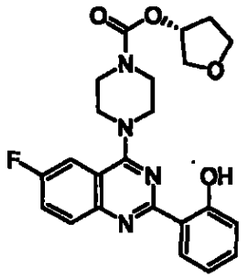
[00772] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (406 mg, 0.898 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) followed by the addition of Et_2O (6 mL) under an N_2 atmosphere. A 2.0 M HCl solution in Et_2O (0.449 mL, 0.898 mmol) was added over a 2 minute period. The reaction solution changed from a clear yellow solution to a turbid white slurry. After complete addition of the HCl solution, the reaction was allowed to stir for an additional 15 minutes. The product was collected by vacuum filtration and dried under vacuum to obtain (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one hydrochloride as a white solid (403 mg, 92%). LC/MS: *m/z* 453.5 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.20 (d, *J* = 8.7 Hz, 1H), 7.71 (s,

1H), 7.60–7.60 (m, 1H), 7.50–7.44 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.87 (t, J = 9.1 Hz, 1H), 4.36–4.33 (m, 1H), 4.25–3.67 (m, 8H), 2.57 (s, 3H), 1.83–1.71 (m, 1H), 1.49–1.35 (m, 2H), 0.91 (d, J = 6.7 Hz, 6H).

[00773] Example 148

[00774] (*R*)-Tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00775]



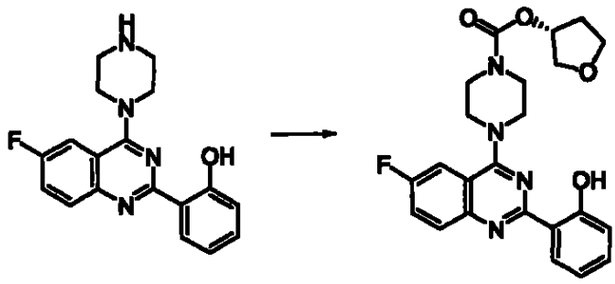
[00776] (*R*)-Tetrahydrofuran-3-yl chloroformate

[00777]

[00778] A stirred solution of (*R*)-tetrahydrofuran-3-ol (7.9 g, 90 mmol) in anhydrous CH_2Cl_2 (50 mL) under an N_2 atmosphere was cooled in an ice bath, and a 20% solution of phosgene in toluene (134 mL, 270 mmol) was slowly added. The reaction was allowed to warm to room temperature overnight, and the solvent was removed under vacuum to afford (*R*)-tetrahydrofuran-3-yl chloroformate (12.1 g, 85%) as a clear liquid.

[00779]

[00780] (*R*)-Tetrahydrofuran -3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate



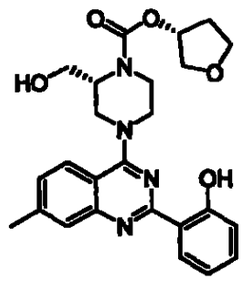
[00781]

[00782] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol), (*R*)-tetrahydrofuran-3-yl chloroformate (12 mg, 0.08 mmol), triethylamine (22 μL, 0.154 mmol) and HATU (38 mg, 0.10 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00783] Example 149

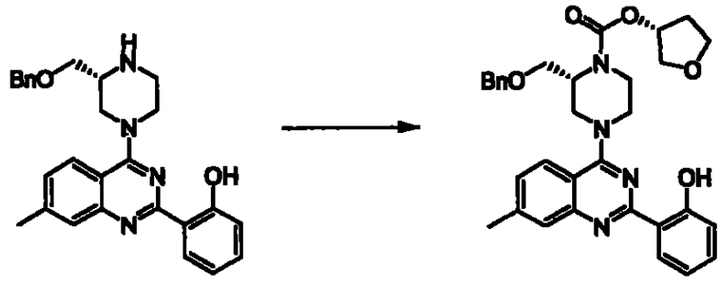
[00784] (2*R*)-(*R*)-Tetrahydrofuran-3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00785]



[00786] (2*R*)-(*R*)-Tetrahydrofuran -3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

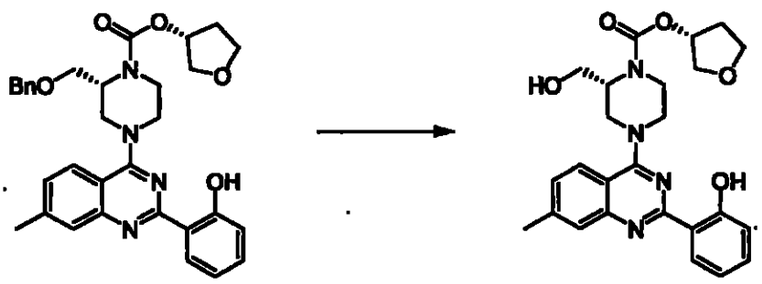
[00787]



[00788] To a solution of 2-(4-((*R*)-3-((benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol (75 mg, 0.17 mmol) in DMF (1 mL) was added triethylamine (47 μL) followed by the dropwise addition of (*R*)-tetrahydrofuran-3-yl chloroformate (25 mg, 0.17 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 455.3 $(M+H)^+$ at 2.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00789] **(2*R*)-(*R*)-Tetrahydrofuran -3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00790]

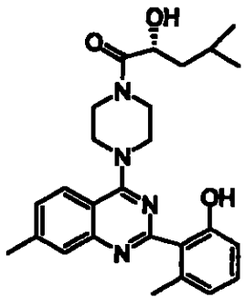


[00791] To a solution of (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate TFA salt (94 mg, 0.17 mmol) in ethanol was added $Pd(OH)_2$ (78 mg), and the reaction was heated at 50 °C under an H_2 atmosphere at ambient pressure. The reaction was filtered, and purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate trifluoroacetate. LC/MS: *m/z* 465.5 $(M+H)^+$ at 2.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00792] Example 150

[00793] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

[00794]



[00795] 2-Methoxy-6-methyl-benzoic acid

[00796]

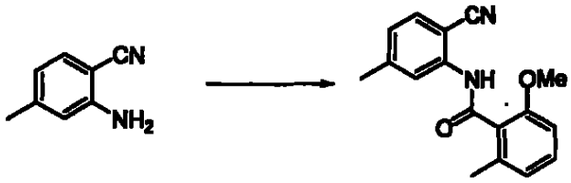
[00797] Ethyl-2-methoxy-6-methylbenzoate (30.4 g, 0.157 mol) was added to 100 mL 3.2 M NaOH (2 equiv) and 150 mL hot EtOH. The mixture was refluxed overnight after which EtOH was removed *in vacuo*. The aqueous mixture was acidified with 5 M HCl to pH 3. CH_2Cl_2 (200 mL) was added, and the layers were separated. The water layer was extracted two times with 200 mL CH_2Cl_2, and the organic layers were combined and dried over Na_2SO_4. Filtering the Na_2SO_4 and concentrating the CH_2Cl_2 to dryness yielded 21.4 g (0.129 mol, 82.3%) of 2-methoxy-6-methyl-benzoic acid.

[00798] 2-Methoxy-6-methyl-benzoyl chloride

[00799]

[00800] 2-Methoxy-6-methyl-benzoic acid (21.4 g, 0.129 mol) was refluxed for 3 hours in 230 mL thionyl chloride. Excess thionyl chloride was removed under reduced pressure. Co-evaporation of the residue with toluene gave 23.8 g of 2-methoxy-6-methyl-benzoyl chloride.

[00801] *N*-(2-Cyano-5-methyl-phenyl)-2-methoxy-6-methyl-benzamide



[00802]

[00803] 2-Amino-4-methyl-benzonitrile (15.4 g, 0.117 mol) was dissolved in 100 mL pyridine and cooled to 0 °C. To this mixture was added dropwise 2-methoxy-6-methylbenzoyl chloride (24 g, 0.13 mol, 1.1 equiv). During the addition the temperature did not exceed 2 °C. The reaction was stirred at room temperature for 48 hours. The mixture was poured into 400 mL ice water, and the precipitate was collected by filtration and washed with water. The crude product was dissolved in 600 mL CH_2Cl_2, and the solution was washed twice with 500 mL of a 1 N HCl solution and once with 400 mL of a saturated aq. NaCl solution. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and concentrated to dryness to yield 25.44 g (0.09 mol, 77.6%) of *N*-(2-cyano-5-methyl-phenyl)-2-methoxy-6-methyl-benzamide.

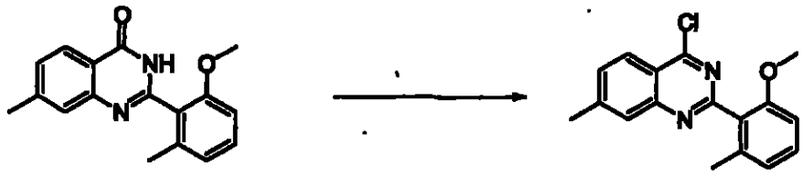
[00804] 2-(2-Methoxy-6-methyl-phenyl)-7-methyl-3*H*-quinazolin-4-one

[00805]

[00806] *N*-(2-Cyano-5-methyl-phenyl)-2-methoxy-6-methyl-benzamide (25 g, 0.09 mol) was suspended in 500 mL EtOH, and 121.3 g of 33% aq. NaOH (1 mol, 11 equiv) was added. To this was added a 35% H_2O_2 solution (50 mL, 0.58 mol), and the reaction was heated to reflux. Additional H_2O_2 was added dropwise until the reaction mixture became clear. EtOH was removed under reduced pressure, and the precipitate formed was removed by filtration. The solution was acidified with acetic acid to pH 5, and the precipitate formed was collected by filtration. The precipitate was washed twice with water and once with diethyl ether. The product was purified over alumina using EtOAc/heptane (1:1) as an eluent. Another purification was performed, over silica gel with the same eluent to yield 2-(2-methoxy-6-methyl-phenyl)-7-methyl-3*H*-quinazolin-4-one (1.61 g).

[00807] 4-Chloro-2-(2-methoxy-6-methyl-phenyl)-7-methyl-quinazoline

[00808]



[00809] 2-(2-Methoxy-6-methyl-phenyl)-7-methyl-3*H*-quinazolin-4-one (1.61 g, 5.74 mmol) was suspended in benzene after which was added *N,N*-dimethylaniline (1.1 mL, 8.62 mmol) and $POCl_3$ (1.61 mL, 17.27 mmol). The reaction mixture was refluxed for 3 hours during which the color changed from yellow to dark red. The reaction mixture was cooled to room temperature, diluted with 40 mL toluene and poured onto ice. Saturated aq. $NaHCO_3$ was carefully added until the pH remained constant at 7 and no more gas formed. The layers were separated, and the water layer was extracted with toluene. The organic layers were combined and washed with respectively 50 mL saturated aq. NaCl, 60 mL 0.5 N HCl , 40 mL 5% $NaHCO_3$ and 50 mL saturated aq. NaCl. The solution was dried over Na_2SO_4 and evaporated to dryness to yield 1.7 g of the impure product. The product was filtered through silica gel and washed with CH_2Cl_2:heptane (2:1) to yield of 4-chloro-2-(2-methoxy-6-methyl-phenyl)-7-methyl-quinazoline (1.22 g, 71%).

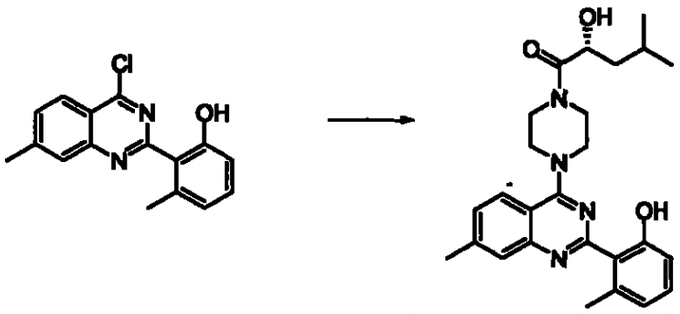
[00810] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-methylphenol

[00811]

[00812] To a solution of 4-chloro-2-(2-methoxy-6-methylphenyl)-7-methylquinazoline (669 mg, 2.24 mmol) in 7 mL CH_2Cl_2 was added dropwise 5 equivalents of a 1 M solution of BBr_3 in CH_2Cl_2 at –78 °C. The reaction was warmed to room temperature and was complete in 30 minutes. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution until the pH was neutral. The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated to obtain 2-(4-chloro-7-methylquinazolin-2-yl)-3-methylphenol. LC/MS: *m/z* 285.1 $(M+H)^+$ at 3.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00813] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00814]

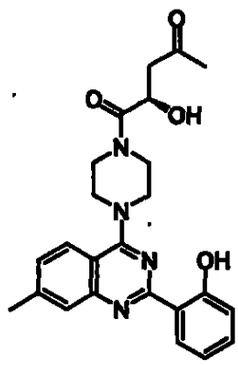


[00815] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-methylphenol (60 mg, 2.1 mmol) in 2 mL CH_2Cl_2 was added triethylamine followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (54.8 mg, 2.73 mmol). The reaction was complete after 1 hour. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

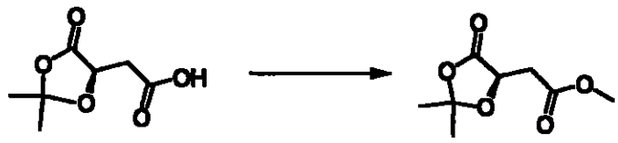
[00816] Example 151

[00817] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentane-1,4-dione

[00818]

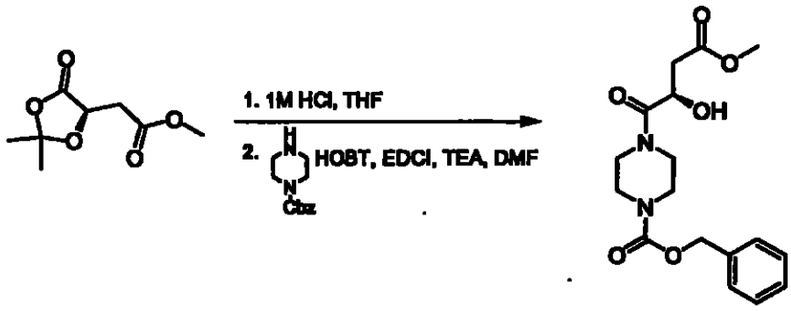


[00819] Methyl 2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate

[00820] 

[00821] 2-((*R*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (15.8 g, 90.9 mmol) in a 3:1 mixture of THF:MeOH (100 mL) was cooled in an ice bath. After adding 2.0 M $TMSCHN_2$ (50 mL, 100 mmol) the bath was removed, and the mixture was stirred at room temperature for 3 h. The solvent was evaporated, and the crude material was purified via silica gel chromatography using 0–50% EtOAc/hexanes to give methyl 2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate. ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (dd, J = 6.6, 3.8 Hz, 1H), 3.74 (s, 3H), 2.95 (dd, J = 17.0, 3.9 Hz, 1H), 2.81 (dd, J = 17.0, 6.6 Hz, 1H), 1.63 (s, 3H), 1.57 (s, 3H).

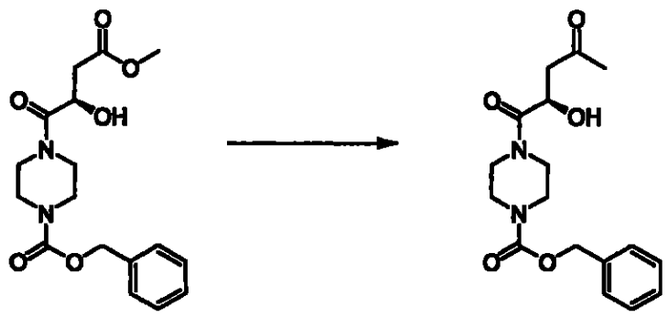
[00822] **4-((*R*)-2-Hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester**

[00823] 

[00824] Methyl 2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate (17.1 g, 90.9 mmol) was stirred in a 1:1 mixture of THF:1 M HCl (200 mL) for 1 h at room temperature. After addition of NaCl to nearly saturate the aqueous layer, the mixture was extracted with EtOAc, and the extracts were dried over Na_2SO_4 and concentrated. To the resulting oil dissolved in dry DMF (500 mL) was added HOBt (13.5 g, 100 mmol) and EDCI (19.2 g, 100 mmol). After stirring for 5 min, benzyl piperazine-1-carboxylate (19.3 mL, 100 mmol) and triethylamine (13.9 mL, 100 mmol) were added to the reaction mixture, which was left stirring at room temperature overnight. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 provided a colorless oil 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (6.71 g, 21%). LC/MS: *m/z* 351.5 $(M+H)^+$ at 2.67 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00825] 4-((*R*)-2-Hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester

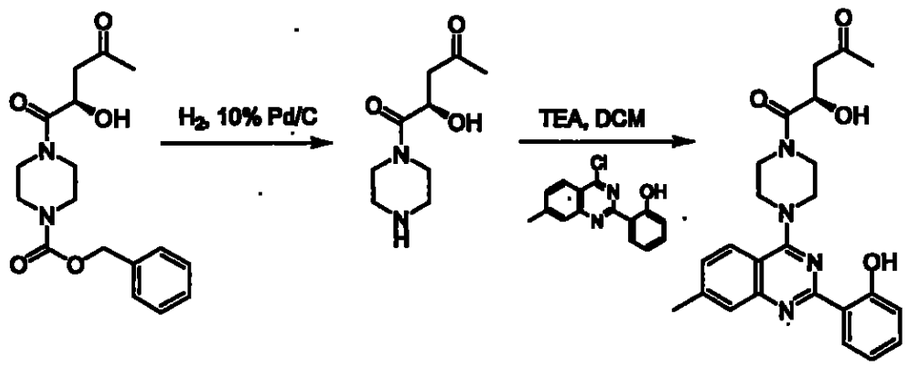
[00826] To a solution of 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (8.5 g, 24.0 mmol) in THF (240 mL) cooled in a dry ice acetone



bath, was added 1.4 M MeMgBr (61 mL, 85 mmol). The reaction was allowed to slowly warm to room temperature overnight. After quenching the mixture with saturated NH_4Cl and extracting with EtOAc, the combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave 4-((*R*)-2-hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester as a colorless oil (0.9 g, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5H), 5.15 (s, 2H), 4.79–4.74 (m, 1H), 4.00 (d, J = 7.8 Hz, 1H), 3.75–3.45 (m, 8H), 2.85 (dd, J = 16.6, 7.3 Hz, 1H), 2.63 (dd, J = 16.6, 3.4 Hz, 1H), 2.26 (s, 3H); LC/MS: *m/z* 335.1 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00827] (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentane-1,4-dione

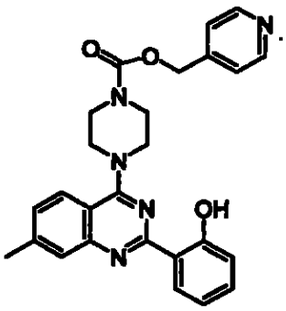
[00828]



[00829] A mixture of 4-((*R*)-2-hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester (0.13 g, 0.39 mmol) and MeOH (4 mL) was stirred with 10 mg of Pd/C (10% wt Pd on carbon)under H_2 atmosphere at ambient pressure overnight. After filtration and evaporation of the solvent, the residue was taken up in CH_2Cl_2, and 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.11 g, 0.39 mmol) and triethylamine (0.11 mL, 0.78 mmol) were added. The reaction mixture was stirred at room temperature overnight, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 provided (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentane-1,4-dione as a yellow solid (91 mg, 54%). LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

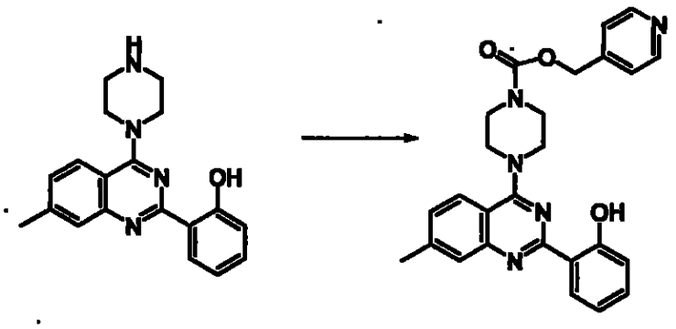
[00830] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00831]



[00832] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate.

[00833]

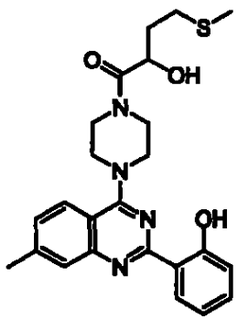


[00834] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (67 mg, 0.32 mmol), and triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 456.5 $(M+H)^+$ at 2.02 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00835] Example 153

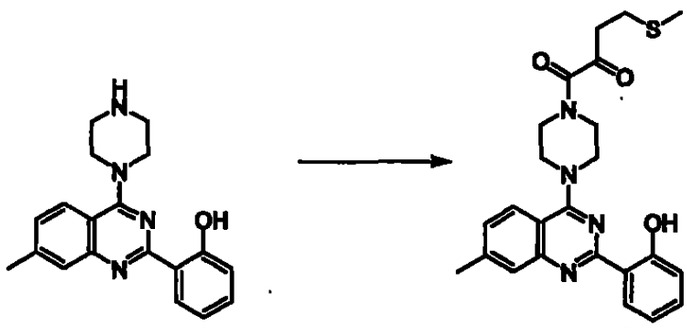
[00836] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butan-1-one**

[00837]



[00838] **1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butane-1,2-dione**

[00839]

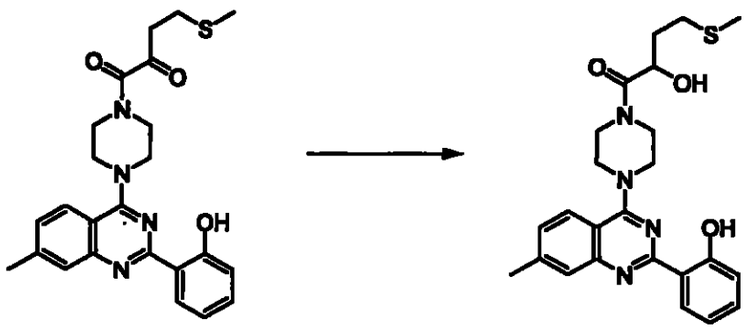


[00840] A mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (200 mg, 0.63 mmol), sodium 4-methylsulfanyl-2-oxo-butyrate (160 mg, 0.94 mmol), BOP (414 mg, 0.94 mmol), and triethylamine (348 μL, 2.5 mmol) in 2.1 mL of CH_2Cl_2 was stirred at room

temperature for 1 h. After adding saturated $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated to give 1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butane-1,2-dione. LC/MS: *m/z* 451.2 $(M+H)^+$ at 3.10 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00841] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butan-1-one**

[00842]



[00843] $NaBH_4$ (34 mg, 0.88 mmol) was added to 1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butane-1,2-dione (200 mg, 0.44 mmol) in 1.5 mL of MeOH, and the reaction mixture was stirred at 0 °C for 20 minutes The reaction mixture was allowed to warm to room temperature, saturated $NaHCO_3$ was added, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Purification using preparative reverse phase HPLC with 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butan-1-one as the TFA salt. (LC/MS: *m/z* 453.4 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00844] Example 154

[00845] **(*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanamide**

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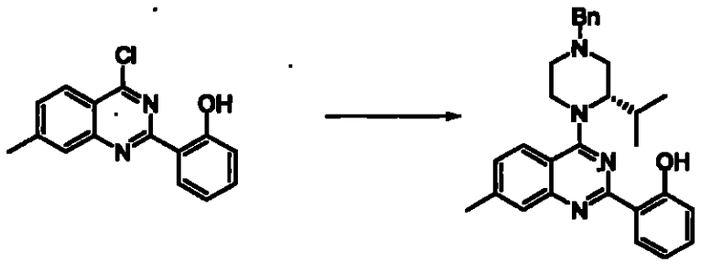
[00852]

[00853] **2-(4-((*S*)-4-Benzyl-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol**

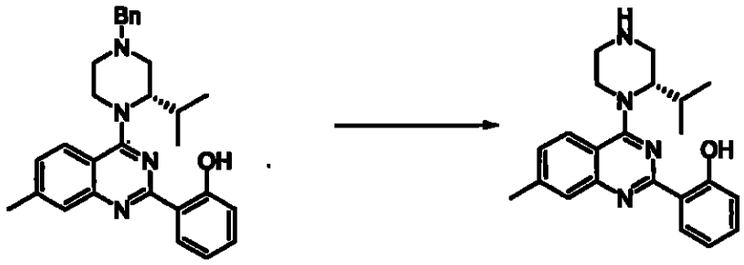
[00854]



[00855] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (200 mg, 0.74 mmol) in 10 mL DMF was added (*S*)-1-benzyl-3-isopropylpiperazine followed by the addition of triethylamine (206 μL). The reaction was heated at 85 °C for two hours. The reaction was quenched with water after cooling it to room temperature. The aqueous layer was extracted twice with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The reaction was purified via silica gel chromatography using 1:1 hexanes:CH_2Cl_2 solvent system to yield 2-(4-((*S*)-4-benzyl-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol (230 mg, 64%). LC/MS: *m/z* 453.5 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00856] **2-(4-((*S*)-2-Isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol**

[00857]

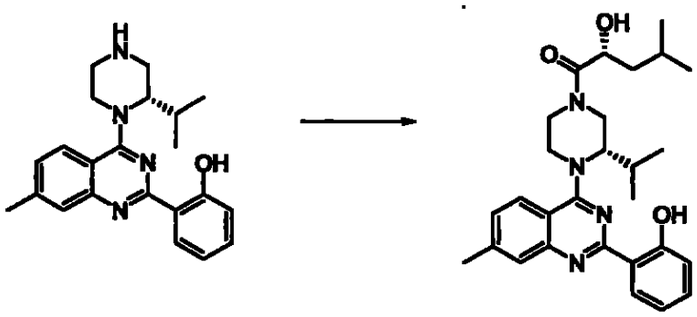


[00858] 20 mg of Pd/C was added to a round-bottom flask, and the flask was flushed with nitrogen followed by evacuation of the atmosphere under vacuum. To the flask was then added a solution of 2-(4-((*S*)-4-benzyl-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol (200 mg, 0.44 mmol) in methanol, followed by the addition of ammonium formate (32 mg, 0.88 mmol). The reaction was refluxed overnight. The reaction was filtered through a bed of Celite

to remove the catalyst. The solvent was evaporated to yield 2-(4-((*S*)-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol (126 mg). LC/MS: *m/z* 363.5 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00859] **(*R*)-2-Hydroxy-1-((*S*)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-3-isopropylpiperazin-1-yl)-4-methylpentan-1-one**

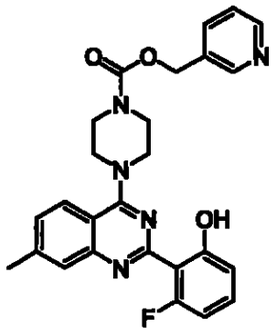
[00860]



[00861] To a solution of 2-(4-((*S*)-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol (70 mg, 0.19 mmol) in DMF (0.5 mL) was added (*R*)-2-hydroxy-4-methylpentanoic acid (32.6 mg, 0.247 mmol). It was followed by the addition of triethylamine (52 μL) and a solution of HATU (94 mg) in 0.5 mL DMF at room temperature. The reaction was complete in an hour. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-((*S*)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-3-isopropylpiperazin-1-yl)-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 477.5 $(M+H)^+$ at 2.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00862] Example 156

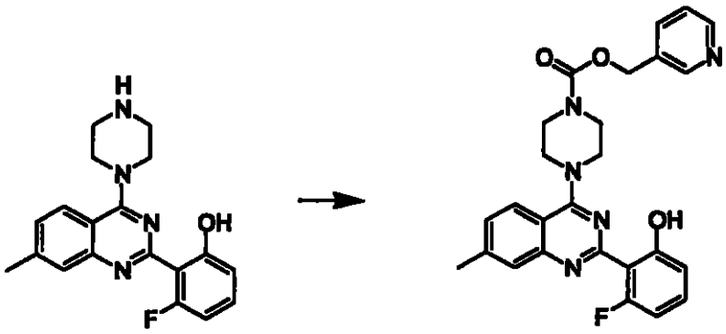
[00863] **(Pyridin-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**



[00864]

[00865] (Pyridin-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00866]

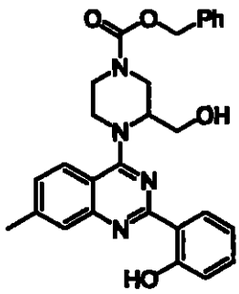


[00867] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.15 mmol), (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (53 mg, 0.26 mmol), triethylamine (30.4 mg, 0.3 mmol) and DMSO (1 mL) were stirred for 18 hours at room temperature. The reaction was purified by preparative reverse phase HPLC to give (pyridin-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 474.30 $(M+H)^+$ at 1.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00868] Example 157

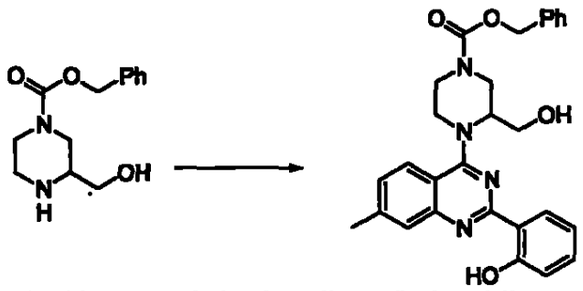
[00869] 3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester

[00870]



[00871] 3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester

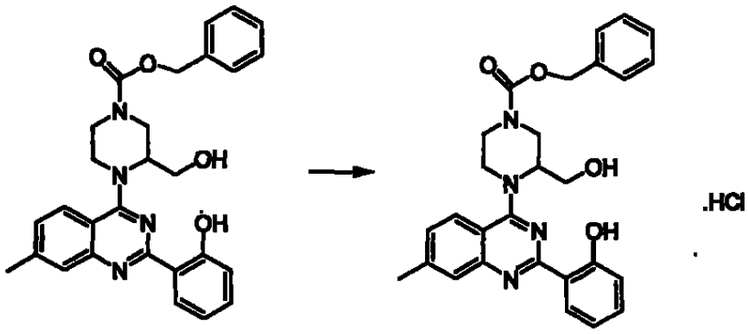
[00872]



[00873] To 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol (245 mg, 0.91 mmol) in 3.0 mL of CH_2Cl_2 was added sequentially 3-hydroxymethyl-piperazine-1-carboxylic acid benzyl ester (336.3 mg, 1.34 mmol) and triethylamine (190 mL, 1.37 mmol), and the reaction mixture was heated at 40 °C for 6 h. The reaction mixture was cooled and extracted with water (2 x 10 mL) and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to give an oil. The residue was purified by normal phase LC (20–85% EtOAc–hexanes) to give 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester (216 mg, 64% yield). LC/MS: *m/z* 485.4 (M+H)+ at 3.02 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00874] **Benzyl 3-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate hydrochloride**

[00875]



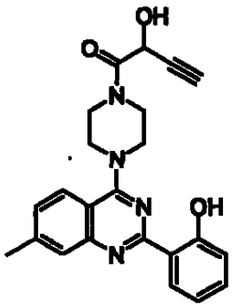
[00876] A 2.0 M HCl solution in Et_2O (212 μL, 0.42 mmol) was slowly added at room temperature to a stirring solution of 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester (206 mg, 0.42 mmol) in 500 μL of CH_2Cl_2. The reaction was stirred for 1 hour. Solvents were removed under reduced pressure, and the residue was triturated with Et_2O and filtered to give benzyl 3-(hydroxymethyl)-4-(2-(2-

hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate hydrochloride. LC/MS: *m/z* 485.5 (M+H)+ at 3.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[00877] Example 158

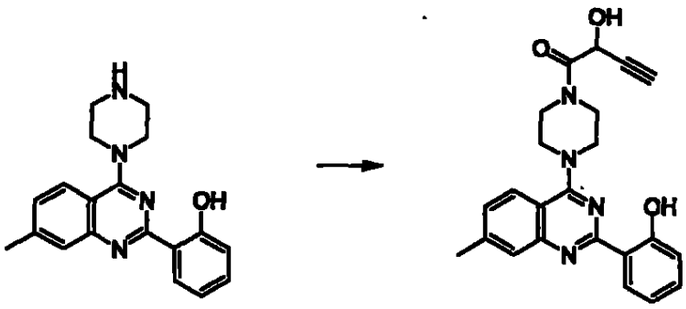
[00878] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)but-3-yn-1-one**

[00879]



[00880] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)but-3-yn-1-one**

[00881]

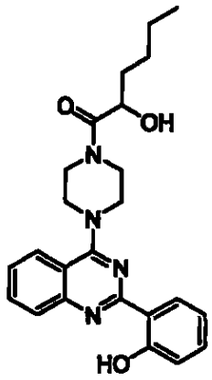


[00882] To a mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (75 mg, 0.23 mmol) in 0.78 ml CH_2Cl_2 were added successively 2-hydroxybut-3-ynoic acid (30 mg, 0.30 mmol), BOP (134 mg, 0.30 mmol), and triethylamine (36 mg, 49 µL, 0.35 mmol). The mixture was stirred at 0 °C for 30 minutes. Purification via silica gel chromatography using 0–100% ethyl acetate/hexanes gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)but-3-yn-1-one. (LC/MS: *m/z* 403.5 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00883] Example 159

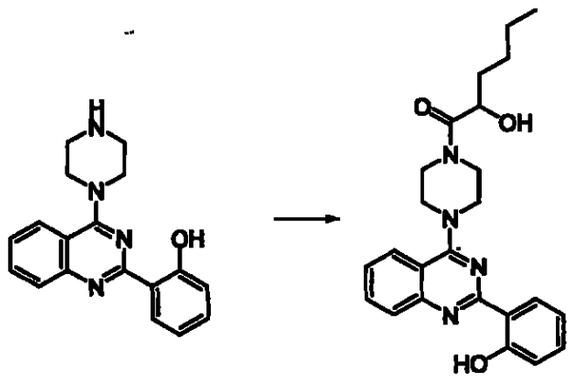
[00884] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00885]



[00886] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00887]

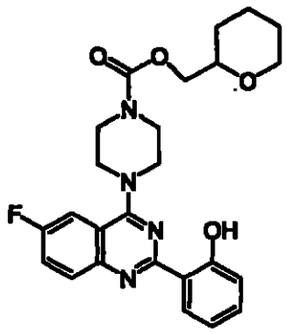


[00888] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-hydroxyhexanoic acid (39.3 mg, 0.297 mmol). Triethylamine (63 μL) was added at room temperature, then a solution of HATU (113 mg) in 0.5 mL DMF. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one. LC/MS: *m/z* 421.3 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00889] Example 160

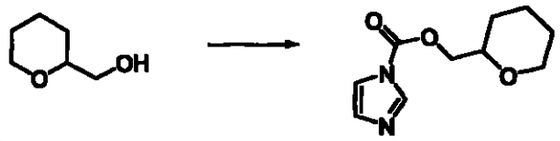
[00890] (Tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00891]



[00892] (Tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate

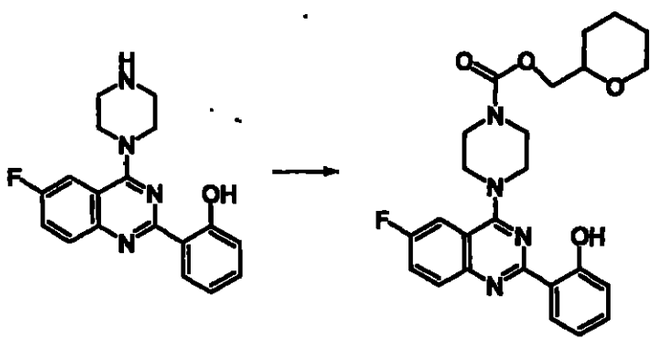
[00893]



[00894] A solution of (tetrahydro-2*H*-pyran-2-yl)methanol (1 g, 8.60 mmol) and di(1*H*-imidazol-1-yl)methanone (2.8 g, 17.2 mmol) in 17 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was quenched with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, J = 0.9 Hz, 1H), 7.44 (t, J = 1.4 Hz, 1H), 7.07 (dd, J = 1.6, 0.8 Hz, 1H), 6.95 (m, 2H), 6.84 (m, 1H), 6.01 (s, 2H), 5.33 (s, 2H)

[00895] (Tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl) quinazolin-4-yl)piperazine-1-carboxylate

[00896]



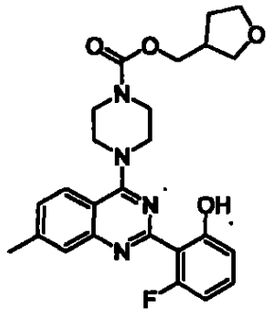
112

[00897] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.077 mmol), (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (48.5 mg, 0.23 mmol), triethylamine (22μL, 0.154 mmol), and HATU (38 mg, 0.10 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. *LC/MS*: *m/z* 467.3 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00898] Example 162

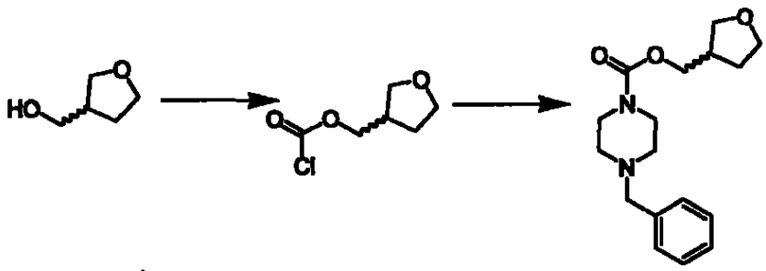
[00899] **(Tetrahydrofuran-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00900]



[00901] **4-Benzyl-piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester**

[00902]

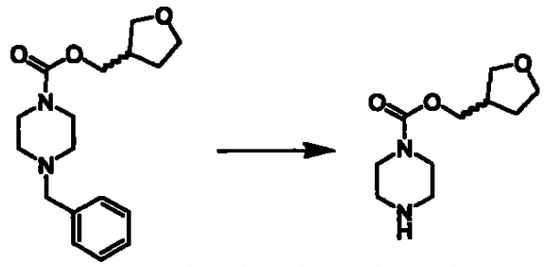


[00903] To a cooled (0 °C) solution of triphosgene (5.0 g, 17 mmol) in 50 ml dichloromethane under a nitrogen atmosphere was added dropwise a solution of tetrahydro-3-furanmethanol (5.4 g, 53 mmol) in 10 ml dichloromethane. Pyridine (4.3 ml, 53 mmol) was added dropwise, and the solution was warmed to room temperature. After 2 hours at room temperature a mixture of triethylamine (7.5 ml, 52 mmol) and *N*-benzylpiperazine (9.5 ml, 54

mmol) was added dropwise with cooling. The resulting mixture was refluxed for 1 hour. The solution was stirred at room temperature overnight under an nitrogen atmosphere. The mixture was washed with aqueous sodium bicarbonate solution (5%, 2 x 50 ml), and with a solution of saturated aqueous NaCl (50 ml). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was co-evaporated three times with toluene (50 ml) to yield 4-benzyl-piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester (13.0 g, 81%) as a brownish oil.

[00904] **Piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester.**

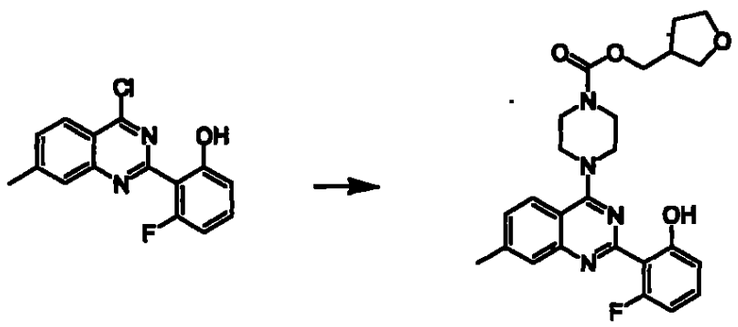
[00905]



[00906] 4-Benzyl-piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester (11.0 g) was dissolved in 100 ml ethanol. Palladium on carbon (10% Pd/C, 0.5 g) was added, and a hydrogen atmosphere was applied overnight at room temperature. The solution was filtered through Celite to remove the catalyst, and the Celite cake was rinsed with 50 ml ethanol. The combined filtrates were evaporated to dryness to yield piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester (8.0 g) as a colorless oil.

[00907] **(Tetrahydrofuran-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00908]



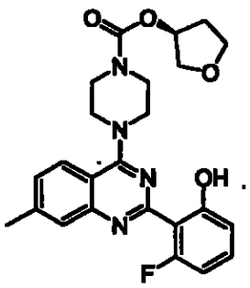
113

[00909] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (50 mg, 0.174 mmol) was dissolved in 1 mL DMF, followed by the addition of triethylamine (35.2 mg, 0.348 mmol). (Tetrahydrofuran-3-yl)methyl piperazine-1-carboxylate (45 mg, 0.21 mmol) was then added. After 1 hour at room temperature, the reaction was complete. It was filtered and purified by reverse phase preparative HPLC to give (tetrahydrofuran-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 467.3 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00910] Example 163

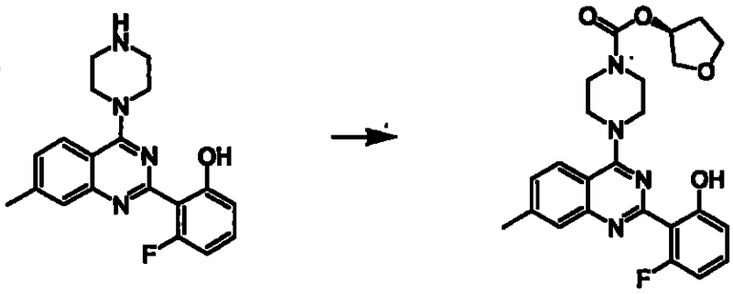
[00911] **(*S*)-Tetrahydrofuran-3-yl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00912]



[00913] **(*S*)-Tetrahydrofuran-3-yl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00914]

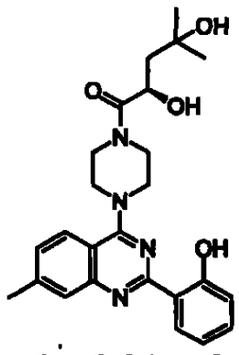


[00915] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.21 mmol) was dissolved in 1 mL anhydrous DMF under an N_2 atmosphere and cooled to 0 °C. (*S*)-Tetrahydrofuran-3-yl chloroformate (34.3 mg, 0.228 mmol) was dissolved in 150 μL anhydrous DMF and added dropwise to the reaction, followed by triethylamine (42 mg, 0.41 mmol). After 1 hour the reaction was complete, and it was filtered and purified by reverse phase HPLC to give (*S*)-tetrahydrofuran-3-yl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00916] Example164

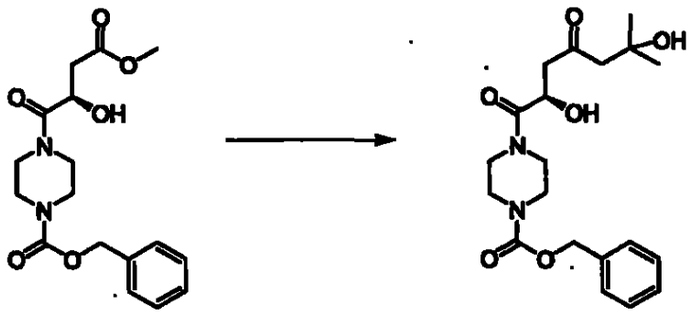
[00917] (*R*)-2,6-Dihydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-6-methylheptane-1,4-dione

[00918]



[00919] 4-((*R*)-2,6-Dihydroxy-6-methyl-4-oxo-heptanoyl)-piperazine-1-carboxylicacid benzyl ester

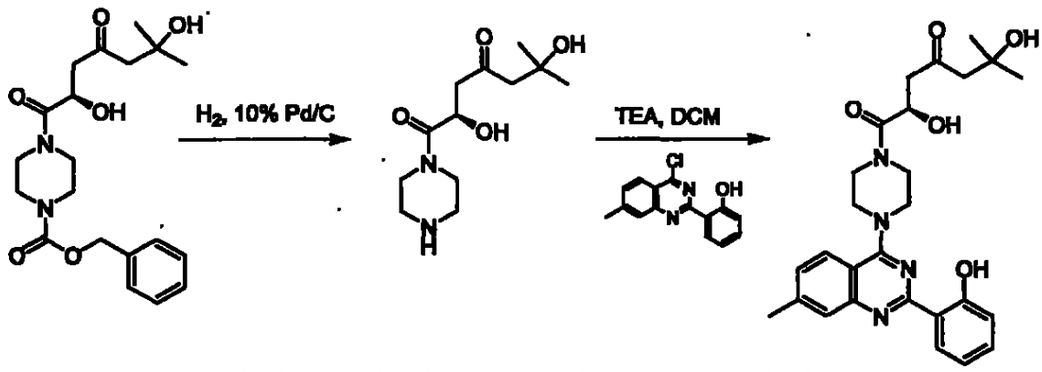
[00920]



[00921] To a solution of 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (5.26 g, 15.0 mmol) in THF (150 mL) cooled in a dry ice acetone bath was added 1.4 M MeMgBr (32 mL, 45 mmol). The reaction was allowed to slowly warm to room temperature overnight. After quenching the mixture with saturated NH_4Cl and extracting with EtOAc, the combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave 4-((*R*)-2-hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester as a colorless oil (0.79 g, 15%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 5.15 (s, 2H), 4.71–4.68 (m, 1H), 4.05 (d, J = 6.8 Hz, 1H), 3.80–3.73 (m, 1H), 3.62–3.42 (m, 6H), 3.31–3.23 (m, 1H), 1.72–1.61 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H); LC/MS: *m/z* 351.3 $(M+H)^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00922] **(*R*)-2,4-Dihydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

[00923]



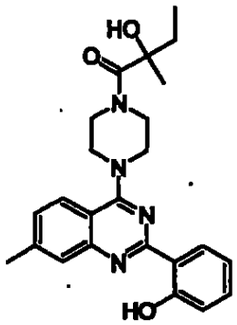
[00924] A mixture of 4-((*R*)-2,6-dihydroxy-6-methyl-4-oxo-heptanoyl)-piperazine-1-carboxylicacid benzyl ester (0.79 g, 2.20 mmol) and MeOH (25 mL) was stirred with 40 mg of Pd/C (10% wt Pd on carbon) under H_2 atmosphere at ambient pressure overnight. After filtration and evaporation of the solvent, the residue was taken up in CH_2Cl_2, and 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.61 g, 2.20 mmol) and triethylamine (0.63 mL, 4.50 mmol) were added. The reaction mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave (*R*)-2,6-dihydroxy-1-(4-(2-(2-

hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-6-methylheptane-1,4-dione as a yellow solid (372 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, J = 7.9, 1.6 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.67 (s, 1H), 7.40–7.36 (m, 1H), 7.29 (dd, J = 8.5, 1.4 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.96–6.92 (m, 1H), 4.81–4.76 (m, 1H), 4.09 (d, J = 6.8 Hz, 1H), 4.03–3.77 (m, 6H), 3.75–3.67 (m, 2H), 3.28 (s, 1H), 2.55 (s, 3H), 1.78–1.69 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 164.0, 161.3, 160.5, 150.1, 144.5, 132.7, 129.2, 127.7, 126.8, 124.4, 119.3, 118.5, 117.7, 112.7, 70.6, 66.4, 49.9, 49.0, 46.1, 44.5, 42.4, 30.6, 29.2, 21.9; LC/MS: *m/z* 451.1 $(M+H)^+$ at 2.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00925] Example 165

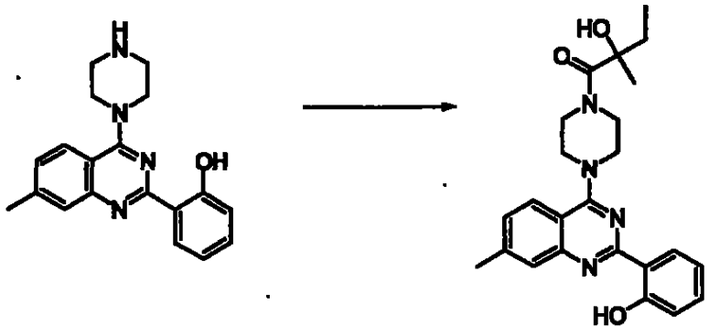
[00926] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one

[00927]



[00928] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one

[00929]

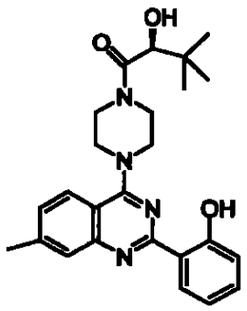


[00930] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxy-2-methylbutanoic acid (33.6 mg, 0.284 mmol). Triethylamine (61 μL) was added, followed by a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 421.3 $(M+H)^+$ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00931] Example 166

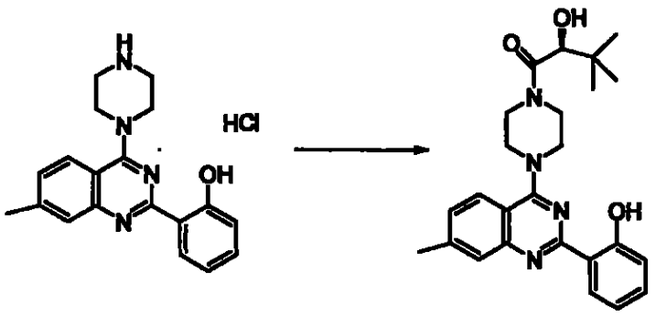
(*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3,3-dimethylbutan-1-one

[00932]



[00933] **(*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3,3-dimethylbutan-1-one**

[00934]



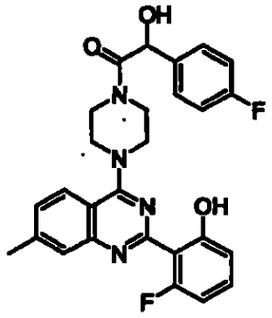
[00935] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol hydrochloride (30 mg, 0.09 mmol), (*S*)-2-hydroxy-3,3-dimethylbutanoic acid (16 mg, 0.12 mmol), triethylamine (37.5μL, 0.27 mmol), and HATU (45.6 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight.

Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3,3-dimethylbutan-1-one as the TFA salt. LC/MS: *m/z* 434.53 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00936] Example 167

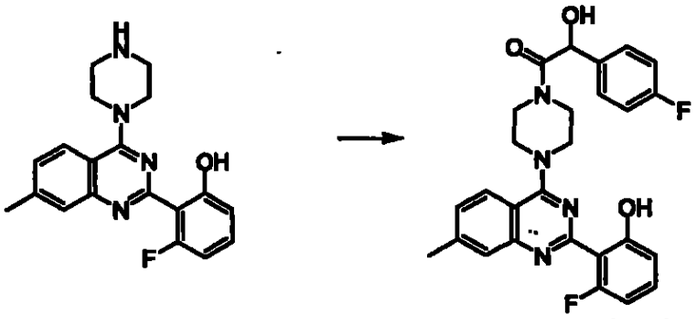
[00937] 1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-(4-fluorophenyl)-2-hydroxyethanone

[00938]



[00939] 1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-(4-fluorophenyl)-2-hydroxyethanone

[00940]



[00941] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol), 2-(4-fluorophenyl)-2-hydroxyacetic acid (19.62 mg, 0.12 mmol), triethylamine (25 μL, 0.18 mmol) and HATU (45.6 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-(4-fluorophenyl)-

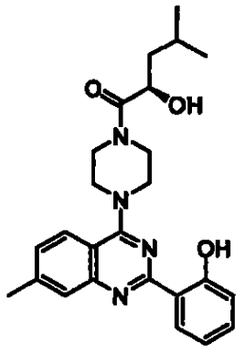
116

2-hydroxyethanone as the TFA salt. LC/MS: *m/z* 491.3 $(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00942] Example 168

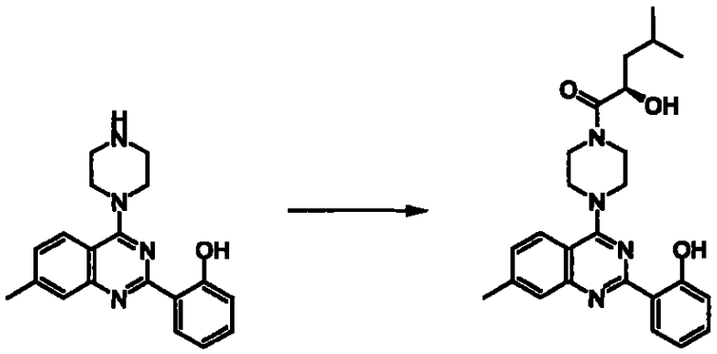
[00943] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00944]



[00945] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00946]

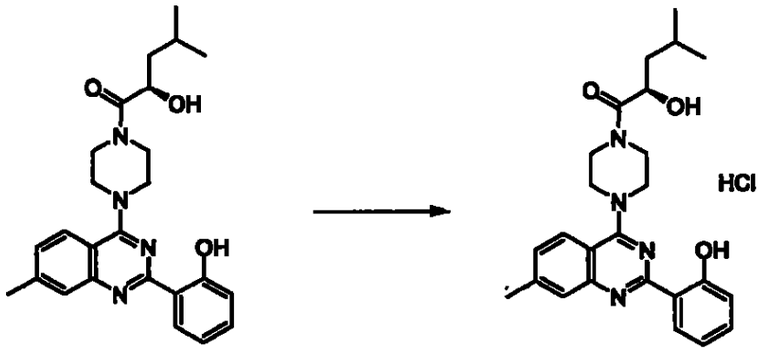


[00947] Under an N_2 atmosphere, BOP (138 mg, 0.31 mmol) was added in a single portion to a stirring solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (100 mg, 0.31 mmol), (*R*)-2-hydroxy-4-methylpentanoic acid (41 mg, 0.31 mmol), and triethylamine (43 µL, 0.31 mmol) in DMF (0.5 ml). After stirring the mixture for 1 h at room temperature, it was partitioned between H_2O and ether. The organic phase was washed with H_2O (3x 20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 20%

EtOAc and 80% CH_2Cl_2 gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one as a light yellow solid (89 mg, 60%). *LC/MS*: *m/z* 435.1 (M+H)+ at 2.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.66 (s, 1H), 7.41–7.37 (m, 1H), 7.30 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.06–7.04 (m, 1H), 6.98–6.94 (m, 1H), 4.51–4.45 (m, 1H), 4.04–3.80 (m, 6H), 3.72–3.62 (m, 3H), 2.56 (s, 3H), 2.12–1.99 (m, 1H), 1.57–1.49 (m, 1H), 1.38–1.32 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H).

[00948] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride

[00949]

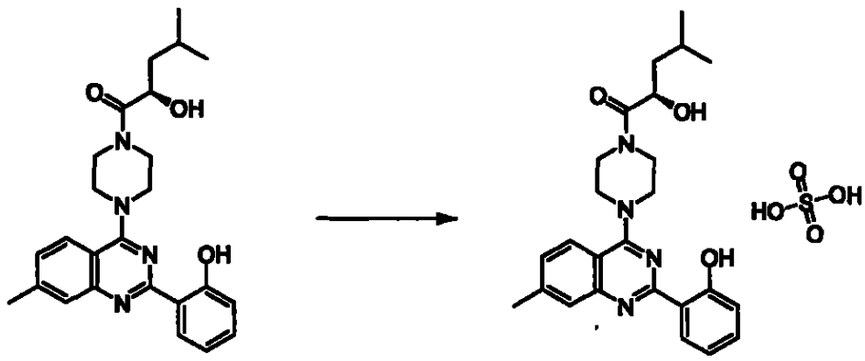


[00950] (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (90 mg, 0.20 mmol) was dissolved in 1 mL CH_2Cl_2 and treated with 1 equivalent of 2.0 M HCl in ether (100 μL, 0.20 mmol). The formed precipitate was filtered and vacuum dried to obtain (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride. *LC/MS*: *m/z* 435.1 (M+H)+ at 2.84 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, CD_3OD) δ 8.39–8.37 (m, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.61–7.55 (m, 2H), 7.15–7.11 (m, 2H), 4.57 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.49–4.32 (m, 4H), 4.07–3.79 (m, 4H), 2.62 (s, 3H), 1.97–1.87 (m, 1H), 1.65–1.58 (m, 1H), 1.53–1.47 (m, 1H), 1.03–1.00 (m, 6H).

[00951] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one sulfate

117

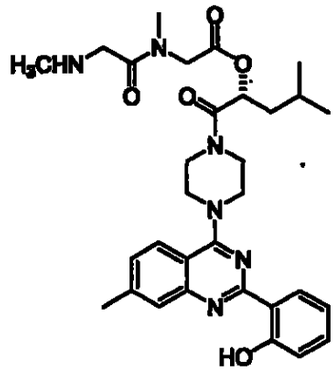
[00952]



[00953] To a stirring yellow solution of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (200 mg, 0.46 mmol) and THF (0.9 mL) under an N_2 atmosphere was added a solution of concentrated H_2SO_4 solution (95.9%) (26 µL, 0.46 mmol) and CH_3CN (0.75 mL) in a single portion. A white precipitate formed slowly over a period of 1 h. The solid was filtered and vacuum dried to obtain (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one sulfate as a white solid (229 mg, 94%). LC/MS: *m/z* 435.3 (M+H)+ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.20 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.53–7.49 (m, 2H), 7.10–7.03 (m, 2H), 4.39–4.35 (m, 1H), 4.30–4.04 (m, 4H), 3.93–3.69 (m, 4H), 2.55 (s, 3H), 1.86–1.73 (m, 1H), 1.52–1.33 (m, 2H), 0.93–0.91 (m, 6H).

[00954] Example 169

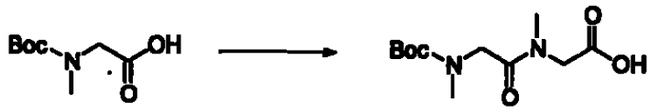
[00955] (*R*)-[Methyl-(2-methylamino-acetyl)-amino]-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester



[00956]

[00957] {[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid

[00958]

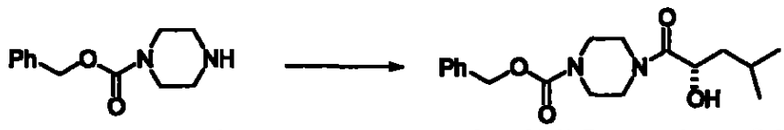


[00959] To (*tert*-butoxycarbonyl-methyl-amino)-acetic acid (2.73 g, 14.4 mmol) in 70 mL of THF was added sequentially diisopropyl ethylamine (7.5 mL, 14.4 mmol) and HBTU (5.47 g, 14.4 mmol), and the reaction mixture was stirred at room temperature for one hour. To this reaction mixture was added methylamino-acetic acid ethyl ester (2.22 g, 14.4 mmol) in one portion, and the reaction mixture was heated at 65 °C for 12 h. The reaction mixture was cooled, diluted with a solution of saturated $NaHCO_3$, and extracted with EtOAc. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid ethyl ester.

The ester was taken up in 49 mL of methanol, and to this was added a 1 M NaOH solution (25.1 mL, 25 mmol). The reaction mixture was heated at 65 °C for 3 h. The reaction mixture was cooled, and methanol was removed under reduced pressure. The residue was diluted with 50 mL of water and acidified with glacial acetic acid until the pH was 5. This solution was extracted with EtOAc (50 mL), and the organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give {[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid as an oil.

[00960] 4-(2(*R*)-Hydroxy-4-methyl-pentanoyl)-piperazine-1-carboxylic acid benzyl ester

[00961]

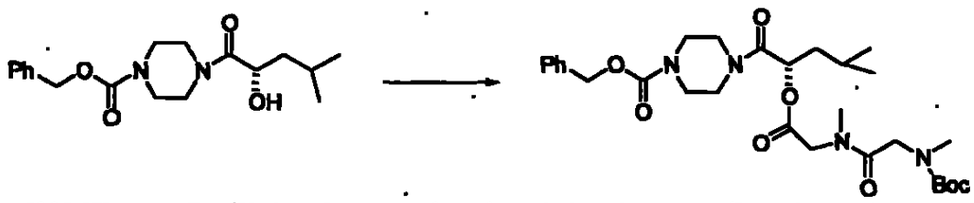


[00962] To (*R*)- 2-hydroxy-4-methyl-pentanoic acid (1.71 g, 12.9 mmol) in 48 mL of DMF was added sequentially triethylamine (4.9 mL, 35. mmol), HOBt (1.75 g, 12.9 mmol), EDCI·HCl (2.48 g, 12.9 mmol) and piperazine-1-carboxylic acid benzyl ester (2.59 g, 11.8 mmol) at room temperature. The reaction mixture was stirred for 4 h and then diluted with EtOAc (50 mL) and extracted with 50 mL of water. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue

was subjected to purification by normal phase LC using 40–85% EtOAc–hexanes to give (1.92 g, 49% yield) of 4-(2(*R*)-hydroxy-4-methyl-pentanoyl)-piperazine-1-carboxylic acid benzyl ester the desired product. LC/MS: *m/z* 335.4 $(M+H)^+$ at 2.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

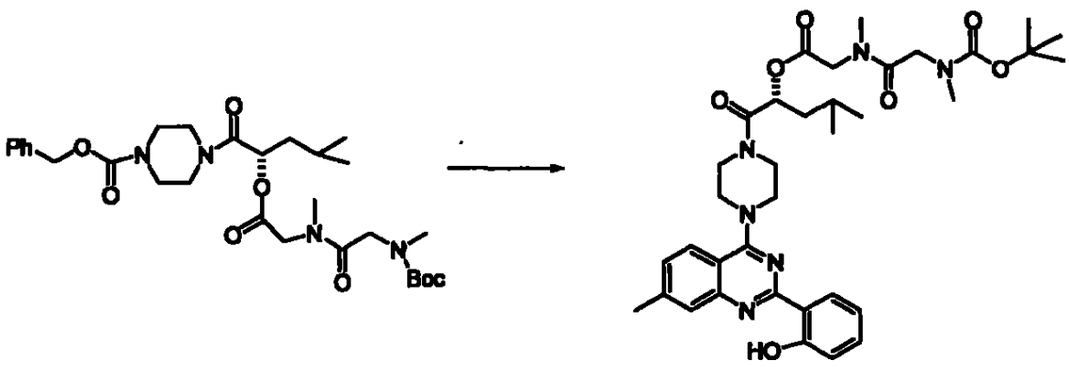
[00963] 4-[2-(2-{[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetoxy)-4-methyl-pentanoyl]-piperazine-1-carboxylic acid benzyl ester

[00964]



[00965] To {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid (427 mg, 1.57 mmol) in 2 mL of THF was added sequentially HBTU (624 mg, 1.2 mmol), diisopropyl ethylamine (860 μL, 4.71 mmol) at room temperature. After 5 min, 4-(2-hydroxy-4-methyl-pentanoyl)-piperazine-1-carboxylic acid benzyl ester (403 mg 1.2 mmol) in 2 mL of THF was added to the reaction mixture, and the solution was heated at 65 °C for 12 h. The reaction mixture was cooled and diluted with 20 mL of CH_2Cl_2 and 10 mL of water. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was subjected to purification by normal phase LC using 30–100% EtOAc–hexanes to give 4-[2-(2-{[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetoxy)-4-methyl-pentanoyl]-piperazine-1-carboxylic acid benzyl ester (283 mg, 41% yield). LC/MS: *m/z* 577 $(M+H)^+$ at 3.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

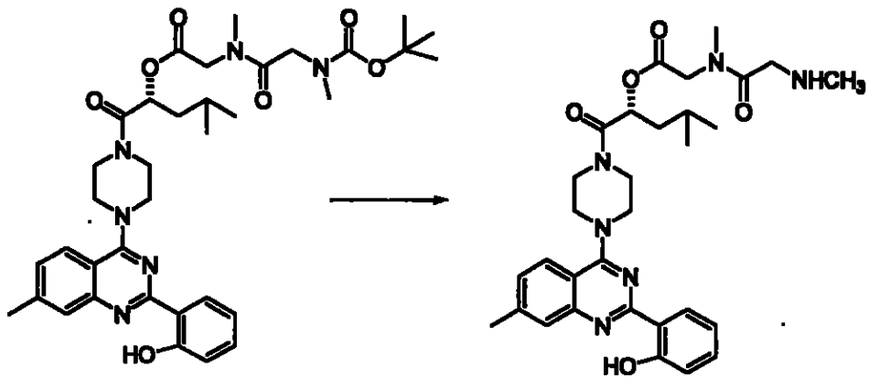
[00966] {[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester.



[00967] To 4-[2-(2-{[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetoxy)-4-methyl-pentanoyl]-piperazine-1-carboxylic acid benzyl ester (208 mg, 0.49 mmol) in 1.6 mL of methanol was added 70 mg of Pd/C (10% wt Pd on carbon). The reaction mixture was hydrogenated using a balloon of H_2 for 4 h at room temperature. The mixture was then filtered through Celite, and the solvent removed to give {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid 3-methyl-1-(piperazine-1-carbonyl)-butyl ester.

The amine was taken up in 1 mL CH_2Cl_2 and treated with 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol (53 mg, 0.19 mmol) and 49 μL of triethylamine, and stirred at room temperature for 3 h. The reaction mixture was diluted with 10 mL of CH_2Cl_2 and 10 mL of water. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester. LC/MS: *m/z* 677.4 $(M+H)^+$ at 3.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00968] [Methyl-(2-methylamino-acetyl)-amino]-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester.



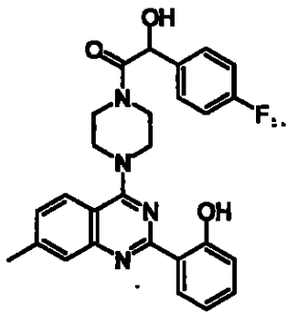
[00969]

[00970] To {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester (42 mg, 0.062 mmol) was added 300 μL of 1.25 M HCl in methanol at room temperature, and the reaction mixture was stirred for 12 h. The solvent was removed, and the residue was purified with reverse phase LC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) as eluent to give [methyl-(2-methylamino-acetyl)-amino]-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester as the TFA salt. LC/MS: *m/z* 577.4 (M+H)+ at 2.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00971] Example 170

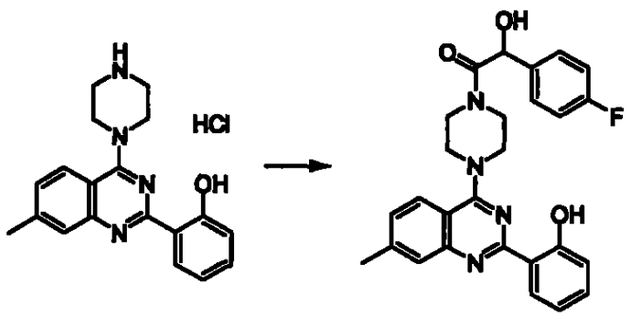
[00972] **2-(4-Fluorophenyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone**

[00973]



[00974] **2-(4-Fluorophenyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone**

[00975]

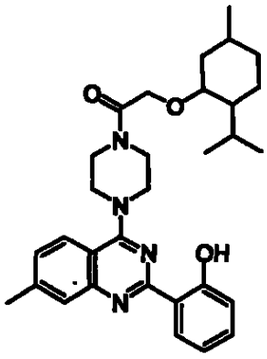


[00976] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol hydrochloride (prepared analogously to 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol, oxalate salt, see Example 130; 30 mg, 0.09 mmol), 2-(4-fluorophenyl)-2-hydroxyacetic acid (20 mg, 0.12 mmol), triethylamine (37.5 μL, 0.27 mmol) and HATU (45 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight. Purification via preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-(4-fluorophenyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone as the TFA salt. LC/MS: *m/z* 473.1 $(M+H)^+$ at 2.63 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00977] Example 171

[00978] 2-(2-Isopropyl-5-methylcyclohexyloxy)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone

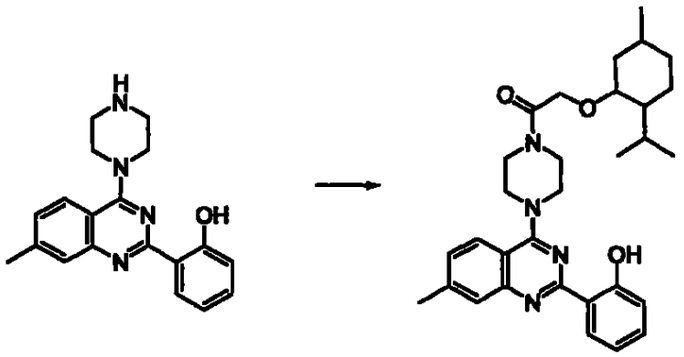
[00979]



[00980] 2-(2-Isopropyl-5-methylcyclohexyloxy)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone

120

[00981]

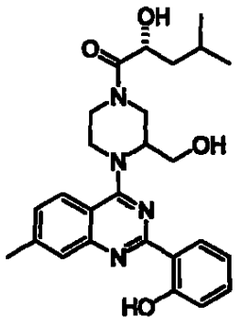


[00982] To a solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added of triethylamine (25 μL) followed by the dropwise addition of 2-(2-isopropyl-5-methylcyclohexyloxy)acetyl chloride (21 μL, 0.09 mmol) at 0 °C. The reaction was warmed to room temperature, and purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-(2-isopropyl-5-methylcyclohexyloxy)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone as the TFA salt. LC/MS: *m/z* 517.5 $(M+H)^+$ at 3.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00983] Example 172

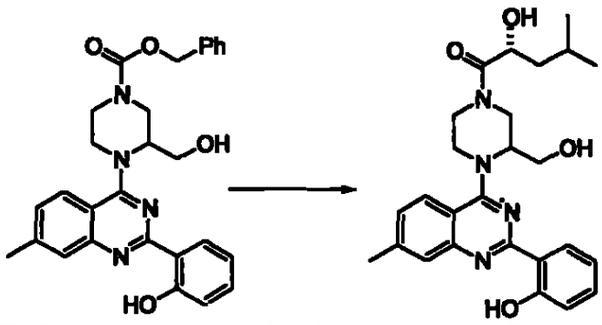
[00984] **(*R*)-2-Hydroxy-1-{3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one**

[00985]



[00986] **(*R*)-2-Hydroxy-1-{3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one**

[00987]

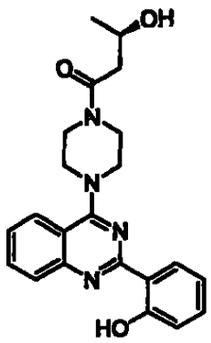


[00988] To 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester (200 mg, 0.41 mmol) in 1.7 mL of methanol was added 39 mg of Pd /C (10% weight Pd on carbon). The reaction mixture was subjected to hydrogenation using a H_2 balloon for 3 h. The reaction mixture was filtered through Celite and the solvent was removed to give 2-[4-(2-hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol. This amine was treated with (*R*)-2-hydroxy-4-methyl-pentanoic acid (60 mg, 0.45 mmol), BOP (200 mg, 0.45 mmol) and 115 µL of triethylamine in 1.6 mL of DMF at room temperature for 12 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and 20 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to purification using 60–100% EtOAc–hexanes to give (*R*)-2-hydroxy-1-{3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one. *LC/MS*: *m/z* 465 (M+H)+ at 2.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00989] Example 173

[00990] **(*R*)-3-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one**

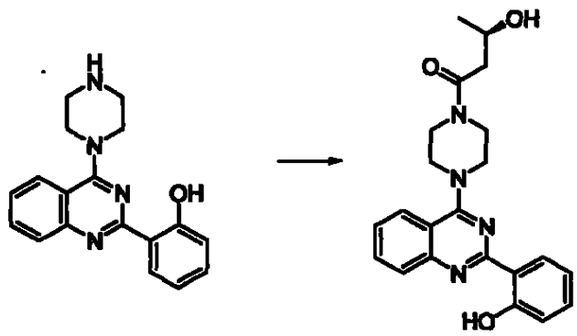
121



[00991]

[00992] (*R*)-3-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00993]

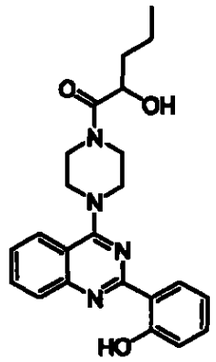


[00994] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*R*)-3-hydroxybutanoic acid (31 mg, 0.30 mmol). Then, triethylamine (63 μL) was added, followed by a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-3-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 393.1 $(M+H)^+$ at 2.03 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00995] Example 174

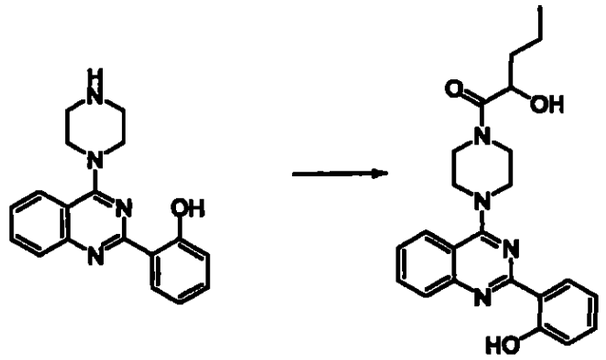
[00996] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)pentan-1-one

[00997]



[00998] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)pentan-1-one

[00999]



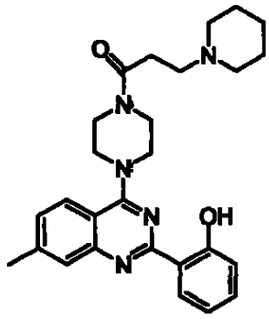
[001000] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-hydroxypentanoic acid (35 mg, 0.30 mmol). This was followed by the addition of triethylamine (63 μL) and a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.41 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001001] Example 175

122

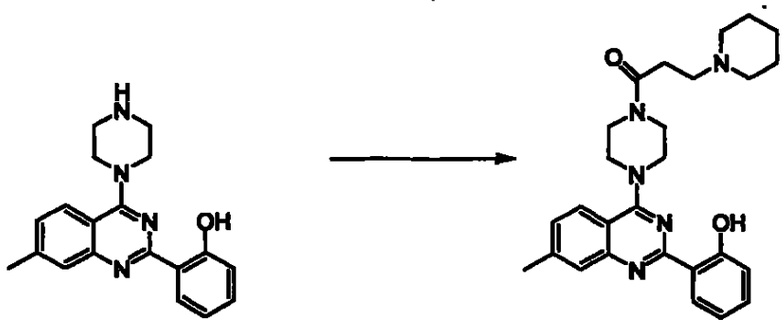
[001002] 1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(piperidin-1-yl)propan-1-one

[001003]



[001004] 1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(piperidin-1-yl)propan-1-one

[001005]

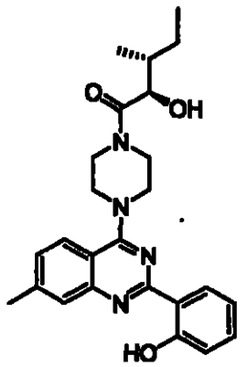


[001006] To 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (53 mg, 0.17 mmol) was added sequentially 3-(piperidin-1-yl)propanoyl chloride (33 mg, 0.19 mmol) in 28 μL of CH_2Cl_2 and triethylamine (28 μL, 0.2 mmol). The mixture was stirred at 0 °C for 20 minutes After adding H_2O and CH_2Cl_2, the phases were separated, and the organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification using preparative reverse phase HPLC with 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 460.5 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001007] Example 176

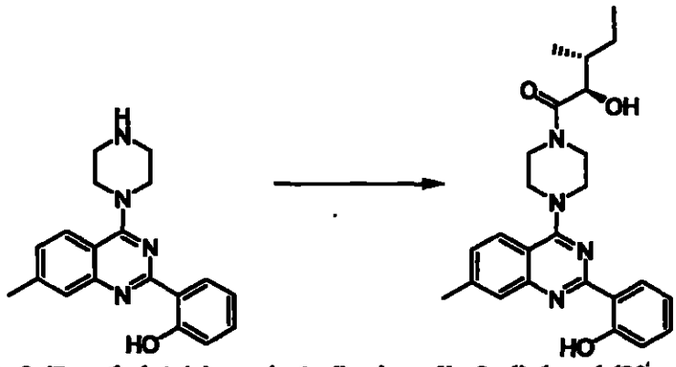
[001008] (2*R*,3*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylpentan-1-one

[001009]



[001010] (2*R*,3*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylpentan-1-one

[001011]



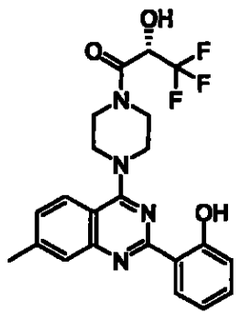
[001012] To 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (80 mg, 0.25 mmol) in 800 μL of CH_2Cl_2 was added sodium of (2*R*,3*R*)-2-hydroxy-3-methyl-pentanoate (50 mg, 0.33 mmol), BOP (144 mg, 0.33 mmol), and triethylamine (52 μL, 0.38 mmol). The reaction mixture was stirred at room temperature for 2 h. After adding H_2O and CH_2Cl_2, the layers were separated, and the organic layer was dried over Na_2SO_4 and concentrated. Purification via preparative reverse phase HPLC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave (2*R*,3*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.62 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001013] Example 177

123

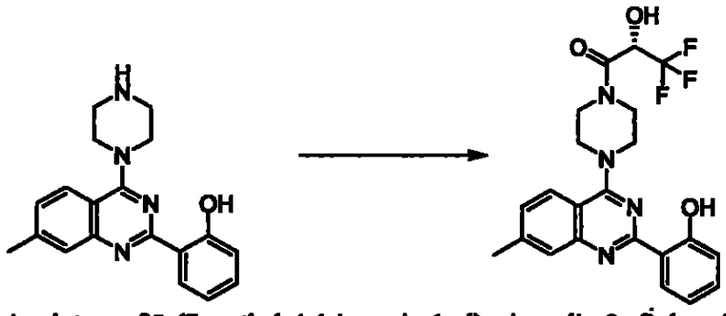
[001014] (*S*)-3,3,3-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[001015]



[001016] (*S*)-3,3,3-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[001017]

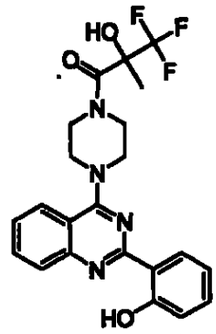


[001018] A mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (64 mg, 0.2 mmol), (*S*)-3,3,3-trifluoro-2-hydroxypropanoic acid (29 mg, 0.2 mmol), HATU (76 mg, 0.2 mmol) and triethylamine (28 μL, 0.2 mmol) in DMF (1 mL) was stirred at room temperature overnight. Purification via preparative HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-3,3,3-trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 447.1 $(M+H)^+$ at 2.53 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001019] Example 178

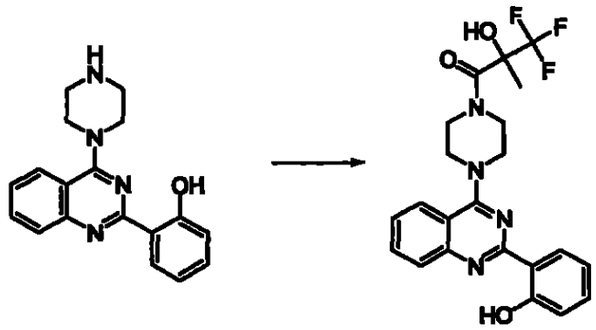
[001020] 2-(Trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl) quinazolin-4-yl)piperazin-1-yl)propan-1-one

[001021]



[001022] 2-(Trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl) quinazolin-4-yl)piperazin-1-yl)propan-1-one

[001023]

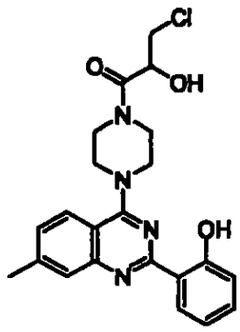


[001024] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-(trifluoromethyl)-2-hydroxypropanoic acid (47.0 mg, 0.297 mmol). Then, triethylamine (63 μL) was added, followed by a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-(trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 447.3 $(M+H)^+$ at 2.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001025] Example 179

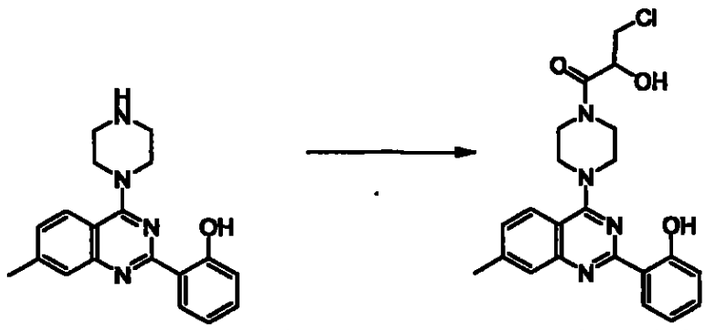
[001026] 3-Chloro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[001027]



[001028] 3-Chloro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[001029]

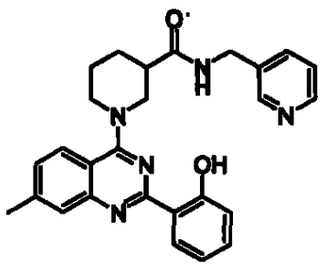


[001030] A mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (121 mg, 0.38 mmol), 3-chloro-2-hydroxypropanoic acid (61 mg, 0.49 mmol), BOP (217 mg, 0.49 mmol), and triethylamine (79 μL, 0.56 mmol) in 1.2 mL of CH_2Cl_2 was stirred at room temperature for 1 h. The reaction was washed with water and the organic layer was dried over Na_2SO_4 and concentrated. Purification via preparative reverse phase HPLC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave 3-chloro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 427.2 $(M+H)^+$ at 2.59 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001031] Example 201

[001032] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)piperidine-3-carboxamide

[001033]



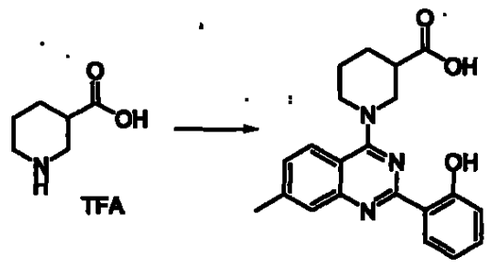
[001034] Piperidine-3-carboxylic acid

[001035]

[001036] To a solution of 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid (500 mg, 2.18 mmol) in CH_2Cl_2 (10 mL) was added TFA (5 ml). The reaction mixture was stirred for an hour. Excess TFA was removed under reduced pressure, and the piperidine-3-carboxylic acid was used without neutralization for the next step. LC/MS: *m/z* 1303 $(M+H)^+$ at 0.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001037] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid

[001038]



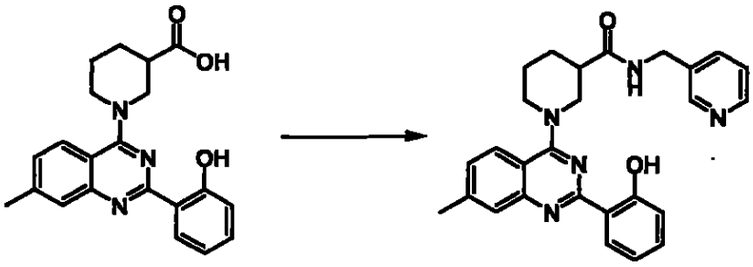
[001039] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.449 mg, 1.66 mmol) in CH_2Cl_2 was added 5 equivalents of triethylamine followed by the addition of piperidine-3-carboxylic acid as a TFA salt. The reaction was stirred for 2 hours and quenched with water. The layers were separated, and the organic extracts were dried over $MgSO_4$, filtered,

125

and concentrated to give 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid which was used without further purification. *LC/MS*: *m/z* 364.3 $(M+H)^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001040] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)piperidine-3-carboxamide

[001041]

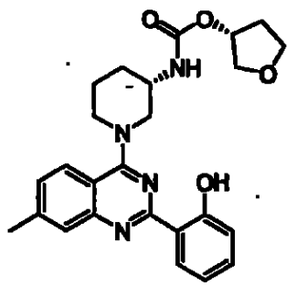


[001042] A solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid (45 mg, 0.12 mmol), (pyridin-3-yl)methanamine (14 μL, 0.136 mmol) and triethylamine (25 mg, 35 μL, 0.25 mmol) in 500 μL DMF was cooled to 0 °C, and HATU (57 mg, 0.15 mmol) was added. The reaction was warmed to room temperature, stirred overnight and purified by reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) giving 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)piperidine-3-carboxamide as the TFA salt. *LC/MS*: *m/z* 454.5 $(M+H)^+$ at 1.87 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001043] Example 203

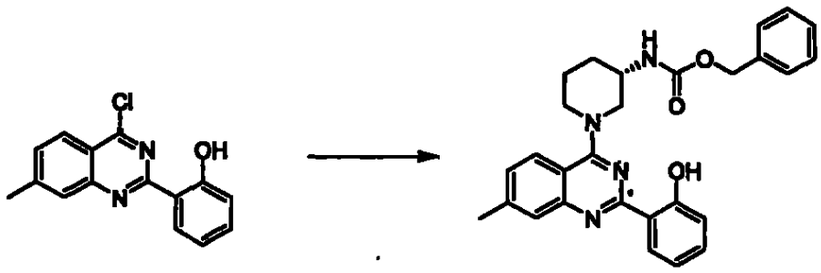
[001044] (*R*)-Tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001045]



[001046] Benzyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

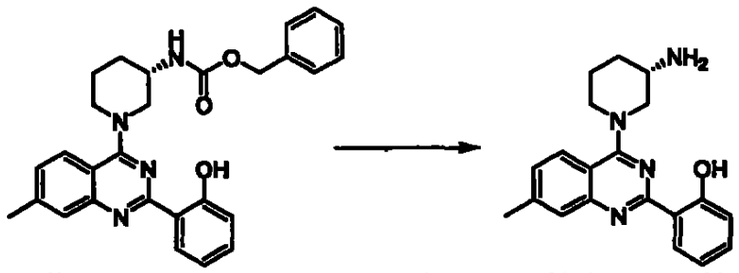
[001047]



[001048] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (1.15 g, 4.26 mmol) in CH_2Cl_2 (25 mL) at 0 °C under inert atmosphere was slowly added a solution of benzyl (*S*)-piperidin-3-ylcarbamate (1.0 g, 4.26 mmol) and triethylamine (1.18 mL, 8.52 mmol) in CH_2Cl_2 (10 mL). The reaction was allowed to warm to room temperature and was then quenched with water. The mixture was extracted with CH_2Cl_2 and the organic layers were combined, dried over $MgSO_4$, and concentrated to obtain benzyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate (2.03 g). This material was used without further purification. LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.86 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001049] 2-(4-((*S*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001050]



[001051] Pd/C (175 mg, 10% weight Pd on carbon) was added to a round bottom flask and the flask was flushed with N_2. To this flask was then added MeOH (10 mL). After purging the flask again with N_2, (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate (1.75 g, 3.74 mmol) dissolved in EtOAc (60 mL) and MeOH (50 mL) was added. After flushing the flask 3 times with N_2, and evacuating it under vacuum, H_2 was passed through

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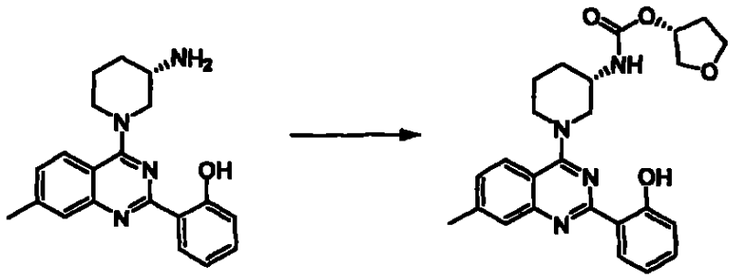
the vigorously stirring mixture for 4 h until hydrogenation was complete. The mixture was filtered through a pad of Celite. The filtrate was concentrated to afford 2-(4-((*S*)-3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.62 g, 50%). *LC/MS*: *m/z* 335.5$(M+H)^+$ at 1.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001052] **(*R*)-Tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate**

[001053]

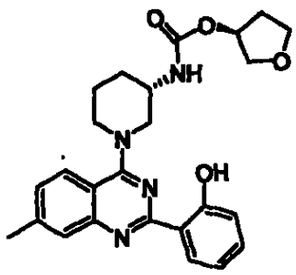


[001054] 2-(4-((*S*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol), (*R*)-tetrahydrofuran-3-yl chloroformate (22.6 mg, 0.15 mmol) and triethylamine (30 mg, 0.3 mmol) were stirred in DMF (1 mL) at 0 °C. After allowing the reaction to warm to room temperature, it was purified via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (*R*)-tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate as the TFA salt. *LC/MS*: *m/z* 449.3.5$(M+H)^+$ at 1.52 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001055] Example 204

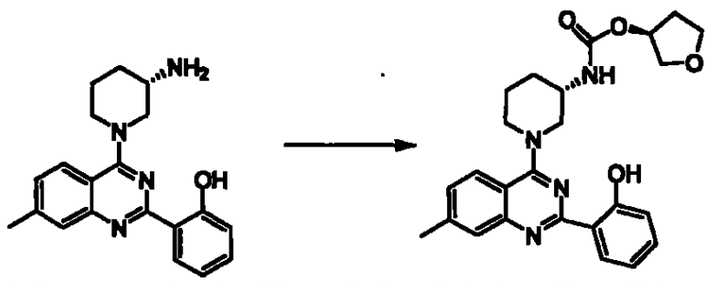
[001056] **(*S*)-Tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate**

[001057]



[001058] (*S*)-Tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001059]

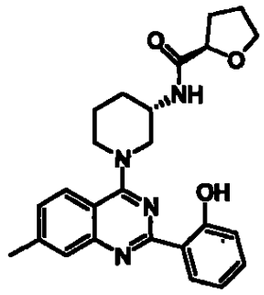


[001060] 2-(4-((*S*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol), (*S*)-tetrahydrofuran-3-yl chloroformate (22.6 mg, 0.15 mmol), and triethylamine (30 mg, 0.3 mmol) were stirred in DMF (1 mL) at 0 °C. After allowing the reaction to warm to room temperature it was purified via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (*S*)-tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001061] Example 205

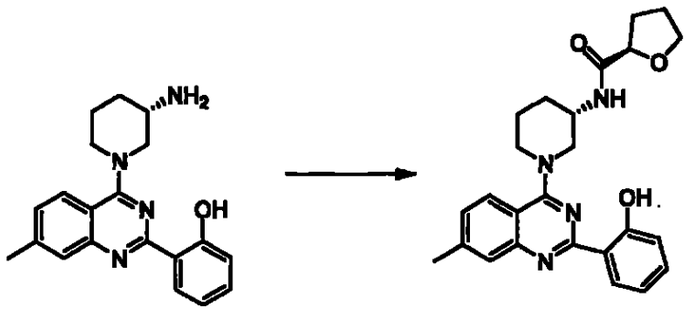
[001062] (2*R*)-Tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide

[001063]



[001064] (2*R*)-Tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide

[001065]

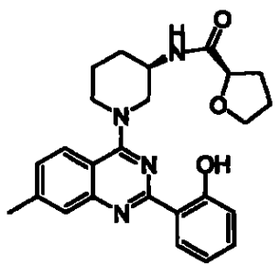


[001066] 2-(4-((*S*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol), (*R*)-tetrahydrofuran-2-carboxylic acid (22.6 mg, 0.195 mmol), triethylamine (30 mg, 0.3 mmol), and HATU (74.14 mg, 0.195 mmol) were stirred at room temperature in DMF for 1 h. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 433.3$(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

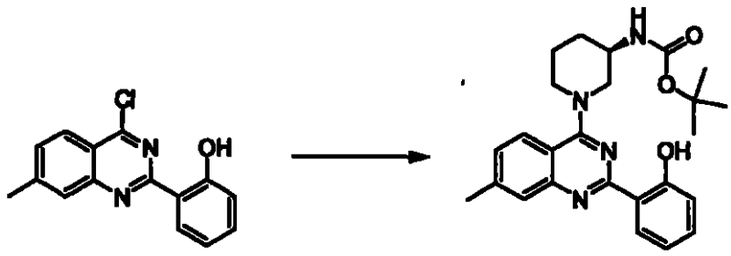
[001067] Example 206

[001068] **(2*R*)-Tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide**

[001069]



[001070] ***tert*-Butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate**

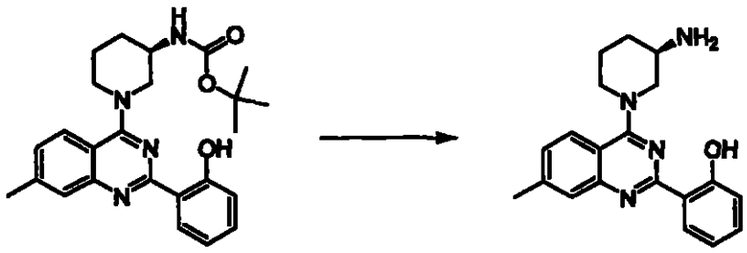


[001071]

[001072] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.5 g, 1.84 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise a solution of *tert*-butyl (*R*)-piperidin-3-ylcarbamate (0.37 g, 1.84 mmol) in CH_2Cl_2 (5 mL), then triethylamine (0.51 mL, 3.68 mmol). The mixture was allowed to warm to room temperature and was stirred for 3 h. After quenching with water, it was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated. Purification via silica gel chromatography using 5:1 CH_2Cl_2: hexanes gave *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate (0.54 g, 68%). LC/MS: *m/z* 435.5$(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001073] **2-(4-((*R*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol.**

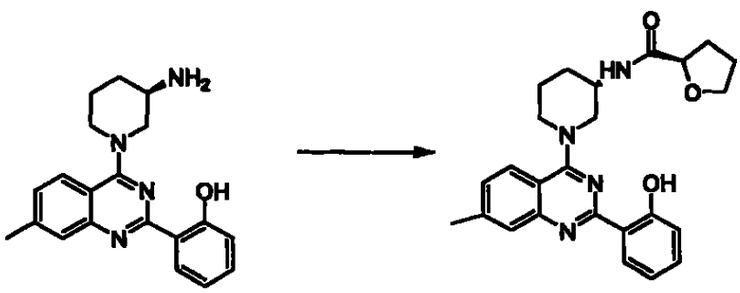
[001074]



[001075] *tert*-Butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate (0.54 g, 1.24 mmol) was dissolved in CH_2Cl_2 (15 mL) followed by the addition of TFA (8 mL). The reaction was stirred for 1.5 h, and the solvents were evaporated to an oily liquid which was diluted with CH_2Cl_2 and neutralized with a 1 M aqueous NaOH solution. The organic layer was separated, and the aqueous layer was washed two times with CH_2Cl_2. After drying the combined organic phases over $MgSO_4$, they were filtered, and concentrated to afford 2-(4-((*R*)-3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol as a solid (0.354 g, 85%). LC/MS: *m/z* 335.7$(M+H)^+$ at 1.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001076] (2*R*)-Tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide

[001077]

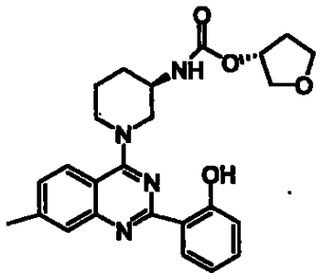


[001078] 2-(4-((*R*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol), (*R*)-tetrahydrofuran-2-carboxylic acid (22.6 mg, 0.15 mmol), triethylamine (30 mg, 0.3 mmol), and HATU (74.14 mg, 0.195 mmol) were stirred at room temperature in DMF for 1 h. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 433.3$(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001079] Example 207

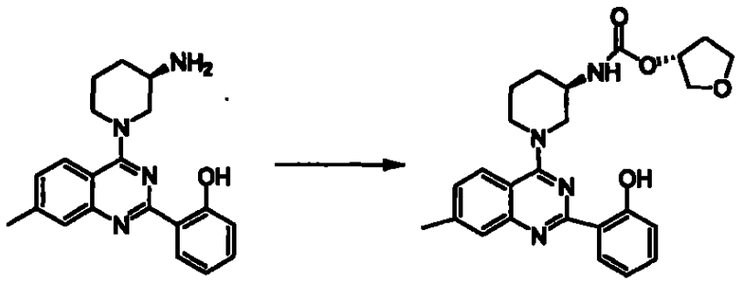
[001080] (*R*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001081]



[001082] (*R*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001083]

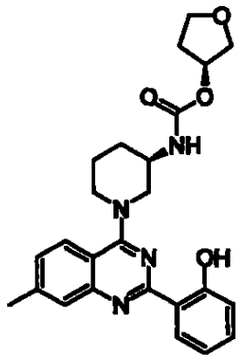


[001084] A solution of 2-(4-((*R*)-3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMF (0.5 mL) was cooled to 0 °C. Then, a solution of triethylamine (30 mg, 0.3 mmol) and (*R*)-tetrahydrofuran-3-yl chloroformate (22.6 mg, 0.15 mmol) in DMF (0.5 mL) was added dropwise. The mixture was allowed to warm to room temperature over a period of 30 min before it was purified using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*R*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 449.5$(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001085] Example 208

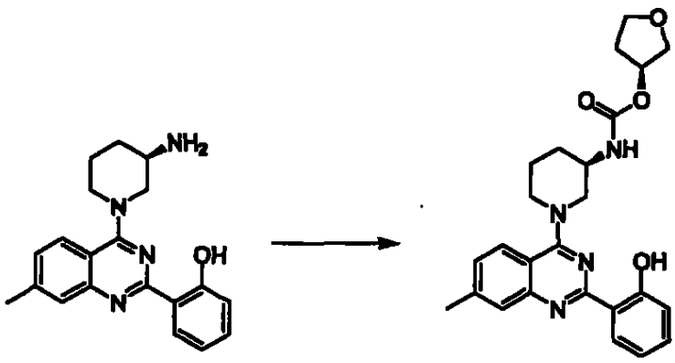
[001086] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001087]



[001088] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001089]

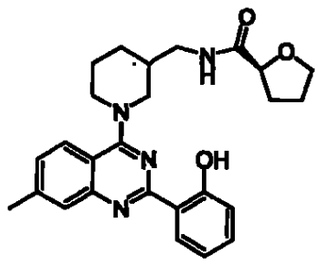


[001090] To a solution of 2-(4-((*R*)-3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMF (0.5 mL) was cooled to 0 °C. A solution of (*S*)-tetrahydrofuran-3-yl chloroformate (22.6 mg, 0.15 mmol) in DMF (0.5 mL) was then added, followed by triethylamine (30 mg, 0.3 mmol). The mixture was allowed to warm to room temperature over a period of 30 min before it was purified using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 449.5$(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

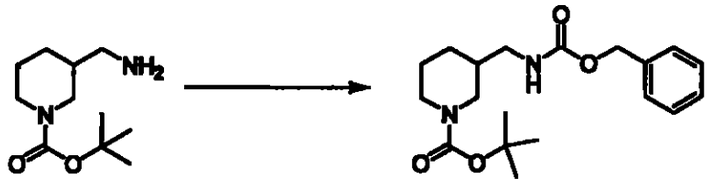
[001091] Example 209

[001092] (2*S*)-Tetrahydro-*N*-((1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)furan-2-carboxamide

[001093]



[001094] 3-(Benzyloxycarbonylamino-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester

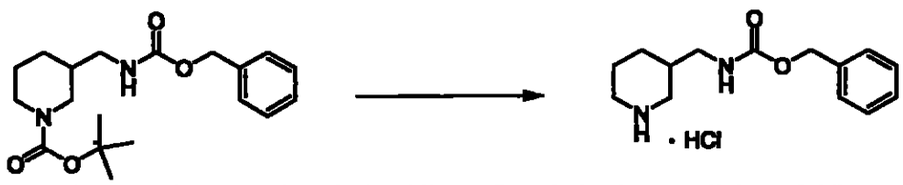


[001095]

[001096] 3-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (3.6 g, 16.8 mmol) was dissolved in 42 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled in an ice water bath. Triethylamine (4.7 mL, 33.6 mmol) was added followed by the dropwise addition of benzyl chloroformate (3.55 mL, 25.2 mmol). After 16 hours, the reaction mixture was partitioned between CH_2Cl_2/H_2O,and separated, and the aqueous layer was extracted twice with CH_2Cl_2. All of the organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to a light yellow oil. Purification by silica gel chromatography using 97% CH_2Cl_2/3% MeOH gave the product as a clear colorless oil (55%). LC/MS: *m/z* 349.3 $(M+H)^+$ at 3.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

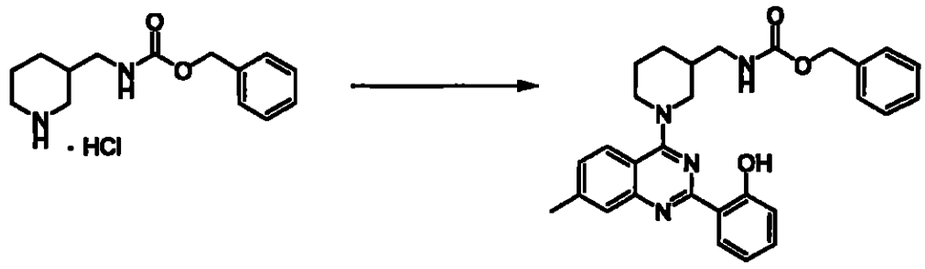
[001097] **Benzyl (piperidin-3-yl)methylcarbamate hydrochloride**

[001098]



[001099] Benzyl (1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate (3.22 g, 9.25 mmol) was treated with a 4.0 M HCl solution in dioxane (11.3 mL, 46.25 mmol). Formation of a white precipitate was observed. After 3 h, the reaction was complete. The solvent and excess HCl were removed under reduced pressure to obtain benzyl (piperidin-3-yl)methylcarbamate hydrochloride as a white solid. LC/MS: *m/z* 249.3 $(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001100] **Benzyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

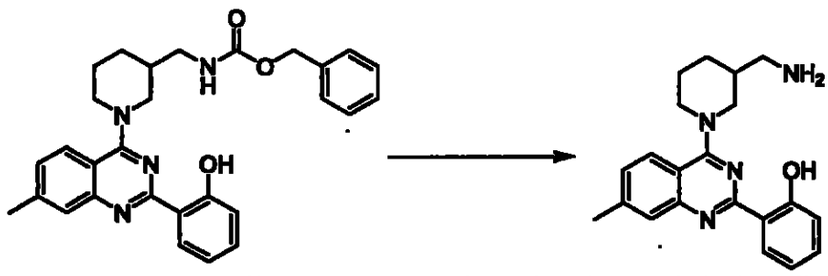


[001101]

[001102] 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (1.5 g, 5.54 mmol) was suspended in anhydrous CH_2Cl_2 (15 mL) and cooled to 0 °C under an N_2 atmosphere. A mixture of benzyl (piperidin-3-yl)methylcarbamate hydrochloride (1.73 g, 6.09 mmol) in CH_2Cl_2 (20 mL), and triethylamine (23 mL, 16.67 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature, and the reaction was complete after one hour. It was then partitioned between CH_2Cl_2/H_2O, and separated, and the organic phase was dried over Na_2SO_4, filtered, and concentrated to an orange solid. Purification by silica gel chromatography using 98% CH_2Cl_2/2% EtOAc gave benzyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as a bright yellow solid (1.75 g, 66%). LC/MS: *m/z* 483.5 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001103] **2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol**

[001104]

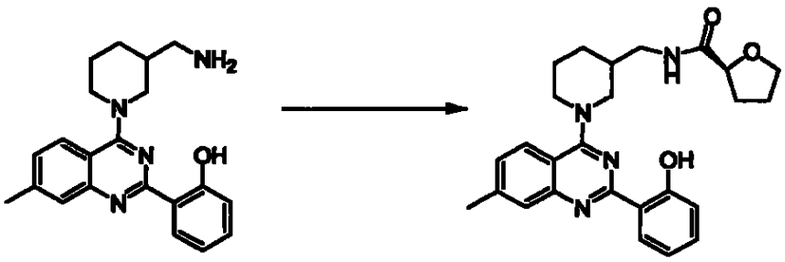


[001105] A mixture of benzyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (1.75 g, 3.63 mmol) and EtOH/EtOAc (50 mL/20 mL) was heated to obtain a homogeneous solution. After cooling to room temperature, Pd/C (175 mg, 10% wt Pd on carbon) was added and the flask was sealed with a septum. The same flask was 3 times charged with N_2 and evacuated under vacuum. The mixture was then stirred under an H_2

atmosphere at ambient pressure for 1 h. The product was collected by filtration through a plug of Celite, eluting with MeOH. The filtrate was concentrated to a yellow solid (1.26 g) to give 2-(4-(3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol. LC/MS: *m/z* 349.3 $(M+H)^+$ at 1.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001106] **(2*S*)-Tetrahydro-*N*-((1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)furan-2-carboxamide**

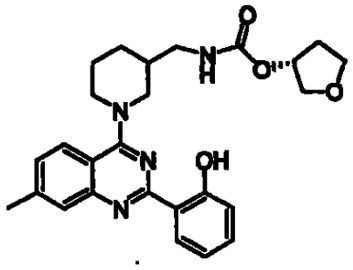
[001107]



[001108] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled in an ice water bath. To this was added (*S*)-tetrahydrofuran-2-carboxylic acid (24.0 mg, 19.8 μL, 0.2 mmol), and triethylamine (50 μL, 0.34 mmol). After 5 minutes, HATU (78.3 mg, 0.2 mmol) was added in one portion, and the reaction was allowed to warm to room temperature overnight. Purification by reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*S*)-tetrahydro-N-((1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 447.5 $(M+H)^+$ at 2.27 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001109] Example 210

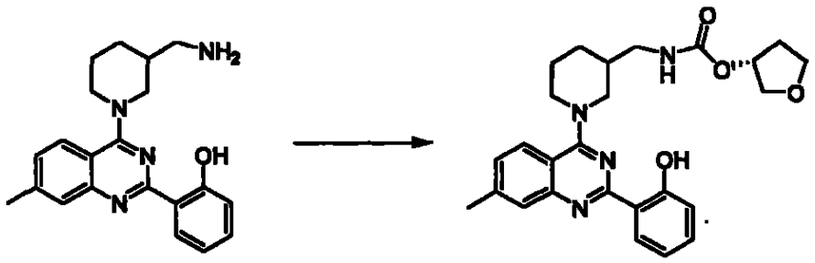
[001110] **(*R*)-Tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



[001111]

[001112] (*R*)-Tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001113]

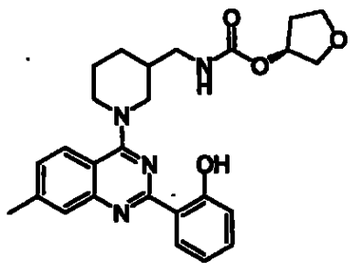


[001114] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in DMF (0.5 mL) and placed into an ice water bath. (*R*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) was dissolved in DMF (0.1 mL) and added dropwise, followed by the addition of triethylamine (50 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001115] Example 211

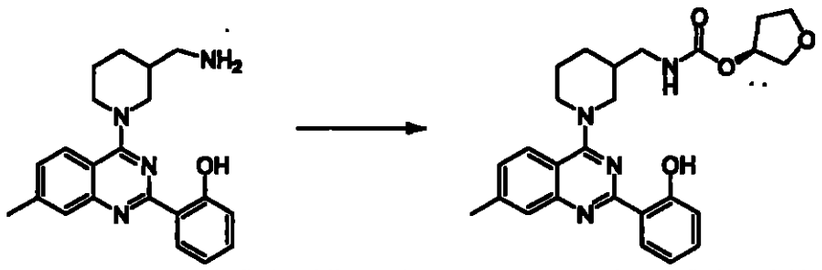
[001116] (*S*)-Tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001117]



[001118] (*S*)-Tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001119]

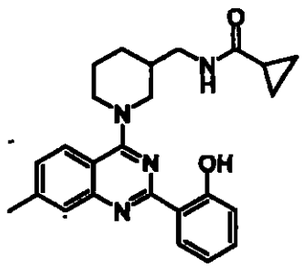


[001120] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) dissolved in DMF (0.5 mL) was cooled to 0 °C. (*S*)-Tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) was dissolved in DMF (0.1 mL) and added dropwise to the reaction mixture, followed by the addition of triethylamine (50 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The reaction was purified by reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*S*)-tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

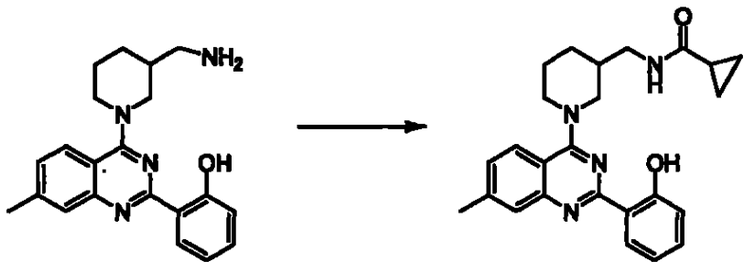
[001121] Example 212

[001122] *N*-((1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide

[001123]



[001124] *N*-((1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide



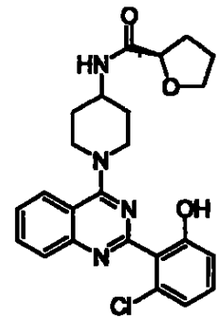
[001125]

[001126] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in DMF (0.5 mL) and cooled to 0 °C. Cyclopropanecarbonyl chloride (15.7 mg, 0.2 mmol) was dissolved in DMF (0.1 mL) and added dropwise, followed by the addition of triethylamine (50 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave *N*-((1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 417.0 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001127] Example 213

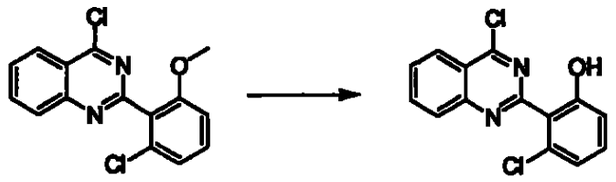
[001128] **(2*R*)-*N*-(1-(2-(2-Chloro-6-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide**

[001129]



[001130] **3-Chloro-2-(4-chloroquinazolin-2-yl)phenol**

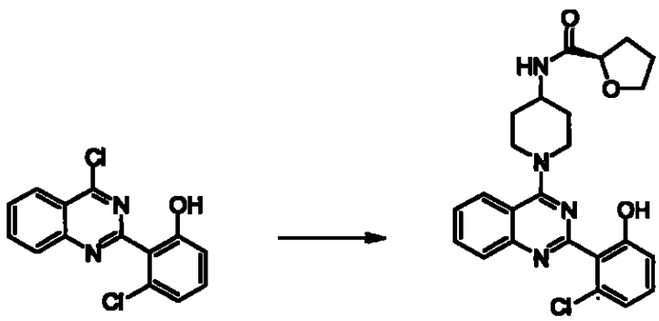
[001131]



[001132] To a solution of 4-chloro-2-(2-chloro-6-methoxyphenyl)quinazoline (0.3 g, 0.98 mmol) in CH_2Cl_2 at –78 °C was added 5 equivalents of 1 M BBr_3 solution (4.9 mL, 4.9 mmol) in CH_2Cl_2. The reaction was complete after 30 minutes After allowing it to warm to room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$ to pH 7, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 2:1 CH_2Cl_2:hexanes yielded 3-chloro-2-(4-chloroquinazolin-2-yl)phenol (0.17 g, 60%). LC/MS: *m/z* 291.1$(M+H)^+$ at 3.16
min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001133] **(2*R*)-*N*-(1-(2-(2-Chloro-6-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide**

[001134]

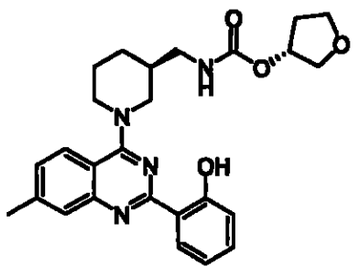


[001135] At 0 °C, to a solution of 3-chloro-2-(4-chloroquinazolin-2-yl)phenol (42 mg, 0.144 mmol) in CH_2Cl_2 was added triethylamine (80 µL, 0.58 mmol) followed by the addition of (*R*)-tetrahydro-*N*-(piperidin-4-yl)furan-2-carboxamide a oxalate. After allowing the reaction to warm to room temperature it was purified via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-*N*-(1-(2-(2-chloro-6-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide as the TFA salt. LC/MS: *m/z* 453.5$(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001136] Example 214

[001137] **(*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

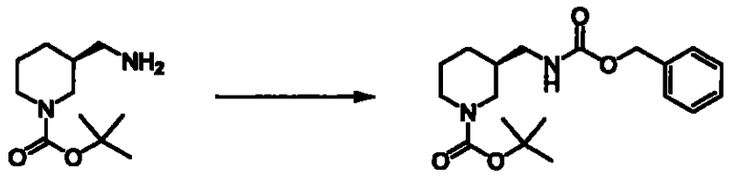
[001138]



[001139] Method 1

[001140] Benzyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate

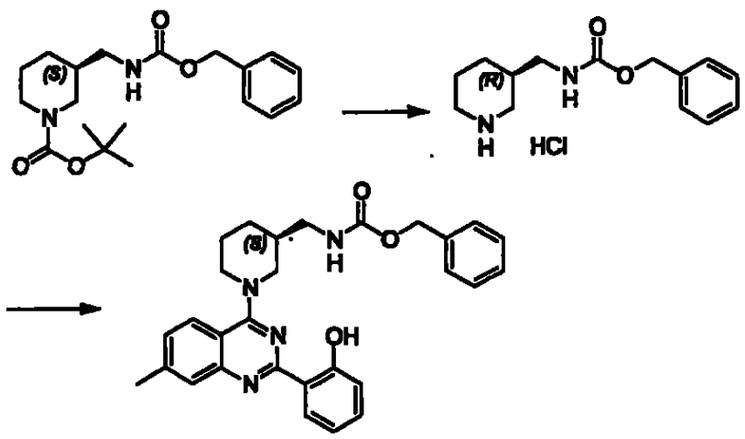
[001141]



[001142] (*S*)-*tert*-Butyl 3-(aminomethyl)piperidine-1-carboxylate (1.00 g, 4.67 mmol) was dissolved in 14 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled to 0 °C. Triethylamine (1.30 mL, 945 mg, 9.34 mmol) was added followed by the dropwise addition of benzyl chloroformate (0.99 mL, 1.20 g, 7.00 mmol). After 16 h, the reaction mixture was partitioned between H_2O and CH_2Cl_2,and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to a light yellow oil. Purification via silica gel chromatography using 97% CH_2Cl_2/3% MeOH gave benzyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate as a clear colorless oil (895 mg, 55%). LC/MS: *m/z* 349.5 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001143] Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

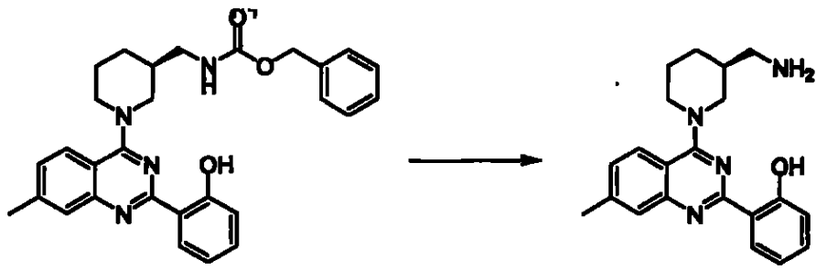
[001144]



[001145] Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (895 mg, 2.57 mmol) was treated with a 4.0 M HCl solution in dioxane (3.2 mL, 12.85 mmol). Formation of a white precipitate was observed. After 3 h, complete conversion of starting material was seen by TLC. The solvent and excess HCl were removed under reduced pressure to obtain benzyl ((*R*)-piperidin-3-yl)methylcarbamate hydrochloride as a white solid.

This solid was suspended in DMF/CH_2Cl_2 (3 mL/3 mL), followed by the addition of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (696 mg, 2.57 mmol), and triethylamine (1.8 mL, 1.3 g, 12.85 mmol). The mixture was stirred at room temperature under an N_2 atmosphere for 16 h. The reaction was then partitioned between H_2O/CH_2Cl_2, and separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography using 0–5% MeOH in CH_2Cl_2 gave benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as a thick yellow oil (610 mg, 49%). LC/MS: *m/z* 483.3 $(M+H)^+$ at 2.83 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001146] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol

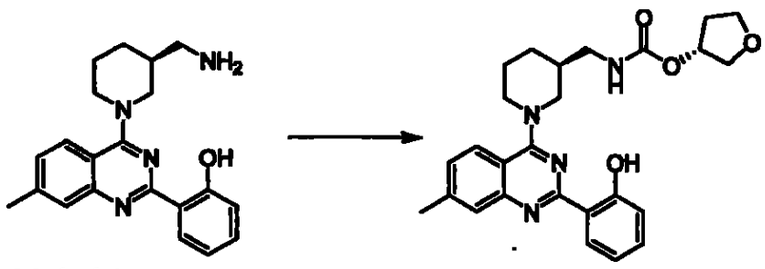


[001147]

[001148] To a mixture of benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (610 mg, 1.26 mmol) and EtOH (15 mL) in a round bottom flask was added Pd/C (61 mg, 10% wt Pd on carbon) and the flask was sealed with a septum. The atmosphere in the flask was evacuated, purged with N_2, and equipped with a balloon charged with H_2. The mixture was then stirred under an H_2 atmosphere at ambient pressure for 3 h. After filtration through a plug of Celite, using MeOH as the eluting solvent, the reaction mixture was concentrated to a yellow solid 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (441 mg). *LC/MS*: *m/z* 349.3 $(M+H)^+$ at 1.52 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.43–8.45 (m, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35–7.39 (m, 2H), 6.92–6.96 (m, 2H), 4.52 (d, *J* = 12.5 Hz, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 3.26–3.29 (m, 2H), 3.02–3.08 (m, 1H), 2.55–2.61 (m, 1H), 2.45–2.48 (m, 1H), 1.84–1.91 (m, 2H), 1.65–1.77 (m, 3H), 1.24–1.36 (m, 1H).

[001149] **(*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001150]



[001151] Method A

[001152] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, and (*R*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) dissolved in DMF (100 μL) was added

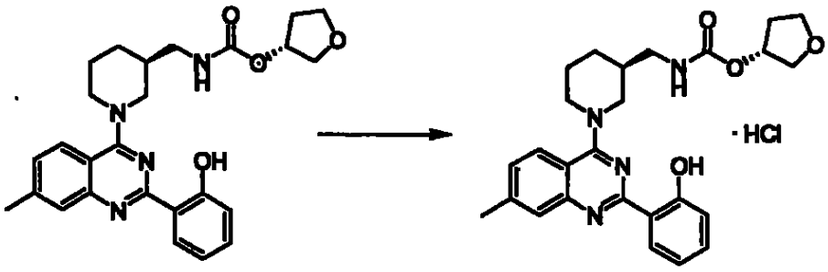
dropwise followed by triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature. The reaction was complete after two hours. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001153] Method B

[001154] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (127 mg, 0.364 mmol) was dissolved in 5 mL anhydrous DMF and cooled to 0 °C, and a solution of (*R*)-tetrahydrofuran-3-yl chloroformate (65.4 mg, 0.436 mmol) in 200 μL DMF was added dropwise followed by the addition of triethylamine (74 mg, 0.10 mL, 0.73 mmol). The reaction was allowed to warm to room temperature. The reaction was complete after two hours. The mixture was partitioned between H_2O and CH_2Cl_2, and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to a yellow solid. Purification via silica gel chromatography using 98% CH_2Cl_2/2% MeOH gave (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as an off white solid (116 mg, 69%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.41–8.43 (m, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 1H), 7.33–7.44 (m, 3H), 6.90–6.95 (m, 2H), 5.11 (dd, *J* = 6.2, 4.6 Hz, 1H), 4.38 (t, *J* = 14.5 Hz, 2H), 3.68–3.79 (m, 3H), 3.60–3.63 (m, 1H), 3.28–3.31 (m, 1H), 2.98–3.07 (m, 3H), 2.50 (s, 3H), 2.06–2.15 (m, 1H), 1.85–1.91 (m, 4H), 1.70 (d, *J* = 12.9 Hz, 1H), 1.24–1.37 (m, 1H).

[001155] **(*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride**

[001156]

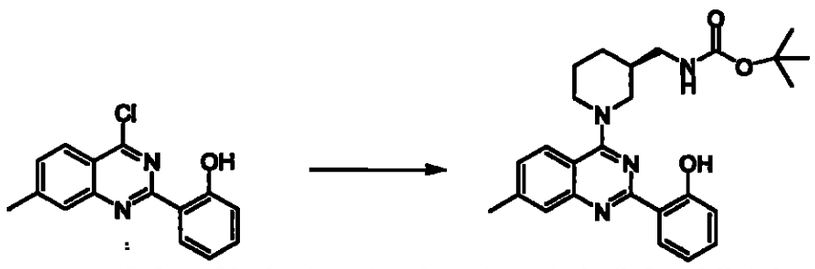


[001157] (*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (116 mg, 0.251 mmol) was suspended in 8 mL anhydrous CH_2Cl_2 and gently heated until an homogenous solution was formed. After the reaction was cooled to room temperature, a 2.0 M solution of HCl in Et_2O (0.126 mL, 0.251 mmol) was added in one portion. The reaction mixture was diluted with 25 mL Et_2O, and the product precipitated from solution. The reaction was stirred for an additional 30 minutes before the solid was filtered and dried to obtain (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride as a light yellow solid (99 mg, 70%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.22 (d, *J* = 7.7 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.75 (s, 1H), 7.42–7.49 (m, 3H), 6.97–7.08 (m, 2H), 5.08 (dd, *J* = 6.1, 4.6 Hz, 1H), 4.52–4.54 (m, 2H), 3.66–3.78 (m, 3H), 3.58–3.60 (m, 1H), 3.48 (t, *J* = 10.7 Hz, 1H), 3.23 (t, *J* = 11.5 Hz, 1H), 3.00 (t, *J* = 6.3 Hz, 2H), 2.53 (s, 3H), 2.05–2.14 (m, 1H), 1.80–1.91 (m, 4H), 1.72 (d, *J* = 9.0 Hz, 1H), 1.34–1.43 (m, 1H).

[001158] Method 2

[001159] *tert*-Butyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001160]

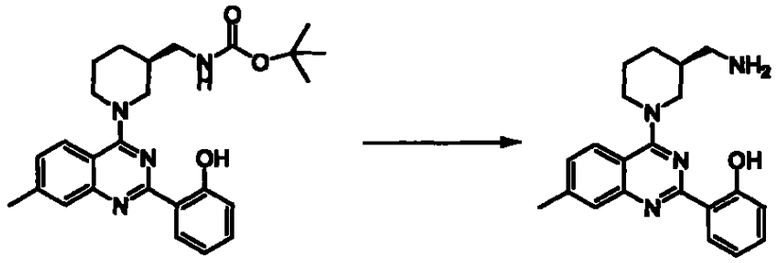


[001161] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.478 g, 1.76 mmol) in CH_2Cl_2 was added triethylamine (0.98 mL, 0.712 g, 7.04 mmol), and the mixture was cooled to 0 °C. To the reaction mixture was added *tert*-butyl ((*R*)-piperidin-3-yl)methylcarbamate oxalate (prepared analogously to 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol, oxalate salt, see Example 130; 700 mg, 2.3 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over

$MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–2% EtOAc in CH_2Cl_2 gave *tert*-butyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (700 mg, 88%). LC/MS: *m/z* 449.5 $(M+H)^+$ at 2.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

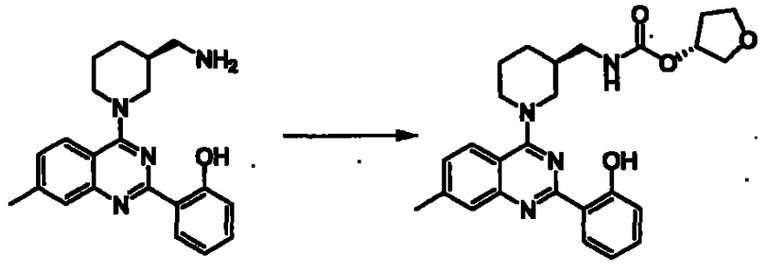
[001162] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001163]



[001164] To ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (700 mg, 1.56 mmol) was added 20 mL CH_2Cl_2 followed by addition of 7 mL of TFA. After the reaction was stirred for 1 hour it was neutralized with a1.0 M aqueous NaOH solution. The mixture was partitioned between H_2O and CH_2Cl_2, and separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (400 mg, 74%). LC/MS: *m/z* 349.3 $(M+H)^+$ at 1.52 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.43–8.45 (m, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35–7.39 (m, 2H), 6.92–6.96 (m, 2H), 4.52 (d, J = 12.5 Hz, 1H), 4.41 (d, J = 13.2 Hz, 1H), 3.26–3.29 (m, 2H), 3.02–3.08 (m, 1H), 2.55–2.61 (m, 1H), 2.45–2.48 (m, 1H), 1.84–1.91 (m, 2H), 1.65–1.77 (m, 3H), 1.24–1.36 (m, 1H).

[001165] (*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate



[001166]

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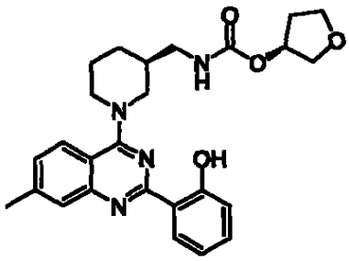
[001167] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (210 mg, 0.6 mmol) in DMF at 0 °C were added (*R*)-tetrahydrofuran-3-yl chloroformate (0.09 g, 0.6 mmol) and triethylamine (167 μL, 1.2 mmol) simultaneously. Ten to fifteen minutes after addition, the reaction was complete, and quenched with water, extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (150 mg, 54%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.41–8.43 (m, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 1H), 7.33–7.44 (m, 3H), 6.90–6.95 (m, 2H), 5.11 (dd, *J* = 6.2, 4.6 Hz, 1H), 4.38 (t, *J* = 14.5 Hz, 2H), 3.68–3.79 (m, 3H), 3.60–3.63 (m, 1H), 3.28–3.31 (m, 1H), 2.98–3.07 (m, 3H), 2.50 (s, 3H), 2.06–2.15 (m, 1H), 1.85–1.91 (m, 4H), 1.70 (d, *J* = 12.9 Hz, 1H), 1.24–1.37 (m, 1H).

[001168] Example 215

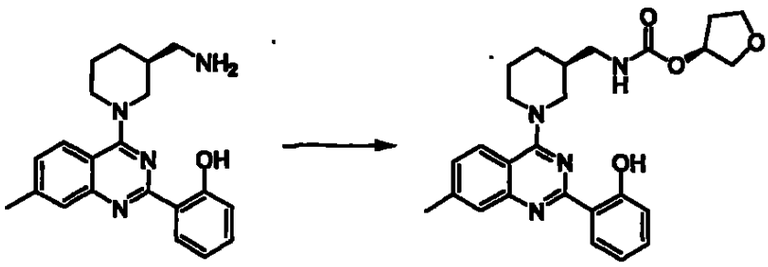
[001169] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001170]



[001171] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001172]



[001173] Method A

[001174] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, and (*S*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) in DMF (100 μL) was added dropwise followed by triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature. The reaction was complete after two hours. Purification using preparative HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001175] Method B

[001176] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (126.8 mg, 0.364 mmol) was dissolved in 5 mL anhydrous DMF and cooled to 0 °C, and a solution of (*S*)-tetrahydrofuran-3-yl chloroformate (65.4 mg, 0.436 mmol) in 200 μl of DMF was added dropwise followed by the addition of triethylamine (74 mg, 0.102 mL, 0.728 mmol). The reaction was allowed to warm to room temperature and was complete after two hours. The mixture was partitioned between H_2O and CH_2Cl_2, separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to a yellow solid. Purification via silica gel chromatography using 98% CH_2Cl_2/2% MeOH gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as an off white solid (116 mg, 69%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).^1H NMR (400 MHz, DMSO–d6) δ 8.42 (dd, J = 8.1, 1.7 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.66 (s, 1H), 7.34–7.43 (m, 3H), 6.91–6.95 (m, 2H), 5.10–5.11 (m, 1H), 4.38 (t, J = 12.4 Hz, 2H), 3.65–3.77 (m, 4H), 2.98–3.08 (m, 3H), 2.04–2.13 (m, 1H), 1.80–1.87 (m, 4H), 1.68–1.74 (m, 1H), 1.30–1.38 (m, 1H).

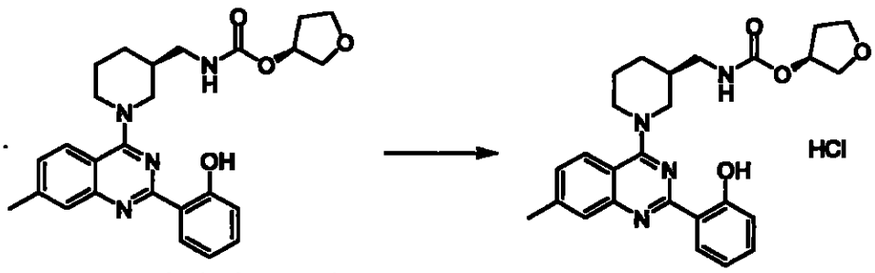
[001177] Method C

[001178] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (175 mg, 0.5 mmol) in DMF at 0 °C were added (*S*)-tetrahydrofuran-3-yl chloroformate (75 mg, 0.5 mmol) and triethylamine (137 μL, 1.0 mmol) simultaneously. Ten to fifteen minutes after addition, the reaction was complete, and it was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated. Purification by chromatography using 98% CH_2Cl_2/2% MeOH gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (150 mg, 54%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.42 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.66 (s, 1H), 7.34–7.43 (m, 3H), 6.91–6.95 (m, 2H), 5.10–5.11 (m, 1H), 4.38 (t, *J* = 12.4 Hz, 2H), 3.65–3.77 (m, 4H), 2.98–3.08 (m, 3H), 2.04–2.13 (m, 1H), 1.80–1.87 (m, 4H), 1.68–1.74 (m, 1H), 1.30–1.38 (m, 1H).

[001179] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001180]

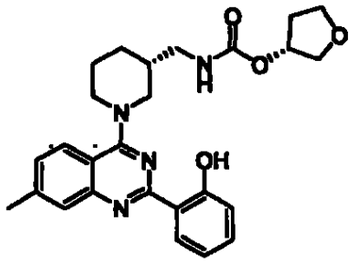


[001181] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (115 mg, 0.251 mmol) was suspended in 8 mL of anhydrous CH_2Cl_2 and gently heated until an homogenous solution was formed. After cooling to room temperature, a 2.0 M solution of HCl in Et_2O (0.126 mL, 0.251 mmol) was added in one portion. The reaction mixture was diluted with 25 mL Et_2O, and the product precipitated from the solution. The reaction was stirred for an additional 30 minutes before the solid was filtered and dried to obtain (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride (108 mg, 86%) as a light yellow solid. LC/MS: *m/z* 463.5$(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).^1H NMR (400 MHz, DMSO–d6) δ 8.18 (d, *J* = 6.6 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.73 (s, 1H), 7.44–7.51 (m, 2H), 7.00–7.07 (m, 2H), 5.06–5.09 (m, 1H), 4.52–4.62 (m, 2H), 3.62–3.74 (m, 4H), 3.23–3.29 (m, 1H), 3.00 (d, *J* = 6.8 Hz, 2H), 2.52 (s, 3H), 2.02–2.11 (m, 1H), 1.61–2.01 (m, 4H), 1.24–1.43 (m, 2H), 0.84–0.89 (m, 1H).

[001182] Example 216

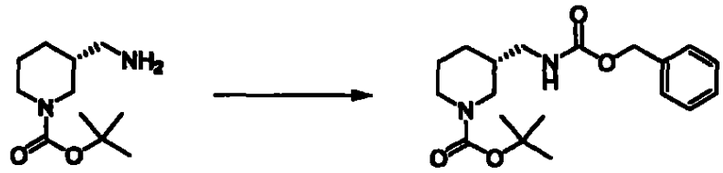
[001183] (*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001184]



[001185] Benzyl ((*R*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate

[001186]



[001187] (*R*)-*tert*-Butyl 3-(aminomethyl)piperidine-1-carboxylate (1.00 g, 4.67 mmol) was dissolved in 14 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled to 0 °C. Triethylamine (1.30 mL, 945 mg, 9.34 mmol) was added followed by the dropwise addition of benzyl chloroformate (0.99 mL, 1.20 g, 7.00 mmol). After 16 h, the reaction was complete. The mixture was partitioned between H_2O and CH_2Cl_2, and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to a light yellow oil. Purification via silica gel chromatography using 97% CH_2Cl_2/3% MeOH gave, benzyl ((*R*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate as a clear colorless oil (1.2 g, 74%). *LC/MS*: *m/z* 349.5 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001188] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

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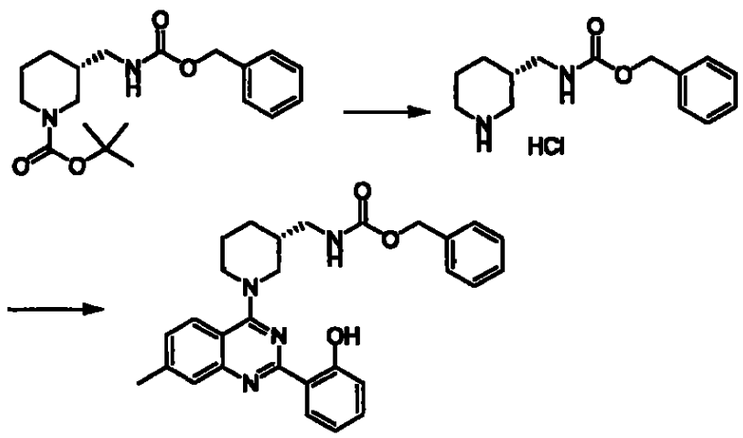
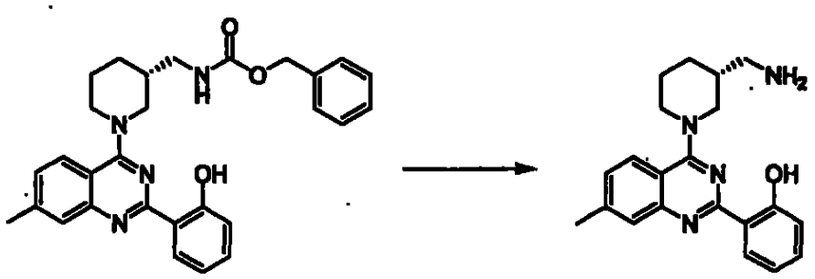
[001189]



[001190] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (1.2 g, 3.54 mmol) was treated with 4.0 M HCl solution in dioxane (4.3 mL, 17.2 mmol). Formation of a white precipitate was observed. The reaction was complete after three hours. The solvent and excess HCl were removed under reduced pressure to obtain benzyl ((*S*)-piperidin-3-yl)methylcarbamate hydrochloride as a white solid. This solid was suspended in DMF/CH_2Cl_2 (3 mL/3 mL), followed by the addition of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (958 mg, 3.54 mmol) and then triethylamine (1.8 mL, 1.3 g, 12.85 mmol). The mixture was stirred at room temperature under an N_2 atmosphere for 16 h. The reaction was then partitioned between H_2O and CH_2Cl_2, separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography using 0–5% MeOH in CH_2Cl_2 gave benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as a thick yellow oil (855 mg, 51%). LC/MS: *m/z* 483.5 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001191] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol

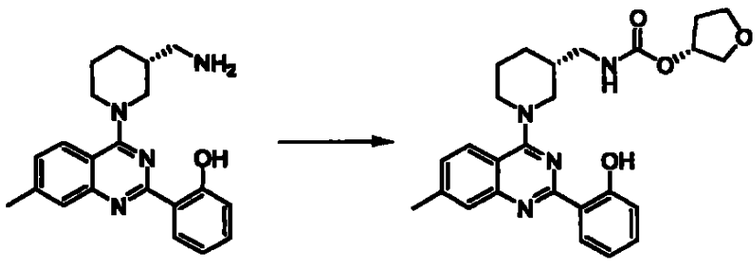
[001192]



[001193] To a mixture of benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (855 mg, 1.77 mmol) and EtOH (15 mL) in a round bottom flask was added Pd/C (86 mg, 10% wt Pd on carbon) and the flask was sealed with a septum. The atmosphere in the flask was evacuated, purged with N_2, and equipped with a balloon charged with H_2. The mixture was stirred under an H_2 atmosphere at ambient pressure for 3 h. After filtration through a plug of Celite using MeOH as the eluting solvent, the reaction mixture was concentrated to 2-(4-((*R*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (625 mg) as a yellow solid. LC/MS: *m/z* 349.3 $(M+H)^+$ at 1.82 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001194] (*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001195]



[001196] Method A

[001197] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which (*R*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by the addition of triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature, and was complete after two hours. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001198] Method B

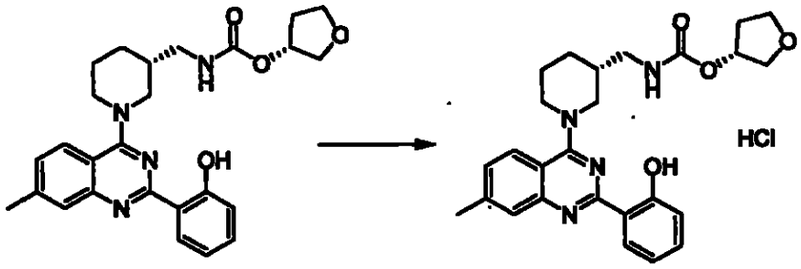
[001199] To a stirred solution of 2-(4-((*R*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (150 mg, 0.43 mmol) under an N_2 atmosphere at 0 °C was added

triethylamine (85 mg, 0.84 mmol) followed by the dropwise addition of (*R*)-tetrahydrofuran-3-yl chloroformate (65 mg, 0.43 mmol). The reaction was allowed to warm to room temperature and was stirred for 2 h. The mixture was partitioned between H_2O and CH_2Cl_2 and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 4:1 CH_2Cl_2:EtOAc afforded (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate. LC/MS: *m/z* 463.5$(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001200] **(*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride**

[001201]

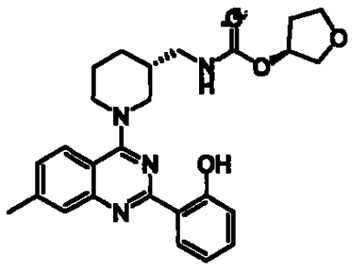
[001202] To a solution of (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-



methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (0.085 g, 0.18 mmol) in 9 mL CH_2Cl_2 was added dropwise a 2.0 M HCl solution in ether (0.09 mL, 0.18 mmol). Ether (20 mL) was then added, leading to the precipitation of (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride which was filtered and dried (85 mg, 95%). LC/MS: *m/z* 463.5$(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001203] Example 217

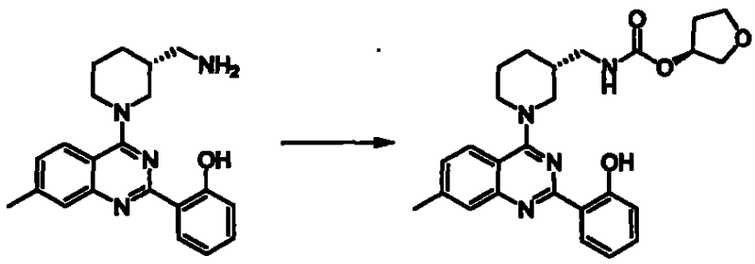
[001204] **(*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



[001205]

[001206] (*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001207]



[001208] Method A

[001209] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which (*S*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

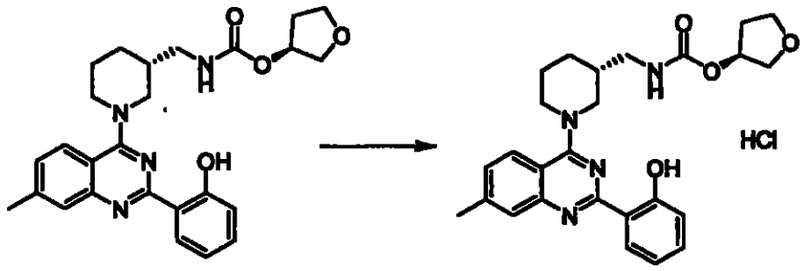
[001210] Method B

[001211] To a stirred solution of 2-(4-((*R*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (200 mg, 0.57 mmol) in DMF under an N_2 atmosphere at 0 °C was added triethylamine (115 mg, 1.14 mmol) followed by the dropwise addition of (*S*)-tetrahydrofuran-3-yl chloroformate (86 mg, 0.57 mmol). The reaction was allowed to warm to room temperature and was stirred for 2 h. The mixture was partitioned between H_2O and CH_2Cl_2 and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were

combined, dried [illegible] and concentrated. Purification via silica gel chromatography using 4:1 CH_2Cl_2:EtOAc afforded (*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate. LC/MS: *m/z* 463.5$(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001212] ((*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001213]

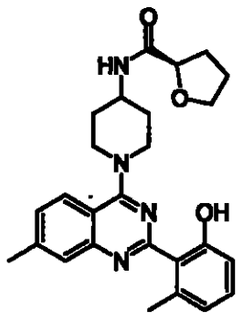


[001214] To a solution of (*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate in 12 mL CH_2Cl_2 was added dropwise 2.0 M HCl solution in ether (0.13 mL, 0.25 mmol). To the solution was then added 20 mL ether leading to the precipitation of ((*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride which was filtered and dried (116 mg, 92%). LC/MS: *m/z* 463.5$(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001215] Example 218

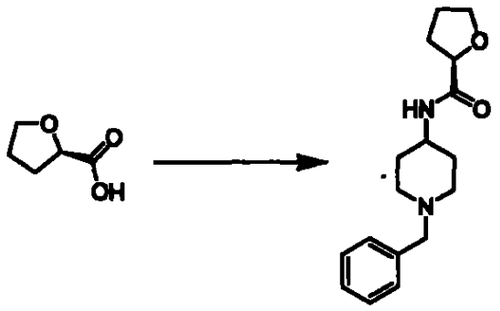
[001216] (2*R*)-Tetrahydro-*N*-(1-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)furan-2-carboxamide

[001217]



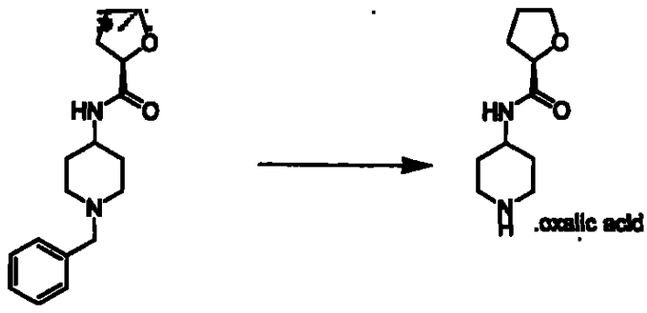
[001218] (*R*)-Tetrahydrofuran-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide

[001219]



[001220] A solution of (*R*)-tetrahydro-2-furoic acid (58.5 g, 504 mmol) and oxalyl chloride (86 mL, 1.0 mol) in 100 mL CH_2Cl_2 were refluxed for 2 hours in a flask equipped with a $CaCl_2$ guard tube. After the solution was cooled to room temperature the solvents and excess oxalyl chloride were removed by evaporation under reduced pressure. The resulting acid chloride was dissolved in 200 mL CH_2Cl_2 and added dropwise to a solution of 1-benzyl-4-amino piperidine dihydrochloride (142 g, 539 mmol) and triethylamine (240 mL, 1.7 mol) in 300 mL CH_2Cl_2 cooled in an ice bath. The resulting mixture was stirred for 2 hours at room temperature and subsequently washed twice with 300 mL portions of 5% aq. $NaHCO_3$ and 300 mL saturated aq. NaCl solution, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The solid residue was triturated with 500 mL heptanes, collected by filtration, and washed twice with 200 mL portions of heptanes. The solid was air-dried at 45 °C to yield (*R*)-tetrahydrofuran-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (128 g, 88%) as an off-white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 5H), 6.58 (bs, 1H), 4.29 (dd, *J*=5.9, 8.4 Hz, 1H), 3.92–3.77 (m, 2H), 3.48 (s, 2H), 2.82–2.74 (m, 2H), 2.32–2.21 (m, 1H), 2.19–1.95 (m, 3H), 1.94–1.78 (m, 4H), 1.58–1.40 (m, 2H) ppm.

[001221] (*R*)-Tetrahydro-furan-2-carboxylic acid piperidin-4-ylamide as an oxalate salt

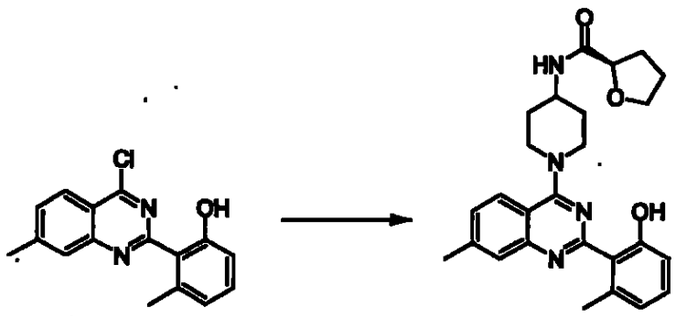


[001222]

[001223] (*R*)-Tetrahydro-furan-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (128 g, 444 mmol) was dissolved in 300 mL ethanol and 50 mL acetic acid. Palladium on activated carbon (5 g) was added. A hydrogen pressure of 5 bars was applied, and hydrogenation was continued until no more hydrogen was consumed (about 5 days). The suspension was filtered through Celite, and the filtrate was evaporated to dryness under reduced pressure. The residue and oxalic acid (50 g, 555 mmol) were suspended in 500 mL 2-propanol and heated to dissolve the solids. Upon cooling, the oxalate salt of *R*-tetrahydro-furan-2-carboxylic acid piperidin-4-ylamide crystallized and was collected by filtration to yield (*R*)-Tetrahydro-furan-2-carboxylic acid piperidin-4-ylamide as an oxalate salt (99.0 g, 77%) as an off-white solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.84 (d, J=7.8 Hz, 1H), 5.90 (bs, 2H), 4.18–4.14 (m, 1H), 3.89–3.67 (m, 3H), 3.25–3.20 (m, 2H), 2.94–2.71 (m, 2H), 2.13–2.00 (m, 1H), 1.56–1.58 (m, 6H) ppm.

[001224] (2*R*)-Tetrahydro-*N*-(1-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)furan-2-carboxamide

[001225]



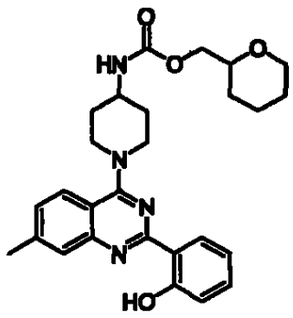
[001226] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-methylphenol (60 mg, 2.1 mmol) in DMF (1 mL) was added triethylamine (1.17 mL, 8.4 mmol) and (*R*)-tetrahydro-*N*-(piperidin-4-yl)furan-2-carboxamide as an oxalate salt (80 mg, 2.73 mmol).. This mixture was

stirred for 2 h at room temperature before it was purified via reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to afford (2*R*)-tetrahydro-*N*-(1-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 447.5$(M+H)^+$ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001227] Example 219

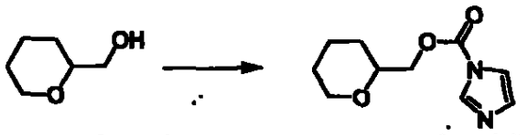
[001228] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid tetrahydro-pyran-2-ylmethyl ester

[001229]



[001230] (Tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate

[001231]



[001232] A mixture of (tetrahydro-2*H*-pyran-2-yl)methanol (369 mg, 3.18 mmol) and di(1*H*-imidazol-1-yl)methanone (1.0 g, 6.36 mmol) in 0.3 M CH_3Cl (10 mL) was stirred at 50 °C for 3 h. After allowing the reaction to cool to room temperature, the solvent was evaporated under reduced pressure giving (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (412 mg) which was used without further purification. *LC/MS*: *m/z* 211.1$(M+H)^+$ at 0.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001233] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid tetrahydro-pyran-2-ylmethyl ester.

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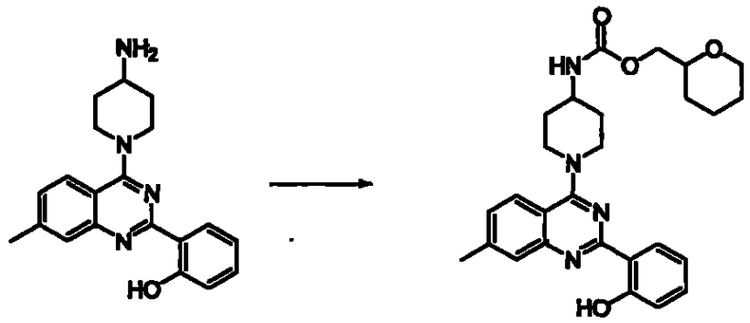
[001234]

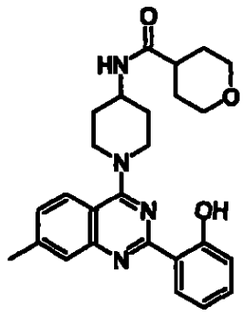


[001235] To 2-[4-(4-amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (100 mg, 0.3 mmol) in 1 mL CH_2Cl_2 was added sequentially triethylamine (62.5 μL, 0.45 mmol) and imidazole-1-carboxylic acid tetrahydro-pyran-2-ylmethyl ester(94 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 12 h and at 45 °C for 3 h. The reaction mixture was cooled and diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was purified by reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) as eluent to give the desired product {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid tetrahydro-pyran-2-ylmethyl ester as the TFA salt. LC/MS: *m/z* 477.4 (M+H)+ at 2.84 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001236] Example 220

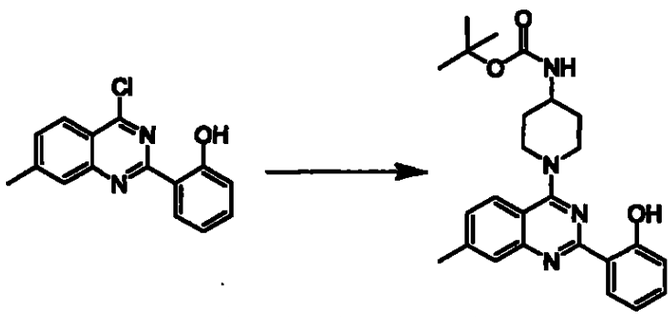
[001237] **Tetrahydro-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2*H*-pyran-4-carboxamide**

[001238]



[001239] [illegible]ylcarbamate

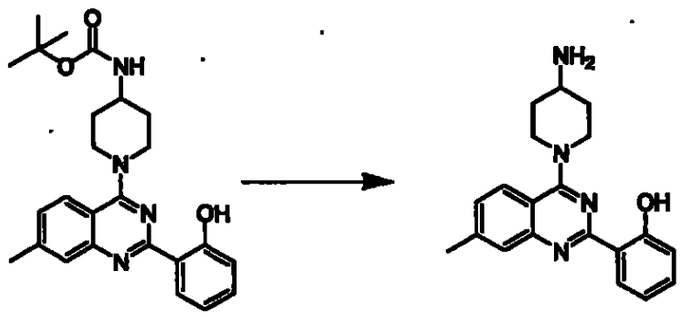
[001240]



[001241] To a cooled (0–5 °C) suspension of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (50.2 g, 186 mmol) in dichloromethane (200 mL) was slowly added a solution of *tert*-butyl piperidin-4-ylcarbamate (39.0 g, 195 mmol) and triethylamine (56 mL, 390 mmol) in dichloromethane (200 mL). The resulting mixture was stirred overnight at room temperature. Water (400 ml) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 200 mL), and the combined organic layers were dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (SiO_2, eluent: dichloromethane/heptanes 4:6–1:0). Two fractions were obtained: 38.7 g of *tert*-butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as a yellow solid, and a less pure fraction (26.1 g) that was purified by recrystallization from methanol to yield *tert*-butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate. Both fractions were combined (17.0 g, 69%).

[001242] 2-(4-(4-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001243]

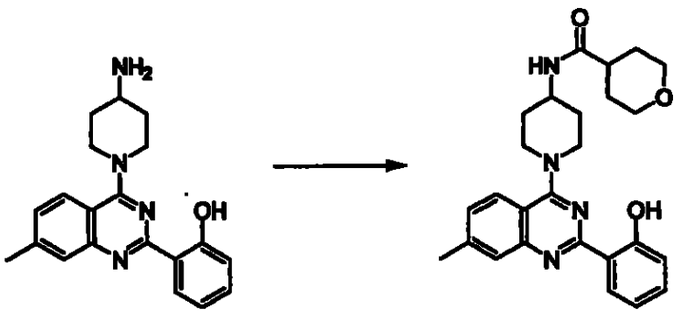


14B

[001244] [illegible] 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (55.7 g, 128 mmol) was dissolved in dichloromethane (200 mL) and trifluoroacetic acid (215 ml) was slowly added (careful: immediate gas evolution!). The resulting solution was stirred overnight at room temperature under a nitrogen atmosphere and evaporated to dryness. To the residue were added equal amounts of water and dichloromethane (300 mL). The obtained emulsion was basified to pH 9 with 33% aq. NaOH. The emulsion was cleared by the addition of methanol, and the layers were separated. The aqueous layer was extracted with dichloromethane (200 mL), and the combined organic extracts were dried over sodium sulfate, filtered, and evaporated to dryness to yield crude 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol. The crude material was purified by column chromatography (SiO_2, 2% methanol in dichloromethane) to yield 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (44 g, 97%) as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.52 (dd, *J*=2.1, 8.1 Hz, 1H), 7.77 (d, *J*=8.4 Hz, 1H), 7.62 (s, 1H), 7.37 (dt, *J*=1.5, 7.2 Hz, 1H), 7.22 (dd, *J*=1.5, 9.0 Hz, 1H), 7.04 (dd, *J*=1.2, 6.9 Hz, 1H), 6.92 (dt, *J*=1.2, 7.2 Hz, 1H), 4.49–4.39 (m, 2H), 3.34 (dt, *J*=2.4, 12.2 Hz, 2H), 3.12–3.02 (m, 1H), 2.54 (s, 3H), 2.09–2.00 (m, 2H), 1.68–1.55 (m, 2H), 1.40–1.25 (m, 2H) ppm.

[001245] **Tetrahydro-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2*H*-pyran-4-carboxamide**

[001246]



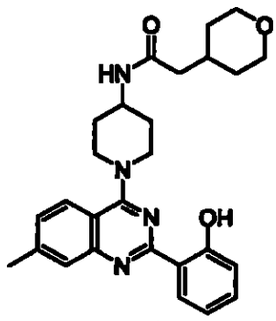
[001247] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added tetrahydro-2*H*-pyran-4-carboxylic acid (17.5 mg, 0.13 mmol) followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (44 mg, 0.117 mmol). The reaction was stirred for 16 h, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford tetrahydro-*N*-(1-(2-(2-

hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2*H*-pyran-4-carboxamide as the TFA salt. LC/MS: *m/z* 447.5(M+H)$^+$ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001248] Example 221

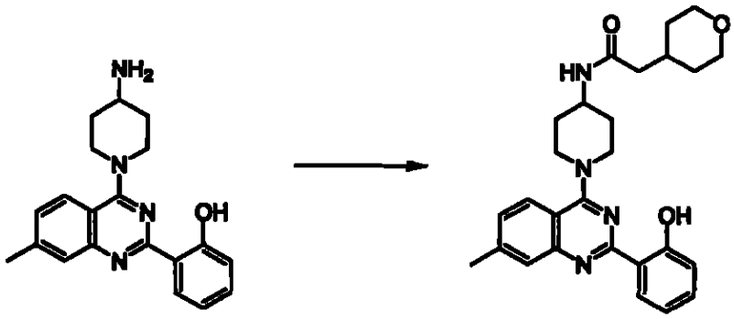
[001249] 2-(Tetrahydro-2*H*-pyran-4-yl)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide

[001250]



[001251] 2-(Tetrahydro-2*H*-pyran-4-yl)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide

[001252]

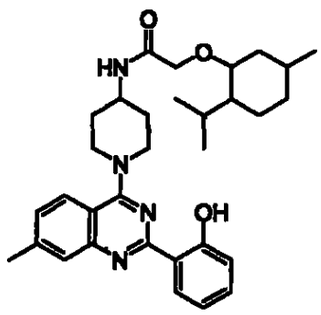


[001253] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (13 mg, 0.09 mmol) followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (44 mg, 0.117 mmol). The reaction was stirred for 16 h, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-(tetrahydro-2*H*-pyran-4-yl)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide as the TFA salt. LC/MS: *m/z* 461.5(M+H)$^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

144

[001254] [redacted]

[001255] 2-(2-Isopropyl-5-methylcyclohexyloxy)-*N*-(1-(2-(2-hydroxyphenyl)-7-



methylquinazolin-4-yl)piperidin-4-yl)acetamide (

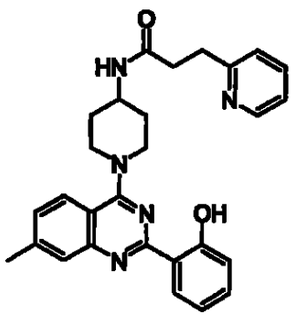
[001256] 2-(2-Isopropyl-5-methylcyclohexyloxy)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide

[001257] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) at 0 °C was added triethylamine (25 μL, 0.18 mmol) followed by the addition of 2-(2-isopropyl-5-methylcyclohexyloxy)acetyl chloride (21 mg, 0.09 mmol). The reaction was stirred for 16 h, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-(2-isopropyl-5-methylcyclohexyloxy)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide as the TFA salt. LC/MS: *m/z* 531.3$(M+H)^+$ at 3.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001258] Example 223

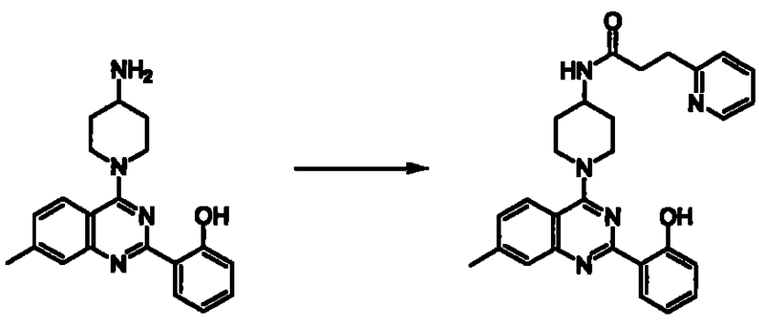
[001259] *N*-(1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-3-(pyridin-2-yl)propanamide

[001260]



[001261] *N*-(1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-3-(pyridin-2-yl)propanamide

[001262]

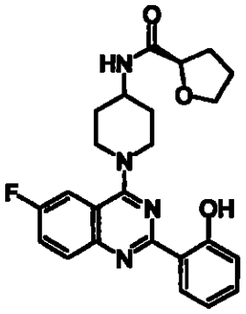


[001263] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added 3-(pyridin-2-yl)propanoic acid (20 mg, 0.13 mmol) followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (44 mg, 0.117 mmol). The reaction was stirred for 16 h, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford *N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-3-(pyridin-2-yl)propanamide as the TFA salt. LC/MS: *m/z* 468.3 $(M+H)^+$ at 1.86 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001264] Example 224

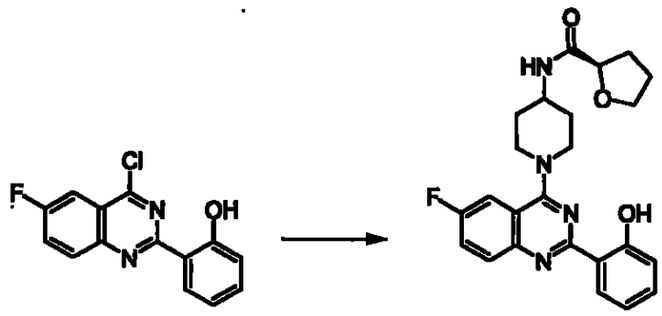
[001265] (2*R*)-*N*-(1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

[001266]



[001267] (2*R*)-*N*-(1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

[001268]

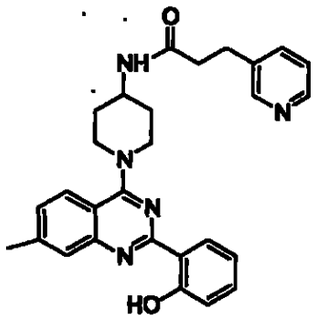


[001269] To a solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (25 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was added (*R*)-tetrahydro-*N*-(piperidin-4-yl)furan-2-carboxamide oxalate (33 mg, 0.117 mmol), followed by the addition of triethylamine (50 μL, 0.36 mmol). The reaction was stirred for 2 h before it was filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-*N*-(1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide as the TFA salt. LC/MS: *m/z* 437.1$(M+H)^+$ at 2.54 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001270] Example 225

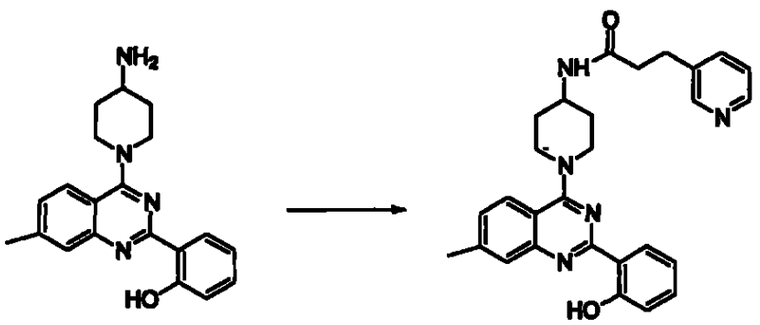
[001271] ***N*-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-3-pyridin-3-yl-propionamide**

[001272]



[001273] ***N*-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-3-pyridin-3-yl-propionamide**

[001274]

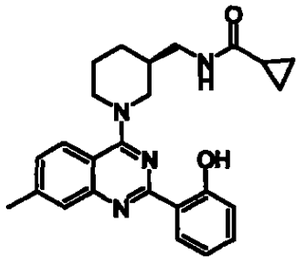


[001275] To 2-[4-(4-amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (238 mg, 0.71 mmol) in 2.4 mL of CH_2Cl_2 was added sequentially 3-pyridin-3-yl-propionic acid (118.3 mg, 0.78 mmol), triethylamine (129 μL, 0.92 mmol), and BOP (346 mg, 0.78 mmol) at room temperature. The reaction mixture was stirred for 40 min and diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was purified by reverse phase LC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) as eluent to give the desired product as the TFA salt. LC/MS: *m/z* 468.6 (M+H)+ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001276] Example 226

[001277] *N*-(((*S*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide

[001278]



[001279] *N*-(((*S*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide

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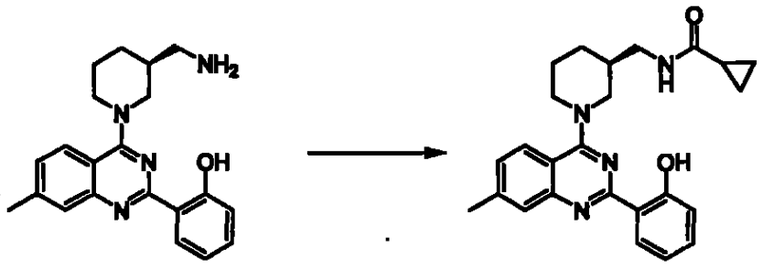


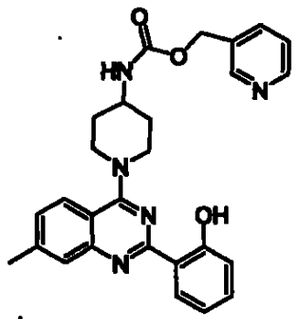
[001280]

[001281] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (35 mg, 0.10 mmol) was dissolved in DMF (1 mL). Cyclopropanecarboxylic acid (9.7 mg, 0.11 mmol) was added, followed by the addition of triethylamine (28 μL, 0.2 mmol), and the mixture was cooled in an ice water bath. HATU (42 mg, 0.11 mmol) was added in one portion, and the reaction was allowed to warm to room temperature while stirring for 16 h. The reaction mixture was filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give N-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 417.5 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001282] Example 227

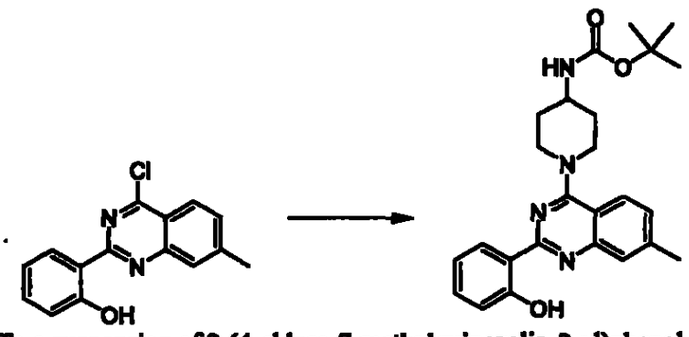
(Pyridin-3-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001283]



[001284] ***tert*-Butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate**

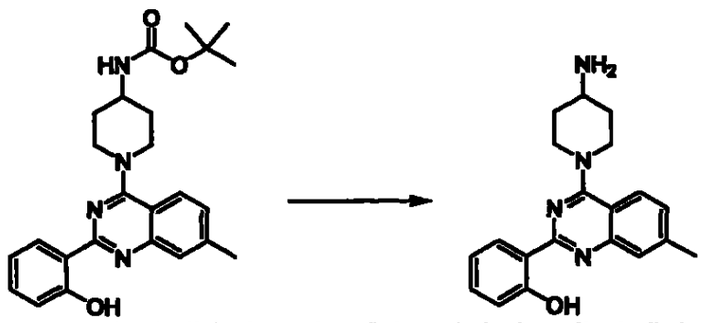
[001285]



[001286] To a suspension of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (2.0 g, 7.38 mmol) in CH_2Cl_2 (25 ml) at 0 °C under an N_2 atmosphere was added dropwise a solution of *tert*-butyl piperidin-4-ylcarbamate (1.92 g, 9.6 mmol) in CH_2Cl_2 (10 ml) and triethylamine (2.0 ml, 14.76 mmol). The reaction was stirred for 6 hours, then it was quenched with water (25 ml), and the layers were separated. The aqueous phase was extracted twice with CH_2Cl_2 (10 ml), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give *tert*-butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as a yellow solid (3.24 g, 100%). LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001287] **2-(4-(4-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol**

[001288]



[001289] *tert*-Butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (3.21 g, 7.39 mmol) was dissolved in CH_2Cl_2 (55 ml). TFA (50 ml) was added and the reaction was stirred for 1 hour. After evaporating the solvents *in vacuo*, the crude material was diluted with CH_2Cl_2 and neutralized with a 1 N NaOH solution. The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (30 ml). The combined organic

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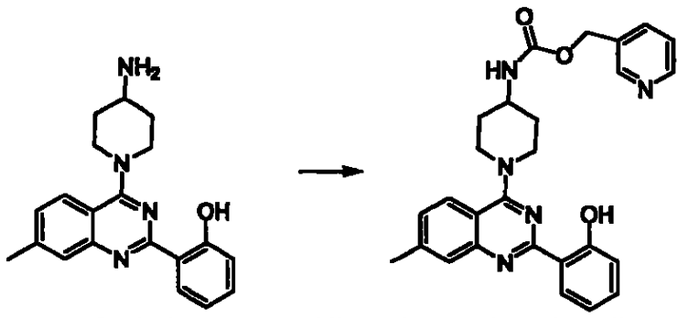
layer [illegible] and concentrated to give 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol as a yellow solid (2.06 g, 83%). LC/MS: *m/z* 335.3 $(M+H)^+$ at 1.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001290] **(Pyridin-3-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate**

[001291]

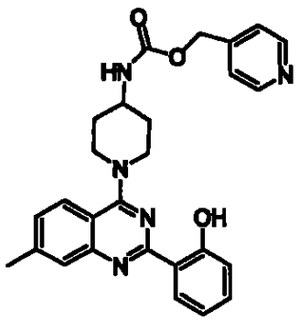


[001292] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMSO (1 mL) was added (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (53 mg, 0.263 mmol) and triethylamine (30.4 mg, 42 μL, 0.3 mmol). The reaction was stirred overnight at room temperature and then purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (pyridin-3-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as the TFA salt. LC/MS: *m/z* 470.5 $(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001293] Example 228

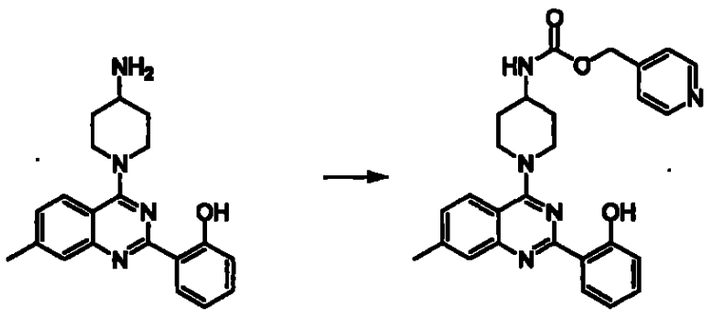
[001294] **(Pyridin-4-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate**

[001295]



[001296] (pyridin-4-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001297]

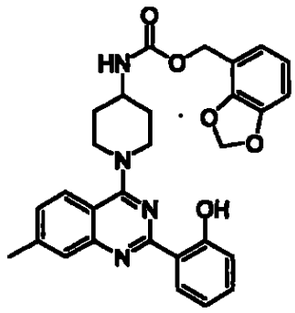


[001298] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMSO (1 mL) was added (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (53 mg, 0.263 mmol) and triethylamine (30.4 mg, 42 μL, 0.3 mmol). The reaction was stirred overnight at room temperature and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (pyridin-4-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as the TFA salt. LC/MS: *m/z* 470.5 $(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001299] Example 229

[001300] (Benzo[d][1,3]dioxol-7-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001301]



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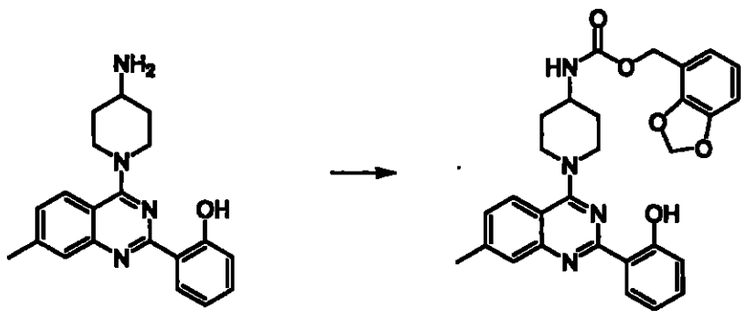
[001302] (Benzo[d][1,3]dioxol-4-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001303]

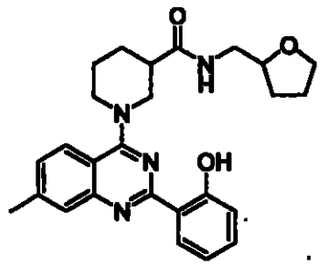


[001304] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMSO (1 mL), was added (benzo[d][1,3]dioxol-4-yl)methyl 1*H*-imidazole-1-carboxylate (65 mg, 0.263 mmol), followed by the addition of triethylamine (30.4 mg, 42 μL, 0.3 mmol). The reaction was stirred overnight at room temperature and then purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (benzo[d][1,3]dioxol-7-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as the TFA salt. LC/MS: *m/z* 513.3 $(M+H)^+$ at 2.82 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001305] Example 230

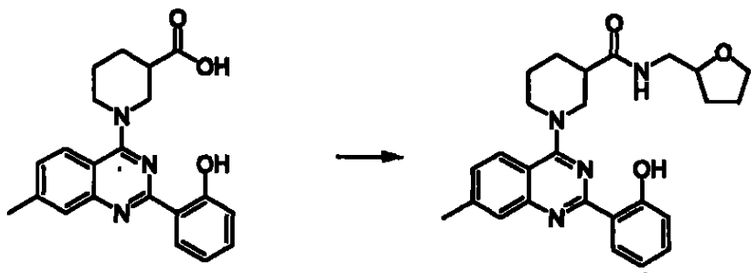
[001306] *N*-((Tetrahydrofuran-2-yl)methyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxamide

[001307]



[001308] *N*-((Tetrahydrofuran-2-yl)methyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxamide

[001309]

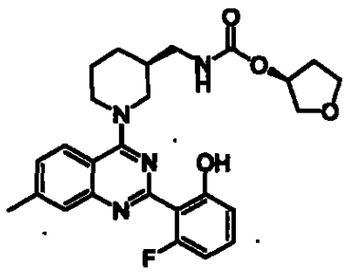


[001310] A solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid (45 mg, 0.12 mmol) in 500 μL DMF was cooled to 0 °C, and (tetrahydrofuran-2-yl)methanamine (13.2 mg, 0.13 mmol) and triethylamine (25 mg, 35 μL, 0.25 mmol) were added. After ten minutes HATU (57 mg, 0.15 mmol) was added to the reaction mixture in one portion .The reaction was allowed to warm to room temperature, stirred overnight, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) yielding *N*-((tetrahydrofuran-2-yl)methyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 447.3 $(M+H)^+$ at 2.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001311] Example 231

[001312] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001313]



[001314] *tert*-butyl piperidin-3-ylmethylcarbamate

[001315]

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[001316] A solution of 1.25 M MeOH (prepared by adding acetyl chloride (13.5 mL, 14.9 g, 0.19 mol) to 1 L of MeOH) was added to a cold solution of *tert*-butyl pyridin-3-ylmethylcarbamate (41.0 grams, 0.20 mol) in MeOH (100 mL). The solution was transferred to a Parr hydrogenation apparatus at 12 °C. PtO_2 (3 g) was added, and 12 bar pressure of H_2 was applied. After 16 hours ^1H NMR of a concentrated sample indicated the reaction to be complete. The catalyst was filtered, and conc. aq. NaOH (20 mL) was added to neutralize the HCl. The solution was concentrated to remove the bulk of the MeOH and extracted with *tert*-butyl methyl ether (4x200 mL). The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated to give the product (40.16 g, 0.187 mol, 95%) as a yellow oil that crystallized upon standing. ^1H NMR (300 MHz, $CDCl_3$): δ 4.62 (bs. s, 1H), 3.06–2.94 (m, 4H), 2.52 (dt, *J*= 12 Hz, 3Hz, 1H), 2.28 (dd, *J*= 12 Hz, 10Hz, 1H), 1.82–1.72 (m, 1H), 1.70–1.51 (m, 3H), 1.49–1.34 (m, 1H), 1.42 (s, 9H), 1.06 (dq, *J*= 12 Hz, 4Hz, 1H).

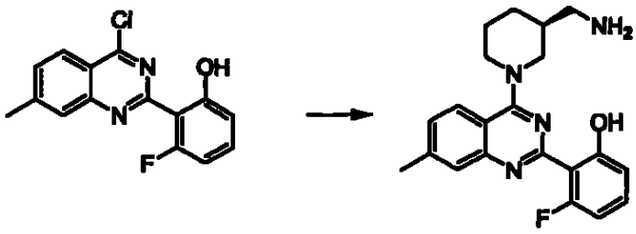
[001317] **(*R*)-*tert*-Butyl piperidin-3-ylmethylcarbamate**

[001318]

[001319] To a solution of *tert*-butyl piperidin-3-ylmethylcarbamate (162 g, 0.758 mol) in EtOH was added (+)-dianisoyltartaric acid (316 g, 0.756 mol). The suspension was heated until clear and allowed to cool to room temperature overnight. The precipitated salt was recrystallized three times from EtOH. The salt was washed with EtOH (2x200 mL) and air-dried. Residual solvent was removed *in vacuo*. The salt was taken up in *tert*-butyl methyl ether and 10% aq. NaOH. The organic layer was separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (3x200 mL). More product was extracted after addition of 30% aq. NaOH to the aqueous layer. The combined organic layers were washed with water and saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated to give (*R*)-*tert*-butyl piperidin-3-ylmethylcarbamate as a white crystalline solid (41.3 g, 0.192 mol, 25%). For ee determinations, samples of the salt were taken up in CH_2Cl_2 and 1 N aq. NaOH. The organic layer was washed with water, dried over Na_2SO_4, and filtered. A drop of 1-naphthyl isocyanate was added, and after 15 minutes a drop of morpholine was added to quench excess isocyanate. Volatiles were evaporated after another 15 minutes. The sample was dissolved in EtOH for chiral HPLC

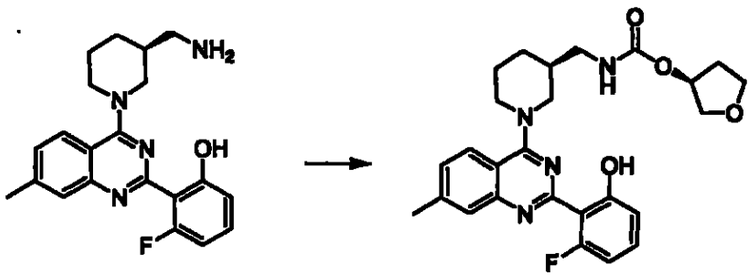
(Chiralpak AD-H, 5 μm, Hexane/EtOH/Et$_2$NH 90/10/0.2; 0.5 mL/min; Rt (*R*): 46 min, Rt (*S*): 57 min, Rt (*N*-(naphthalen-1-yl)morpholine-4-carboxamide): 64 min.

[001320] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol



[001321] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (1.0 g, 3.46 mmol) was dissolved in 15 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled using an ice bath and piperidin-3-ylmethyl-carbamic acid *tert*-butyl ester/oxalic acid (1.16 g, 3.81 mmol) was added in portions, followed by triethylamine (1.05 g, 1.45 mL, 10.4 mmol). The reaction was allowed to warm to room temperature and was complete after 1.5 hour. The mixture was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted once more with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to a yellow solid. This solid was suspended in 40 mL CH_2Cl_2 and 20 mL of TFA were added. The reaction was complete after 1 hour. The solvent and the excess TFA were removed *in vacuo*, the residue was re-dissolved in CH_2Cl_2, and the pH was adjusted to 7 using an aqueous 1 M solution of NaOH. The reaction was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted once more with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to yield of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (900 mg, 71% overall yield) as a yellow solid. LC/MS: *m/z* 367.3 $(M+H)^+$ at 1.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001322] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate



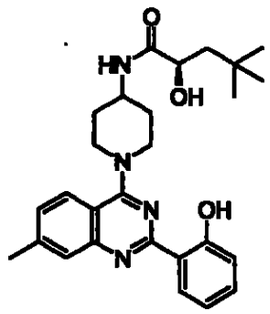
[001323]

[001324] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.11 mmol) was dissolved in anhydrous DMF (800 μL) and cooled to 0 °C, upon which (*S*)-tetrahydrofuran-3-yl chloroformate (16.3 mg, 0.12 mmol) dissolved in DMF (100 μL) was added dropwise followed by triethylamine (22 mg, 30.3 μL, 0.218 mmol). The reaction was allowed to warm to room temperature, and after 2 h the reaction was complete. The mixture was purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to yield (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 481.1 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001325] Example 232

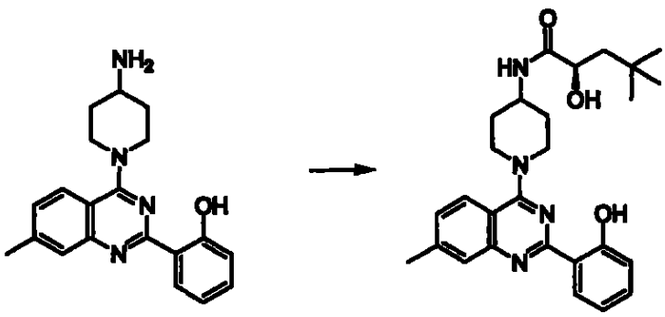
[001326] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-4,4-dimethylpentanamide

[001327]



[001328] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-4,4-dimethylpentanamide

[001329]

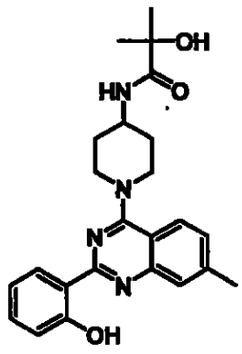


[001330] 2-(4-(4-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) was dissolved in DMF (1 mL) and cooled to 0 °C. (2*R*)-Hydroxy-4,4-dimethyl-pentanoic acid (26.3 mg, 0.18 mmol) was added followed by the addition of triethylamine (42 μL, 0.3 mmol). After ten minutes, HATU (68 mg, 0.18 mmol) was added in one portion. The reaction was stirred at 0 °C for 10 minutes, and then allowed to warm to room temperature. The reaction was complete after 40 minutes, then filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (2*R*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-4,4-dimethylpentanamide as the TFA salt. LC/MS: *m/z* 463.3 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001331] Example 233

[001332] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide

[001333]



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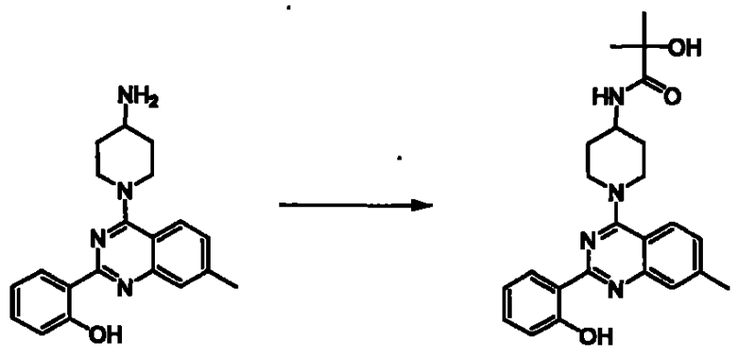
[001334] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide

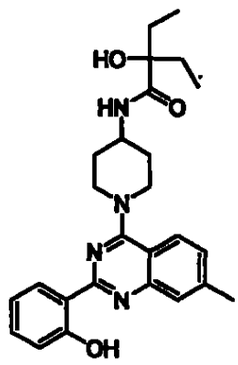
[001335]



[001336] To 2-hydroxy-2-methylpropanoic acid (28 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide as the TFA salt. *LC/MS*: *m/z* 421.2$(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

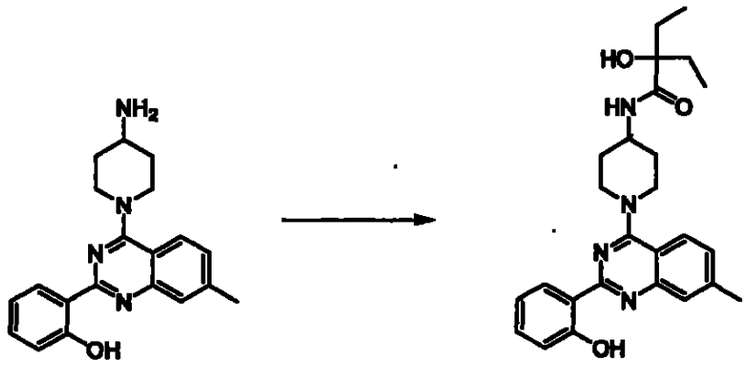
[001337] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001338]



[001339] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001340]

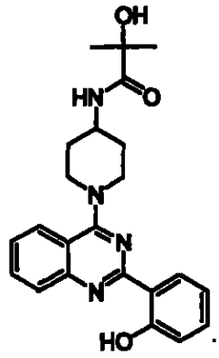


[001341] To 2-ethyl-2-hydroxybutanoic acid (36 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 449.2$(M+H)^+$ at 2.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001342] Example 235

[001343] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide

[001344]



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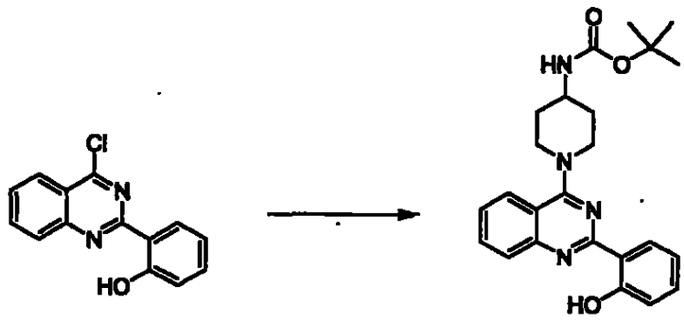
[001345] tert-Butyl 1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate

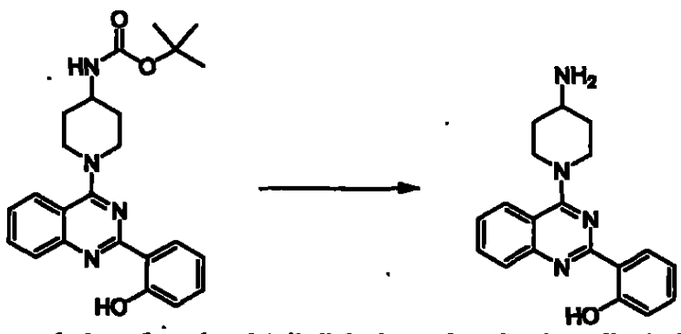
[001346]



[001347] To a suspension of 2-(4-chloroquinazolin-2-yl)phenol (2.0 g, 7.79 mmol) in CH_2Cl_2 (25 mL) at 0 °C under an N_2 atmosphere, was added dropwise *tert*-butyl piperidin-4-ylcarbamate (2.08 g, 10.13 mmol) and triethylamine (2.20 mL, 15.8 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred overnight, quenched with water and extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford *tert*-butyl 1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate (3.27 g, 100% –solvent residue). LC/MS: *m/z* 421.3$(M+H)^+$ at 2.70 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001348] 2-(4-(4-Aminopiperidin-1-yl)quinazolin-2-yl)phenol

[001349]

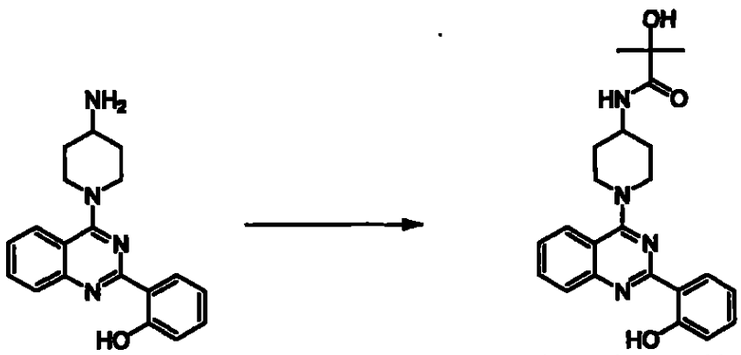


[001350] To a solution of *tert*-butyl 1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate (3.27 g, 8.09 mmol) in CH_2Cl_2 (75 mL) was added TFA (50 mL). The reaction was complete after 45 minutes After evaporating the solvents *in vacuo*, the crude material was diluted with CH_2Cl_2 and neutralized by adding a 1 N aqueous NaOH solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 2-(4-(4-aminopiperidin-1-

yl)quinazolin-2-yl)phenol as a solid (0.089 g, 84%). LC/MS: *m/z* 321.3$(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001351] **2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide**

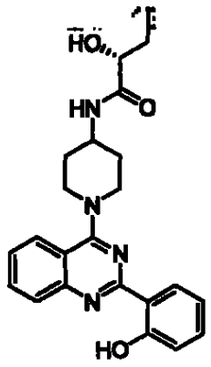
[001352]



[001353] To 2-hydroxy-2-methylpropanoic acid (27 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide as the TFA salt. LC/MS: *m/z* 407.5$(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001354] Example 236

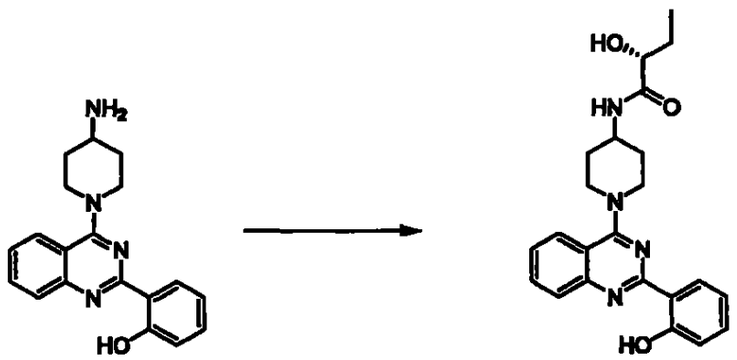
[001355] **(2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide**



[001356]

[001357] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001358]

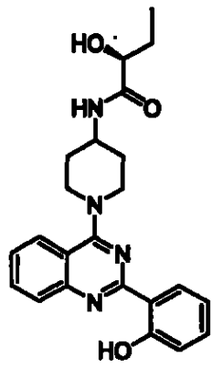


[001359] To (*R*)-2-hydroxybutanoic acid (30 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) dissolved in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 407.3$(M+H)^+$ at 2.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001360] Example 237

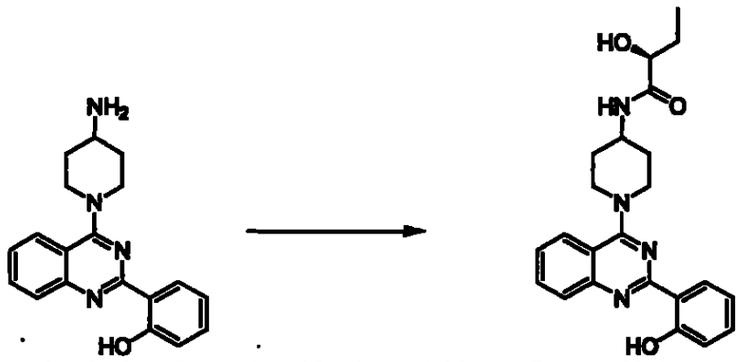
[001361] (2*S*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[0013[2]



[001363] (2*S*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001364]



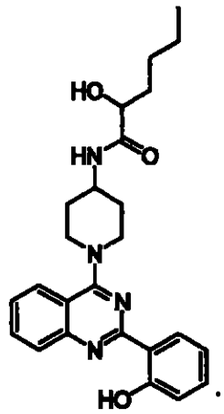
[001365] To (*S*)-2-hydroxybutanoic acid (30 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*S*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 407.3$(M+H)^+$ at 2.09 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001366] Example 238

[001367] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)hexanamide

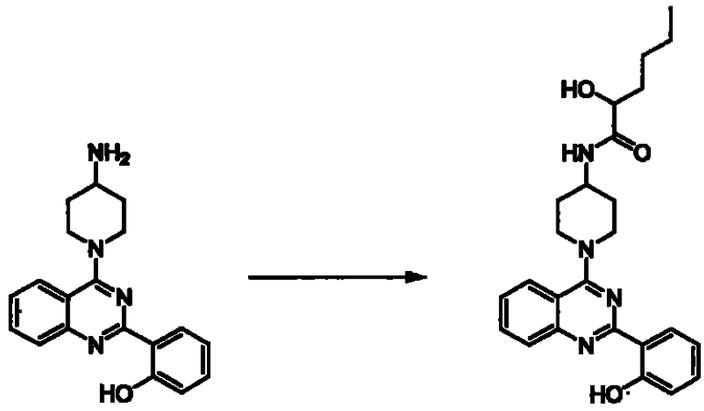
154

[001368]



[001369] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)hexanamide

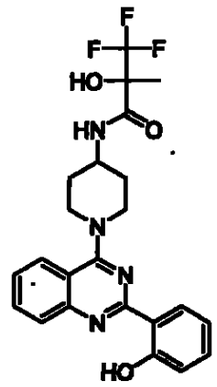
[001370]



[001371] To 2-hydroxyhexanoic acid (38 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)hexanamide as the TFA salt. LC/MS: *m/z* 435.3$(M+H)^+$ at 2.4 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

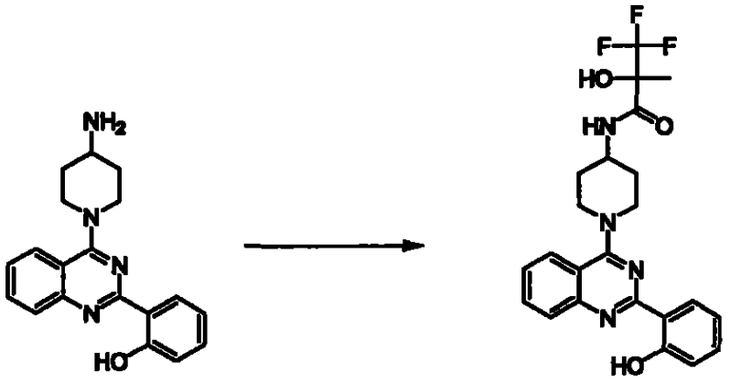
[001372] Example 239

[001373] 2-(Trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)propanamide



[001374] 2-(Trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)propanamide

[001375]



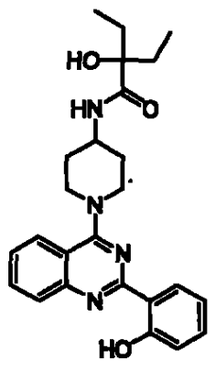
[001376] To 2-(trifluoromethyl)-2-hydroxypropanoic acid (45 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) dissolved in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-(trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)propanamide as the TFA salt. LC/MS: *m/z* 461.1$(M+H)^+$ at 2.4 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001377] Example 240

155

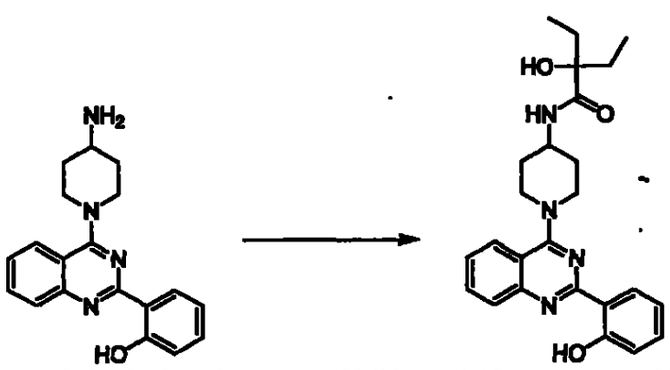
[001378] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001379]



[001380] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001381]

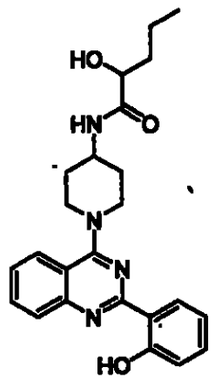


[001382] To 2-ethyl-2-hydroxybutanoic acid (38 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 435.5$(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001383] Example 241

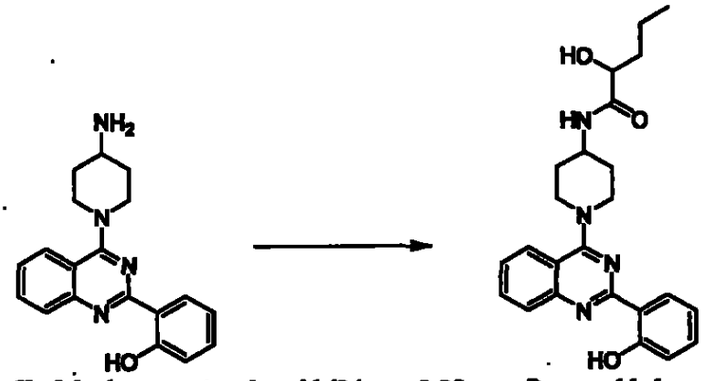
[001384] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)pentanamide

[001385]



[001386] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)pentanamide

[001387]



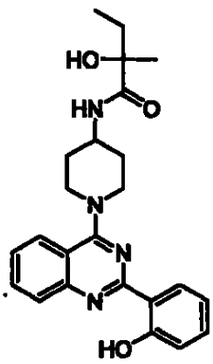
[001388] To 2-hydroxypentanoic acid (34 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)pentanamide as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001389] Example 242

156

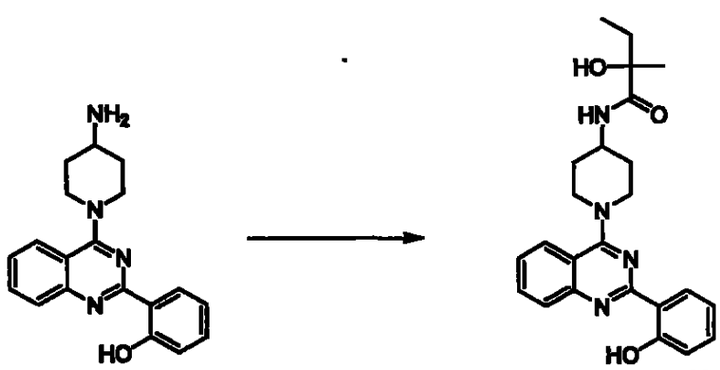
[001390] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide

[001391]



[001392] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide

[001393]

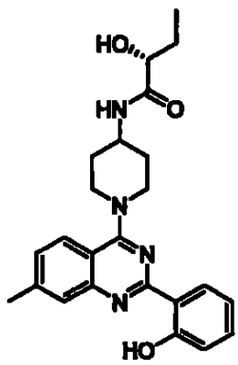


[001394] To 2-hydroxy-2-methylbutanoic acid (34 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide as the TFA salt. LC/MS: *m/z* 421.3$(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001395] Example 243

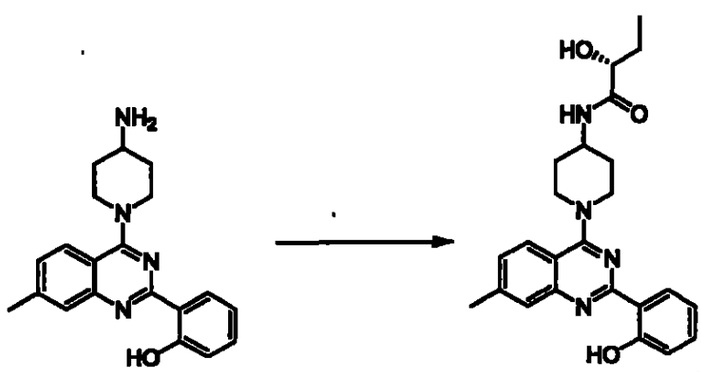
[0013[illegible] [illegible]-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001397]



[001398] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001399]



[001400] To (*R*)-2-hydroxybutanoic acid (28 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 421.3$(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001401] Example 244

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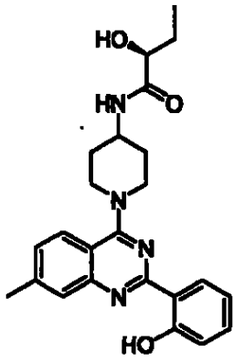
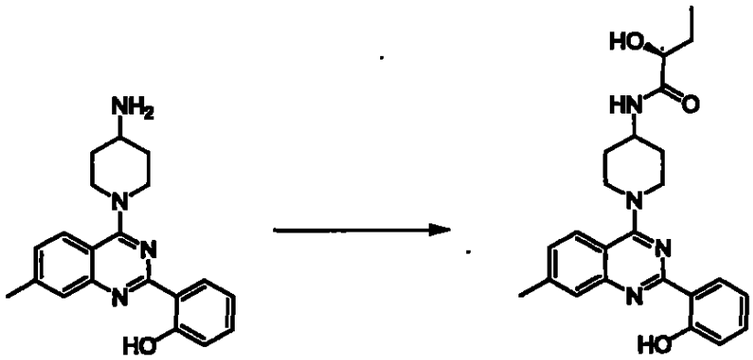
[001402] (2S)-2-Hydroxy-N-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001403]



[001404] (2*S*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001405]

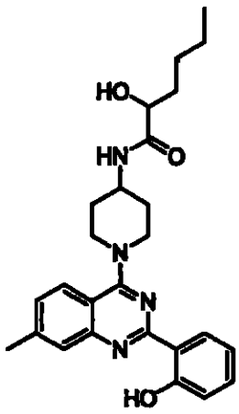


[001406] To (*S*)-2-hydroxybutanoic acid (28 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, then filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*S*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 421.3$(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001407] Example 245

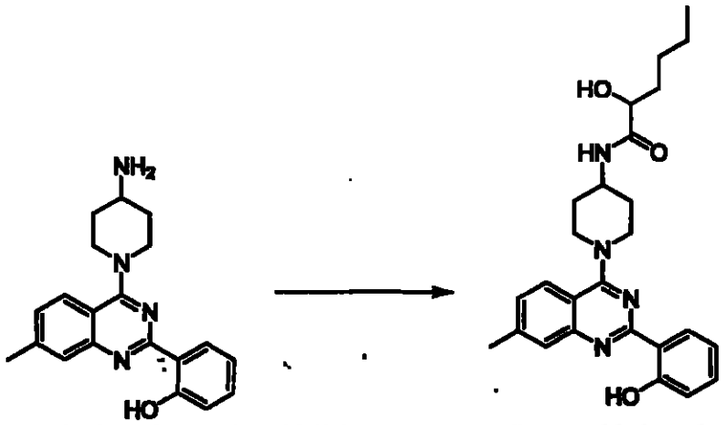
[001408] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)hexanamide

[001409]



[001410] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)hexanamide

[001411]



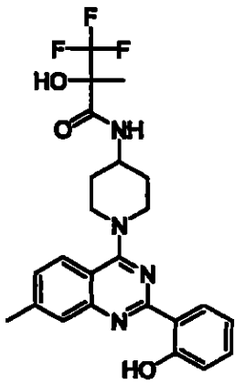
[001412] To 2-hydroxyhexanoic acid (36 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)hexanamide as the

TFA [illegible] 2.45 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001413] Example 246

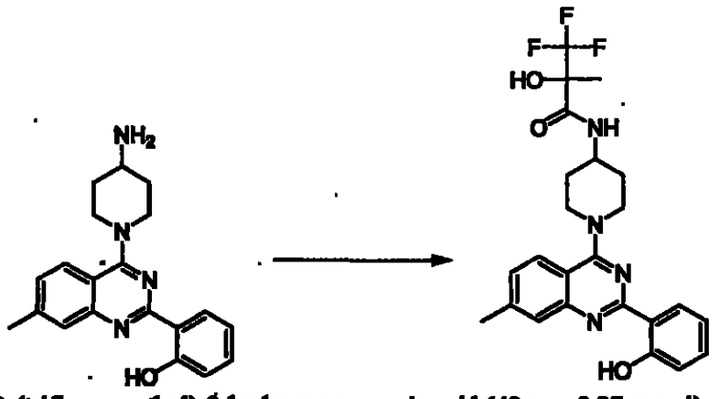
[001414] 2-(Trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)propanamide

[001415]



[001416] 2-(Trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)propanamide

[001417]



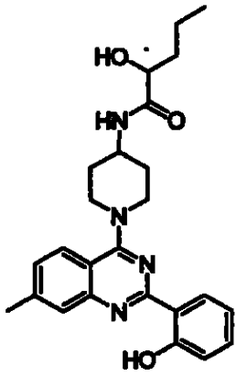
[001418] To 2-(trifluoromethyl)-2-hydroxypropanoic acid (43 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

to afford 2-trifluoroacetyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)propanamide as the TFA salt. LC/MS: *m/z* 475.1$(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001419] Example 247

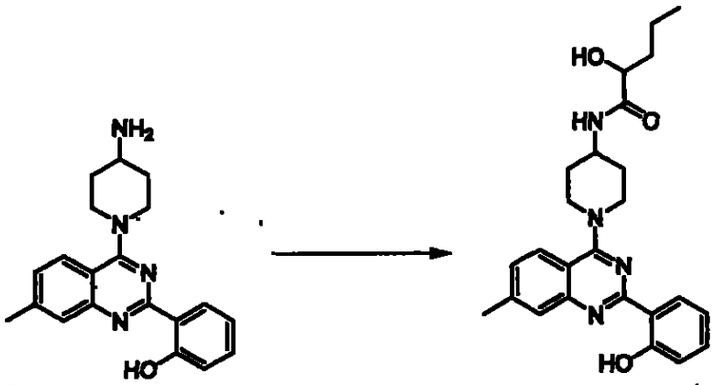
[001420] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)pentanamide

[001421]



[001422] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)pentanamide

[001423]



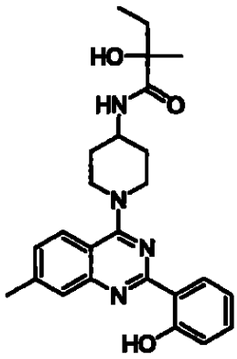
[001424] To 2-hydroxypentanoic acid (32 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified

using [illegible] CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)pentanamide as the TFA salt. LC/MS: *m/z* 435.3$(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001425] Example 248

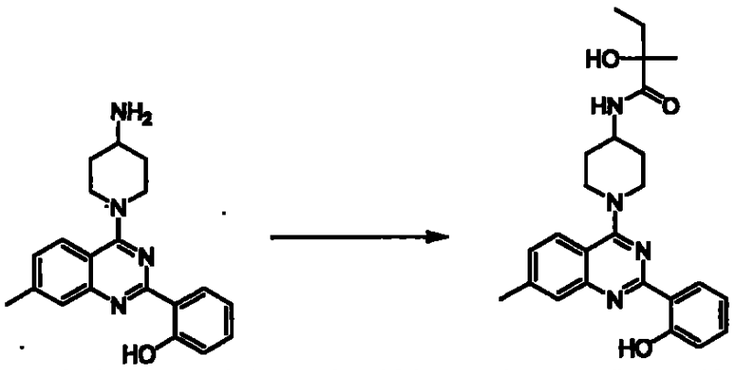
[001426] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide

[001427]



[001428] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide

[001429]



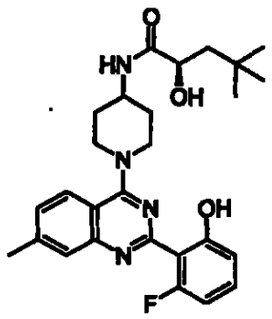
[001430] To 2-hydroxy-2-methylbutanoic acid (32 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and

purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide as the TFA salt. LC/MS: *m/z* 435.3$(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001431] Example 249

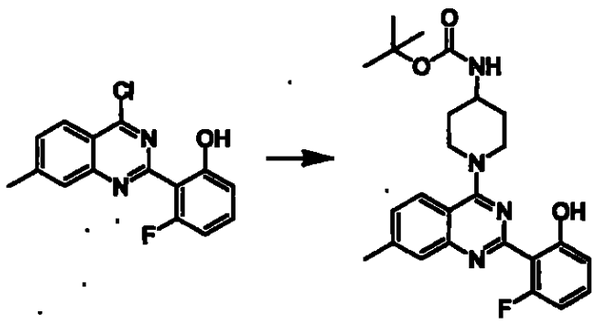
[001432] (2*R*)-*N*-(1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-hydroxy-4,4-dimethylpentanamide

[001433]



[001434] *tert*-Butyl 1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001435]

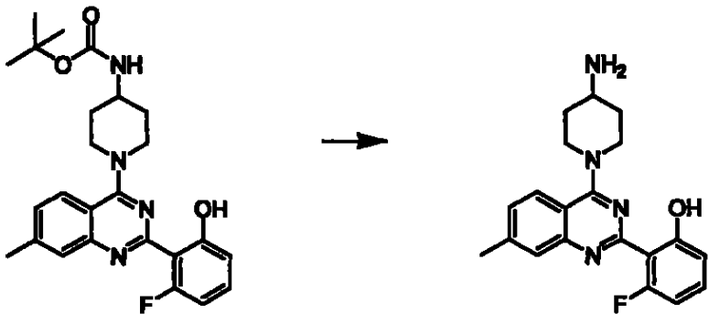


[001436] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (700 mg, 2.42 mmol) in 10 ml CH_2Cl_2 at 0 °C was added triethylamine (0.67 mL, 4.8 mmol) followed by the addition of *tert*-butyl piperidin-4-ylcarbamate (630 mg, 3.14 mmol) under an N_2 atmosphere. The reaction was gradually warmed to room temperature and stirred overnight. The reaction mixture was then quenched with water, and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered,

1GD

and concentrated to obtain *tert*-butyl 1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (1.05 g, 96%) LC/MS: *m/z* 453.3$(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

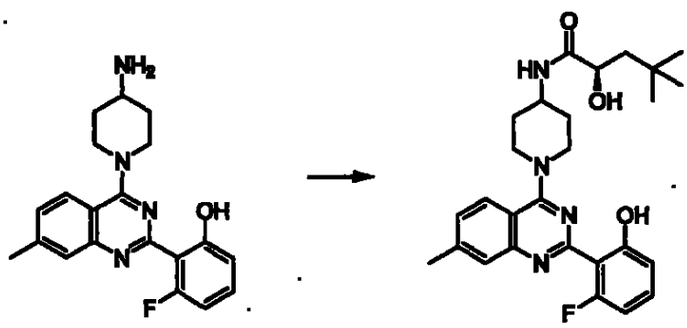
[001437] 2-(4-(4-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol



[001438] To a solution of *tert*-butyl 1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (1.05 g, 2.3 mmol) in 20 ml CH_2Cl_2 was slowly added TFA (5 mL). The reaction was stirred for one hour before it was evaporated to dryness. To the residue was added CH_2Cl_2, and the reaction was neutralized using an aqueous 1 M NaOH solution. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried over MgSO4, filtered, and concentrated to obtain 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.75 g, 92%). LC/MS: *m/z* 353.3$(M+H)^+$ at 1.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001439] (2*R*)-*N*-(1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-hydroxy-4,4-dimethylpentanamide

[001440]

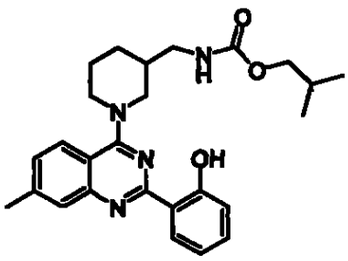


[001441] To a solution of 2-(4-(3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (50 mg, 0.14 mmol) in 1 mL DMF at 0 °C was added (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (25 mg, 0.17 mmol), followed by the addition of triethylamine (29 mg, 0.28 mmol). HATU (65 mg, 0.17 mmol) was then added, and the reaction was stirred at 0 °C for an additional 10 minutes and then warmed to room temperature. The reaction was complete after 40 minutes, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (2*R*)-*N*-(1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-hydroxy-4,4-dimethylpentanamide as the TFA salt. LC/MS: *m/z* 481.3 $(M+H)^+$ at 2.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001442] Example 250

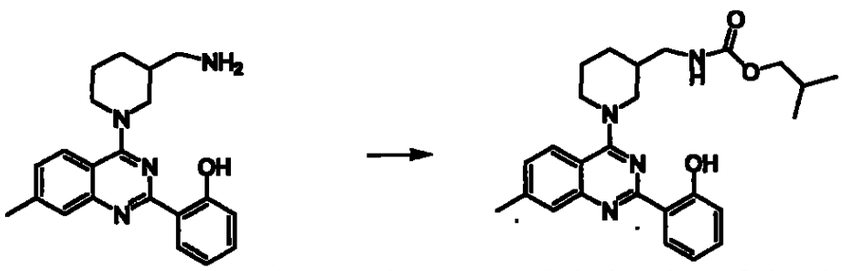
[001443] Isobutyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001444]



[001445] Isobutyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001446]



[001447] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which isobutyl chloroformate (27 μL, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by

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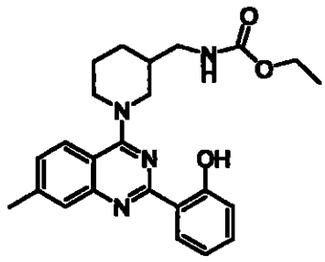
triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature, and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.5 $(M+H)^+$ at 2.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001448] Example 251

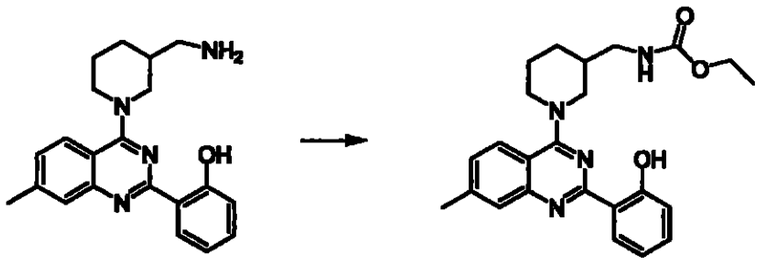
[001449] Ethyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001450]



[001451] Ethyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001452]



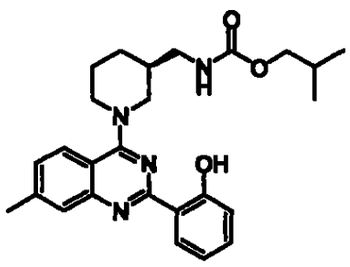
[001453] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which ethyl chloroformate (20μL, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by the addition of triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave ethyl (1-(2-(2-hydroxyphenyl)-7-

methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 421.0 $(M+H)^+$ at 2.48 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001454] Example 252

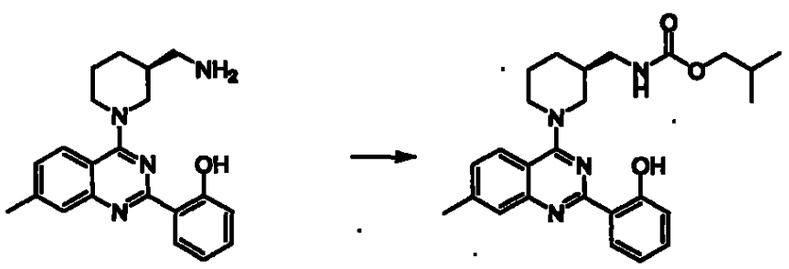
[001455] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001456]



[001457] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001458]



[001459] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which isobutyl chloroformate (27 μL, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by the addition of triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. *LC/MS*: *m/z* 449.3 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001460] Example 253

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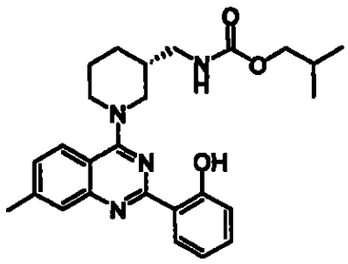
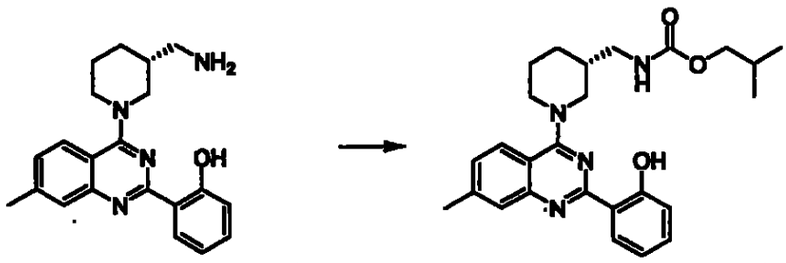
[001461] Isobutyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001462]



[001463] Isobutyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001464]

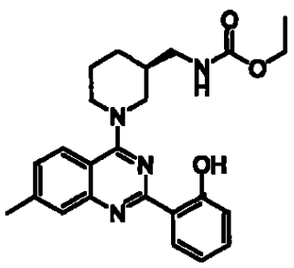


[001465] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.172 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which isobutyl chloroformate (27 μL, 0.21 mmol) dissolved in DMF (100 μL) was added dropwise followed by the addition of triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature, and it was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.78 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001466] Example 254

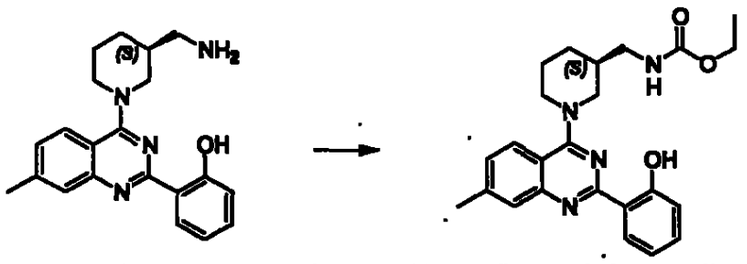
[001467] Ethyl((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001468]



[001469] Ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001470]

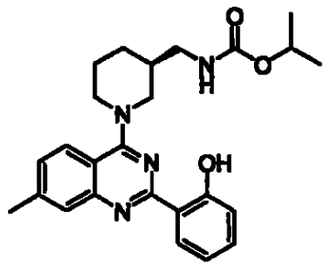


[001471] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (35 mg, 0.10 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which ethyl chloroformate (10.5 μL, 0.11 mmol) dissolved in DMF (100 μL) was added dropwise followed by triethylamine (20.2 mg, 27.8 μL, 0.2 mmol). The reaction was allowed to warm to room temperature, and it was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001472] Example 255

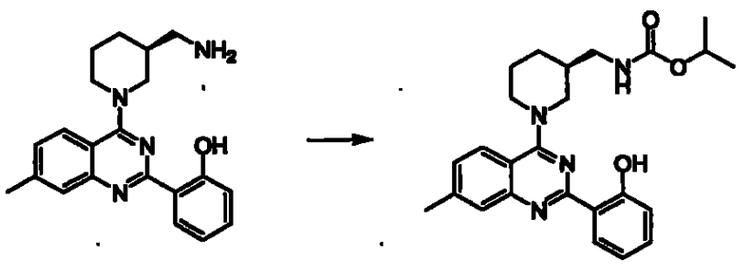
[001473] Isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001474]



[001475] Isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

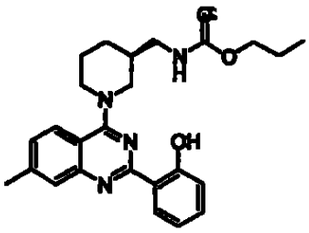
[001476]



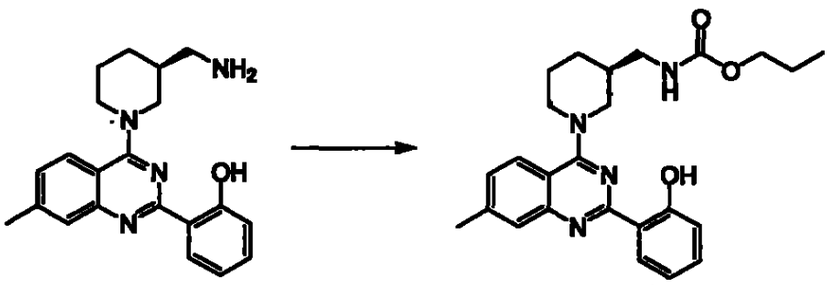
[001477] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (35 mg, 0.10 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which isopropyl chloroformate (1 M solution in toluene, 98.1 mg, 110 μL, 0.11 mmol) was dissolved in DMF (100 μL) and added dropwise, followed by triethylamine (20.2 mg, 27.8 μL, 0.2 mmol). The reaction was allowed to warm to room temperature, and it was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001478] Example 256

[001479] Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate



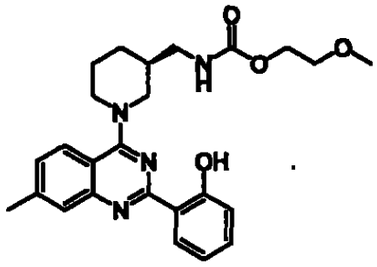
[001474] **Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



[001475] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (35 mg, 0.10 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which propyl chloroformate (12.4 μL, 0.11 mmol) dissolved in DMF (100 μL) was added dropwise followed by triethylamine (20.2 mg, 27.8 μL, 0.2 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001476] Example 257

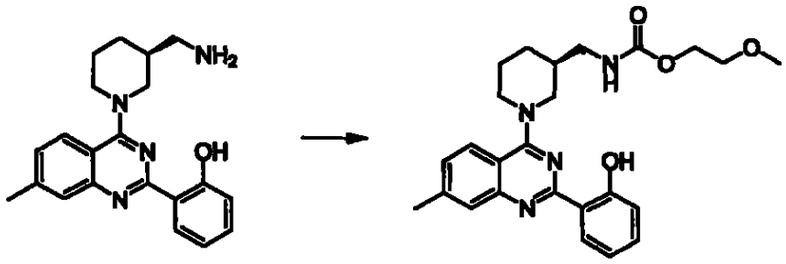
[001477] **2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



164

[001487] 2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001488]

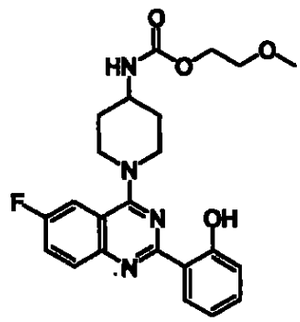


[001489] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (35 mg, 0.1 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which 2-methoxyethyl chloroformate (11.6μL, 0.1 mmol) dissolved in DMF (100 μL) was added dropwise followed by triethylamine (20.2 mg, 27.8 μL, 0.2 mmol). The reaction was allowed to warm to room temperature, and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 451.1 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001490] Example 258

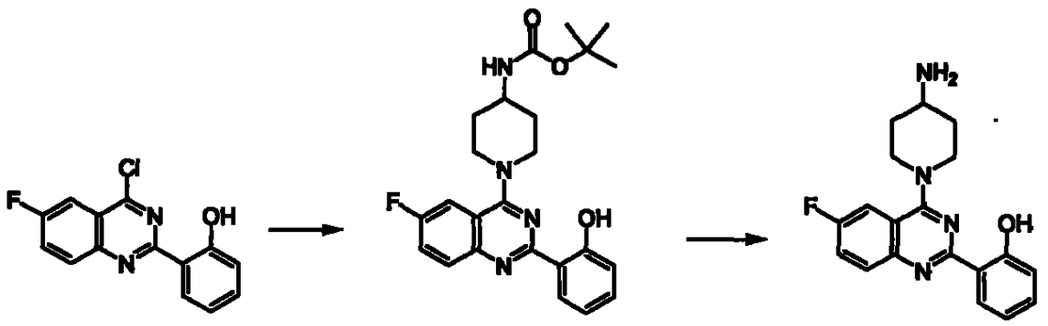
[001491] 2-Methoxyethyl 1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate

[001492]



[001493] 2-(4-(4-Aminopiperidin-1-yl)-6-fluoroquinazolin-2-yl)phenol

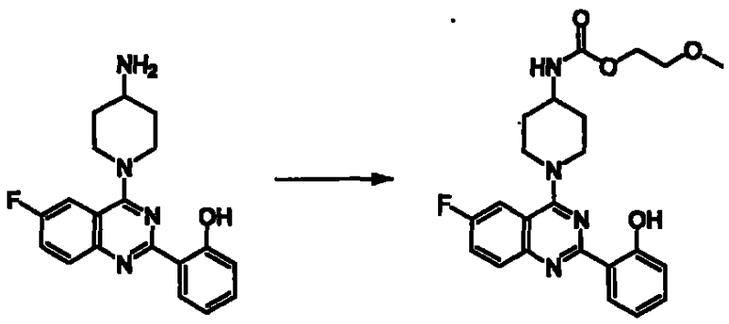
[001494]



[001495] To a stirred solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (0.20 g, 0.73 mmol) in CH_2Cl_2 (5mL) was added dropwise a solution of *tert*-butyl piperidin-4-ylcarbamate (0.19 g, 0.95 mmol) and triethylamine (203 μL, 147 mg, 1.46 mmol) in CH_2Cl_2. The reaction was stirred for 3 h and then quenched with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to obtain *tert*-butyl 1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate. The residue was dissolved in 10 mL CH_2Cl_2 and 3 mL TFA. The reaction was stirred for 2 hours and neutralized with a 1.0 *M* aqueous NaOH solution. The mixture was partitioned between H_2O/CH_2Cl_2 and separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to obtain 2-(4-(4-aminopiperidin-1-yl)-6-fluoroquinazolin-2-yl)phenol. LC/MS: *m/z* 339.3$(M+H)^+$ at 1.87 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001496] **2-Methoxyethyl 1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate**

[001497]



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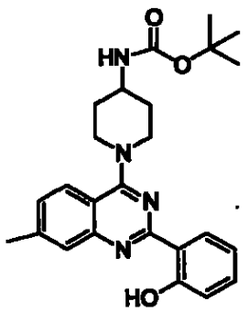
[001498] A solution of 2-(4-(3-Trimethylpiperidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMF (1 mL) was cooled to –40 °C (external temp). To it was added triethylamine (41 μL, 30 mg, 0.29 mmol) and a solution of 2-methoxyethyl chloroformate (17 μL, 20 mg, 0.15 mmol) in 100 μL DMF dropwise. The reaction was allowed to warm to room temperature and was stirred for 2 h. Purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl 1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate as the TFA salt. LC/MS: *m/z* 441.5$(M+H)^+$ at 2.6 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001499] Example 259

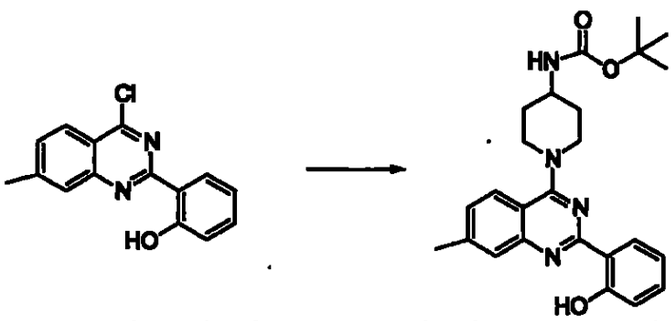
[001500] **{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester**

[001501]



[001502] **{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester**

[001503]



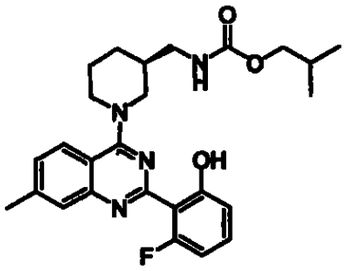
[001504] To piperidin-4-yl-carbamic acid *tert*-butyl ester (887 mg, 4.4 mmol) in 10 mL of was CH_2Cl_2 was added sequentially triethylamine (720 μL, 5.2 mmol) and 2-(4-chloro-7-methyl-

quinazolin-2-yl]-phenol (1.0 g, 3.7 mmol). The reaction mixture was stirred at room temperature for 2 h and then diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester as the TFA salt. *LC/MS*: *m/z* 435.2 (M+H)+ at 3.03 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001505] Example 260

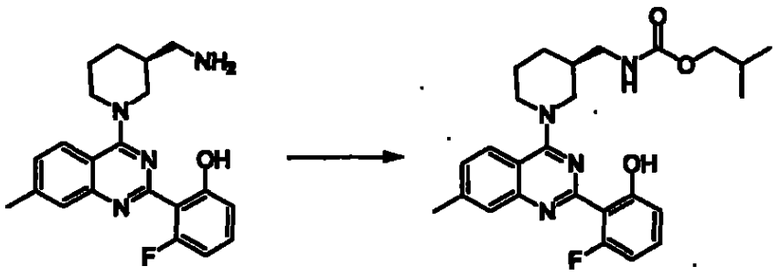
[001506] Isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001507]



[001508] Isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001509]



[001510] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.11 mmol) in DMF (400 μL) at 0 °C was added dropwise isobutyl chloroformate (15.7 μL, 0.12 mmol) in DMF (400 μL), followed by the addition of triethylamine

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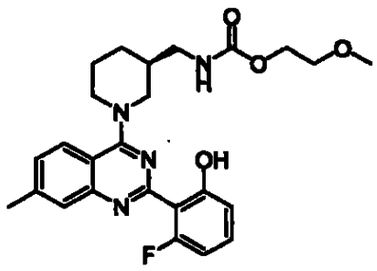
(30 μL, 0.22 mmol). The reaction was allowed to warm to room temperature and was complete after 2h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 467.1 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001511] Example 261

[001512] **2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

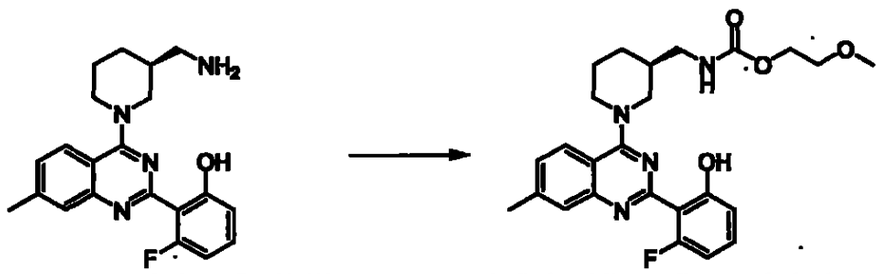
[001513]



[001514] Method A

[001515] **2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001516]



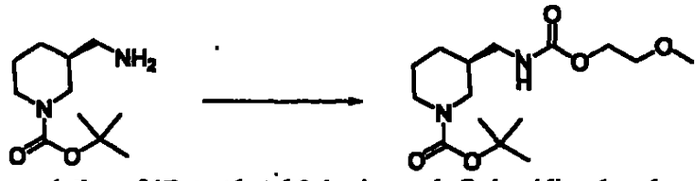
[001517] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.11 mmol) in DMF (400 μL) at 0 °C was added dropwise 2-methoxyethyl chloroformate (12.6 μL, 0.11 mmol) in DMF (400 μL), followed by the addition of triethylamine (30 μL, 0.22 mmol). The reaction was allowed to warm to room temperature and was complete after 2h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-

methylquinazolin-4-yl)piperidin-3-yl]methylcarbamate as the TFA salt. LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.20 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001518] Method B

[001519] **2-Methoxyethyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate**

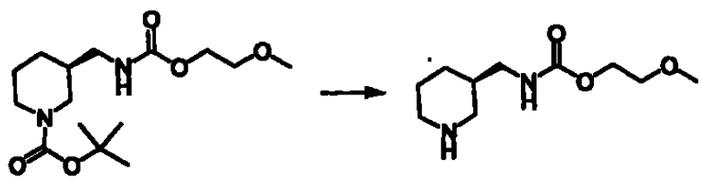
[001520]



[001521] To a solution of (*S*)-*tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (500 mg, 2.33 mmol) in CH_2Cl_2 at –10 °C was added triethylamine (650 µL, 4.66 mmol) followed by the dropwise addition of 2-methoxyethyl chloroformate (325 µL, 2.79 mmol). The reaction was warmed to room temperature and quenched with water. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, and evaporated. Purification via silica gel chromatography using 0 to 10% EtOAc in CH_2Cl_2 afforded 2-methoxyethyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate (496 mg, 67%). LC/MS: *m/z* 317.3 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001522] **2-Methoxyethyl ((*R*)-piperidin-3-yl)methylcarbamate**

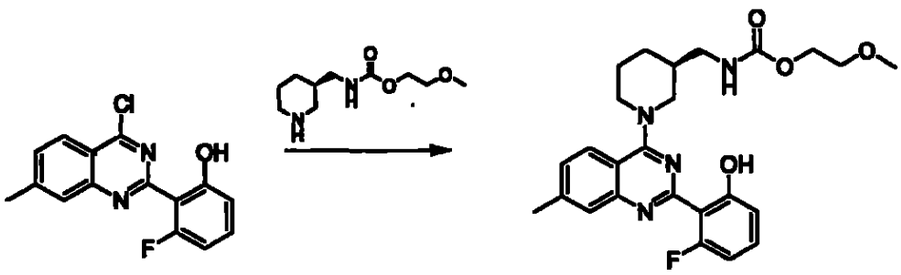
[001523]



[001524] To 2-methoxyethyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate (496 mg, 1.6 mmol) dissolved in 10 mL CH_2Cl_2 was added 5 mL TFA, and the reaction was stirred for 1 hour. After neutralizing the mixture with a 1 N NaOH solution it was extracted with CH_2Cl_2, and the combined organic layers were dried over MgSO4, filtered, and concentrated to give 2-methoxyethyl ((*R*)-piperidin-3-yl)methylcarbamate (300 mg, 87%) which was used without further purification. LC/MS: *m/z* 217.5 $(M+H)^+$ at 0.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001525] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

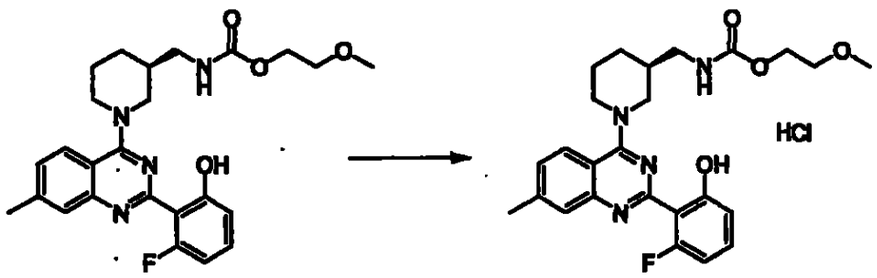
[001526]



[001527] To a solution of 2-methoxyethyl ((*R*)-piperidin-3-yl)methylcarbamate (0.24 g, 1.1 mmol) and 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (250 mg, 0.865 mmol) in CH_2Cl_2 was added triethylamine (2.41 mL, 1.73 mmol). After stirring the reaction at room temperature for 2 h, it was quenched with water and then extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0%–10% EtOAc in CH_2Cl_2 yielded 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (357 mg, 88%). LC/MS: *m/z* 469.5 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (m, 3H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.71 (m, 2H), 4.40 (d, *J* = 12.7 Hz, 2H), 4.05 (m, 2H), 3.48 (m, 2H), 3.30 (m, 1H), 3.25 (s, 3H), 3.05 (m, 3H), 1.82 (m, 3H), 1.63 (m, 1H), 1.32 (m, 1H).

[001528] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001529]



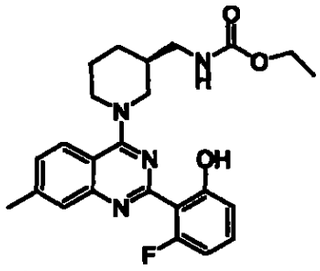
[001530] To a solution of ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (352 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) was added dropwise

a 2.0 M HCl solution in ether (0.375 mL, 0.75 mmol) under an N_2 atmosphere. It was followed by the addition of 20 mL ether which lead to the precipitation of 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride (350 mg, 92%) which was then filtered and dried. LC/MS: *m/z* 469.5 $(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 7.97 (d, *J* = 7.9 Hz, 1H), 7.63 (s, 1H), 7.45 (m, 3H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.82 (t, *J* = 9.5 Hz, 1H), 4.54 (s, 1H), 4.03 (d, *J* = 2.7 Hz, 2H), 3.47 (t, *J* = 4.6 Hz, 4H), 3.24 (s, 3H), 2.99 (m, 2H), 2.54 (s, 3H), 1.89 (m, 3H), 1.70 (m, 1H), 1.38 (m, 1H)

[001531] Example 262

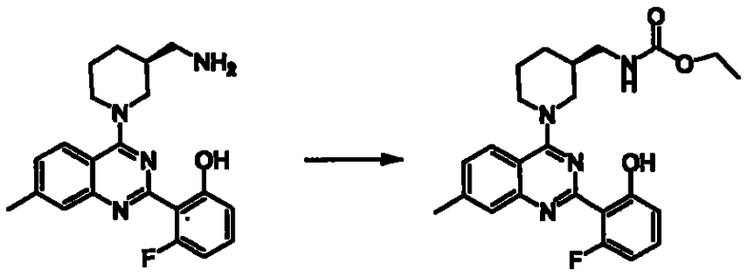
[001532] Ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001533]



[001534] Ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001535]



[001536] Method A

[001537] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.11 mmol) in DMF (400 μL) at 0 °C was added dropwise ethyl chloroformate (10.4 μl, 0.10 mmol) in DMF (400 μL), followed by the addition of triethylamine

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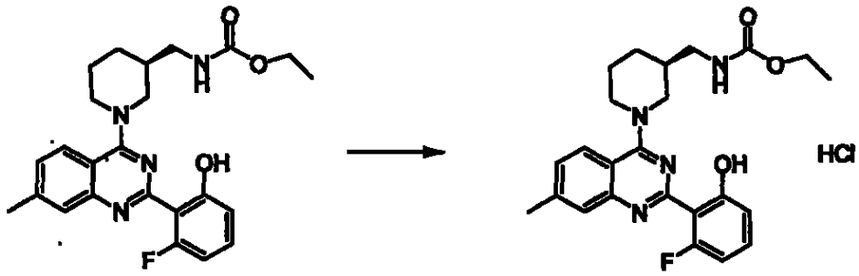
(30 μL, 0.22 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001538] Method B

[001539] To a stirred solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (200 mg, 0.54 mmol) in 12 mL THF was added diisopropyl ethylamine (188 μL, 1.08 mmol) at room temperature. The mixture was cooled to –60 °C, and a solution of ethyl chloroformate (52 μL, 0.54 mmol) in 0.6 mL THF was added dropwise. After allowing the reaction to warm to room temperature, the mixture was partitioned between H_2O and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted twice more with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 hexanes:CH_2Cl_2 gave ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (92 mg, 38%). LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 7.87 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (m, 2H), 7.21 (m, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.70 (m, 1H), 4.40 (m, 2H), 3.98 (m, 2H), 3.27 (m, 1H), 3.05 (m, 1H), 2.97 (m, 2H), 1.84 (d, J = 11.0 Hz, 3H), 1.67 (d, J = 9.4 Hz, 1H), 1.32 (dd, J = 20.8, 11.3 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H)

[001540] Ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001541]

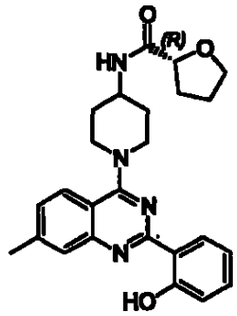


[001542] To a solution of ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (89 mg, 0.2 mmol) in 2 mL CH_2Cl_2 under an N_2 atmosphere was added ether (10 mL) followed by the dropwise addition of a 2.0 M solution of HCl in ether (0.1 mL, 0.2 mmol) which resulted in precipitation of ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride which was then filtered and dried (85 mg, 90%). LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.26 (d, *J* = 8.5 Hz, 1H), 7.57 (s, 1H), 7.45 (m, 2H), 6.81 (m, 2H), 4.57 (m, 2H), 3.89 (m, 2H), 3.52 (m, 1H), 3.36 (m, 1H), 2.95 (s, 2H), 2.52 (s, 3H), 1.86 (m, 3H), 1.66 (m, 1H), 1.39 (m, 1H), 1.07 (t, *J* = 6.6 Hz, 3H).

[001543] Example 276

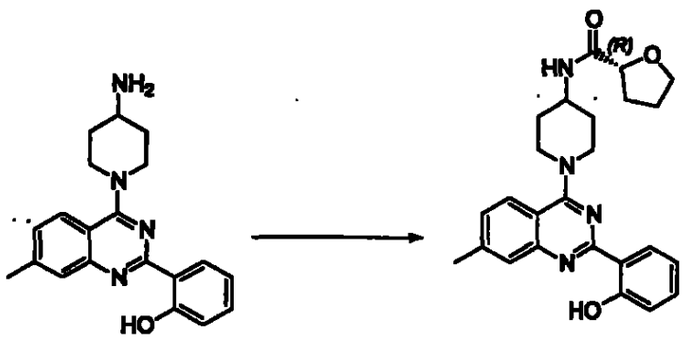
[001544] **(*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide**

[001545]



[001546] **(*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide**

[001547]

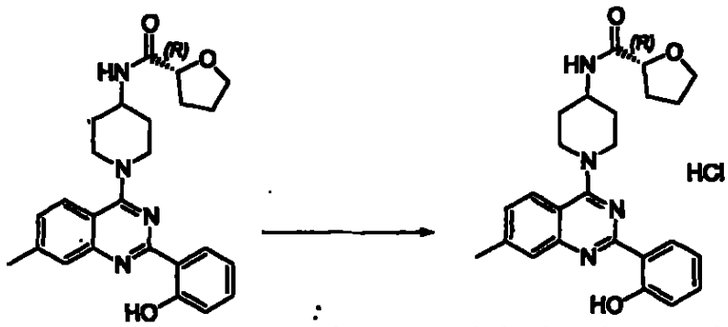


[001548] Method A: (*R*)-Tetrahydrofuran-2-carboxylic acid (23 mg, 0.20 mmol) and HATU (84 mg, 0.22 mmol) were dissolved in 0.75 mL DMF, then triethylamine (40 mg, 55 μL, 0.40 mmol) was added, followed immediately by 2-[4-(4-Amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (67 mg, 0.20 mmol). The reaction was then stirred for 30 min at room temperature, diluted with 0.75 mL 1:1 methanol / DMSO, filtered, and purified by reverse phase HPLC (2–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide as the TFA salt. LC/MS: *m/z* 433.2 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001549] Method B: (*R*)-Tetrahydrofuran-2-carboxylic acid (193 mg, 1.66 mmol) was dissolved in DMF (6 mL), followed by the addition of HATU (696 mg, 1.83 mmol). The mixture was then stirred for 15 min at room temperature under an N_2 atmosphere. The 2-[4-(4-Amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (556 mg, 1.66 mmol) was dissolved in DMF (8 mL) and added to the mixture, followed by triethylamine (336 mg, 0.463 mL, 3.32 mmol). After 30 min, theDMF was removed *in vacuo* and the crude product partitioned between water and ethyl acetate. The aqueous layer was separated, washed with ethyl acetate, and the combined organic layers dried over $MgSO_4$, filtered, and concentrated to give crude product as an orange oil. Purification via silica gel chromatography (20% ethyl acetate / 80% 1:1 CH_2Cl_2:hexane) gave pure (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide (303 mg, 42%). ^1H NMR (400 MHz, DMSO-d6) δ 8.44 (dd, J = 8.2, 1.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.67 (s, 1H), 7.40–7.36 (m, 2H), 6.97–6.93 (m, 2H), 4.48–4.45 (m, 2H), 4.20 (dd, J = 8.2, 5.3 Hz, 1H), 4.06–3.96 (m, 1H), 3.88 (dd, J = 14.3, 6.6 Hz, 1H), 3.74 (dd, J = 14.5, 6.7 Hz, 1H), 3.43–3.32 (m, 2H), 2.51 (s, 3H), 2.16–2.07 (m, 1H),

1.89–1.69 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d6) δ 171.7, 162.8, 160.7, 159.5, 149.3, 144.1, 132.5, 129.0, 127.3, 125.7, 125.4, 118.9, 118.4, 117.2, 111.9, 77.6, 68.5, 48.3, 45.5, 31.3, 31.2, 30.0, 24.9, 21.2.

[001550] **(*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide hydrochloride**

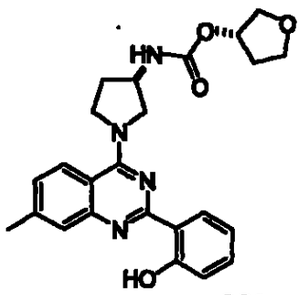


[001551] (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide (303 mg, 0.701 mmol) was dissolved in 9 mL 2:1 dry ether / dry CH_2Cl_2 and 2.0 M HCl in ether added dropwise (0.35 mL, 0.70 mmol), producing a white precipitate which was collected by filtration to give (*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide hydrochloride (268 mg, 82%). LC/MS: *m/z* 433.5 $(M+H)^+$ at 2.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^{1}H NMR (400 MHz, DMSO-d6) δ 8.20 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.80–7.79 (m, 2H), 7.51–7.47 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.05–7.01 (m, 1H), 4.66–4.63 (m, 2H), 4.21 (dd, *J* = 8.2, 5.2 Hz, 1H), 4.12–4.03 (m, 1H), 3.91–3.84 (m, 1H), 3.78–3.70 (m, 1H), 3.59 (t, *J* = 12.3 Hz, 2H), 2.54 (s, 3H), 2.16–2.05 (m, 1H), 1.97–1.94 (m, 2H), 1.89–1.72 (m, 5H).

[001552] Example 301

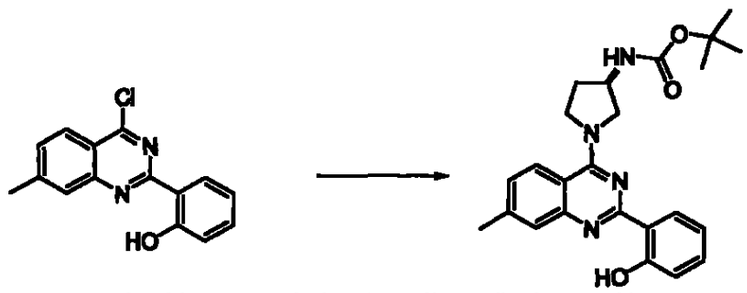
[001553] **(*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

[001554]



[001555] *tert*-Butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

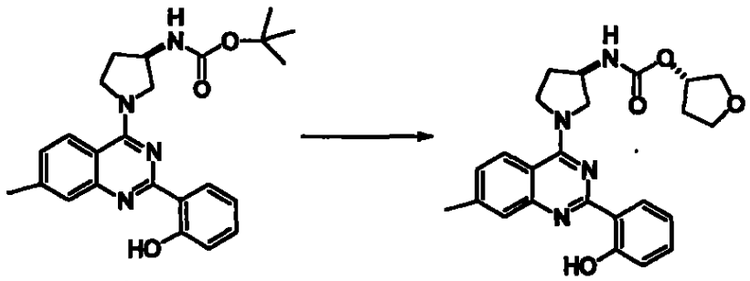
[001556]



[001557] To 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol (644 mg, 2.4 mmol) in 2.9 mL of DMF at room temperature was added sequentially (*R*)- pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (857 mg, 4.6 mmol) and triethylamine (662 μL, 4.8 mmol), and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and dried (Na_2SO_4), and the residue was purified by silica gel chromatography with 25–85% ethyl acetate/hexanes to give *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (856 mg, 86%). LC/MS: *m/z* 421 $(M+H)^+$ at 2.82 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001558] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001559]



[001560] Method A

[001561] To *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (850 mg, 2.02 mmol) was added at room temperature 4 mL of 1:1 TFA:CH_2Cl_2. The reaction mixture was stirred for 50 min, diluted with 20 mL of CH_2Cl_2, and washed with 15 mL of satd. $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4, and the

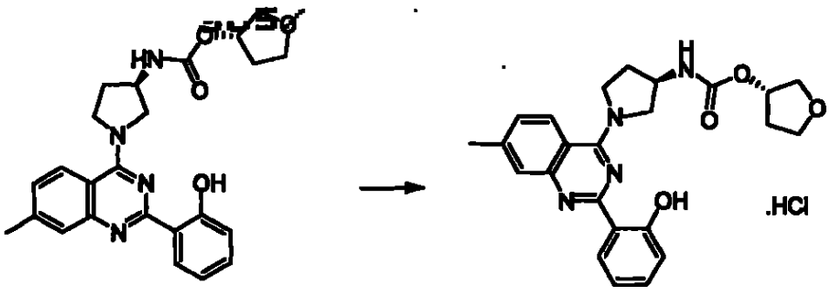
solvent was removed under reduced pressure to give (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol as an oil which was used without further purification.

To 45.9 mg (0.14 mmol) of the amine from above procedure was added 570 μL of CH_2Cl_2 and the solution was cooled to 0 °C. To this solution was added sequentially 24 μL (0.17 mmol) of triethylamine and 19.4 mg (0.13 mmol) of (*S*)- tetrahydro-furan-3-ol chloroformate. The reaction mixture was stirred at 0 °C for 45 min, diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 435 $(M+H)^+$ at 2.41 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001562] Method B

[001563] To *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (907.2 mg, 2.16 mmol) was added 4 mL of 1:1 TFA:CH_2Cl_2. The mixture was stirred at room temperature for 5 hours. The reaction was diluted with a solution of saturated aqueous $NaHCO_3$ and CH_2Cl_2: The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to give 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol. To this free amine (640 mg, 2 mmol) was added 8 ml of CH_2Cl_2 and triethylamine (335 μL, 2.4 mmol). After cooling the mixture to 0 °C, (*S*)-tetrahydrofuran-3-yl chloroformate (271 mg, 1.8 mmol) was added, and the reaction was allowed to stir for 30 minutes. Purification on silica gel using 30–100% ethyl acetate/hexanes gave (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. ^1H NMR (400 MHz, $CDCl_3$) δ 14.8 (bs, 1H), 8.34 (d, J = 6.4 Hz, 1H), 7.83 (d, J = 4.0 Hz, 1H), 7.48 (bs, 1H), 7.27 (m, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 5.21 (s, 1H), 5.06 (s, 1H), 4.37 (s, 1H), 4.15 (m, 1H), 4.02 (s, 1H), 3.97 (d, J = 5.6 Hz, 1H), 3.87–3.77 (m, 5H), 2.42 (s, 3H), 2.24 (t, J = 6.0 Hz, 1H), 2.15–2.06 (m, 1H), 1.98 (q, J = 9.3 Hz, 2H).

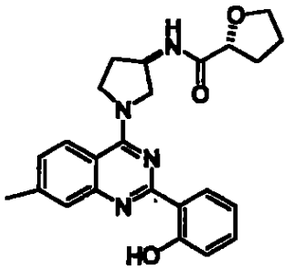
[001564] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride



[001556] A 2.0 M HCl solution in Et_2O (192 μL, 0.38 mmol) was slowly added at –20 °C to a stirring solution of (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (167 mg, 0.38 mmol) in 700 μL of CH_2Cl_2. The reaction was allowed to warm to room temperature and was stirred for 25 minutes. Solvents were removed under reduced pressure, and the residue was triturated with Et_2O and filtered to give (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride. LC/MS: *m/z* 435.2 $(M+H)^+$ at 2.41 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

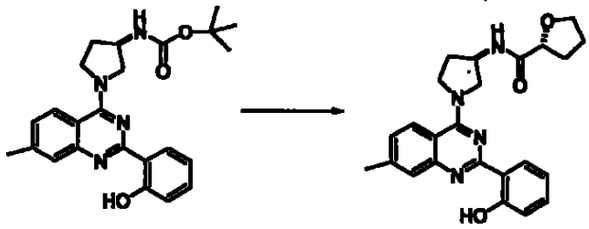
[001557] Example 302

[001558] **(*R,R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide**



[001559] **(*R, R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide.**

[001560]



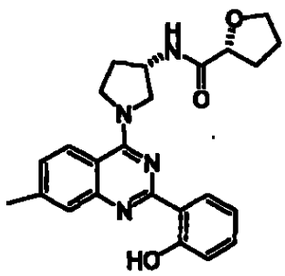
[001572] To 850 mg (2.52 mmol) of (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester was added at room temperature 4 mL of 1:1 TFA: CH_2Cl_2. The reaction mixture was stirred for 50 min and diluted with 20 mL of CH_2Cl_2 and extracted with 15 mL of satd. $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol as an oil which was used without further purification.

To 52.6 mg (0.16 mmol) of the amine from above procedure was added 600 μL of CH_2Cl_2. To this solution was added sequentially 27.4 μL (0.19 mmol) of triethylamine and 20.9 mg (0.18 mmol) of (*R*)- tetrahydro-furan-2-carboxylic acid, 24.2 mg (0.18 mmol) of HOBt, 34.6 mg (0.18 mmol) of EDCI at room temperature. The reaction mixture was stirred for 12 h, then diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*, *R*)-tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide as the TFA salt. *LC/MS*: *m/z* 419 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001573] Example 303

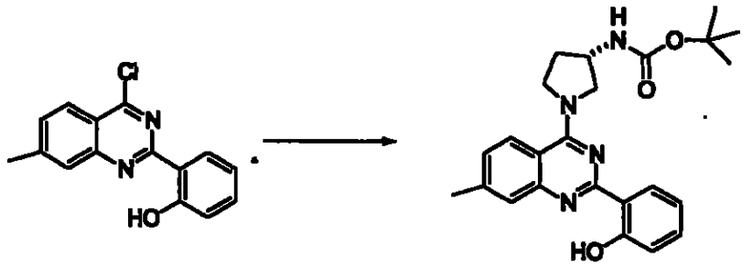
[001574] (2*R*)-Tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)furan-2-carboxamide

[001575]



[001576] (*S*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester

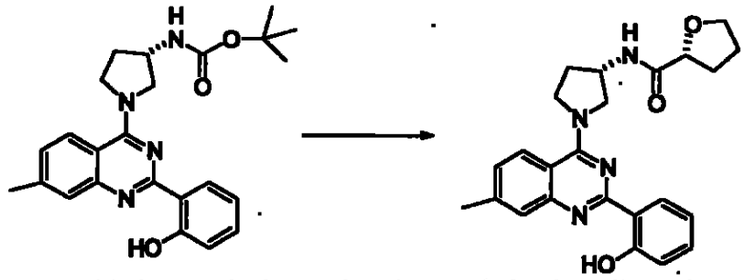
[001577]



[001578] To 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol(551 mg, 2.03 mmol) in 2.5 mL of DMF at room temperature was added sequentially (*S*)- pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (740 mg, 3.9 mmol) and triethylamine (567 μL, 4.0 mmol), and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and dried (Na_2SO_4), and the residue was purified via silica gel chromatography with 25–85% ethyl acetate/hexanes to give of (*S*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (694 mg, 81%). LC/MS: *m/z* 421 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001579] (2*R*)-Tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)furan-2-carboxamide

[001580]



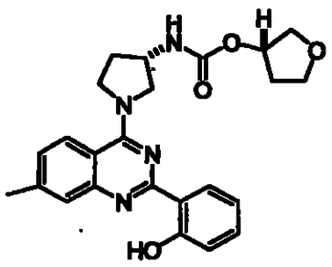
[001581] To (*S*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (690 mg, 1.64 mmol) was added at room temperature 3 mL of 1:1 TFA:CH_2Cl_2. The reaction mixture was stirred for 55 min, diluted with 20 mL of CH_2Cl_2 and washed with 15 mL of satd. $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*S*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol as an oil which was used without further purification.

To the [illegible] mixture (133.3 mg, 0.42 mmol) was added 1.6 mL of CH_2Cl_2. To this solution was added sequentially triethylamine (174 μL, 1.25 mmol) and (*R*)-tetrahydro-furan-2-carboxylic acid (57.9 mg, 0.5 mmol), HOBt (67.5 mg 0.5 mmol), EDCI (95.8 mg 0.5 mmol) at room temperature. The reaction mixture was stirred for 12 h and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (2*R*)-tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 419 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001582] Example 304

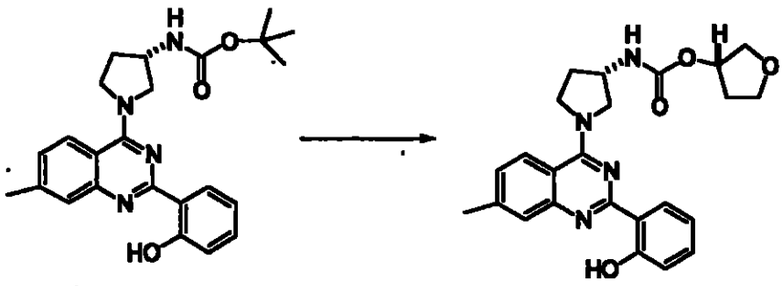
[001583] (*S*, *S*)- {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid tetrahydro-furan-3-yl ester

[001584]



[001585] (*S*, *S*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid tetrahydro-furan-3-yl ester

[001586]



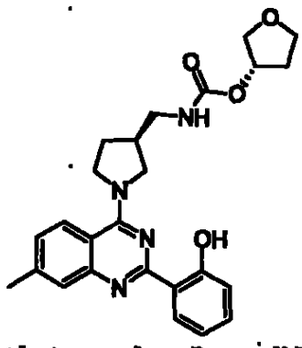
[001587] To (*S*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (690 mg, 1.64 mmol) was added at room temperature, 3 mL of 1:1 TFA:CH_2Cl_2. The reaction mixture was stirred for 55 min, diluted with 20 mL of CH_2Cl_2, and washed with 15 mL of satd. $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*S*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol as an oil which was used without further purification.

To the amine from above procedure (134.7 mg, 0.42 mmol) was added 1.6 mL of CH_2Cl_2, and the solution was cooled to 0 °C. To this solution was added sequentially . triethylamine (88 μL, 0.63 mmol) and (*S*)- tetrahydro-furan-3-ol chloroformate(82.3 mg, 0.55 mmol). The reaction mixture was stirred and allowed to warm from 0 °C to room temperature over 12 h and was diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*S*, *S*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid tetrahydro-furan-3-yl ester as the.TFA salt. LC/MS: *m/z* 435 $(M+H)^+$ at 2.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001588] Example 305

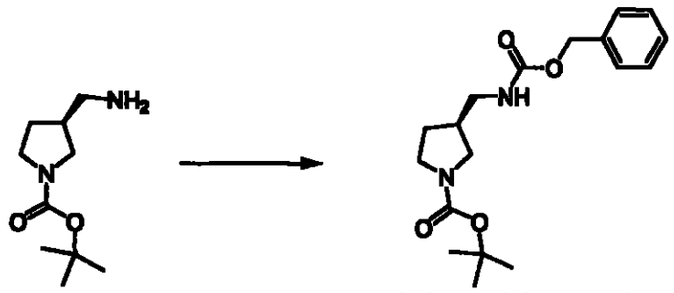
[001589] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001590]



[001591] Benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate

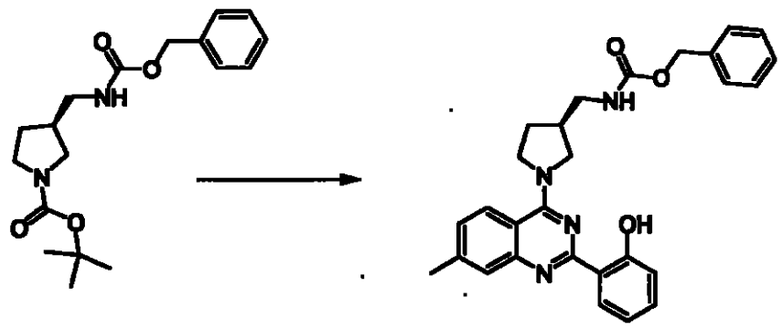
[001592]



[001593] A mixture of (*S*)-*tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (1.0 g, 5.0 mmol) and 50 mL THF was cooled in an ice bath. To this was added benzyl chloroformate (0.77 mL, 5.5 mmol), followed by triethylamine (1.39 mL, 10 mmol). After removing the ice bath, the reaction was stirred for 4 h. The mixture was poured into ice water and extracted with EtOAc. The organic extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using EtOAc in hexanes (0–40%) gave benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.29 g, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.10 (s, 2H), 4.87 (s, 1H), 3.52–2.95 (m, 6H), 2.41–2.35 (m, 1H), 2.10—1.79 (m, 2H), 1.45 (s, 9H).

[001594] **Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[001595]



[001596] A solution of benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (0.20 g, 0.60 mmol) and 4 M HCl in dioxane (10 mL) was stirred for 3 h at room temperature. After evaporating the solvent under reduced pressure, the solid was triturated with Et_2O and dried under vacuum, then taken up in CH_2Cl_2 (10 mL). To this solution was added 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.16 g, 0.60 mmol) and triethylamine (0.25 mL, 1.8 mmol).

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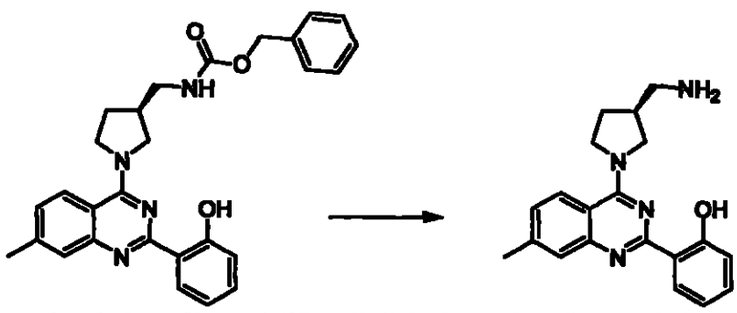
The reaction mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 and washed with water. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in hexanes gave benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as a colorless oil (0.19 g, 68%). LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001597] **2-(4-((*S*)-3-(Aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol**

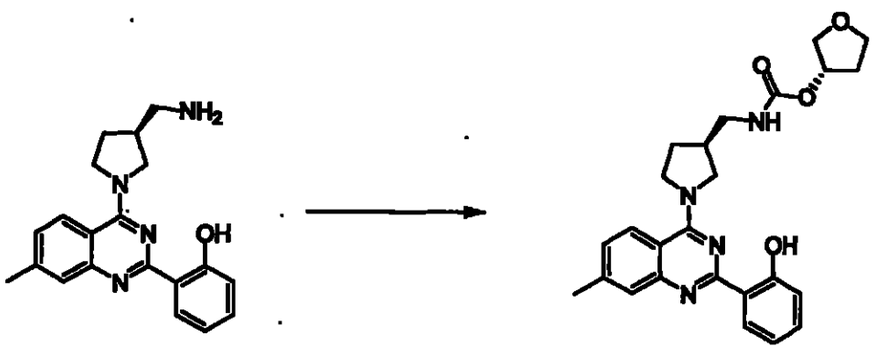
[001598]



[001599] A solution of benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.19 g, 0.41 mmol) and MeOH (5 mL) was stirred with Pd/C (20 mg, 10% weight of Pd on carbon) under an H_2 atmosphere at ambient pressure at ambient pressure overnight. Purification via silica gel chromatography using MeOH in CH_2Cl_2 (0–10%) gave 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (27 mg, 19%). LC/MS: *m/z* 335.5 $(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001600] **(*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[001601]

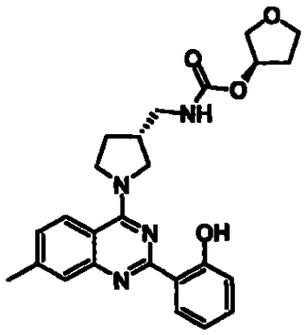


[001602] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (13 mg, 0.04 mmol) and CH_2Cl_2 (0.5 mL) was cooled in an ice bath. To this mixture was added (*S*)-tetrahydrofuran-3-yl chloroformate (6 μL, 0.04 mmol), followed by triethylamine (11 μL, 0.08 mmol). After removing the ice bath, the reaction was stirred for 3 h at room temperature. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001603] Example 306

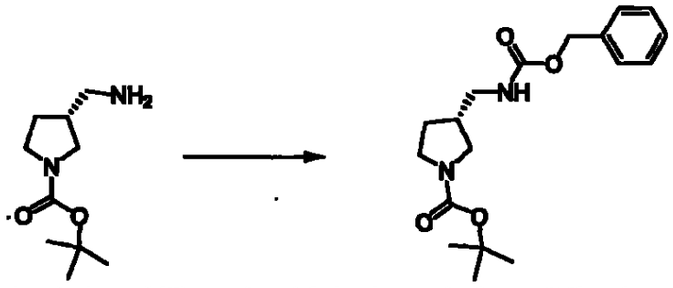
[001604] (*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001605]



[001606] Benzyl ((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate

[001607]

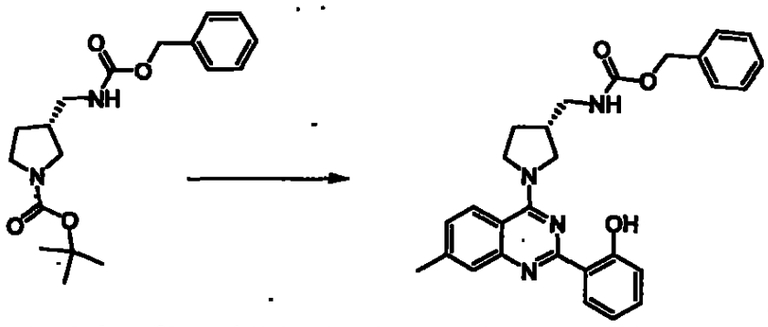


[001608] A solution of (*R*)-*tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (1.0 g, 5.0 mmol) and 50 mL THF was cooled in an ice bath. To this mixture was added benzyl

chloroformate (0.77 mL, 5.5 mmol), followed by triethylamine (1.39 mL, 10 mmol). After removing the ice bath, the reaction was stirred for 4 h. The mixture was poured into ice water and extracted with EtOAc. The organic extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using EtOAc in hexanes (0–40%) gave benzyl ((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.29 g, 77%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.10 (s, 2H), 4.87 (s, 1H), 3.52–2.95 (m, 6H), 2.41–2.35 (m, 1H), 2.10—1.79 (m, 2H), 1.45 (s, 9H).

[001609] **Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

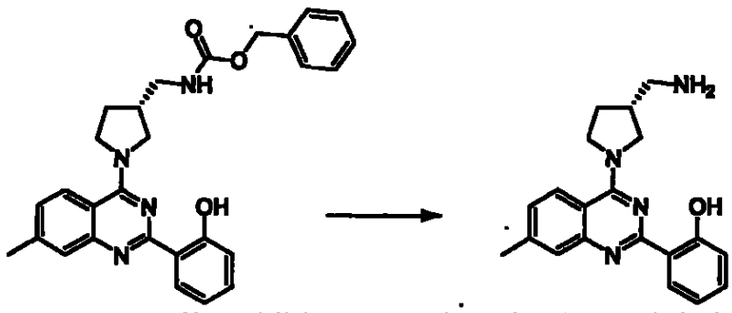
[001610]



[001611] A solution of benzyl ((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (0.20 g, 0.60 mmol) and 4 M HCl in dioxane (10 mL) was stirred for 3 h at room temperature. After evaporating the solvent under reduced pressure, the resulting solid was triturated with Et_2O and dried under vacuum, then taken up in CH_2Cl_2 (10 mL). To this solution was added 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.16 g, 0.60 mmol) and triethylamine (0.25 mL, 1.8 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 and washed with water. The CH_2Cl_2 solution was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in hexanes gave benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as a colorless oil (0.19 g, 68%). LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001612] **2-(4-((*R*)-3-(Aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol**

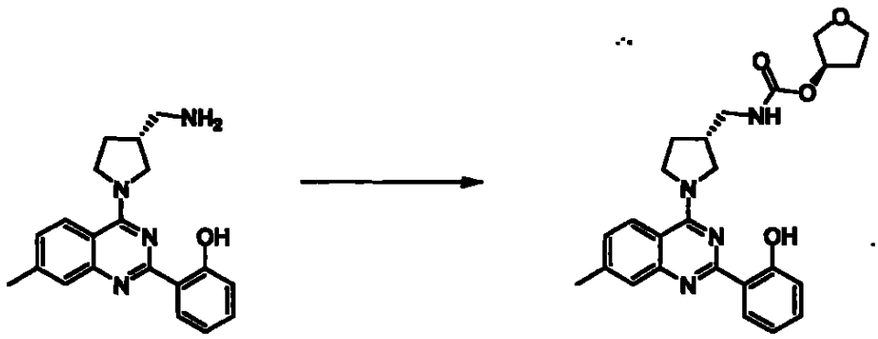
[001613]



[001614] A solution of benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.19 g, 0.41 mmol) and MeOH (5 mL) was stirred with Pd/C (20 mg, 10% weight of Pd on carbon) under an H_2 atmosphere at ambient pressure overnight. Purification via silica gel chromatography using MeOH in CH_2Cl_2 (0–10%) gave 2-(4-((*R*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (63 mg, 45%). LC/MS: *m/z* 335.7 $(M+H)^+$ at 1.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001615] (*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001616]



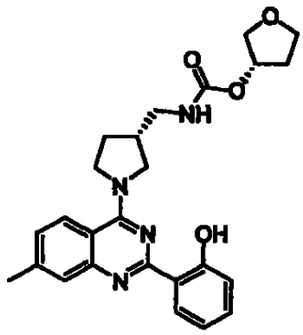
[001617] A solution of 2-(4-((*R*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (15 mg, 0.045 mmol) and CH_2Cl_2 (0.5 mL) was cooled in an ice bath. To this mixture was added (*R*)-tetrahydrofuran-3-yl chloroformate (7 μL, 0.045 mmol), followed by triethylamine (13 μL, 0.090 mmol). After removing the ice bath, the reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-

methylquinazolin-4-yl)pyrrolidin-3-yl]methylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001618] Example 307

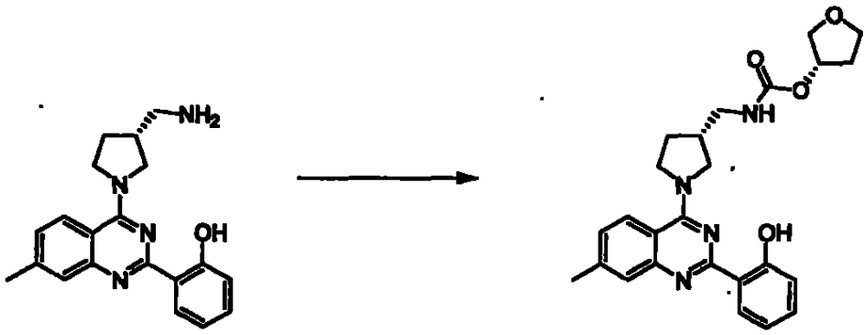
[001619] (*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001620]



[001621] (*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001622]



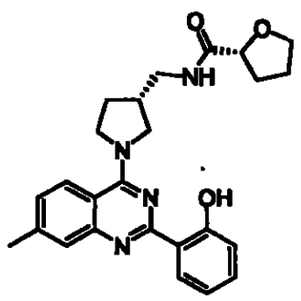
[001623] A mixture of 2-(4-((*R*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (15 mg, 0.045 mmol) and CH_2Cl_2 (0.5 mL) was cooled in an ice bath. To this was added (*S*)-tetrahydrofuran-3-yl chloroformate (7 μL, 0.045 mmol), followed by triethylamine (13 μL, 0.090 mmol). After removing the ice bath, the reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-

yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001624]. Example 308

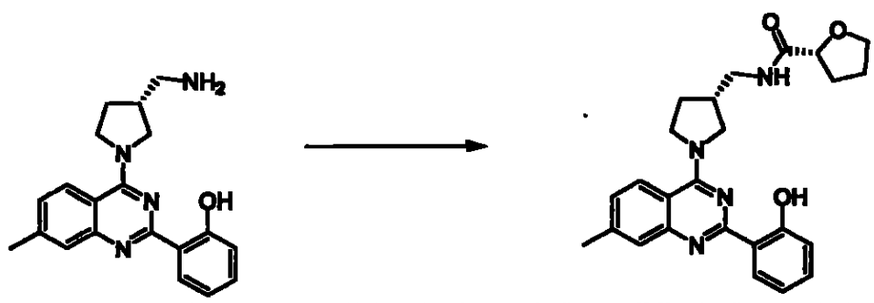
[001625] (2*R*)-Tetrahydro-*N*-(((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide

[001626]



[001627] (2*R*)-Tetrahydro-*N*-(((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide

[001628]



[001629] To a solution of 2-(4-((*R*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (15 mg, 0.045 mmol) and DMF (0.5 mL) was added (*R*)-tetrahydrofuran-2-carboxylic acid (6 μL, 0.062 mmol), followed by the addition of HATU (26 mg, 67 mmol) and triethylamine (13 μL, 0.090 mmol). The reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-tetrahydro-*N*-(((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 433.5 $(M+H)^+$ at 2.11 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001630] Example 309

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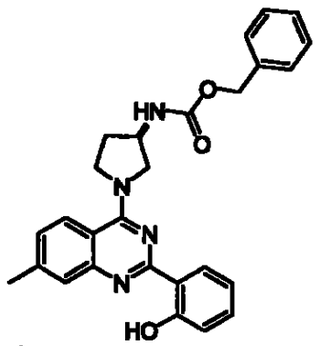
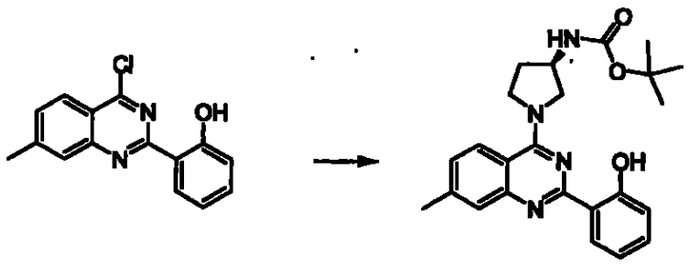
[001631] (3*R*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid benzyl ester

[001632]



[001633] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3*R*-yl}-carbamic acid *tert*-butyl ester

[001634]

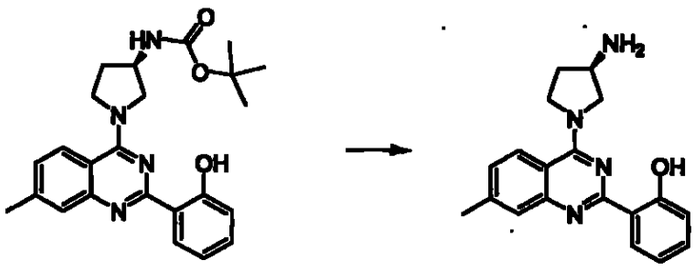


[001635] To a cooled (–15 °C) solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (43.8 g, 0.15 mol) in CH_2Cl_2 (125 mL) was added dropwise a solution of (3*R*)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine (30 g, 0.16 mol) and triethylamine (38 mL, 0.27 mol) in CH_2Cl_2 (170 mL). The addition, during which the temperature stayed below 30 °C, was completed in 20 minutes. The external cooling was removed and the reaction mixture was stirred at room temperature overnight. Water (1 L) and CH_2Cl_2 (1 L) were added. The resulting precipitate was collected by filtration, washed with water and CH_2Cl_2, and air-dried to yield 33 g of pure {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3*R*-yl}-carbamic acid *tert*-butyl ester. The filtrates were evaporated to give another batch of crude {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3*R*-yl}-carbamic acid *tert*-butyl ester which was purified by trituration with CH_2Cl_2. Total yield: 43.5 g (70%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ

8.45 (dd, J = 8.5 Hz, 1.7 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.57 (s, 1H), 7.37–7.31 (m, 1H), 7.18 (dd, J = 8.5 Hz, 1.7, 1H), 7.0 (dd, J = 8.3 Hz, 1.1 Hz, 1H), 6.9 (dt, J = 8.9 Hz, 1.4 Hz, 1H), 4.77 (bs, 1H), 4.40 (bs, 1H), 4.27–4.21 (m, 1H), 4.14–4.03 (m, 2H), 3.86 (dd, J = 11.8 Hz, 4.4 Hz, 1H), 2.50 (s, 3H), 2.34–2.28 (m, 1H), 2.08–2.02 (m, 1H), 1.46 (s, 9H) ppm.

[001636] **2-(4-(3*R*-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol**

[001637]

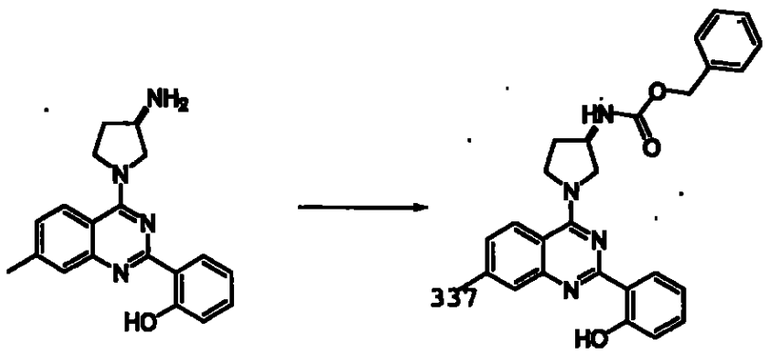


[001638] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3*R*-yl}-carbamic acid *tert*-butyl ester (43.5 g, 100 mmol) was stirred with CF_3CO_2H (142 mL) in CH_2Cl_2 (300 mL) at room temperature overnight. The solution was concentrated to dryness, and the residue was suspended in 10% aq. Na_2CO_3 (900 mL) and stirred for 2 hours. The suspension was filtered, and the yellow solid was washed with water several times. The product was air-dried at 45 °C to yield 2-(4-(3*R*-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (34.2 g) as a light-yellow solid. ^{1}H-NMR (300 MHz, CD_3OD): δ 8.41 (dd, J = 7.4 Hz, 1.4 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.34–7.28 (m, 1H), 7.23 (dd, J = 8.8 Hz, 1.9 Hz, 1H), 6.91–6.85 (m, 2H), 4.16–4.09 (m, 2H), 4.00–3.94 (m, 1H), 3.73–3.64 (m, 2H), 2.48 (s, 3H), 2.26–2.20 (m, 1H), 1.92–1.86 (m, 1H) ppm.

[001639] **(*R*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid benzyl ester**

[001640] Method A

[001641]



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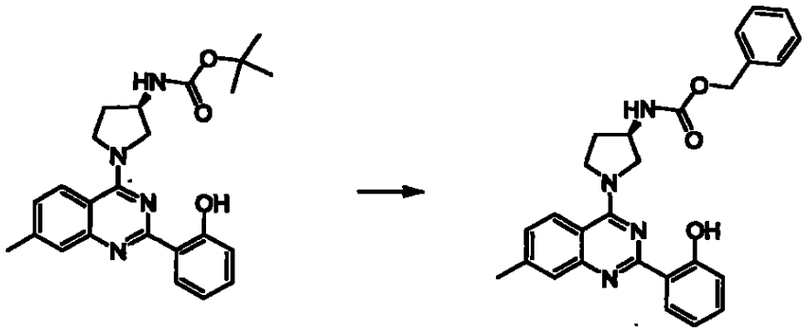
[001642] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (50.8 mg, 0.16 mmol) was added 500 μL of CH_2Cl_2 and the solution was cooled to 0 °C. To this solution was added sequentially triethylamine (33.2 μL, 0.24 mmol) and benzyl chloroformate (29.2 mg, 0.17 mmol). The reaction mixture was stirred from 0 °C to 5 °C over 45 min, then diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid benzyl ester. LC/MS: *m/z* 455.2 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001643] Method B

[001644] **Benzyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

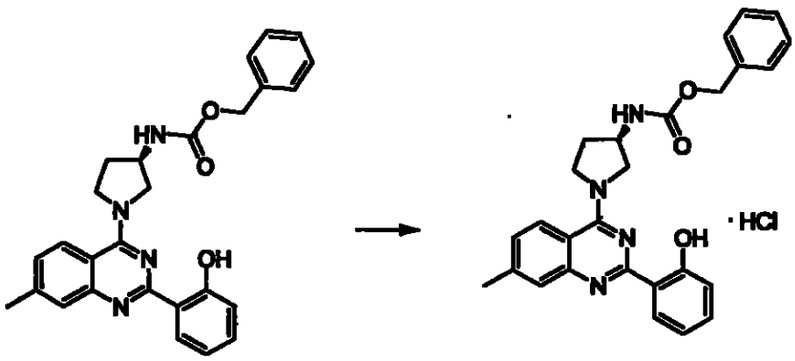
[001645]



[001646] To *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (398 mg, 0.94 mmol) was added 3 mL of 1:1 TFA: CH_2Cl_2. The mixture was then stirred at room temperature for 30 minutes. The reaction mixture was diluted with a solution of saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, washed with a solution of extracted 1 N NaOH, dried over Na_2SO_4 and evaporated under reduced pressure to give the intermediate amine. To this amine (300 mg, 0.94 mmol) were added 3 ml of CH_2Cl_2 and triethylamine (145 μL, 1.04 mmol). After cooling the mixture to 0 °C, benzyl chloroformate (161.6 mg, 0.94 mmol) was added, and the reaction was stirred for 30 minutes. Purification via silica gel chromatography using 20–100% ethyl acetate/hexanes gave benzyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 455.2 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001647] (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride

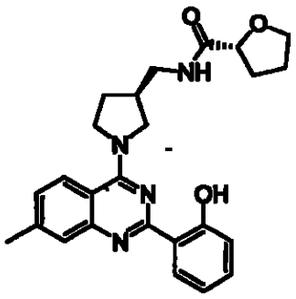
[001648]



[001649] A 2.0 M HCl solution in Et_2O (318 μL, 0.636 mmol) was slowly added to a stirring solution of benzyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (289 mg, 0.636 mmol) in 2.1 mL of CH_2Cl_2. Solvents were removed under reduced pressure and the residue was triturated with Et_2O and filtered to give benzyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride. LC/MS: *m/z* 455.2 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

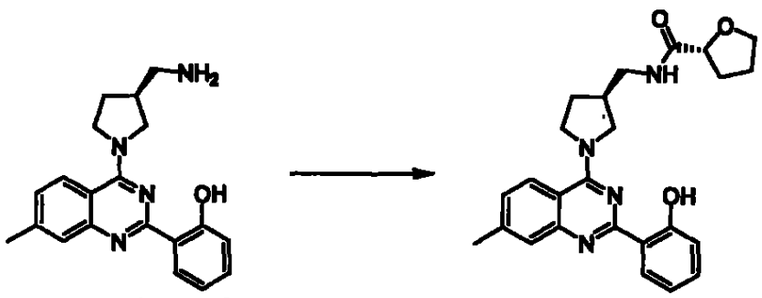
[001650] Example 310

[001651] (2*R*)-Tetrahydro-*N*-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide



[001652] (2*R*)-Tetrahydro-*N*-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide

[001653]

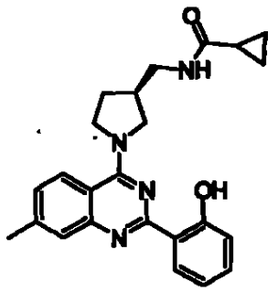


[001654] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) and DMF (0.5 mL) was added (*R*)-tetrahydrofuran-2-carboxylic acid (8.6 μL, 0.09 mmol), followed by the addition of HATU (34 mg, 0.09 mmol) and triethylamine (21 μL, 0.15 mmol). The reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-tetrahydro-*N*-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide as the TFA salt. *LC/MS*: *m/z* 433.5 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

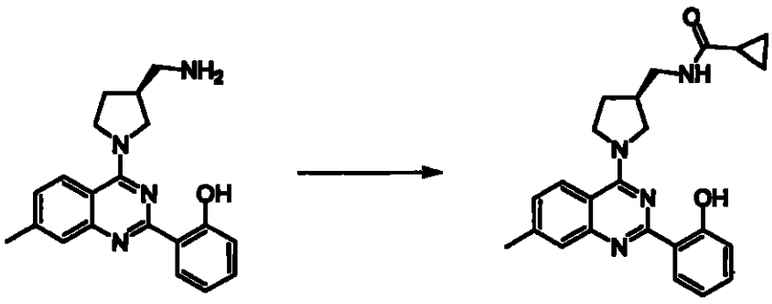
[001655] Example 311

[001656] ***N*-(((*S*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide**

[001657]



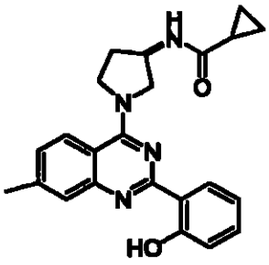
[001658] ***N*-(((*S*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide**



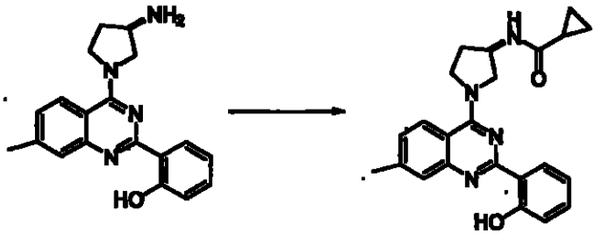
[001648] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) and CH_2Cl_2 (0.5 mL) was cooled in an ice bath. To this mixture was added cyclopropanecarbonyl chloride (7.5 μL, 82 mmol), followed by triethylamine (21 μL, 0.15 mmol). After removing the ice bath, the reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave *N*-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 403.7 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001649] Example 312

[001650] **(*R*)-Cyclopropanecarboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide**



[001651] **(*R*)-Cyclopropanecarboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide.**



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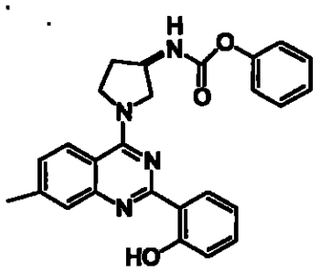
[001666] [illegible]rolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (49.3 mg, 0.15 mmol) was added 500 μL of CH_2Cl_2 and the solution was cooled to 0 °C. To this solution was added sequentially triethylamine (21.5 μL, 0.15 mmol) and cyclopropanecarbonyl chloride (16.1 mg, 0.15 mmol). The reaction mixture was stirred from 0 °C to 5 °C over 40 min and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-cyclopropanecarboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide as the TFA salt. LC/MS: *m/z* 389 $(M+H)^+$ at 2.38 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001667] Example 313

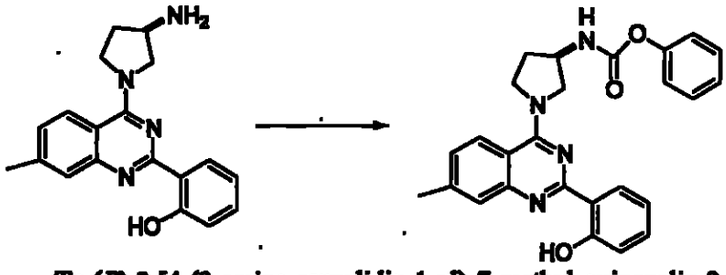
[001668] **(*R*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid phenyl ester**

[001669]



[001670] **(*R*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid phenyl ester.**

[001671]



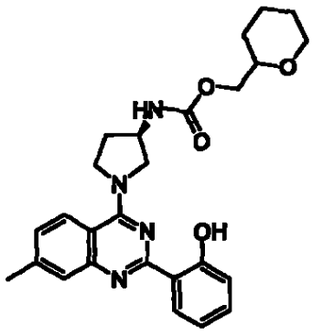
[001672] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (48 mg, 0.15 mmol) was added 500 μL of CH_2Cl_2, and the solution was cooled to 0 °C. To this solution

was added sequentially triethylamine (21 μL, 0.15 mmol) and phenyl chloroformate (22.8 mg, 0.15 mmol). The reaction mixture was stirred from 0 °C to 5 °C over 40 min, diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid phenyl ester as the TFA salt. LC/MS: *m/z* 441 $(M+H)^+$ at 2.78 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001673] Example 314

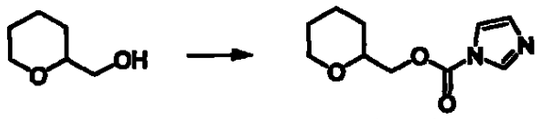
[001674] **(Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

[001675]



[001676] **(Tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate**

[001677]

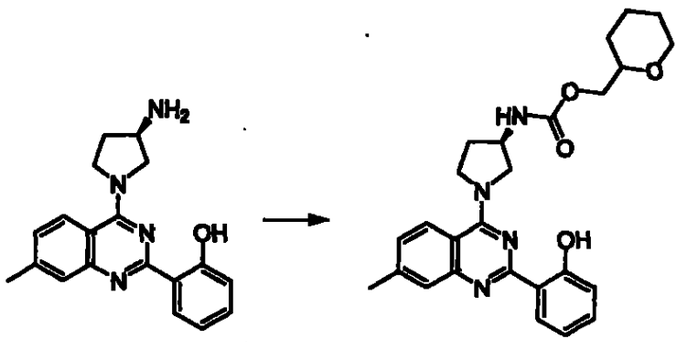


[001678] To a mixture of (tetrahydro-2*H*-pyran-2-yl)methanol (369 mg, 3.17 mmol) and di(1*H*-imidazol-1-yl)methanone (1.03 g, 6.35 mmol) was added 10.5 mL of CH_2Cl_2. The reaction was stirred at 50 °C for 3 hours. The reaction mixture was used without further purification. LC/MS: *m/z* 211.1 $(M+H)^+$ at 0.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001679] **(Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

181

[001680]

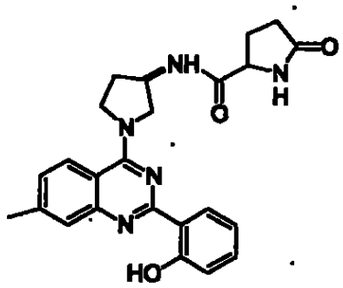


[001681] To a mixture of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (100 mg, 0.31 mmol) and (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (98 mg, 0.47 mmol) was added 1.04 mL CH_2Cl_2 and triethylamine (65 μL, 47 mg, 0.46 mmol). The mixture was stirred at room temperature overnight. An additional equivalent of (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (100 mg, 0.47 mmol) was added to the mixture, and the reaction was heated at 45 °C for 4 hours. Purification via silica gel chromatography using 10%–100% ethyl acetate/hexanes gave (tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 463.4 $(M+H)^+$ at 2.66 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001682] Example 315

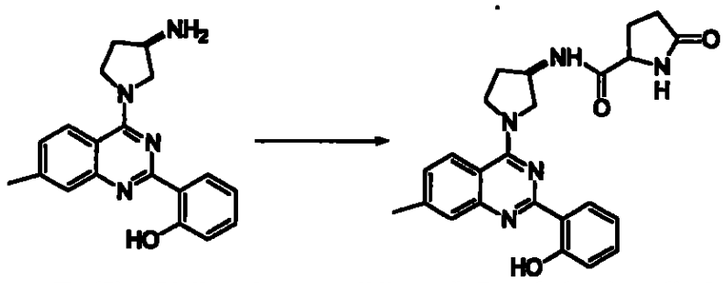
[001683] (*R*)-5-Oxo-pyrrolidine-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide

[001684]



[001685] (*R*)-5-Oxo-pyrrolidine-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide

[001686]

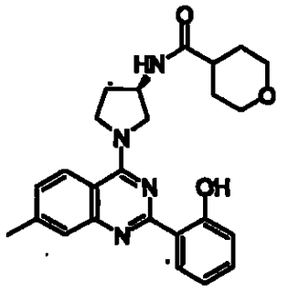


[001687] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (71 mg, 0.22 mmol) was added 890 μL of CH_2Cl_2. To this solution was added sequentially triethylamine (47 μL, 0.34 mmol) and 5-oxo-pyrrolidine-2-carboxylic acid (34.8 mg, 0.27 mmol) and BOP (119 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 2 h and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*R*)-5-oxo-pyrrolidine-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide. LC/MS: *m/z* 432.5 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001688] Example 316

[001689] Tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2*H*-pyran-4-carboxamide

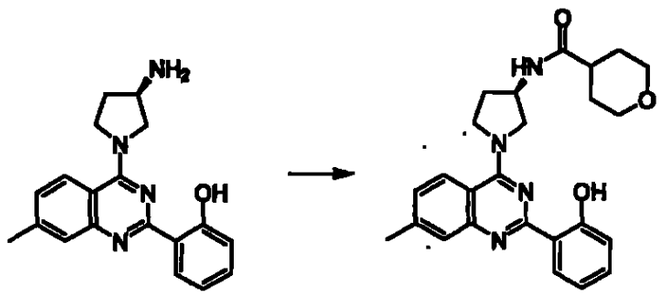
[001690]



[001691] Tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2*H*-pyran-4-carboxamide

182

[001692]

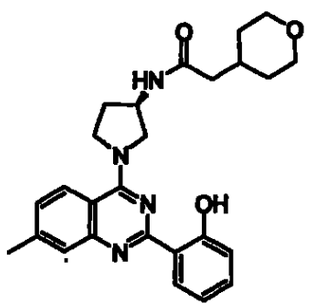


[001693] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in 1 mL of DMF was cooled to 0 °C and tetrahydro-2*H*-pyran-4-carboxylic acid (24 mg, 0.19 mmol) was added, followed by the addition of triethylamine (32 mg, 44 μL, 0.31 mmol) and HATU (71.1 mg, 0.187 mmol). The reaction was stirred at 0 °C for 10 minutes, then gradually warmed to room temperature, then filtered. Purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2*H*-pyran-4-carboxamide as the TFA salt. *LC/MS*: *m/z* 433.5 $(M+H)^+$ at 2.05 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001694] Example 317

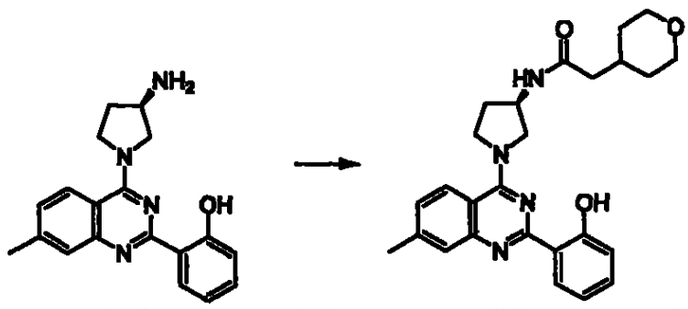
[001695] **2-(Tetrahydro-2*H*-pyran-4-yl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide**

[001696]



[001697] **2-(Tetrahydro-2*H*-pyran-4-yl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide**

[001698]

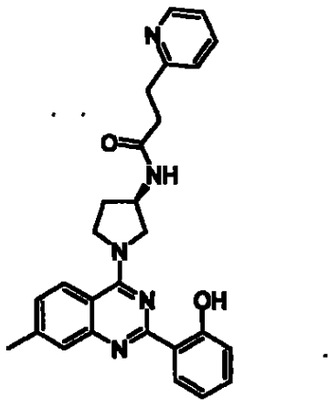


[001699] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in 1 mL of DMF cooled to 0 °C was added 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (27 mg, 0.19 mmol), followed by the addition of triethylamine (32 mg, 44 μL, 0.31 mmol) and HATU (71.1 mg, 0.187 mmol). The reaction was stirred at 0 °C for 10 minutes, then gradually warmed to room temperature. Filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 2-(tetrahydro-2*H*-pyran-4-yl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide as the TFA salt. LC/MS: *m/z* 477.3 $(M+H)^+$ at 2.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001700] Example 318

[001701] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-2-yl)propanamide

[001702]



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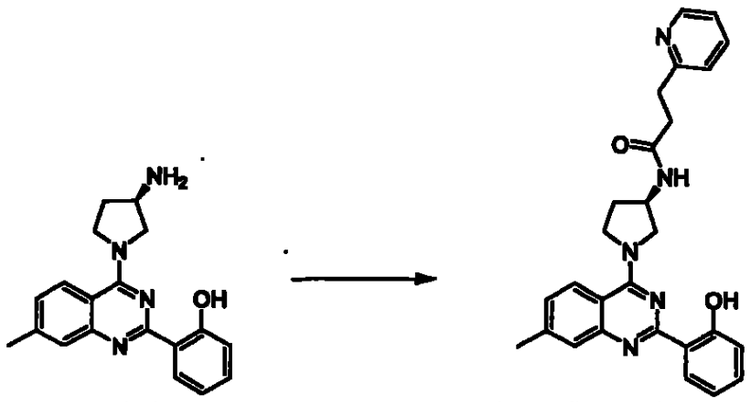
[001703] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-2-yl)propanamide

[001704]

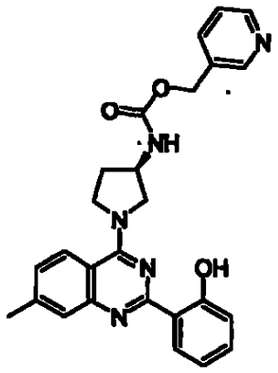


[001705] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.05 g, 0.15 mmol) in DMF (1 mL) was added 3-(pyridin-2-yl)propanoic acid (30 mg, 0.195 mmol), followed by the addition of triethylamine (42 μL, 0.30 mmol) and HATU (74 mg, 0.195 mmol). The reaction was stirred at room temperature for 2 h and then purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-2-yl)propanamide as the TFA salt. LC/MS: *m/z* 454.3 $(M+H)^+$ at 1.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001706] Example 319

[001707] (Pyridin-3-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

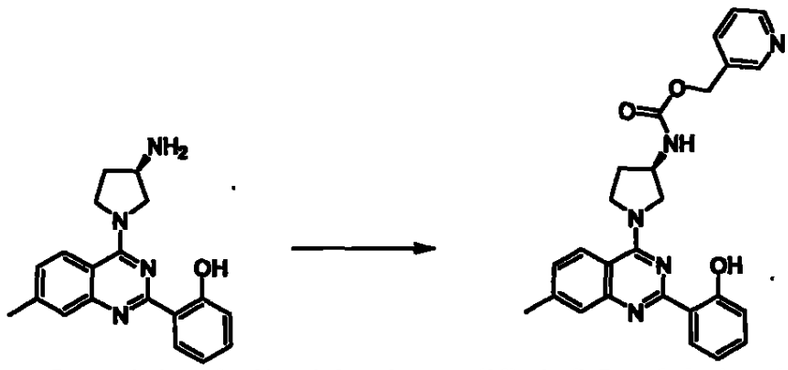
[001708]



[001709] [illegible]

yl)pyrrolidin-3-ylcarbamate

[001710]

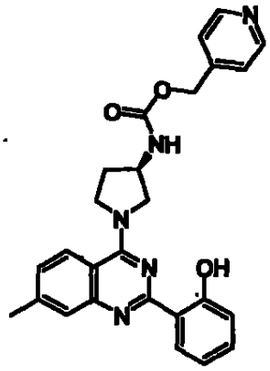


[001711] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) at room temperature was added triethylamine (43 μL, 0.31 mmol), followed by the addition of (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (63 mg, 0.31 mmol). The reaction was stirred at room temperature overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (pyridin-3-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 456.5 $(M+H)^+$ at 1.85 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001712] Example 320

[001713] (Pyridin-4-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001714]



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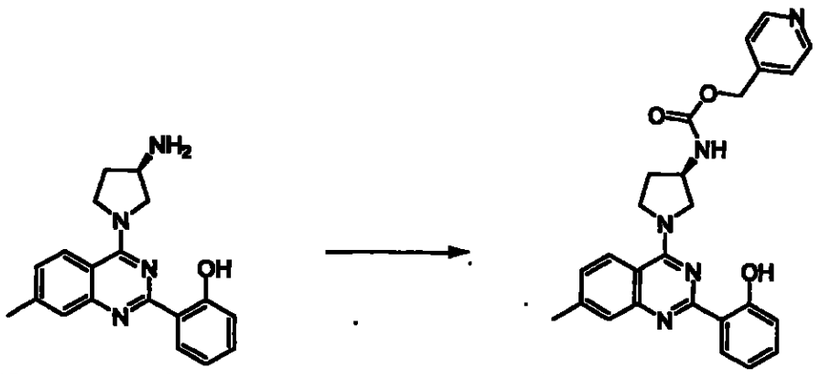
[001715] (Pyridin-4-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001716]

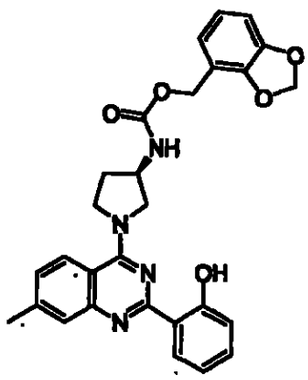


[001717] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) at room temperature was added triethylamine (43 μL, 0.31 mmol), followed by the addition of (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (63 mg, 0.31 mmol). The reaction was stirred at room temperature overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (pyridin-4-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 456.5 $(M+H)^+$ at 1.84 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001718] Example 321

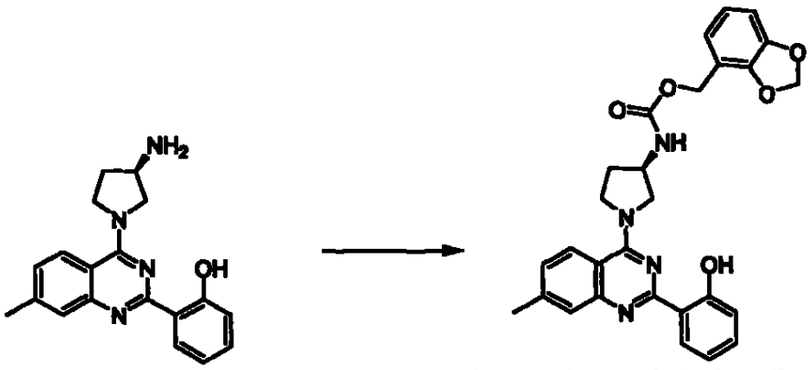
[001719] (Benzo[d][1,3]dioxol-7-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001720]



[001721] (benzo[d][1,3]dioxol-4-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001722]

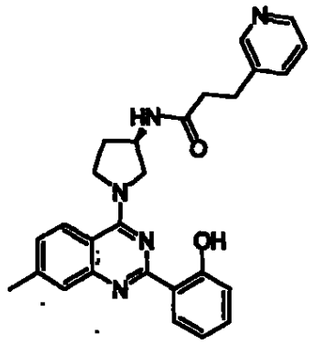


[001723] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) was added triethylamine (43 µl, 0.31 mmol), followed by the addition of (benzo[d][1,3]dioxol-4-yl)methyl 1*H*-imidazole-1-carboxylate (77 mg, 0.31 mmol). The reaction was stirred at room temperature overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (benzo[d][1,3]dioxol-7-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. *LC/MS*: *m/z* 499.3 $(M+H)^+$ at 2.57 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001724] Example 322

[001725] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-3-yl)propanamide

[001726]



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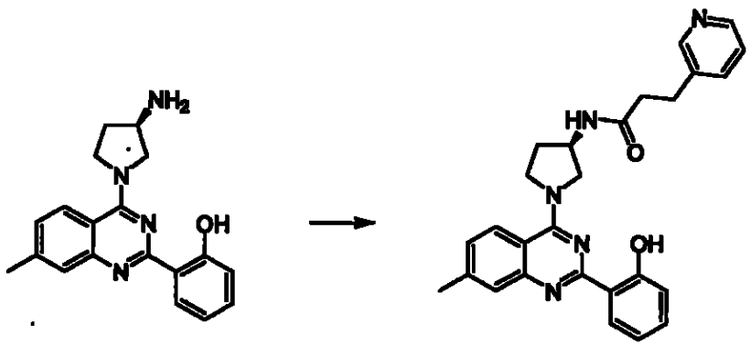
[001727] N-((R)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-3-yl)propanamide

[001728]

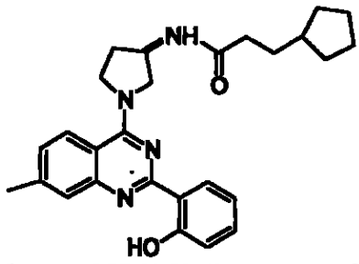


[001729] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (249 mg, 0.778 mmol) was dissolved in 2.6 mL of CH_2Cl_2. 3-(Pyridin-3-yl)propanoic acid (129 mg, 0.85 mmol) was added followed by triethylamine (102 mg, 141 μL, 1.01 mmol) and BOP (378 mg, 0.85 mmol). After stirring the reaction for 35 minutes at room temperature, it was filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-3-yl)propanamide as the TFA salt. LC/MS: *m/z* 454.4 $(M+H)^+$ at 2.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001730] Example 323

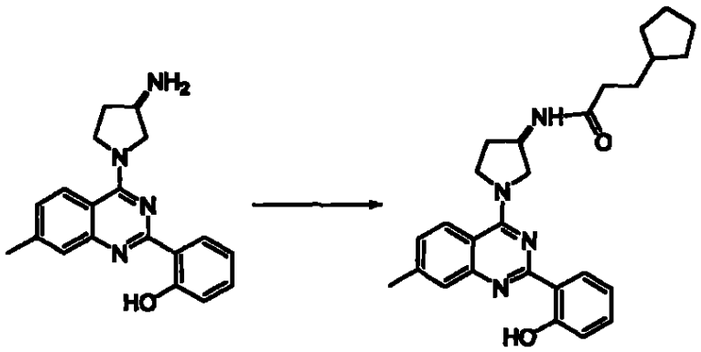
[001731] (*R*)-3-Cyclopentyl-N-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-propionamide

[001732]



[001733] (*R*)-3-Cyclopentyl-N-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-propionamide

[001734]

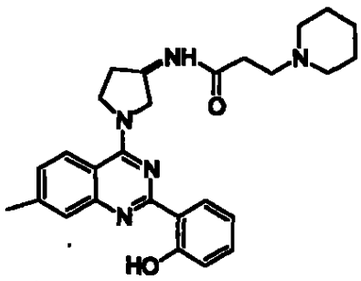


[001735] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (100 mg, 0.31 mmol) was added 1 mL of CH_2Cl_2, and the solution was cooled to 0 °C. To this solution was added sequentially triethylamine (56.6 µL, 0.41 mmol) and 3-cyclopentyl-propionyl chloride (57 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 2 h, then diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give ((*R*)-3-cyclopentyl-*N*-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-propionamide as the TFA salt. *LC/MS*: *m/z* 445.4 $(M+H)^+$ at 2.85 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001736] Example 324

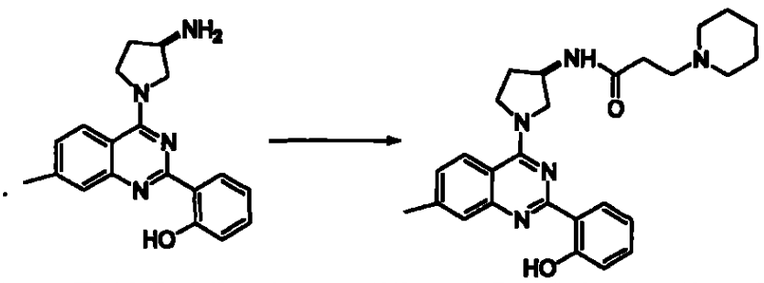
[001737] (*R*)-N-{1-[2-(2-Hydroxy-phenyl)-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide

[001738]



[001739] (*R*)-N-{1-[2-(2-Hydroxy-phenyl)-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide

[001740]

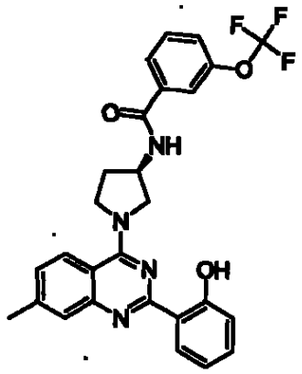


[001741] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (58.6 mg, 0.18 mmol) was added 700 μL of CH_2Cl_2. To this solution was added sequentially triethylamine (38.3 μL, 0.27 mmol), 3-piperidin-1-yl-propionic acid (37.4 mg, 0.24 mmol) and BOP (119 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 2 h and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-*N*-{1-[2-(2-hydroxy-phenyl)-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide as the TFA salt. LC/MS: *m/z* 460.4 $(M+H)^+$ at 2.1 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001742] Example 325

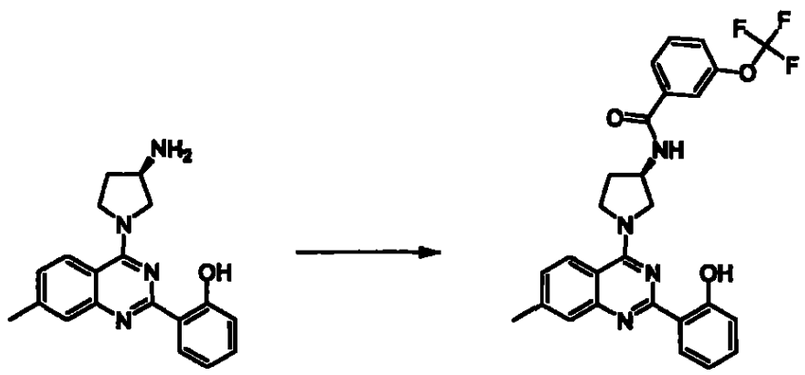
[001743] ***N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(trifluoromethoxy)benzamide**

[001744]



[001745] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(trifluoromethoxy)benzamide

[001746]

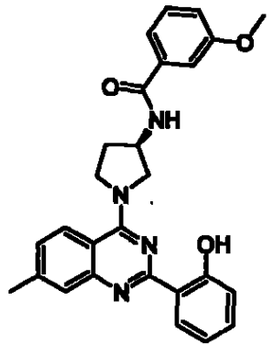


[001747] To a stirring solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (32 mg, 0.10 mmol) and DMF (1.0 mL) was added 3-(trifluoromethoxy)benzoyl chloride (19 μL, 0.10 mmol), followed by the addition of triethylamine (28 μL, 0.2 mmol). The reaction was stirred at room temperature overnight, filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(trifluoromethoxy)benzamide as the TFA salt. LC/MS: *m/z* 509.5 $(M+H)^+$ at 2.71 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001748] Example 326

[001749] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-methoxybenzamide

[001750]



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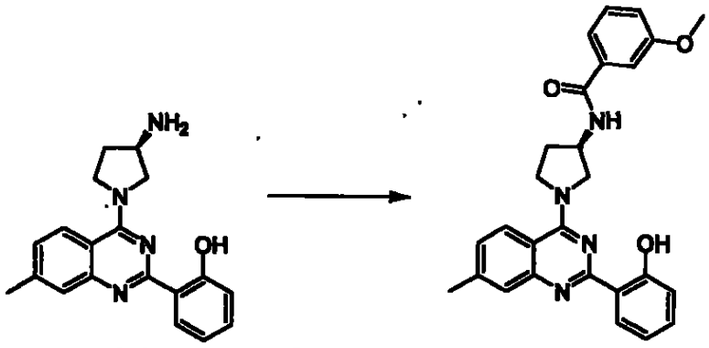
[001751] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-methoxybenzamide

[001752]

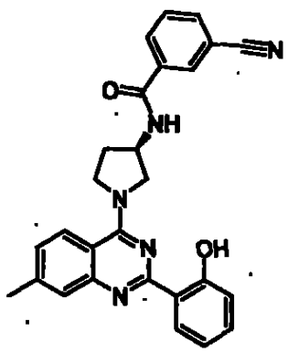


[001753] To a stirring solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (32 mg, 0.10 mmol) and DMF (1.0 mL) was added 3-methoxybenzoyl chloride (14 μL, 0.1 mmol), followed by the addition of triethylamine (28 μL, 0.2 mmol). The reaction was stirred at room temperature overnight, then filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-methoxybenzamide as the TFA salt. LC/MS: *m/z* 455.3 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001754] Example 327

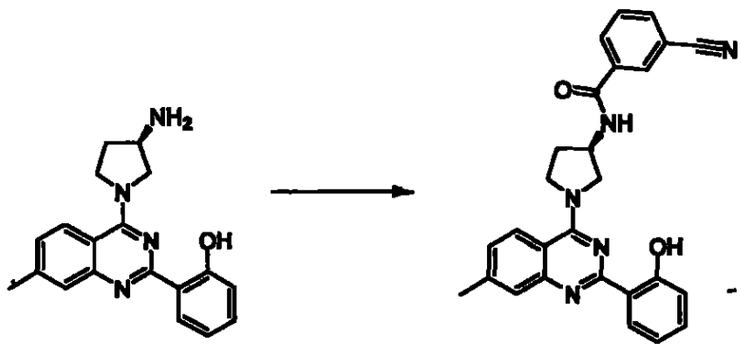
[001755] 3-Cyano-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001756]



[001757] 3-Cyano-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001758]

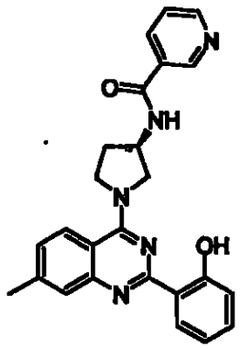


[001759] To a stirring solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (32 mg, 0.10 mmol) and DMF (1.0 mL) was added 3-cyanobenzoyl chloride (17 mg, 0.10 mmol), followed by the addition of triethylamine (28 μL, 0.20 mmol). The reaction was stirred at room temperature overnight, then filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-cyano-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 450.3 $(M+H)^+$ at 2.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001760] Example 328

[001761] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001762]



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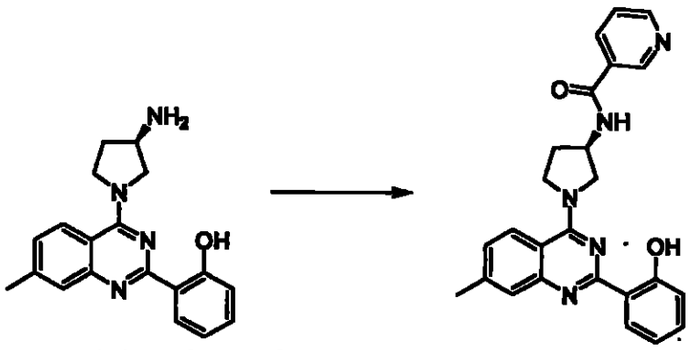
[001763] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001764]

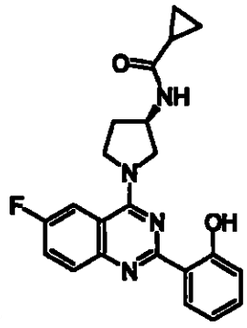


[001765] To a stirring solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (32 mg, 0.1 mmol) and DMF (1.0 mL) was added nicotinoyl chloride (18 mg, 0.1 mmol), followed by the addition of triethylamine (28 μL, 0.2 mmol). The reaction was stirred at room temperature overnight, then filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide as the TFA salt. *LC/MS*: *m/z* 426.3 $(M+H)^+$ at 1.91 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001766] Example 329

[001767] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001768]



[001769] Method A

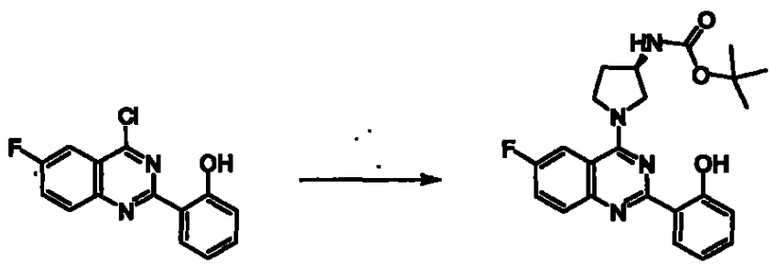
[001770] 2-(4-Chloro-6-fluoroquinazolin-2-yl)phenol

[001771]

[001772] A solution of 4-chloro-6-fluoro-2-(2-methoxyphenyl)quinazoline (3.0 g, 10.39 mmol) in CH_2Cl_2 (15 mL) was cooled to –78 °C. To it was added a 1.0 M BBr_3 solution in CH_2Cl_2 (52 mL, 52 mmol) dropwise. The reaction was allowed to warm to room temperature. It was neutralized with a saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 5–20% CH_2Cl_2/hexanes gave 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (1.68 g, 60%). LC/MS: *m/z* 275.3 $(M+H)^+$ at 3.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001773] ***tert*-Butyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate**

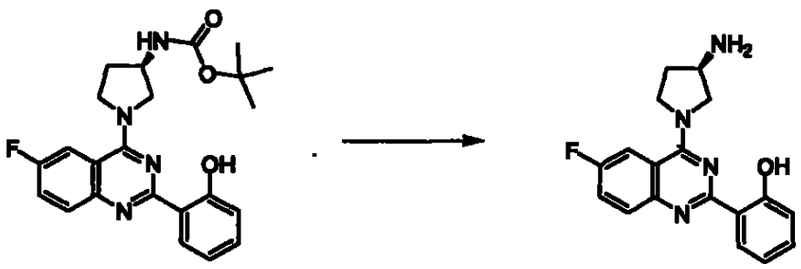
[001774]



[001775] At 0 °C under an N_2 atmosphere, a solution of *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate (264 mg, 1.42 mmol) and triethylamine (0.33 mL, 2.36 mmol) in CH_2Cl_2 was rapidly added to a stirring solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (325 mg, 1.18 mmol) in 15 mL CH_2Cl_2. The reaction mixture was stirred for 1 h before it was quenched with water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc/CH_2Cl_2 yielded *tert*-butyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 425.5 $(M+H)^+$ at 2.74 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001776] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol

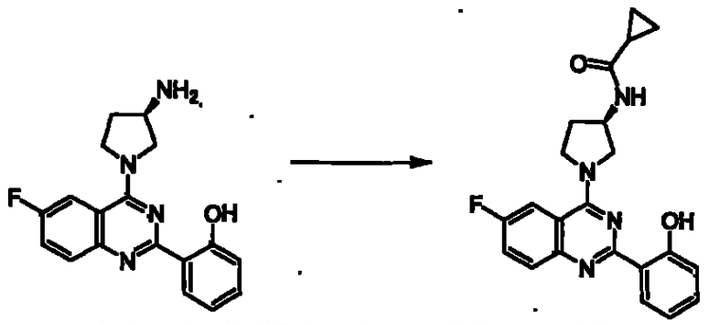
[001777]



[001778] To a solution of *tert*-butyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate (480 mg, 1.11 mmol) in CH_2Cl_2 (10 mL) was added TFA (4 mL). The reaction was stirred for an hour, diluted with 10 mL CH_2Cl_2, and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 3–20% EtOAc/CH_2Cl_2 gave 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol. LC/MS: *m/z* 325.5 $(M+H)^+$ at 1.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001779] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001780]



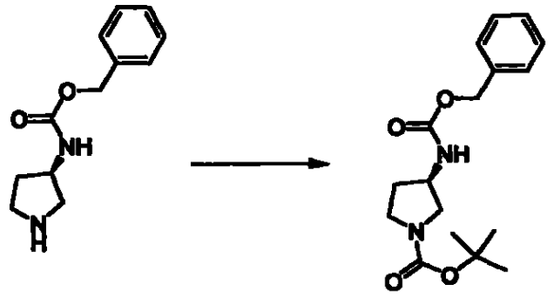
[001781] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.025 g, 0.08 mmol) in DMF (1.0 mL) was added cyclopropanecarboxylic acid (10 mg, 0.12 mmol), followed by the addition of triethylamine (22 μL, 0.16 mmol) and HATU (40 mg, 0.1 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-

fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001782] Method B

[001783] **Benzyl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate**

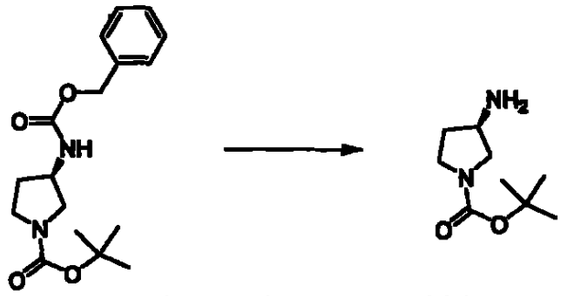
[001784]



[001785] At –10 °C, triethylamine (2.3 mL, 16.6 mmol) was added to a solution of benzyl (*R*)-pyrrolidin-3-ylcarbamate oxalate (2.0 g, 6.4 mmol) in MeOH, followed by the slow addition of Boc_2O (1.92 mL, 8.3 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was quenched with water and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in CH_2Cl_2 gave benzyl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate (1.85 g, 90%). LC/MS: *m/z* 321.3 $(M+H)^+$ at 3.01 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001786] **(*R*)-*tert*-Butyl 3-aminopyrrolidine-1-carboxylate**

[001787]

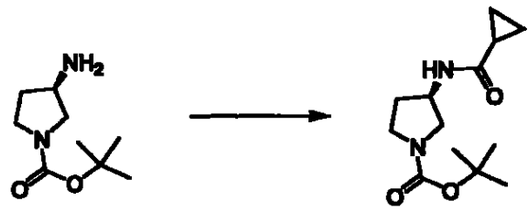


[001788] Under an N_2 atmosphere, a solution of benzyl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate (1.85 g, 5.75 mmol) in 10 mL MeOH was added to a

flask containing Pd/C (185 mg, 10% weight Pd on carbon). After evacuating the flask under vacuum and purging it twice with N_2, the reaction was stirred for 3 h under an H_2 atmosphere at ambient pressure. The reaction was filtered through a bed of Celite, and the solvent was evaporated under reduced pressure to obtain (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate which was used without further purification. LC/MS: *m/z* 187.3 $(M+H)^+$ at 1.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001789] **(*R*)-*tert*-Butyl 3-(cyclopropanecarboxamido)pyrrolidine-1-carboxylate**

[001790]



[001791] To a mixture of (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (500 mg, 2.68 mmol) in CH_2Cl_2 (10 mL) was added cyclopropanecarboxylic acid (276 μL, 3.48 mmol), followed by the addition of HATU (1.3 g, 3.48 mmol) and triethylamine (725 μL, 5.2 mmol). The reaction was complete after stirring for 1 h. After quenching with water, the aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified via silica gel chromatography 0–20% EtOAc/CH_2Cl_2 to afford (*R*)-*tert*-butyl 3-(cyclopropanecarboxamido)pyrrolidine-1-carboxylate (500 mg, 73%). LC/MS: *m/z* 255.3 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001792] ***N*-((*R*)-Pyrrolidin-3-yl)cyclopropanecarboxamide**

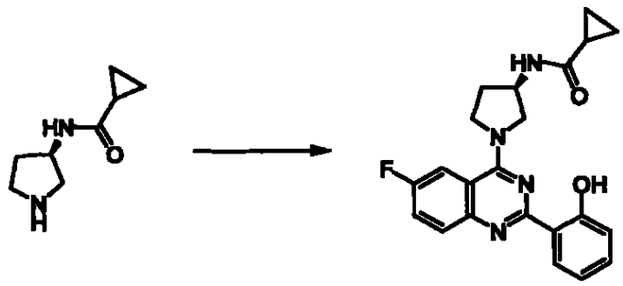
[001793]

[001794] TFA (1 mL) was added to a solution of (*R*)-*tert*-butyl 3-(cyclopropanecarboxamido)pyrrolidine-1-carboxylate (500 mg, 1.96 mmol) in 5 mL CH_2Cl_2. After stirring for 30 min, the reaction was quenched with 1M NaOH solution till neutral and

extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to yield *N*-((*R*)-pyrrolidin-3-yl)cyclopropanecarboxamide (250 mg) which was used without further purification. *LC/MS*: *m/z* 155.3 $(M+H)^+$ at 0.6 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

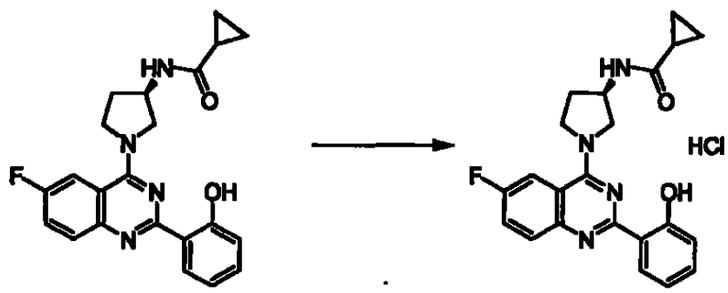
[001795] ***N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide**

[001796]



[001797] A mixture of *N*-((*R*)-pyrrolidin-3-yl)cyclopropanecarboxamide (250 mg, 0.86 mmol), 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (250 mg, 0.86 mmol) and triethylamine (0.240 mL, 1.72 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature. The reaction was complete after one hour. The reaction was quenched with water, the aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc/CH_2Cl_2 gave *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide (230 mg, 68%). LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H-NMR (400 MHz, DMSO-d6) δ 8.42–8.46 (m, 2H), 8.03 (dd, J = 10.5, 2.6 Hz, 1H), 7.88–7.92 (m, 1H), 7.74–7.79 (m, 1H), 7.35–7.39 (m, 1H), 6.92–6.96 (m, 2H), 4.44–4.47 (m, 1H), 4.01–4.28 (m, 3H), 3.83–3.87 (m, 1H), 2.20–2.28 (m, 1H), 1.99–2.06 (m, 1H), 1.51–1.57 (m, 1H), 0.63–0.73 (m, 4H).

[001798] ***N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide hydrochloride**



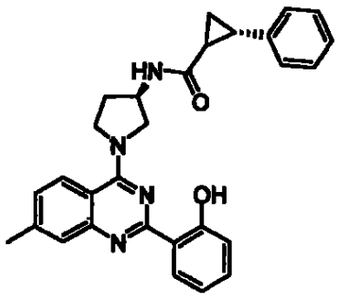
[001799]

[001800] To a solution of *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide (225 mg, 0.57 mmol) in 5 mL CH_2Cl_2 was added a 2 M HCl solution in ether (0.28 mL, 0.57 mmol), which resulted in the precipitation of a solid. After the addition of 20 mL ether, the reaction mixture was stirred for 1 h. The solvents were evaporated under reduced pressure to afford *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide hydrochloride (225 mg, 91%). LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.23 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 10.6 Hz, 1H), 7.91–7.94 (m, 1H), 7.79–7.83 (m, 1H), 7.44–7.48 (m, 1H), 7.00–7.03 (m, 2H), 4.44 (t, *J* = 4.9 Hz, 1H), 4.09–4.23 (m, 3H), 3.87–3.90 (m, 1H), 2.25–2.34 (m, 1H), 2.02–2.09 (m, 1H), 1.49–1.55 (m, 1H), 0.68–0.71 (m, 4H).

[001801] Example 330

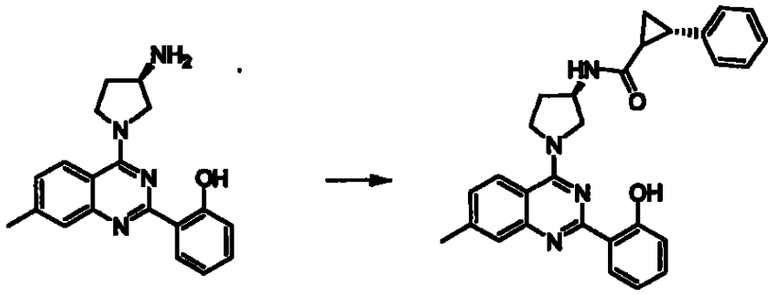
[001802] (2*S*)-*N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-phenylcyclopropanecarboxamide

[001803]



[001804] (2*S*)-*N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-phenylcyclopropanecarboxamide

[001805]

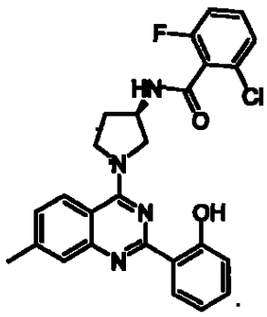


[001806] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. (2*R*)-2-Phenylcyclopropanecarbonyl chloride (31 mg, 0.17 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (2*S*)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-phenylcyclopropanecarboxamide as the TFA salt. LC/MS (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)), LC/MS: *m/z* 465.4 $(M+H)^+$ at 2.88 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001807] Example 331

[001808] 2-Chloro-6-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

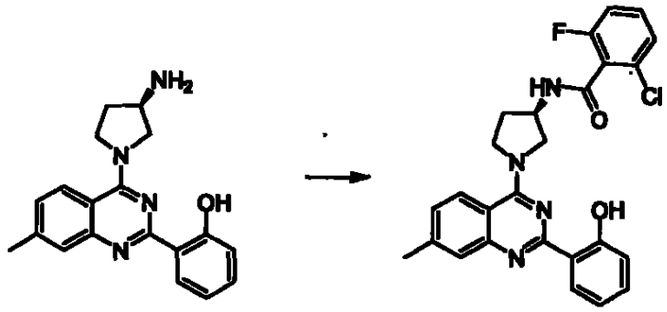
[001809]



[001810] 2-Chloro-6-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

192

[001811]

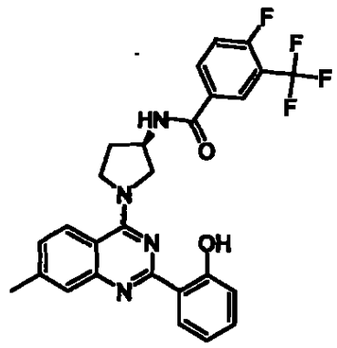


[001812] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-Chloro-6-fluorobenzoyl chloride (36 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 2-chloro-6-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 477.3 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001813] Example 332

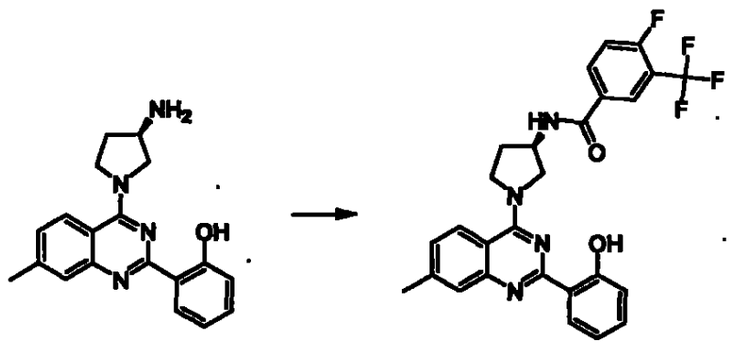
[001814] 4-Fluoro-3-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001815]



[001816] 4-Fluoro-3-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001817]

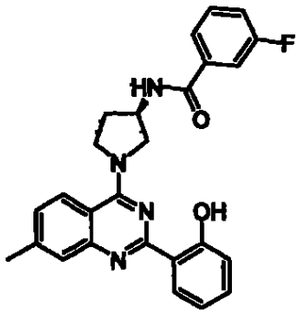


[001818] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 4-Fluoro-3-(trifluoromethyl)benzoyl chloride (42 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 4-fluoro-3-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 511.5 $(M+H)^+$ at 3.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001819] Example 333

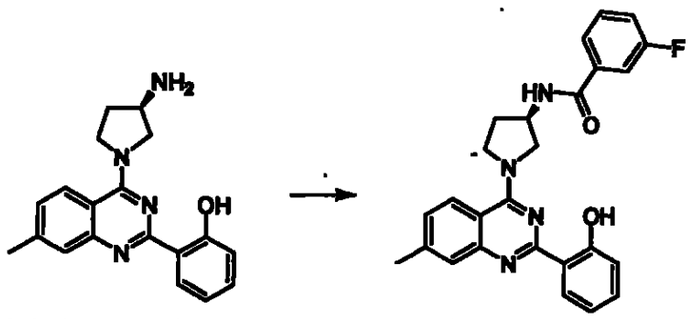
[001820] 3-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001821]



[001822] 3-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001823]

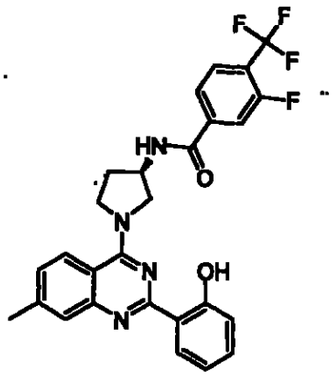


[001824] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 3-Fluorobenzoyl chloride (30 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 443.5 $(M+H)^+$ at 2.83 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001825] Example 334

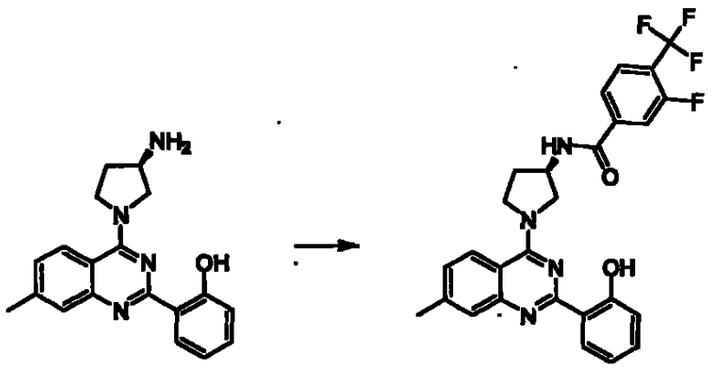
[001826] 3-Fluoro-4-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001827]



[001828] 3-Fluoro-4-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001829]

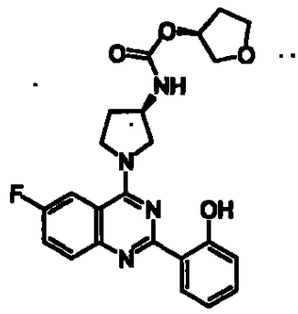


[001830] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 3-Fluoro-4-(trifluoromethyl)benzoyl chloride (42 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-fluoro-4-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 511.5 $(M+H)^+$ at 3.1 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001831] Example 335

[001832] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

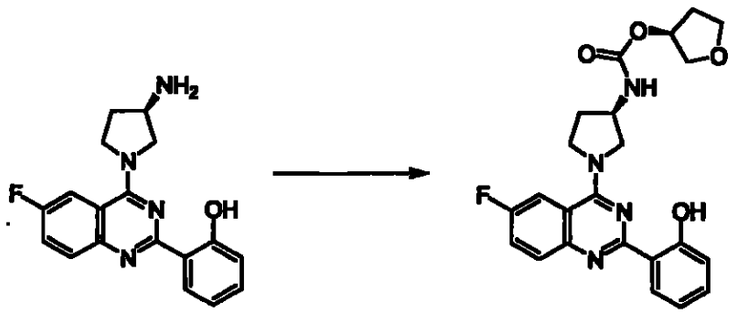
[001833]



[001834] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

194
194

[001835]

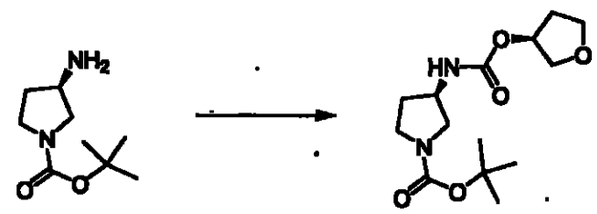


[001836] A solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.092 mmol) in DMF (1.0 mL) was cooled to –40 °C. To this mixture was added triethylamine (26 μL, 0.184 mmol), followed by the addition of (*S*)-tetrahydrofuran-3-yl chloroformate (0.014 g, 0.092 mmol). After allowing the reaction to warm to room temperature the mixture was filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*S*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001837] Method B

[001838] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate

[001839]

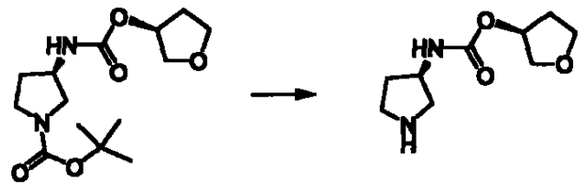


[001840] To a solution of (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (500 mg, 2.6 mmol) in 5 mL CH_2Cl_2 was added triethylamine (0.73 mL, 5.2 mmol), and the reaction was cooled to –20 °C. (*S*)-tetrahydrofuran-3-yl chloroformate (525 mg, 3.48 mmol) was added in portions over a period of 10 minutes to the above reaction mixture. After allowing the reaction to warm to room temperature, it was quenched with water and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford (*S*)-

tetrahydrofuran-3-yl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate. Purification via silica gel chromatography using 0–20% EtOAc in CH_2Cl_2 gave (*S*)-tetrahydrofuran-3-yl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate (490 mg, 63%). LC/MS: *m/z* 301.3 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001841] (*S*)-Tetrahydrofuran-3-yl (*R*)-pyrrolidin-3-ylcarbamate

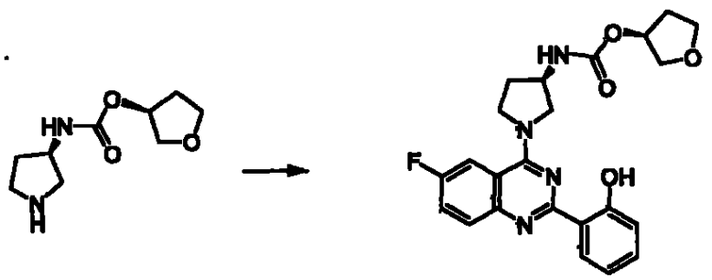
[001842]



[001843] TFA (1 mL) was added to a solution of (*S*)-tetrahydrofuran-3-yl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate (490 mg, 1.63 mmol) in 5 mL CH_2Cl_2. After stirring for 30 min, the reaction was quenched with NaOH and extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to yield (*S*)-tetrahydrofuran-3-yl (*R*)-pyrrolidin-3-ylcarbamate (230 mg) which was used without further purification. LC/MS: *m/z* 201.3 $(M+H)^+$ at 0.59 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001844] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001845]

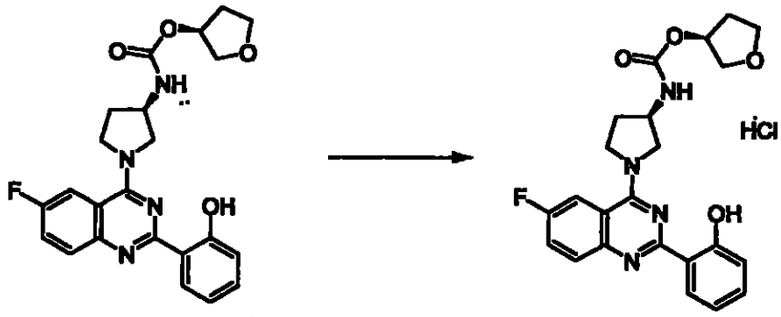


[001846] A mixture of (*S*)-tetrahydrofuran-3-yl (*R*)-pyrrolidin-3-ylcarbamate (225 mg, 1.12 mmol), 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (250 mg, 0.86 mmol), and triethylamine (0.240 mL, 1.72 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature. The reaction was complete in one hour. The reaction was quenched with water, the aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and

concentrated. Purification via silica gel chromatography using 0–10% EtOAc/CH_2Cl_2 gave (*S*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate (250 mg, 66%). LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.43 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.99 (d, *J* = 2.6 Hz, 1H), 7.87–7.91 (m, 1H), 7.74–7.79 (m, 1H), 7.70 (d, *J* = 6.2 Hz, 1H), 7.35–7.39 (m, 1H), 6.91–6.96 (m, 2H), 5.15 (s, 1H), 4.21–4.25 (m, 2H), 4.12–4.14 (m, 1H), 4.01–4.06 (m, 1H), 3.87–3.89 (m, 1H), 3.65–3.78 (m, 4H), 2.02–2.26 (m, 3H), 1.82–1.89 (m, 1H).

[001847] **(*S*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride**

[001848]

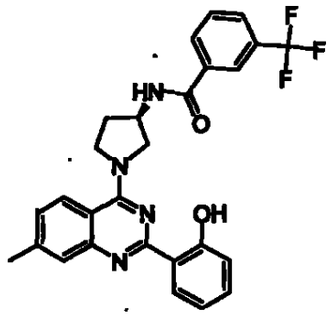


[001849] To a mixture of (*S*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate (250 mg, 0.57 mmol) and CH_2Cl_2 (25 mL) was added a 2.0 M HCl solution in ether (0.285 mL, 0.57 mmol). After the addition of ether (40 mL), the reaction was stirred for 1 h. The resulting solid was filtered and dried to afford (*S*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.18 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.00 (d, *J* = 9.6 Hz, 1H), 7.90–7.94 (m, 1H), 7.78–7.83 (m, 1H), 7.45–7.49 (m, 1H), 7.00–7.03 (m, 2H), 5.10 (s, 1H), 4.09–4.25 (m, 4H), 3.90–3.92 (m, 1H), 3.62–3.75 (m, 4H), 2.22–2.27 (m, 1H), 2.03–2.14 (m, 2H), 1.83–1.91 (m, 1H).

[001850] Example 336

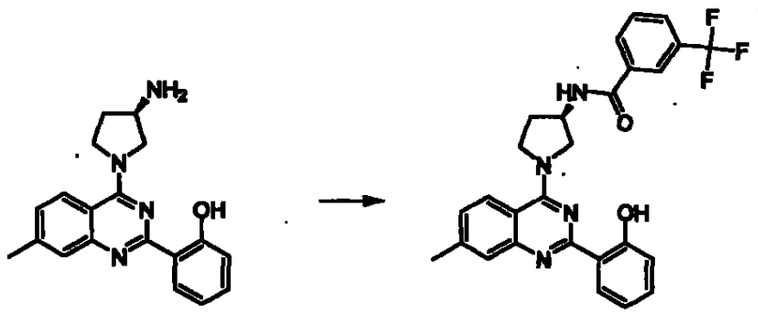
[001851] **3-(Trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide**

[001852]



[001853] 3-(Trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001854]

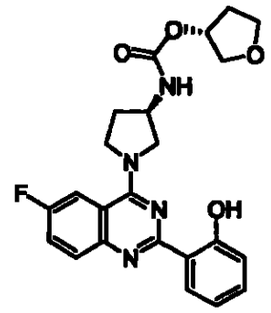


[001855] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (130 mg, 0.406 mmol) was dissolved in 0.7 mL anhydrous CH_2Cl_2 and cooled to 0 °C. 3-(Trifluoromethyl)benzoyl chloride (42 mg, 0.18 mmol) dissolved in 0.7 mL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (53 mg, 74 μL, 0.52 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 493.5 $(M+H)^+$ at 3.03 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001856] Example 337

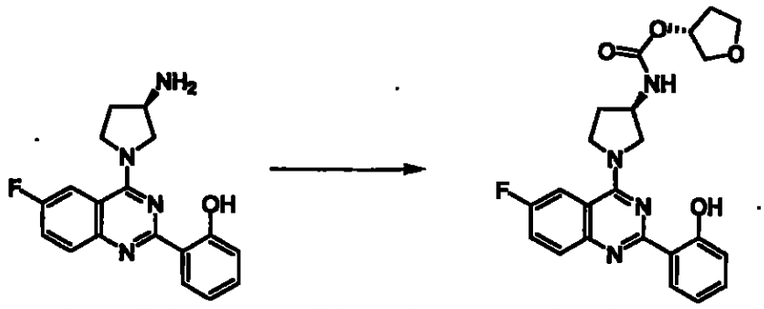
[001857] (*R*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001858]



[001859] (*R*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001860]

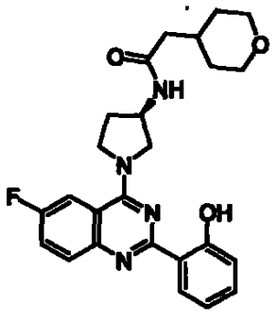


To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.092 mmol) in DMF (1.0 mL) was cooled to –40 °C, triethylamine (26 μL, 0.184 mmol) was added, followed by the addition of (*R*)-tetrahydrofuran-3-yl chloroformate (0.014 g, 0.092 mmol). After warming to room temperature, the mixture was filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*R*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001861] Example 338

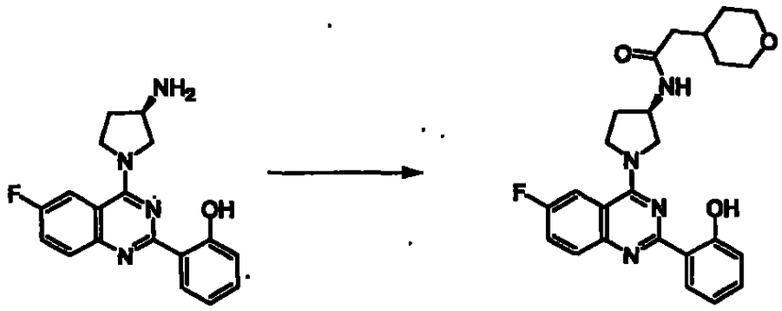
[001862] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)acetamide

[001863]



[001864] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)acetamide

[001865]

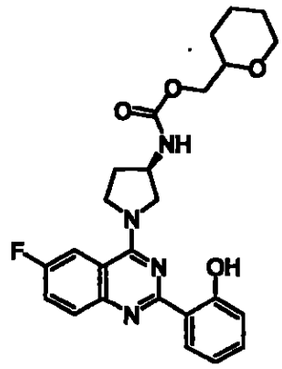


To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.092 mmol) in DMF (1.0 mL) was added 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (0.017 g, 0.12 mmol), followed by the addition of triethylamine (25.6 μL, 0.184 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)acetamide as the TFA salt. LC/MS: *m/z* 451.5 $(M+H)^+$ at 2.15 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001866] Example 339

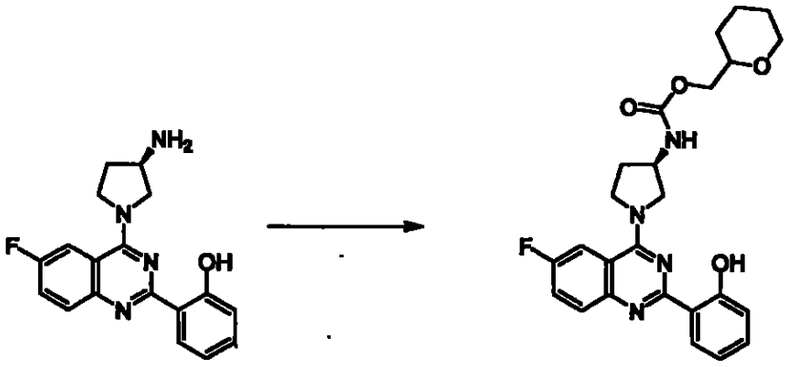
[001867] (Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001868]



[001869] (Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001870]

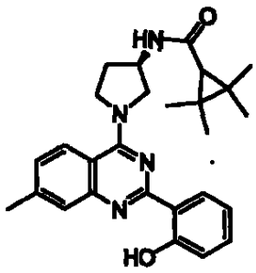


[001871] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) at room temperature was added triethylamine (43 μL, 0.31 mmol), followed by the addition of (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (39 mg, 0.13 mmol). The reaction was stirred at room temperature overnight, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 467.3 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001872] Example 340

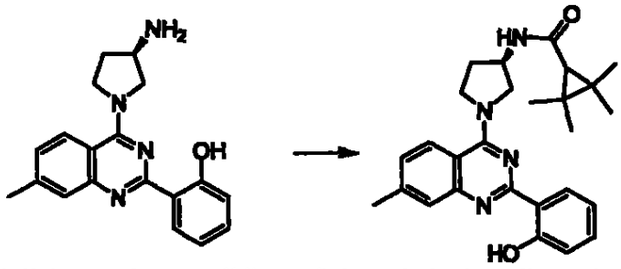
[001873] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2,2,3,3-tetramethylcyclopropanecarboxamide

[001874]



[001875] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2,2,3,3-tetramethylcyclopropanecarboxamide

[001876]



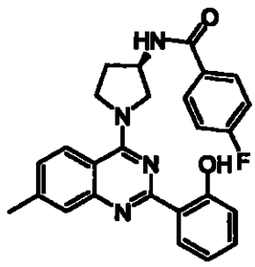
[001877] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.156 mmol) was dissolved in 0.52 mL of anhydrous CH_2Cl_2. 2,2,3,3-Tetramethylcyclopropanecarboxylic acid (26.63 mg, 0.18 mmol) was added, followed by triethylamine (22.14 mg, 30.49 μL, 0.22 mmol) and BOP (82.93 mg, 0.18 mmol). After stirring the mixture for 30 minutes at room temperature, it was filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2,2,3,3-tetramethylcyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 445.4 $(M+H)^+$ at 2.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001878] Example 341

[001879] 4-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

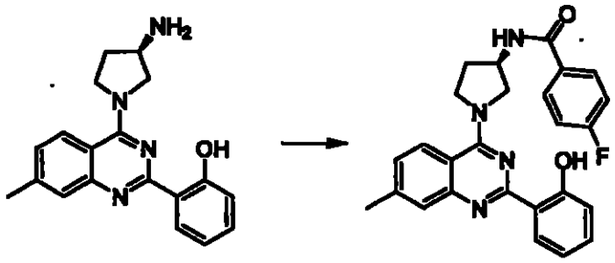
198

[001880]



[001881] 4-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

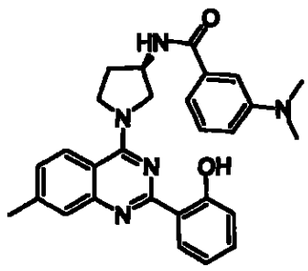
[001882]



[001883] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 4-Fluorobenzoyl chloride (25 mg, 0.15 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (19 mg, 26 μL, 0.18 mmol). The reaction was stirred for 15 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 4-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 443.4 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001884] Example 342

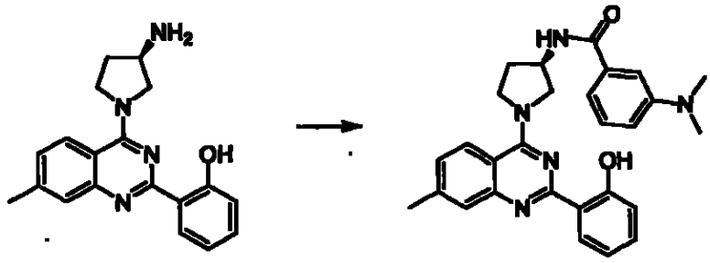
[001885] 3-(Dimethylamino)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide



[001886]

[001887] 3-(Dimethylamino)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

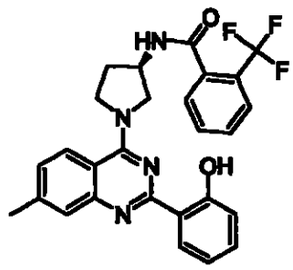
[001888]



[001889] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 3-(Dimethylamino)benzoyl chloride hydrochloride (34 mg, 0.15 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (32 mg, 44 μL, 0.31 mmol). The reaction was stirred for 1.5 hour at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-(dimethylamino)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 468.4 $(M+H)^+$ at 2.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001890] Example 343

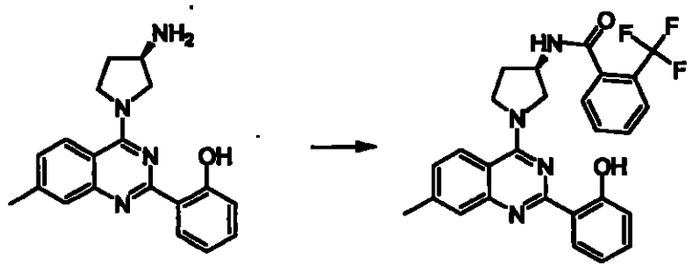
[001891] 2-(Trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide



[001892]

[001893] 2-(Trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

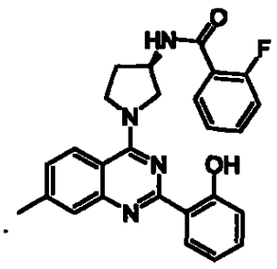
[001894]



[001895] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-(Trifluoromethyl)benzoyl chloride (39 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 2-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 493.4 $(M+H)^+$ at 2.76 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001896] Example 344

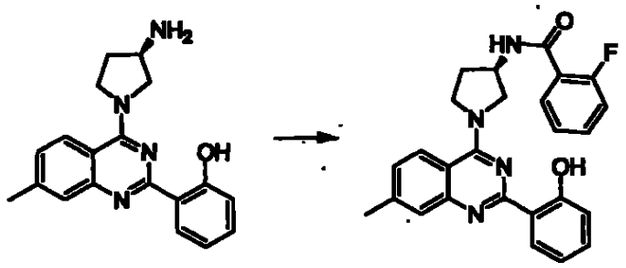
[001897] 2-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide



[001898]

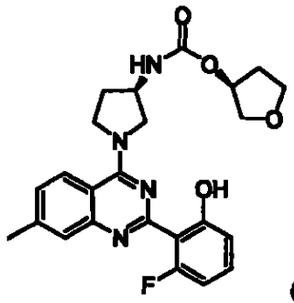
[001899] 2-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001900]



[001901] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50.6 mg, 0.158 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-Fluorobenzoyl chloride (27 mg, 0.17 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 15 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 2-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 443.4 $(M+H)^+$ at 2.69 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001902] Example 345

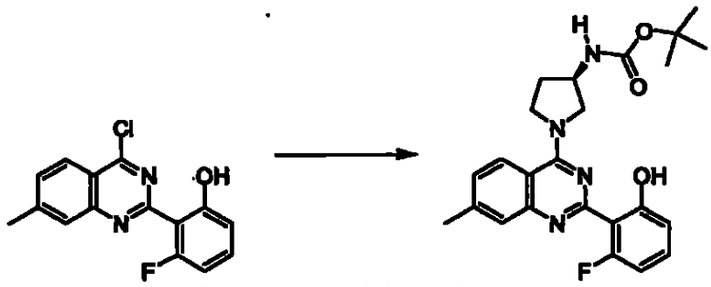


[001903] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001904]

[001905] *tert*-Butyl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

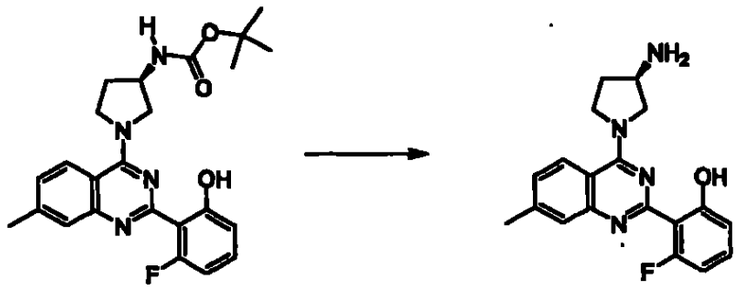
[001906]



[001907] A solution of *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate (368 mg, 1.97 mmol) and triethylamine (0.46 mL, 3.28 mmol) in CH_2Cl_2 was rapidly added to a stirring solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (475 mg, 1.65 mmol) in 15 mL CH_2Cl_2 at 0 °C under an N_2 atmosphere. The reaction was stirred for 1 h before it was quenched with water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc/CH_2Cl_2 yielded *tert*-butyl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001908] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol

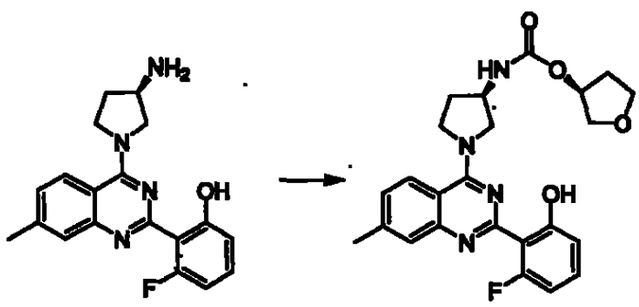
[001909]



[001910] To a solution of *tert*-butyl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (500 mg, 1.14 mmol) in CH_2Cl_2 (15 mL) was added TFA (5 mL). The mixture was stirred for 1 h and then neutralized with a 1 M NaOH solution, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 3–20% EtOAc/CH_2Cl_2 gave 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol. LC/MS: *m/z* 339.5 $(M+H)^+$ at 0.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001911] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001912]



[001913] Method A

[001914] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.12 mmol) in 800 μL of anhydrous DMF cooled to 0 °C was added (*S*)-tetrahydrofuran-3-yl chloroformate (20 mg, 19 μL, 0.13 mmol) dropwise, followed by the addition of triethylamine (24 mg, 33 μL, 0.23 mmol). The reaction was warmed to room temperature and stirred overnight, and the product purified via reverse phase HPLC (10%–99%

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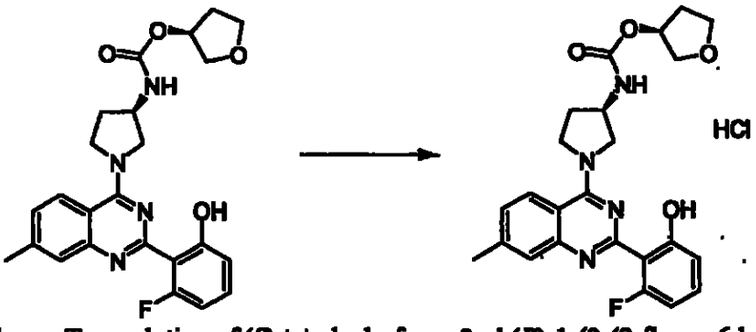
CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.05 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001915] Method B

[001916] At room temperature, *N*-ethyl-*N*-isopropylpropan-2-amine (155 mL, 0.88 mmol) was added to a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (150 mg, 0.40 mmol) in THF. The mixture was cooled in an ice bath, and (*S*)-tetrahydrofuran-3-yl chloroformate (63 mg, 0.42 mmol) was added slowly over a period of 10 minutes. After warming to room temperature, the reaction was quenched with water and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in CH_2Cl_2/hexanes (1:1) gave (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (160 mg, 84%). LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.18 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 6.3 Hz, 1H), 7.58 (s, 1H), 7.29–7.38 (m, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.67–6.72 (m, 1H), 5.14 (s, 1H), 4.23–4.24 (m, 1H), 3.99–4.13 (m, 3H), 3.64–3.85 (m, 5H), 2.50 (s, 3H), , 2.07–2.22 (m, 2H), 2.00–2.03 (m, 1H), 1.85–1.90 (m, 1H).

[001917] **(*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride**

[001918]



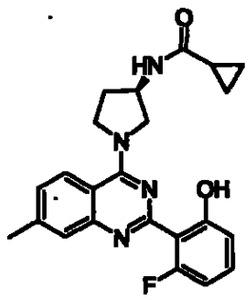
[001919] To a solution of (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (160 mg, 0.35 mmol) in 2 mL CH_2Cl_2 was added 2 M HCL solution in ether (0.176 mL, 0.35 mmol) resulting in precipitation of a solid. After the addition of 10 mL ether, the reaction was stirred for 30 minutes, filtered and the

resulting solid was dried to obtain (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride (130 mg, 76%).). LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.29 (s, 1H), 7.57 (s, 2H), 7.43–7.49 (m, 1H), 6.83–6.89 (m, 2H), 5.08 (s, 1H), 4.23–4.42 (m, 4H), 3.62–3.73 (m, 5H), 2.24–2.34 (m, 1H), 2.04–2.11 (m, 2H), 1.86–1.92 (m, 1H).

[001920] Example 346

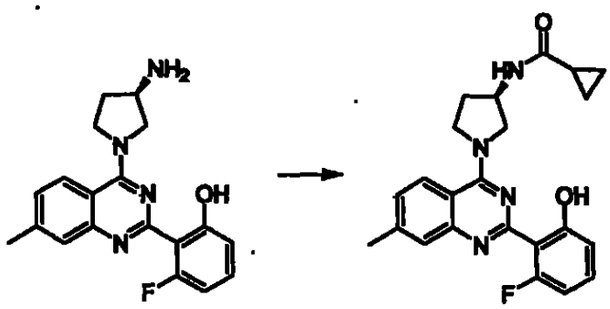
[001921] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001922]



[001923] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001924]



[001925] Method A

[001926] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.12 mmol) in 800 μL of anhydrous DMF at 0 °C was added cyclopropanecarboxylic acid (11 mg, 0.13 mmol), followed by the addition of triethylamine (24

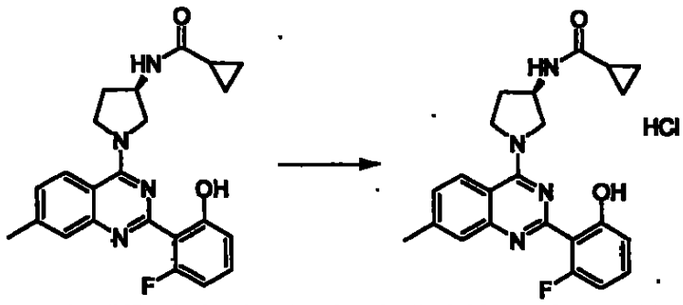
mg, 33 μL, 0.24 mmol) and HATU (60 mg, 0.16 mmol). The mixture was allowed to warm to room temperature and was stirred overnight. Filtration and purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.2 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001927] Method B

To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (100 mg, 0.295 mmol) in 10 mL DMF, at –20 °C, was added cyclopropanecarboxylic acid (23 μL, 0.30 mmol), followed by the addition of triethylamine (82 μL, 0.59 mmol) and a solution of HATU (124 mg, 0.32 mmol) in 4 mL DMF. The mixture was warmed to room temperature and stirred for 1 h. Cold water was added to the reaction mixture which resulted in the formation of a precipitate which was collected by filtration and dissolved in CH_2Cl_2. The solution was then dried over $MgSO_4$, filtered, and concentrated to afford *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide (80 mg, 66%) LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001928] ***N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide hydrochloride**

[001929]



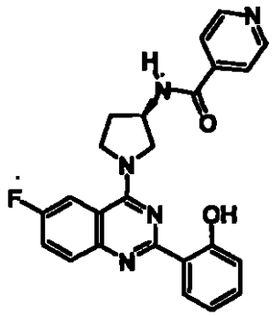
[001930] A 2 M HCl solution in ether (0.16 mL, 0.32 mmol) was added to a solution of *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide (133 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) under an N_2 atmosphere. Additional ether was then added (15 mL) and the reaction mixture was stirred for an hour. The formed precipitate was then filtered and dried to afford *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-

7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide hydrochloride (135 mg, 95%). LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.32 (d, *J* = 7.6 Hz, 1H), 7.56–7.58 (m, 2H), 7.43–7.49 (m, 1H), 6.83–6.88 (m, 2H), 3.94–4.41 (m, 5H), 2.52 (s, 3H), 2.25–2.36 (m, 1H), 1.91–2.13 (m, 1H), 1.47–1.54 (m, 1H), 0.63–0.69 (m, 4H)

[001931] Example 347

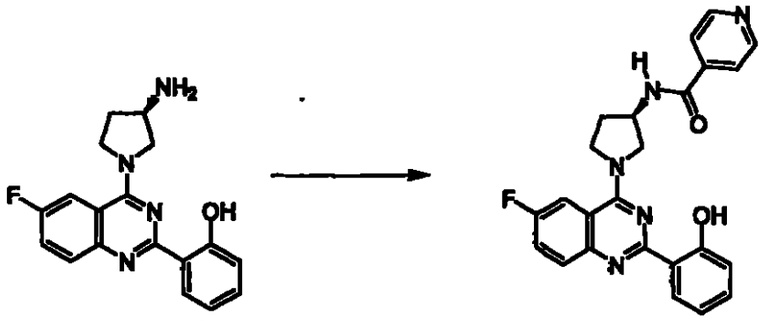
[001932] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001933]



[001934] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001935]



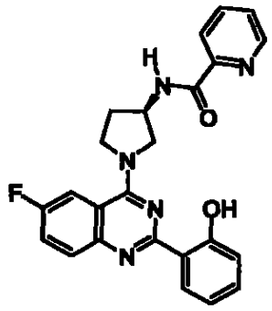
[001936] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added isonicotinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-

hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide as the TFA salt. LC/MS: *m/z* 430.5 $(M+H)^+$ at 1.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001937] Example 348

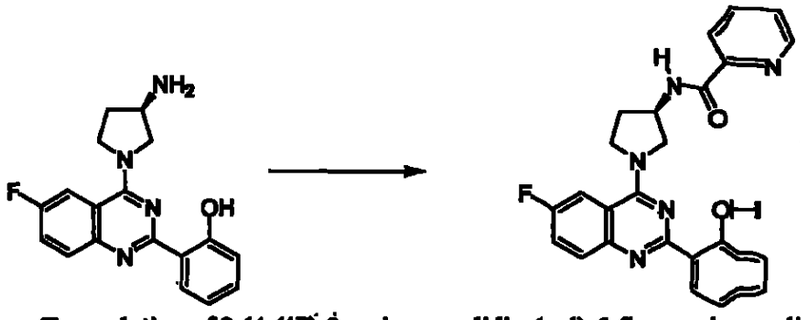
[001938] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001939]



[001940] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001941]

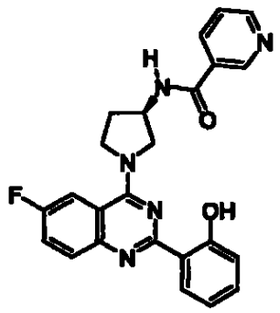


[001942] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added picolinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)picolinamide as the TFA salt. LC/MS: *m/z* 430.5 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001943] Example 349

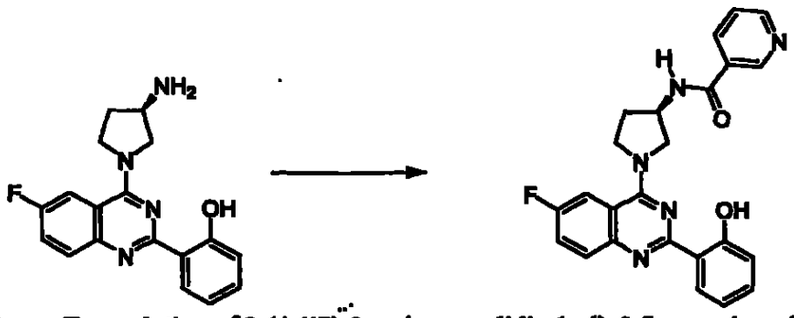
[001944] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001945]



[001946] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001947]



[001948] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added nicotinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)nicotinamide as the TFA salt. LC/MS: *m/z* 430.5 $(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001949] Example 350

[001950] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

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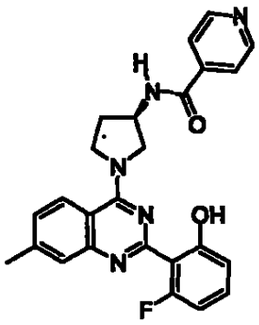
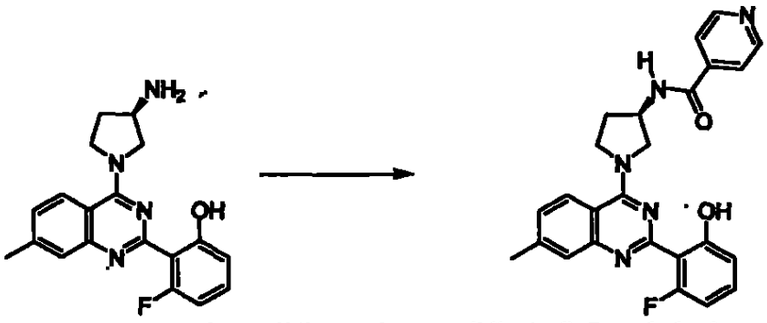
[001951]



[001952] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001953]

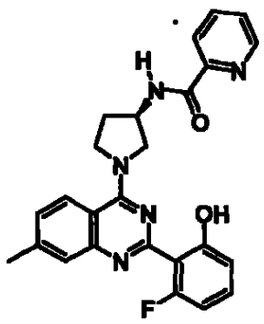


[001954] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) in DMF (0.5 mL) was added isonicotinic acid (0.014 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide as the TFA salt. LC/MS: *m/z* 444.5 $(M+H)^+$ at 1.85 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001955] Example 351

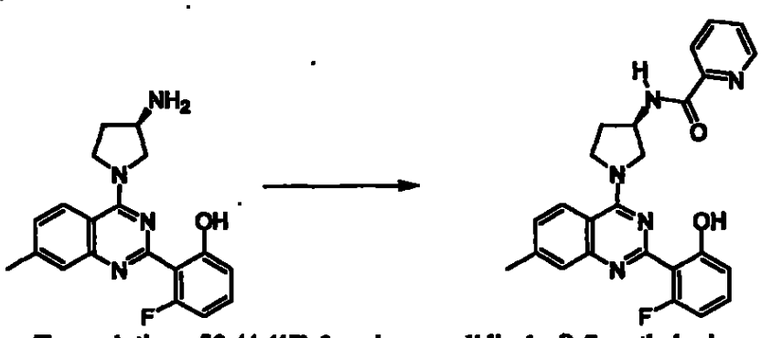
[001956] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001957]



[001958] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001959]

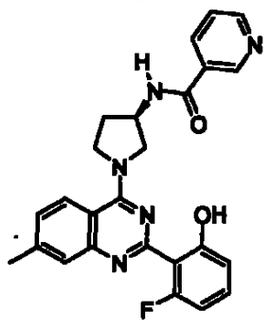


[001960] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added picolinic acid (0.014 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide as the TFA salt. LC/MS: *m/z* 444.5 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001961] Example 352

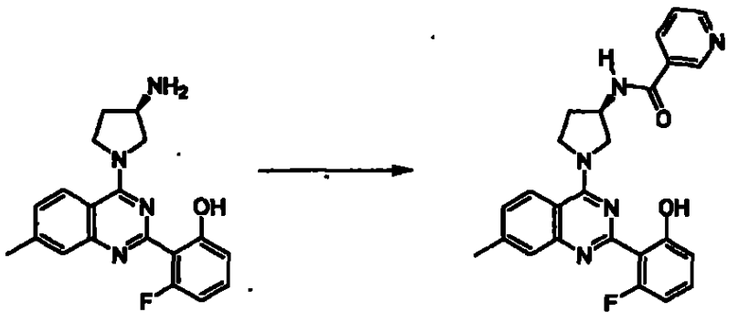
[001962] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001963]



[001964] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001965]

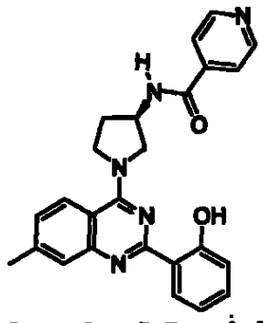


[001966] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added nicotinic acid (0.014 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide as the TFA salt. LC/MS: *m/z* 444.5 $(M+H)^+$ at 1.89 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001967] Example 353

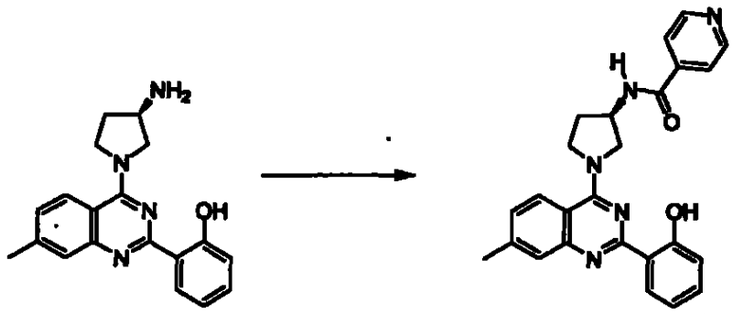
[001968] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001969]



[001970] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001971]

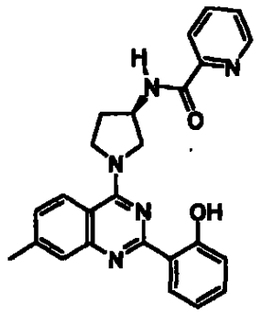


[001972] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added isonicotinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide as the TFA salt. LC/MS: *m/z* 426.1 $(M+H)^+$ at 1.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001973] Example 354

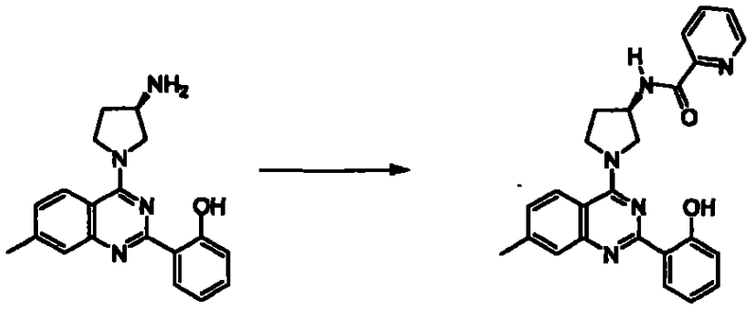
[001974] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001975]



[001976] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001977]

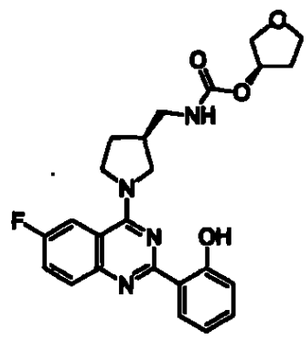


[001978] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added picolinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide as the TFA salt. LC/MS: *m/z* 426.1 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001979] Example 355

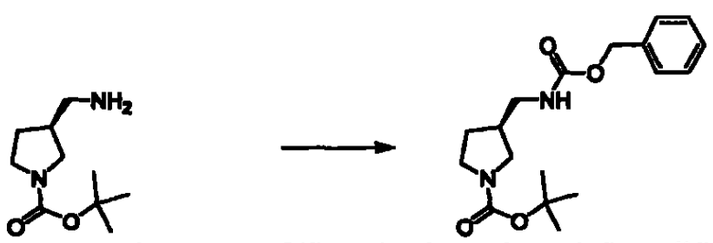
[001980] (*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001981]



[001982] **Benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate**

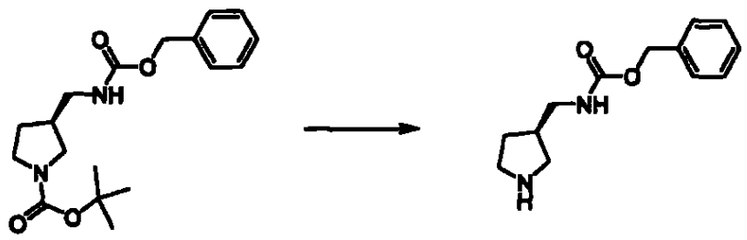
[001983]



[001984] To a stirring solution of (*S*)-*tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (1.5 g, 7.5 mmol) in 25 mL CH_2Cl_2 was added triethylamine (2.1 mL, 15 mmol) at 0 °C, followed by the dropwise addition of benzyl chloroformate (1.58 mL, 11.2 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was quenched with water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 3% MeOH in CH_2Cl_2 gave benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.5 g, 60%). LC/MS: *m/z*: 335.5 $(M+H)^+$ at 3.01 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001985] **Benzyl ((*R*)-pyrrolidin-3-yl)methylcarbamate**

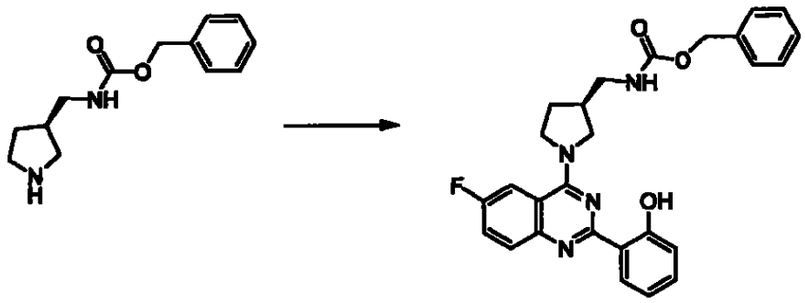
[001986]



[001987] To a stirred solution of ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.5 g, 4.48 mmol) in CH_2Cl_2 (20 mL) was slowly added TFA (5 mL). The reaction was stirred for 2 h. After removing the solvents under reduced pressure, the mixture was neutralized with a 1 M NaOH solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford benzyl ((*R*)-pyrrolidin-3-yl)methylcarbamate (800 mg, 76%). *LC/MS*: *m/z* 335.3 $(M+H)^+$ at 1.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

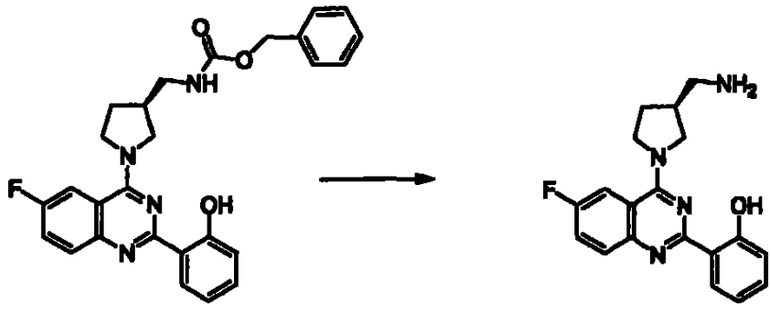
[001988] **Benzyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[001989]



[001990] A solution of triethylamine (507 μL, 3.64 mmol) and benzyl ((*R*)-pyrrolidin-3-yl)methylcarbamate (0.47 g, 2 mmol) in CH_2Cl_2 was added dropwise to a solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (0.5 g, 1.82 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred at room temperature for 3 h. After quenching the reaction with water, the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 5–10% EtOAc in CH_2Cl_2 yielded benzyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate. *LC/MS*: *m/z* 473.1 $(M+H)^+$ at 2.91 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001991] **2-(4-((*S*)-3-(Aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol**

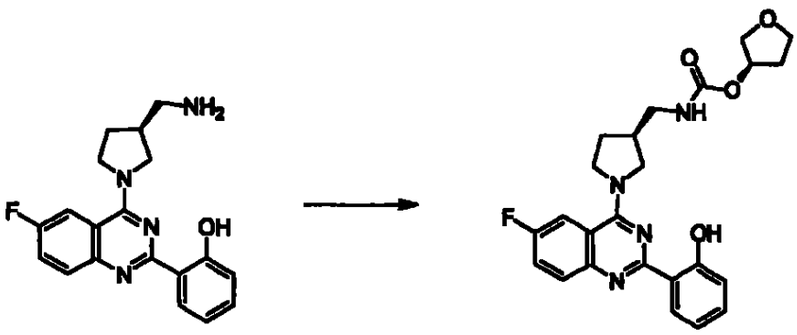


[001992]

[001993] Under an N_2 atmosphere, a mixture of benzyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.770 g, 1.6 mmol) and MeOH (5 mL) was added to Pd/C (77 mg, 10 % weight Pd on carbon) weighed into a 100 mL flask. After the atmosphere in the flask was evacuated and purged with N_2 three times, the reaction mixture was vigorously stirred under an H_2 atmosphere at ambient pressure overnight and then filtered through a pad of Celite, concentrated, and dried to obtain 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.45 g, 81%). LC/MS: *m/z* 459.5 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001994] (*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001995]



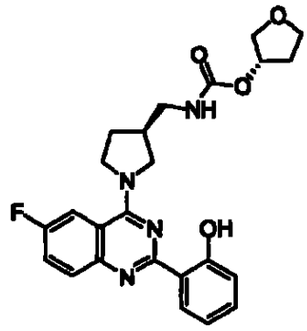
[001996] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol) and (*R*)-tetrahydrofuran-3-yl chloroformate (13 mg, 0.09 mmol). The reaction was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the

TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001997] Example 356

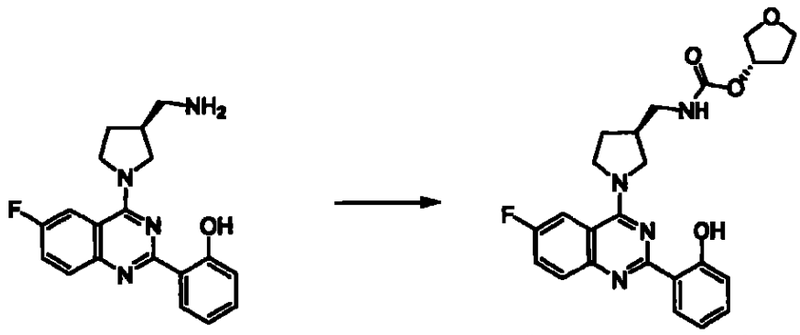
[001998] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001999]



[002000] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002001]



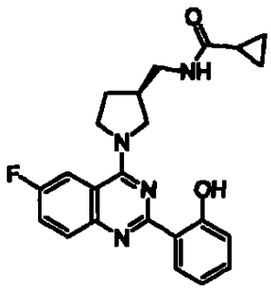
[002002] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol) and (*S*)-tetrahydrofuran-3-yl chloroformate (13 mg, 0.09 mmol). The reaction was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the

TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002003] Example 357

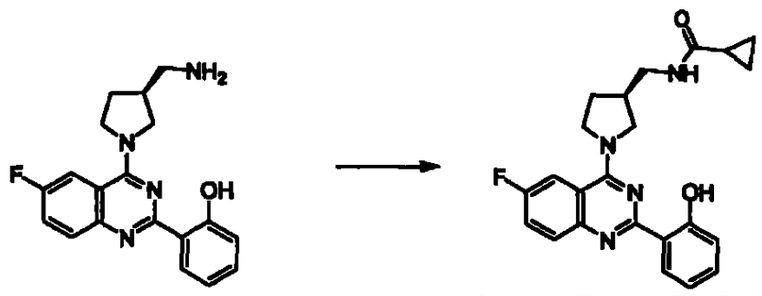
[002004] *N*-(((*S*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide

[002005]



[002006] *N*-(((*S*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide

[002007]



[002008] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) and cyclopropanecarboxylic acid (10 mg, 0.12 mmol) in *DMF* (1.0 mL) was added triethylamine (25 μL, 0.18 mmol) followed by the addition of HATU (45 mg, 0.117 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-(((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 407.3 $(M+H)^+$ at 2.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002009] Example 358

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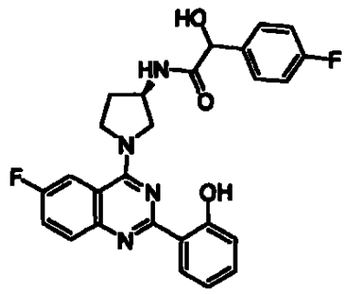
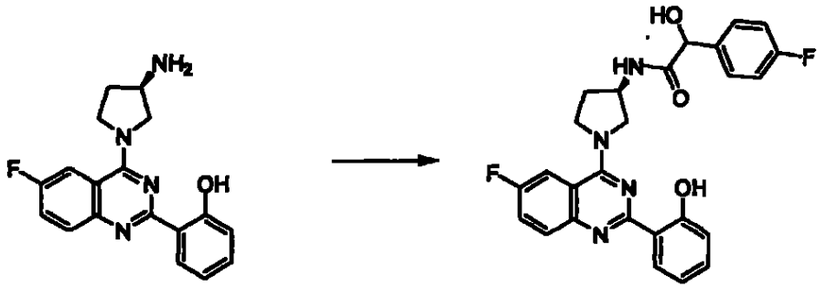
[002010] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[002011]



[002012] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[002013]

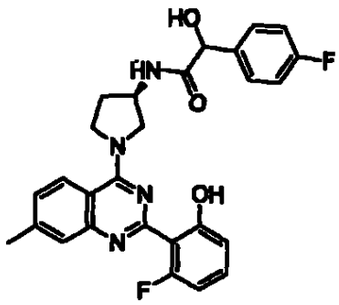


[002014] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added 2-(4-fluorophenyl)-2-hydroxyacetic acid (20 mg, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide as the TFA salt. LC/MS: *m/z* 477.3 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002015] Example 359

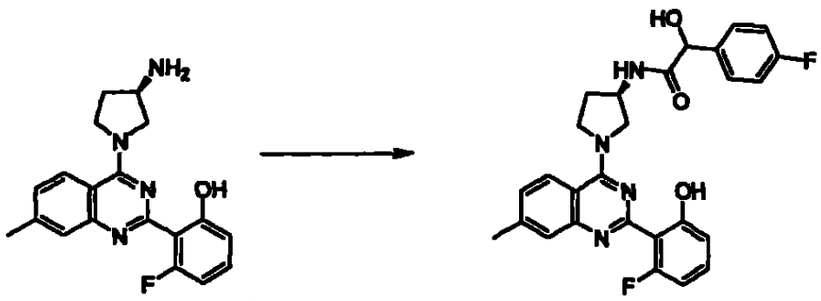
[002016] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[002017]



[002018] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[002019]



[002020] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added 2-(4-fluorophenyl)-2-hydroxyacetic acid (0.020 g, 0.12 mmol), followed by the addition of triethylamine (25.6 μL, 0.184 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide as the TFA salt. LC/MS: *m/z* 4491.3 $(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002021] Example 360

[002022] 2-(4-Fluorophenyl)-2-hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide

[002023]

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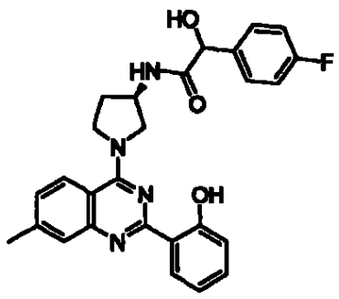
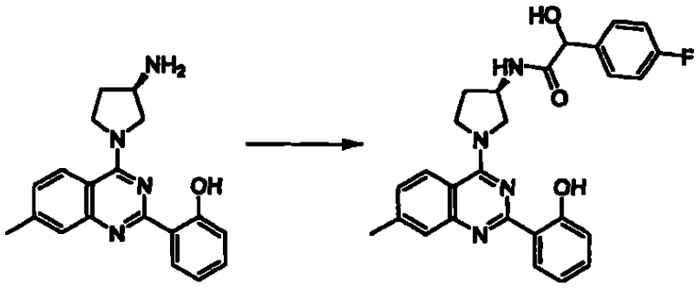


[002024] 2-(4-Fluorophenyl)-2-hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide

[002025]

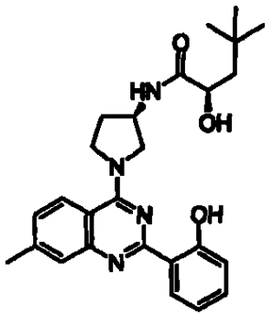


[002026] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added 2-(4-fluorophenyl)-2-hydroxyacetic acid (0.02 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain 2-(4-fluorophenyl)-2-hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide as the TFA salt. *LC/MS*: *m/z* 473.1 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002027] Example 361

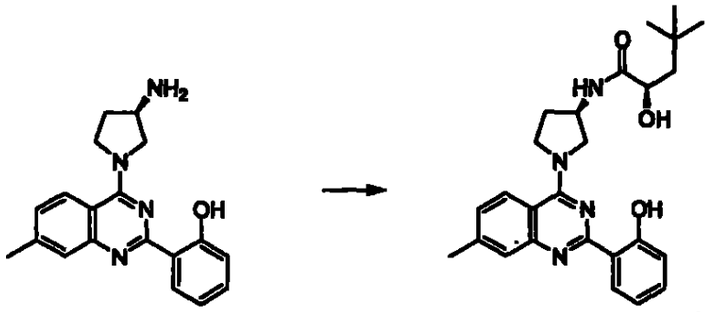
[002028] (2*R*)-2-Hydroxy-*N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-4,4-dimethylpentanamide

[002029]



[002030] (2*R*)-2-Hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-4,4-dimethylpentanamide

[002031]



[002032] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in 1 mL of DMF cooled at 0 °C was added (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (27.3 mg, 0.187 mmol), followed by the addition of triethylamine (32 mg, 44 μL, 0.31 mmol), then HATU (71.1 mg, 0.187 mmol). The reaction was stirred at 0 °C for 10 minutes, warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-2-hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-4,4-dimethylpentanamide as the TFA salt. *LC/MS*: *m/z* 449.3 $(M+H)^+$ at 2.4 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002033] Example 362

[002034] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

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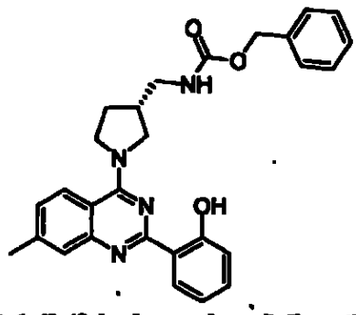
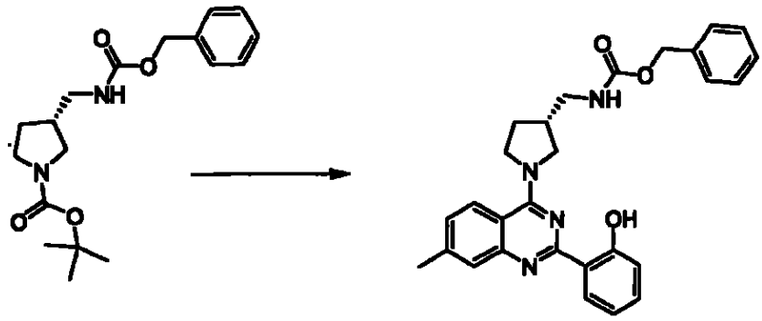
[002035]



[002036] **Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[002037]

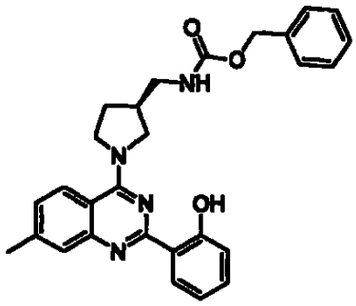


[002038] A mixture of benzyl ((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (0.20 g, 0.60 mmol) and 4 M HCl (10 mL) in dioxane was stirred at room temperature for 3 h. After evaporating the solvent under reduced pressure, the solid was triturated with Et_2O, dried under vacuum, and taken up in CH_2Cl_2 (10 mL). 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (0.16 g, 0.60 mmol) was added to this solution, followed by the addition of triethylamine (0.25 mL, 1.8 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 and washed with water. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in hexanes gave benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as a colorless oil (0.19 g, 68% yield). LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002039] Example 363

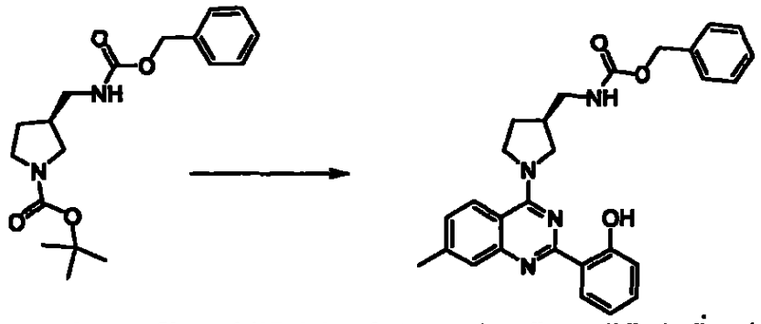
[002040] Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002041]



[002042] Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002043]

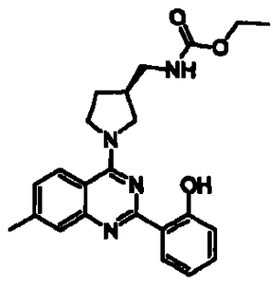


[002044] A mixture of benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (0.20 g, 0.60 mmol) and 4 M HCl in dioxane (10 mL) was stirred for 3 h at room temperature. After evaporating the solvent under reduced pressure, the solid was triturated with Et_2O, dried under vacuum, and taken up in CH_2Cl_2 (10 mL). 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (0.16 g, 0.60 mmol) was added to this solution, followed by the addition of triethylamine (0.25 mL, 1.8 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 and washed with water. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in hexanes gave benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as a colorless oil (0.19 g, 68% yield). LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002045] Example 364

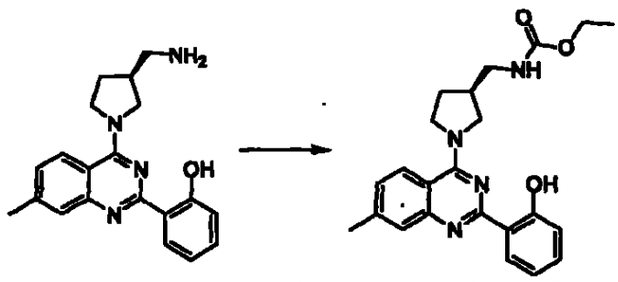
[002046] Ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002047]



[002048] Ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002049]

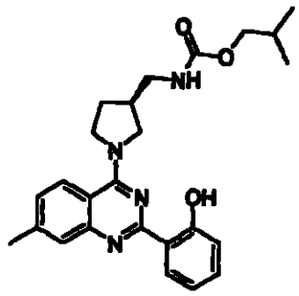


[002050] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) in CH_2Cl_2 (1.0 mL) was cooled in an ice bath. To this mixture was added ethyl chloroformate (7.8 μL, 0.082 mmol), followed by triethylamine (21 μL, 0.15 mmol). After removing the ice bath, the reaction was stirred for 3 h at room temperature. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 407.1 $(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002051] Example 365

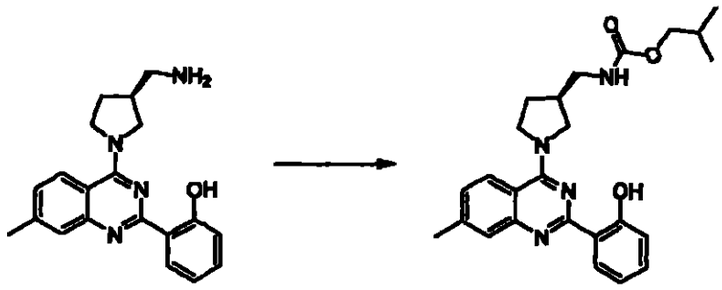
[002052] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002053]



[002054] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002055]



[002056] Method A

[002057] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) in CH_2Cl_2 (1.0 mL) was cooled in an ice bath. To this mixture was added isobutyl chloroformate (11 μL, 0.082 mmol), followed by the addition of triethylamine (21 μL, 0.15 mmol). After removing the ice bath, the reaction was stirred for 3 h at room temperature. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.55 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002058] Method B

[002059] A mixture of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (200 mg, 0.6 mmol), THF (6.0 mL), and CH_2Cl_2 was stirred under an N_2 atmosphere. Triethylamine (0.166 mL, 1.2 mmol) was added, and the reaction was cooled in an ice bath. To

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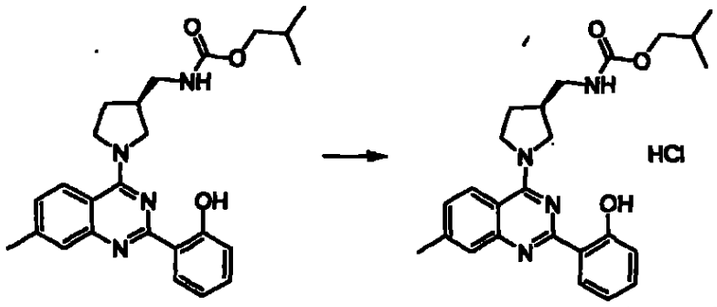
this was added 1 M isobutyl chloroformate solution (78 μL in 600 μL THF, 0.6 mmol). After allowing the reaction mixture to warm to room temperature, CH_2Cl_2 was added, and the organic solution washed twice with water, then dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–20% EtOAc in CH_2Cl_2/hexanes (1:1) gave isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (183 mg, 70%). LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.63 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). LC/MS: *m/z* 435 $(M+H)^+$ at 2.63 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.43 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.22 (d, *J* = 8.7 Hz, 1H), 7.58 (s, 1H), 7.42–7.31 (m, 3H), 6.93–6.89 (m, 2H), 4.17–3.91 (m, 3H), 3.80–3.69 (m, 3H), 3.34–3.30 (m, 1H), 3.21–3.07 (m, 2H), 2.49 (s, 3H), 2.16–2.08 (m, 1H), 1.88–1.74 (m, 2H), 0.88 (d, *J* = 6.7 Hz, 6H).

[002060] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride

[002061]



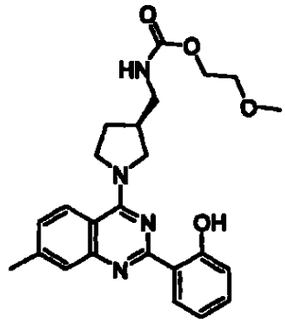
[002062] A solution of isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (183 mg, 0.42 mmol) in CH_2Cl_2 (1.5 mL) was stirred under an N_2 atmosphere. A 1.0 M HCl solution in ether (0.42 ml, 0.42 mmol) was added dropwise to this solution. After 10 minutes, 5 mL ether was added, and a precipitate formed which was filtered and dried to obtain isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (169 mg, 85%). *LC/MS*: *m/z* 435.5 $(M+H)^+$ at 2.64 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.24 (d, *J* = 6.8 Hz, 1H), 7.80 (s, 1H), 7.53–7.45 (m, 2H), 7.41–7.38 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 7.05–7.02 (m, 1H), 4.36–3.85 (m, 5H), 3.77–3.70

(m, 2H), 3.22–3.06 (m, 2H), 2.54 (s, 3H), 2.18–2.13 (m, 1H), 1.87–1.77 (m, 2H), 0.87 (d, J = 6.7 Hz, 6H).

[002063] Example 366

[002064] 2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002065]



[002066] 2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002067] Method A

[002068] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) in anhydrous CH_2Cl_2 was cooled in an ice bath. Then 2-methoxyethyl chloroformate (8.6 μL, 0.075 mmol) was added, followed by the addition of triethylamine (16 μL, 0.11 mmol). After removing the ice bath, the reaction was stirred at room temperature for 4 h. Water and saturated aqueous $NaHCO_3$ solution were added, and the reaction mixture was stirred at room temperature overnight. After separation of the aqueous and organic layers, the organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)), *m/z*: M+1 *obs* = 437.3; t_R = 2.18 minutes

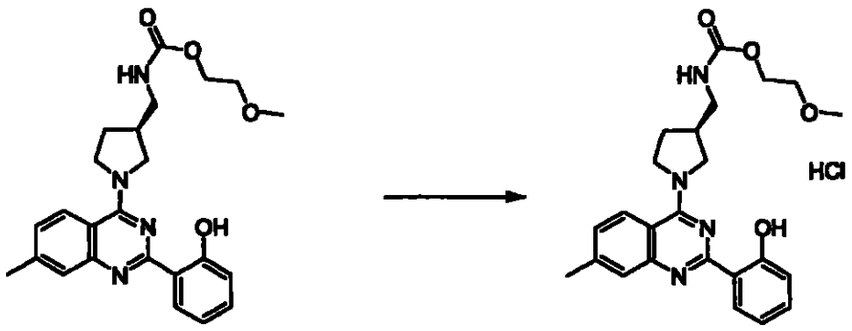
[002069] Method B

[002070] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.12 g, 0.35 mmol) and triethylamine (98 μL, 0.7 mmol) in anhydrous DMF (4.0 mL) was cooled in an ice bath. 2-Methoxyethyl chloroformate (40 mL, 0.35 mmol) was added, and

the ice bath was removed. The solution was stirred at room temperature overnight. Purification via silica gel chromatography using 0–10% MeOH in CH_2Cl_2 gave 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.12 g, 80%). LC/MS: *m/z* 437.5 $(M+H)^+$ at 2.20 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002071] 2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride

[002072]

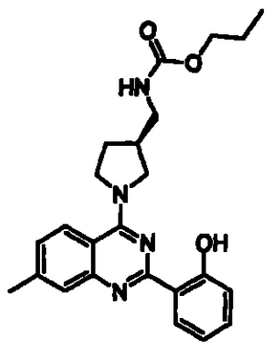


[002073] A 1.0 M HCl solution in Et_2O (0.27 mL, 0.27 mmol) was slowly added to a stirring solution of 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.12 g, 0.27 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 30 minutes at room temperature, then Et_2O was slowly added to the solution until a precipitate formed. After stirring for 1 h, the solid was filtered and washed with Et_2O to obtain 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (0.10 g, 77%). LC/MS: *m/z* 437.1 $(M+H)^+$ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.24 (d, *J* = 7.3 Hz, 1H), 7.77 (s, 1H), 7.52–7.48 (m, 3H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.05–7.02 (m, 1H), 4.22–4.12 (m, 2H), 4.08–4.05 (m, 3H), 3.87–3.83 (m, 1H), 2H), 3.24 (s, 3H), 3.23–3.12 (m, 2H), 2.54 (s, 3H), 2.55–2.52 (m, 1H), 2.17–2.13 (m, 1H), 1.84–1.77 (m, 1H).

[002074] Example 367

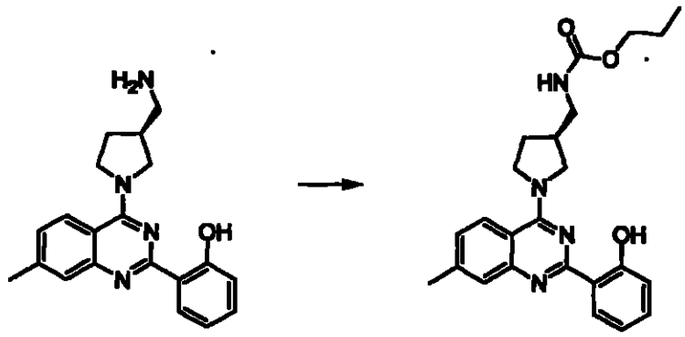
[002075] Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002076]



[002077] Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002078]



[002079] Method A

[002080] Propyl chloroformate (12 mg, 0.10 mmol) and triethylamine (30 mg, 42 μL, 0.30 mmol) were added to 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (33 mg, 0.10 mmol) in 1 mL anhydrous DMF. The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

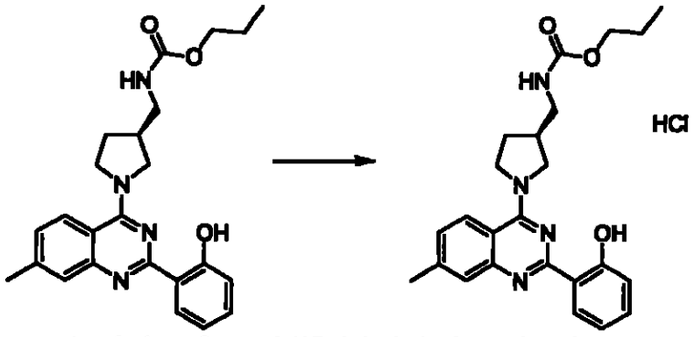
[002081] Method B

[002082] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (301 mg, 0.9 mmol) in CH_2Cl_2 (10 ml) was stirred under an N_2 atmosphere. Triethylamine (0.25 mL, 1.8 mmol) was added, and the solution was cooled to –30 °C. A 1 M

propyl chloroformate solution (0.1 mL in 0.9 mL CH_2Cl_2, 0.9 mmol) was added, and the reaction mixture was allowed to warm to room temperature over a period of 30 minutes. After adding CH_2Cl_2 to the reaction mixture, it was washed 2 times with water, before it was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–20% EtOAc in CH_2Cl_2 gave propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (236 mg, 62%). LC/MS: *m/z* 421 $(M+H)^+$ at 2.54 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.43 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.21 (d, *J* = 8.7 Hz, 1H), 7.58 (s, 1H), 7.39–7.31 (m, 3H), 6.93–6.89 (m, 2H), 4.09–3.86 (m, 6H), 3.78–3.73 (m, 1H), 3.21–3.09 (m, 2H), 2.49 (s, 3H), 2.15–2.09 (m, 1H), 1.83–1.74 (m, 1H), 1.62–1.48 (m, 2H), 0.89–0.86 (m, 3H).

[002083] Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride

[002084]



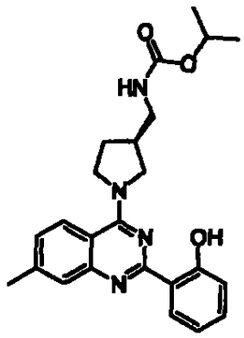
[002085] A solution of propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (232 mg, 0.552 mmol) in CH_2Cl_2 (2 mL) was stirred under an N_2 atmosphere. A 2.0 M HCl solution in ether (0.276 mL, 0.552 mmol) was added dropwise to this solution. After 10 minutes, ether (8 mL) was added until a precipitate formed, which was filtered and dried to obtain propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (223 mg, 88%). LC/MS: *m/z* 421 $(M+H)^+$ at 2.54 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.24 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.82 (s, 1H), 7.54–7.49 (m, 2H), 7.41–7.37 (m, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.06–7.02 (m, 1H), 4.29–3.78 (m, 7H), 3.24–3.08

(m, 2H), 2.54 (s, 3H), 2.18–2.12 (m, 1H), 1.84–1.79 (m, 1H), 1.59–1.50 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H).

[002086] Example 368

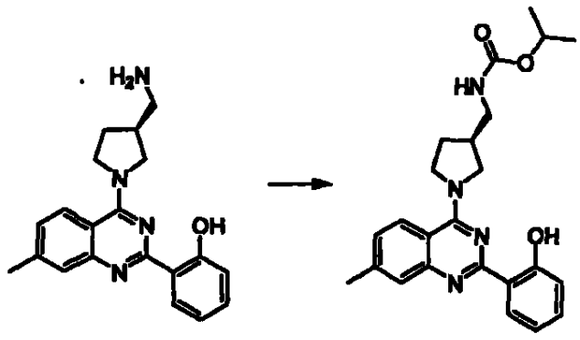
[002087] Isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002088]



[002089] Isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002090]



[002091] Isopropyl chloroformate (12 mg, 0.10 mmol) and triethylamine (30 mg, 42 μL, 0.30 mmol) were added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (33 mg, 0.10 mmol) in 1 mL anhydrous DMF. The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-

methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

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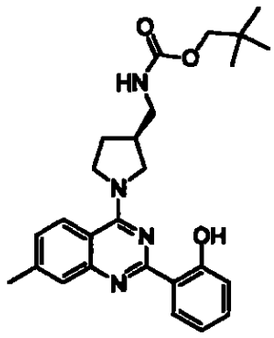
[002092] Example 369

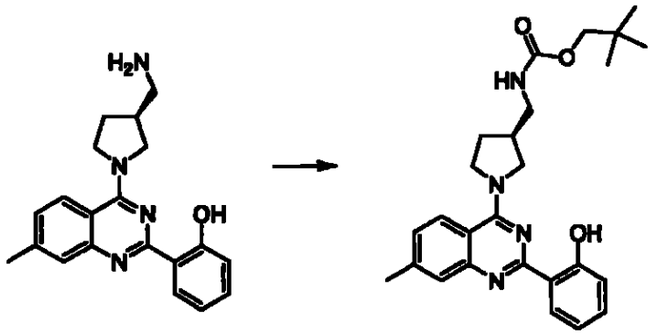
[002093] **Neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[002094]



[002095] **Neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[002096]



[002097] Method A

[002098] Neopentyl chloroformate (15 mg, 0.10 mmol) and triethylamine (30 mg, 42 μL, 0.30 mmol) were added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (33 mg, 0.10 mmol) in 1 mL anhydrous DMF. The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-

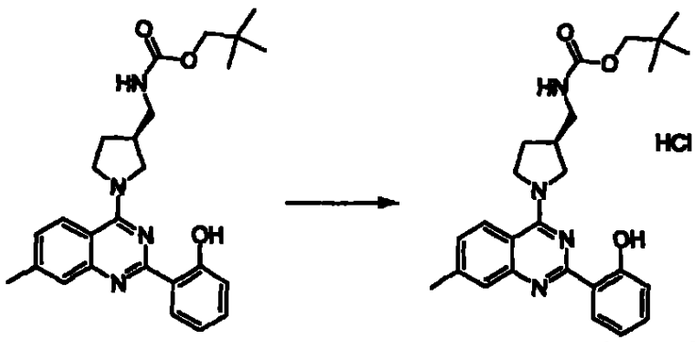
methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.67 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002099] Method B

[002100] A mixture of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (200 mg, 0.6 mmol), THF (6.0 mL), and DMF (1 mL) was stirred under an N_2 atmosphere. Triethylamine (0.166 mL, 1.2 mmol) was added, and the reaction was cooled in an ice bath. To this was added 1 M neopentyl chloroformate solution (89 μL in 600 μL THF, 0.6 mmol). After allowing the reaction mixture to warm to room temperature over a period of 30 minutes, CH_2Cl_2 was added to the reaction mixture, and it was washed once with water before it was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–20% EtOAc in CH_2Cl_2/hexanes (1:1) gave neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (222 mg, 94%). LC/MS: *m/z* 449 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, acetic acid-d4) δ 8.42 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.20 (d, *J* = 8.7 Hz, 1H), 7.57 (s, 1H), 7.40–7.29 (m, 3H), 6.92–6.89 (m, 2H), 4.11–3.92 (m, 3H), 3.78–3.61 (m, 3H), 3.33–3.28 (m, 1H), 3.23–3.10 (m, 2H), 2.49 (s, 3H), 2.16–2.08 (m, 1H), 1.83–1.75 (m, 1H), 0.89 (s, 9H).

[002101] **Neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride**

[002102]



[002103] A solution of neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (215 mg, 0.48 mmol) in CH_2Cl_2 (2 ml) was stirred under an N_2 atmosphere. A 1.0 M HCl solution in ether (0.48 ml, 0.48 mmol) was added dropwise to this solution. After 10 minutes, ether (8 ml) was added until a precipitate formed, which was filtered

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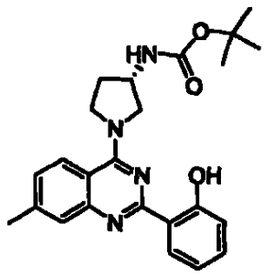
and dried to obtain neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (214 mg, 92%). LC/MS: *m/z* 449 $(M+H)^+$ at 2.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.31 (d, *J* = 8.7 Hz, 1H)1H), 7.85 (s, 1H), 7.54–7.49 (m, 2H), 7.47–7.45 (m, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.05–7.02 (m, 1H), 4.33–3.74 (m, 5H), 3.70–3.64 (m, 2H), 3.19–3.16 (m, 2H), 2.53 (s, 3H), 2.18–2.13 (m, 1H), 1.87–1.81 (m, 1H), 0.88 (s, 9H).

[002104] Example 370

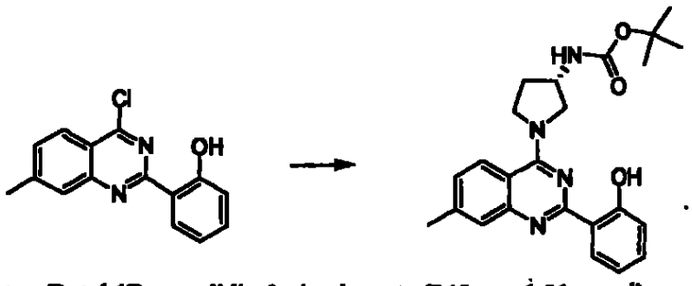
[002105] *tert*-Butyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[002106]



[002107] *tert*-Butyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[002108]



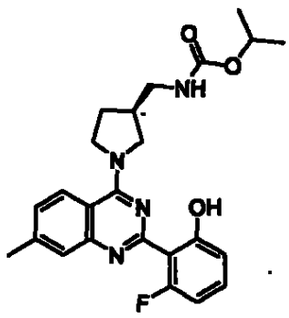
[002109] *tert*-Butyl (*S*)-pyrrolidin-3-ylcarbamate (245 mg, 1.31 mmol) was dissolved in 1.8 mL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (300 mg, 1.1 mmol) dissolved in 1.8 mL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (134 mg, 184 μL, 1.32 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. Purification via silica gel chromatography using

10–100% ethyl acetate/hexanes gave *tert*-butyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 421.0 $(M+H)^+$ at 2.84 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002110] Example 371

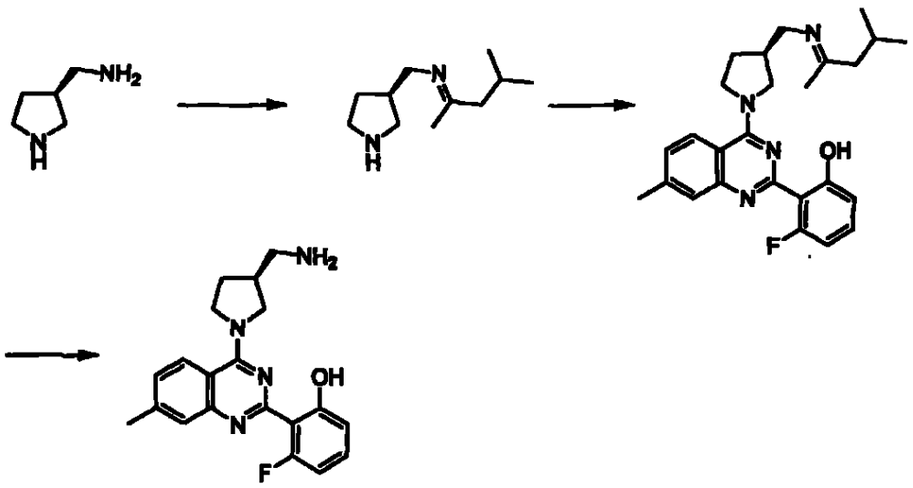
[002111] Isopropyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002112]



[002113] 2-(4-((*S*)-3-(Aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol

[002114]



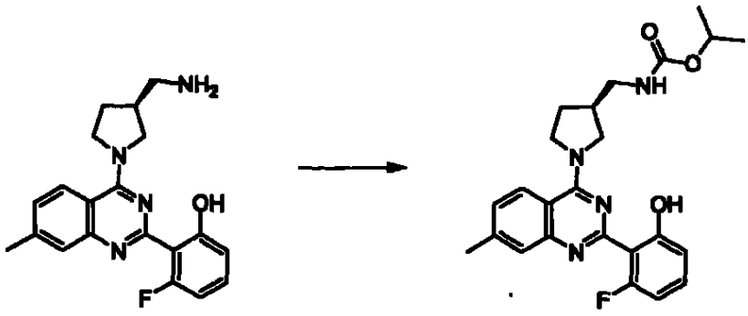
[002115] A mixture of ((*S*)-pyrrolidin-3-yl)methanamine (0.6 g, 6.0 mmol), Na_2CO_3 (2.2 g, 21 mmol) and methyl isobutyl ketone (12 mL, 6.0 mmol) under an N_2 atmosphere was refluxed overnight using a Dean Stark apparatus. After allowing the reaction to cool to room temperature,

2 18

2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (1.73 g, 5.99 mmol) was added, and the mixture was stirred overnight at room temperature under an N_2 atmosphere. The reaction was then quenched with water. The aqueous layer was extracted twice with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to obtain a crude material containing 2-(4-((*S*)-3-((*E*)-(4-methylpentan-2-ylideneamino)methyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol which was then hydrolyzed by heating at 50 °C in 80 mL of a water/isopropanol mixture (1:1) for 6 hours. The reaction was cooled to room temperature, and the aqueous layer was extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 5–20% MeOH and CH_2Cl_2 afforded 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (400 mg, 19% after 3 steps). *LC/MS*: *m/z* 353.1 $(M+H)^+$ at 1.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002116] ***Isopropyl ((S)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate***

[002117]

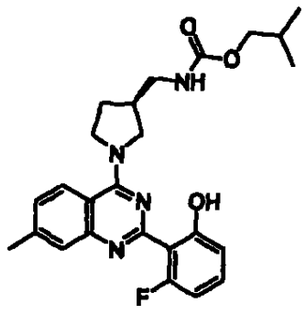


[002118] Isopropyl chloroformate (10 mg, 0.09 mmol) was added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) and triethylamine (25 mL, 0.18 mmol) in DMF (0.6 mL) at –78 °C (external temperature). The reaction mixture was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford isopropyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002119] Example 372

[002120] Isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002121]



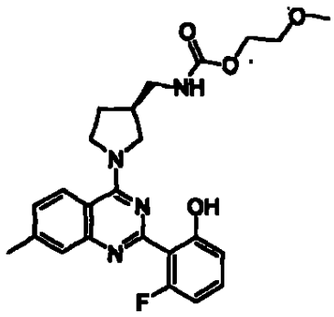
[002122] *Isobutyl* ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002123] Isobutyl chloroformate (12 mg, 0.09 mmol) was added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) and triethylamine (25 mL, 0.18 mmol) in DMF (0.6 mL) at –70 °C (external temperature). The reaction mixture was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 453.5 $(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002124] Example 373

[002125] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

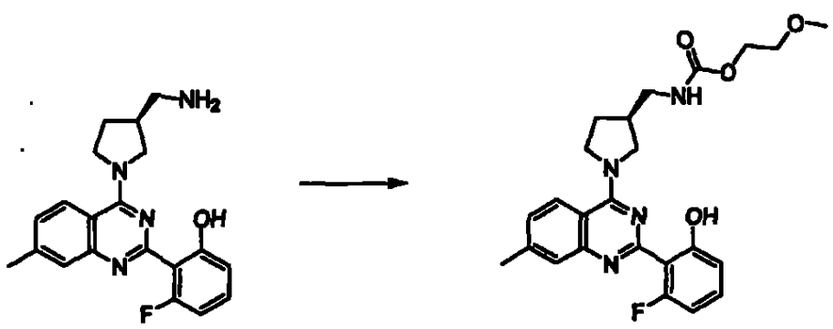
[002126]



219.

[002127] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002128]

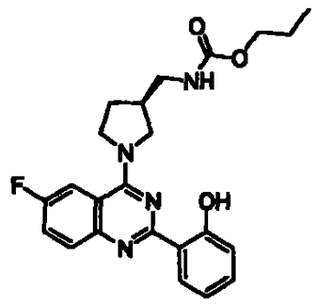


[002129] 2-Methoxyethyl chloroformate (12 mg, 0.09 mmol) was added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) and triethylamine (25 mL, 0.18 mmol) in DMF (0.6 mL) at –78 °C. The reaction mixture was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. *LC/MS*: *m/z* 455.5 $(M+H)^+$ at 2.11 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002130] Example 374

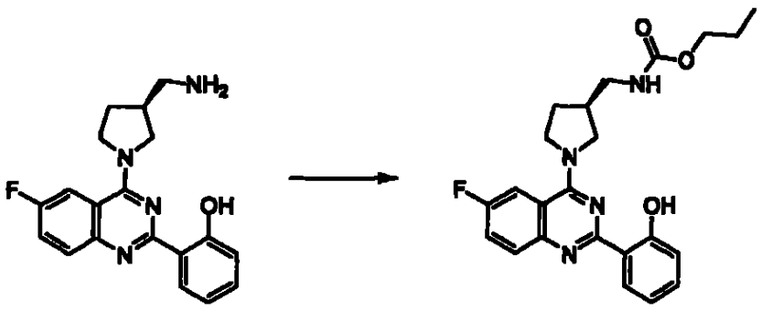
[002131] Propyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002132]



[002133] Propyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002134]

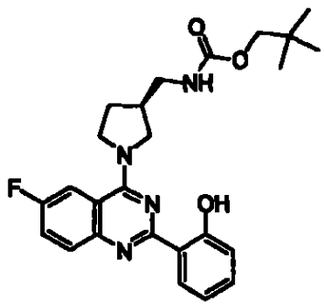


[002135] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol), followed by the addition of propyl chloroformate (11 mg, 0.09 mmol). The reaction was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford propyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 425.3 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002136] Example 375

[002137] Neopentyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002138]



[002139] Neopentyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

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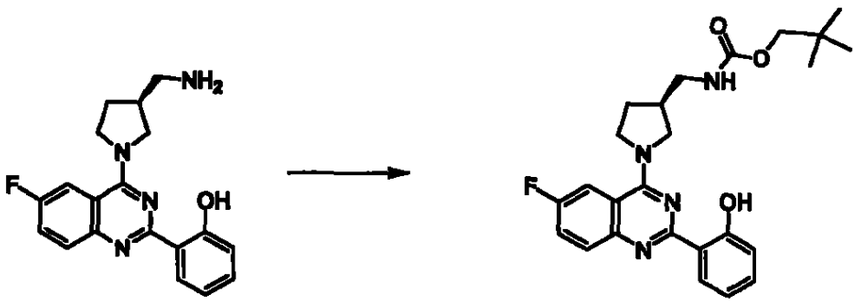
[002140]

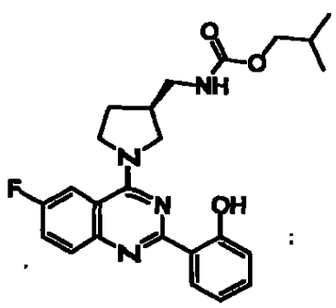


[002141] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol), followed by the addition of neopentyl chloroformate (13 mg, 0.09 mmol). The reaction was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford neopentyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 453.5 $(M+H)^+$ at 2.88 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002142] Example 376

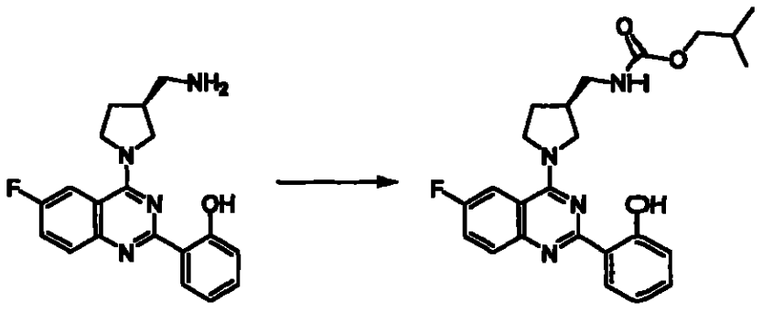
[002143] **Isobutyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[002144]



[002145] **Isobutyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[002146]

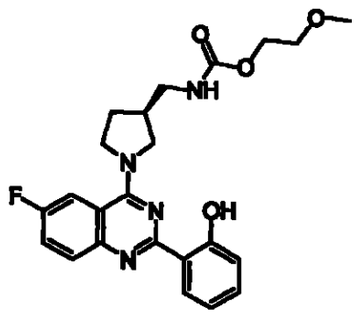


[002147] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol), followed by the addition of isobutyl chloroformate (12 mg, 0.09 mmol). The reaction was warmed to room temperature, and filtered and purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.76 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002148] Example 377

[002149] 2-Methoxyethyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002150]



[002151] 2-Methoxyethyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

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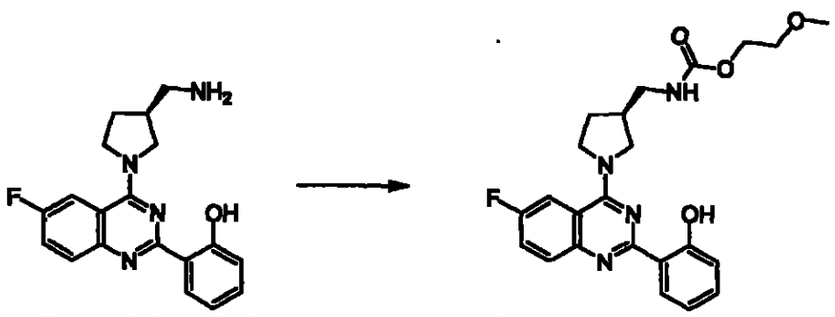
[002152]

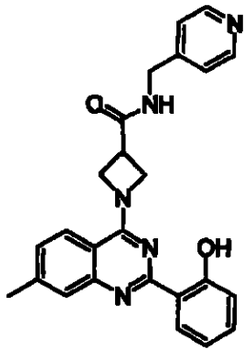


[002153] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol), followed by the addition of 2-methoxyethyl chloroformate (12 mg, 0.09 mmol). The reaction was warmed to room temperature, and filtered and purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ((*S*)-1-(6-fluoro-2- (2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 441.5 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002154] Example 401

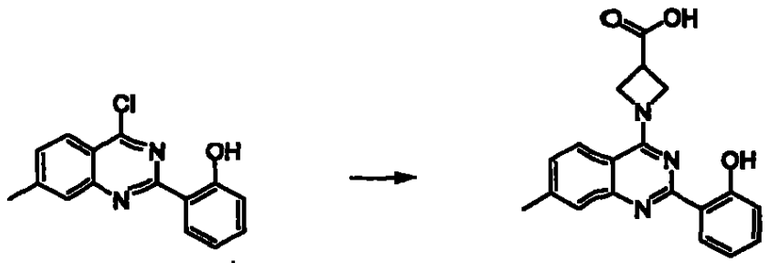
[002155] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-4-yl)methyl)azetidine-3-carboxamide

[002156]



[002157] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid

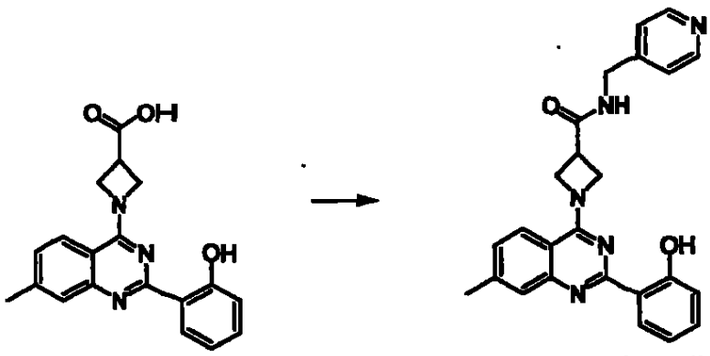
[002158]



[002159] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (2.84 g, 10.5 mmol) and azetidine-3-carboxylic acid (1.06 g, 10.5 mmol) in DMF (100 mL) was added triethylamine (3.18 g, 4.39 mL, 31.5 mmol). The reaction was stirred at room temperature overnight then diluted with H_2O (400 mL). The pH of the solution was adjusted to 3–4 by addition of an aqueous 1 M HCl solution. The white precipitate then obtained was filtered, washed with H_2O, and purified by silica gel chromatography using 0–15% MeOH–CH_2Cl_2 giving 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid. LC/MS: *m/z* 336.3 $(M+H)^+$ at 1.97 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002160] **1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-4-yl)methyl)azetidine-3-carboxamide**

[002161]



[002162] To a solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid (34 mg, 0.1 mmol) and HATU (57 mg, 0.15 mmol) in DMF (1 mL) was added (pyridin-4-yl)methanamine (32 mg, 30μL, 0.30 mmol). The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) giving 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-

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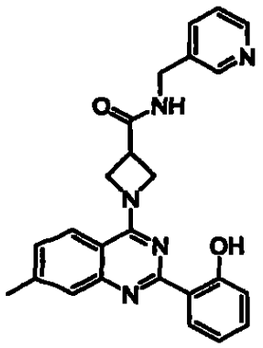
((pyridin-4-yl)methyl)azetidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 426.3 $(M+H)^+$ at 1.72 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002163] Example 402

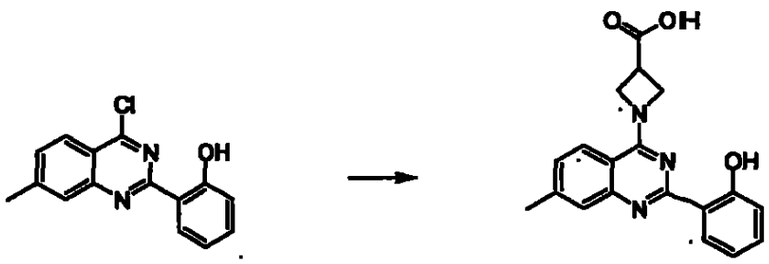
[002164] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)azetidine-3-carboxamide

[002165]



[002166] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid

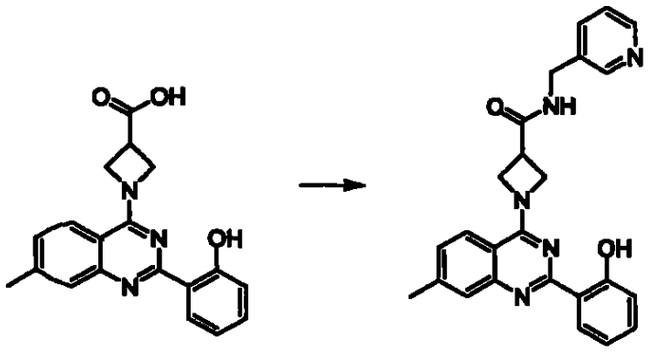
[002167]



[002168] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (2.84 g, 10.5 mmol) and azetidine-3-carboxylic acid (1.06 g, 10.5 mmol) in DMF (100 mL) was added triethylamine (3.18 g, 4.39 mL, 31.5 mmol). The reaction was stirred at room temperature overnight then diluted with H_2O (400 mL). The pH of the solution was adjusted to 3–4 by addition of an aqueous 1 M HCl solution. The white precipitate then obtained was filtered, washed with H_2O, and purified by silica gel chromatography using 0–15% MeOH–CH_2Cl_2 giving 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid. LC/MS: *m/z* 336.3 $(M+H)^+$ at 1.97 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002169] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)azetidine-3-carboxamide

[002170]

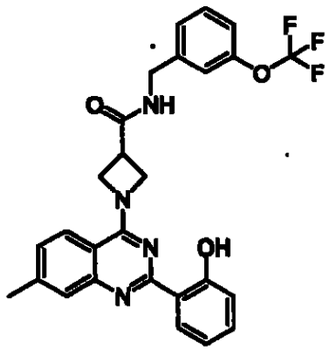


[002171] To a solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid (34 mg, 0.1 mmol) and HATU (57 mg, 0.15 mmol) in DMF (1 mL) was added (pyridin-3-yl)methanamine (32 mg, 30μL, 0.30 mmol). The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)azetidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 426.3 $(M+H)^+$ at 1.72 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002172] Example 403

[002173] *N*-(3-(Trifluoromethoxy)benzyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxamide

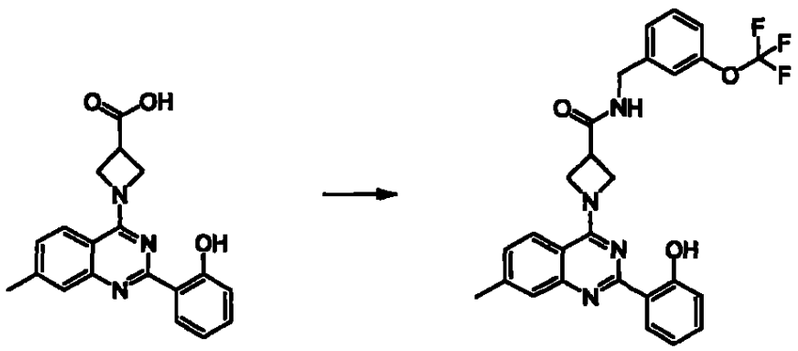
[002174]



[002175] *N*-(3-(Trifluoromethoxy)benzyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxamide

253

[002176]

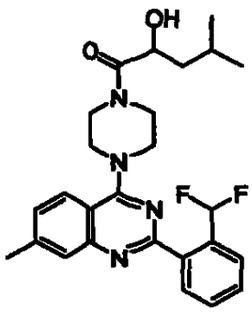


[002177] To a solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid (34 mg, 0.10 mmol) and HATU (57 mg, 0.15 mmol) in DMF (1 mL) was added (3-(trifluoromethoxy)phenyl)methanamine (57 μL, 0.30 mmol). The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-(3-(trifluoromethoxy)benzyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 509.3 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

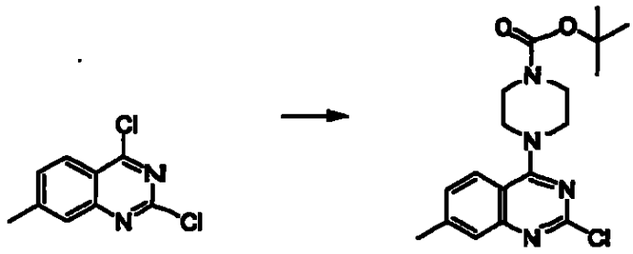
[002178] Example 501

[002179] 1-(4-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[002180]



[002181] *tert*-Butyl 4-(2-chloro-7-methylquinazolin-4-yl)piperazine-1-carboxylate

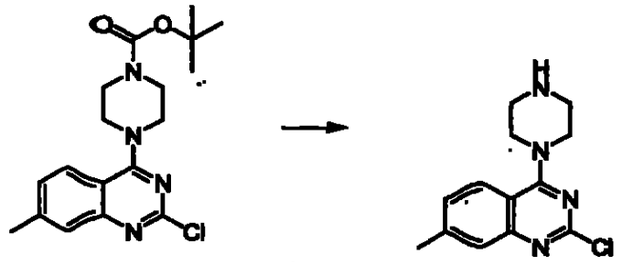


[002182]

[002183] A solution of 2,4-dichloro-7-methylquinazoline (0.43 g, 2.0 mmol), *tert*-butyl piperazine-1-carboxylate (0.37 g, 2.0 mmol), and triethylamine (0.56 mL, 4.0 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature overnight. The solution was washed with water, dried over Na_2SO_4, and evaporated to give *tert*-butyl 4-(2-chloro-7-methylquinazolin-4-yl)piperazine-1-carboxylate (0.72 g, 99%). LC/MS: *m/z* 363.1 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002184] **2-chloro-7-methyl-4-(piperazin-1-yl)quinazoline dihydrochloride**

[002185]



[002186] *tert*-Butyl 4-(2-chloro-7-methylquinazolin-4-yl)piperazine-1-carboxylate (0.72 g, 2.0 mmol) in 4 M HCl in dioxane (10 mL) was stirred at room temperature for five hours. The solvent was evaporated to give 2-chloro-7-methyl-4-(piperazin-1-yl)quinazoline dihydrochloride (0.67 g, 100%). LC/MS: *m/z* 263.3 $(M+H)^+$ at 1.75 min (10%—99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002187] **1-(4-(2-Chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

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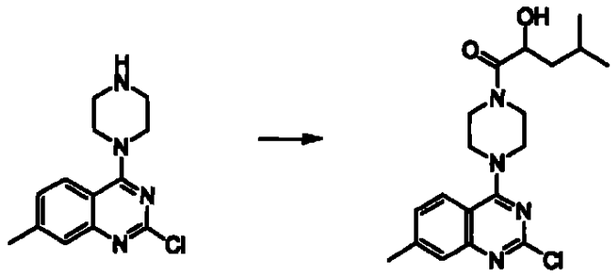
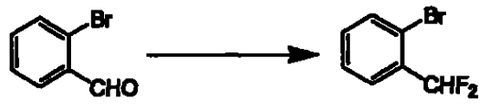


[002188]

[002189] A solution of 2-chloro-7-methyl-4-(piperazin-1-yl)quinazoline dihydrochloride (127 mg, 0.38 mmol), 2-hydroxy-4-methylpentanoic acid (55 mg, 0.42 mmol), HATU (158 mg, 0.42 mmol), and triethylamine (163 μL, 1.2 mmol) in DMF (4 mL) was stirred at room temperature for four hours. The reaction was diluted with water and was extracted with EtOAc. The combined extracts were washed with saturated aqueous NaCl and water, dried over Na_2SO_4, and evaporated. Purification via silica gel chromatography using 0–50% EtOAc in hexanes gave 1-(4-(2-chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (23 mg, 16%). LC/MS: *m/z* 377.3 $(M+H)^+$ at 2.71 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002190] **1-Bromo-2-(difluoromethyl)benzene**

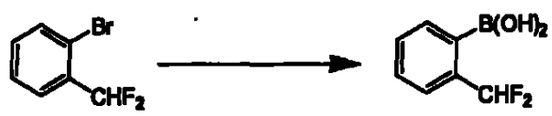
[002191]



[002192] A mixture of 2-bromo benzaldehyde (27.1 g, 0.15 mol) and (diethylamino)sulfur trifluoride (52 g, 0.32 mol) in anhydrous benzene (250 mL) was heated to reflux overnight under an N_2 atmosphere. The mixture was treated with $NaHCO_3$ (sat. aq.) and CH_2Cl_2, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with water and saturated aq. NaCl. Removal of the solvent gave 1-bromo-2-difluoromethylbenzene (16 g, 52%). ^1H NMR($CDCl_3$): δ 7.68 (d, 1H, J = 7.6), 7.62 (d, 1 H, J = 7.6), 7.43 (t, 1 H, J = 7.6), 7.34 (t, 1 H, J = 7.6), 7.06–6.79 (t, 1 H, J = 55.2).

[002193] **2-(Difluoromethyl)phenylboronic acid**

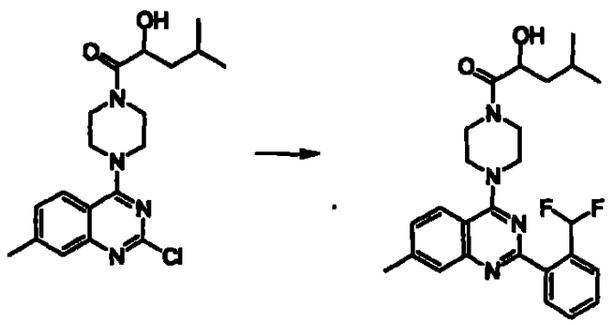
[002194]



[002195] To a solution of 1-bromo-2-difluoromethylbenzene (16 g, 0.077 mol) in THF (300 mL) was added *n*-BuLi (2.5 M, 46 mL, 0.12 mol) dropwise at –78 °C. After one hour, trimethyl borate (16 g, 0.15 mol) was added dropwise. The mixture was warmed to room temperature slowly overnight, and then the mixture was treated with water and ethyl acetate. The organic layer was extracted with a 10% aqueous NaOH solution. The aqueous solution was acidified with dilute aq. HCl and extracted with ethyl acetate. Removal of the solvent gave 2-(difluoromethyl)phenylboronic (0.7 g, 5.3%). ^{1}H NMR($CDCl_3$): δ 8.28 (d, 1 H, J = 7.2), 7.86 (d, 1H, J = 7.2), 7.58–7.79 (m, 1 H), 7.73 (t, 1 H, J = 7.2), 7.65 (t, 1 H).

[002196] **1-(4-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[002197]

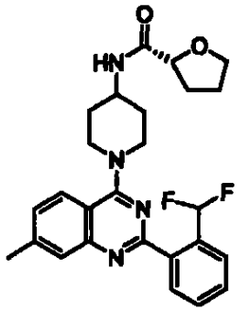


[002198] A mixture of 1-(4-(2-chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (23 mg, 61 μmol), 2-(difluoromethyl)phenylboronic acid (13 mg, 73 μmol), $Pd(dppf)Cl_2$ (3 mg, 3.7 μmol), and K_2CO_3 (17 mg, 122 μmol) in DMF (1 mL) and H_2O (0.5 mL) was heated in a sealed microwave vial at 170 °C for 6 minutes. After filtration and evaporation of the solvents, the mixture was purified using preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 1-(4-(2-(2-(difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 469.3 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002199] Example 502

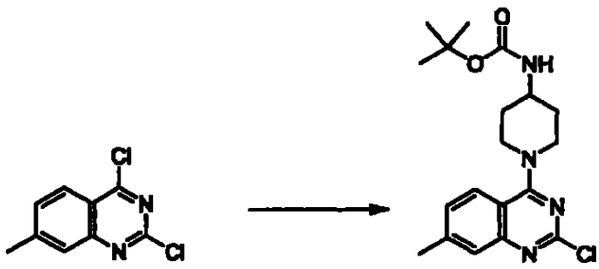
[002200] **(2*R*)-*N*-(1-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide**

[00220T]



[002202] *tert*-Butyl 1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

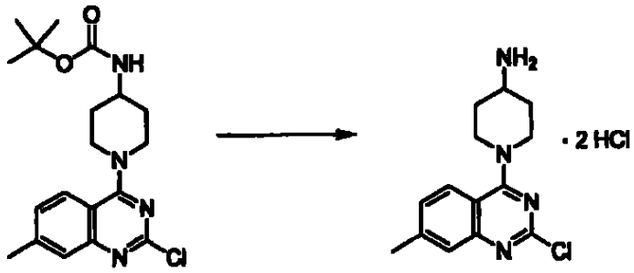
[002203]



[002204] To a solution of 2,4-dichloro-7-methylquinazoline (1.06 g, 5.0 mmol) in CH_2Cl_2 (20 mL) cooled in an ice bath under an N_2 atmosphere was added *tert*-butyl piperidin-4-ylcarbamate (1.0 g, 5.0 mmol) dissolved in CH_2Cl_2 (30 mL). To this was added triethylamine (1.4 mL, 10.0 mmol), and the reaction was allowed to warm to room temperature. After stirring for 1 h, the solution was washed with water and dried over Na_2SO_4. The solvents were evaporated to obtain *tert*-butyl 1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as a yellow solid (1.6 g, 85%). LC/MS: *m/z* 377.5 $(M+H)^+$ at 2.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002205] 1-(2-Chloro-7-methylquinazolin-4-yl)piperidin-4-amine dihydrochloride

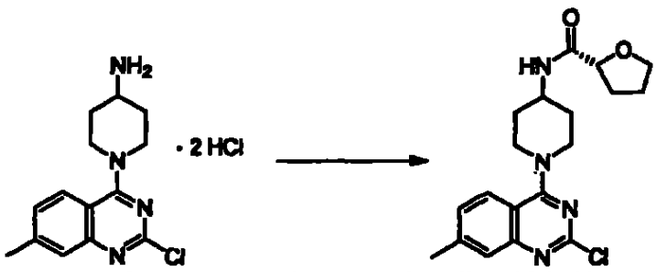
[002206]



[002207] Under an N_2 atmosphere, a 4 M HCl solution in dioxane (50 mL) was added to *tert*-butyl 1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (1.06 g, 2.82 mmol), and the mixture was stirred for 3 h. After evaporating the solvents, the resulting solid was taken up in CH_2Cl_2 and EtOAc and concentrated to yield 1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-amine dihydrochloride as a pale pink powder (985 mg, 100%). LC/MS: *m/z* 277.3 $(M+H)^+$ at 1.57 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002208] **(*R*)-*N*-(1-(2-Chloro-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide**

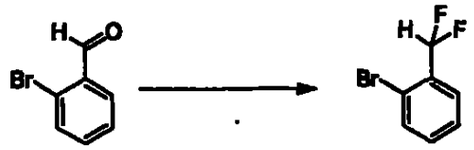
[002209]



[002210] To a mixture of (*R*)-tetrahydrofuran-2-carboxylic acid (0.13 mL, 1.58 mmol) in CH_2Cl_2 (2 mL) was added HATU (0.5 g, 1.58 mmol). After adding triethylamine (0.74 mL, 5.28 mmol), the solution was stirred for 30 min. 1-(2-Chloro-7-methylquinazolin-4-yl)piperidin-4-amine dihydrochloride (460 mg, 1.32 mmol) was added and the reaction was stirred overnight. The yellow, cloudy solution was washed 4 times with H_2O, and the aqueous layer was re-extracted with CH_2Cl_2. After concentrating the combined organic phases, purification via silica gel chromatography using 0–100% EtOAc in hexanes provided (*R*)-*N*-(1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide (0.17 g, 33%). LC/MS: *m/z* 475.3 $(M+H)^+$ at 2.20 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002211] **1-Bromo-2-difluoromethyl-benzene**

[002212]



[002213] A solution of 2-bromobenzaldehyde (55.5 g, 300 mmol) and (diethylamino)sulfur trifluoride (75.0 g, 467 mmol) in 250 ml dichloromethane was refluxed under a nitrogen

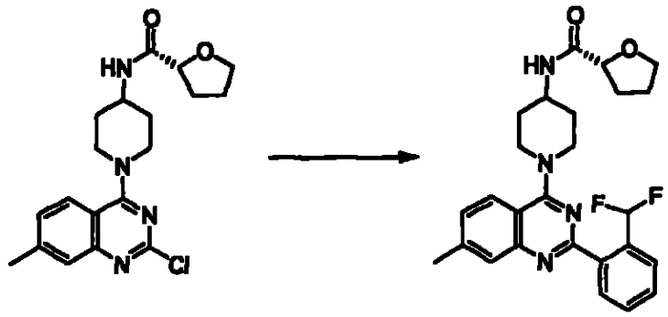
atmosphere overnight. The cooled solution was poured into 0.5 L aqueous 15% $NaHCO_3$ and stirred until no more CO_2 was produced. The layers were separated, and the aqueous layer was extracted with 250 ml dichloromethane. The combined organic layers were washed with 250 ml 5% aq. $NaHCO_3$ and saturated aq. NaCl, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The crude material was purified by vacuum distillation, and the fraction boiling at 62–63 °C at 12 mbar was collected, yielding 1-bromo-2-difluoromethyl-benzene (42.6 g, 69%) as a light-yellow oil.

[002214] 2-(2-Difluoromethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

[002215]

[002216] To a solution of 1-bromo-2-difluoromethyl-benzene (19.8 g, 95.7 mmol) in dry THF (200 ml) at –78 °C under a nitrogen atmosphere was added 2.5 M *n*-BuLi in hexanes (42 ml, 105 mmol) slowly. After completion of the addition, the resulting dark solution was stirred for an additional hour at –78 °C. Subsequently, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25 ml, 123 mmol) was added, and the solution was slowly warmed to room temperature. After stirring overnight at room temperature under a nitrogen atmosphere the solution was poured into 400 ml water. Ethyl acetate (300 ml) was added and the layers were separated. The aqueous layer was extracted twice with ethyl acetate (150 ml and 50 ml respectively), and the combined organic layers were washed with water, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The resulting brown oil (21 g) was purified by bulb-to-bulb-distillation at $3x10^{-3}$ mbar at 90–95 °C to yield 2-(2-difluoromethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (14.4 g, 59%) as a slightly yellow oil.

[002217] (2*R*)-*N*-(1-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide



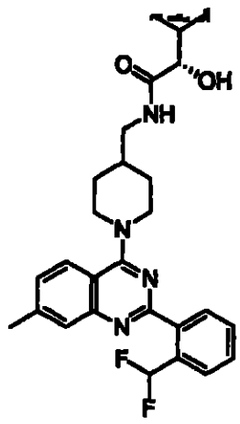
[002218]

[002219] To a mixture of (*R*)-*N*-(1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide (65.2 mg, 0.17 mmol), 2-(2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.09 mL, 0.35 mmol), $Pd(dppf)Cl_2$ (17.1 mg, 0.02 mmol), and K_2CO_3 (48.1 mg, 0.35 mmol) was added DMF (3.3 mL), and the reaction was heated in a microwave synthesizer at 170 °C for 6 min. Since LC/MS showed that reaction was not complete, another 2 equivalents of 2-(2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.09 mL, 0.38 mmol) were added, and the reaction was heated to 170 °C in a microwave synthesizer for 6 minutes The solution was diluted with EtOAc and washed with H_2O. The aqueous fraction was re-extracted with EtOAc and the organic layers were combined, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0-40% EtOAc in CH_2Cl_2/hexanes (1:1) gave (2*R*)-*N*-(1-(2-(2-(difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide (38 mg, 47%). *LC/MS*: *m/z* 467.3 $(M+H)^+$ at 2.20 min (10%-99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002220] Example 503

[002221] (2*S*)-*N*-((1-(2-(2-(Difluoromethyl)pheayl)-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide

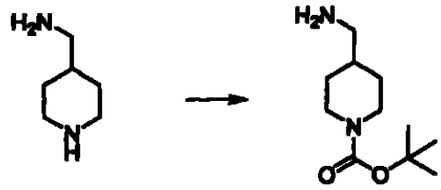
227



[002222]

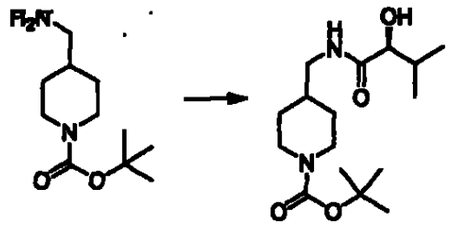
[002223] *tert*-Butyl 4-(aminomethyl)piperidine-1-carboxylate

[002224]



[002225] A solution of 4-(aminomethyl)-piperidine (25.3 g, 222 mmol) and benzaldehyde (23.5 g, 222 mmol) in 250 mL toluene was refluxed overnight under a nitrogen atmosphere in a flask equipped with a Dean-Stark trap. The solution was cooled to 0–5 °C in an ice bath, and Boc_2O (53.2 g, 244 mmol) was added in one portion. The ice bath was removed, and stirring at room temperature was continued for 6 hours. The mixture was evaporated to dryness under reduced pressure, and the residue was stirred overnight with potassium bisulphate in water (33.2 g $KHSO_4$ in 244 mL water). The solution was extracted twice with 200 ml portions of diethyl ether and was made alkaline with 50 ml 30% aqueous sodium hydroxide solution. After saturation of the solution with sodium chloride, it was extracted with dichloromethane (1x 150 ml, 2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness, yielding *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (41.8 g, 88%) as an orange oil.

[002226] 4-[((*S*)-2-Hydroxy-3-methyl-butyrylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester

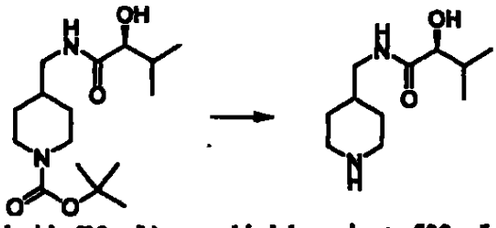


[002227]

[002228] HOBt (23.5 g, 174 mmol) and EDCI·HCl (33.5 g, 174 mmol) were added to a mixture of *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (37.3 g, 174 mmol), (*S*)-(+)-2-hydroxy-3-methyl-butanoic acid (20.6 g, 174 mmol), and triethylamine (50 mL, 349 mmol) in a mixture of dichloromethane (500 mL) and DMF (250 mL) cooled in an ice bath. The reaction was stirred overnight at room temperature. An additional portion of EDCI·HCl (5 g) and triethylamine (4 mL) were added, and stirring was continued for another 4 hours. The mixture was diluted to 1 L by the addition of dichloromethane and was washed with 500 mL portions of water, 1 N HCl solution, 5% aq. $NaHCO_3$ solution, water, and saturated aqueous NaCl solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure yielding 52 g of the crude product. This crude material was stirred with 200 mL diisopropyl ether, and the solid was collected by filtration and washed twice with 100 mL portions of diisopropyl ether to yield to 33 g (64%) of 4-[((*S*)-2-hydroxy-3-methyl-butyrylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester.

[002229] **(*S*)-2-Hydroxy-3-methyl-*N*-piperidin-4-ylmethyl-butyramide**

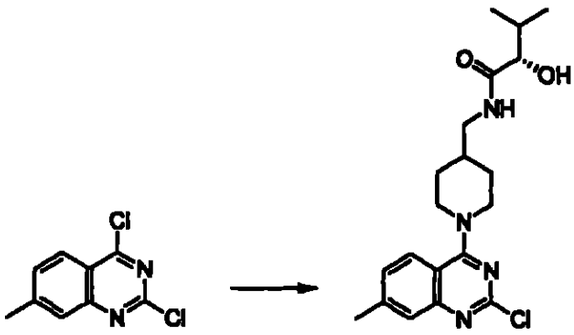
[002230]



[002231] Acetyl chloride (30 mL) was added dropwise to 500 mL methanol cooled in an ice bath, and after completion of the addition the solution was stirred at room temperature for 30 minutes. 4-[((*S*)-2-hydroxy-3-methyl-butyrylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester (33 g) in 150 mL methanol was added, and stirring was continued for 2 hours at room temperature. The solution was evaporated to dryness to yield to 26.6 g of (*S*)-2-hydroxy-3-methyl-*N*-piperidin-4-ylmethyl-butyramide hydrochloride as a white solid.

[002232] (*S*)-*N*-((1-(2-Chloro-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide

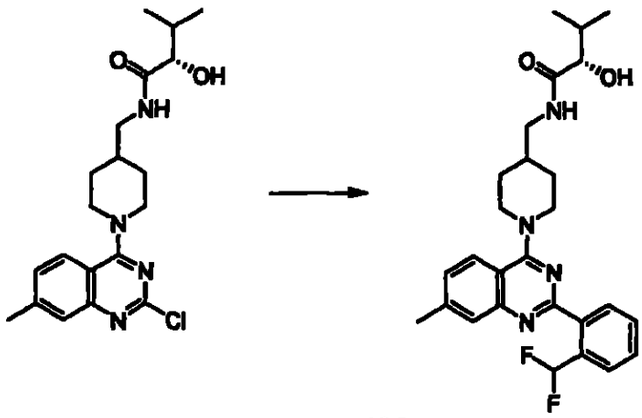
[002233]



[002234] A solution of 2,4-dichloro-7-methylquinazoline (1.07 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was cooled in an ice bath. (*S*)-2-Hydroxy-3-methyl-N-((piperidin-4-yl)methyl)butanamide hydrochloride (1.25 g, 5.0 mmol) suspended in 30 mL of CH_2Cl_2 was added in portions, followed by the addition of triethylamine (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and was stirred for 1.5 h. After washing the mixture 4 times with H_2O, the aqueous portion was re-extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and dried under vacuum to obtain (*S*)-*N*-((1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide as a yellow solid (1.83 g, 94%). LC/MS: *m/z* 391.3 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002235] (2*S*)-*N*-((1-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide

[002236]



[002237] To a solution of (*S*)-*N*-((1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide (200 mg, 0.51 mmol), 2-(2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (195 μL, 0.77 mmol), and K_2CO_3 (142 mg, 1.02 mmol) in a DMF:H_2O mixture (4:1) was added $Pd(dppf)Cl_2$ (25.3 mg, 0.03 mmol). The reaction mixture was heated in a microwave synthesizer at 170 °C for 6 minutes The reaction was diluted with EtOAc and washed with 30 mL saturated aqueous NaCl solution. The organic portion was 3 times washed with H_2O, and the combined aqueous layers were re-extracted 3 times with EtOAc. All combined organic portions were then dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–70% EtOAc in CH_2Cl_2:hexanes (1:1) yielded 177 mg (71%) of (2*S*)-*N*-((1-(2-(2-(difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide which crystallized as a white solid after freezing it for 1 h. *LC/MS*: *m/z* 483.3 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002238] Table 3 below recites analytical data for exemplary compounds of the present invention.

Table 3

Cmpd No.	LCMS m/z	LC RT min
101	449.3	2.79
102	421	2.48
103	499.3	2.97
104	464.5	2.03
105	447.1	2.32
106	465.5	2.47
107	442.5	1.97
108	407.5	2.21
109	393.1	2.04
110	461.1	2.56
111	453.5	3.21
112	461.3	2.49
113	421.1	2.76
114	474.3	1.19
115	421.3	2.51
116	442.5	1.96
117	439.5	2.79
118	393.3	2.22
119	465.2	2.5

Cmpd No.	LCMS m/z	LC RT min
120	435.3	2.65
121	393.3	2.21
122	435.3	2.56
123	465.3	2.5
124	407.5	2.29
125	453.4	2.79
126	471.2	2.93
127	445.5	3.32
128	451.5	2.62
129	407.5	2.31
130	469.3	2.87
131	469.4	2.88
132	456.5	2.04
133	454.3	1.94
134	421.1	2.46
135	467.1	2.59
136	453.3	3.02
137	407.3	2.28
138	453.3	2.43

Cmpd No.	LCMS m/z	LC RT min
139	439.5	2.95
140	485.5	2.94
141	459.3	2.13
142	448.3	3.17
143	439.5	2.99
144	435.3	2.9
145	437.3	2.04
146	455.5	2.45
147	453.3	2.4
148	439.5	2.8
149	485.5	2.23
150	449.3	2.22
151	435.5	2.13
152	466.5	2.02
153	453.4	2.73
154	436.3	1.94
155	477.5	2.96
156	474.3	1.19
157	485.4	3.02

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Cmpd No.	LC-MS M+1	LC-RT min
156	403.5	2.34
159	421.3	2.6
160	467.3	3.13
162	467.3	2.33
163	453.3	2.25
164	451.3	2.16
165	421.3	2.4
166	434.53	2.61
167	491.3	2.46
168	435.3	2.91
169	577.4	2.5
170	473.1	2.63
171	517.5	3.49
172	466	2.77
173	393.1	2.03
174	407.5	2.41
175	460.5	2.33
176	435.5	2.62
177	447.1	2.53
178	447.3	2.5
179	427.2	2.59
180	436.2	2.86
181	436.3	2.69
182	435.3	2.5
183	436.3	2.5
184	449.3	2.5
185	449.3	2.56
201	454.5	1.87
203	449.3	2.34
204	449.3	2.33
205	433.3	2.33
206	433.5	2.34
207	449.5	2.34
208	449.5	2.33
209	447.5	2.27
210	463.5	2.34
211	463.5	2.34
212	417	2.3
213	453.5	1.96
214	463.5	2.32
215	463.5	2.36
216	463.5	2.35
217	463.6	2.35
218	447.5	2.02

Cmpd No.	LC-MS M+1	LC-RT min
219	477.4	2.64
220	447.5	2.19
221	461.5	2.22
222	531.3	3.06
223	468.3	1.86
224	437.1	2.64
225	468.6	2.19
226	417.5	2.3
227	470.5	1.96
228	470.5	1.96
229	513.3	2.82
230	447.3	2.21
231	461.1	2.17
232	463.3	2.58
233	421.2	2.17
234	449.2	2.42
235	407.5	2.04
236	407.3	2.08
237	407.5	2.09
238	435.3	2.4
239	461.1	2.4
240	435.5	2.29
241	421.1	2.24
242	421.3	2.18
243	421.3	2.18
244	421.3	2.18
245	449.3	2.45
246	475.1	2.46
247	435.3	2.31
248	435.3	2.24
249	461.3	2.42
250	449.5	2.77
251	421	2.46
252	449.3	2.8
253	449.5	2.76
254	421.1	2.5
255	435.5	2.61
256	435.5	2.61
257	451.1	2.34
258	441.5	2.8
259	435.2	3.03
260	467.1	2.56
261	469.1	2.2
262	439.3	2.31

Cmpd No.	LC-MS M+1	LC-RT min
264	435.1	2.6
265	449.3	2.72
266	449.2	2.55
267	449.3	2.58
268	449.1	2.54
269	449.5	2.57
270	435.2	2.88
271	447.2	2.48
272	449.2	2.57
273	449.2	2.57
274	463.4	2.42
275	463.4	2.43
276	433.2	2.33
277	433.2	2.32
278	449.2	2.85
279	435.4	2.61
301	436	2.41
302	419	2.35
303	419	2.34
304	435	2.39
305	449.3	2.18
306	449.3	2.16
307	449.3	2.18
308	433.5	2.11
309	455.2	2.61
310	433.5	2.13
311	403.7	2.17
312	389.2	2.36
313	441	2.78
314	463.4	2.66
315	432.5	2.24
316	433.5	2.05
317	447.3	2.07
318	454.3	1.79
319	456.5	1.85
320	456.5	1.84
321	469.3	2.57
322	454.4	2.08
323	445.4	2.85
324	480.4	2.1
325	509.5	2.71
326	455.3	2.43
327	450.3	2.39
328	426.3	1.91

Cmpd No.	LC/MS [M+1]	LC/MS Rt min
329	393.3	2.23
330	465.4	2.66
331	477.3	2.81
332	511.5	3.07
333	443.5	2.63
334	511.5	3.1
335	439.5	2.25
336	493.5	3.03
337	439.5	2.25
338	451.5	2.15
339	467.3	2.5
340	445.4	2.95
341	443.4	2.73
342	466.4	2.39
343	493.4	2.76
344	443.3	2.69
345	453.3	2.05
346	407.5	2.2
347	430.5	1.95
348	430.5	2.43
349	430.5	1.98
350	444.5	1.85
351	444.5	2.24
352	444.5	1.89
353	426.1	1.93
354	426.1	2.33
355	453.3	2.29
356	453.3	2.29

Cmpd No.	LC/MS [M+1]	LC/MS Rt min
357	407.3	2.26
358	477.3	2.8
359	491.3	2.24
360	473.1	2.32
361	449.3	2.4
362	469.1	2.58
363	469.1	2.58
364	407.7	2.3
365	435.3	2.57
366	437.3	2.18
367	421.1	2.44
368	421.1	2.43
369	449.3	2.67
370	421	2.84
371	439.5	2.31
372	453.5	2.46
373	455.5	2.11
374	425.3	2.31
375	453.5	2.88
376	439.5	2.76
377	441.5	2.3
401	426.3	1.72
402	426.3	1.72
403	509.3	2.73
404	393.2	1.95
405	421.2	2.29
406	421.2	2.2
407	435.4	2.23

Cmpd No.	LC/MS [M+1]	LC/MS Rt min
408	435.4	2.18
409	421.2	2.15
410	421.1	2.4
411	435.2	2.24
412	405.2	2.09
413	435.4	2.18
414	435.2	2.17
415	449.2	2.25
416	435.3	2.25
417	419.4	2.06
418	421.2	2.57
419	423.2	2.15
420	407.2	2.42
501	467.3	2.14
502	469.3	2.44
503	483.3	2.24
504	455.4	2.91
505	367.9	2.79
506	339.9	2.36
507	469.3	2.97
508	441.3	2.54
509	455.5	2.13
510	469.5	2.37
511	471.3	2.28
512	467.3	2.14
513	483.3	2.26
514	483.3	2.24

[002239] Methods:

[002240] (A) Micromass MUX LCT 4 channel LC/MS, Waters 60F pump, Gilson 215 4 probe autosampler, Gilson 849 injection module, 1.5 mL/min/column flow rate, 10-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 columns (50 x 4.60 mm), Waters MUX UV-2488 UV detector, Cedex 75 ELSD detectors.

[002241] (B) PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 10-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.

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[002242] (C) PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 40-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.

[002243] ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUNDS

[002244] A) Optical methods for assaying NaV inhibition properties of compounds:

[002245] Compounds of the invention are useful as antagonists of voltage-gated sodium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the NaV of interest were placed into microtiter plates. After an incubation period, the cells were stained with fluorescent dyes sensitive to the transmembrane potential. The test compounds were added to the microtiter plate. The cells were stimulated with either a chemical or electrical means to evoke a NaV dependent membrane potential change from unblocked channels, which was detected and measured with trans-membrane potential-sensitive dyes. Antagonists were detected as a decreased membrane potential response to the stimulus. The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR®) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today 4(9): 431-439).

[002246] B) VIPR® optical membrane potential assay method with chemical stimulation

[002247] Cell Handling and Dye Loading

[002248] 24 hours before the assay on VIPR, CHO cells endogenously expressing a NaV1.2 type voltage-gated NaV are seeded in 96-well poly-lysine coated plates at 60,000 cells per well. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

1) On the day of the assay, the drug is aspirated and cells are washed twice with 225 µL of Bath Solution #2 (BS#2).
2) A 15 uM CC2-DMPE solution is prepared by mixing 5 mM coumarin stock solution with 10% Pluronic 127 1:1 and then dissolving the mix in the appropriate volume of BS#2.
3) After bath solution is removed from the 96-well plates, the cells are loaded with 80 µL of the CC2-DMPE solution. Plates are incubated in the dark for 30 minutes at room temperature.
4) While the cells are being stained with coumarin, a 15 µL oxonol solution in BS#2 is prepared. In addition to $DiSBAC_2(3)$, this solution should contain 0.75 mM ABSC1 and 30 µL veratridine (prepared from 10 mM EtOH stock, Sigma #V-5754).
5) After 30 minutes, CC2-DMPE is removed and the cells are washed twice with 225 µL of BS#2. As before, the residual volume should be 40 µL.
6) Upon removing the bath, the cells are loaded with 80 µL of the $DiSBAC_2(3)$ solution, after which test compound, dissolved in DMSO, is added to achieve the desired test concentration to each well from the drug addition plate and mixed thoroughly. The volume in the well should be roughly 121 µL. The cells are then incubated for 20-30 minutes.
7) Once the incubation is complete, the cells are ready to be assayed on VIPR® with a sodium addback protocol. 120 µL of Bath solution #1 is added to stimulate the NaV dependent depolarization. 200 µL tetracaine was used as an antagonist positive control for block of the NaV channel.

[002249] Analysis of VIPR® Data:

[002250] Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

$$(\text{intensity}_{460\,nm} - \text{background}_{460\,nm})$$

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$$R(t) = \frac{}{(\text{intensity}_{580\,nm} - \text{background}_{580\,nm})}$$

[002251] The data is further reduced by calculating the initial (R_i) and final (R_f) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus $R = R_f/R_i$ is then calculated. For the Na^+ addback analysis time windows, baseline is 2-7 sec and final response is sampled at 15-24 sec.

[002252] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative (N) and positive (P) controls are calculated as above. The compound antagonist activity A is defined as:

$A = \frac{R-P}{N-P} * 100$. where R is the ratio response of the test compound

Solutions [mM]

Bath Solution #1: NaCl 160, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.4 with NaOH

Bath Solution #2 TMA-Cl 160, $CaCl_2$ 0.1, $MgCl_2$ 1, HEPES 10, pH 7.4 with KOH (final K concentration ~ 5 mM)

CC2-DMPE: prepared as a 5 mM stock solution in DMSO and stored at -20°C

$DiSBAC_2(3)$: prepared as a 12 mM stock in DMSO and stored at -20°C

ABSC1: prepared as a 200 mM stock in distilled H_2O and stored at room temperature

[002253] Cell Culture

[002254] CHO cells are grown in DMEM (Dulbecco's Modified Eagle Medium; GibcoBRL #10569-010) supplemented with 10% FBS (Fetal Bovine Serum, qualified; GibcoBRL #16140-071) and 1% Pen-Strep (Penicillin-Streptomycin; GibcoBRL #15140-122). Cells are grown in

vented tap flasks, in 90% humidity and 10% CO_2, to 100% confluence. They are usually split by trypsinization 1:10 or 1:20, depending on scheduling needs, and grown for 2-3 days before the next split.

[002255] C) VIPR® optical membrane potential assay method with electrical stimulation

[002256] The following is an example of how NaV1.3 inhibition activity is measured using the optical membrane potential method#2. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

[002257] HEK293 cells stably expressing NaV1.3 are plated into 96-well microtiter plates. After an appropriate incubation period, the cells are stained with the voltage sensitive dyes CC2-DMPE/DiSBAC2(3) as follows.

[002258] *Reagents:*

100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

10 mM DiSBAC$_2$(3) (Aurora #00-100-010) in dry DMSO

10 mM CC2-DMPE (Aurora #00-100-008) in dry DMSO

200 mM ABSC1 in H_2O

Hank's Balanced Salt Solution (Hyclone #SH30268.02) supplemented with 10 mM HEPES (Gibco #15630–080)

[002259] *Loading protocol:*

[002260] 2X CC2-DMPE = 20 μM CC2-DMPE: 10 mM CC2-DMPE is vortexed with an equivalent volume of 10% pluronic, followed by vortexing in required amount of HBSS containing 10 mM HEPES. Each cell plate will require 5 mL of 2X CC2-DMPE. 50 μL of 2X CC2-DMPE is to wells containing washed cells, resulting in a 10 μM final staining concentration. The cells are stained for 30 minutes in the dark at RT.

[002261] 2X DISBAC$_2$(3) with ABSC1 = 6μM DISBAC$_2$(3) and 1 mM ABSC1: The required amount of 10 mM DISBAC$_2$(3) is added to a 50 ml conical tube and mixed with 1 μL 10% pluronic for each mL of solution to be made and vortexed together. Then HBSS/HEPES is added to make up 2X solution. Finally, the ABSC1 is added.

[002262] The 2X DiSBAC$_2$(3) solution can be used to solvate compound plates. Note that compound plates are made at 2X drug concentration. Wash stained plate again, leaving residual

volume of 50 µL. Add 50 µl/well of the 2X DiSBAC$_2$(3) w/ ABSC1. Stain for 30 minutes in the dark at RT.

[002263] The electrical stimulation instrument and methods of use are described in ION Channel Assay Methods PCT/US01/21652, herein incorporated by reference. The instrument comprises a microtiter plate handler, an optical system for exciting the coumarin dye while simultaneously recording the coumarin and oxonol emissions, a waveform generator, a current- or voltage-controlled amplifier, and a device for inserting electrodes in well. Under integrated computer control, this instrument passes user-programmed electrical stimulus protocols to cells within the wells of the microtiter plate.

[002264] Reagents

[002265] Assay buffer #1

140 mM NaCl, 4.5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 10 mM glucose, pH 7.40, 330 mOsm

Pluronic stock (1000X): 100 mg/mL pluronic 127 in dry DMSO
Oxonol stock (3333X): 10 mM DiSBAC$_2$(3) in dry DMSO
Coumarin stock (1000X): 10 mM CC2-DMPE in dry DMSO
ABSC1 stock (400X): 200 mM ABSC1 in water

[002266] Assay Protocol

1. Insert or use electrodes into each well to be assayed.
2. Use the current-controlled amplifier to deliver stimulation wave pulses for 3 s. Two seconds of pre-stimulus recording are performed to obtain the un-stimulated intensities. Five seconds of post-stimulation recording are performed to examine the relaxation to the resting state.

[002267] Data Analysis

[002268] Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which

there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

$$R(t) = \frac{(\text{intensity}_{460\,nm} - \text{background}_{460\,nm})}{(\text{intensity}_{580\,nm} - \text{background}_{580\,nm})}$$

[002269] The data is further reduced by calculating the initial (R_i) and final (R_f) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus $R = R_f/R_i$ is then calculated.

[002270] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative (N) and positive (P) controls are calculated as above. The compound antagonist activity A is defined as:

$A = \frac{R-P}{N-P} * 100$. where R is the ratio response of the test compound.

[002271] ELECTROPHYSIOLOGY ASSAYS FOR NaV ACTIVITY AND INHBITION OF TEST COMPOUNDS

[002272] Patch clamp electrophysiology was used to assess the efficacy and selectivity of sodium channel blockers in dorsal root ganglion neurons. Rat neurons were isolated from the dorsal root ganglions and maintained in culture for 2 to 10 days in the presence of NGF (50 ng/ml) (culture media consisted of NeurobasalA supplemented with B27, glutamine and antibiotics). Small diameter neurons (nociceptors, 8-12 μm in diameter) have been visually identified and probed with fine tip glass electrodes connected to an amplifier (Axon Instruments). The "voltage clamp" mode has been used to assess the compound's IC50 holding the cells at – 60 mV. In addition, the "current clamp" mode has been employed to test the efficacy of the compounds in blocking action potential generation in response to current injections. The results of these experiments have contributed to the definition of the efficacy profile of the compounds.

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[002273] VOLTAGE-CLAMP assay in DRG neurons

[002274] TTX-resistant sodium currents were recorded from DRG somata using the whole-cell variation of the patch clamp technique. Recordings were made at room temperature (~22° C) with thick walled borosilicate glass electrodes (WPI; resistance 3-4 MΩ) using an Axopatch 200B amplifier (Axon Instruments). After establishing the whole-cell configuration, approximately 15 minutes were allowed for the pipette solution to equilibrate within the cell before beginning recording. Currents were lowpass filtered between 2-5 kHz and digitally sampled at 10 kHz. Series resistance was compensated 60-70% and was monitored continuously throughout the experiment. The liquid junction potential (-7 mV) between the intracellular pipette solution and the external recording solution was not accounted for in the data analysis. Test solutions were applied to the cells with a gravity driven fast perfusion system (SF-77; Warner Instruments).

[002275] Dose-response relationships were determined in voltage clamp mode by repeatedly depolarizing the cell from the experiment specific holding potential to a test potential of +10mV once every 60 seconds. Blocking effects were allowed to plateau before proceeding to the next test concentration.

[002276] Solutions

[002277] Intracellular solution (in mM): Cs-F (130), NaCl (10), $MgCl_2$ (1), EGTA (1.5), $CaCl_2$ (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[002278] Extracellular solution (in mM): NaCl (138), $CaCl_2$ (1.26), KCl (5.33), KH_2PO_4 (0.44), $MgCl_2$ (0.5), $MgSO_4$ (0.41), $NaHCO_3$ (4), Na_2HPO_4 (0.3), glucose (5.6), HEPES (10), CdCl2 (0.4), NiCl2 (0.1), TTX (0.25×10^{-3}).

[002279] CURRENT-CLAMP assay for NaV channel inhibition activity of compounds

[002280] Cells were current-clamped in whole-cell configuration with a Multiplamp 700A amplifier (Axon Inst). Borosilicate pipettes (4-5 MOhm) were filled with (in mM):150 K-gluconate, 10 NaCl, 0.1 EGTA, 10 Hepes, 2 $MgCl_2$, (buffered to pH 7.34 with KOH). Cells were bathed in (in mM): 140 NaCl, 3 KCl, 1 MgCl , 1 CaCl , and 10 Hepes). Pipette potential was zeroed before seal formation; liquid junction potentials were not corrected during acquisition. Recordings were made at room temperature.

[002281] Following these procedures, representative compounds of the present invention were found to possess desired voltage gated sodium channel activity and selectivity.

[002282] ASSAYS FOR DETECTING AND MEASURING L-Type CaV 1.2 INHIBITION PROPERTIES OF COMPOUNDS

[002283] A) Optical methods for assaying CaV inhibition properties of compounds:

[002284] Compounds of the invention are useful as antagonists of voltage-gated calcium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the CaV of interest were placed into microtiter plates. After an incubation period, the cells were stained with fluorescent dyes sensitive to the transmembrane potential. The test compounds were added to the microtiter plate. The cells were stimulated with electrical means to evoke a CaV dependent membrane potential change from unblocked channels, which was detected and measured with trans-membrane potential-sensitive dyes. Antagonists were detected as a decreased membrane potential response to the stimulus. The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR®) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today 4(9): 431-439).

[002285] VIPR® optical membrane potential assay method with electrical stimulation

Positive Control (100% Block)

The positive control for this assay was 125uM mibefradil, achieved by adding 25uL of 250uM solution to the assay plates containing 25uL of assay buffer. Each assay plate included positive control wells.

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Negative Control (No Block)

The negative (baseline) control for this assay was DMSO. This was achieved by adding 25uL of 1% DMSO (in assay buffer) to the assay plates containing 25uL of assay buffer. Each assay plate included negative control wells.

Background Subtraction

Fluorescence background from plastic in assay plates (or from the assay buffer) was assessed by running a cell-free plate through the EVIPR under the same optical configuration. The average background values for each row and each wavelength were subtracted in MOD3 prior to ratio change and activity calculations.

Reagents

Assay Buffers:

Bath Y (Prepared by Vertex Lab Support)

140mM TMA-Cl

4.5mM KCl

1mM $MgCl_2$

10mM HEPES, pH7.4

10mM glucose

Osmolarity = 295mOsm (280-310 acceptable range)

500mM $BaCl_2$ (Sigma #B0750), in H_2O

100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

10mM $DiSBAC_2(3)$ (Aurora #00-100-010) in dry DMSO

10mM CC2-DMPE (Aurora #00-100-008) in dry DMSO

200mM Acid Yellow 17 (Aurora #VABSC) in H_2O

Assay Volume

50uL

DMSO Conc in Assay

0.5% (1uL of 75% DMSO/25% water, dilution factor of 160)

Incubation Time of Compound

20-25 minutes

Instrumentation

This screen was conducted on the Allegro™ system. The system is diagrammed below: The Allegro™ is equipped with a compound plate storage unit (stacker). The stacker holds a set of trays (each tray holds 12 compound plates). The libraries were received from Compound Management, as pre-spotted (1uL/well of compound and controls) intermediate plates in 384-well format, as a 1.6mM stock solution in 75% DMSO/25% de-ionized H_2O. The plates are diluted in 80uL oxonol dye solution to create a 2X stock. Three EVIPR readers are integrated to the Allegro system by a Mitsubishi robotic arm. Only one EVIPR was used per run.

Instrumentation Settings

Optical:

Read Frequency: 10Hz

Excitation Wavelength: 400nm

Emission Wavelengths: 460nm and 560nm

Electrical Stimulation:

Pulse Width: 11.1 ms

Stimulation Current: 0.8 amps

Stimulation Frequency: 90Hz

Pre-stimulation time: 2 s

Stimulation time: 3 s

Post-stimulation time: 1 s

Waveform: Biphasic Square Wave

Plate Washer Settings:

Settings for ELx405 washer will leave a residual volume of 25uL.

Plate Type: 384

# of cycles: 3

Soak/shake: No

Dispense: dispense volume 100

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	dispense flow rate	1
	dispense height	80
	horizontal disp pos	-20
	horiz y disp pos	-5
Aspirate:	aspirate height	48
	horizontal aspr pos	-18
	horiz y asp pos	-5
	aspiration rate	0
	aspiration delay	0
	final asp delay	500

Assay Procedure

Procedure run on HTS Allegro™:

1. **Carousel:** Assay plates (Cell plates) loaded into carousel module #1 (CO_2 = 5%, ambient temperature and Rh)
2. **Barrier:** Assay plates retrieved from carousel and passed through environmental barrier (The remaining steps are conducted at room temperature and ambient CO_2)
3. **Washer:** Assay plates washed with Bath Y on Biotek ELx405.
4. **MultiReagent Dispenser (MRD):** 25uL of CC2-DMPE (and equal volume Pluronic) in Bath Y added to each well to make 10uM.
5. **Barrier:** Assay plates passed through barrier.
6. **Carousel:** 30-minute incubation at room temperature.
7. **Barrier:** Assay plates passed through barrier.
8. **Washer:** Assay plates washed with Bath Y on Biotek ELx405
9. **High Density Transfer Station:**
    a. 80uL oxonol dye loading solution (4uM DiSBAC2(3), 1mM VABSC and 30mM $BaCl_2$ in BathY) added to compound plates (pre-spotted with 1uL compound) using a MultiDrop (offline)

b. Plates mixed (3 times 20uL) on CyBiWell (offline). Plates loaded onto compound tray.

c. Compound tray retrieved from compound tray stacker and compound plate barcodes read.

d. Assay plate barcode read and moved to SciClone deck

e. 25uL compound plus oxonol aspirated from compound plate on SciClone deck and transferred to assay plate.

i. Final assay volume = 50uL

ii. Final compound concentration = 10uM

f. SciClone tips washed in DMSO and 5% ethanol in water to remove external carry-over.

10. **Carousel:** Assay plates incubated for 20 minutes at RT

11. **Barrier:** Assay plates passed through final barrier

12. **Mitsubishi Robotic Arm:** Retrieves assay plate from barrier output, delivers cell plates to EVIPR 384-1, and sends command to initiate EVIPR run.

Assay Window

Assay window criteria:

Passing plates ≤0.5, rejected plates > 0.5

$$\textit{Assay Window} = \frac{3(SD_{FullStock} + SD_{Baseline})}{(AVE_{Baseline} - AVE_{FullStock})} = 1 - Z'$$

Data Reduction

The EVIPR files were reduced to decrease the amount of data pumped into the database. Two "windows" of interest were filtered out of each EVIPR file. Each window is a slice of the response measured in each well. The first window is measured before stimulation. The second

window samples the peak of the response. The ratio of the two is used to determine the response size.

Data Analysis

Once the data were collected on the VIPR, they were archived and uploaded, in reduced form, to Mod3. Once in Mod3, each individual assay plate was QC'ed (looking for acceptable window and dynamic range).

[002286] **HERG Assay**

[002287] hERG-inhibition was assayed in a Chinese Hamster Lung cell line (CHL) stably transduced with the structural gene for hERG. Cells express high numbers of hERG channels resulting in 500pA to 1.5nA of hERG outward K^+ currents. The method used a planar patch instrument (IonWorks HT, Molecular Devices) that allowed medium-throughput electrophysiology measurements in 384-well format. The potency of hERG inhibition was measured at 1.1 μM, 3.3μM, 10μM, and 30μM of the compound studied. The compound was added from a 3x aqueous addition buffer.

[002288] The compounds of the present invention exhibit a desirably low activity against hERG.

[002289] **CYP-450 Isozyme assay**

[002290] Compound preparation:

1. The desired compound was plated (2mM in 75% DMSO/25% H_2O) with a Piezo Sample Distribution Robot (PSDR™) at 8nL per well.
2. The compound was centrifuged briefly at approximately 1000rpm to shift the compound drop to the bottom of the well.
3. PVP 10K (excipient, 0.2% in 75% DMSO/25% H_2O) was plated with a PSDR™ at 100nL per well.
4. The compound and PVP 10K were centrifuged briefly at approximately 1000rpm to ensure an adequate mix of compound and excipient.
5. The dry-down of the plates was initiated using house vacuum for at least 3 hours.
6. The plates were transferred to a high vacuum (50millitorr) apparatus and the dry-down process was continued for at least 15 hours.

[002291] The following assay protocol was employed for a desired CYP-450 isozyme (CYP3A4, CYP2C9, CYP1A2, CYP2C19, or CYP2D6).

[002292] Assay Protocol

All reagents below were added using a Flying Reagent Dispenser (FRD™).

1. 800 nL of dH_2O was added to the 100% activity control, compound, and background control wells.
2. 800 nL of the appropriate control drug (3A4:clotrimazole, 2C9:miconazole, 1A2:ticlopidine, 2C19:lansoprazole, or 2D6:propanolol; 10uM final dissolved in dH_2O) was added to the drug control wells.
3. 200 nL of 500mM K^+ Phosphate buffer (pH 8.4)was added to the 100% activity control, drug control, and compound wells.
4. 600 nL of Control Insect Baculosomes (PanVera P2315) in 500mM K^+ Phosphate Buffer (pH 8.4) was added to the background control wells. The calculation for this reagent was based on the protein concentration of the 100% activity control wells.
5. The plate was scanned for compound fluorescence using a NanoPlate™ Fluorescence Plate Reader (NPR™).
6. 200 nL of $NADP^+$ (Sigma, 100 μM final) and substrate in 100mM K^+ Phosphate buffer (50mM K^+ Phosphate buffer for 2C9 and 2C19) was added to all wells. Fluorogenic substrate (3A4:5 μM Vivid™ 3A4 Red, 2C9:1μM Vivid™ 2C9 Green, 1A2:2μM Vivid™ 1A2 Blue, 2C19:10μM Vivid™ 2C19 Blue, and 2D6: 10μM Vivid™ 2D6 Blue) was added at a final concentration corresponding to the K_m of the substrate for its pertinent CYP450 isozyme.
7. 400 nL of the desired CYP450 isozyme and recycling buffer (3.3mM glucose-6-phosphate, 0.4units/ml glucose-6-phosphate dehydrogenase, 100mM $MgCl_2$, and 0.00025% Antifoam 289; reagents obtained from Sigma) in 100mM K^+ Phosphate Buffer (50mM K^+ Phosphate buffer for 2C9 and 2C19) were added to the 100% activity control, drug control, and compound wells. The desired isozyme was added to obtain the following final concentrations of the desired isozyme: 5nM CYP3A4, 10nM CYP2C9, 5nM CYP1A2, 5nM CYP2C19, or 20nM CYP2D6.
8. The plate was incubated for 60 minutes at room temperature.

9. The plate was scanned for solution fluorescence using a NanoPlate™ Fluorescence Plate Reader (NPR™).
10. The NPR™ data was converted into a format compatible with importation into a data visualizer and complete the analysis of data acquired.

[002293] The compounds of the present invention exhibit a desirably low activity against one or more of the CYP450 isozymes.

[00229-4] The activity of selected compounds of the present invention against NaV 1.8 channel is shown below in Table 4. In Table 4, the symbols have the following meaning:

"+++" means < 2 μM; "++" means between 2 μM and 10 μM; and "+" means > 10μM.

[00229-5] Table 4

Example	IC50
101	+++
102	++
103	+
104	+
105	++
106	+
107	++
108	++
109	++
110	+
111	+
112	+
113	++
114	++
115	+
116	++
117	++
118	++
119	+
120	++
121	++
122	++
123	+
124	+
125	+
126	+
127	+++
128	++
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151	+
152	+
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158	+
159	++
160	+
162	++
163	++
164	+
165	++
166	+
167	+
168	++
169	+
170	+
172	+
173	+
174	++
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176	+
177	++
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276	++
277	++
278	+
279	++
301	++
302	+
303	++
304	+
305	++
306	+
307	+
308	+
309	+++
310	++
311	+++
312	++
314	++
315	+
316	+
317	++
318	+
319	++
320	++
321	+
322	+

238

Cmpd #	IC50
323	+
324	+
325	+
326	+
327	+
328	+
329	++
335	++
337	++
338	+
339	++
340	+++
342	+
345	++
346	++
347	+

Cmpd #	IC50
348	+
349	+
350	+
351	++
352	+
353	+
354	++
355	+
356	+
357	+
358	+
359	+
360	+
361	++
362	+
363	++

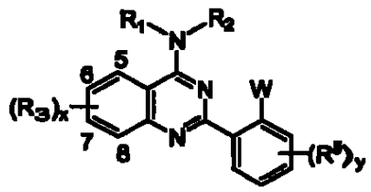
Cmpd #	IC50
364	+++
365	+++
366	++
367	+++
368	++
369	+++
370	+++
371	+++
372	+++
373	++
374	+
375	+
376	+
377	++
401	+
402	+

Cmpd #	IC50
403	+
404	+
405	+
406	+
407	+
408	+
409	+
410	+
411	++
412	+
413	++
414	++
415	++
416	+
417	+
418	++

Cmpd #	IC50
419	++
420	+++
501	++
502	++
503	++
504	++
505	++
506	++
507	++
508	++
509	+
510	++
511	++
512	++
513	+
514	++

CLAIMS

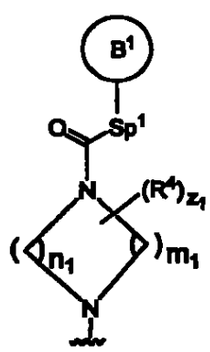
1. A compound of formula I:



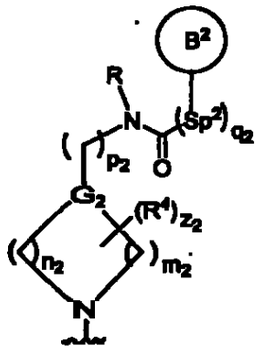
I;

or a pharmaceutically acceptable salt or derivative thereof, wherein:

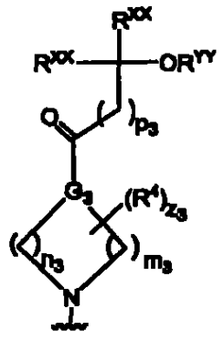
R^1 and R^2, taken together with the nitrogen atom, form a substituted ring selected from:



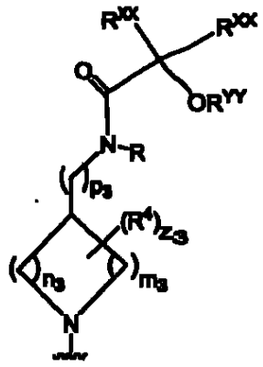
(A)



(B)

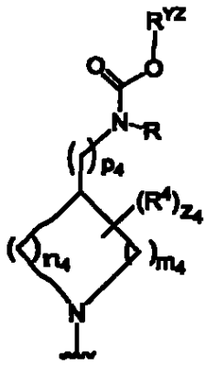


(C)



(D)

or



(E);

wherein, in ring (A):

each of m_1 and n_1 is independently 0-3, provided that m_1+n_1 is 2-6;

~~z_1 is 0-4;~~

Sp^1 is –O-, -S-, -NR'-, or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, –S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO_2-, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, -SO_2-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-, provided that Sp^1 is attached to the carbonyl group through an atom other than carbon;

ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w_1 independent occurrences of -R^{11}, wherein w_1 is 0-4;

wherein, in ring (B):

G_2 is -N-, or CH;

each of m_2 and n_2 is independently 0-3, provided that $m_2 + n_2$ is 2-6;

p_2 is 0-2; provided that when G_2 is N, then p_2 is not 0;

q_2 is 0 or 1;

z_2 is 0-4;

Sp^2 is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO_2-, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, -SO_2-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-;

ring B^2 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of –R^{12}, wherein w_2 is 0-4;

wherein, in ring (C) or ring (D):

G_3 is -N-, -CH-NH-, or -CH-CH_2-NH-;

each of m_3 and n_3 is independently 0-3, provided that m_3+n_3 is 2-6;

p_3 is 0-2;

z_3 is 0-4;

each R^{XX} is hydrogen, C_{1-6} aliphatic group, a 3–8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently

selected from nitrogen, oxygen, or sulfur; wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3;

provided that both R^{XX} are not simultaneously hydrogen;

R^{YY} is hydrogen, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or $-PO(R')$;

wherein, in ring (E):

each of m_4 and n_4 is independently 0-3, provided that $m_4 + n_4$ is 2-6;

p_4 is 1-2;

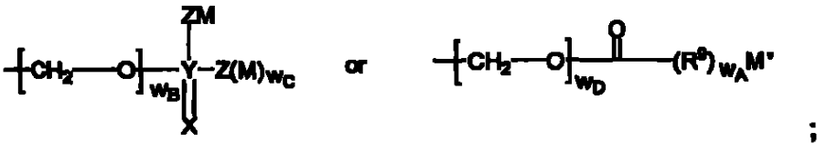
z_4 is 0-4;

R^{YZ} is C_1-C_6 aliphatic group, optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3;

x and y, each, is independently 0-4;

W is OR^{XY};

R^{XY} is hydrogen or a group selected from:



;

wherein:

each of w_A, w_B, w_C, and w_D is independently 0 or 1;

each M is independently selected from hydrogen, Li, Na, K, Mg, Ca, Ba, $-N(R^7)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^7$, $-R^7$, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, $-CO_2R^7$, $-C(O)-N(R^7)_2$, $S(O)_2-N(R^7)_2$, $N(R^7)-C(O)-R^7$, $C(O)R^7$, $-S(O)_n-R^7$, OCF_3, $-S(O)_n-R^6$, $N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$, or $-NO_2$;

n is 0-2;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a

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substituent selected from C_1-C_4 R^7, - R^7, -$N(R^7)_2$, $N(R^7)_3$, - R^7OH, -CN, -CO_2 R^7, -C(O)-$N(R^7)_2$, -$S(O)_2$-$N(R^7)_2$, -$N(R^7)$-C(O)- R^7, -C(O) R^7, -$S(O)_n$- R^7, -OCF_3, -$S(O)_n$-R^6, -$N(R^7)$-$S(O)_2(R^7)$, halo, -CF_3, or -NO_2;

Z is -CH_2-, -O-, -S-, -$N(R^7)_2$-; or,

when M is absent, then Z is hydrogen, =O, or =S;

Y is P or S, wherein when Y is S, then Z is not S;

X is O or S;

each R^7 is independently selected from hydrogen, or C_1-C_4 aliphatic, optionally substituted with up to two Q_1;

each Q_1 is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more hetero atom or heteroatom group selected from O, N, NH, S, SO, or SO_2; wherein Q_1 is optionally substituted with up to three substituents selected from oxo, -OH, -O(C_1-C_4 aliphatic), -C_1-C_4 aliphatic, -NH_2, NH(C_1-C_4 aliphatic), -N(C_1-C_4 aliphatic)$_2$, -N(C_1-C_4 aliphatic)-C(O)- C_1-C_4 aliphatic, -(C_1-C_4 aliphatic)-OH, -CN, -CO_2H, -CO_2(C_1-C_4 aliphatic), -C(O)-NH_2, -C(O)-NH(C_1-C_4 aliphatic), -C(O)-N(C_1-C_4 aliphatic)$_2$, halo or -CF_3;

R^6 is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, $S(O)_n$ or $N(R^7)$; and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C_1-C_4 alkyl, O-C_1-C_4 alkyl or O-C(O)-C_1-C_4 alkyl;

R^9 is $C(R^7)_2$, O or $N(R^7)$;

each occurrence of R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4, and R^5 is independently Q-R^X; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by -NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -$NRCO_2$-, -SO_2NR-, -$NRSO_2$-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -$NRSO_2NR$-, -SO-, -SO_2-, -PO-, -PO_2-, -OP(O)(OR)-, or -POR-; and each occurrence of R^X is independently selected from -R^*, halogen, =O, =NR', -NO_2, -CN, -OR', -SR', -N(R')$_2$, -NR'COR', -NR'CON(R')$_2$, -NR'CO_2R', -COR', -CO_2R', -OCOR', -CON(R')$_2$, -OCON(R')$_2$, -

SOR', $-SO_2R'$, $-SO_2N(R')_2$, $-NR'SO_2R'$, $-NR'SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, or $-OPO(R')_2$; and

each occurrence of R is independently hydrogen or C_{1-6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

2. The compound according to claim 1, wherein W is OH.

3. The compound according to claim 1, wherein x is 1 and R^3 is present at the 6- or 7-position of the quinazoline ring.

4. The compound according to claim 3, wherein R^3 is selected from -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

5. The compound according to claim 4, wherein x is 1 and R^3 is at the 7-position of the quinazoline ring and is $-CH_3$.

6. The compound according to claim 1, wherein y is 0.

7. The compound according to claim 1, wherein y is 1, and R^5 is halo.

8. The compound according to claim 7, wherein R^5 is halo at the 6-position.

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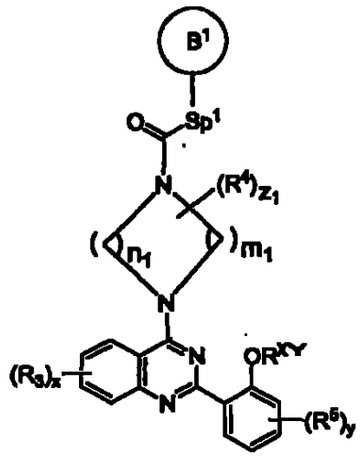
9. The compound according to claim 1, wherein z_1, z_2, z_3, and z_4 each is 0.

10. The compound according to claim 1, wherein said compound has formula I-A:



I-A.

11. The compound according to claim 10, wherein Sp^1 is -O-, -O-CH_2-, -S-, or -NH-, or -NH-CH_2-.

12. The compound according to claim 10, wherein each of m_1 and n_1 is 2.

13. The compound according to claim 10, wherein ring B^1 is a 5-6 membered, saturated, monocyclic heterocyclic ring having having 1-2 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w independent occurrences of $-R^{11}$, wherein w_1 is 0-4.

14. The compound according to claim 13, wherein ring B1 is tetrahydrofuranyl, tetrahydro-[*2H*]-pyranyl, pyridyl, or phenyl.

15. The compound according to claim 10, wherein Sp^1 is a bond, O, or –O-CH_2-; R is hydrogen; and n_1 and m_1 are both simultaneously 2.

16. The compound according to claim 10, wherein:

n_1 and m_1 each is 2;

R^{XY} is hydrogen;

y is 0 or 1 and R^5 is fluoro;

x is 1 and R^3 is Me at 7-position or fluoro at 6-position;

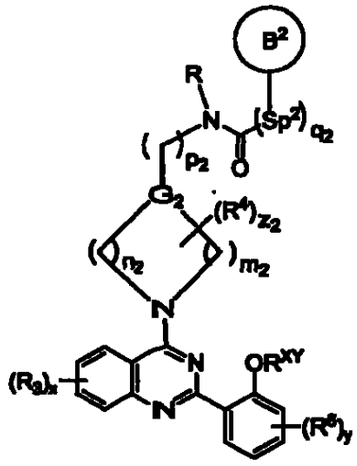
z_1 is 0;

Sp^1 is –O-CH_2-;

w_1 is 0; and

ring B^1 is tetrahydrofuran-3-yl, phenyl, pyridine-3-yl, pyridine-4-yl, or tetrahydro[2H]-pyran-4-yl.

17. The compound according to claim 1, wherein said compound has formula I-B:



I-B.

18. The compound according to claim 17, wherein G_2 is CH and p_2 is 1 or 2.

19. The compound according to claim 17, wherein m_2 and n_2 each is 1 or 2.

20. The compound according to claim 17, wherein m_2 is 1 and n_2 each is 2.

21. The compound according to claim 17, wherein n_2 is 1, and m_2 is 3.

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22. The compound according to claim 17, wherein Sp^2 is -O- or $-O-CH_2-$.

23. The compound according to claim 17, wherein ring B^2 is a 5-6 membered, saturated, monocyclic heterocyclic ring having having 1-2 heteroatoms selected from O, S, or N, wherein ring B^2 is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4.

24. The compound according to claim 23, wherein ring B^2 is tetrahydrofuranyl, tetrahydro[2*H*]pyranyl, or pyridyl.

25. The compound according to claim 17, wherein

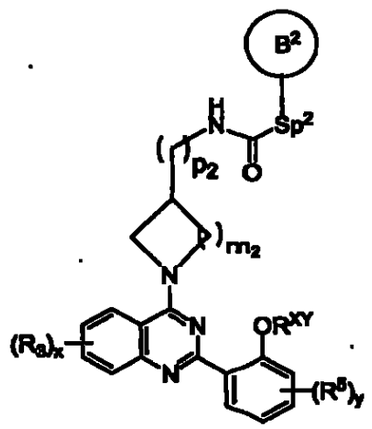
Sp^2 is a bond, O, or $-O-CH_2-$;

p_2 is 1;

R is hydrogen; and

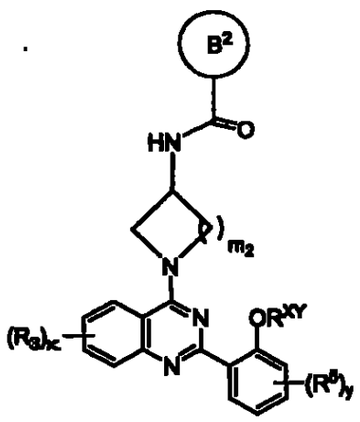
n_2 is 1 and m_2 is 2 or 3.

26. The compound according to claim 17, wherein said compound has formula I-B-i or formula I-B-ii:



I-B-i

or



I-B-ii;

wherein:

m_2 is 2 or 3; and

Sp^2 is –O- or -O-CH_2.

27. The compound of formula I-B-I according to claim 26, wherein:

p_2 is 1;

m_2 is 3;

Sp^2 is -O-;

y is 0 or 1, and R^5 is fluoro;

x is 1 and R^3 is 7-Me; and

ring B^2 is tetrahydrofuranyl.

28. The compound of formula I-B-I according to claim 26, wherein:

p_2 is 0 or 1;

m_2 is 2;

Sp^2 is -O- or -O-CH_2-;

y is 0;

x is 1 and R^3 is 7-Me; and

ring B^2 is tetrahydrofuranyl, tetrahydro[2H]pyranyl, pyridyl, or phenyl.

29. The compound of formula I-B-II according to claim 26, wherein:

p_2 is 0;

m_2 is 2;

Sp^2 is a bond;

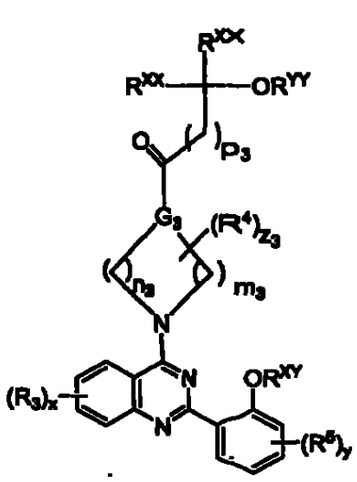
y is 0 or 1, and R^5 is fluoro;

x is 1 and R^3 is 7-Me or 6-F; and

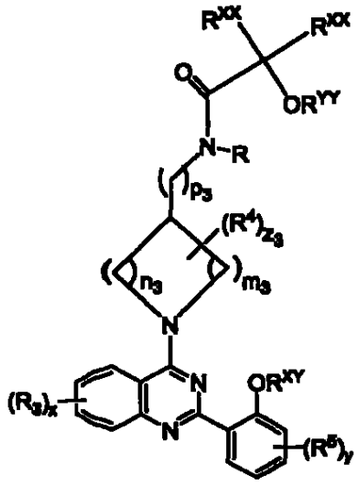
ring B^2 is cyclopropyl optionally substituted with C1-C4 alkyl, or pyridyl.

30. The compound of formula I-B-I or formula I-B-II according to claim 17, wherein R^{XY} is hydrogen.

31. The compound according to claim 1, wherein said compound has formula I-C or formula I-D:



I-C



I-D.

32. The compound according to claim 31, wherein one R^{XX} is hydrogen and the other R^{XX} is not hydrogen.

33. The compound according to claim 31, wherein one R^{XX} is hydrogen and the other R^{XX} is C1-C6 alkyl optionally substituted with halo.

34. The compound according to claim 31, wherein both R^{XX} are simultaneously C1-C6 alkyl.

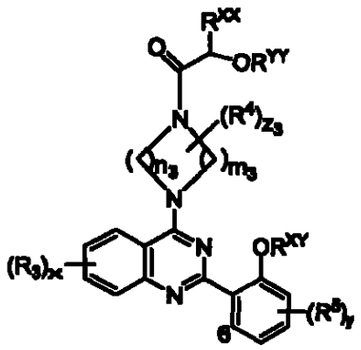
35. The compound according to claims 33 or 34, wherein said alkyl is selected from methyl, ethyl, isopropyl, *n*-propyl, *n*-butyl, *sec*-butyl, or *t*-butyl.

36. The compound according to claim 31, wherein p_3 is 0.

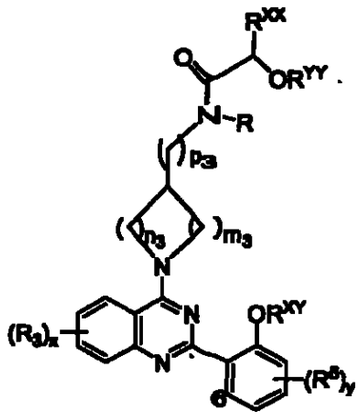
37. The compound according to claim 31, wherein m_3 and n_3 each is 2.

38. The compound according to claim 31, wherein R^{YY} is hydrogen.

39. The compound according to claim 31, wherein said compound has formula I-C-1 or formula I-D-1:



I-C-1



I-D-1

40. The compound according to claim 39, wherein R^{XX} is C1-C6 alkyl.

41. The compound according to claim 39, wherein x is 1, and R^3 is C1-C4 alkyl at the 7-position.

42. The compound according to claim 39, wherein x is 1 and R^3 is F, CN, or CF_3 at the 6-position.

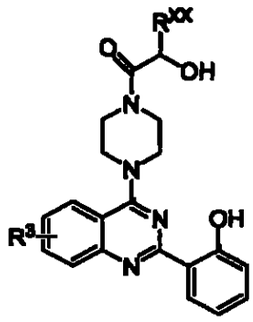
43. The compound according to claim 39, wherein R^{XX} is methyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, or *t*-butyl.

44. The compound according to claim 41, wherein R^3 is methyl, *n* -propyl, isopropyl, *n* -butyl, *sec*-butyl, or *t*-butyl.

45. The compound according to claim 39, wherein R^{XY} is hydrogen, and y is 0.

46. The compound according to claim 39, wherein R^{XY} is hydrogen, y is 1 and R^5 is 6-F.

47. The compound according to claim 31, wherein said compound has formula I-C-ii:

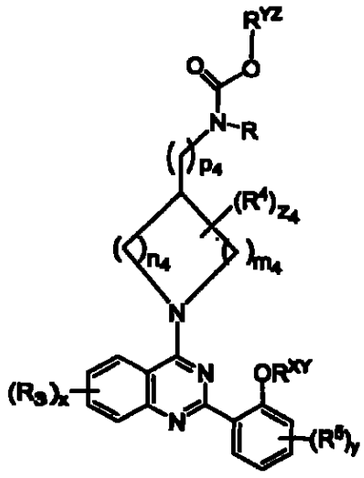


I-C-ii.

48. The compound according to claim 47, wherein R^3 is methyl at the 7-position of the quinazoline ring.

49. The compound according to claim 47, wherein R^{XX} is $CH_2C(O)OH$ or $CH_2C(O)NH_2$.

50. The compound according to claim 1, wherein said compound has formula I-E:



I-E.

51. The compound according to claim 50, wherein p_4 is 1.

52. The compound according to claim 50, wherein m_4 and n_4 each is 2.

53. The compound according to claim 50, wherein n_4 is 1, m_4 is 3, z_4 is 0, p_4 is 1, y is 0 or 1, and x is 1.

54. The compound according to claim 50, wherein n_4 is 1, m_4 is 2, z_4 is 0, p_4 is 1, y is 0 or 1, and x is 1.

55. The compound according to claim 50, wherein n_4 is 1, m_4 is 3, z_4 is 0, p_4 is 1, y is 0 or 1, x is 1, and R and R^{XY} both are hydrogen.

56. The compound according to claim 50, wherein n_4 is 1, m_4 is 2, z_4 is 0, p_4 is 1, y is 0 or 1, x is 1, and R and R^{XY} both are hydrogen.

57. The compound according to claim 50, wherein R^{YZ} is C1-C4 alkyl group optionally substituted with w_4 independent occurrences of -R^{14}, wherein w_4 is 0-3.

58. The compound according to claim 50, wherein:

n_4 is 1 and m_4 is 3;

p_4 is 1;

z_4 is 0;

R^{YZ} is C1-C6 alkyl, wherein up to two -CH_2- groups therein is optionally replaced by -O-;

y is 0 or 1, and R^5 is 6-fluoro; and

x is 1 and R^3 is C1-C4 alkyl.

59. The compound according to claim 50, wherein:

n_4 is 1 and m_4 is 2;

p_4 is 1;

z_4 is 0;

R^{YZ} is C1-C6 alkyl, wherein up to two -CH_2- groups therein is optionally replaced by -O-;

y is 0 or 1, and R^5 is 6-fluoro; and

x is 1 and R^3 is C1-C4 alkyl.

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60. The compound according to claim 50, wherein:

n_4 is 1 and m_4 is 3;

p_4 is 1;

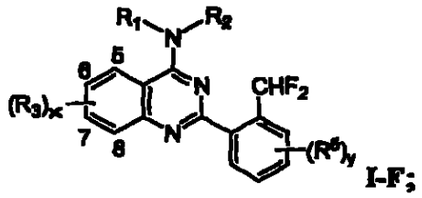
z_4 is 0;

R^{YZ} is benzyl;

y is 0 or 1, and R^5 is 6-fluoro; and

x is 1 and R^3 is C1-C4 alkyl.

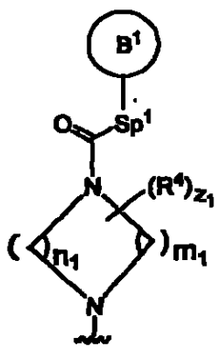
61. A compound according having formula I-F:



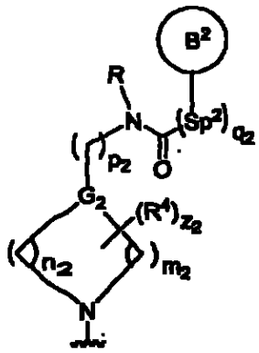
I-F;

wherein:

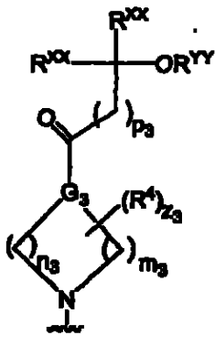
R^1 and R^2, taken together with the nitrogen atom, form a substituted ring selected from:



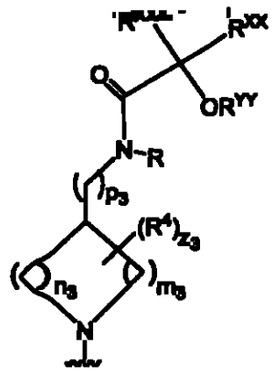
(A)



(B)

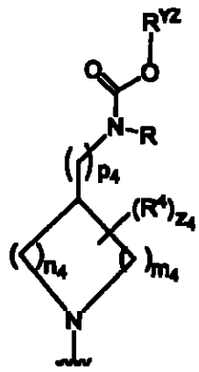


(C)



(D)

or



(E);

wherein, in ring (A):

each of m_1 and n_1 is independently 0-3, provided that m_1+n_1 is 2-6;

z_1 is 0-4;

Sp^1 is –O-, -S-, –NR'-, or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR'-, -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$, provided that Sp^1 is attached to the carbonyl group through an atom other than carbon;

ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, mono cyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w_1 independent occurrences of $-R^{11}$, wherein w_1 is 0-4;

wherein, in ring (B):

G_2 is -N-, or CH;

each of m_2 and n_2 is independently 0-3, provided that $m_2 + n_2$ is 2-6;

p_2 is 0-2; provided that when G_2 is N, then p_2 is not 0;

q_2 is 0 or 1;

z_2 is 0-4;

Sp^2 is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR'-, -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$;

ring B is a 4-8 membered saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1 -4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4;

wherein, in ring (C) or ring (D):

G_3 is -N-, -CH-NH-, or -CH-CH_2-NH-;

each of m_3 and n_3 is independently 0-3, provided that m_3+n_3 is 2-6;

p_3 is 0-2;

z_3 is 0-4;

each R^{XX} is hydrogen, C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3;

provided that both R^{XX} are not simultaneously hydrogen;

R^{YY} is hydrogen, -COR', $-CO_2R'$, -CON(R')$_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', -$COCH_2COR'$, -P(O)(OR')$_2$, -$P(O)_2OR'$, or -PO(R');

wherein, in ring (E):

each of m_4 and n_4 is independently 0-3, provided that m_4+n_4 is 2-6;

p_4 is 1-2;

z_4 is 0-4;

R^{YZ} is C_1-C_6 aliphatic group, optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3;

x and y, each, is independently 0-4;

each occurrence of R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4, and R^5 is independently Q-R^X; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by –NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, -OP(O)(OR)-, or -POR-; and each occurrence of R^X is independently selected from -R', halogen, =O, =NR', $-NO_2$, -CN, -OR', -SR', -N(R')$_2$, -NR'COR', -NR'CON(R')$_2$, $-NR'CO_2R'$, -COR', $-CO_2R'$, -OCOR', -CON(R')$_2$, -OCON(R')$_2$, -

SO$_2$R', SO$_2$R', -NR'SO$_2$N(R')$_2$, -NR'SO$_2$R', -NR'SO$_2$N(R')$_2$, -COCOR', -COCH$_2$COR', -OP(O)(OR')$_2$, -P(O)(OR')$_2$, -OP(O)$_2$OR', -P(O)$_2$OR', -PO(R')$_2$, or -OPO(R')$_2$; and

each occurrence of R is independently hydrogen or C$_{1-6}$ aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C$_{1-6}$ aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

62. The compound according to claim 1, wherein said compound is selected from Table 2.

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

64. A method for treating or lessening the severity of a disease, disorder, or condition selected from acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain, said method comprising the step of administering to said patient an effective amount of a composition according to claim 62.

65. The method according to claim 63, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated sodium channels.

66. The method according to claim 64, wherein the disease, condition, or disorder is acute, chronic, neuropathic, or inflammatory pain.

67. The method according to claim 64, wherein the disease, condition, or disorder is radicular pain, sciatica, back pain, head pain, or neck pain.

68. The method according to claim 64, wherein the disease, condition, or disorder is severe or intractable pain, acute pain, postsurgical pain, back pain, or cancer pain.

69. The method according to claim 64, wherein said disease is selected from femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, including, abdominal; pancreatic; IBS pain; chronic headache pain; migraine; tension headache, including, cluster headaches; chronic neuropathic pain, including, post-herpetic neuralgia; diabetic neuropathy; HIV- associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phanton pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac Pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, including, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); or prostatitis.

A. CLASSIFICATION OF SUBJECT MATTER
C07D239/94 C07D401/04 C07D401/12 C07D401/14 C07D403/04
C07D403/12 C07D403/14 C07D405/12 C07D405/14 A61P9/06
A61P25/00 A61K31/498

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data., BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/32632 A (ELI LILLY AND COMPANY; AMBLER, SAMANTHA, JAYNE; BAKER, STEPHEN, RICHAR) 10 May 2001 (2001-05-10) page 19 - page 29; claims 1-32; table I	1, 61,63, 64
P,X	WO 2004/078733 A (VERTEX PHARMACEUTICALS INCORPORATED; GONZALES, JESUS, E., III; WILSON,) 16 September 2004 (2004-09-16) cited in the application claims 1-249	1-69

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2006	09/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Megido, B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/031146

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. [X] Claims Nos.: 64–69
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 64–69 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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 an additional fees, this Authority did not invite payment of 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 document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0132632	A	10-05-2001	AU	1071301 A	14-05-2001
			EP	1230225 A2	14-08-2002
WO 2004078733	A	16-09-2004	AU	2004217891 A1	16-09-2004
			CA	2517844 A1	16-09-2004
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60/607,245	2 September 2004 (02.09.2004)	US
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(74) Agent: GOVINDASWAMY, Nandakumar; Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02139 (US).

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

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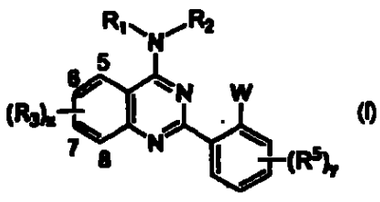
(54) Title: QUINAZOLINES USEFUL AS MODULATORS OF ION CHANNELS



(I)

(57) Abstract: The present invention relates to compounds useful as inhibitors of voltage-gated sodium channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

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

QUINAZOLINES USEFUL AS MODULATORS OF ION CHANNELS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119 to United States Provisional application serial no. 60/607,150, filed September 2, 2004, United States Provisional application serial no. 60/607,037, filed September 2, 2004, United States Provisional application serial no. 60/607,033, filed September 2, 2004, United States Provisional application serial no. 60/607,036, filed September 2, 2004, and United States Provisional application serial no. 60/607,245, filed September 2, 2004, the entire contents of each of the above application being incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to compounds useful as inhibitors of ion channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0003] Na channels are central to the generation of action potentials in all excitable cells such as neurons and myocytes. They play key roles in excitable tissue including brain, smooth muscles of the gastrointestinal tract, skeletal muscle, the peripheral nervous system, spinal cord and airway. As such they play key roles in a variety of disease states such as epilepsy (See, Moulard, B. and D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents 12(1): 85-91)), pain (See, Waxman, S. G., S. Dib-Hajj, et al. (1999) "Sodium channels and pain" Proc Natl Acad Sci U S A 96(14): 7635-9 and Waxman, S. G., T. R. Cummins, et al. (2000) "Voltage-gated sodium channels and the molecular pathogenesis of pain: a review" J Rehabil Res Dev 37(5): 517-28), myotonia (See, Meola, G. and V. Sansone (2000) "Therapy in myotonic disorders and in muscle channelopathies" Neurol Sci 21(5): S953-61 and Mankodi, A. and C. A. Thornton (2002) "Myotonic syndromes" Curr Opin Neurol 15(5): 545-52), ataxia (See,

Meisler, M. H., J. A. Kearney, et al. (2002) "Mutations of voltage-gated sodium channels in movement disorders and epilepsy" Novartis Found Symp 241: 72-81), multiple sclerosis (See, Black, J. A., S. Dib-Hajj, et al. (2000) "Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of mice with experimental allergic encephalomyelitis and humans with multiple sclerosis" Proc Natl Acad Sci U S A 97(21): 11598-602, and Renganathan, M., M. Gelderblom, et al. (2003) "Expression of Na(v)1.8 sodium channels perturbs the firing patterns of cerebellar purkinje cells" Brain Res 959(2): 235-42), irritable bowel (See, Su, X., R. E. Wachtel, et al. (1999) "Capsaicin sensitivity and voltage-gated sodium currents in colon sensory neurons from rat dorsal root ganglia" Am J Physiol 277(6 Pt 1): G1180-8, and Laird, J. M., V. Souslova, et al. (2002) "Deficits in visceral pain and referred hyperalgesia in Nav1.8 (SNS/PN3)- null mice" J Neurosci 22(19): 8352-6), urinary incontinence and visceral pain (See, Yoshimura, N., S. Seki, et al. (2001) "The involvement of the tetrodotoxin-resistant sodium channel Na(v)1.8 (PN3/SNS) in a rat model of visceral pain" J Neurosci 21(21): 8690-6), as well as an array of psychiatry dysfunctions such as anxiety and depression (See, Hurley, S. C. (2002) "Lamotrigine update and its use in mood disorders" Ann Pharmacother 36(5): 860-73).

[0004] Voltage gated Na channels comprise a gene family consisting of 9 different subtypes (NaV1.1-NaV1.9). These subtypes show tissue specific localization and functional differences (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol 63: 871-94). Three members of the gene family (NaV1.8, 1.9, 1.5) are resistant to block by the well-known Na channel blocker TTX, demonstrating subtype specificity within this gene family. Mutational analysis has identified glutamate 387 as a critical residue for TTX binding (See, Noda, M., H. Suzuki, et al. (1989) "A single point mutation confers tetrodotoxin and saxitoxin insensitivity on the sodium channel II" FEBS Lett 259(1): 213-6).

[0005] In general, voltage-gated sodium channels (NaVs) are responsible for initiating the rapid upstroke of action potentials in excitable tissue in nervous system, which transmit the electrical signals that compose and encode normal and aberrant pain sensations. Antagonists of NaV channels can attenuate these pain signals and are useful for treating a variety of pain conditions, including but not limited to acute, chronic, inflammatory, and neuropathic pain. Known NaV antagonists, such as TTX, lidocaine (See, Mao, J. and L. L. Chen (2000) "Systemic lidocaine for neuropathic pain relief" Pain 87(1): 7-17.) bupivacaine, phenytoin (See, Jensen, T. S. (2002) "Anticonvulsants in neuropathic pain: rationale and clinical evidence" Eur J Pain 6

(Suppl A): 61-8), lamotrigine (See, Rozen, T. D. (2001) "Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia" Headache 41 Suppl 1: S25-32 and Jensen, T. S. (2002) "Anticonvulsants in neuropathic pain: rationale and clinical evidence" Eur J Pain 6 (Suppl A): 61-8.), and carbamazepine (See, Backonja, M. M. (2002) "Use of anticonvulsants for treatment of neuropathic pain" Neurology 59(5 Suppl 2): S14-7), have been shown to be useful attenuating pain in humans and animal models.

[0006] Hyperalgesia (extreme sensitivity to something painful) that develops in the presence of tissue injury or inflammation reflects, at least in part, an increase in the excitability of high-threshold primary afferent neurons innervating the site of injury. Voltage sensitive sodium channels activation is critical for the generation and propagation of neuronal action potentials. There is a growing body of evidence indicating that modulation of NaV currents is an endogenous mechanism used to control neuronal excitability (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol 63: 871-94.). Several kinetically and pharmacologically distinct voltage-gated sodium channels are found in dorsal root ganglion (DRG) neurons. The TTX-resistant current is insensitive to micromolar concentrations of tetrodotoxin, and displays slow activation and inactivation kinetics and a more depolarized activation threshold when compared to other voltage-gated sodium channels. TTX-resistant sodium currents are primarily restricted to a subpopulation of sensory neurons likely to be involved in nociception. Specifically, TTX-resistant sodium currents are expressed almost exclusively in neurons that have a small cell-body diameter, and give rise to small-diameter slow-conducting axons and that are responsive to capsaicin. A large body of experimental evidence demonstrates that TTX-resistant sodium channels are expressed on C-fibers and are important in the transmission of nociceptive information to the spinal cord.

[0007] Intrathecal administration of antisense oligo-deoxynucleotides targeting a unique region of the TTX-resistant sodium channel (NaV1.8) resulted in a significant reduction in PGE_2-induced hyperalgesia (See, Khasar, S. G., M. S. Gold, et al. (1998) "A tetrodotoxin-resistant sodium current mediates inflammatory pain in the rat" Neurosci Lett 256(1): 17-20). More recently, a knockout mouse line was generated by Wood and colleagues, which lacks functional NaV1.8. The mutation has an analgesic effect in tests assessing the animal's response to the inflammatory agent carrageenan (See, Akopian, A. N., V. Souslova, et al. (1999) "The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways" Nat

Neurosci 2(6): 541-8.). In addition, deficit in both mechano- and thermoreception were observed in these animals. The analgesia shown by the Nav1.8 knockout mutants is consistent with observations about the role of TTX-resistant currents in nociception.

[0008] Immunohistochemical, in-situ hybridization and in-vitro electrophysiology experiments have all shown that the sodium channel NaV1.8 is selectively localized to the small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Akopian, A. N., L. Sivilotti, et al. (1996) "A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons" Nature 379(6562): 257-62.). The primary role of these neurons is the detection and transmission of nociceptive stimuli. Antisense and immunohistochemical evidence also supports a role for NaV1.8 in neuropathic pain (See, Lai, J., M. S. Gold, et al. (2002) "Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8" Pain 95(1-2): 143-52, and Lai, J., J. C. Hunter, et al. (2000) "Blockade of neuropathic pain by antisense targeting of tetrodotoxin- resistant sodium channels in sensory neurons" Methods Enzymol 314: 201-13.). NaV1.8 protein is upregulated along uninjured C-fibers adjacent to the nerve injury. Antisense treatment prevents the redistribution of NaV1.8 along the nerve and reverses neuropathic pain. Taken together the gene-knockout and antisense data support a role for NaV1.8 in the detection and transmission of inflammatory and neuropathic pain.

[0009] Several Na channel blockers are currently used or being tested in the clinic to treat epilepsy (See, Moulard, B. and D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents 12(1): 85-91.); acute (See, Wiffen, P., S. Collins, et al. (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev 3), chronic (See, Wiffen, P., S. Collins, et al. (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev 3, and Guay, D. R. (2001) "Adjunctive agents in the management of chronic pain" Pharmacotherapy 21(9): 1070-81), inflammatory (See, Gold, M. S. (1999) "Tetrodotoxin-resistant Na+ currents and inflammatory hyperalgesia." Proc Natl Acad Sci U S A 96(14): 7645-9), and neuropathic pain (See, Strichartz, G. R., Z. Zhou, et al. (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain" Novartis Found Symp 241: 189-201, and Sandner-Kiesling, A., G. Rumpold Seitlinger, et al. (2002) "Lamotrigine monotherapy for control of neuralgia after nerve section" Acta Anaesthesiol Scand 46(10): 1261-4); cardiac arrhythmias (See, An, R. H., R. Bangalore, et al.

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(1996) "Lidocaine block of LQT-3 mutant human Na+ channels" Circ Res 79(1): 103-8, and Wang, D. W., K. Yazawa, et al. (1997) "Pharmacological targeting of long QT mutant sodium channels" J Clin Invest 99(7): 1714-20); neuroprotection (See, Taylor, C. P. and L. S. Narasimhan (1997) "Sodium channels and therapy of central nervous system diseases" Adv Pharmacol 39: 47-98) and as anesthetics (See, Strichartz, G. R., Z. Zhou, et al. (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain." Novartis Found Symp 241: 189-201).

[0010] Various animal models with clinical significance have been developed for the study of sodium channel modulators for numerous different pain indications. E.g., malignant chronic pain, see, Kohase, H., et al., Acta Anaesthesiol Scand. 2004; 48(3):382-3; femur cancer pain (see, Kohase, H., et al., Acta Anaesthesiol Scand. 2004; 48(3):382-3); non-malignant chronic bone pain (see, Ciocon, J. O. et al., J Am Geriatr Soc. 1994; 42(6):593-6); rheumatoid arthritis (see, Calvino, B. et al., Behav Brain Res. 1987; 24(1):11-29); osteoarthritis (see, Guzman, R. E., et al., Toxicol Pathol. 2003; 31(6):619-24); spinal stenosis (see, Takenobu, Y. et al., J Neurosci Methods. 2001; 104(2):191-8); Neuropathic low back pain (see, Hines, R., et al., Pain Med. 2002; 3(4):361-5; Massie, J. B., et al., J Neurosci Methods. 2004; 137(2):283-9; neuropathic low back pain (see, Hines, R., et al., Pain Med. 2002; 3(4):361-5; Massie, J. B., et al., J Neurosci Methods. 2004; 137(2):283-9); myofascial pain syndrome (see, Dalpiaz & Dodds, J Pain Palliat Care Pharmacother. 2002; 16(1):99-104; Sluka KA et al., Muscle Nerve. 2001; 24(1):37-46); fibromyalgia (see, Bennet & Tai, Int J Clin Pharmacol Res. 1995;15(3):115-9); temporomandibular joint pain (see, Ime H, Ren K, Brain Res Mol Brain Res. 1999; 67(1):87-97); chronic visceral pain, including, abdominal (see; Al-Chaer, E. D., et al., Gastroenterology. 2000; 119(5):1276-85); pelvic/perineal pain, (see, Wesselmann et al., Neurosci Lett. 1998; 246(2):73-6); pancreatic (see, Vera-Portocarrero, L. B., et al., Anesthesiology. 2003; 98(2):474-84); IBS pain (see, Verne, G. N., et al., Pain. 2003; 105(1-2):223-30; La JH et al., World Gastroenterol. 2003; 9(12):2791-5); chronic headache pain (see, Willimas & Stark, Cephalalgia. 2003; 23(10):963-71); migraine (see, Yamamura, H., et al., J Neurophysiol. 1999; 81(2):479-93); tension headache, including, cluster headaches (see, Costa, A., et al., Cephalalgia. 2000; 20(2):85-91); chronic neuropathic pain, including, post-herpetic neuralgia (see, Attal, N., et al., Neurology. 2004; 62(2):218-25; Kim & Chung 1992, Pain 50:355); diabetic neuropathy (see, Beidoun A et al., Clin J Pain. 2004; 20(3):174-8; Courteix, C., et al., Pain. 1993; 53(1):81-8);

HIV- associated neuropathy (see, Portegies & Rosenberg, Ned Tijdschr Geneeskd. 2001; 145(15):731-5; Joseph EK et al., Pain. 2004; 107(1-2):147-58; Oh, S. B., et al., J Neurosci. 2001; 21(14):5027-35); trigeminal neuralgia (see, Sato, J., et al., Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004; 97(1):18-22; Imamura Y et al., Exp Brain Res. 1997; 116(1):97-103); Charcot-Marie Tooth neuropathy (see, Sereda, M., et al., Neuron. 1996; 16(5):1049-60); hereditary sensory neuropathies (see, Lee, M. J., et al., Hum Mol Genet. 2003; 12(15):1917-25); peripheral nerve injury (see, Attal, N., et al., Neurology. 2004; 62(2):218-25; Kim & Chung 1992, Pain 50:355; Bennett & Xie, 1988, Pain 33:87; Decostered, I. & Woolf, C. J., 2000, Pain 87:149; Shir, Y. & Seltzer, Z. 1990; Neurosci Lett 115:62); painful neuromas (see, Nahabedian & Johnson, Ann Plast Surg. 2001; 46(1):15-22; Devor & Raber, Behav Neural Biol. 1983; 37(2):276-83); ectopic proximal and distal discharges (see, Liu, X. et al., Brain Res. 2001; 900(1):119-27); radiculopathy (see, Devers & Galer, (see, Clin J Pain. 2000; 16(3):205-8; Hayashi N et al., Spine. 1998; 23(8):877-85); chemotherapy induced neuropathic pain (see, Aley, K. O., et al., Neuroscience. 1996; 73(1):259-65); radiotherapy-induced neuropathic pain; post-mastectomy pain (see, Devers & Galer, Clin J Pain. 2000; 16(3):205-8); central pain (Cahana, A., et al., Anesth Analg. 2004; 98(6):1581-4), spinal cord injury pain (see, Hains, B. C., et al., Exp Neurol. 2000; 164(2):426-37); post-stroke pain; thalamic pain (see, LaBuda, C. J., et al., Neurosci Lett. 2000; 290(1):79-83); complex regional pain syndrome (see, Wallace, M. S., et al., Anesthesiology. 2000; 92(1):75-83; Xantos D et al., J Pain. 2004; 5(3 Suppl 2):S1); phantom pain (see, Weber, W. E., Ned Tijdschr Geneeskd. 2001; 145(17):813-7; Levitt & Heyback, Pain. 1981; 10(1):67-73); intractable pain (see, Yokoyama, M., et al., Can J Anaesth. 2002; 49(8):810-3); acute pain, acute post-operative pain (see, Koppert, W., et al., Anesth Analg. 2004; 98(4):1050-5; Brennan, T. J., et al., Pain. 1996; 64(3):493-501); acute musculoskeletal pain; joint pain (see, Gotoh, S., et al., Ann Rheum Dis. 1993; 52(11):817-22); mechanical low back pain (see, Kehl, L. J., et al., Pain. 2000; 85(3):333-43); neck pain; tendonitis; injury/exercise pain (see, Sesay, M., et al., Can J Anaesth. 2002; 49(2):137-43); acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc (see, Giambernardino, M. A., et al., Pain. 1995; 61(3):459-69); chest pain, including, cardiac Pain (see, Vergona, R. A., et al., Life Sci. 1984; 35(18):1877-84); pelvic pain, renal colic pain, acute obstetric pain, including, labor pain (see, Segal, S., et al., Anesth Analg. 1998; 87(4):864-

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9); cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, including, endometriosis (see, Cason, A. M., et al.,Horm Behav. 2003; 44(2):123-31); acute herpes zoster pain; sickle cell anemia; acute pancreatitis (see, Toma, H; Gastroenterology. 2000; 119(5):1373-81); breakthrough pain; orofacial pain, including, sinusitis pain, dental pain (see, Nusstein, J., et al., J Endod. 1998; 24(7):487-91; Chidiac, J. J., et al., Eur J Pain. 2002; 6(1):55-67); multiple sclerosis (MS) pain (see, Sakurai & Kanazawa, J Neurol Sci. 1999; 162(2):162-8); pain in depression (see, Greene B, Curr Med Res Opin. 2003; 19(4):272-7); leprosy pain; behcet's disease pain; adiposis dolorosa (see, Devillers & Oranje, Clin Exp Dermatol. 1999; 24(3):240-1); phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain (see, Legroux-Crespel, E., et al., Ann Dermatol Venereol. 2003; 130(4):429-33); Fabry's disease pain (see, Germain, D. P., J Soc Biol. 2002;196(2):183-90); Bladder and urogenital disease, including, urinary incontinence (see, Berggren, T., et al., J Urol. 1993; 150(5 Pt 1):1540-3); hyperactivity bladder (see, Chuang, Y. C., et al., Urology. 2003; 61(3):664-70); painful bladder syndrome (see, Yoshimura, N., et al., J Neurosci. 2001; 21(21):8690-6); interstitial cystitis (IC) (see, Giannakopoulos& Campilomatos, Arch Ital Urol Nefrol Androl. 1992; 64(4):337-9; Boucher, M., et al., J Urol. 2000; 164(1):203-8); and prostatitis (see, Mayersak, J. S., Int Surg. 1998; 83(4):347-9; Keith, I. M., et al., J Urol. 2001; 166(1):323-8).

[0011] Unfortunately, as described above, the efficacy of currently used sodium channel blockers and calcium channel blockers for the disease-states described above has been to a large extent limited by a number of side effects. These side effects include various CNS disturbances such as blurred vision, dizziness, nausea, and sedation as well more potentially life threatening cardiac arrhythmias and cardiac failure. Such undesirable side effects may be avoided by using a Na channel blocker that exhibit a degree of selectivity in its activity against a Na channel subtype. However, Na channel blockers currently in the market lack such selectivity. Perhaps because of this lack of molecular selectivity, drugs currently in the market exhibit use-dependent block and generally show higher affinity at depolarized potentials resulting in the preferential targeting of actively firing neurons, believed to be a key factor in the therapeutic window of existing Na channel blocking drugs. While every drug has it own unique therapeutic profile, current Na channel blockers are generally associated with central nervous system (CNS) and cardiovascular (CV) side-effects, including blood pressure changes, which are often dose-

limiting. Dizziness, sedation, nausea, ataxia, and confusion are some of the specific side-effects observed for phenytoin™, mexiletine™, and lidocaine™.

[0012] There is also a need to develop Na channel blockers that have minimal or no inhibitory activity against the hERG channel. hERG (human ether a-go-go related gene) encodes a potassium ion channel (hERG channel) that is involved in cardiac repolarization. See, e.g., Pearlstein, R., R. Vaz, et al. (2003). "Understanding the Structure-Activity Relationship of the Human Ether-a-go-go-Related Gene Cardiac K(+) Channel. A Model for Bad Behavior." J Med Chem 46(11): 2017-22. Interaction with with the hERG channel is one indicator of potential cardaic toxicity. hERG-block increases the likelihood of cardiac QT-interval prolongation and dispersion. A subset of compounds that prolong the QT interval can cause ventricular fibrillation and cardiac failure. Belardinelli, L., C. Antzelevitch and M.A. Vos (2003). "Assessing predictors of drug-induced torsade de pointes". Trends Pharmacol Sci. 24 (12): 619-25; Al-Khatib, S. M., N. M. LaPointe, et al. (2003). "What clinicians should know about the QT interval." Jama 289(16): 2120-7; http://www.fenichel.net/pages/site_map.htm.

[0013] There is also a need to develop Na channel blockers that have minimal or no inhibitory activity against the Cytochrome P450 enzyme family. Within this family, CYP 3A4 isoform is believed to be the major isoform present in the liver and small intestines. Other key isoforms include CYP 2D6, CYP 2C9, and CYP 1A2. See, e.g., United States patent 6,514,687, the disclosure whereof is incorporated herein by reference. A Na channel blocker that inhibits one or more of the isoforms can cause undesirable side effect or can cause undesirable drug-drug interactions when administered with another drug that interacts with that isoform. See, e.g, Davit, B., et al. (1999), "FDA Evaluations Using In Vitro Metabolism to Predict and Interpret In Vivo Metabolic Drug-Drug Interactions: Impact on Labeling," J. Clin. Pharmacol., 39: 899-910; "Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, Dept. of Health and Human Services, U.S.F.D.A (http://www.fda.gov/cder/guidance.htm).

[0014] There is also a need to develop Na channel blockers that exhibit selectivity against a certain sub-type of Na channel. Particularly useful are compounds that have a desirably low activity against NaV 1.2.

[0015] There is also a need to develop Na channel blockers that have a desirably low activity against L-type calcium channel 1.2. CaV1.2 calcium channels are abundantly expressed in smooth and striated muscle, especially in the heart, brain and endocrine cells. Blocking these

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channels can be therapeutically useful, but it can also result in significant side effects. The most significant concerns are impairment of cardiac contractility (that is, a negative inotropic effect) and slowing of electrical conduction in the pacemaker regions of the heart. See, e.g., Kizer, J. R., et al., "Epidemiologic Review of the Calcium Channel Blocker Drugs," Arch. Intern Med. 2001; 161: 1145-1158.

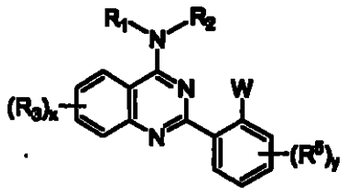
[0016] There is also a need to Na channel blockers that have a desirably low activity against potassiums channel 1.5 ("Kv1.5"; also known as KCNA5). Kv1.5 is found primarily in human atrial cells, but also in brain. See, e.g., Gutman, G. A., et al., "Compendium of Voltage-Gated Ion Channels: Potassium Channels," Pharmacol. Rev., 55: 583-585 (2003). Unwanted block of Kv1.5 could produce convulsion or ataxia.

[0017] There is also a need to develop Na channel blockers that have improved pharmacokinetic and/or pharmacodynamic properties and, therefore, are better suited for *in-vivo* administration for therapeutic purposes. Such properties include aqueous solubility, bioavailability, clearance kinetics, etc. See, e.g., Shargel, L., Yu, A., Ed's "Applied Biopharmaceutics & Pharmacokinetics", 4th Ed., McGraw-Hill, New York, 1999; Yacobi, A., Skelly, J.P., Shah, V.P., Benet, L.Z., Ed's. "Integration of Pharmacokinetics, Pharmacodynamics, and Toxicokinetics in Rational Drug Development", Plenum Press, New York, 1993; Lee, J.S., Obach, R.S., Fisher, M.B., Ed's. "Drug Metabolizing Enzymes Cytochrome P450 and Other Enzymes in Drug Discovery and Development", Marcel Dekker, New York, 2003; Birkett, D.J. "Pharmacokinetics Made Easy", McGraw-Hill Australia, Roseville, Australia, 2002; Katzung, B.G. "Basic & Clinical Pharmacology", McGraw-Hill, New York, 2001; Welling, P.G., Tse, F.L.S., Ed's. "Pharmcokinetics", Marcel Dekker, New York, 1988; Thomas, G. "Medicinal Chemistry An Introduction", Wiley & Sons, New York, 2000; and Gennaro, A. R., et al., "Remington: The Science and Practice of Pharmacy," 20th Ed., Lippincott, Williams, & Wilkins (2003).

[0018] Na channel blocker that meets one or more of the above unmet needs would be a very desirable improvement over the currently marketed Na channel blockers and would greatly benefit patients in need of a therapy therewith.

SUMMARY OF THE INVENTION

[0019] The present invention provides compounds of formula I:



I;

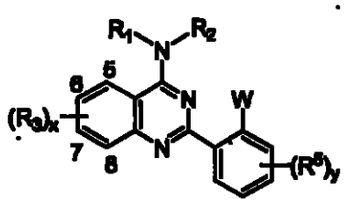
or a pharmaceutically acceptable salt or derivative thereof.

[0020] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain.

DETAILED DESCRIPTION OF THE INVENTION

[0021] *I. General Description of Compounds of the Invention:*

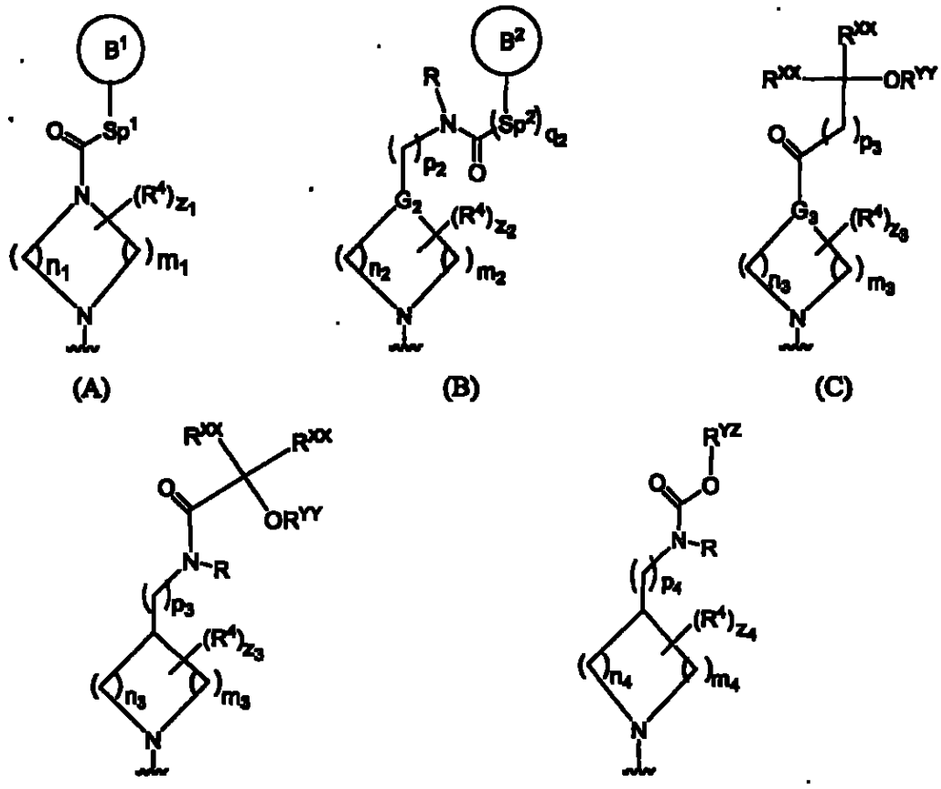
[0022] The present invention provides a compound of formula I:



I;

or a pharmaceutically acceptable salt or derivative thereof, wherein:

R^1 and R^2, taken together with the nitrogen atom, form a substituted ring selected from:



(A) (B) (C)

(D) or (E);

wherein, in ring (A):

each of m_1 and n_1 is independently 0-3, provided that m_1+n_1 is 2-6;

z_1 is 0-4;

Sp^1 is –O-, -S-, -NR'-, or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO_2-, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, -SO_2-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-, provided that Sp^1 is attached to the carbonyl group through an atom other than carbon;

ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w_1 independent occurrences of -R^{11}, wherein w_1 is 0-4;

wherein, in ring (B):

G_2 is -N-, or CH;

each of m_2 and n_2 is independently 0-3, provided that $m_2 + n_2$ is 2-6;

p_2 is 0-2; provided that when G_2 is N, then p_2 is not 0;

q_2 is 0 or 1;

z_2 is 0-4;

Sp^2 is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$;

ring B^2 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4;

wherein, in ring (C) or ring (D):

G_3 is -N-, -CH-NH-, or $-CH-CH_2-NH-$;

each of m_3 and n_3 is independently 0-3, provided that m_3+n_3 is 2-6;

p_3 is 0-2;

z_3 is 0-4;

each R^{XX} is hydrogen, C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3;

provided that both R^{XX} are not simultaneously hydrogen;

R^{YY} is hydrogen, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or $-PO(R')$;

wherein, in ring (E):

each of m_4 and n_4 is independently 0-3, provided that $m_4 + n_4$ is 2-6;

p_4 is 1-2;

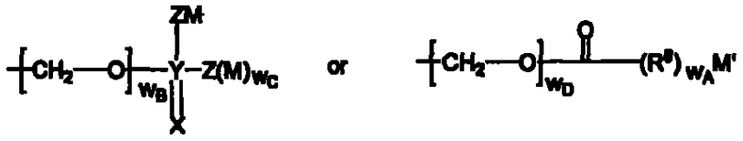
z_4 is 0-4;

R^{YZ} is C_1-C_6 aliphatic group, optionally substituted with w_4 independent occurrences of -R^{14}, wherein w_4 is 0-3;

x and y, each, is independently 0-4;

W is OR^{XY};

R^{XY} is hydrogen or a group selected from:



;

wherein:

each of w_A, w_B, w_C, and w_D is independently 0 or 1;

each M is independently selected from hydrogen, Li, Na, K, Mg, Ca, Ba, -$N(R^7)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or -R^6; wherein 1 to 4 –CH_2 radicals of the alkyl or alkenyl group, other than the –CH_2 that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, -OR^7, -R^7, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, -CO_2R^7, -$C(O)$-$N(R^7)_2$, $S(O)_2$-$N(R^7)_2$, $N(R^7)$-$C(O)$-R^7, $C(O)R^7$, -$S(O)_n$-R^7, OCF_3, -$S(O)_n$-R^6, $N(R^7)$-$S(O)_2(R^7)$, halo, -CF_3, or -NO_2;

n is 0-2;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or -R^6; wherein 1 to 4 –CH_2 radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, -OR^7, -R^7, -$N(R^7)_2$, $N(R^7)_3$, -R^7OH, -CN, -CO_2R^7, -$C(O)$-$N(R^7)_2$, -$S(O)_2$-$N(R^7)_2$, -$N(R^7)$-$C(O)$-R^7, -$C(O)R^7$, -$S(O)_n$-R^7, -OCF_3, -$S(O)_n$-R^6, -$N(R^7)$-$S(O)_2(R^7)$, halo, -CF_3, or -NO_2;

Z is -CH_2-, -O-, -S-, -$N(R^7)_2$-; or,

when M is absent, then Z is hydrogen, =O, or =S;

Y is P or S, wherein when Y is S, then Z is not S;

X is O or S;

each R^7 is independently selected from hydrogen, or C_1-C_4 aliphatic, optionally substituted with up to two Q_1;

each Q_1 is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatom or heteroatom group selected from O, N, NH, S, SO, or SO_2; wherein Q_1 is optionally substituted with up to three substituents selected from oxo, -OH, -O(C_1-C_4 aliphatic), -C_1-C_4 aliphatic, -NH_2, NH(C_1-C_4 aliphatic), -N(C_1-C_4 aliphatic)$_2$, -N(C_1-C_4 aliphatic)-C(O)- C_1-C_4 aliphatic, -(C_1-C_4 aliphatic)-OH, -CN, -CO_2H, -CO_2(C_1-C_4 aliphatic), -C(O)-NH_2, -C(O)-NH(C_1-C_4 aliphatic), -C(O)-N(C_1-C_4 aliphatic)$_2$, halo or -CF_3;

R^6 is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)$_n$ or N(R^7); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C_1-C_4 alkyl, O-C_1-C_4 alkyl or O-C(O)-C_1-C_4 alkyl;

R^9 is C(R^7)$_2$, O or N(R^7);

each occurrence of R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4, and R^5 is independently Q-R^X; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO_2-, -SO_2NR-, -NRSO_2-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO_2NR-, -SO-, -SO_2-, -PO-, -PO_2-, -OP(O)(OR)-, or -POR-; and each occurrence of R^X is independently selected from -R', halogen, =O, =NR', -NO_2, -CN, -OR', -SR', -N(R')$_2$, -NR'COR', -NR'CON(R')$_2$, -NR'CO_2R', -COR', -CO_2R', -OCOR', -CON(R')$_2$, -OCON(R')$_2$, -SOR', -SO_2R', -SO_2N(R')$_2$, -NR'SO_2R', -NR'SO_2N(R')$_2$, -COCOR', -$COCH_2$COR', -OP(O)(OR')$_2$, -P(O)(OR')$_2$, -$OP(O)_2$OR', -$P(O)_2$OR', -PO(R')$_2$, or -OPO(R')$_2$; and

each occurrence of R is independently hydrogen or C_{1-6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four

substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0023] *2. Compounds and Definitions:*

[0024] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0025] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not

substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0026] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0027] The term "heteroaliphatic", as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" groups.

[0028] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members are an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[0029] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0030] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0031] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[0032] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

[0033] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[0034] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0035] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are generally selected from halogen; $-R^\circ$; $-OR^\circ$; $-SR^\circ$; phenyl (Ph) optionally substituted with R°; $-O(Ph)$ optionally substituted with R°; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R°; -

CH=CH(Ph), optionally substituted with R°; $-NO_2$; -CN; $-N(R^\circ)_2$; $-NR^\circ C(O)R^\circ$; $-NR^\circ C(S)R^\circ$; $-NR^\circ C(O)N(R^\circ)_2$; $-NR^\circ C(S)N(R^\circ)_2$; $-NR^\circ CO_2R^\circ$; $-NR^\circ NR^\circ C(O)R^\circ$; $-NR^\circ NR^\circ C(O)N(R^\circ)_2$; $-NR^\circ NR^\circ CO_2R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-CO_2R^\circ$; $-C(O)R^\circ$; $-C(S)R^\circ$; $-C(O)N(R^\circ)_2$; $-C(S)N(R^\circ)_2$; $-OC(O)N(R^\circ)_2$; $-OC(O)R^\circ$; $-C(O)N(OR^\circ)R^\circ$; $-C(NOR^\circ)R^\circ$; $-S(O)_2R^\circ$; $-S(O)_3R^\circ$; $-SO_2N(R^\circ)_2$; $-S(O)R^\circ$; $-NR^\circ SO_2N(R^\circ)_2$; $-NR^\circ SO_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(=NH)-N(R^\circ)_2$; $-P(O)_2R^\circ$; $-PO(R^\circ)_2$; $-OPO(R^\circ)_2$; $-(CH_2)_{0-2}NHC(O)R^\circ$; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R°; or -CH=CH(Ph), optionally substituted with R°; wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or $-CH_2(Ph)$, or, notwithstanding the definition above, two independent occurrences of R°, on the same substituent or different substituents, taken together with the atom(s) to which each R° group is bound, to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0036] . Optional substituents on the aliphatic group of R° are selected from NH_2, $NH(C_{1-4}$aliphatic), $N(C_{1-4}$aliphatic$)_2$, halogen, C_{1-4}aliphatic, OH, $O(C_{1-4}$aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$aliphatic), O(haloC_{1-4} aliphatic), or haloC_{1-4}aliphatic, wherein each of the foregoing C_{1-4}aliphatic groups of R° is unsubstituted.

[0037] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2$(alkyl), $=NNHSO_2$(alkyl), or $=NR^*$, where each R^* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group.

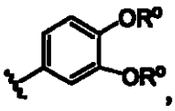
[0038] Unless otherwise defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring are generally selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally

substituted phenyl, optionally substituted -O(Ph), optionally substituted -CH_2(Ph), optionally substituted -$(CH_2)_{1-2}$(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R^+, on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

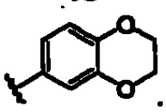
[0039] Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from -NH_2, -NH(C_{1-4} aliphatic), -N(C_{1-4} aliphatic)$_2$, halogen, C_{1-4} aliphatic, -OH, -O(C_{1-4} aliphatic), -NO_2, -CN, -CO_2H, -CO_2(C_{1-4} aliphatic), -O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R^+ is unsubstituted.

[0040] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation and has two points of attachment to the rest of the molecule.

[0041] As detailed above, in some embodiments, two independent occurrences of R° (or R^+, R, R' or any other variable similarly defined herein), are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0042] Exemplary rings that are formed when two independent occurrences of R° (or R^+, R, R', or any other variable similarly defined herein), are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R° (or R^+, R, R' or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, N(R°)$_2$, where both occurrences of R° are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R° (or R^+, R, R' or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR°  , these two occurrences of R° are taken together with

the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:



. It will be appreciated that a variety of other rings can be formed when two independent occurrences of R^o (or R^+, R, R' or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0043] *3. Description of Exemplary Compounds:*

[0044] In one embodiment, R is hydrogen. Or, R is C1-C6 aliphatic. Exemplary R includes C1-C6 alkyl, e.g., methyl, ethyl, propyl, or butyl.

[0045] In one embodiment, R' is hydrogen.

[0046] In one embodiment, R' is a C1-C8 aliphatic group, optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, or $OCHF_2$, wherein up to two methylene units of said C1-C8 aliphatic is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, -CO_2-, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, -SO_2N(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[0047] In one embodiment, R' is a 3-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen,

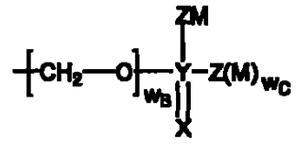
oxygen, or sulfur, wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with -CO-, -CONH(C1-C4 alkyl)-, $-CO_2-$, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, $-SO_2N$(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[0048] In one embodiment, R' is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, $-CO_2-$, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, $-SO_2N$(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[0049] In one embodiment, two occurrences of R' are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' is optionally substituted with up to 3 substituents selected from halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$, or C1-C6 alkyl, wherein up to two methylene units of said C1-C6 alkyl is optionally replaced with –CO-, -CONH(C1-C4 alkyl)-, $-CO_2-$, -OCO-, -N(C1-C4 alkyl)CO_2-, -O-, -N(C1-C4 alkyl)CON(C1-C4 alkyl)-, -OCON(C1-C4 alkyl)-, -N(C1-C4 alkyl)CO-, -S-, -N(C1-C4 alkyl)-, $-SO_2N$(C1-C4 alkyl)-, N(C1-C4 alkyl)SO_2-, or -N(C1-C4 alkyl)SO_2N(C1-C4 alkyl)-.

[0050] In another embodiment, W is OH.

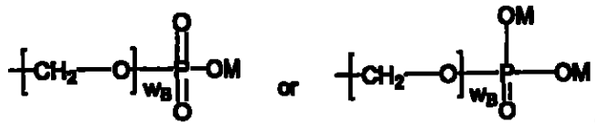
[0051] In still another embodiment, R^{XY} is:



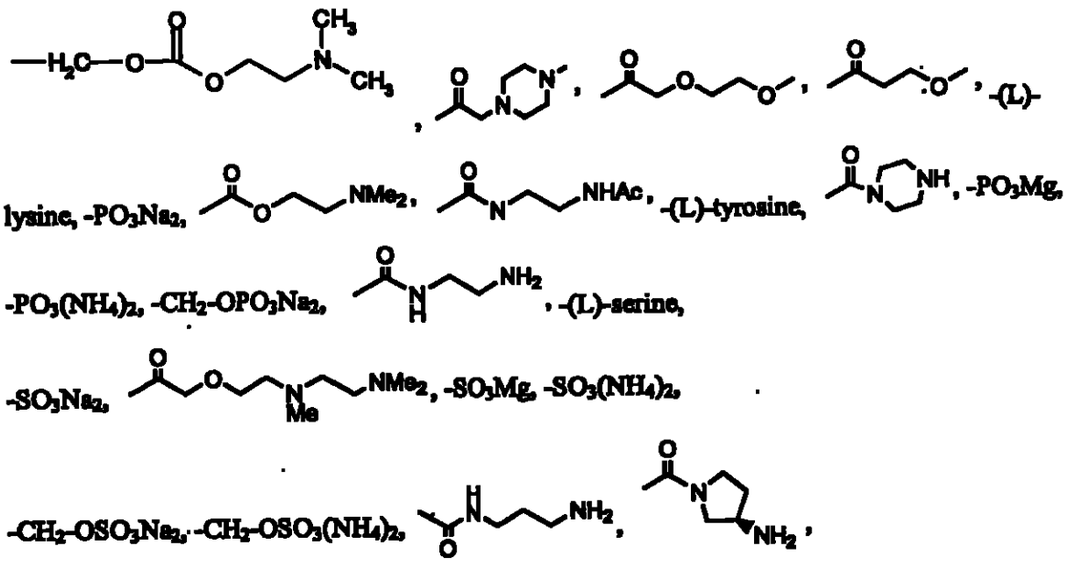
[0052] In certain embodiment, Y is P and X is O.

[0053] In another embodiment, each Z is –O-.

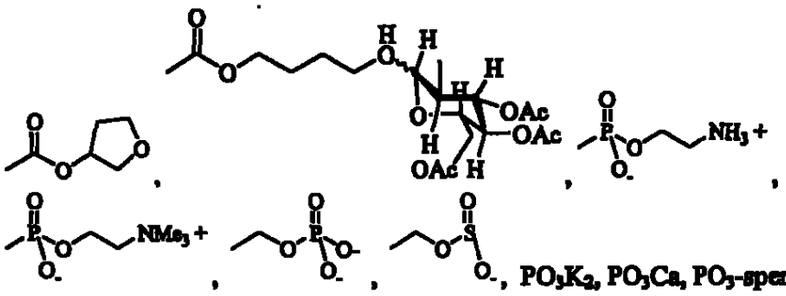
[0054] In yet another embodiment, R^{XY} is selected from:



[0055] In yet another embodiment, R^{XY} is selected from:

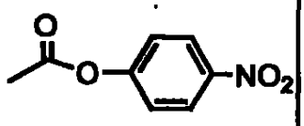
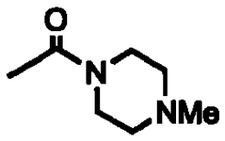
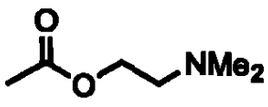
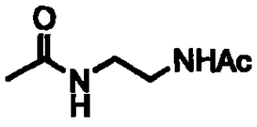
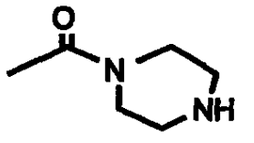


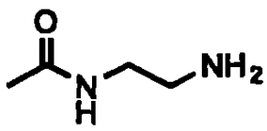
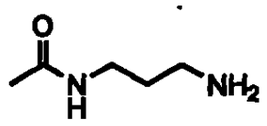
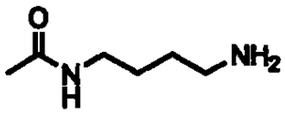
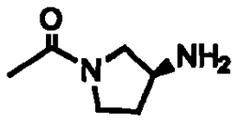
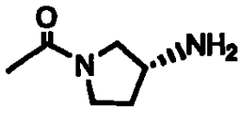
lysine, -PO_3Na_2, , -(L)-tyrosine, , -PO_3Mg, -$PO_3(NH_4)_2$, -CH_2-OPO_3Na_2, , -(L)-serine, -SO_3Na_2, , -SO_3Mg, -$SO_3(NH_4)_2$, -CH_2-OSO_3Na_2, -CH_2-$OSO_3(NH_4)_2$, , , , , , acetyl, , , -(L)-valine, -(L)-glutamic acid, -(L)-aspartic acid, -(L)-γ-t-butyl-aspartic acid, , -(L)-3-pyridylalanine, -(L)-histidine, -CHO, ,

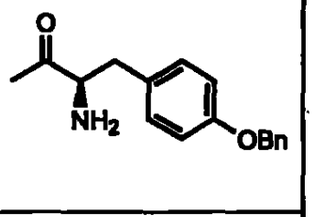
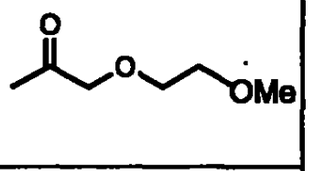
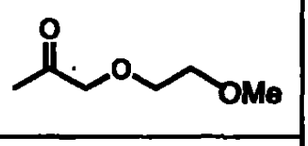
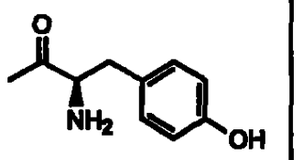
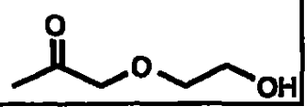


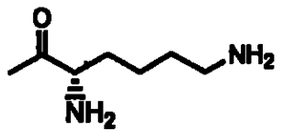
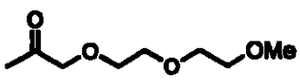
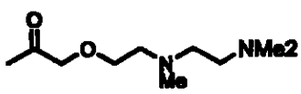
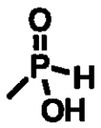
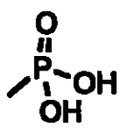
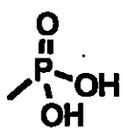
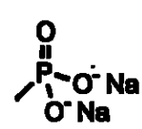
, PO_3K_2, PO_3Ca, PO_3-spermine, PO_3-(spermidine)$_2$ or PO_3-(meglamine)$_2$.

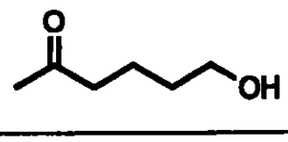
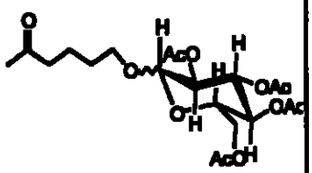
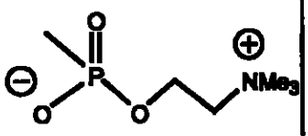
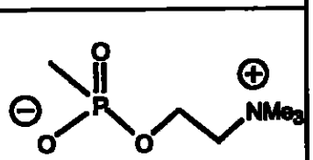
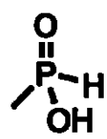
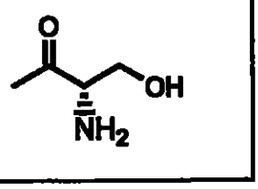
[0056] In yet another embodiment, R^{XY} is selected from:

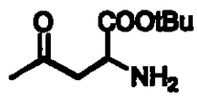
R^{XY}






R^{XY}






R^{XY}






R^{XY}








R^{XY}


-SO_3H
-SO_3H





R^{XY}
PO_3K_2
PO_3Ca
PO_3Mg


[0057] In one embodiment, x is 0-2. Or, x is 1 or 2. Or, x is 1.

[0058] In one embodiment, R^3 is present at the 6- or 7-position of the quinazoline ring.

[0059] In another embodiment, R^3 is selected from halo, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0060] In one embodiment, R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(cyclopropyl), $-CONHCH_3$, $-CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

[0061] In another embodiment, each R^3 group is independently halogen, CN, optionally substituted C_1-C_6alkyl, OR', $N(R')_2$, $CON(R')_2$, or NRCOR'.

[0062] In one embodiment, x is 1 or 2, and each R^3 group is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

[0063] In yet another embodiment, x is 1 and R^3 is at the 6-position of the quinazoline ring and is selected from -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or –CN.

[0064] In yet another embodiment, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

[0065] In one embodiment, R^3 is at the 6-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'.

[0066] In another embodiment, x is 1 and R^3 is at the 7-position of the quinazoline ring and is selected from -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

[0067] In yet another embodiment, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$. Or, x is 1 and R^3 is at the 7-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'.

[0068] In one embodiment, y is 0-4 and R^3 is independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, - -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -

COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0069] In another embodiment, R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), $-COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0070] In certain embodiments, each of z_1, z_2, z_3, or z_4 is independently 0-2. In other embodiments, each of z_1, z_2, z_3, or z_4 is 0 and the ring is unsubstituted. Preferred R^4 groups, when present, are each independently halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl. Other exemplary R^4 groups are Cl, Br, F, CF_3, CH_3, $-CH_2CH_3$, CN, -COOH, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2(CH_2)_3CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)NHCH_2CH(CH_3)_2$, $-NHCOOCH_3$, $-C(O)C(CH_3)_3$, $-COO(CH_2)_2CH_3$, $-C(O)NHCH(CH_3)_2$, $-C(O)CH_2CH_3$, or an optionally substituted group selected from piperidinyl, piperizinyl, morpholino, C_{1-4}alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, $-CH_2$cyclohexyl, pyridyl, $-CH_2$pyridyl, or $-CH_2$thiazolyl

[0071] In certain embodiments, x is 0-2. In other embodiments, x is 1 or 2. In still other embodiments x is 1 and R^3 is substituted at the 6- or 7-position of the quinazoline ring. When the quinazoline ring is substituted (x is 1-4), R^3 groups are halogen, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, -COOR', -NRCOR', $-CON(R')_2$, $-OCON(R')_2$, COR', -NHCOOR', $-SO_2R'$, $-SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl. In still other embodiments, each occurrence of R^3 is independently Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, -

CH_2OH, -$NHCOCH_3$, -$NHCOCH(CH_3)_2$, -SO_2NH_2, -CONH(cyclopropyl), -$CONHCH_3$, -$CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy. In still other embodiments, x is 1 or 2 and each R^3 group is independently halogen, CN, optionally substituted C_1-C_6alkyl, OR', $N(R')_2$, $CON(R')_2$, or NRCOR'. In yet other embodiments, x is 1 or 2, and each R^3 group is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -$CONHCH_3$, -$CONHCH_2CH_3$, -CONH(cyclopropyl), -OCH_3, -NH_2, -OCH_2CH_3, or -CN. In still other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -$CONHCH_3$, -$CONHCH_2CH_3$, -CONH(cyclopropyl), -OCH_3, -NH_2, -OCH_2CH_3, or –CN. IN yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -$CONHCH_3$, -$CONHCH_2CH_3$, -CONH(cyclopropyl), -OCH_3, -NH_2, -OCH_2CH_3, or -CN. In other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -OCH_3, or -OCH_2CH_3. In still other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -OCH_3, or -OCH_2CH_3. In other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is –$CON(R')_2$, or NRCOR'. In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is –$CON(R')_2$, or NRCOR'.

[0072] In some embodiments, y is 0-4 and R^5 group, when present, is each independently halogen, CN, NO_2, -$N(R')_2$, -$CH_2N(R')_2$, -OR', -CH_2OR', -SR', -CH_2SR', - -NRCOR', -$CON(R')_2$, -$S(O)_2N(R')_2$, -OCOR', -COR', -CO_2R', -$OCON(R')_2$, -NR'SO_2R', -$OP(O)(OR')_2$, -$P(O)(OR')_2$, -$OP(O)_2OR'$, -$P(O)_2OR'$, -$PO(R')_2$, -$OPO(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0073] In yet other embodiments, y is 0-4 and each occurrence of R^5 is independently Cl, Br, F, CF_3, Me, Et, CN, -COOH, -NH_2, –$N(CH_3)_2$, -$N(Et)_2$, -$N(iPr)_2$, -$O(CH_2)_2OCH_3$, -$CONH_2$, -$COOCH_3$, -OH, -OCH_3, -OCH_2CH_3, -CH_2OH, -$NHCOCH_3$, -SO_2NH_2, -$SO_2NHC(CH_3)_2$, -$OCOC(CH_3)_3$, -$OCOCH_2C(CH_3)_3$, -$O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-yl, $OCOCH(CH_3)_2$, OCO(cyclopentyl), -$COCH_3$, optionally substituted phenoxy, or optionally substituted benzyloxy.

[0074] In yet another embodiment, each of z_1, z_2, z_3, or z_4 is 0-4, and R^4 groups, when present, are each independently halogen, CN, NO_2, -$N(R')_2$, -$CH_2N(R')_2$, -OR', -CH_2OR', -SR',

-CH_2SR', -COOR', -NRCOR', -$CON(R')_2$, -$OCON(R')_2$, COR', -NHCOOR', -SO_2R', -$SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0075] In still other embodiments, each of z_1, z_2, z_3, or z_4 is 0-4 and R^4 groups are each independently Cl, Br, F, CF_3, CH_3, -CH_2CH_3, CN, -COOH, -$N(CH_3)_2$, -$N(Et)_2$, -$N(iPr)_2$, -$O(CH_2)_2OCH_3$, -$CONH_2$, -$COOCH_3$, -OH, -CH_2OH, -$NHCOCH_3$, -SO_2NH_2, -$SO_2(CH_2)_3CH_3$, -$SO_2CH(CH_3)_2$, -$SO_2N(CH_3)_2$, -$SO_2CH_2CH_3$, -$C(O)OCH_2CH(CH_3)_2$, -$C(O)NHCH_2CH(CH_3)_2$, -$NHCOOCH_3$, -$C(O)C(CH_3)_3$, -$COO(CH_2)_2CH_3$, -$C(O)NHCH(CH_3)_2$, -$C(O)CH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, C_{1-4}alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, -CH_2cyclohexyl, pyridyl, -CH_2pyridyl, or -CH_2thiazolyl.

[0076] For compounds described directly above, in some embodiments, x is 0-4, and R^3 groups, when present, are each independently halogen, CN, NO_2, -$N(R')_2$, -$CH_2N(R')_2$, -OR', -CH_2OR', -SR', -CH_2SR', -COOR', -NRCOR', -$CON(R')_2$, -$OCON(R')_2$, COR', -NHCOOR', -SO_2R', -$SO_2N(R')_2$, or an optionally substituted group selected from C_1-C_6aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC_1-C_6alkyl, heteroarylC_1-C_6alkyl, cycloaliphaticC_1-C_6alkyl, or heterocycloaliphaticC_1-C_6alkyl.

[0077] In yet other embodiments, x is 1 or 2, and each occurrence of R^3 is independently Cl, Br, F, CF_3, -OCF_3, Me, Et, CN, -COOH, -NH_2, -$N(CH_3)_2$, -$N(Et)_2$, -$N(iPr)_2$, -$O(CH_2)_2OCH_3$, -$CONH_2$, -$COOCH_3$, -OH, -OCH_3, -OCH_2CH_3, -CH_2OH, -$NHCOCH_3$, -$NHCOCH(CH_3)_2$, -SO_2NH_2, -CONH(cyclopropyl), -$CONHCH_3$, -$CONHCH_2CH_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzyloxy.

[0078] In still other embodiments, x is 1 or 2 and each R^3 group is independently halogen, CN, optionally substituted C_1-C_6alkyl, OR', $N(R')_2$, $CON(R')_2$, or NRCOR'.

[0079] In yet other embodiments, x is 1 or 2, and each R^3 group is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -$CONHCH_3$, -$CONHCH_2CH_3$, -CONH(cyclopropyl), -OCH_3, -NH_2, -OCH_2CH_3, or -CN.

[0080] In still other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, -CH_3, -CH_2CH_3, -F, -CF_3, -OCF_3, -$CONHCH_3$, -$CONHCH_2CH_3$, -CONH(cyclopropyl), -OCH_3, -NH_2, -OCH_2CH_3, or -CN.

[0081] In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

[0082] In still other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

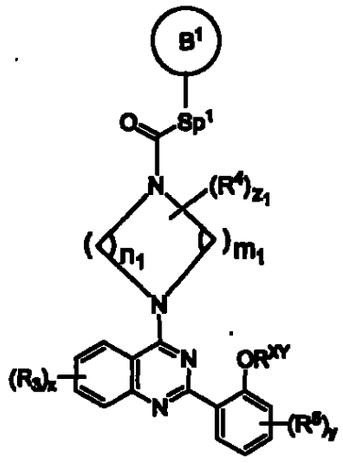
[0083] In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

[0084] In still other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'.

[0085] In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$.

[0086] In yet other embodiments for compounds described directly above, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN. In still other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN. In yet other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$. In still other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$, or $-OCH_2CH_3$. In yet other embodiments, x is 1 and R^3 is at the 6-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'. In yet other embodiments, x is 1 and R^3 is at the 7-position of the quinazoline ring and is $-CON(R')_2$, or NRCOR'.

[0087] In one embodiment, the present invention provides compounds of formula I-A:



I-A;

wherein x, y, n_1, m_1, z_1, R^{XY}, R^4, R^5, Sp^1, and ring B^1 are as defined above.

[0088] In one embodiment, Sp^1 is selected from -O-, -S-, or –NR'-. Or, Sp^1 is –O-. Or, Sp^1 is –O-CH_2-. In another embodiment, Sp^1 is –NR'-. Or, Sp^1 is –NH-. Or, Sp^1 is -NH-CH_2-.

[0089] In one embodiment, each of m_1 and n_1 is 1. In another embodiment, each of m_1 and n_1 is 2.

[0090] In one embodiment, ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w independent occurrences of -R^{11}, wherein w_1 is 0-4.

[0091] In another embodiment, ring B^1 is a 4-8 membered, saturated, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w independent occurrences of -R^{11}, wherein w_1 is 0-4.

[0092] In yet another embodiment, ring B^1 is a 5-6 membered, saturated, monocyclic heterocyclic ring having having 1-2 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w independent occurrences of -R^{11}, wherein w_1 is 0-4.

[0093] In one embodiment, w_1 is 0.

[0094] In another embodiment, ring B^1 is tetrahydrofuranyl.

[0095] In yet another embodiment, Sp^1 is a bond, O, or –O-CH_2-; R is hydrogen; and n_1 and m_1 are both simultaneously 1 or 2.

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[0096] In one embodiment, R is hydrogen. Or, R is C1-C6 alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[0097] In another embodiment, z_1 is 0.

[0098] According to another embodiment, ring B^1 is tetrahydrofuranyl, tetrahydro-[*2H*]-pyranyl, pyridyl, or phenyl.

[0099] According to yet another embodiment, Sp^1 is a bond, -O-, $-O-CH_2-$, or $-NH-CH_2$.

[00100] In one embodiment:

n_1 and m_1 each is 2;

R^{XY} is hydrogen;

y is 0 or 1 and R^5 is fluoro;

x is 1 and R^3 is Me at 7-position or fluoro at 6-position;

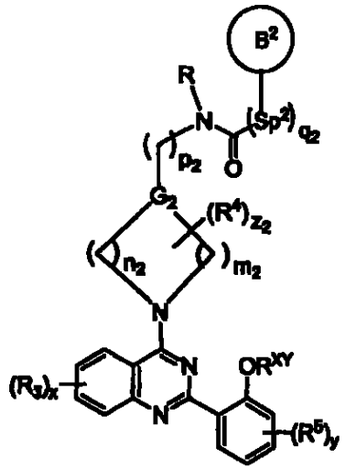
z_1 is 0;

Sp^1 is $-O-CH_2-$;

w_1 is 0; and

ring B^1 is tetrahydrofuran-3-yl, phenyl, pyridine-3-yl, pyridine-4-yl, or tetrahydro[2H]-pyran-4-yl.

[00101] According to another embodiment, the present invention provides compounds of formula I-B:



I-B;

wherein x, y, n_2, m_2, z_2, q_2, R, Sp^2, ring B^2, R^{XY}, R^3, R^4, and R^5 are as defined above.

[00102] In one embodiment, G_2 is N. Or, G_2 is CH.

[00103] In one embodiment, p_2 is 0. Or, p_2 is 1. Or, p_2 is 2.

[00104] In another embodiment, q_2 is 0. Or, q_2 is 1..

[00105] In one embodiment, p_2 is 1, and q_2 is 1.

[00106] In another embodiment, G_2 is CH, p_2 is 0, and q_2 is 1.

[00107] In one embodiment, m_2 and n_2 each is 1. Or, m_2 and n_2 each is 2. Or, n_2 is 1 and m_2 is 2. Or, n_2 is 1, and m_2 is 3.

[00108] In another embodiment, Sp^2 is selected from -O-, -S-, or –NR'-. In one embodiment, Sp^2 is –O-. Or, Sp^2 is –NR'-. Or, Sp^2 is –NH-.

[00109] In one embodiment, ring B^2 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4.

[00110] In another embodiment, ring B^2 is a 4-8 membered, saturated, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^2 is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4.

[00111] In yet another embodiment, ring B^2 is a 5-6 membered, saturated, monocyclic heterocyclic ring having having 1-2 heteroatoms selected from O, S, or N, wherein ring B^2 is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4.

[00112] In one embodiment, w_2 is 0.

[00113] According to yet another embodiment, Sp^2 is a bond, -O-, or $-O-CH_2-$.

[00114] In another embodiment, ring B^2 is tetrahydrofuranyl, tetrahydro[2*H*]pyranyl, or pyridyl.

[00115] In yet another embodiment,

i) Sp^2 is a bond, O, or $-O-CH_2-$;

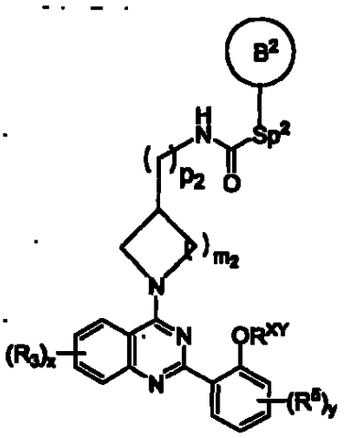
ii) p_2 is 1;

iii) R is hydrogen; and

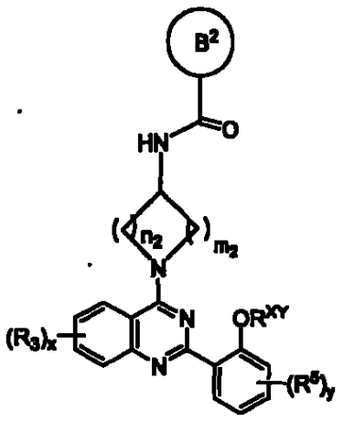
iv) n_2 is 1 and m_2 is 2 or 3.

[00116] In one embodiment, R is hydrogen. Or, R is C1-C6 alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[00117] In one embodiment, compounds of formula I-B have formula I-B-i or formula I-B-ii:



I-B-i



I-B-ii.

[00118] In one embodiment of formula I-B-i:

i) p_2 is 1;

ii) m_2 is 3;

iii) Sp^2 is -O-;

iv) y is 0 or 1, and R^5 is fluoro;

v) x is 1 and R^3 is 7-Me; and

vi) ring B^2 is tetrahydrofuranyl.

[00119] In another embodiment of formula I-B-i:

i) p_2 is 0 or 1;

ii) m_2 is 1 or 2, preferably 2;

iii) Sp^2 is -O- or -O-CH_2-;

iv) y is 0;

v) x is 1 and R^3 is 7-Me; and

vi) ring B^2 is tetrahydrofuranyl, tetrahydro[2H]pyranyl, pyridyl, or phenyl.

[00120] In one embodiment of formula I-B-ii:

(i) n_2 is 1, m_2 is 1 or 2, preferably 2;

(ii) y is 0 or 1, and R^5 is fluoro;

(iii) x is 1 and R^3 is 7-Me or 6-F; and

(iv) ring B^2 is cyclopropyl optionally substituted with C1-C4 alkyl, or pyridyl.

[00121] In one embodiment of formula I-B-ii:

(i) n_2 and m_2 both are 2;

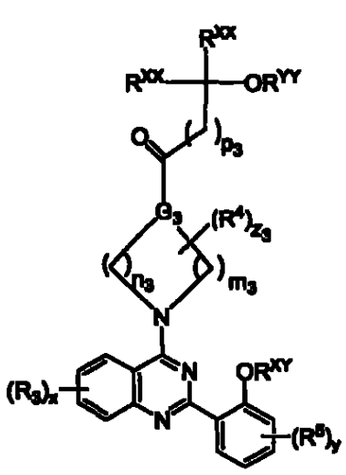
(ii) y is 0;

(iii) x is 1 and R^3 is C1-C4 alkyl at the 7-position; and

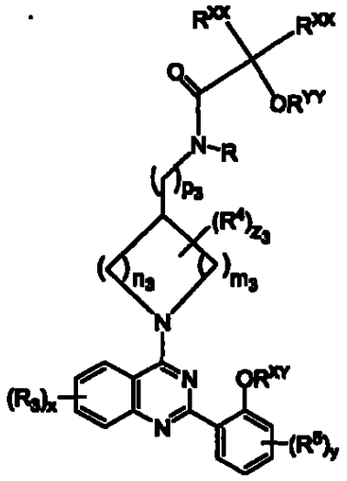
(iv) ring B^2 is an optionally substituted tetrahydrofuranyl.

[00122] In one embodiment of formula I-B-i or formula I-B-ii, R^{XY} is hydrogen.

[00123] According to one embodiment, the present invention provides compounds of formula I-C or formula I-D:



I-C



I-D;

wherein x, y, n_3, m_3, z_3, p_3, R^{XX}, R^{YY}, R^{XY}, R^3, R^4, and R^5 are as defined above.

[00124] In one embodiment of the present invention, one R^{XX} is hydrogen and the other R^{XX} is not hydrogen.

[00125] In another embodiment of the present invention, both R^{XX} are not hydrogen.

[00126] In another embodiment, one R^{XX} is hydrogen and the other R^{XX} is C1-C6 alkyl optionally substituted with halo. Or, both R^{XX} are simultaneously C1-C6 alkyl. Exemplary alkyl include methyl, ethyl, isopropyl, *n*-propyl, *n*-butyl, *sec*-butyl, or *t*-butyl.

[00127] In one embodiment of the present invention, p_3 is 0. Or, p_3 is 1. Or, p_3 is 2.

[00128] In one embodiment of the present invention, m_3 and n_3 each is 1. Or, m_3 and n_3 each is 2. Or, m_3 and n_3 each is 3.

[00129] In one embodiment of the present invention, R^{XX} is C_{1-6} aliphatic group, wherein R^{XX} is optionally substituted with w independent occurrences of $-R^{13}$, wherein w_3 is 0-3. Or, R^{XX} is

C1-C6 alkyl group optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3.

[00130] In one embodiment of the present invention, R^{XX} is C1-C6 alkyl group.

[00131] In another embodiment of the present invention, R^{XX} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3.

[00132] In another embodiment, R^{XX} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^{XX} is optionally substituted with w independent occurrences of $-R^{13}$, wherein w_3 is 0-3.

[00133] In another embodiment, R^{XX} is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3.

[00134] In another embodiment, R^{YY} is hydrogen, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or -PO(R').

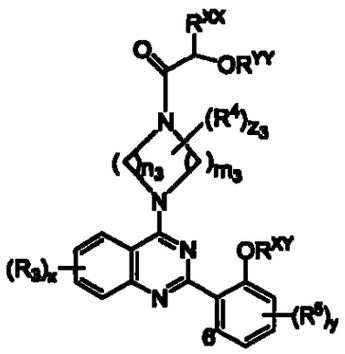
[00135] Or, R^{YY} is hydrogen.

[00136] In another embodiment, R^{YY} is -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or -PO(R').

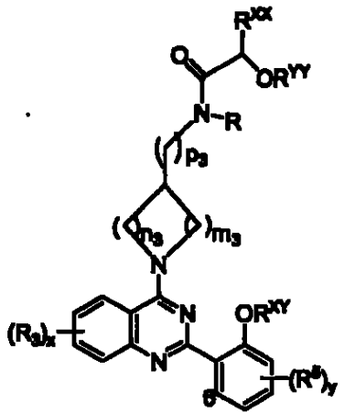
[00137] In another embodiment, R^{YY} is R^{XY}.

[00138] In one embodiment, R is hydrogen. Or, R is C1-C6 alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[00139] In one embodiment, the present invention provides a compound of formula I-C-1 or formula I-D-1:



I-C-i



I-D-i;

wherein x, y, n_3, m_3, z_3, p_3, R^{XX}, R^{YY}, R^{XY}, R^3, R^4, and R^5 are as defined above.

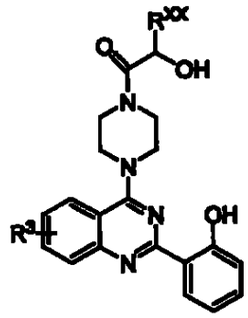
[00140] In one embodiment of I-C-i or I-D-i, R^{XX} is C1-C6 alkyl. In another embodiment, x is 1, and R^3 is C1-C4 alkyl at the 7-position. Or, x is 1 and R^3 is F, CN, or CF_3 at the 6-position.

[00141] In one embodiment, R^{XX} is methyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, or *t*-butyl.

[00142] In one embodiment, R^3 is C1-C6 alkyl. Or, R^3 is methyl, *n* -propyl, isopropyl, *n* -butyl, *sec*-butyl, or *t*-butyl.

[00143] In one embodiment of I-C-i or I-D-i, R^{XY} is hydrogen, and y is 0. Or, R^{XY} is hydrogen, y is 1 and R^5 is 6-F.

[00144] In another embodiment, the present invention provides a compound of formula I-C-ii:



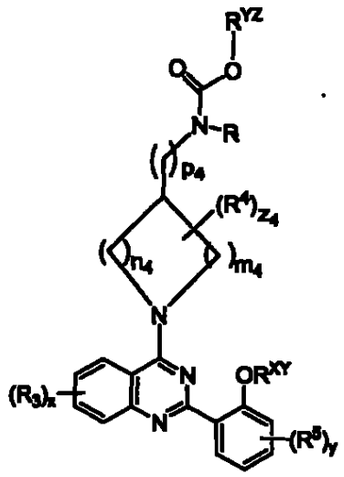
I-C-ii;

wherein R^3 and R^{XX} are as defined above.

[00145] In another embodiment, R^3 is methyl at the 6- or 7-position of the quinazoline ring.

[00146] In another embodiment of formula I-C-ii, R^{XX} is $CH_2C(O)OH$ or $CH_2C(O)NH_2$.

[00147] According to one embodiment, the present invention provides a compound of formula I-E:



I-E;

wherein x, y, n_4, m_4, z_4, p_4, R^{YZ}, R^{XY}, R^3, R^4, and R^5 are as defined above.

[00148] In one embodiment, p_4 is 1. Or, p_4 is 2.

[00149] In one embodiment, m_4 and n_4 each is 1. Or, m_4 and n_4 each is 2. Or, m_4 and n_4 each is 3. In one embodiment, n_4 is 1 and m_4 is 3. In another embodiment, n_4 is 1 and m_4 is 2.

[00150] In one embodiment, n_4 is 1, m_4 is 3, z_4 is 0, p_4 is 1, y is 0 or 1, and x is 1.

[00151] In another embodiment, n_4 is 1, m_4 is 2, z_4 is 0, p_4 is 1, y is 0 or 1, and x is 1.

[00152] In one embodiment, n_4 is 1, m_4 is 3, z_4 is 0, p_4 is 1, y is 0 or 1, x is 1, and R and R^{XY} both are hydrogen.

[00153] In another embodiment, n_4 is 1, m_4 is 2, z_4 is 0, p_4 is 1, y is 0 or 1, x is 1, and R and R^{XY} both are hydrogen.

[00154] In one embodiment, R^{YZ} is C1-C6 alkyl, optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3. In another embodiment, R^{YZ} is C1-C4 alkyl group optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3. Or, R^Y is C1-C6 alkyl group.

[00155] In one embodiment, R is hydrogen. Or, R is C1-C6 alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[00156] In another embodiment:

(i) n_4 is 1 and m_4 is 3;

(ii) p_4 is 1;

(iii) z_4 is 0;

(iv) R^{YZ} is C1-C6 alkyl, wherein up to two $-CH_2-$ groups therein is optionally replaced by -O-;

(v) y is 0 or 1, and R^5 is 6-fluoro; and

(vi) x is 1 and R^3 is C1-C4 alkyl.

[00157] In another embodiment:

(i) n_4 is 1 and m_4 is 2;

(ii) p_4 is 1;

(iii) z_4 is 0;

(iv) R^{YZ} is C1-C6 alkyl, wherein up to two $-CH_2-$ groups therein is optionally replaced by -O-;

(v) y is 0 or 1, and R^5 is 6-fluoro; and

(vi) x is 1 and R^3 is C1-C4 alkyl.

[00158] In another embodiment:

(i) n_4 is 1 and m_4 is 3;

(ii) p_4 is 1;

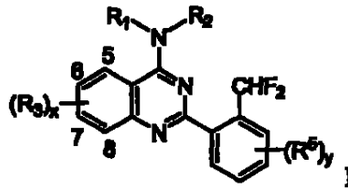
(iii) z_4 is 0;

(iv) R^{YZ} is benzyl;

(v) y is 0 or 1, and R^5 is 6-fluoro; and

(vi) x is 1 and R^3 is C1-C4 alkyl.

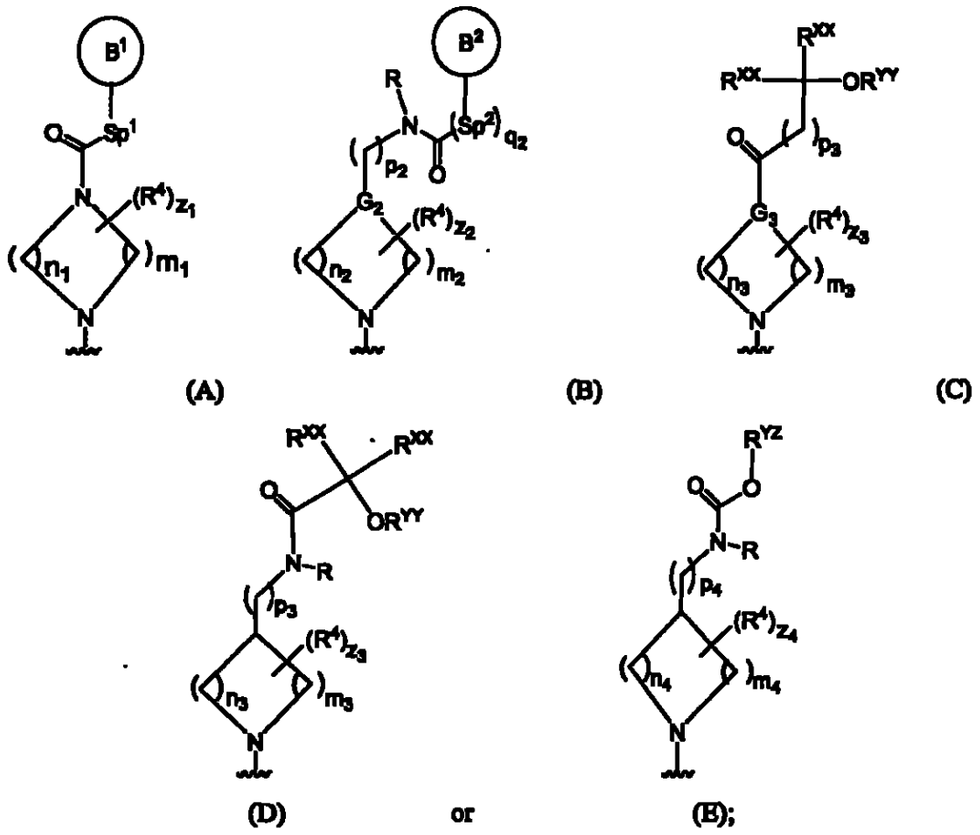
[00159] In another embodiment, the present invention provides compounds of formula I-F:



I-F;

wherein:

R^1 and R^2, taken together with the nitrogen atom, form a substituted ring selected from:



(A) (B) (C)

(D) or (E);

wherein, in ring (A):

each of m_1 and n_1 is independently 0-3, provided that m_1+n_1 is 2-6;

z_1 is 0-4;

Sp^1 is -O-, -S-, -NR'-, or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$, provided that Sp^1 is attached to the carbonyl group through an atom other than carbon;

ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w_1 independent occurrences of $-R^{11}$, wherein w_1 is 0-4;

wherein, in ring (B):

G_2 is -N-, or CH;

each of m_2 and n_2 is independently 0-3, provided that $m_2 + n_2$ is 2-6;

p_2 is 0-2; provided that when G_2 is N, then p_2 is not 0;

q_2 is 0 or 1;

z_2 is 0-4;

Sp^2 is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO_2-, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, -SO_2-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-;

ring B^2 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4;

wherein, in ring (C) or ring (D):

G_3 is -N-, -CH-NH-, or -CH-CH_2-NH-;

each of m_3 and n_3 is independently 0-3, provided that m_3+n_3 is 2-6;

p_3 is 0-2;

z_3 is 0-4;

each R^{XX} is hydrogen, C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3;

provided that both R^{XX} are not simultaneously hydrogen;

R^{YY} is hydrogen, -COR', -CO_2R', -CON(R')$_2$, -SOR', -SO_2R', -SO_2N(R')$_2$, -COCOR', -$COCH_2$COR', -P(O)(OR')$_2$, -$P(O)_2$OR', or -PO(R')$_2$;

wherein, in ring (E):

each of m_4 and n_4 is independently 0-3, provided that $m_4 + n_4$ is 2-6;

p_4 is 1-2;

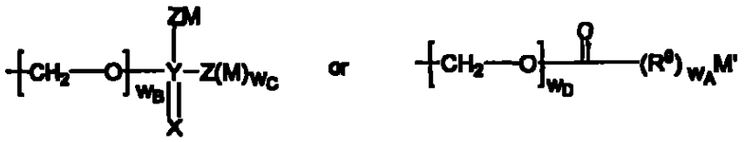
z_4 is 0-4;

R^{YZ} is C_1-C_6 aliphatic group, optionally substituted with w_4 independent occurrences of -R^{14}, wherein w_4 is 0-3;

x and y, each, is independently 0-4;

W is OR^{XY};

R^{XY} is hydrogen or a group selected from:



;

wherein:

each of w_A, w_B, w_C, and w_D is independently 0 or 1;

each M is independently selected from hydrogen, Li, Na, K, Mg, Ca, Ba, -$N(R^7)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or -R^6; wherein 1 to 4 –CH_2 radicals of the alkyl or alkenyl group, other than the –CH_2 that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, -OR^7, -R^7, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, -CO_2R^7, -C(O)-$N(R^7)_2$, $S(O)_2$-$N(R^7)_2$, $N(R^7)$-C(O)-R^7, $C(O)R^7$, -$S(O)_n$-R^7, OCF_3, -$S(O)_n$-R^6, $N(R^7)$-$S(O)_2(R^7)$, halo, -CF_3, or -NO_2;

n is 0-2;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or -R^6; wherein 1 to 4 –CH_2 radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, -OR^7, -R^7, $N(R^7)_2$, $N(R^7)_3$, -R^7OH, -CN, -CO_2R^7, -C(O)-$N(R^7)_2$, $S(O)_2$-$N(R^7)_2$, -$N(R^7)$-C(O)-R^7, $C(O)R^7$, -$S(O)_n$-R^7, $-OCF_3$, -$S(O)_n$-R^6, -$N(R^7)$-$S(O)_2(R^7)$, halo, -CF_3, or -NO_2;

Z is -CH_2-, -O-, -S-, -$N(R^7)_2$-; or,

when M is absent, then Z is hydrogen, =O, or =S;

Y is P or S, wherein when Y is S, then Z is not S;

X is O or S;

each R^7 is independently selected from hydrogen, or C_1-C_4 aliphatic, optionally substituted with up to two Q_1;

each Q_1 is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatom or heteroatom group selected from O, N, NH, S, SO, or SO_2; wherein Q_1 is optionally substituted with up to three substituents selected from oxo, -OH, -O(C_1-C_4 aliphatic), -C_1-C_4 aliphatic, -NH_2, NH(C_1-C_4 aliphatic), -N(C_1-C_4 aliphatic)$_2$, -N(C_1-C_4 aliphatic)-C(O)- C_1-C_4 aliphatic, -(C_1-C_4 aliphatic)-OH, -CN, -CO_2H, -CO_2(C_1-C_4 aliphatic), -C(O)-NH_2, -C(O)-NH(C_1-C_4 aliphatic), -C(O)-N(C_1-C_4 aliphatic)$_2$, halo or -CF_3;

R^6 is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)$_n$ or N(R^7); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C_1-C_4 alkyl, O-C_1-C_4 alkyl or O-C(O)-C_1-C_4 alkyl;

R^9 is C(R^7)$_2$, O or N(R^7);

each occurrence of R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4, and R^5 is independently Q-R^X; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO_2-, -SO_2NR-, -NRSO_2-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO_2NR-, -SO-, -SO_2-, -PO-, -PO_2-, -OP(O)(OR)-, or -POR-; and each occurrence of R^X is independently selected from -R', halogen, =O, =NR', -NO_2, -CN, -OR', -SR', -N(R')$_2$, -NR'COR', -NR'CON(R')$_2$, -NR'CO_2R', -COR', -CO_2R', -OCOR', -CON(R')$_2$, -OCON(R')$_2$, -SOR', -SO_2R', -SO_2N(R')$_2$, -NR'SO_2R', -NR'SO_2N(R')$_2$, -COCOR', -$COCH_2$COR', -OP(O)(OR')$_2$, -P(O)(OR')$_2$, -OP(O)$_2$OR', -P(O)$_2$OR', -PO(R')$_2$, or -OPO(R')$_2$; and

each occurrence of R is independently hydrogen or C_{1-6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s)

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to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00160] In compounds of formula I-F, exemplary embodiments of n_1, m_1, n_2, m_2, n_3, m_3, n_4, m_4, x, y, z_1, z_2, z_3, z_4, q_2, p_3, p_4, R^{XY}, R^{XX}, R^{YY}, R^{YZ}, R^3, R^4, R^5, R^{11}, R^{12}, R^{13}, R^{14}, R, Sp^1, Sp^2, ring B^1, ring B^2, etc., are as defined above for compounds of formula I-A through formula I-E.

[00161] In one embodiment, the present invention provides compounds shown below in Table 2.

Table 2

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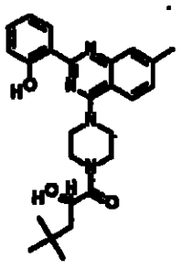	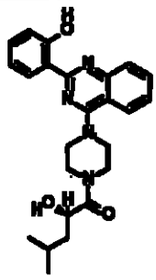	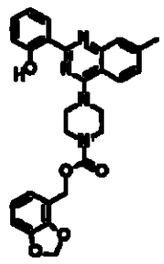
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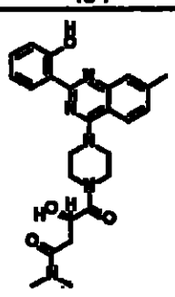	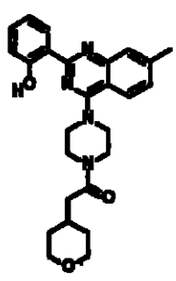	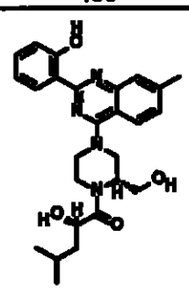
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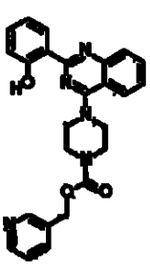	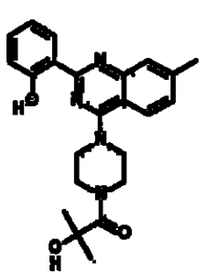	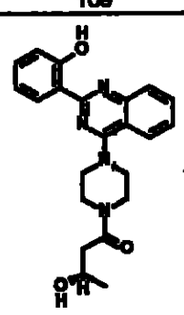
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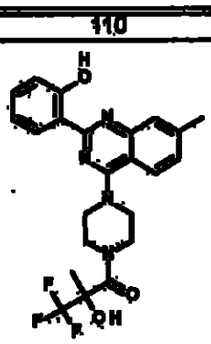	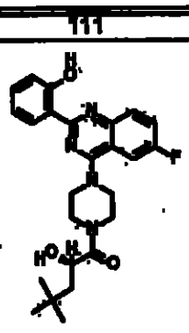	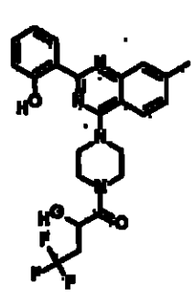

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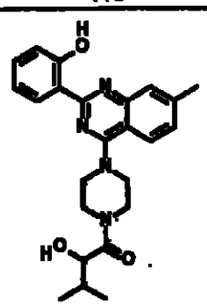	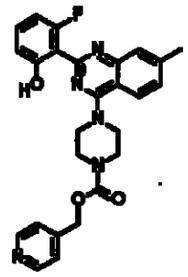	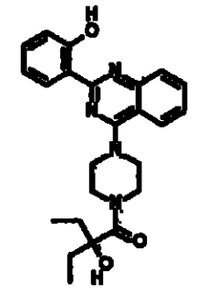
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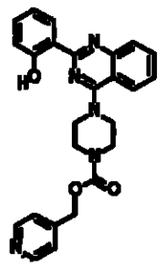	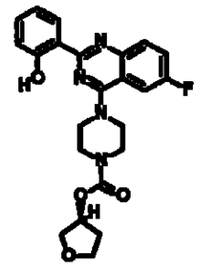	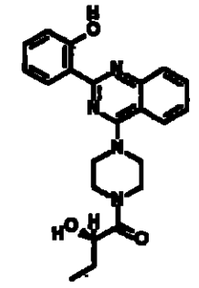
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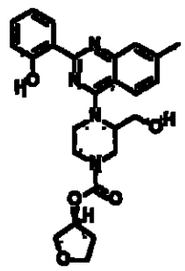	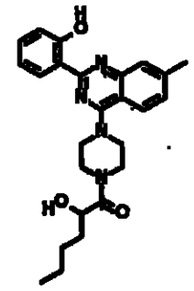	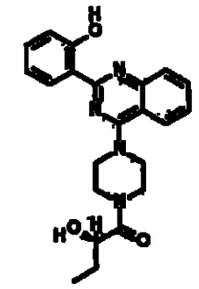
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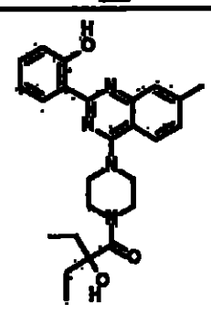	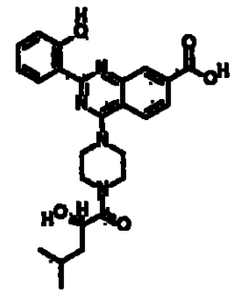	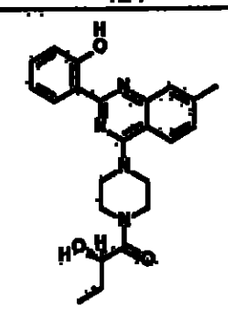

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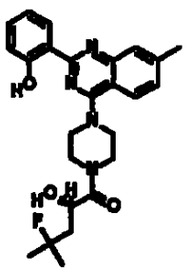	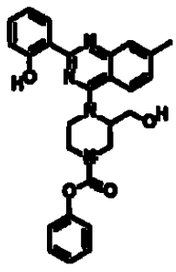	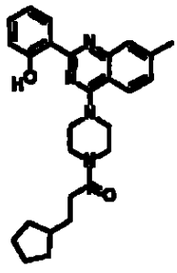
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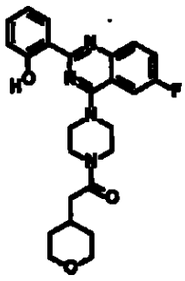	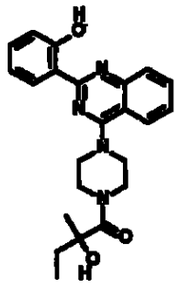	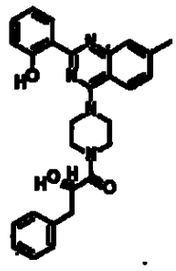
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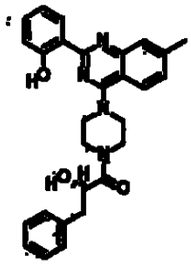	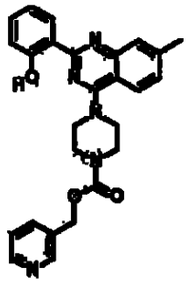	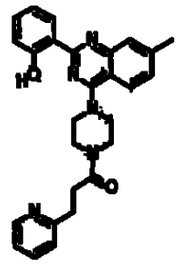
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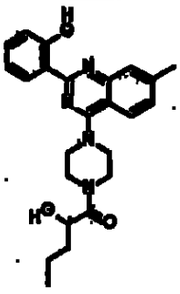	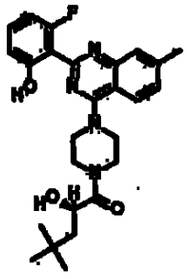	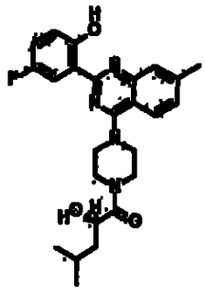

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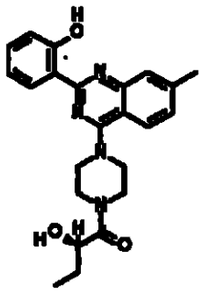	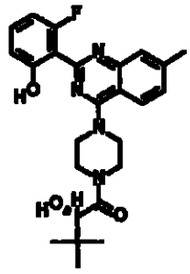	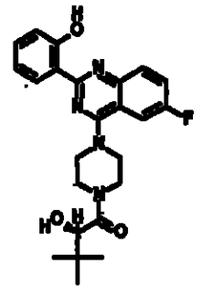
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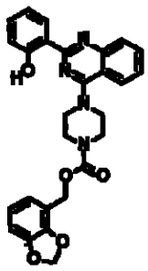	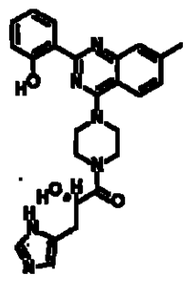	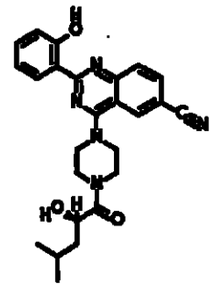
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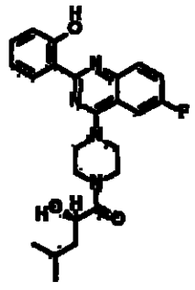	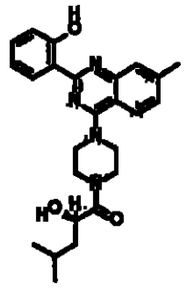	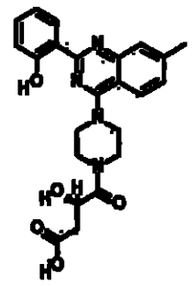
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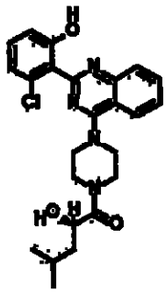	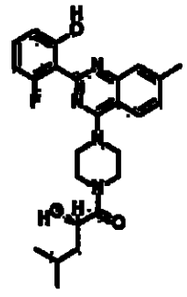	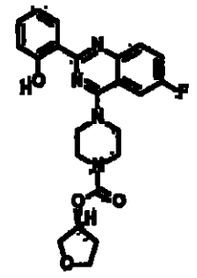

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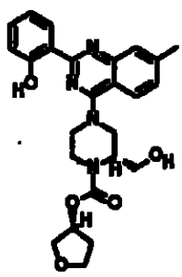	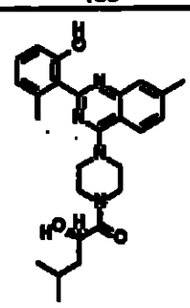	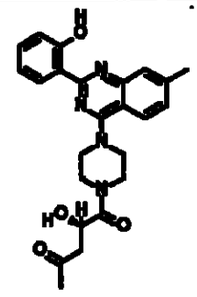
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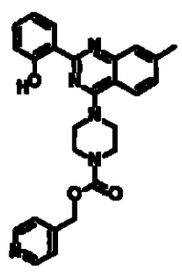	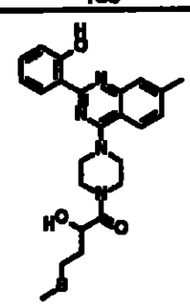	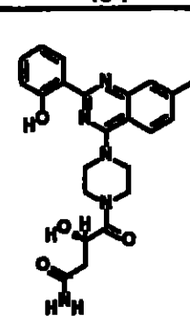
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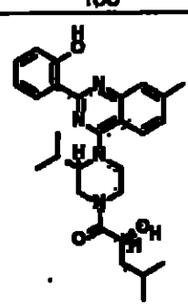	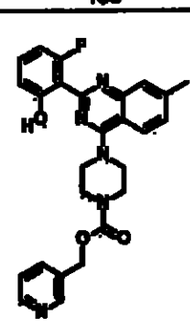	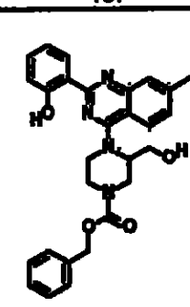
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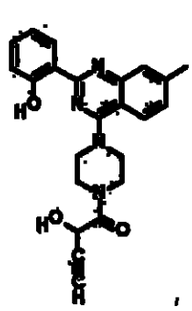	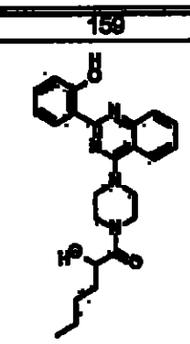	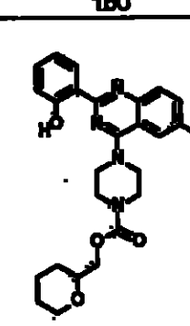

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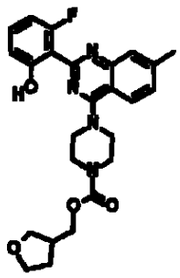	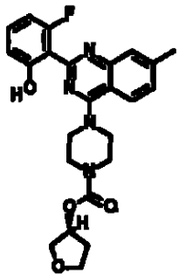	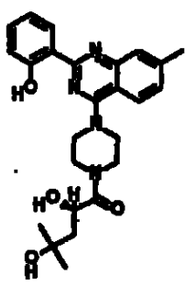
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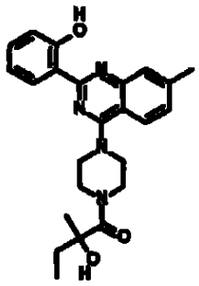	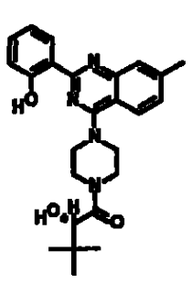	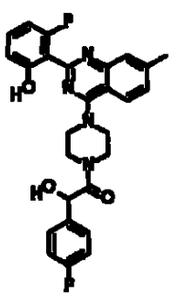
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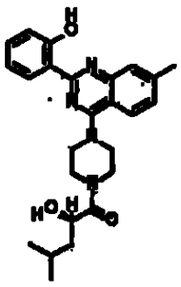	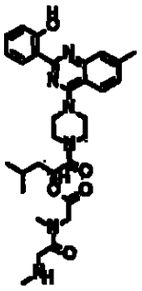	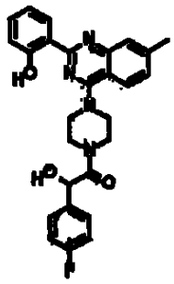
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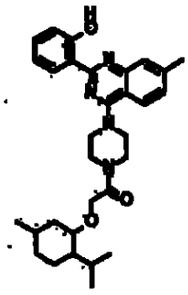
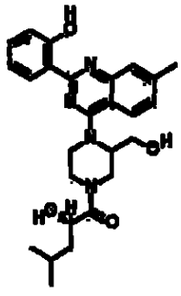
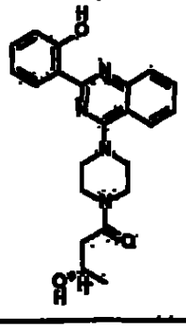
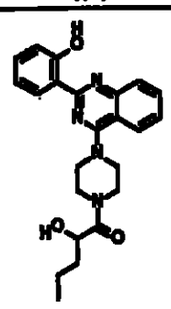
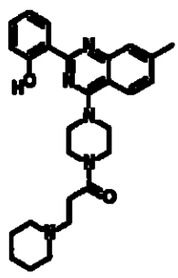
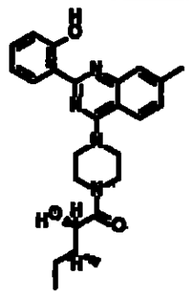
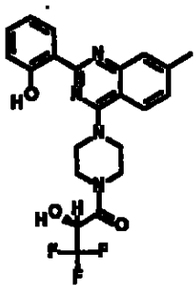
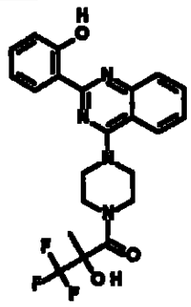
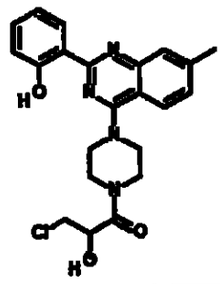
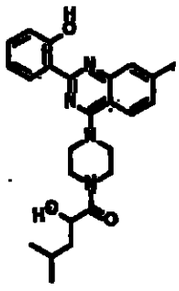
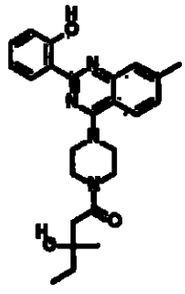
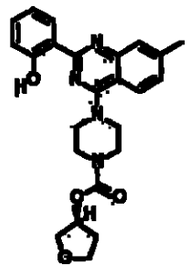
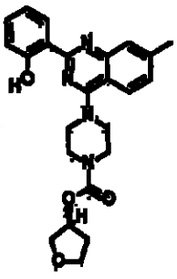
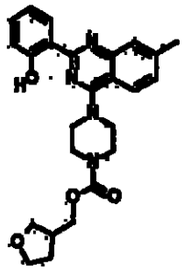
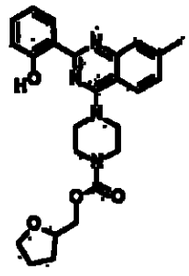
		

174 	175 	176 
177 	178 	179 
180 	181 	182 
183 	184 	185 

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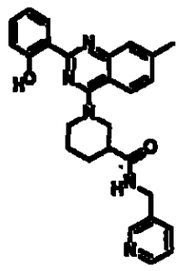	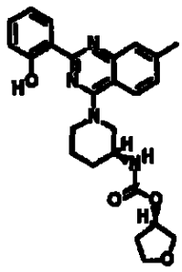	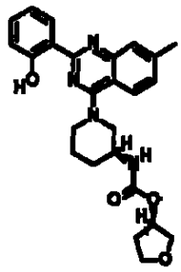
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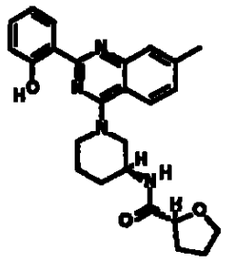	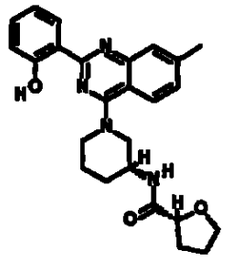	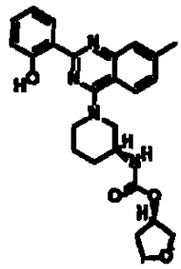
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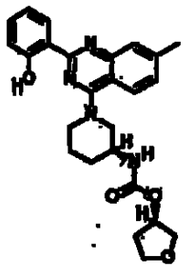	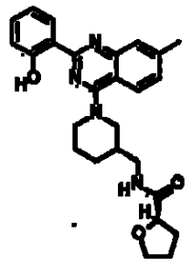	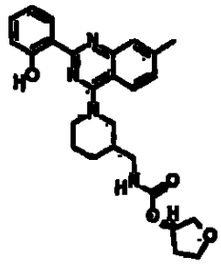
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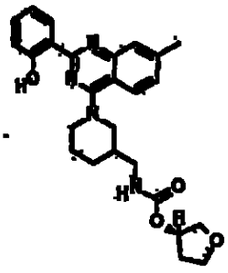	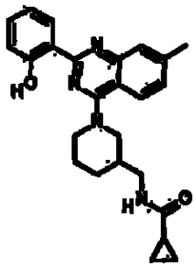	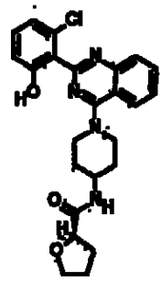

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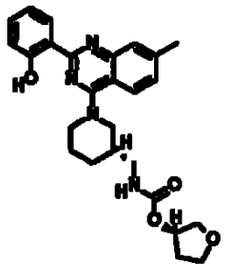	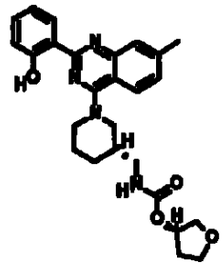	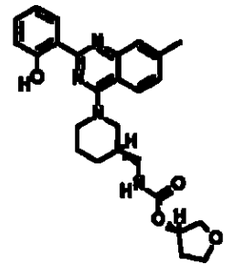
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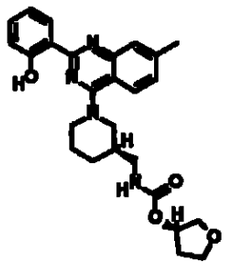	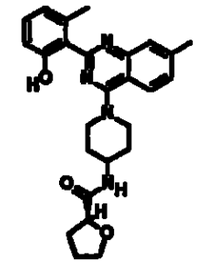	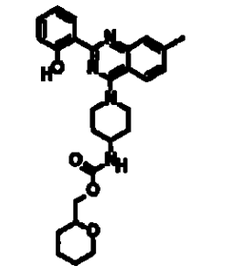
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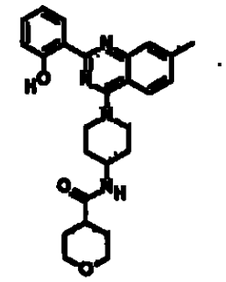	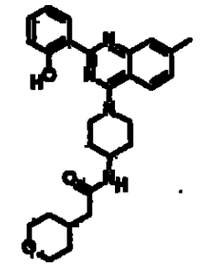	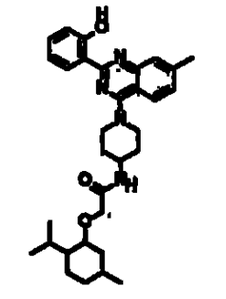
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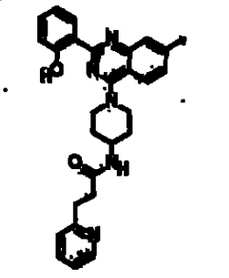	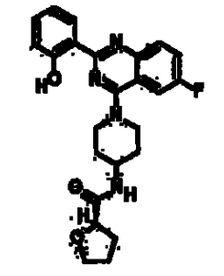	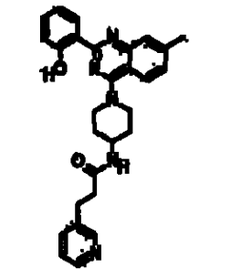

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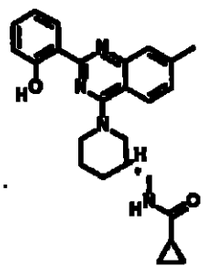	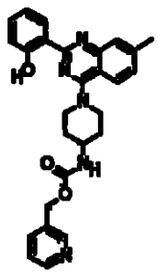	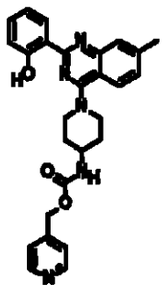
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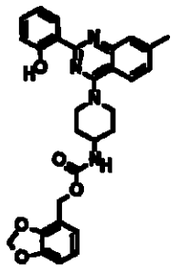	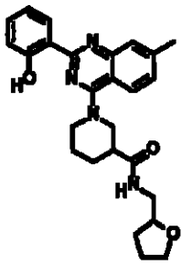	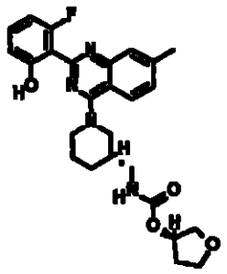
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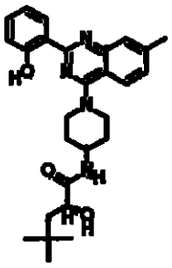	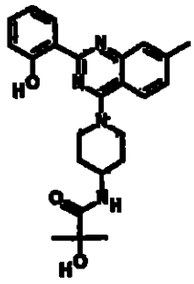	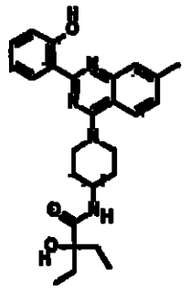
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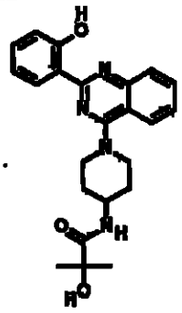	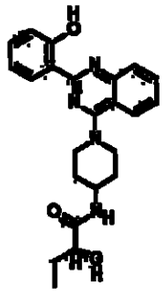	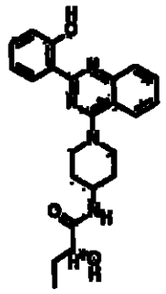

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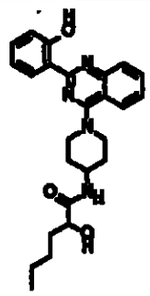	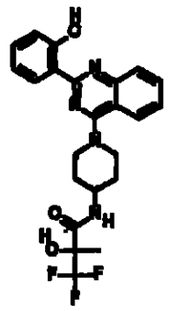	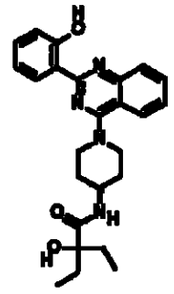
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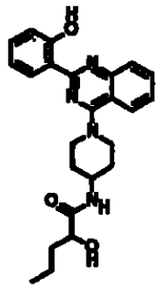	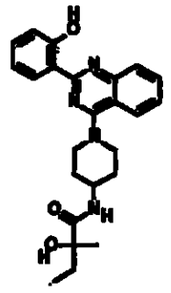	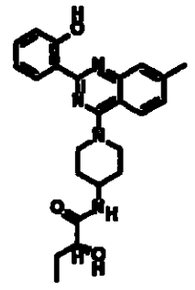
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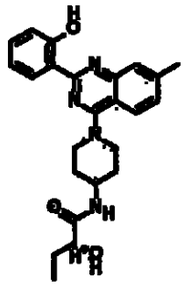	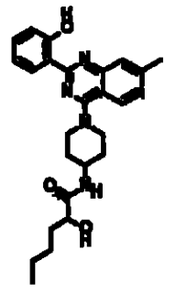	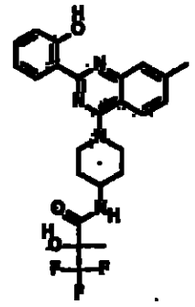
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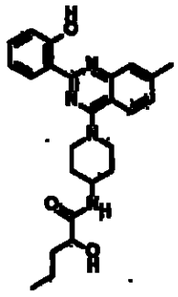	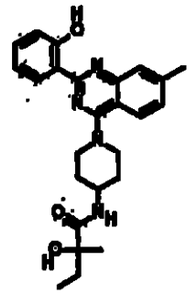	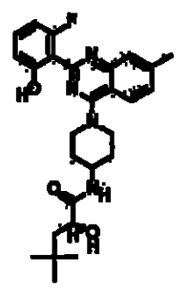

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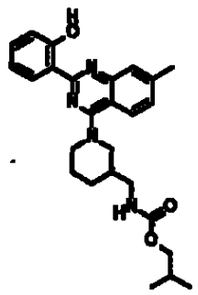	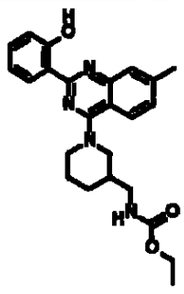	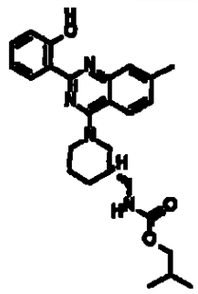
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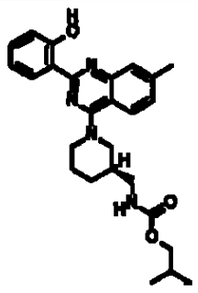	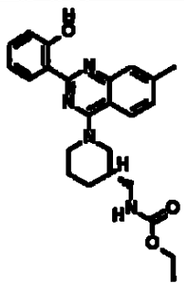	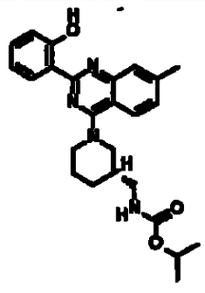
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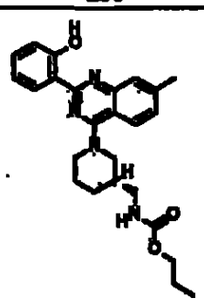	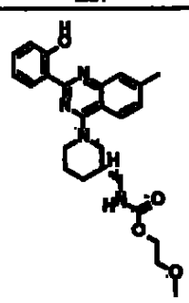	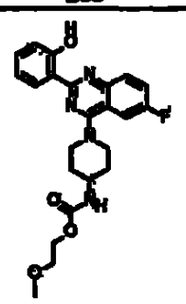
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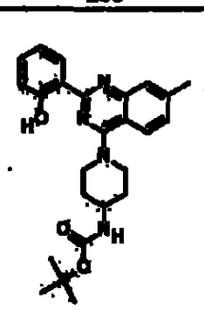	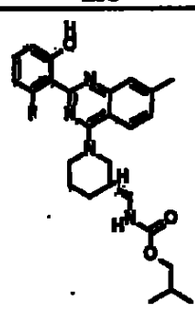	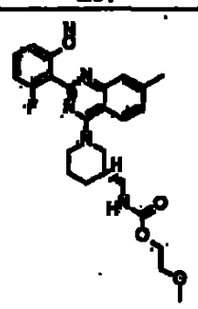

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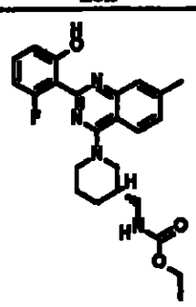	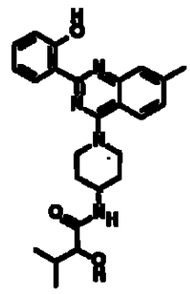	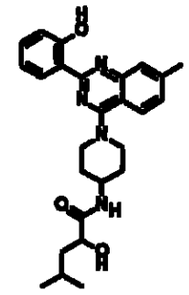
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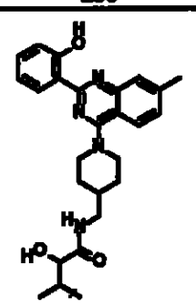	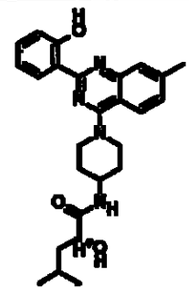	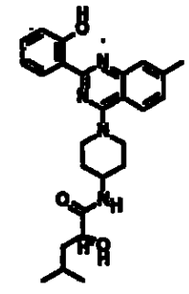
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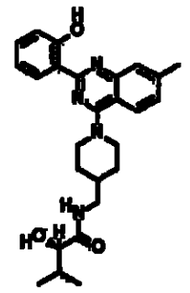	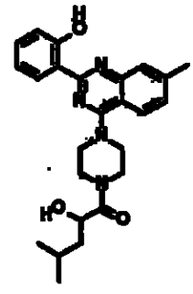	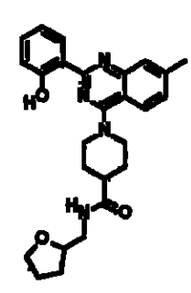
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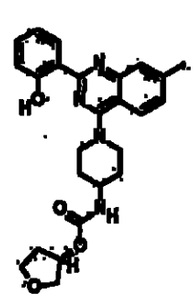	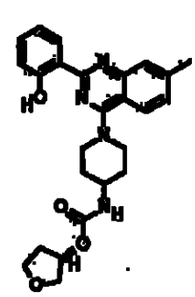	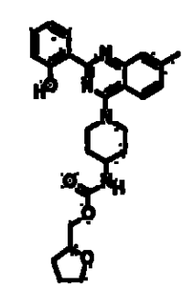

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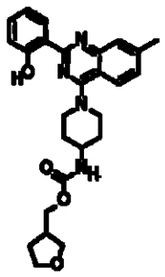	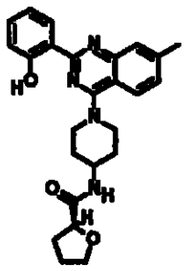	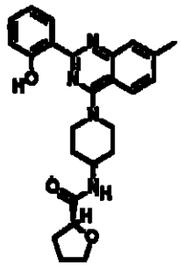
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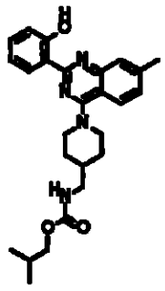	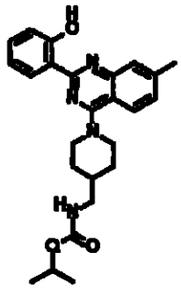	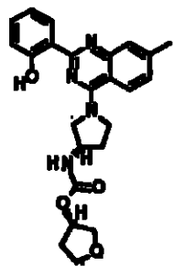
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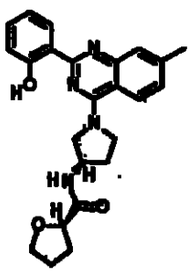	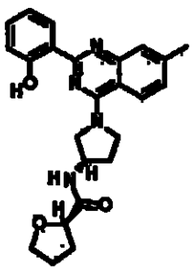	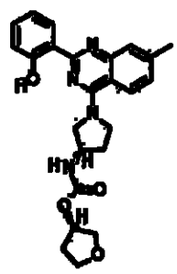
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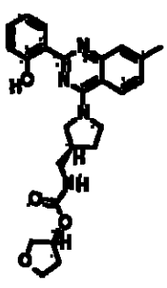	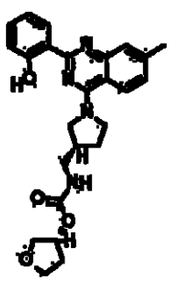	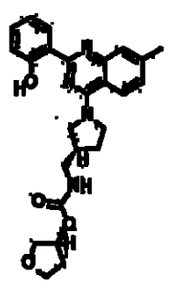

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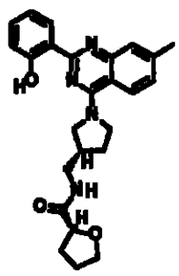	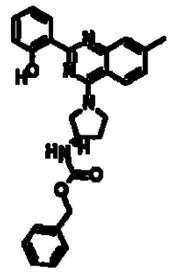	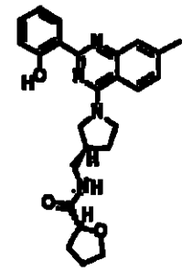
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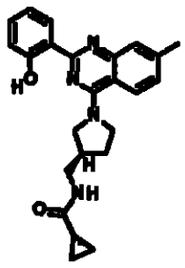	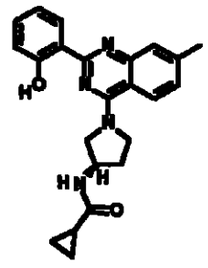	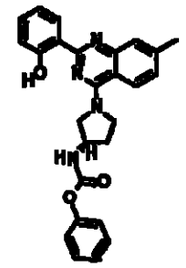
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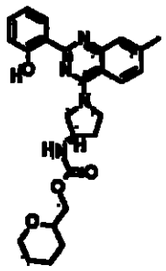	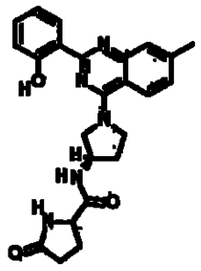	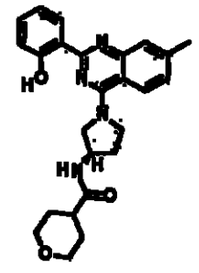
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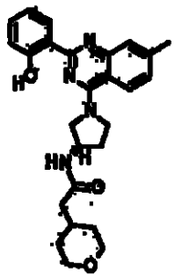	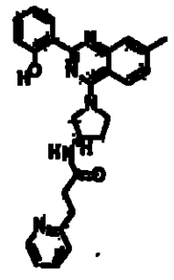	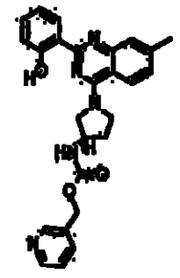

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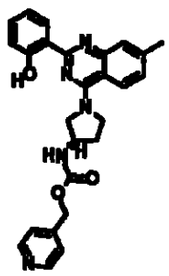	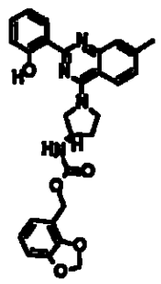	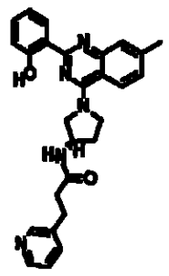
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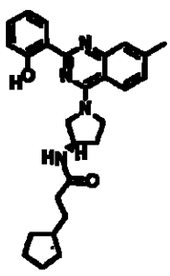	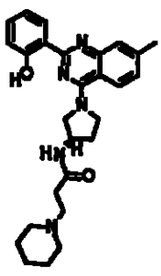	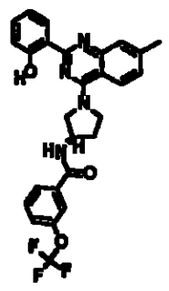
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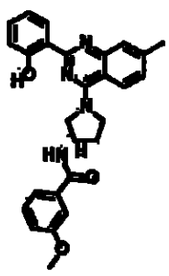	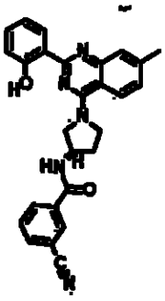	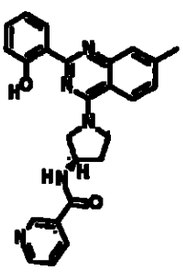
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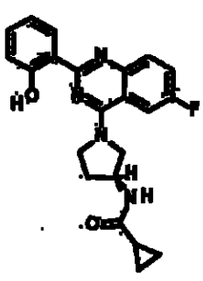	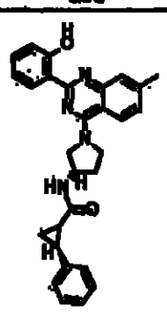	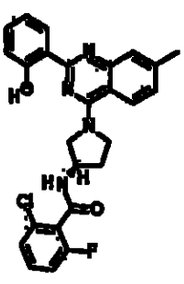

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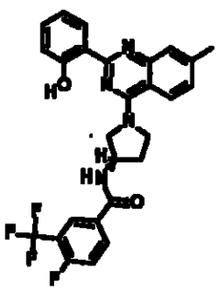	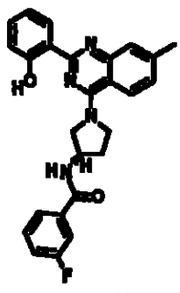	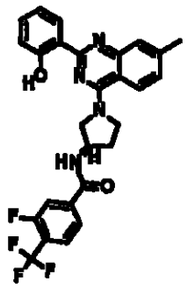
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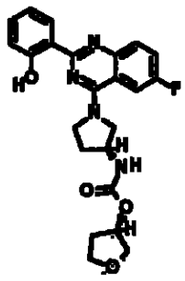	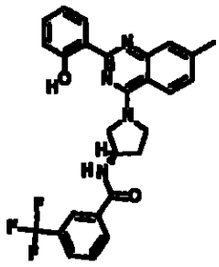	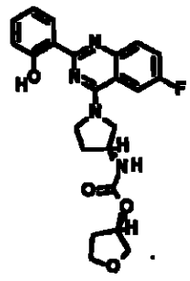
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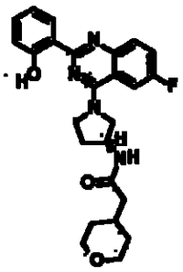	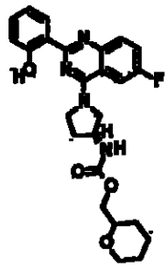	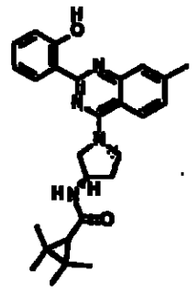
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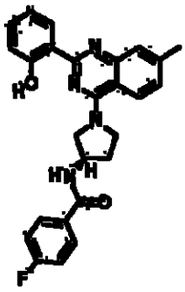	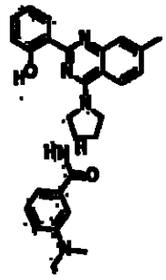	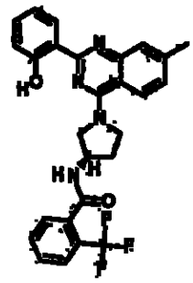

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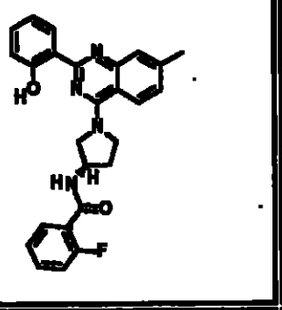
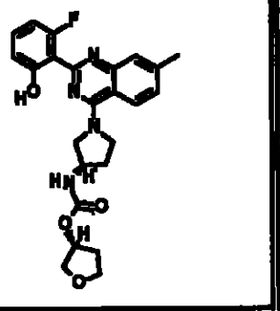
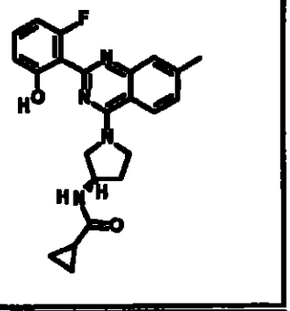
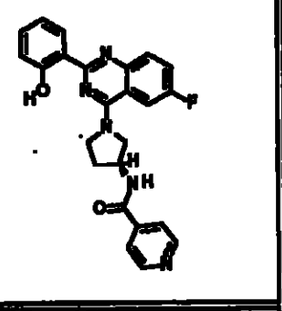
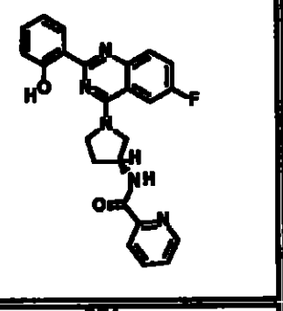
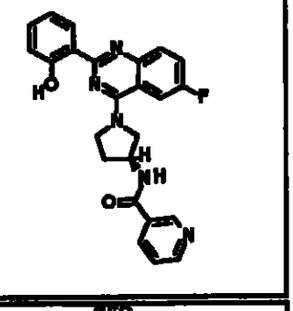
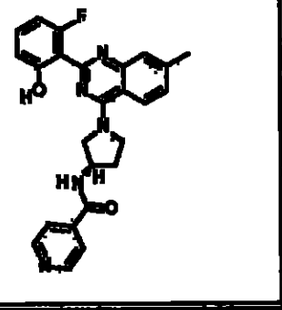
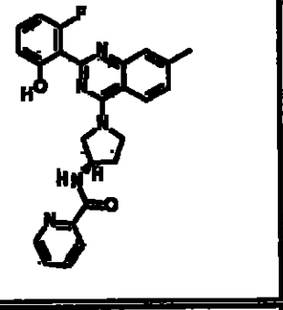
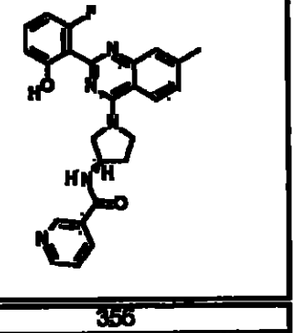
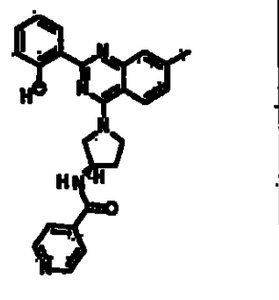
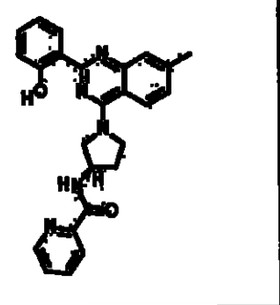
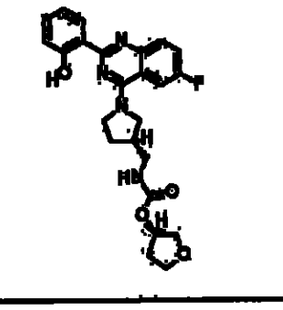
344 	345 	346 
347 	348 	349 
350 	351 	352 
353 	354 	356 

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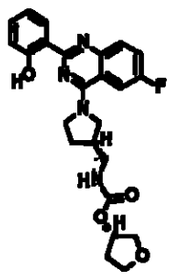	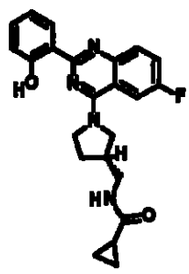	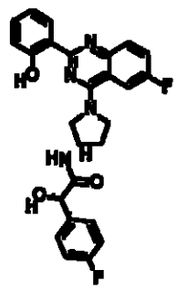
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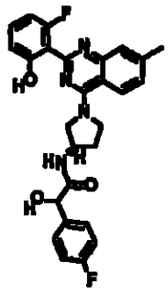	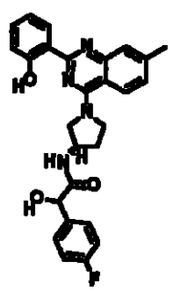	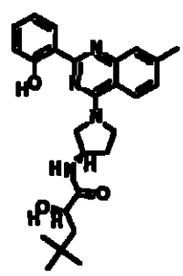
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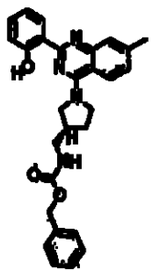	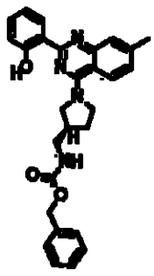	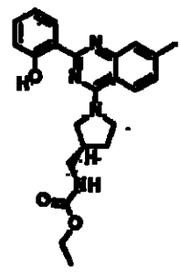
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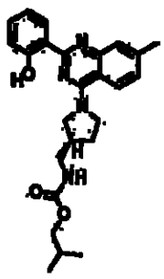	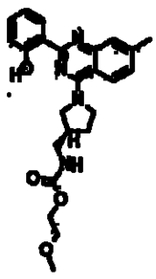	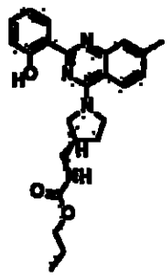

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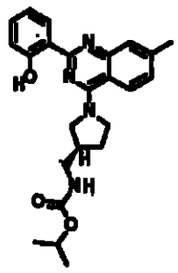	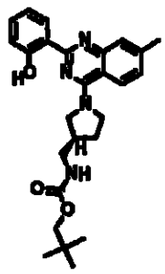	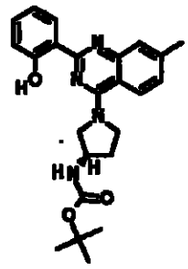
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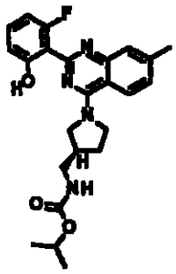	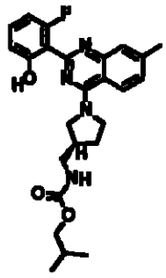	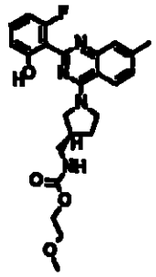
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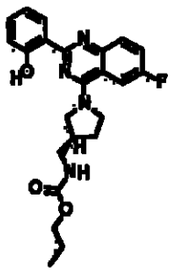	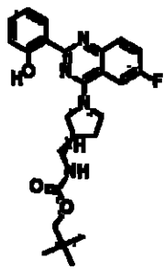	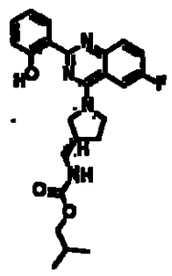
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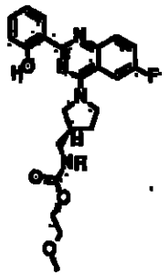	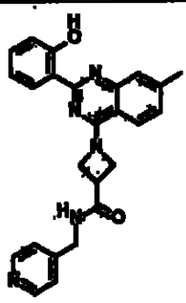	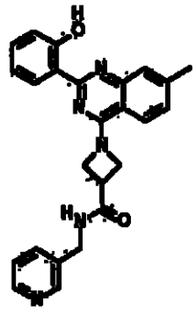

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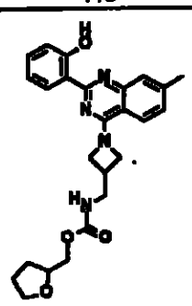	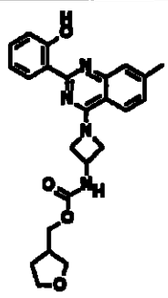	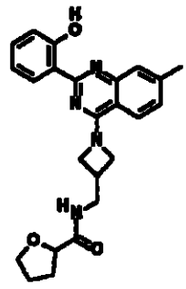
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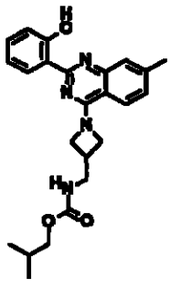	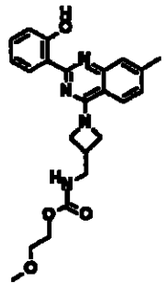	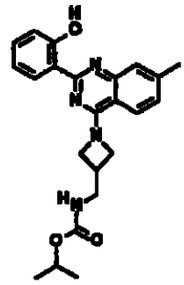

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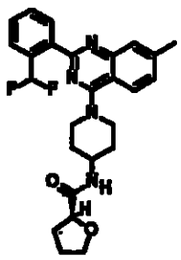	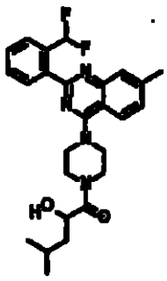	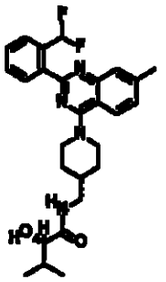
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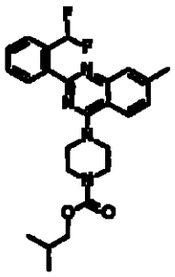	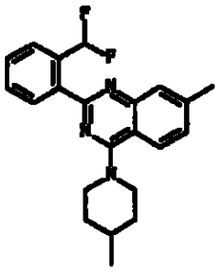	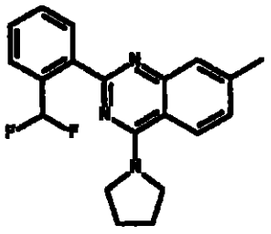
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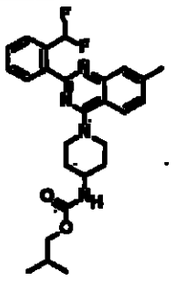	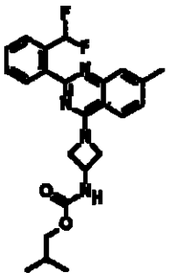	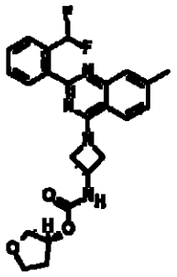
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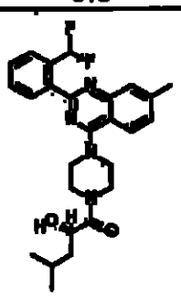	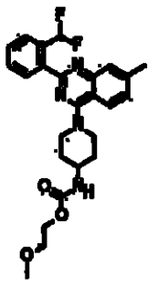	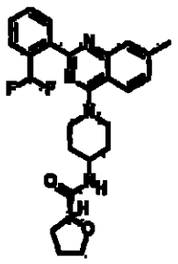

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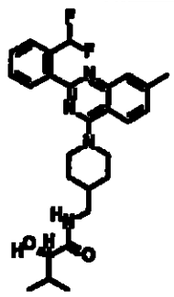
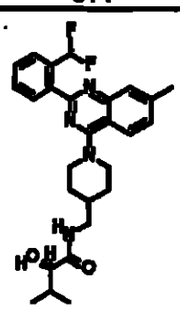
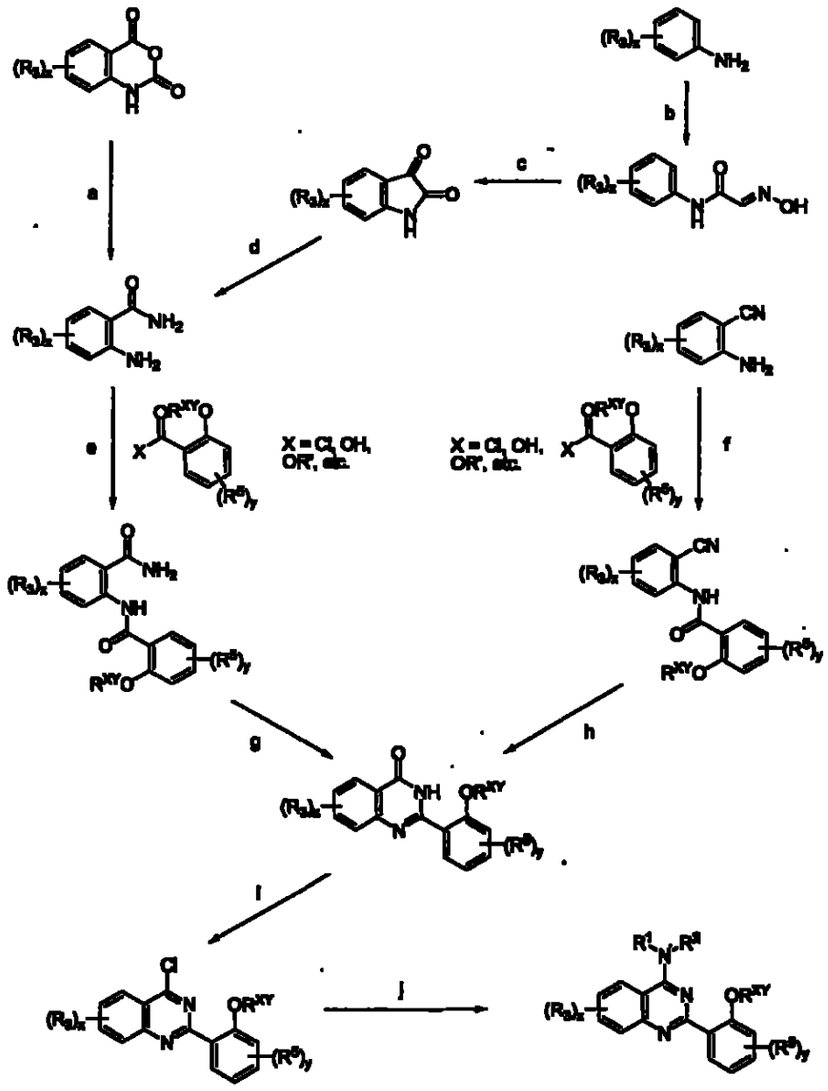
	

[00162] *4. General Synthetic Methodology:*

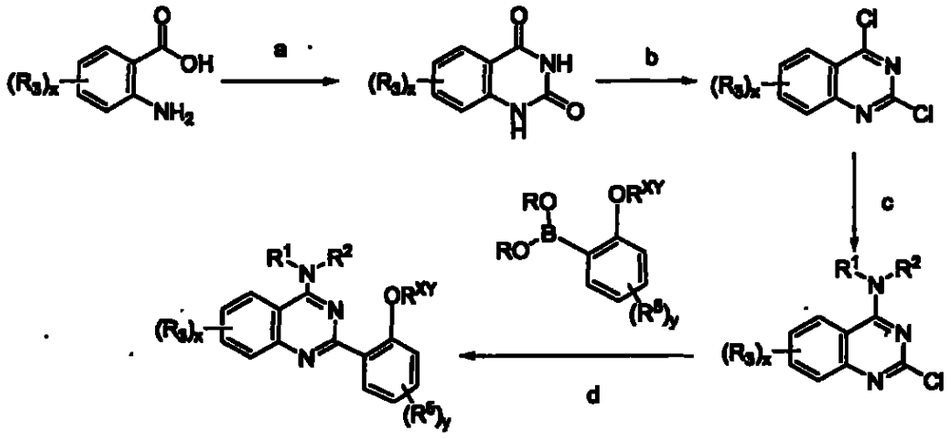
[00163] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general schemes below, and the preparative examples that follow.

[00164] Scheme A: General Preparations via 4-Chloroquinazolines



[00165] Conditions: a) aq. NH_4OH; b) chloral hydrate, HCl, Na_2SO_4, $HONH_2$*HCl c) H_2SO_4; d) acetic acid, H_2SO_4, aq. H_2O_2; e) Et_3N, THF; f) Et_3N, DMAP, CH_2Cl_2; g) aq. NaOH; h) aq. NaOH, aq. H_2O_2 i) $POCl_3$, N,N-dimethylaniline, benzene; j) R^1R^2NH, Et_3N, CH_2Cl_2

[00166] Scheme B: General Preparations via 2,4-Dichloroquinazolines



[00167] Conditions: a) AcOH, KOCN; b) $POCl_3$; c) Et_3N, DCM, R^1R^2NH; d) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, H_2O

[00168] Scheme I-A for formula I-A:

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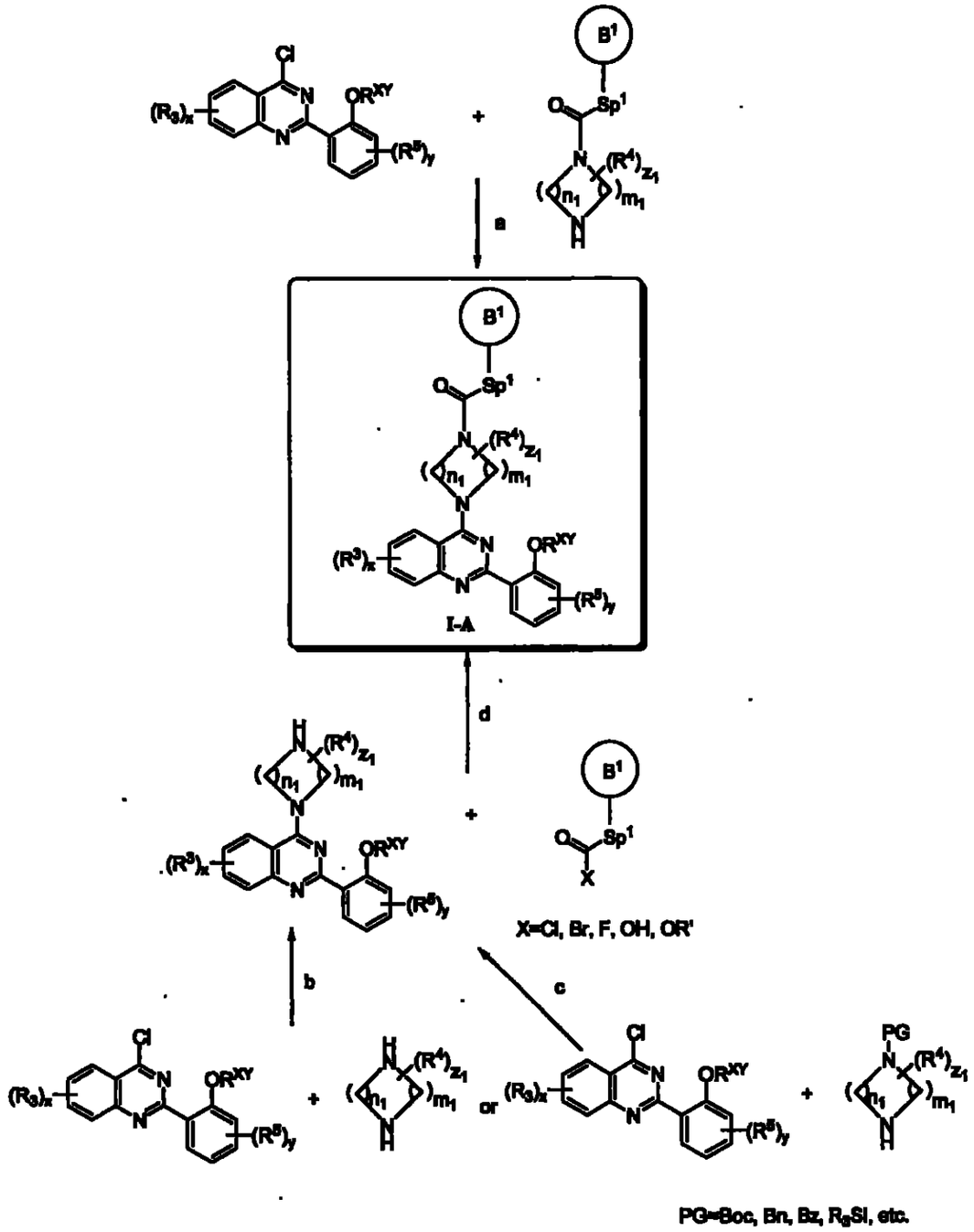
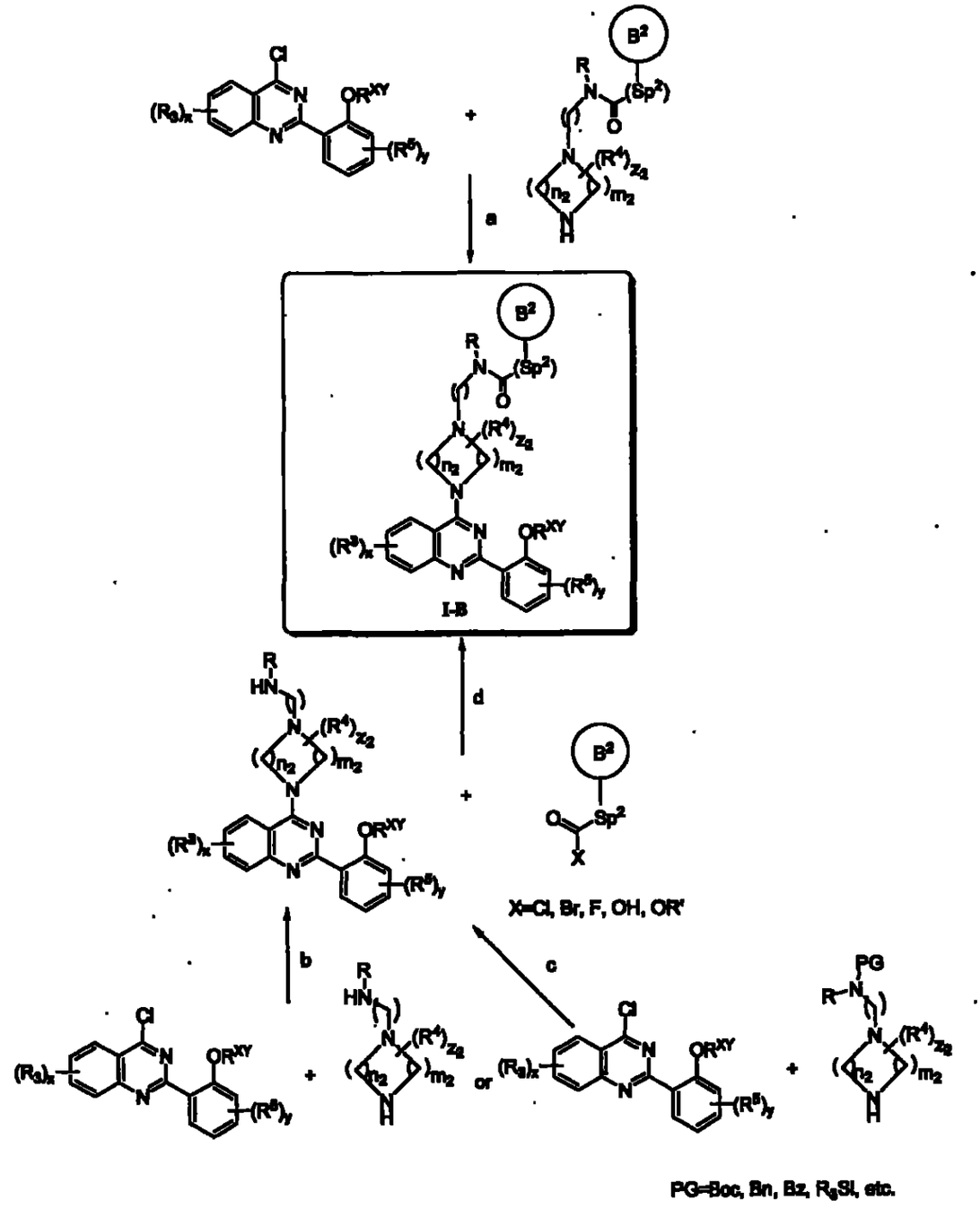


[00169] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For acid halides, DCM or THF, triethylamine; for carboxylic acids, EDC, HOBt, triethylamine, DMF; for X=OR', THF or DMF, heat.

285

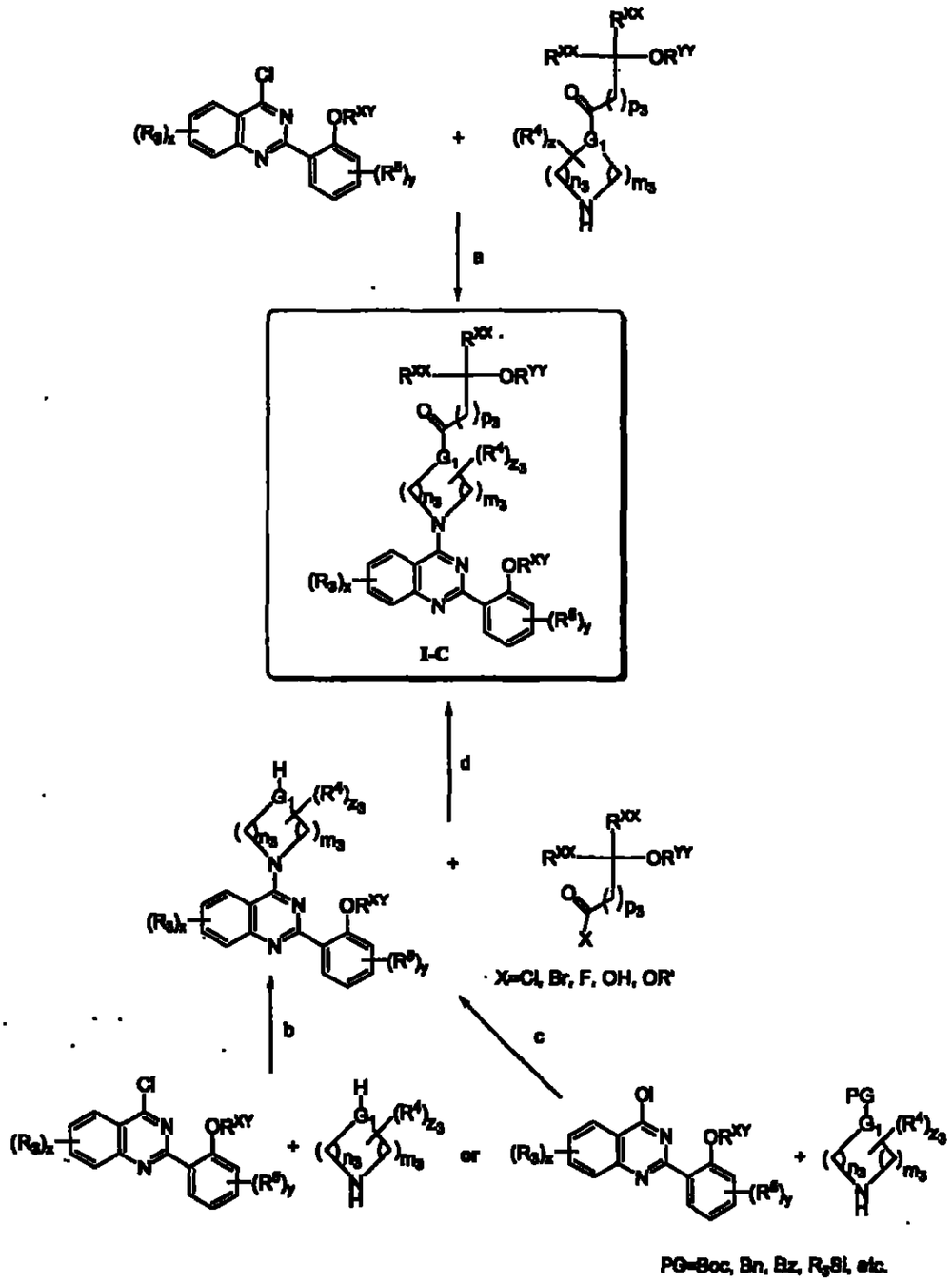
[00170] Scheme I-B for compounds of formula I-B:



[00171] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For acid halides, DCM or THF, triethylamine; for carboxylic acids, EDC, HOBt, triethylamine, DMF; for X=OR', THF or DMF, heat.

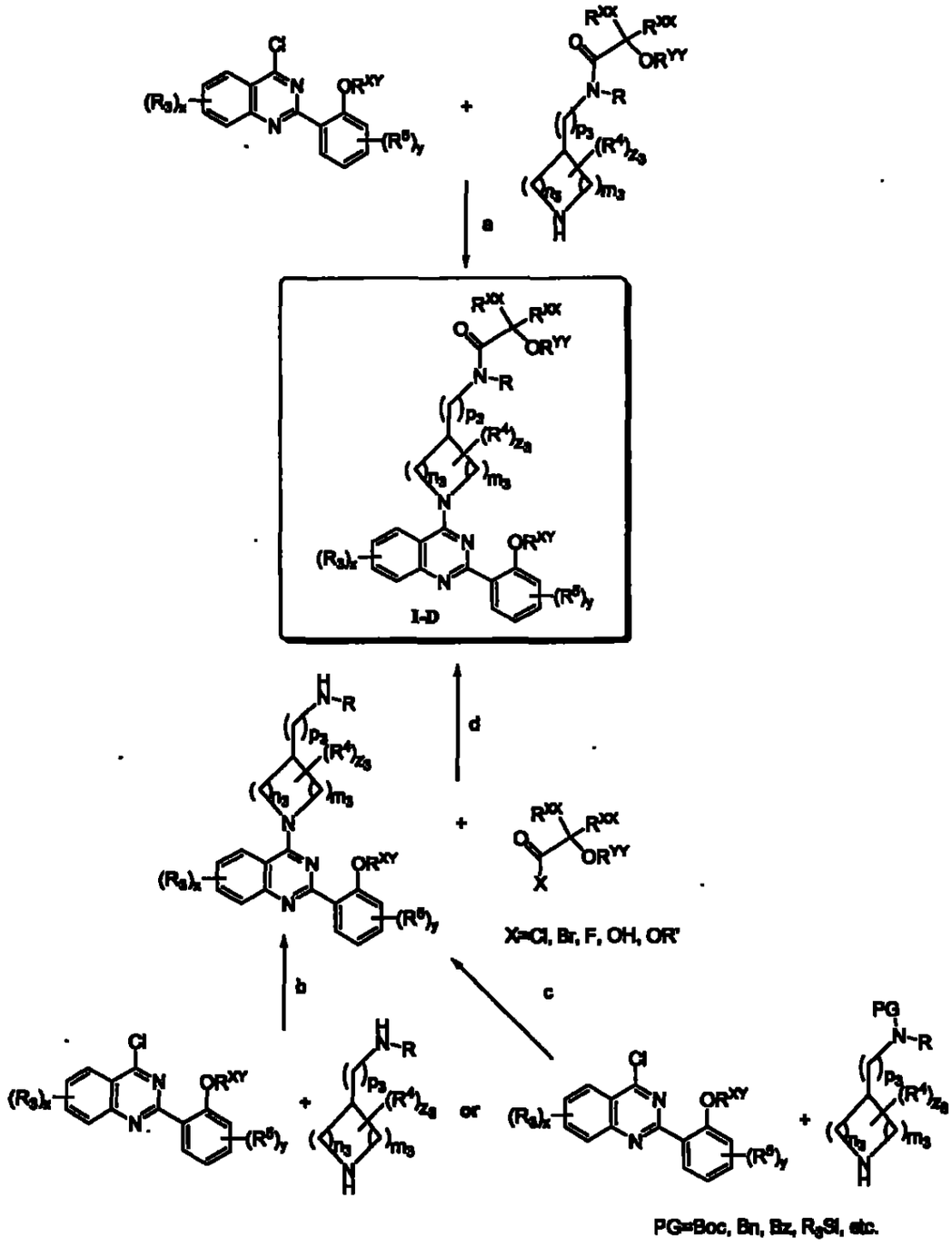
286

[00172] Scheme I-C for formula I-C:



[00173] *Conditions*: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For acid halides, DCM or THF, triethylamine; for carboxylic acids, EDC, HOBt, triethylamine, DMF; for X=OR', THF or DMF, heat.

[00174] Scheme I-D for formula I-D:



[00175] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For acid halides, DCM or THF, triethylamine; for carboxylic acids, EDC, HOBt, triethylamine, DMF; for X=OR', THF or DMF, heat.

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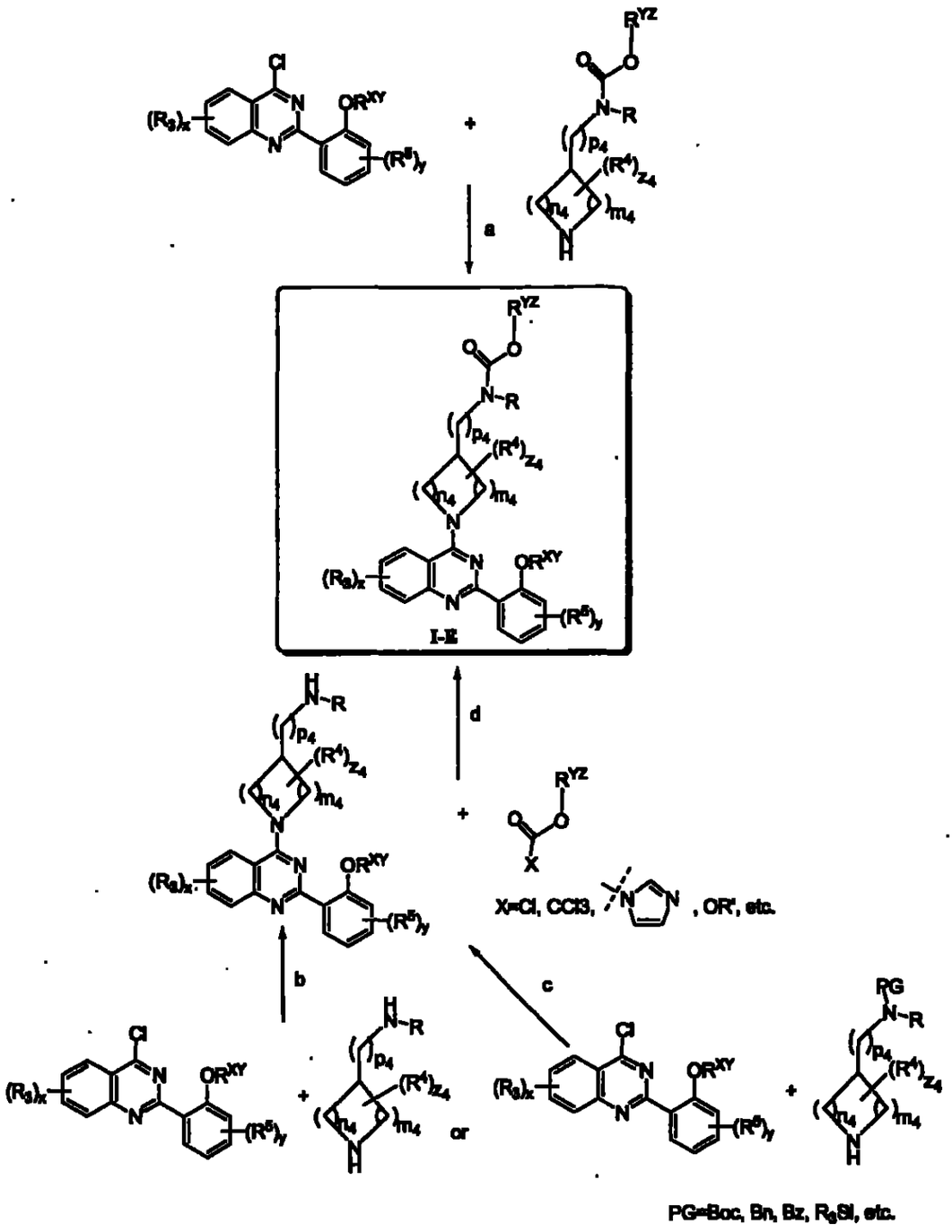
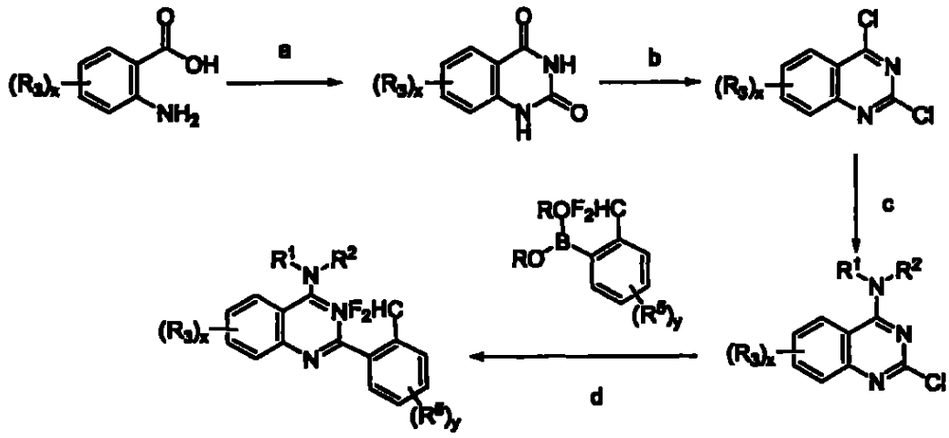
[00176] Scheme I-E for formula I-E:



[00177] Conditions: a) DCM or THF, triethylamine, 0 °C to room temperature; b) DCM or THF, triethylamine, 0 °C to room temperature; c) i. DCM or THF, triethylamine, 0 °C to room temperature, ii. Deprotect: 1:1 TFA / DCM, rt, for Boc; H_2, Pd / C for Bn; NaOH for Bz, TBAF for R3Si, etc.; d) For X=Cl, CCl_3, imidazolyl, OR', etc., DCM or THF, triethylamine, rt or heat.

[00178] Scheme I-F for preparing compounds of formula I-F:



[00179] Conditions: a) AcOH, KOCN; b) $POCl_3$; c) Et_3N, DCM, R^1R^2NH; d) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, H_2O.

[00180] *5. Uses, Formulation and Administration*

[00181] WO 2004/078733 discloses a genus of sodium channel blockers that encompasses the compounds of the present invention. However, the compounds of the present invention exhibit unexpected properties set forth below that render them therapeutically more useful.

[00182] In one embodiment, certain compounds of the present invention are useful as improved inhibitors of sodium channels.

[00183] In another embodiment, certain compounds of the present invention possess improved selectivity in inhibiting one sodium channel, e.g., NaV 1.8, over one or more of the other sodium channels. Particularly useful are compounds that have a desirably low activity against NaV 1.2 or NaV 1.5.

[00184] In another embodiment, certain compounds of the present invention are improved inhibitors of NaV 1.8.

[00185] In another embodiment, certain compounds of the present invention have improved aqueous solubility, e.g., at physiologically relevant pH.

[00186] In yet another embodiment, certain compounds of the present invention have improved pharmacokinetic and/or pharmacodynamic properties and, therefore, are better suited for *in-vivo* administration for therapeutic purposes. Such properties include oral bioavailability, clearance kinetics, efficacy, etc.

[00187] In another embodiment, certain compounds of the present invention have desirably low activity against the hERG channel.

[00188] In another embodiment, certain compounds of the present invention have desirably low activity against the key isoforms of the cytochrome P450 enzyme family, including isozymes CYP3A4, CYP2C9, CYP1A2, CYP2C19, or CYP2D6.

[00189] In another embodiment, certain compounds of the present invention have desirably low activity against the CaV 1.2 channel and/or Kv 1.5.

[00190] Thus, in one embodiment of the present invention, the compounds have one or more of the following unexpected and therapeutically beneficial features: potent inhibition of NaV 1.8 channel, selectivity for one sodium channel, e.g., NaV 1.8 over one or more of the other sodium channels, improved aqueous solubility, improved pharmacokinetic and/or pharmacodynamic properties, desirably low activity against the hERG channel, desirably low activity against the key isoforms of the cytochrome P450 enzyme family, or desirably low activity against L-type CaV 1.2 and/or Kv1.5. The presence of such features, individually or in combination, renders the compounds more suitable for administration to humans to treat various diseases as set forth below.

[00191] The phrase "desirably low activity" as used herein means a level of activity of a compound against a target/enzyme that is low enough such that said activity would be considered advantageous (e.g., mitigating a risk factor), when evaluating the suitability of said compound for administration in humans.

[00192] The present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias,

epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, and incontinence. Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00193] According to one embodiment, the compounds of the present invention are useful for treating a disease selected from femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, including, abdominal; pancreatic; IBS pain; chronic headache pain; migraine; tension headache, including, cluster headaches; chronic neuropathic pain, including, post-herpetic neuralgia; diabetic neuropathy; HIV- associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phanton pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac Pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, including, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain, including, sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); and prostatitis.

[00194] In another embodiment, the compounds of the present invention are useful in treating lower urinary tract disorders. See, e.g., International Patent Publication No. WO 2004/066990, the contents of which are incorporated herein by reference.

[00195] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00196] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of the targeted channel.

[00197] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, *66*, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate,

heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00198] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates,

waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00199] *Uses of Compounds and Pharmaceutically Acceptable Compositions*

[00200] In yet another aspect, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In certain other embodiments, a method for the treatment or lessening the severity of radicular pain, sciatica, back pain, head pain, or neck pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In still other embodiments, a method for the treatment or lessening the severity of severe or intractable pain, acute pain, postsurgical pain, back pain, or cancer pain is provided comprising administering an

effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof.

[00201] In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain.

[00202] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the

specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00203] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00204] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00205] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For

this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00206] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00207] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00208] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00209] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar–agar, calcium carbonate, potato or tapioca starch, alginic acid, certain

silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00210] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00211] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00212] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants

or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00213] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated". For example, exemplary additional therapeutic agents include, but are not limited to: nonopioid analgesics (indoles such as Etodolac, Indomethacin, Sulindac, Tolmetin; naphthylalkanones such as Nabumetone; oxicams such as Piroxicam; para-aminophenol derivatives, such as Acetaminophen; propionic acids such as Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Naproxen sodium, Oxaprozin; salicylates such as Asprin, Choline magnesium trisalicylate, Diflunisal; fenamates such as meclofenamic acid, Mefenamic acid; and pyrazoles such as Phenylbutazone); or opioid (narcotic) agonists (such as Codeine, Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Propoxyphene, Buprenorphine, Butorphanol, Dezocine, Nalbuphine, and Pentazocine). Additionally, nondrug analgesic approaches may be utilized in conjunction with administration

of one or more compounds of the invention. For example, anesthesiologic (intraspinal infusion, neural blocade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Seventeenth Edition, Ed. Mark H. Beers and Robert Berkow, Merck Research Laboratories, 1999, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[00214] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00215] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00216] Another aspect of the invention relates to inhibiting NaV1.8 activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of the present invention or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00217] Inhibition of NaV1.8 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium ion channels in biological and pathological phenomena; and the comparative evaluation of new sodium ion channel inhibitors.

[00218] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

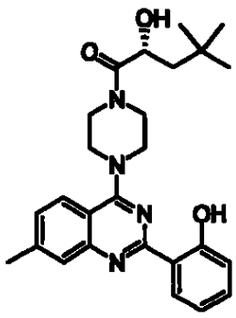
[00219] General LC/MS Methods

[00220] LC/MS data were acquired using a PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 10-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.

[00221] Example 101

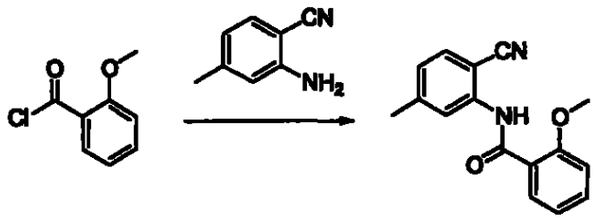
[00222] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one

[00223]



[00224] *N*-(2-Cyano-5-methyl-phenyl)-2-methoxy-benzamide

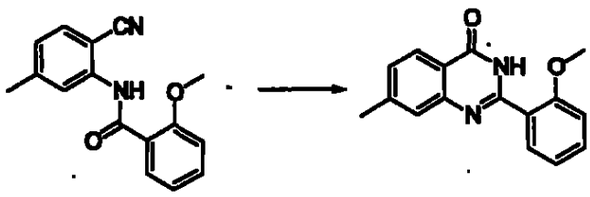
[00225]



[00226] To a stirred solution of 4-methyl-2-aminobenzonitrile (100 g, 0.75 mol) in 800 mL CH_2Cl_2 was added triethylamine (77.4 g, 0.76 mol) and dimethylaminopyridine (4.62 g, 0.037 mol). The solution was cooled to 0–5 °C, and *o*-anisoyl chloride (129 g, 0.75 mol) was added over 1 h while maintaining the reaction temperature at 0–5 °C. The reaction was then stirred at 30–40 °C for 3 h. Water (400 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (600 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to yield a solid residue, to which 800 mL hexane were added. The slurry was stirred and filtered to give *N*-(2-cyano-5-methyl-phenyl)-2-methoxy-benzamide as a yellow powder (180 g, 90%). mp 147–149 °C. ^{1}H NMR ($CDCl_3$) δ 2.429 (s, 3H), 4.2 (s, 3H), 6.8–7.2 (m, 3H), 7.4–7.6 (m, 2H), 8.2–8.4 (d, 1H), 8.6 (s, 1H), 10.8 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 22.68, 55.7, 99, 111.27, 116.7, 120.3, 121.1, 124.15, 131.7, 132.25, 133.67, 141.32, 141.1, 157.2, 163. M/z (obs., $[m+H]^+$) = 268.

[00227] 2-(2-Methoxyphenyl)-7-methyl-3*H*-quinazolin-4-one

[00228]

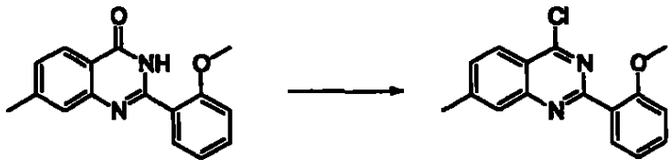


[00229] To a mechanically stirred suspension of *N*-(2-cyano-5-methylphenyl)-2-methoxybenzamide (180 g, 0.67 mol) in 1.8 L ethanol under an N_2 atmosphere was added 6 N sodium hydroxide solution (310 g in 1.25 L water). To the above mixture, 30% hydrogen peroxide (350 mL, 3.64 mol) was slowly added. The solution was then slowly heated to 80 °C

and maintained at this temperature for 4 h. The reaction mixture was concentrated under reduced pressure to remove ethanol, giving a suspension which was quenched with ice cold water (1.8 L) and acidified with acetic acid to pH 5–6 to give a solid residue. The solid was filtered and washed with water, then dissolved in 5.5 L CH_2Cl_2 and washed with water (2x18 L). The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure to give a light yellow solid (100 g, 54%). mp165–170 °C. ^{1}H NMR ($CDCl_3$) δ 2.429 (s, 3H), 4.2 (s,3), 6.8–7.2 (m, 3H), 7.4–7.6 (m, 2H), 8.2–8.4 (d, 1H), 8.6 (s, 1H), 10.8 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 21.68, 55.6, 111.3, 118.2, 119.6, 121.1, 125.7, 127.14, 127.64, 130.96, 132.56, 144.9, 149.06, 150.42, 157.25, 161.52. M/z (obs., $[m+H]^+$) = 268.

[00230] 4-Chloro-2-(2-methoxy-phenyl)-7-methyl-quinazoline

[00231]

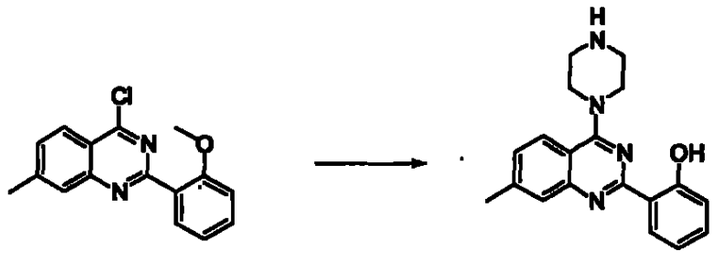


[00232] To a mechanically stirred suspension of 2-(2-methoxyphenyl)-7-methyl-3*H*-quinazolin-4-one (100 g, 0.37 mol) in 1 L toluene was added diisopropyl ethylamine (100 mL), followed by phosphorus oxychloride (69 g, 0.45 mol). The reaction was then heated to 80 °C for 4 h. The reaction mixture was distilled under reduced pressure to remove toluene, and the resulting residue was dissolved in 2.2 L CH_2Cl_2. Ice water was added, and the pH was adjusted to 8–9 with saturated aqueous sodium bicarbonate solution while maintaining the temperature below 20 °C. The resulting organic layer was separated and the aqueous solution extracted with CH_2Cl_2, then the combined the organic layers were dried over sodium sulfate and distilled under reduced pressure. The crude product was dissolved 2:1 CH_2Cl_2/hexane, and the solution was passed through silica gel (2.5 kg, 60–120 mesh), followed by washing the silica bed with 2:1 CH_2Cl_2/hexane until the product eluted. The pure fractions were collected and combined, and the solvent was removed under reduced pressure. Hexane (500 mL) was added, and the mixture was stirred and filtered to give 4-chloro-2-(2-methoxy-phenyl)-7-methyl-quinazoline as a white to off-white solid (77 g, 72%). mp 161–164 °C. ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3H), 3.9 (s, 3H), 6.9–7.2 (m, 2H), 7.4–7.6 (m, 2H), 7.7–8 (d, 2H), 8.2 (d,1H); ^{13}C NMR ($CDCl_3$) δ 22.23, 56.06, 112.2, 120.26, 120.69, 125.34, 127.94, 130.45, 131.08, 131.08. M/z (obs., $[m+H]^+$) = 285.

296

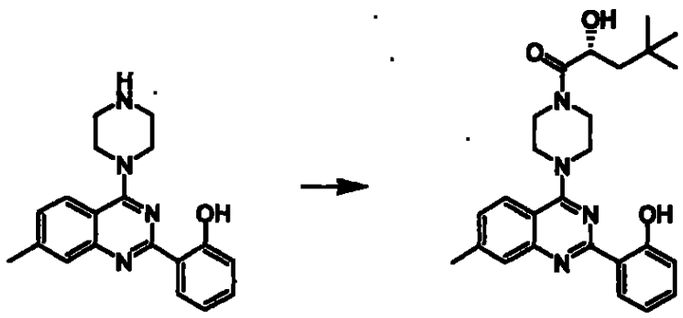
[00233] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol

[00234]



[00235] A stirring solution of 4-chloro-2-(2-methoxyphenyl)-7-methylquinazoline (91 g, 320 mmol) and CH_2Cl_2 (2.0 L) under an N_2 atmosphere was cooled to –30 °C. Boron tribromide (957 mL, 957 mmol, 1.0 M in CH_2Cl_2) was added dropwise over a period of 30 minutes at –30 to –40 °C. The cooling bath was removed, and the mixture was allowed to warm to 25 °C. The mixture was carefully poured into a stirring solution of saturated aqueous $NaHCO_3$ (4.0 L). The organic portion was separated, dried over $MgSO_4$, and evaporated to dryness. The resulting solid was suspended in CH_2Cl_2 (400 mL) under an N_2 atmosphere, followed by the addition of triethylamine (64.8 g, 640 mmol). The solution was cooled to –10 °C. A solution of piperazine (55.0 g, 640 mmol) in CH_2Cl_2 (400 mL) was added in a single portion, and the solution was stirred at ambient temperature for 1 hour. The solution temperature rose to 23 °C upon addition of the piperazine. The solution was partitioned between CH_2Cl_2 and H_2O. The organic portion was dried over $MgSO_4$ and evaporated to dryness. The residue was purified via silica gel chromatography using 5% MeOH in CH_2Cl_2 to obtain a tan solid. The resulting solid was triturated with 1:1 Et_2O/hexanes to obtain a yellow solid which was vacuum dried to give 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol as a light yellow solid (93.0 g, 290 mmol, 91%). LC/MS: *m/z* 321.1 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00236] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one



[00237] Method A

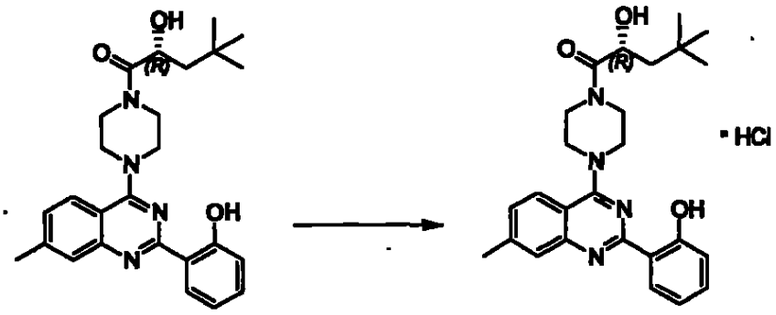
[00238] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol) was placed in a tube charged with a stir bar followed by (*R*)-2-hydroxy-4,4-dimethylpentanoic acid in 1 ml of DMF and triethylamine (31.57 mg, 0.312 mmol), and the reaction was cooled to 0 °C. HATU (71 mg, 0.187 mmol) was then added, and the reaction was allowed to stir at 0 °C for 10 minutes and then allowed to warm to room temperature. The reaction was complete after 40 minutes, filtered, and purified by reverse phase HPLC to give the TFA salt of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00239] Method B

[00240] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.74 mmol) was suspended in anhydrous DMF (5 mL) and cooled to 0 °C internal temperature. Under an N_2 atmosphere, (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (125.4 mg, 0.858 mmol) was added followed by triethylamine (0.218 mL, 1.56 mmol). To this stirring solution was added HATU (356 mg, 0.936 mmol). After the complete addition of HATU, the mixture was allowed to warm to 10 °C. After 45 min the reaction was complete, and it was quenched with an equal portion of ice water. A yellow precipitate formed which was collected by vacuum filtration and dissolved in CH_2Cl_2. This solution was desiccated with Na_2SO_4, filtered, and concentrated to give a viscous yellow-orange oil. The crude material was purified via silica gel chromatography using 88% CH_2Cl_2–hexanes (1:1) and 12% EtOAc to afford (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one as a faint yellow foam (265 mg, 76%). LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.46 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.70 (s, 1H), 7.41–7.37 (m, 2H), 6.97–6.93 (m, 2H), 4.89 (d, *J* = 7.2 Hz, 1H), 4.49–

4.44 (m, 1H), 4.06–3.67 (m,8), 2.52 (s, 3H), 1.56 (dd, J = 14.3, 3.0 Hz, 1H), 1.42 (dd, J = 14.3, 8.8 Hz, 1H), 0.97 (s, 9H)

[00241] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one hydrochloride

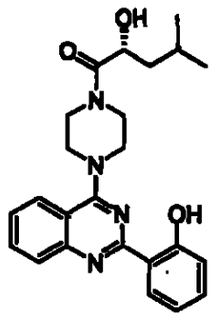


[00242] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one (265 mg, 0.367 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) followed by the addition of Et_2O (6 mL) under an N_2 atmosphere. A 2.0 M HCl solution in Et_2O (0.296 mL, 0.591 mmol) was added over a 1 minute period. The reaction solution changed from a clear yellow solution to a creamy off white slurry. After complete addition of the HCl solution, the reaction was allowed to stir for an additional 10 minutes. The product was collected by vacuum filtration, washed with 3 mL of Et_2O and dried under vacuum to obtain (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4,4-dimethylpentan-1-one hydrochloride as a white solid (261 mg, 91%). LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.33 (d, J = 7.6 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.75 (s, 1H), 7.47–7.43 (m, 2H), 7.04–6.98 (m, 2H), 4.47–4.44 (m, 1H), 4.13–4.04 (m, 4H), 3.91–3.68 (m, 4H), 2.54 (s, 3H), 1.57 (dd, J = 14.3, 3.1 Hz, 1H), 1.42 (dd, J = 14.3, 8.8 Hz, 1H), 0.97 (s, 9H).

[00243] Example 102

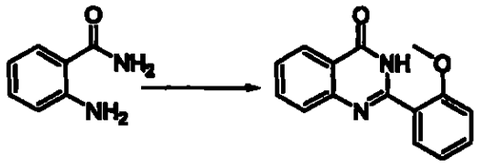
[00244] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00245]



[00246] 2-(2-Methoxyphenyl)quinazolin-4(3*H*)-one

[00247] Method A



[00248] To a cooled (0–5 °C) mixture of anthranilamide (350 g, 2.57 mol) and triethylamine (286 g, 2.83 mol) in THF (2.5 L) was added dropwise *o*-anisoyl chloride (437 g, 2.57 mol) while maintaining the temperature between 0–20 °C. The resulting suspension was stirred at room temperature overnight. The solvent was evaporated *in vacuo*, and the residue was washed several times with water. The wet residue was suspended in 2 M aq. NaOH (13 L), and the mixture was heated to reflux. After 20 minutes a clear solution was obtained. After 1 h of reflux the clear solution was cooled in an ice water bath and then acidified to pH 6 with conc. aq. HCl. The suspension was filtered, and the residue was washed thoroughly with water. The white solid was dried by azeotropic distillation with toluene. 2-(2-Methoxyphenyl)quinazolin-4(3*H*)-one (567 g) was obtained in 82%. ^{1}H-NMR (200 MHz, Me_2SO-d_6): δ 3.90 (s, 3 H), 7.20 (m, 2 H), 7.60 (t, 2 H), 7.85 (m, 3 H), 8.20 (d, 1 H), 12.20 (s, 1 H).

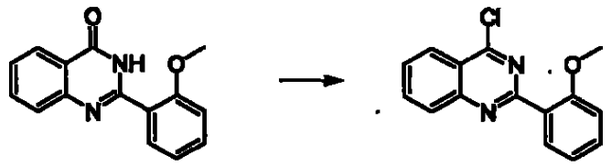
[00249] Method B

[00250] In a 2 L three-necked round-bottomed flask equipped with an overhead stirrer and reflux condenser, anthranilamide (20.0 g, 147 mmol) and potassium carbonate (28.4 g, 206 mmol) were suspended in 1 L dry ether and heated to reflux. *o*-Anisoyl chloride (32.5 g, 191 mmol) was added slowly to the refluxing mixture. After 3 hours at reflux, the reaction mixture was allowed to cool to room temperature, the ether was removed under reduced pressure, and the

resulting residue was filtered and washed with water. The resulting solid was then suspended in 600 mL of 5% aq. NaOH solution and boiled for one hour. The reaction was allowed to cool to room temperature, and it was neutralized with acetic acid, upon which 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one was precipitated. The product was collected by filtration, washed with water, and dried overnight *in vacuo* to yield 27 g (73%) of pure 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one. *LC/MS*: *m/z* 253.0 $(M+H)^+$ at 3.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (DMSO) δ 3.86 (s, 3H), δ 7.09 (t, 1H), δ 7.18 (d, 1H), δ 7.53 (m, 2H), δ 7.70 (m, 2H), δ 7.80 (m, 1H), δ 8.14 (d, 1H), δ 12.11 (s, 1H); ^{13}C NMR (DMSO) δ 55.75, δ 111.86, δ 120.89, δ 120.97, δ 122.74, δ 125.75, δ 126.45, δ 127.26, δ 130.41, δ 132.13, δ 134.32, δ 148.97, δ 152.48, δ 157.12, δ 161.35

[00251] **4-Chloro-3,4-dihydro-2-(2-methoxyphenyl)quinazoline**

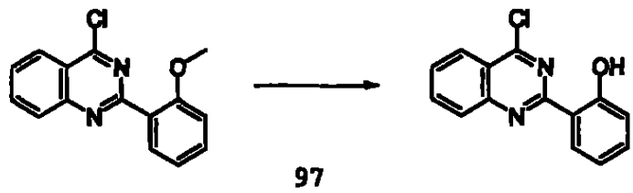
[00252]



[00253] A suspension of 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one (567 g, 2.1 mol) in phosphoryl chloride (2 L, 21 mol) and a catalytic amount of *N,N*-dimethyl aniline was brought to reflux. The reaction started immediately with the evolution of gas (HCl) upon the addition of *N,N*-dimethyl aniline. After the production of gas had ceased the mixture was cooled to room temperature. The excess $POCl_3$ was evaporated. The resulting dark solution was cooled to room temperature and slowly poured on ice and water, while maintaining the temperature below 5 °C. The cold suspension was extracted with dichloromethane. The extract was dried over sodium sulfate and filtered, and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (silica gel, CH_2Cl_2). Yield: 189 g (33%) of 4-chloro-3,4-dihydro-2-(2-methoxyphenyl)quinazoline. ^1H-NMR (300 MHz, Me_2SO-d_6): δ 3.85 (s, 3 H), 7.15 (t, 1 H), 7.25 (d, 1 H), 7.60 (t, 2 H), 7.70 (d, 1 H), 7.8 (d, 1 H), 7.9 (t, 1 H), 8.2 (d, 1 H).

[00254] **2-(4-Chloroquinazolin-2-yl)phenol**

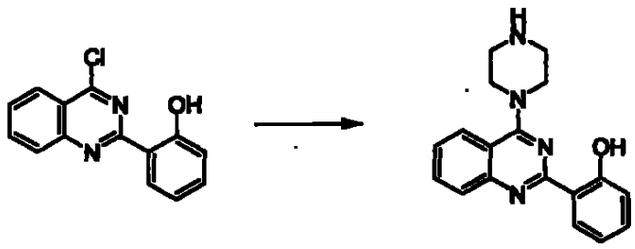
[00255]



[00256] To a solution of 4-chloro-2-(2-methoxyphenyl)quinazoline (1.0 g, 3.7 mmol) in 40 mL CH_2Cl_2 at –78 °C was added 5 equivalents of 1 M BBr_3 dropwise. After complete addition the cooling bath was removed and the reaction was quenched with $NaHCO_3$ after 90 minutes. The product was extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 60:40 CH_2Cl_2: hexanes gave 2-(4-chloroquinazolin-2-yl)phenol (700 mg, 74%). LC/MS: *m/z* 257.1 $(M+H)^+$ at 3.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.44 (m, 1H), 8.24 (m, 3H), 7.89 (m, 1H), 7.49 (m, 1H), 7.05 (m, 2H).

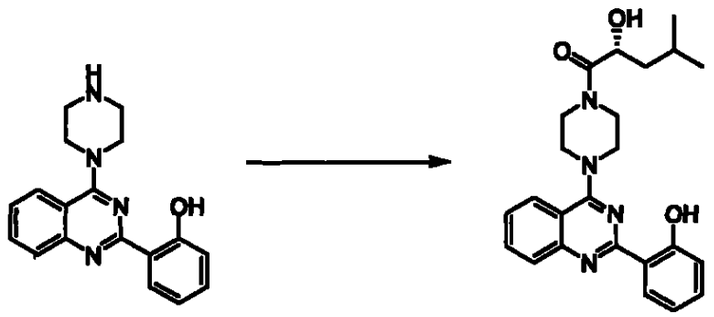
[00257] 2-(4-(Piperazin-1-yl)quinazolin-2-yl)phenol

[00258]



[00259] To a solution of 2-(4-chloroquinazolin-2-yl)phenol (2.0 g, 7.8 mmol) in CH_2Cl_2 at 0 °C was rapidly added a solution of piperazine (2.01 g, 23.4 mmol) and triethylamine (2.17 mL, 15.6 mmol) in 10 mL CH_2Cl_2. The reaction was warmed to room temperature and stirred for 5 hours. The reaction was quenched with 25 mL of water and extracted with (3×15) mL of CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (1.98 g, 83%). LC/MS: *m/z* 307.3 $(M+H)^+$ at 1.47 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.43 (d, J = 10.1 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.85 (m, 2H), 7.53 (m, 1H), 7.38 (m, 1H), 6.95 (m, 2H), 3.85 (t, J = 4.8 Hz, 4H), 2.94 (t, J = 4.8 Hz, 4H).

[00260] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

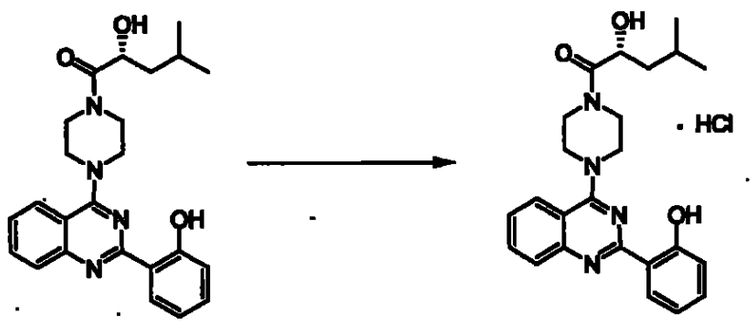


[00261]

[00262] To a solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.82 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (227 μL, 1.63 mmol) followed by the addition of (*R*)-2-hydroxy-4-methylpentanoic acid (140 mg, 1.06 mmol) and HATU (403 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (265 mg, 77%). LC/MS: *m/z* 421.30 $(M+H)^+$ at 2.57 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). H NMR (400 MHz, DMSO-d6) δ 8.47 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H) 7.88 (m, 2H), 7.57 (m, 1H), 7.40 (m, 1H), 6.96 (m, 2H), 4.92 (d, *J* = 7.2 Hz, 1H), 4.39 (m, 1H), 3.95 (m, 4H), 3.76 (m, 4H), 1.80 (m, 1H), 1.43 (m, 2H), 0.92 (q, *J* = 3.8 Hz, 6H).

[00263] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride**

[00264]



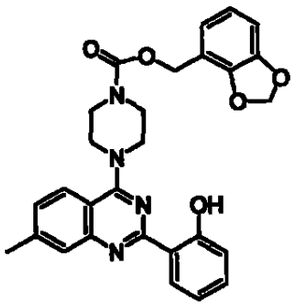
[00265] To a solution of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (265 mg, 0.63 mmol) in CH_2Cl_2 (3 mL) under inert

atmosphere was added 10 mL of ether followed by the dropwise addition of 2 M HCl (0.315 mL, 0.63 mmol).The reaction was stirred for 30 min before the formed precipitate was filtered to afford (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride (261 mg, 91%). *LC/MS*: *m/z* 421.3 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.28 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 3.9 Hz, 2H), 7.65 (m, 1H), 7.48 (m, 1H), 7.04 (m, 2H), 4.37 (m, 1H), 4.10 (m, 4H), 3.80 (m, 4H), 1.77 (m, 1H), 1.41 (m, 2H), 0.91 (dd, *J* = 6.6, 3.1 Hz, 6H).

[00266] Example 103

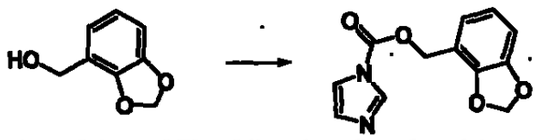
[00267] (Benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00268]



[00269] (Benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate

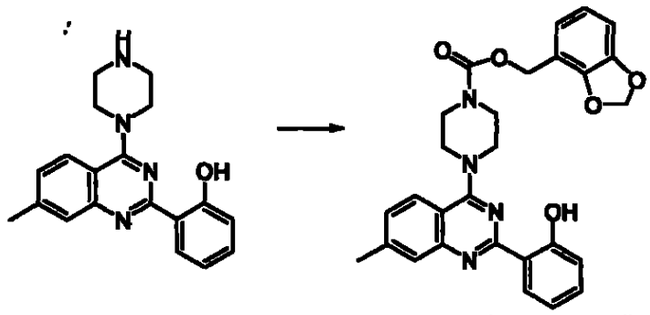
[00270]



[00271] A solution of (benzo[d][1,3]dioxol-7-yl)methanol (2 g, 13.14 mmol) and di(1*H*-imidazol-1-yl)methanone (4.26 g, 26.28 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C. The reaction was quenched with water, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (2.8 g, 86%).

[00272] (Benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00273]

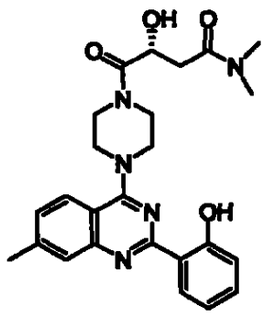


[00274] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (78 mg, 0.32 mmol) and triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 499.3 $(M+H)^+$ at 2.97 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00275] Example 104

[00276] **(*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-N,N-dimethyl-4-oxobutanamide**

[00277]



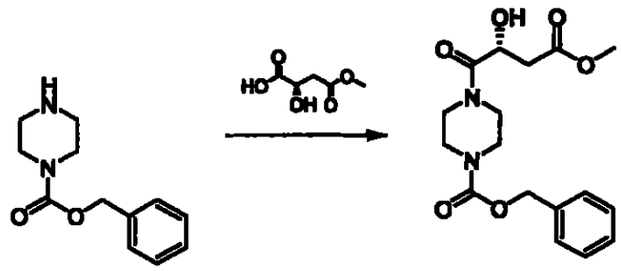
[00278] **(*R*)-3-(Methoxycarbonyl)-2-hydroxypropanoic acid**

[00279]

[00280] Methyl 2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate (17.1 g, 90.9 mmol) was stirred in a 1:1 mixture of THF:1 M HCl (200 mL) for 1 h at room temperature. After addition of NaCl to nearly saturate the aqueous layer, the mixture was extracted with EtOAc, and the extracts were dried over Na_2SO_4 and concentrated to obtain (*R*)-3-(methoxycarbonyl)-2-hydroxypropanoic acid as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58–4.55 (m, 1H), 3.75 (s, 3H), 2.98–2.84 (m, 2H).

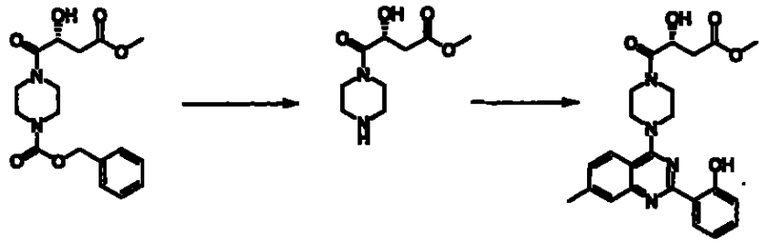
[00281] **4-((*R*)-2-Hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester**

[00282]



[00283] EDCI (3.6 g, 19 mmol) was added to a solution of (*R*)-3-(methoxycarbonyl)-2-hydroxypropanoic acid (2.8 g, 19 mmol) and HOBt (2.6 g, 19 mmol) in DMF (200 mL). After stirring this mixture for 5 min, benzyl piperazine-1-carboxylate (4.2 g, 3.6 mL, 19 mmol) and triethylamine (2.6 mL, 19 mmol) were added and stirred for 3 days at room temperature. The reaction mixture was poured into water and extracted with EtOAc. After washing the organic layers with brine and water, drying over Na_2SO_4 and concentrating, purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester as an oil (2.19 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 5.15 (s, 2H), 4.79–4.74 (m, 1H), 3.95 (d, J = 8.0 Hz, 1H), 3.79–3.74 (m, 1H), 3.74 (s, 3H), 3.71–3.44 (m, 7H), 2.62 (d, J = 5.8 Hz, 2H).

[00284] **(*R*)-Methyl 3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoate**



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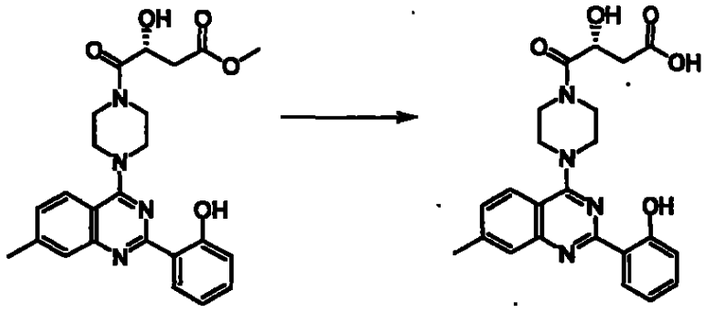
[00286] 4-((*R*)-2-Hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (0.52 g, 1.5 mmol) and MeOH (15 mL) were stirred with 10% Pd/C under an H_2 atmosphere at ambient pressure overnight. After filtration and evaporation of the solvent the residue was taken up in CH_2Cl_2, and 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.40 g, 1.50 mmol) plus triethylamine (0.41 mL, 3.00 mmol) were added. The reaction mixture was stirred at room temperature overnight, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/ CH_2Cl_2 provided (*R*)-methyl 3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoate (0.38 g, 57%). *LC/MS*: *m/z* 451.1 $(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00287] (*R*)-3-Hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid

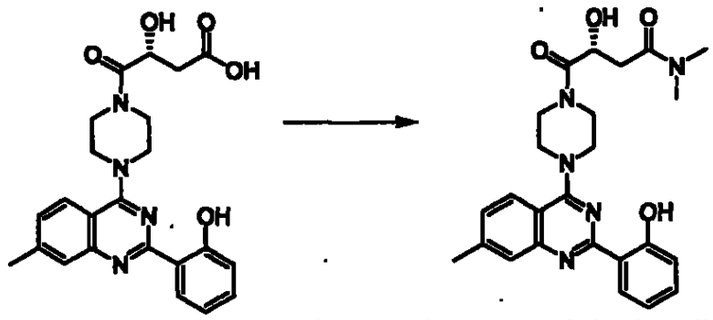
[00288]



[00289] $LiOH·H_2O$ (19.8 mg, 0.47 mmol) was added to a solution of (*R*)-3-hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid methyl ester (71 mg, 0.16 mmol) in 2 mL THF:H_2O (1:1) and stirred at room temperature for 3 h. The reaction mixture was acidified with 1 M HCl and then extracted with EtOAc. After drying the organic layer over Na_2SO_4, it was concentrated and then purified via silica gel chromatography using 0–15% MeOH/CH_2Cl_2 to provide (*R*)-3-hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid (52 mg, 75%). *LC/MS*: *m/z* 437.3 $(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00290] (*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-*N*,*N*-dimethyl-4-oxobutanamide

[00291]

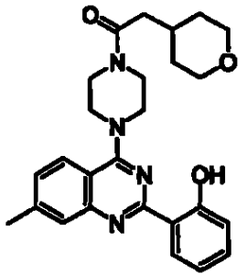


[00292] (*R*)-3-Hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid (17 mg, 0.039 mmol) and HATU (16 mg, 0.043 mmol) were stirred in DMF (0.5 mL). After adding dimethylamine (2 M in THF, 0.10 mL, 0.19 mmol), the reaction mixture was stirred at room temperature for 5 h. Purification via preparative reverse-phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-N,N-dimethyl-4-oxobutanamide as the TFA salt. LC/MS: *m/z* 436.3 $(M+H)^+$ at 1.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00293] Example 105

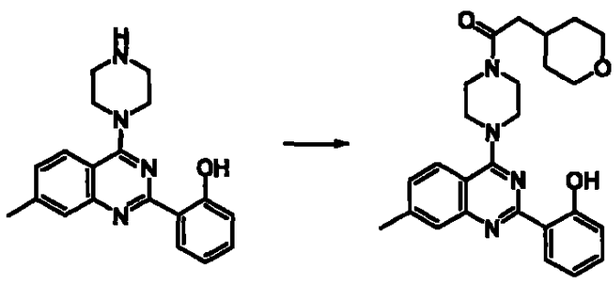
[00294] (2-(Tetrahydro-2*H*-pyran-4-yl)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone

[00295]



[00296] (2-(Tetrahydro-2*H*-pyran-4-yl)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone

[00297]

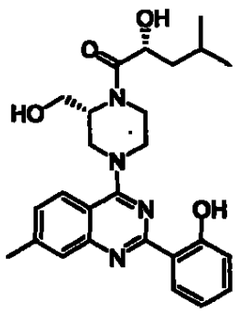


[00298] To a solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (13.5 mg, 0.09 mmol) followed by the addition of triethylamine (25 μL), then HATU (44 mg) at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2-(tetrahydro-2*H*-pyran-4-yl)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone as the TFA salt. LC/MS: *m/z* 447.10 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

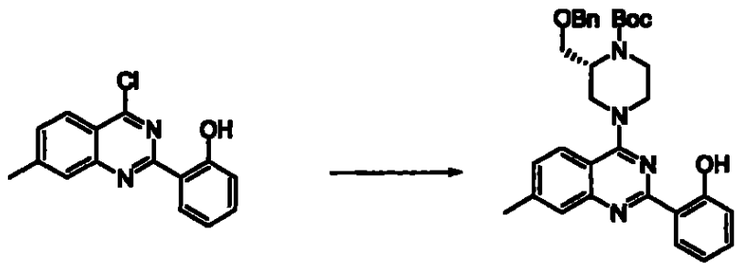
[00299] Example 106

[00300] (*R*)-2-Hydroxy-1-((*R*)-2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00301]



[00302] (*R*)-*tert*-Butyl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

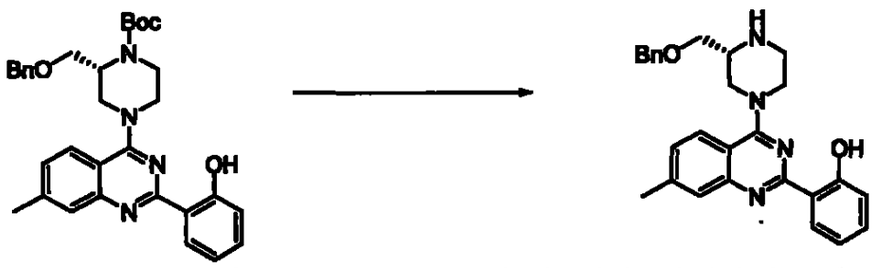


[00303]

[00304] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (450 mg, 1.66 mmol) in 10 mL DMF was added a solution of (*R*)-*tert*-butyl 2-((benzyloxy) methyl) piperazine-1-carboxylate (610 mg, 1.99 mmol) in DMF and triethylamine (0.46 mL). The reaction mixture was then refluxed at 85 °C for 30 minutes, quenched with water, extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated to give (*R*)-*tert*-butyl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate (760 mg, 85%). This material was used in the next step without further purification. LC/MS: *m/z* 541.5 $(M+H)^+$ at 3.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00305] 2-(4-((*R*)-3-((Benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol

[00306]



[00307] To a solution of (*R*)-*tert*-butyl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate (760 mg, 1.72 mmol) in 15 mL CH_2Cl_2 was added 10 mL of TFA. The reaction was stirred for 1 hour. TFA was removed under vacuum and the reaction was neutralized using a 1 M NaOH solution. The aqueous layer was extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to obtain 2-(4-((*R*)-3-((benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol (570 mg, 92%). This material was used in the next step without further purification. LC/MS: *m/z* 441.5 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

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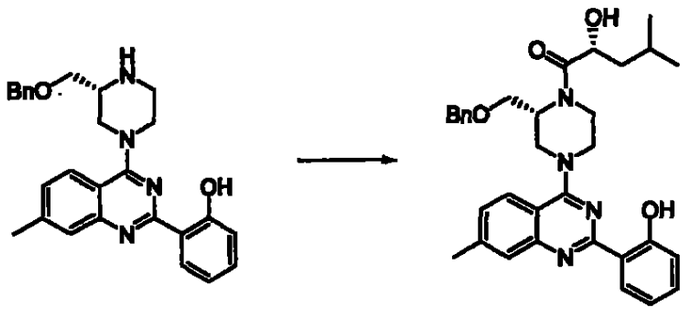
[00308] (*R*)-1-((*R*)-2-((Benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

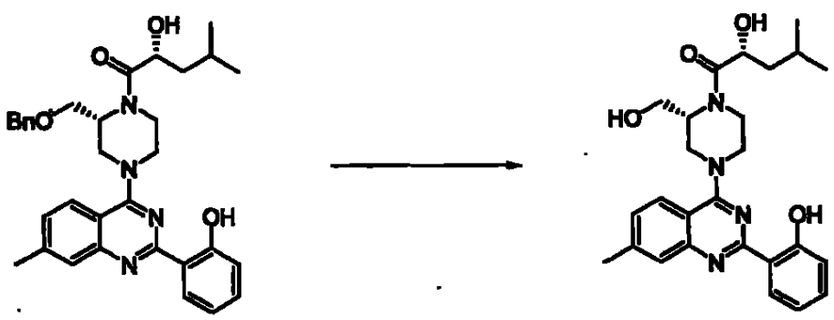
[00309]



[00310] To a solution of 2-(4-((*R*)-3-((benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol (100 mg, 0.22 mmol) in DMF (1 mL) was added (*R*)-2-hydroxy-4-methylpentanoic acid (30 mg, 0.22 mmol) followed by the addition of triethylamine (61 μL), then HATU (109 mg) at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-1-((*R*)-2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 555.7 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00311] (*R*)-2-Hydroxy-1-((*R*)-2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00312]



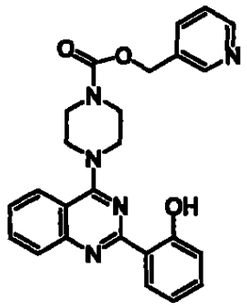
[00313] To a solution of (*R*)-1-((*R*)-2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one trifluoroacetate (29.6 mg, 0.053 mmol) in ethanol was added $Pd(OH)_2$ (188 mg), and the reaction was heated at 50 °C

under H_2 atmosphere at ambient pressure. The reaction was filtered, and purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-((*R*)-2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one as the TFA salt. *LC/MS*: *m/z* 465.50 $(M+H)^+$ at 2.47 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00314] Example 107

[00315] (Pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00316]



[00317] (Pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate

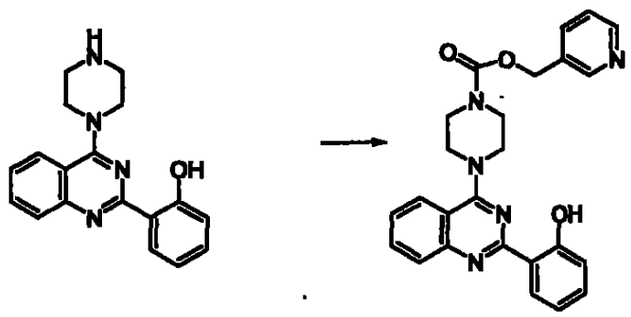
[00318]

[00319] A solution of (pyridin-3-yl)methanol (2 g, 18.32 mmol) and di(1*H*-imidazol-1-yl)methanone (5.94 g, 36.65 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C. The reaction was quenched with water, extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (3.1 g, 84%). *LC/MS*: *m/z* 204.1 $(M+H)^+$ at 0.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.9 Hz, 1H), 8.68 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.16 (s, 1H), 7.81 (m, 1H), 7.44 (s, 1H), 7.38 (m, 1H), 7.09 (s, 1H), 5.46 (s, 2H).

[00320] (Pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

304

[00321]

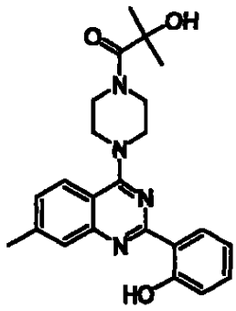


[00322] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (67 mg, 0.32 mmol) and triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 442.50 $(M+H)^+$ at 1.97 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00323] Example 108

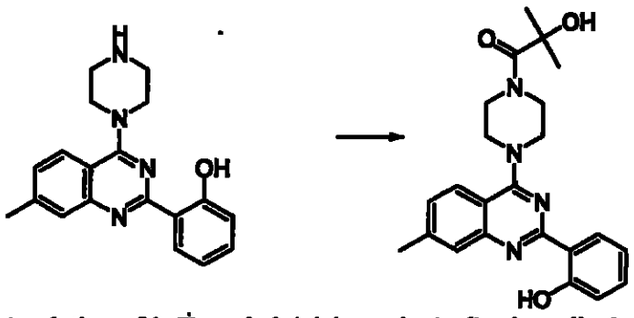
[00324] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylpropan-1-one

[00325]



[00326] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylpropan-1-one

[00327]

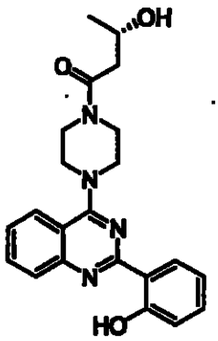


[00328] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxy-2-methylpropanoic acid (29.6 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylpropan-1-one as the TFA salt. LC/MS: *m/z* 407.50 $(M+H)^+$ at 2.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00329] Example 109

[00330] (*S*)-3-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

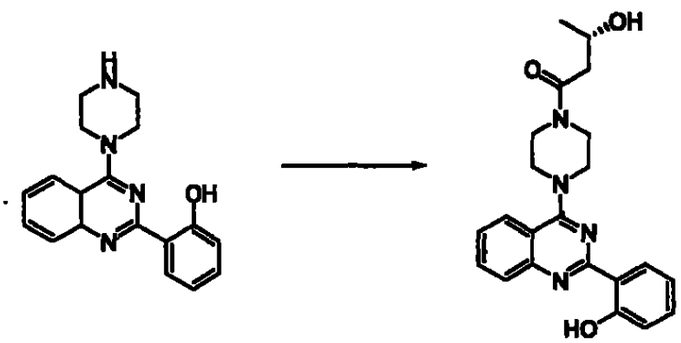
[00331]



[00332] (*S*)-3-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

305

[00333]

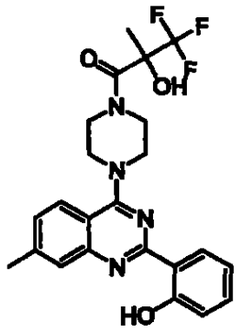


[00334] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*S*)-3-hydroxybutanoic acid (31.0 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-3-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 393.1 $(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00335] Example 110

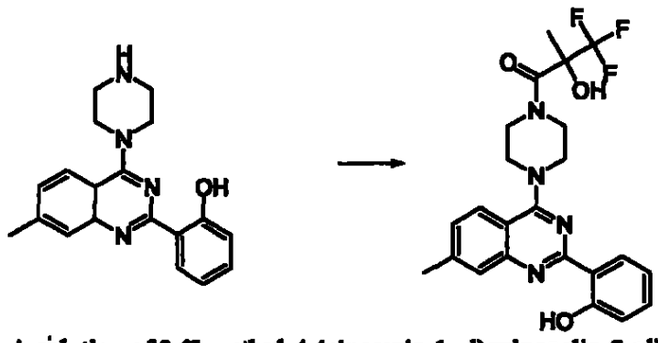
[00336] **2-(Trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one**

[00337]



[00338] **2-(Trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one**

[00339]

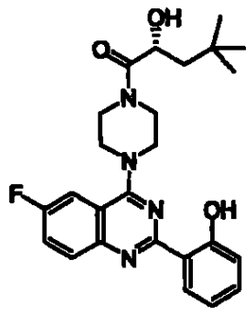


[00340] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-(trifluoromethyl)-2-hydroxypropanoic acid (45 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-(trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 461.1 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

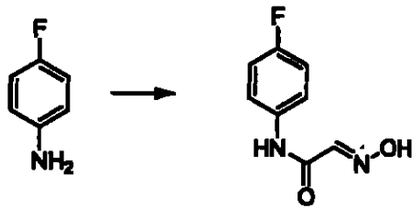
[00341] Example 111

[00342] **(*E*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one**

[00343]



[00344] **(*E*)-*N*-(4-Fluorophenyl)-2-(hydroxyimino)acetamide**

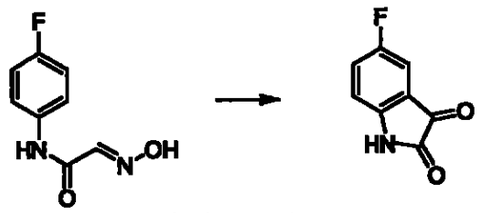


[00345]

[00346] 4-Fluoroaniline (58.2 g, 0.50 mol) was added slowly to 10% aqueous HCl solution. This suspension was added to a mixture of chloral hydrate (95 g, 0.55 mol) and sodium sulfate (0.5 kg) in 750 mL water with mechanical stirring. Hydroxylamine hydrochloride (116 g, 1.63 mol) dissolved in water (250 mL) was added, and the resulting slurry was heated at 100 °C. After this temperature was reached, the heating mantle was removed immediately, and the solution was cooled to room temperature. The formed precipitate was collected by filtration, washed with water (2x300 mL), and dried in a vacuum oven at 60 °C. Yield: 78.2 g of *N*-(4-fluorophenyl)-2-hydroxyiminoacetamide as an off-white solid.

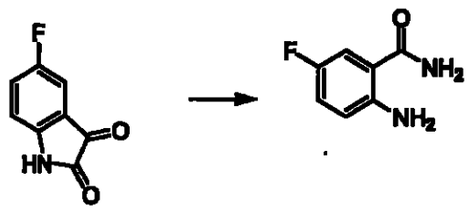
[00347] 5-Fluoroindoline-2,3-dione

[00348]



[00349] Concentrated sulfuric acid (200 mL) was heated at 50 °C, and *N*-(4-fluorophenyl)-2-hydroxyiminoacetamide was slowly added. The black solution was carefully heated at 90 °C. At this temperature, some slight cooling was necessary to keep the temperature at 90 °C. When no more heat had developed, the reaction mixture was heated at 90 °C for an additional half hour. The dark-red solution was cooled to room temperature and poured onto 3 L ice water and 1 L ethyl acetate with vigorous stirring. The layers were separated, and the aqueous layer was extracted with ethyl acetate (1x1 L, 1x0.5 L). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated to dryness. Yield: 35.3 g (52%) of a dark red solid, 5-fluoro-1*H*-indole-2,3-dione.

[00350] 2-Amino-5-fluorobenzamide

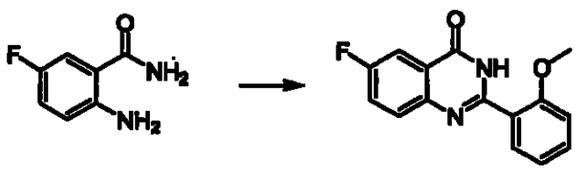


[00351]

[00352] 5-Fluoro-1*H*-indole-2,3-dione (35.3 g, 213 mmol) was heated in acetic acid (300 mL), 1 mL concentrated sulfuric acid, and 22 mL 35% aq. hydrogen peroxide at 70 °C. The solution was kept at that temperature one and a half hours during which time a solid formed in the reaction mixture. After cooling to room temperature this solid was collected by filtration and was washed three times with water. The wet solid was suspended in 150 mL water, and 40 mL of a 25% aq. ammonia solution was added. This mixture was stirred at room temperature 3 days. The formed solid was collected by filtration and was washed twice with water. The solid was dried by azeotropic distillation with toluene (3 x 100 mL) to yield 2-amino-5-fluorobenzamide (9.5 g). The combined filtrates were extracted with ethyl acetate (2x100 mL). The combined extracts were dried over sodium sulfate, filtered, and evaporated to dryness to yield 2-amino-5-fluorobenzamide (3.5 g) as an off-white solid. Both fractions were combined for use in the next reaction step.

[00353] 6-Fluoro-2-(2-methoxyphenyl)-3*H*-quinazolin-4-one

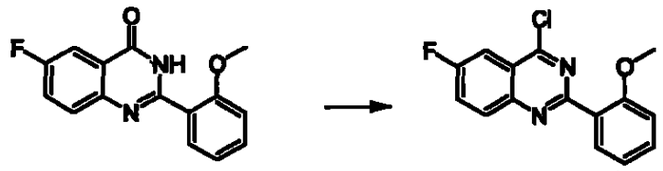
[00354]



[00355] *o*-Anisoyl chloride (15.7 g, 92 mmol) was added dropwise to a solution of aminobenzamide 2-amino-5-fluorobenzamide (13.0 g, 84 mmol) and triethylamine (16 mL, 110 mmol) in tetrahydrofuran (100 mL) cooled in an ice bath. Immediately a precipitate started forming. Stirring of the solution was continued for 5 hours at room temperature. The formed precipitate was collected by filtration and was washed twice with diethyl ether and dried at 50 °C *in vacuo*. The dried solid was suspended in 2 N aqueous sodium hydroxide solution (250 mL) and heated at reflux until a clear solution was obtained (3 hours). The reaction mixture was cooled to room temperature and filtered. The filtrate was acidified to pH<1 with concentrated aqueous HCl. The formed precipitate was collected by filtration and washed twice with water,

twice with methanol, and twice with diethyl ether. The solid was dried in an oven at 45 °C to yield 6-fluoro-2-(2-methoxyphenyl)-3*H*-quinazolin-4-one (18.2 g, 80%) as a white solid.

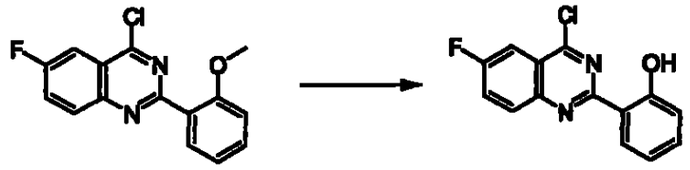
[00356] **4-Chloro-6-fluoro-2-(2-methoxyphenyl)quinazoline**



[00357] A suspension of 6-fluoro-2-(2-methoxyphenyl)-3*H*-quinazolin-4-one (14.0 g, 52 mmol), *N,N*-dimethylaniline (6.6 mL, 52 mmol), and phosphorus oxychloride (4.8 mL, 52 mmol) in benzene (100 mL) was heated at reflux until a clear, dark solution was obtained (1 hour). The reaction mixture was cooled to room temperature, and the volume was reduced under reduced pressure. The black, oily residue was poured into 300 g of ice. Dichloromethane (600 mL) was added with vigorous stirring, and the temperature was kept below 5 °C at all times. The pH was monitored, and aqueous 1 N sodium hydroxide was added until the pH was 10–11. The mixture was stirred for one hour at a temperature below 5 °C, and the pH was kept between 10–11 by addition of 1 N aqueous sodium hydroxide. The layers were separated, and the organic layer was washed with ice cold 1 N aqueous sodium hydroxide (2x200 mL). Heptanes (300 mL) were added to the organic layer. This mixture was filtered through a short plug of silica gel and eluted with dichloromethane/heptanes (2:1). All fractions containing product were combined and evaporated to dryness. The residue was triturated with heptanes to yield 4-chloro-6-fluoro-2-(2-methoxyphenyl)-quinazoline (11.5 g, 76%) as a white solid.

[00358] **2-(4-Chloro-6-fluoroquinazolin-2-yl)phenol**

[00359]

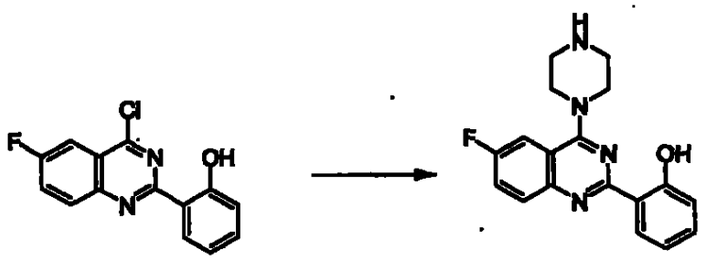


[00360] A solution of 4-chloro-6-fluoro-2-(2-methoxyphenyl)quinazoline (3.0 g, 10.3 mmol) in CH_2Cl_2 (15 mL) was cooled to –78 °C. Then, 1 M BBr_3 (51.95 mL, 59.95 mmol) was added dropwise. The reaction was warmed to room temperature and was quenched with $NaHCO_3$ and extracted twice with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered,

and concentrated. Purification via silica gel chromatography using 5–20% CH_2Cl_2 in hexanes gave 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (1.61 g, 57%). LC/MS: *m/z* 275.1 $(M+H)^+$ at 3.8 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

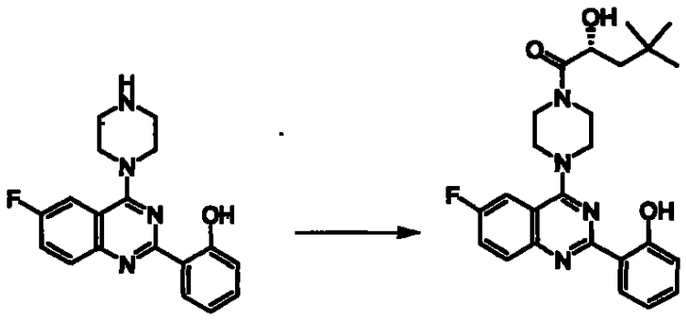
[00361] **2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol**

[00362]



[00363] To a stirring solution of 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (500 mg, 1.82 mmol) in CH_2Cl_2 (20 mL) at 0 °C, under an N_2 atmosphere was rapidly added a solution of piperazine (0.263 g, 7.28 mmol) and triethylamine (0.35 mL, 2.55 mmol) in CH_2Cl_2. The mixture was stirred for 1 h and then quenched with H_2O, extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–5% MeOH in CH_2Cl_2 gave 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (400 mg, 68%). LC/MS: *m/z* 325.5 $(M+H)^+$ at 2.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.42 (m, 1H), 7.97 (m, 1H), 7.78 (m, 2H), 7.39 (m, 1H), 6.95 (m, 2H), 3.83 (t, J = 4.9 Hz, 4H), 2.92 (t, J = 4.9 Hz, 4H).

[00364] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one**



[00365]

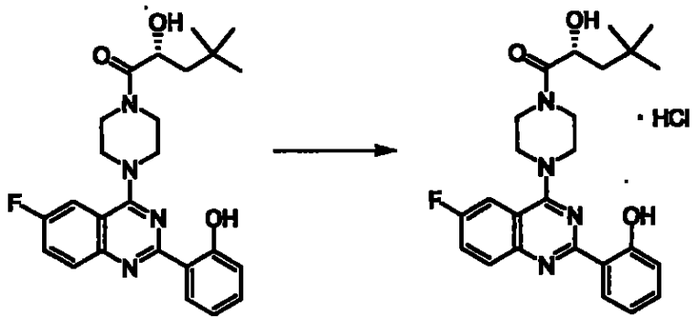
[00366] <u>Method A</u>

[00367] To a solution of 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol) in DMF (1 mL) was added (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (20.28 mg, 0.14 mmol) followed by the addition of triethylamine (25 μL), then HATU (44 mg) at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))–H_2O) gave (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one as the TFA salt. LC/MS: *m/z* 453.52 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00368] Method B

[00369] To a solution of 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (200 mg, 0.61 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (170 μL, 1.22 mmol) followed by the addition of (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (116 mg, 0.79 mmol), then HATU (301 mg, 0.79 mmol). An additional 3 mL of CH_2Cl_2 were added, and the reaction was stirred for 3 h. After quenching with water, the mixture was extracted twice with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes yielded (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one (240 mg, 86%). *m/z*: M+1 *obs* = 453.5; t_R = 3.19 minutes ^1H NMR (400 MHz, DMSO-d6) δ 8.46 (m, 1H), 8.01 (m, 1H), 7.84 (m, 2H), 7.40 (m, 1H), 6.96 (m, 2H), 4.89 (d, *J* = 7.1 Hz, 1H), 4.45 (m, 1H), 3.97 (m, 4H), 3.76 (m, 4H), 1.56 (m, 1H), 1.42 (m, 1H), 0.97 (s, 9H).

[00370] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride**



[00371]

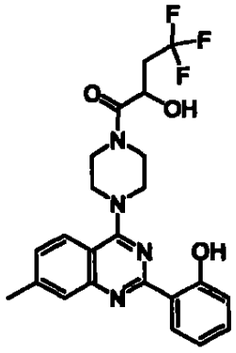
[00372] To a solution of (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2- hydroxy-4,4-dimethylpentan-1-one (230 mg, 0.51 mmol) in CH_2Cl_2 (3 mL)

under an inert atmosphere was added dropwise a 2 M HCl solution in ether (2.55 mL, 0.51 mmol). To it was then added ether (15 mL) which resulted in formation of a precipitate that was allowed to stir for an hour. The product was collected by vacuum filtration and dried to afford (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride (230 mg, 92%). LCMS: *m/z* 453.5 $(M+H)^+$ at 3.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.40 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.04 (m, 1H), 7.88 (m, 2H), 7.43 (m, 1H), 6.99 (m, 2H), 4.45 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.02 (m, 4H), 3.79 (m, 4H), 1.56 (m, 1H), 1.42 (m, 1H), 0.97 (s, 9H).

[00373] Example 112

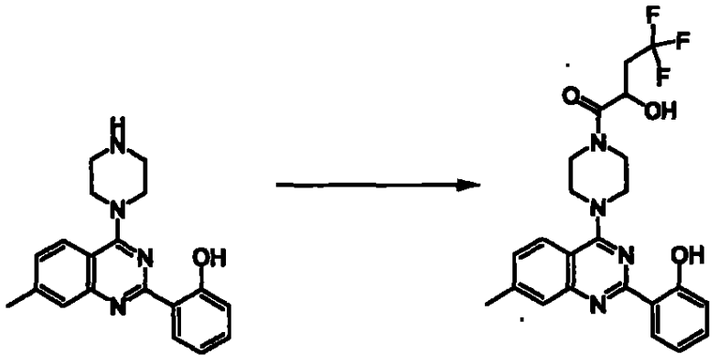
[00374] **4,4,4-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one**

[00375]



[00376] **4,4,4-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one**

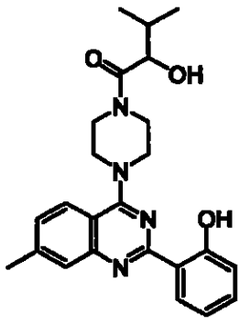
[00377]



[00378] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (87 mg, 0.27 mmol), 4,4,4-trifluoro-2-hydroxybutanoic acid (43 mg, 0.27 mmol), HATU (0.12 g, 0.33 mmol) and triethylamine (45 μL, 0.33 mmol) were stirred in DMF (3 mL) at room temperature overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and water, dried over Na_2SO_4 and concentrated. Purification via silica gel chromatography using 0–20% EtOAc in 1:1 CH_2Cl_2: hexanes gave 4,4,4-trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one as an off-white solid (86 mg, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, J = 8.0, 1.7 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.41–7.37 (m, 1H), 7.31 (dd, J = 8.5, 1.5 Hz, 1H), 7.05–7.03 (m, 1H), 6.97–6.93 (m, 1H), 4.80–4.75 (m, 1H), 4.07–3.68 (m, 9H), 2.56 (s, 3H), 2.50–2.39 (m, 2H); LC/MS: *m/z* 461.3 $(M+H)^+$ at 2.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

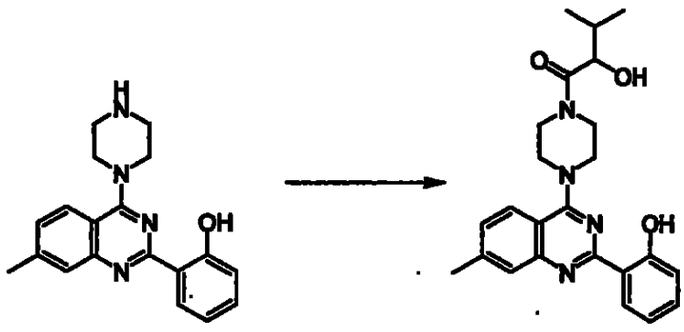
[00379] Example 113

[00380] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one**



[00381]

[00382] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one**



[00383]

[00384] Method A

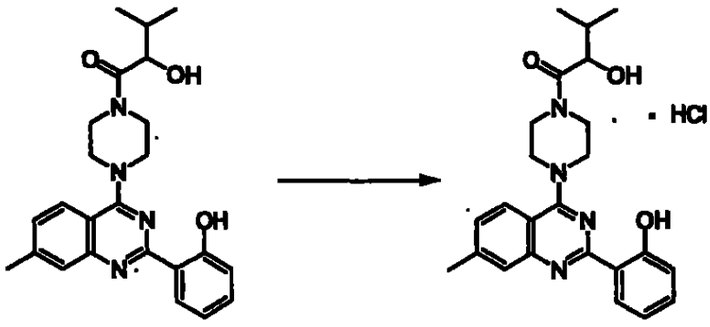
[00385] Under an N_2 atmosphere, a mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol), 2-hydroxy-3-methylbutanoic acid (9 mg, 0.08 mmol), BOP (35 mg, 0.08 mmol), triethylamine (22 μL, 0.16 mmol) and DMF (0.2 mL) was stirred at room temperature for 1 hour. The reaction mixture was then purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 421.10 $(M+H)^+$ at 2.76 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00386] Method B

[00387] To a solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.78 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (217 μL, 1.56 mmol) followed by the addition of 2-hydroxy-3-methylbutanoic acid (120 mg, 1.0 mmol) and HATU (380 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one (230 mg, 70%). LC/MS: *m/z* 421.3 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.45 (m, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.39 (m, 2H), 6.95 (m, 2H), 4.79 (d, J = 7.2 Hz, 1H), 4.11 (dd, J = 7.0, 5.9 Hz, 1H), 3.87 (m, 8H), 2.52 (s, 3H), 1.91 (m, 1H), 0.88 (dd, J = 22.8, 6.7 Hz, 6H).

[00388] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one hydrochloride

[00389]

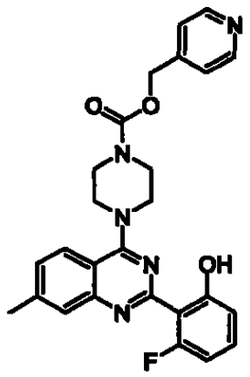


[00390] To a solution of 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one (230 mg, 0.54 mmol) in CH_2Cl_2 (3 mL) under an inert atmosphere was added ether (12 mL) followed by the dropwise addition of 2 M HCl solution in ether (0.27 mL, 0.54 mmol) which resulted in the formation of a precipitate which was stirred for an hour and then collected by vacuum filtration and dried to afford 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylbutan-1-one hydrochloride (205 mg, 83%). *LC/MS*: *m/z* 421.3 $(M+H)^+$ at 2.48 min (10%-99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.25 (d, J = 7.9 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.48 (t, J = 6.6 Hz, 2H), 7.04 (m, 2H), 4.10 (m, 5H), 3.79 (m, 4H), 2.53 (s, 3H), 1.90 (m, 1H), 0.87 (dd, J = 16.3, 6.7 Hz, 6H)

[00391] Example 114

[00392] (Pyridin-4-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

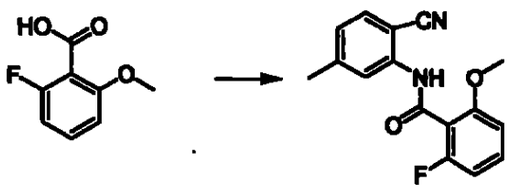
[00393]



[00394]

[00395] *N*-(2-Cyano-5-methyl-phenyl)-2-fluoro-6-methoxy-benzamide

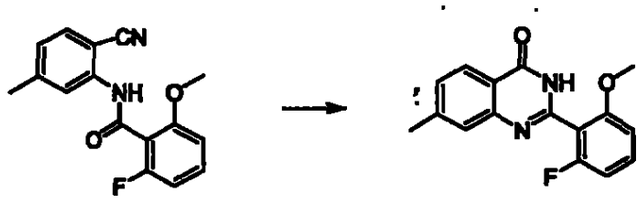
[00396]



[00397] 6-Fluoro-2-anisoic acid (110 g, 0.70 mol) was added in portions over 15 minutes to a mixture of thionyl chloride (230 ml, 3.2 mol), toluene (200 mL), and DMF (1 mL). The resulting mixture was stirred overnight at room temperature. The solution was evaporated to dryness and added dropwise to an ice-bath cooled solution of anthranilonitrile (92.5 g, 0.70 mol) in pyridine (200 mL). The dropping funnel was rinsed with a minimal amount of acetonitrile. The resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere and was subsequently poured into 2 L ice water. The resulting slurry was stirred vigorously for 1 hour. The formed solid was collected by filtration and was washed twice with water. The filter cake was dissolved in 2 L dichloromethane, and this solution was washed with 1 N aq. HCl (400 mL) and with saturated aq. NaCl (400 mL), dried over sodium sulfate, filtered, and evaporated to dryness to give *N*-(2-cyano-5-methylphenyl)-2-fluoro-6-methoxybenzamide (186 g, 93%) as a brownish solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 9.09 (s, 1H), 8.58 (s, 1H), 7.59–7.42 (m, 2H), 7.09–7.02 (m, 1H), 6.94–6.83 (m, 2H), 4.11 (s, 3H), 2.57 (s, 3H) ppm.

[00398] **2-(2-Fluoro-6-methoxy-phenyl)-7-methyl-3*H*-quinazolin-4-one**

[00399]



[00400] To a suspension of *N*-(2-cyano-5-methylphenyl)-2-fluoro-6-methoxybenzamide (31.5 g, 111 mmol) in ethanol (626 mL) was added 6 *M* aqueous NaOH solution (205 mL). After 10 minutes, 30% aqueous H_2O_2 (60 mL) was added, forming a slurry. The reaction was heated to reflux for 18 h and cooled to room temperature. NaOH (22.2 g, 0.56 mol) and 30% aqueous H_2O_2 (26 mL) were added, and the reaction was heated to reflux for six hours. The reaction cooled to room temperature, 30% aqueous H_2O_2 (45 mL) was added, and the reaction was heated to reflux for 18 h. The reaction was cooled to room temperature, NaOH (10 g, 0.25 mol) and 30% aqueous H_2O_2 (70 mL) were added, and the reaction was heated to reflux for six hours. The reaction was cooled to room temperature and poured over ice (800 mL). The pH was adjusted to 3–4 by addition of conc. HCl solution, and the precipitated off-white solid was filtered and washed with water (3 x 40 mL). The solid was dried under vacuum to provide 2-(2-fluoro-6-methoxy-phenyl)-7-methyl-3*H*-quinazolin-4-one (28 g, 89%).

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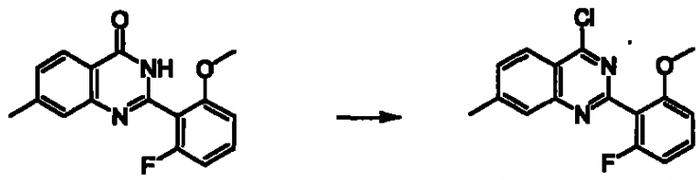
[00401] 4-Chloro-2-(2-fluoro-6-methoxyphenyl)-7-methylquinazoline

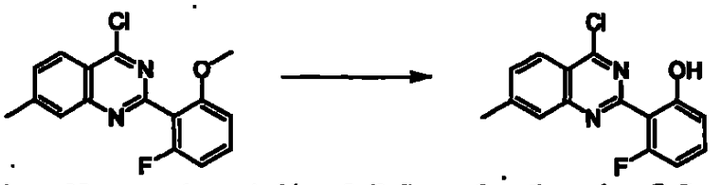
[00402]



[00403] Under an N_2 atmosphere, 2-(2-fluoro-6-methoxyphenyl)-7-methylquinazolin-4(3*H*)-one (20 g, 70.35 mmol) was suspended in benzene (300 mL), followed by the addition of *N,N*-dimethylaniline (26.8 mL, 211.05 mmol), then $POCl_3$ (13.11 mL, 140.7 mmol). The reaction was heated at reflux, and completion of product formation was observed after 1.5 h. After cooling to room temperature, the mixture was slowly poured over 1 liter of ice. The solution was then diluted with CH_2Cl_2, and the pH was adjusted to 7 using a saturated aqueous $NaHCO_3$ solution. The layers were partitioned, separated and extracted with CH_2Cl_2. All organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to a dark oil. The crude material was purified by silica gel chromatography using 75% CH_2Cl_2/ 25% hexanes to obtain 4-chloro-2-(2-fluoro-6-methoxyphenyl)-7-methylquinazoline as a yellow solid (18.82 g, 88%). LC/MS: *m/z* 302.9 $(M+H)^+$ at 3.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 7.60 (dd, J = 8.6, 1.5 Hz, 1H), 7.42–7.40 (m, 1H), 6.86–6.84 (m, 2H), 3.81 (s, 3H), 2.64 (s, 3H)

[00404] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol

[00405]

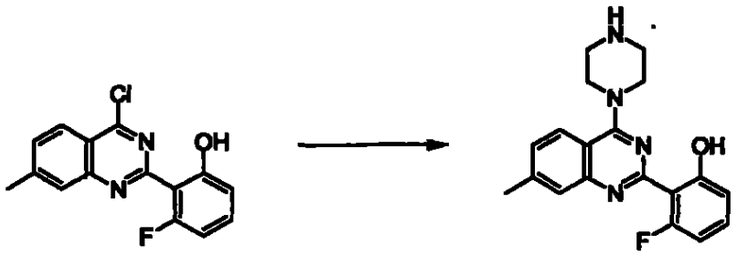


[00406] Under an N_2 atmosphere, 4-chloro-2-(2-fluoro-6-methoxyphenyl)-7-methylquinazolin (7.0 g, 23.12 mmol) was dissolved in CH_2Cl_2 (110 mL) and cooled to –50 °C internal temperature using a dry ice/acetone bath. A 1.0 M solution of BBr_3 in CH_2Cl_2 (115.6 mL, 115.6 mmol) was added dropwise via an addition funnel while maintaining the internal temperature at –50 °C. The reaction mixture was allowed to warm to 0 °C, and the reaction was complete after 1.5 h. It was then slowly quenched with saturated aqueous $NaHCO_3$ solution to

pH 7. After partitioning between CH_2Cl_2 and H_2O, the mixture was separated and the aqueous layer was twice extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to a brown solid. Purification via silica gel chromatography using 75% CH_2Cl_2/ 25% hexanes gave 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol as a yellow solid (4.37 g, 66%). LC/MS: *m/z* 289.1 $(M+H)^+$ at 3.71 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 7.60 (dd, J = 8.6, 1.5 Hz, 1H), 7.42–7.36 (m, 1H), 6.86–6.82 (m, 2H), 3.81 (s, 3H), 2.64 (s, 3H)

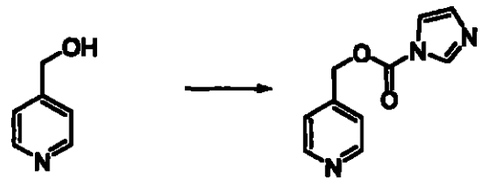
[00407] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol

[00408]



[00409] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (4.37 g, 15.14 mmol) was suspended in CH_2Cl_2 (65 mL) under an N_2 atmosphere and placed into an ice water bath. To this solution was added a solution of piperazine (4.00 g, 45.42 mmol) and triethylamine (4.2 mL, 30.28 mmol) in CH_2Cl_2 (15 mL) in one portion. After stirring the reaction for 30 minutes, it was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted twice more with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated to a bright yellow solid which was purified via silica gel chromatography using a 95%/5% mixture of CH_2Cl_2/MeOH to afford 3-fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (4.32 g, 85%) as a bright yellow solid. LC/MS: *m/z* 339.3 $(M+H)^+$ at 1.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 7.92 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.39–7.30 (m, 2H), 6.78 (d, J = 8.3 Hz, 1H), 6.74–6.69 (m, 1H), 3.83 (t, J = 4.8 Hz, 4H), 2.88 (t, J = 4.9 Hz, 4H).

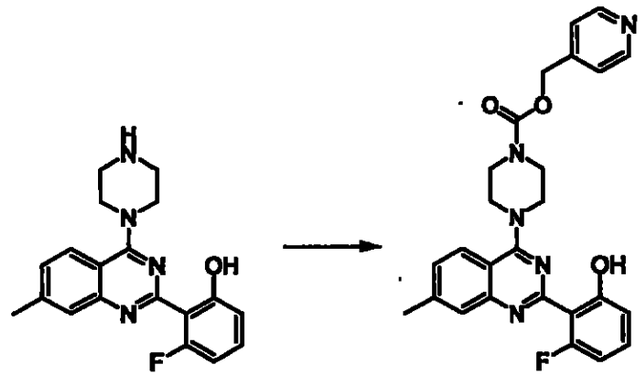
[00410] (Pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate



[00411]

[00412] A solution of (pyridin-4-yl)methanol (2.0 g, 18.3 mmol) and di(1*H*-imidazol-1-yl)methanone (5.94 g, 36.6 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was quenched with water, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (3 g, 81%). LC/MS: *m/z* 204.3 $(M+H)^+$ at 0.38 min (v). ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, J = 4.4, 1.6 Hz, 2H), 8.20 (t, J = 0.9 Hz, 1H), 7.47 (t, J = 1.5 Hz, 1H), 7.34 (dd, J = 4.4, 1.6 Hz, 2H), 7.11 (dd, J = 1.6, 0.8 Hz, 1H), 5.45 (s, 2H).

[00413] **(Pyridin-4-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**



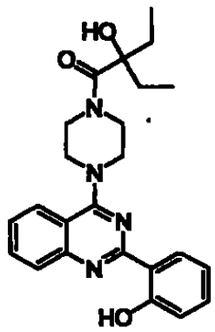
[00414]

[00415] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.15 mmol), (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (53 mg, 0.26 mmol) and triethylamine (30.4 mg, 0.3 mmol) were added into a tube, followed by the addition of DMSO (1 mL). The mixture was stirred at room temperature for 18 h and then filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) giving (pyridin-4-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate. LC/MS: *m/z* 474.30 (M+H)+ at 1.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00416] Example 115

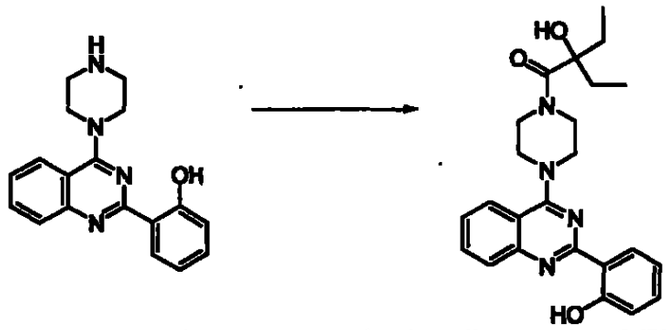
[00417] 2-Ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00418]



[00419] 2-Ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00420]



[00421] To a solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added 2-ethyl-2-hydroxybutanoic acid (39.30 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 421.3 $(M+H)^+$ at 2.51 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00422] Example 116

[00423] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

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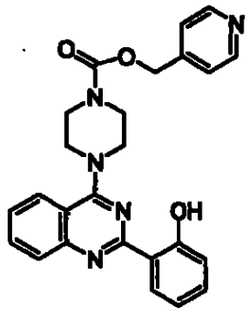
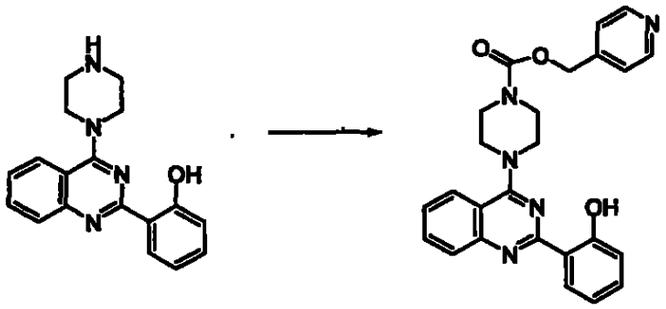
[00424]



[00425] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00426]

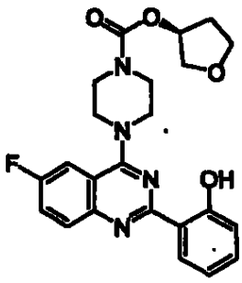


[00427] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (67 mg, 0.32 mmol) and triethylamine (45 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 442.50 $(M+H)^+$ at 1.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00428] Example 117

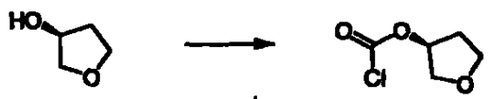
[00429] (*S*)-Tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl) quinazolin-4-yl)piperazine-1-carboxylate

[00430]



[00431] **(*S*)-Tetrahydrofuran-3-yl chloroformate**

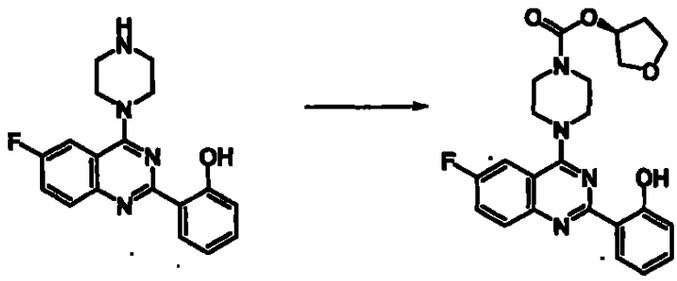
[00432]



[00433] A stirred solution of (*S*)-tetrahydrofuran-3-ol (7.9 g, 90 mmol) in anhydrous CH_2Cl_2 (50 mL) under an N_2 atmosphere was cooled in an ice bath, and a 20% solution of phosgene in toluene (134 mL, 270 mmol) was slowly added. The reaction was allowed to warm to room temperature overnight, and the solvent was removed under vacuum to afford (*S*)-tetrahydrofuran-3-yl chloroformate (12.1 g, 85%) as a clear liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 5.42–5.39 (m, 1H), 4.01–3.84 (m, 4H), 2.31–2.13 (m, 2H).

[00434] **(*S*)-Tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl) quinazolin-4-yl)piperazine-1-carboxylate**

[00435]



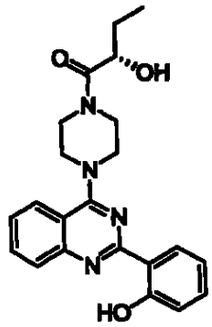
[00436] To a solution of 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol) in DMF (1 mL) was added triethylamine (22 μL, 0.16 mmol) followed by the dropwise addition of (*S*)-tetrahydrofuran-3-yl chloroformate (12 mg, 0.08 mmol) at 0 °C. The reaction was complete immediately after the addition of the chloroformate. Purification using

reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. *LC/MS*: *m/z* 439.5 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00437] Example 118

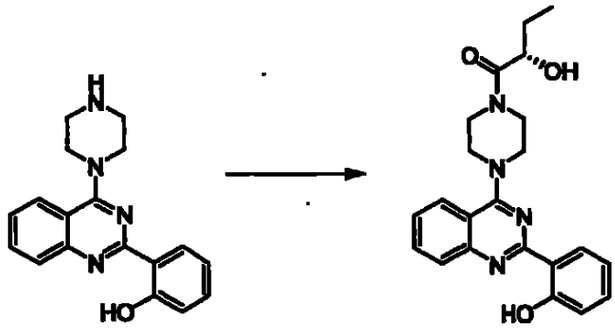
[00438] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00439]



[00440] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00441]



[00442] Method A

[00443] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*R*)-2-hydroxybutanoic acid (31 mg, 0.297 mmol), followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-(4-(2-(2-

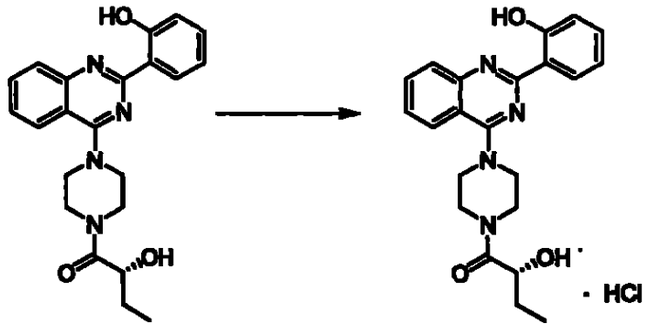
hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 421.30 $(M+H)^+$ at 2.51 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00444] Method B

[00445] To a solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.82 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (227 μL, 1.63 mmol) followed by the addition of (*R*)-2-hydroxybutanoic acid (110 mg, 1.06 mmol) and HATU (380 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one (280 mg, 88%). LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.47 (m, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.89 (m, 2H), 7.57 (m, 1H), 7.40 (m, 1H), 6.96 (m, 2H), 4.92 (d, *J* = 7.1 Hz, 1H), 3.88 (m, 8H), 1.67 (m, 1H), 1.51 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

[00446] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride**

[00447]



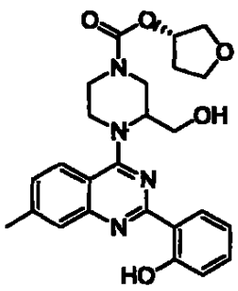
[00448] To a solution of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one (280 mg, 0.71 mmol) in CH_2Cl_2 under an N_2 atmosphere was added a 2 M HCl solution in ether (0.355 mL, 0.71 mmol), followed by the addition of ether which resulted in the formation of precipitate which was stirred for an hour and then filtered and dried to afford (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride (272 mg, 90%). LC/MS: *m/z* 393.1 $(M+H)^+$ at 2.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.27 (dd, *J* = 7.9, 1.6 Hz,

1H), 8.19 (d, J = 8.4 Hz, 1H), 7.96 (m, 2H), 7.65 (m, 1H), 7.48 (m, 1H), 7.04 (m, 2H), 4.26 (dd, J = 7.7, 4.8 Hz, 1H), , 4.03 (m, 4H), 3.79 (m, 5H), 1.65 (m, 1H), 1.50 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H).

[00449] Example 119

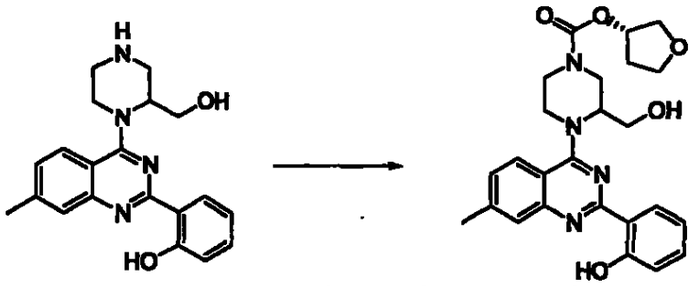
[00450] (*S*)-3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid tetrahydro-furan-3-yl ester

[00451]



[00452] (*S*)-3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid tetrahydro-furan-3-yl ester

[00453]

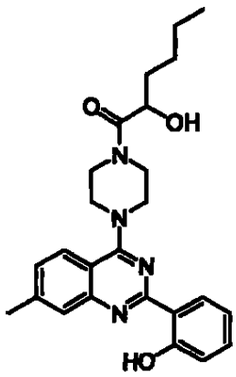


[00454] To 2-[4-(2-hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (69.2 mg, 0.19 mmol) in 650 µL of CH_2Cl_2 at 0 °C was added (*S*)-tetrahydro-furan-3-ol-chloroformate (26.8 mg, 0.17 mmol), followed by triethylamine (30 µL, 0.22 mmol). The reaction mixture was stirred for an hour and then diluted with 5 mL of CH_2Cl_2 and 5 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to purification using 30–100% EtOAc–hexanes to give the desired product. LC/MS: *m/z* 465.2 $(M+H)^+$ at 2.5 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00455] Example 120

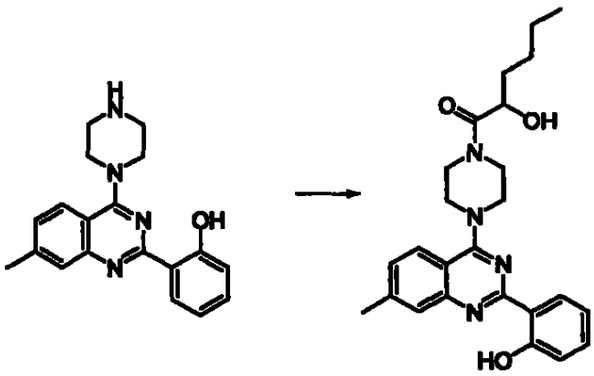
[00456] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00457]



[00458] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00459]



[00460] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxyhexanoic acid (37.5 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one as the TFA salt. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.65 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00461] Example 121

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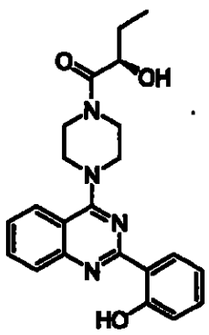
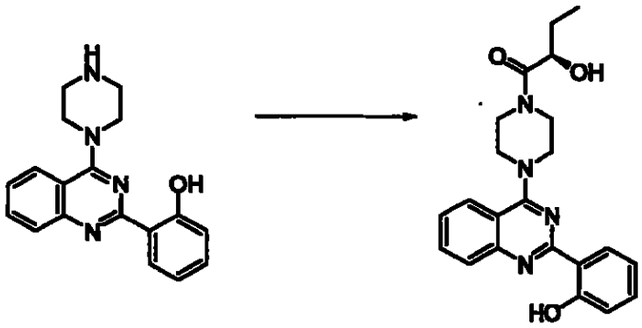
[00462] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00463]



[00464] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00465]

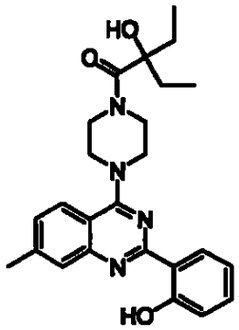


[00466] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*R*)-2-hydroxybutanoic acid (31 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00467] Example 122

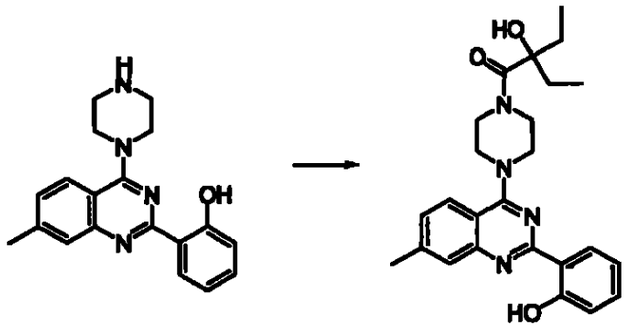
[00468] 2-Ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00469]



[00470] 2-Ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00471]



[00472] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-ethyl-2-hydroxybutanoic acid (37.5 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-ethyl-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00473] Example 123

[00474] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-7-carboxylic acid

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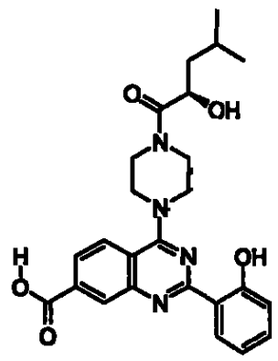
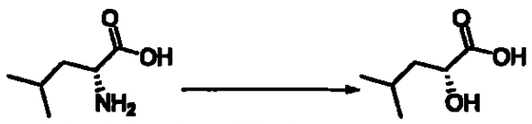
[00475]



[00476] (*R*)-α-hydroxyisocaproic acid

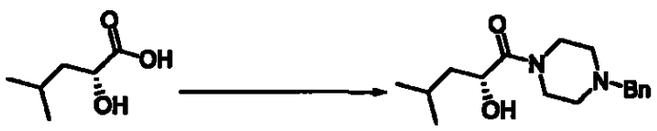
[00477]



[00478] To a cooled solution (0–5 °C) of D-leucine (200 g, 1.5 mol) in sulfuric acid (3 L, 1 M) was added dropwise a solution of sodium nitrite (240 g, 3.5 mol) in water (1 L) while maintaining the temperature between 0–5 °C. The reaction mixture was stirred at room temperature overnight. The solution was saturated with sodium chloride and extracted with *tert*-butyl methyl ether (3x). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. (*R*)-α-hydroxyisocaproic acid was isolated as a white solid in a yield of 67% (132 g).

[00479] 1-(4-Benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one

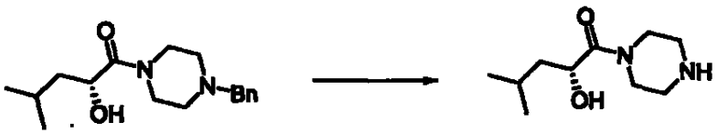
[00480]



[00481] To a cooled solution (0–5 °C) of (*R*)-α-hydroxyisocaproic acid (64.5 g, 0.5 mol), 1-benzylpiperazine (88 g, 0.5 mol) and triethylamine (71 ml, 0.5 mol) in CH_2Cl_2 (850 ml) was added in portions HOBt (68 g, 0.5 mol) and EDCI·HCl (96 g, 0.5 mol). The reaction mixture was stirred at room temperature overnight. The organic layer was washed with water (3x) and once with brine, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. Crude

1-(4-benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one (132 g, 91%) was used in the next step without further purification

[00481] 2-Hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one



[00482] To a solution of 1-(4-benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one (132 g) in methanol (1 L) was added Pd/C (20 g,10% weight Pd on carbon). The reaction mixture was stirred at room temperature overnight under an atmosphere of hydrogen. The reaction mixture was filtered through Celite, and the solvent was removed *in vacuo*. 2-Hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one was obtained as an oil (68 g, 74%).

[00483] 1,2,3,4-Tetrahydro-2,4-dioxoquinazoline-7-carboxylic acid

[00484] To a stirring mixture of dimethyl 2-aminobenzene-1,4-dioate (10.5 g, 50 mmol) and AcOH (3.4 mL, 60 mmol) in H_2O (200 mL) was added KOCN (8.1 g, 100 mmol). The reaction mixture was heated at 100 °C for 3 h. After cooling in an ice bath, NaOH (24 g, 600 mmol) was slowly added to the mixture and stirred for another 3 h at room temperature. Acidification with concentrated HCl resulted in formation of a yellow solid which was filtered, washed with water and dried under vacuum (8.3 g). NMR data showed that the solid consisted of a 3:1 mixture of the desired 1,2,3,4-tetrahydro-2,4-dioxoquinazoline-7-carboxylic acid and a side product. This mixture was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.98 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.67 (dd, J = 8.2, 1.4 Hz, 1H).

[00485] 2,4-Dichloroquinazoline-7-carboxylic acid

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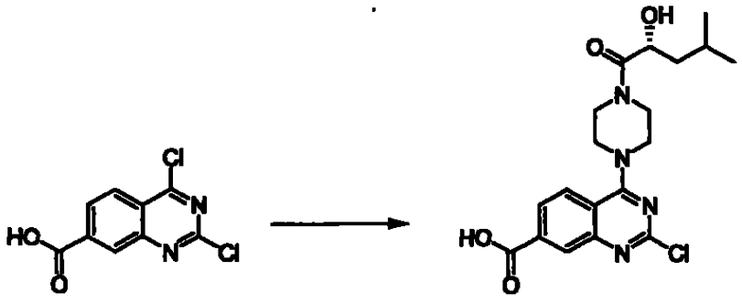
[00490] A mixture of 1,2,3,4-tetrahydro-2,4-dioxoquinazoline-7-carboxylic acid (1.0 g, 4.9 mmol), $POCl_3$ (10 mL) and dimethylaniline (0.5 mL, 3.94 mmol) was heated at 90 °C for 3 h. After cooling and pouring the reaction mixture over ice, it was extracted with EtOAc. The combined extracts were washed with water, dried over Na_2SO_4 and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 provided 2,4-dichloroquinazoline-7-carboxylic acid as a yellow solid (0.45 g, 38%). ^1H NMR (400 MHz, DMSO-d6) δ 8.46 (d, J = 1.4 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.30 (dd, J = 8.6, 1.5 Hz, 1H); LC/MS: *m/z* 243.1 $(M+H)^+$ at 2.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00491] **2-Chloro-4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-quinazoline-7-carboxylic acid**

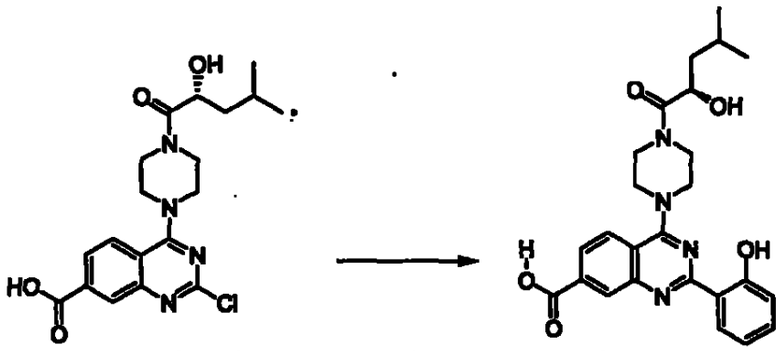
[00492]



[00493] To a solution of 2,4-dichloroquinazoline-7-carboxylic acid (0.45 g, 1.9 mmol) in CH_2Cl_2 (20 mL) was added (*R*)-2-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one (0.37 g, 1.9 mmol) and triethylamine (0.52 mL, 3.7 mmol). The reaction mixture was stirred overnight at room temperature and then purified via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 to obtain 2-chloro-4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-quinazoline-7-carboxylic acid (0.58 g, 77%). LC/MS: *m/z* 407.3 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00494] **4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-7-carboxylic acid**

[00495]

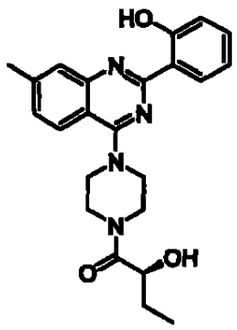


[00496] A mixture of 2-chloro-4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-quinazoline-7-carboxylic acid (114 mg, 0.28 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (88 μL, 0.42 mmol) $Pd(dppf)Cl_2$ (14 mg, 0.017 mmol) and K_2CO_3 (155 mg, 1.1 mmol) in DMF (4 mL) and H_2O (1 mL) was heated in a sealed microwave vial at 170 °C for 6 minutes. After filtration and evaporation of the solvents, the mixture was purified using preparative HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-7-carboxylic acid as the TFA salt. LC/MS: *m/z* 465.3 $(M+H)^+$ at 2.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00497] Example 124

[00498] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00499]



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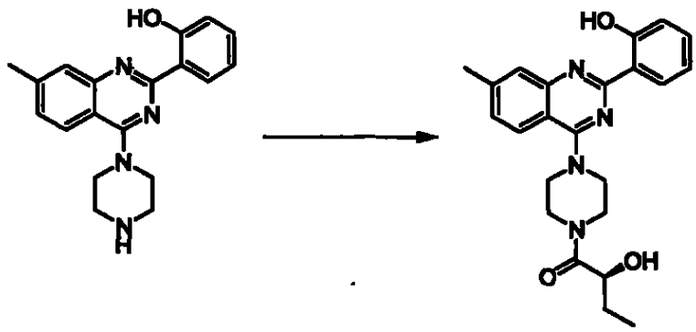
[00500] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00501]

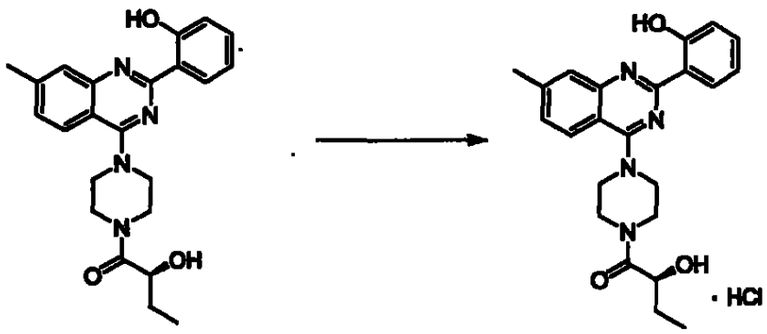


[00502] Method A: A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to (*S*)-2-hydroxybutanoic acid (31 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00503] Method B: To a solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.78 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (217 μL, 1.56 mmol) followed by the addition of (*S*)-2-hydroxybutanoic acid (105 mg, 1.0 mmol) and HATU (380 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one (300 mg, 95%). LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.45 (m, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.39 (m, 2H), 6.95 (m, 2H), 4.92 (d, J = 7.0 Hz, 1H), 4.28 (q, J = 6.5 Hz, 1H), 3.89 (m, 8H), 2.52 (s, 3H), 1.67 (m, 1H), 1.51 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H)

[00504] **(*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride**

[00505]

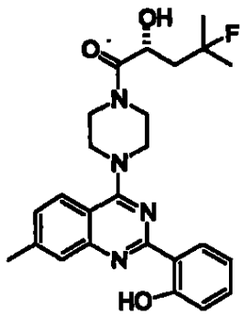


[00506] To a solution of (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one (300 mg, 0.73 mmol) in CH_2Cl_2 was added a 2 M HCl solution in ether (0.365 mL, 0.73 mmol), followed by the addition of ether until the salt precipitated out, which was stirred for an hour, collected by vacuum filtration and dried to afford (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride (270 mg, 84%). LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.26 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.73 (s, 1H), 7.47 (m, 2H), 7.03 (m, 2H), 4.26 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.08 (m, 4H), 3.79 (m, 4H), 2.53 (s, 3H), 1.65 (m, 1H), 1.50 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H).

[00507] Example 125

[00508] **(*R*)-4-Fluoro-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one**

[00509]



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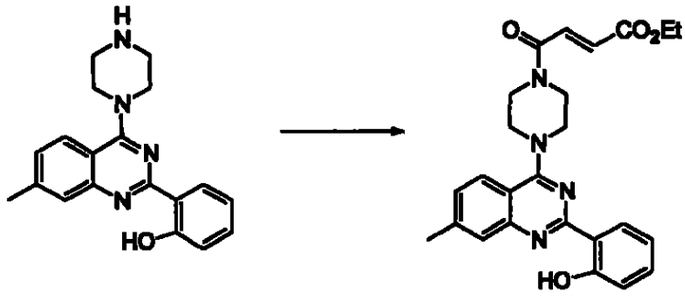
[00510] **4-{4-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-but-2-enoic acid ethyl ester**

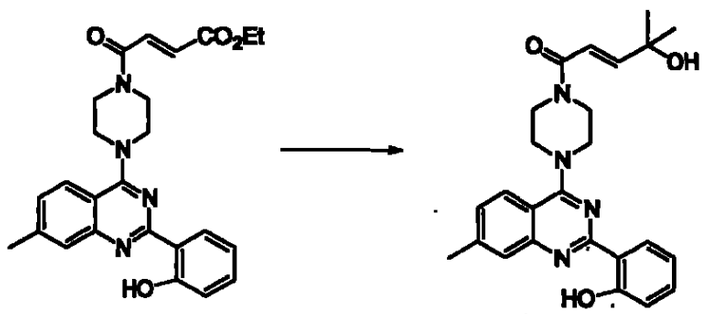
[00511]



[00512] To 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (787 mg, 2.46 mmol) in 8 mL of CH_2Cl_2 at room temperature was added sequentially but-2-enedioic acid monoethyl ester (531 mg, 3.69 mmol), triethylamine(686 μL, 4.92 mmol), BOP (1.63 g, 3.69 mmol). The reaction mixture was stirred for 20 min and diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was subjected to purification by normal phase LC using 10–100% EtOAc–hexanes to give 4-{4-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-but-2-enoic acid ethyl ester (1.00 g, 91% yield). LC/MS: *m/z* 447.3 $(M+H)^+$ at 2.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00513] **4-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1- one**

[00514]

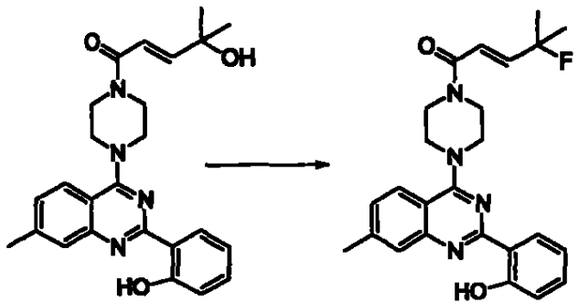


[00515] To 4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-but-2-enoic acid ethyl ester (655 mg, 1.47 mmol) in 2 mL of diethyl ether at –20 °C was added methyl magnesium bromide (8.4 mL, 11.7 mmol, 1.4 M THF/Toluene), and the reaction mixture

was allowed to warm to 0 °C over 15 minutes The mixture was diluted with 10 mL of water and 15 mL of CH_2Cl_2. The resulting emulsion was filtered, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the alcohol. LC/MS: *m/z* 433.5 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00516] 4-Fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1-one

[00517]



[00518] To 4-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1- one (330 mg, 0.76 mmol) at –78 °C in 3 mL of CH_2Cl_2 was added (diethylamino)sulfur trifluoride (185 mg, 1.15 mmol). The reaction mixture was stirred –78 °C for 2.5 h. The reaction mixture was diluted with 10 mL of water and 10 mL of CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was subjected to purification by normal phase LC using 10–100% EtOAc–hexanes to give 4-fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1-one (133 mg, 40% yield). *LC/MS*: *m/z* 435.4.3 $(M+H)^+$ at 2.92 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00519] 4-Fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one

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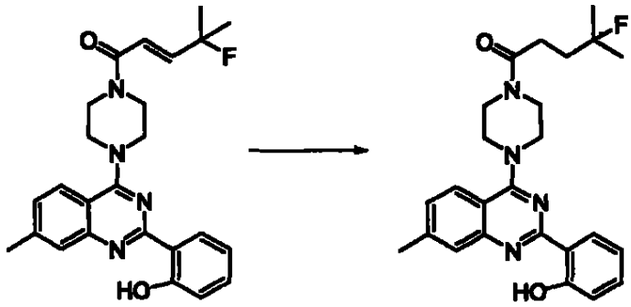
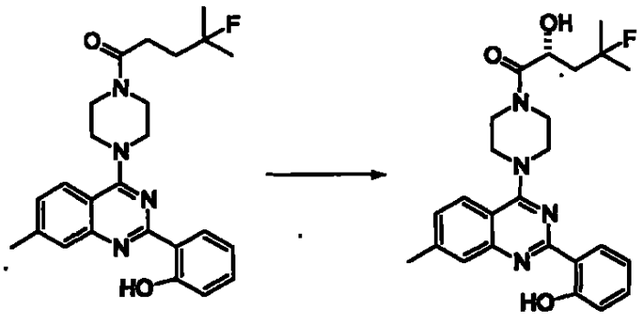


[00520]

[00521] To 4-fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pent-2-en-1-one (228 mg) in 1.5 mL of methanol was added Pd/C (34 mg, 10% weight Pd on carbon), and the reaction mixture was hydrogenated with a hydrogen balloon for 1 h. The resulting mixture was filtered through Celite, and the solvent was removed to give 4-fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one. LC/MS: *m/z* 437.4 $(M+H)^+$ at 2.86 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00522] **(*R*)-4-Fluoro-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one**

[00523]



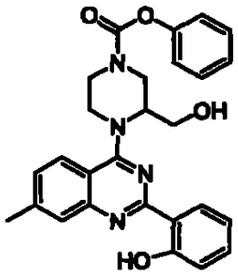
[00524] To 4-fluoro-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one (225 mg, 0.53 mmol) in 500 μL of THF was added a 2.7 M LDA solution (0.8 mL, 2.1 mmol) at –78 °C. The resulting solution was stirred at –78 °C for 25 min, and then (1*R*)-(-)-(10-camphorsulfonyl)oxaziridine (361 mg, 1.6 mmol) in 1.5 mL of THF was added slowly. The reaction mixture was allowed to warm to –45 °C over 30 min, and then diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by preparative reverse

phase HPLC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-4-fluoro-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one as the TFA salt. LC/MS: *m/z* 453.4 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00525] Example 126

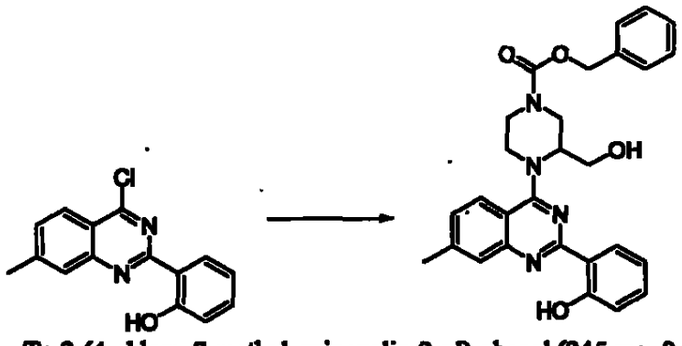
[00526] 3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid phenyl ester

[00527]



[00528] 3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester

[00529]



[00530] To 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol (245 mg, 0.91 mmol) in 3.0 mL of CH_2Cl_2 was added 3-hydroxymethyl-piperazine-1-carboxylic acid benzyl ester (226 mg, 0.58 mmol) and triethylamine (190 μL, 1.37 mmol). The reaction mixture was stirred for 12 hours at room temperature, and additional 3-hydroxymethyl-piperazine-1-carboxylic acid benzyl ester (100 mg, 0.4 mmol) and triethylamine (200 μL, 1.4 mmol) was added, and the reaction mixture was heated at 40 °C for 6 h. The reaction mixture was cooled, and diluted with 5 mL of CH_2Cl_2

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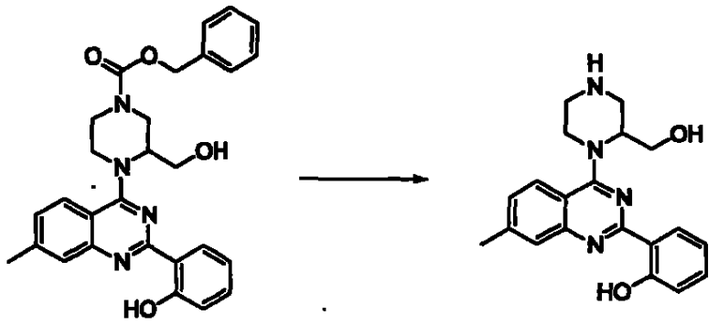
and 5 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography eluting with 20–85% EtOAc/hexanes to give 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester(216 mg, 65 %). LCMS: *m/z* 485 $(M+H)^+$ at 3.03 min (10%-99% CH_3CN/H_2O)

[00531] **2-[4-(2-Hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol**

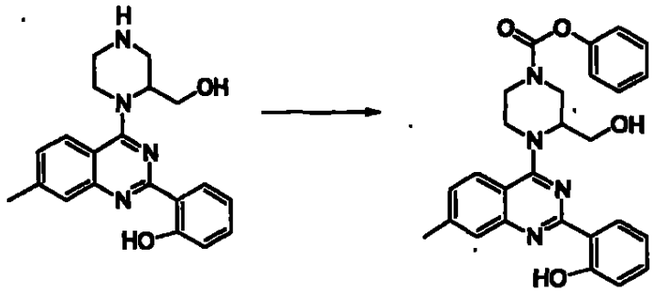
[00532]



[00533] To 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester (200 mg, 0.41 mmol) in 1.7 mL of methanol was added 39 mg of Pd/C (10% wt Pd on carbon). The reaction mixture was stirred under a hydrogen atmosphere for 3 h. The mixture was filtered through Celite, and the solvent was removed to give 2-[4-(2-hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol. LCMS: *m/z* 351.2 $(M+H)^+$ at 2.11 min (10%-99% CH_3CN/H_2O).

[00534] **3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid phenyl ester**

[00535]

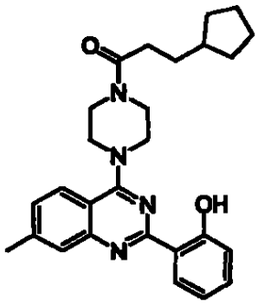


[00536] To 2-[4-(2-hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (31.9 mg, 0.091 mmol) in 300 μL of CH_2Cl_2 was added at 0 °C sequentially triethylamine (13.9 μL) and phenyl chloroformate (14.3 mg, 0.091 mmol). The reaction mixture was stirred for 30 min and was warmed to room temperature and stirred for an additional 40 minutes At the end of this period, the solvent was removed, and the residue was dissolved in DMSO and purified by preparative reverse phase HPLC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) as eluent to give 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid phenyl ester as the TFA salt. LC/MS: *m/z* 471.2 (M+H)+ at 2.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00537] Example 127

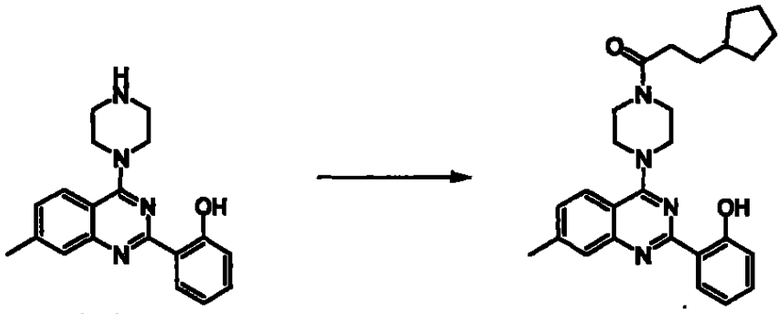
[00538] 3-Cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[00539]



[00540] 3-Cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[00541]



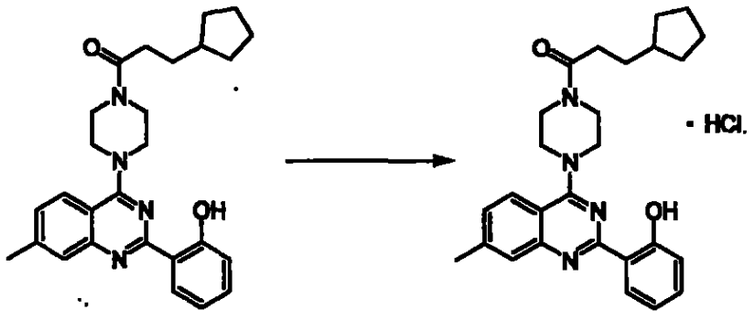
[00542] Method A

[00543] To 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (53 mg, 0.17 mmol) was added sequentially 3-cyclopentylpropanoyl chloride (29 mg, 0.19 mmol) in 550 μL of CH_2Cl_2 and triethylamine (28 μL, 0.2 mmol). The mixture was stirred at 0 °C for 20 minutes After adding H_2O and CH_2Cl_2, the phases were separated, and the organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification using preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 445.5 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00544] Method B

[00545] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (200 mg, 0.62 mmol) in CH_2Cl_2 (6.0 mL) was stirred under an N_2 atmosphere. Then triethylamine (170 μL, 1.24 mmol) was added, and the reaction was cooled to –10 to –20 °C. After adding 3-cyclopentylpropanoyl chloride (96 μL in 600 μL THF, 0.62 mmol), the reaction mixture was stirred for 30 minutes. CH_2Cl_2 was added, and the organic phase was washed 2x with H_2O, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2: hexanes gave 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one (240 mg, 86%). LC/MS: *m/z* 445.50 $(M+H)^+$ at 3.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.45 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.39 (m, 2H), 6.95 (m, 2H), 3.95 (dd, *J* = 19.9, 5.6 Hz, 4H), 3.74 (m, 4H), 2.52 (s, 3H), 2.38 (t, *J* = 7.8 Hz, 2H), 1.76 (m, 3H), 1.55 (m, 6H), 1.16 (m, 2H).

[00546] **3-Cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one hydrochloride**

[00547] 

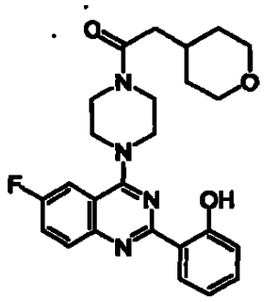
Under an N_2 atmosphere, a 1 M HCl solution in diethyl ether (0.54 mL, 0.54 mmol) was added dropwise to a stirring solution of 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one (240 mg, 0.54 mmol) in CH_2Cl_2 (20 mL). After 10 min, ether was added until a precipitate formed. The solid was collected by filtration and dried under vacuum to give 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one hydrochloride (230 mg, 88%). LC/MS: *m/z* 445.30 $(M+H)^+$ at 3.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.26 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.78 (s, 1H), 7.50–7.46 (m, 2H), 7.09 (d, J = 8.1 Hz, 1H), 7.04–7.00 (m, 1H), 4.15–4.11 (m, 4H), 3.79–3.74 (m, 4H), 2.54 (s, 3H), 2.37 (t, J = 7.7 Hz, 2H), 1.82–1.74 (m, 3H), 1.60–1.45 (m, 6H), 1.12–1.08 (m, 2H)

[00548]

[00549] Example 128

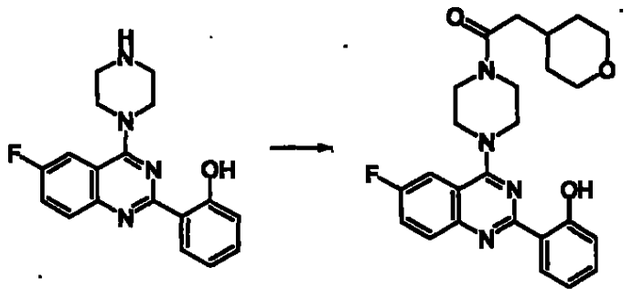
[00550] 1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanone

[00551]



[00552] 1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanone

[00553]



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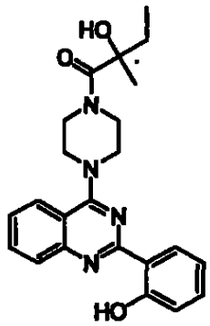
[00554] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.077 mmol), 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (14.3 mg, 0.10 mmol), triethylamine (22μL, 0.154 mmol), and HATU (38 mg, 0.10 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanone. LC/MS: *m/z* 451.5 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00555] Example 129

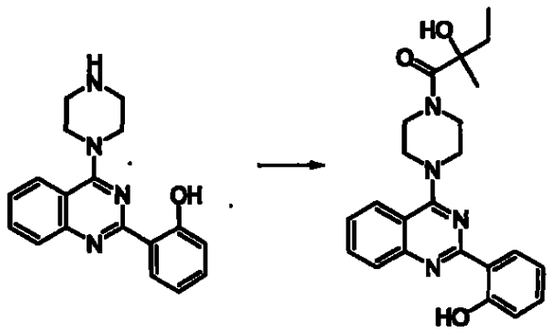
[00556] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one

[00557]

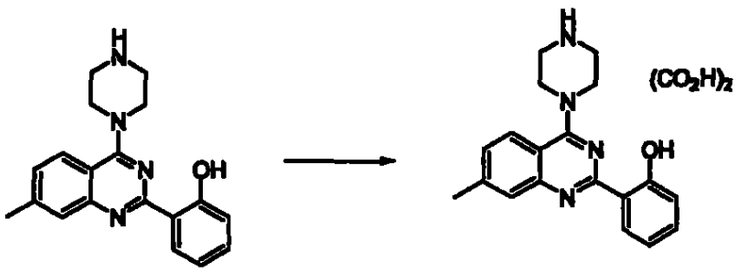


[00558] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one

[00559]



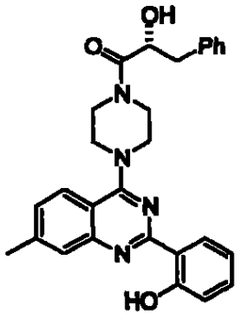
[00560] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-hydroxy-2-methylbutanoic acid (39.3 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL) and a solution of HATU (113 mg) in 0.5 mL



[00557] DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00558] Example 130

[00559] (*R*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone

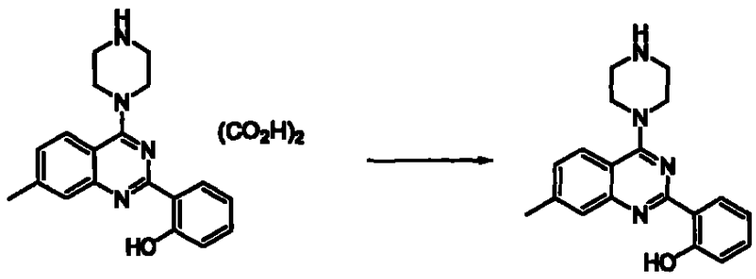


[00560] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol, oxalate salt

[00561] To 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (30.6 g, 95.4 mmol) in 900 mL CH_2Cl_2 was added oxalic acid (9.45 g, 105 mmol, 1.1 eq.) dissolved in 36 mL of methanol. The resulting cloudy solution was stirred for 3h and the resulting solid was filtered, washed with hexanes, and dried to give 29.3 g (75 %) the oxalate salt of 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol. LC/MS: *m/z* 321.2 $(M+H)^+$ at 2.36 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00562] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol

325

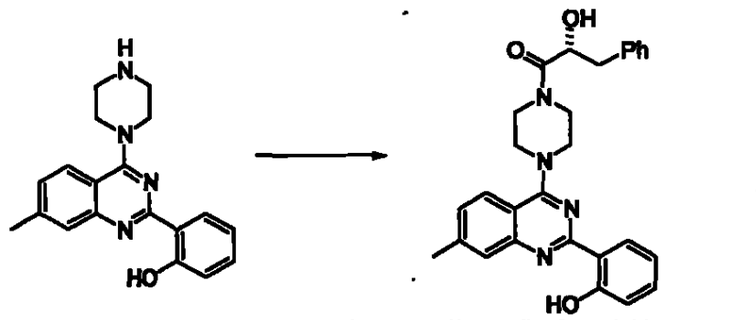


[00568]

[00569] To the oxalate salt of 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (1.32 g, 3.2 mmol) in 10 mL of CH_2Cl_2 was added triethylamine (2.2 mL, 16.0 mmol) at room temperature. The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with 10 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol as an oil which was used without further purification.

[00570] **(*R*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone**

[00571]

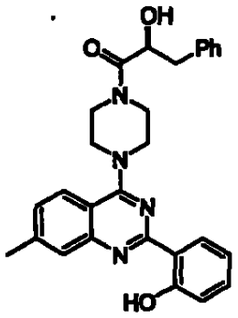


[00572] To 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (64 mg, 0.19 mmol) in 600 μL of CH_2Cl_2 was added sequentially 3-(*R*)-phenyl lactic acid (35 mg, 0.21 mmol), BOP (93 mg, 0.21 mmol), and triethylamine (27.7 μL, 0.2 mmol) at room temperature. The reaction mixture was stirred for 1.5 h, diluted with 10 mL of methylene chloride, and washed with water (2 x 10 mL). The solvent was removed under reduced pressure to give an oil which was purified by normal phase LC (35%–100% EtOAc/ hexanes) to give (*R*)-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone. LC/MS: *m/z* 469.3 $(M+H)^+$ at 2.87 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00573] Example 131

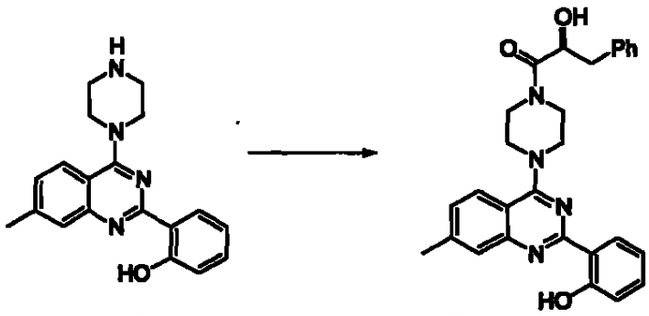
[00574] (*S*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone

[00575]



[00576] (*S*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone

[00577]



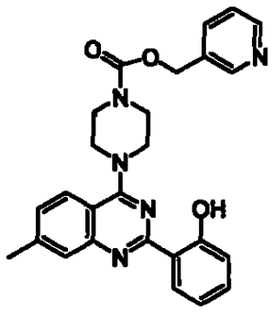
[00578] To 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (79.9 mg, 0.25 mmol) in 800 μL of CH_2Cl_2 was added sequentially 3-(*R*)-phenyl lactic acid(41.4 mg, 0.25 mmol), BOP(110 mg, 0.25 mmol), triethylamine (34.7 μL, 0.25 mmol) at room temperature. The reaction mixture was stirred for 1.5 h, diluted with 10 mL of methylene chloride, and washed with water (2 x 10 mL). The solvent was removed under reduced pressure to give an oil which was purified by normal phase LC (35%-100% EtOAc/hexanes) to give (*S*)-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone. LC/MS: *m/z* 469.4 $(M+H)^+$ at 2.88 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00579] Example 132

326

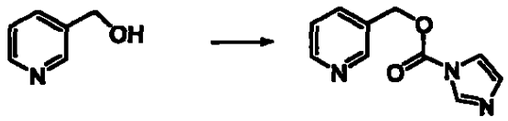
[00580] (Pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00581]



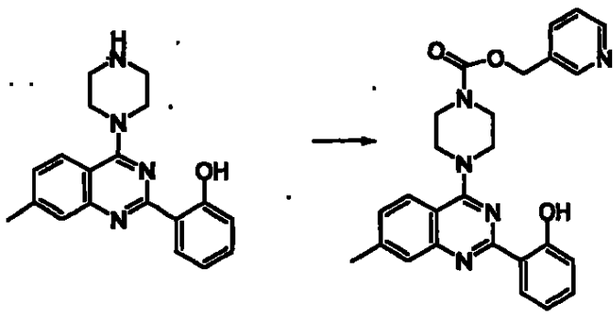
[00582] (Pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate

[00583]



[00584] A solution of (pyridin-3-yl)methanol (2 g, 18.32 mmol) and di(1*H*-imidazol-1-yl)methanone (5.94 g, 36.65 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was washed with water, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (3 g, 81%). *LC/MS*: *m/z* 204.1 $(M+H)^+$ at 0.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.9 Hz, 1H), 8.68 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.16 (s, 1H), 7.81 (m, 1H), 7.44 (s, 1H), 7.38 (m, 1H), 7.09 (s, 1H), 5.46 (s, 2H).

[00585] (Pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate



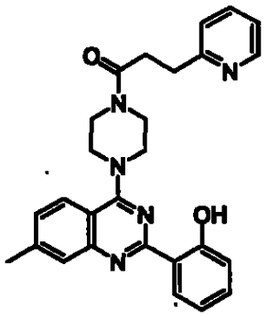
[00586]

[00587] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (67 mg, 0.32 mmol), and triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (pyridin-3-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. *LC/MS*: *m/z* 456.5 $(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00588] Example 133

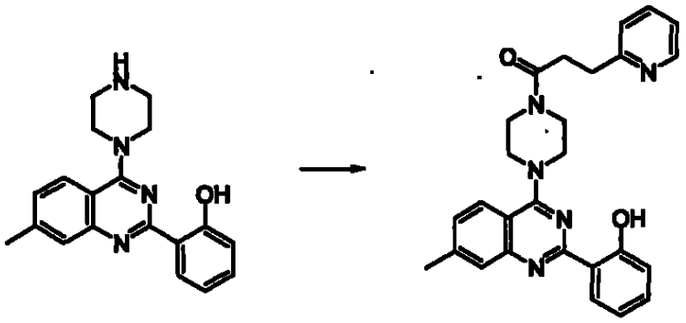
[00589] **1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(pyridin-2-yl)propan-1-one**

[00590]



[00591] **1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(pyridin-2-yl)propan-1-one**

[00592]



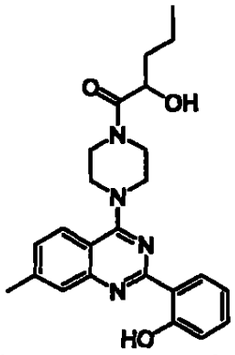
327

[00593] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (0.5 mL) was added to 3-(pyridin-2-yl)propanoic acid (21.23 mg, 0.14 mmol). Triethylamine (25 μL) was added, followed by a solution of HATU (45 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(pyridin-2-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 454.3 $(M+H)^+$ at 1.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00594] Example 134

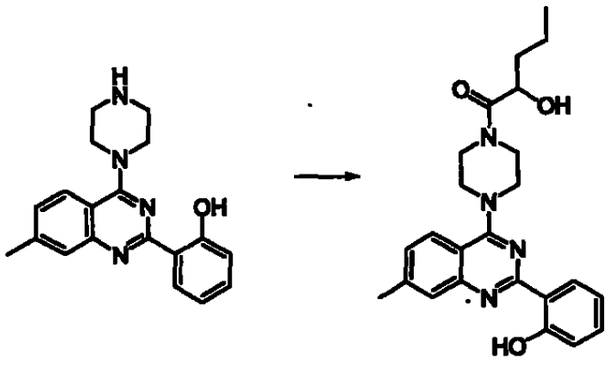
[00595] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentan-1-one

[00596]



[00597] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentan-1-one

[00598]

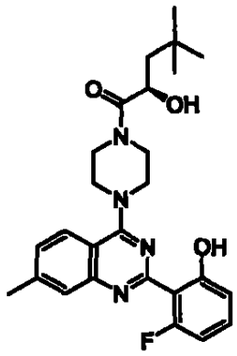


[00599] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxypentanoic acid (33.6 mg, 0.28 mmol). It was followed by the addition of triethylamine (61 μL), and a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentan-1-one as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00600] Example 135

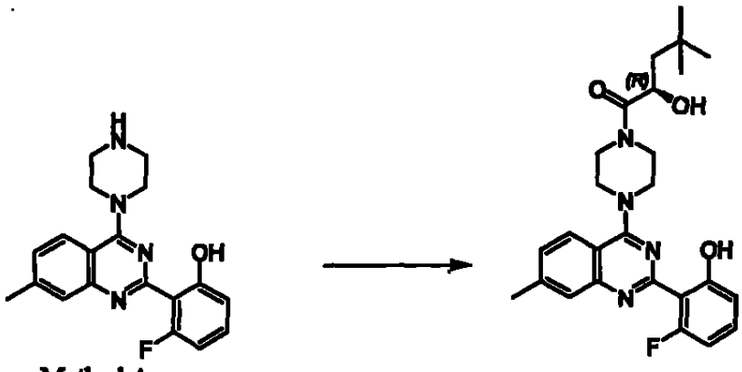
[00601] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one

[00602]



[00603] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one

[00604]



[00605] Method A

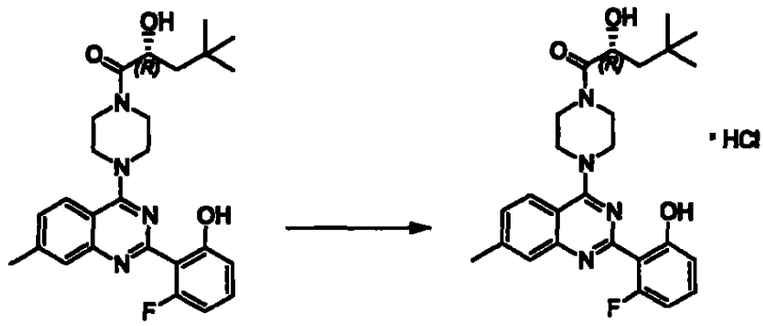
[00606] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.15 mmol) was placed in a tube charged with a stir bar, (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (26 mg, 0.18 mmol) in1 ml of DMF, and triethylamine (30 mg, 41 µL, 0.29 mmol), and the tube was cooled to 0 °C. HATU (68 mg, 0.18 mmol) was added, and the reaction was stirred at 0 °C for 10 minutes and then allowed to warm to room temperature. After 40 minutes, the reaction was filtered, and purified by reverse phase HPLC to give the TFA salt of (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one. *LC/MS*: *m/z* 467.1 $(M+H)^+$ at 2.59 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00607] Method B

[00608] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.74 mmol) was suspended in anhydrous DMF (5 mL) and cooled to 0 °C (internal temperature). Under an N_2 atmosphere, (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (118.4 mg, 0.81 mmol) was added followed by triethylamine (0.207 mL, 1.48 mmol). To this stirring solution was added HATU (337 mg, 0.888 mmol). After the complete addition of HATU, the mixture was allowed to warm to 10 °C. After 45 min the reaction was complete, and it was quenched with an equal portion of ice water. A yellow precipitate formed which was collected by vacuum filtration, dissolved in CH_2Cl_2, and the CH_2Cl_2 solution was desiccated with Na_2SO_4, filtered, and concentrated to a viscous yellow-orange oil. The crude material was purified via silica gel chromatography using 70% CH_2Cl_2/hexanes (1:1) and 30% EtOAc to afford (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one as a yellow solid (171 mg, 50%). *LC/MS*: *m/z* 467.1 $(M+H)^+$ at 2.63 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.02 (d, *J* = 8.6 Hz, 1H), 7.69 (s, 1H), 7.43 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.37–7.32 (m, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.76–6.71 (m, 1H), 4.87 (d, *J* = 7.2 Hz, 1H), 4.47–4.43 (m, 1H), 4.01–3.75 (m, 8H), 2.52 (s, 3H), 1.55 (dd, *J* = 14.3, 3.0 Hz, 1H), 1.40 (dd, *J* = 14.3, 8.8 Hz, 1H), 0.96 (s, 9H)

[00609] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride

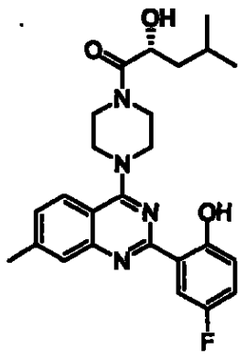
[00610]



[00611] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one (171 mg, 0.367 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) followed by the addition of Et_2O (6 ml) under an N_2 atmosphere. A 2.0 M HCl solution in Et_2O (0.184 mL, 0.367 mmol) was added over a 1 minute period. The reaction solution changed from a clear yellow solution to a milky white slurry. After complete addition of the HCl solution, the reaction was allowed to stir for an additional 10 minutes. The product was collected by vacuum filtration and dried under vacuum to obtain (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride as a light yellow solid (170 mg, 92%). LC/MS: *m/z* 467.3 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.66 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.48–7.43 (m, 1H), 6.92–6.83 (m, 2H), 4.44–4.41 (m, 1H), 3.87–3.68 (m, 8H), 2.56 (s, 3H), 1.55 (dd, *J* = 14.3, 3.0 Hz, 1H), 1.41 (dd, *J* = 14.3, 8.8 Hz, 1H), 0.96 (s, 9H).

[00612] Example 136

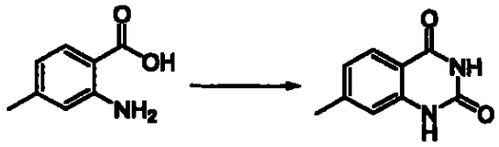
[00613] (*R*)-1-(4-(2-(5-Fluoro-2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one



[00614]

[00615] **7-Methylquinazoline-2,4(1*H*,3*H*)-dione**

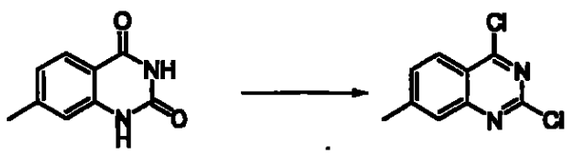
[00616]



[00617] To a suspension of 2-amino-4-methylbenzoic acid (58.9 g, 390 mmol) in water (1.5 L) and glacial acetic acid (50 ml) was added dropwise a solution of potassium cyanate (80.5 g, 993 mmol) in water (300 ml). After completion of the addition and stirring at room temperature for half an hour, sodium hydroxide pellets (500 g) were added at such a rate that the temperature was kept below 50 °C (with ice cooling). During the addition the mixture became a clear solution for a short period, and upon continuation of the sodium hydroxide addition a cream precipitate started forming. The suspension was cooled to 0–5 °C and the precipitate was collected by filtration and washed twice with water (150 ml). The solid was poured in water (1 L) and was acidified with concentrated aqueous HCl (30%, 150 ml). The solid was collected by filtration and washed with water (150 ml) to yield 7-methylquinazoline-2,4(1*H*,3*H*)-dione (57.0 g, 83%) after drying at 45°C under vacuum.

[00618] **2,4-Dichloro-7-methyl-quinazoline**

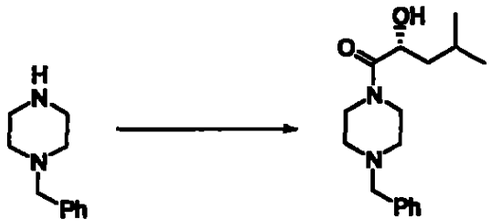
[00619]



[00620] 7-Methylquinazoline-2,4(1*H*,3*H*)-dione (57.0 g, 324 mmol) was refluxed overnight in phosphorus oxychloride (250 ml) in a flask equipped with a calcium chloride guard tube. The clear, dark solution was cooled in an ice bath and poured slowly into 2 L of ice water. The chocolate brown solid was collected by filtration and washed with cold water (150 ml). The solid was dissolved in dichloromethane (500 ml) and filtered. The filtrate was washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and evaporated to dryness yielding 43.0 g of crude 2,4-dichloro-7-methyl-quinazoline. This material was dissolved in hot heptanes (0.5 L),and filtered while hot, and after cooling to room temperature, the precipitated solid was collected by filtration and washed with pentane (100 ml). The solid was purified by chromatography on silica gel with dichloromethane as the eluent to yield 2,4-dichloro-7-methyl-quinazoline (28.5 g, 41%) as an off-white solid.

[00621] 1-(4-benzyl-piperazin-1-yl)-2-(*R*)-hydroxy-4-methyl-pentan-1-one

[00622]



[00623] (R)-α-hydroxyisocaproic acid (52.1 g, 0.394 mol) was added to a solution of 1-benzylpiperazine (69.46 g, 0.394 mol) in CH_2Cl_2 (500 mL). The mixture was cooled in ice and Et_3N (57 mL, 0.5 mol) was added, followed by HOBt (53.25 g, 0.394 mol) and EDCIHCl (76.0 g, 0.396 mol). The reaction mixture was allowed to warm to room temperature overnight. The organic layer was washed with water (3x200 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were washed with water (3x20 mL), dried over Na_2SO_4 and concentrated to give 1-(4-benzyl-piperazin-1-yl)-2-(*R*)-hydroxy-4-methyl-pentan-1-one as a brown oil (109 g, 0.375 mol, 95%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.24 (m, 5H); 4.35 (dd, *J*= 10 Hz, 2 Hz, 1H); 3.77-3.55 (m, 4H); 3.52 (s, 2H); 3.36 (m, 2H); 4.45 (m, 4H); 1.97 (m, 1H); 1.47-1.38 (m, 1H); 1.29-1.21 (m, 1H); 0.96 (d, *J*= 6 Hz, 3H); 0.94 (d, *J*= 6 Hz, 3H).

[00624] 2-(R)-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one

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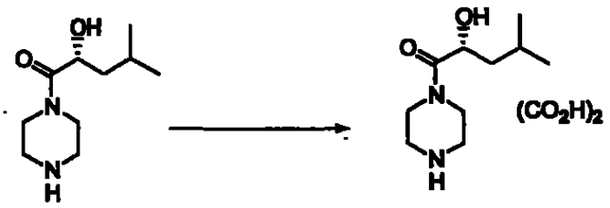
[00625]

[00626] 1-(4-benzyl-piperazin-1-yl)-2-(*R*)-hydroxy-4-methyl-pentan-1-one (109 g, 0.375 mol) was dissolved in MeOH (0.5 L). Crystals formed upon addition of 10% Pd/C (16 grams). The mixture was hydrogenated under 1-4 bar hydrogen pressure for two days. The catalyst was filtered off, the filtrate was concentrated to give 2-(R)-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one as a brownish oil (72.7 g, 0.363 mol, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (dd, *J*= 10 Hz, 2 Hz, 1H); 3.76-3.66 (m, 1H); 3.62-3.52 (m, 1H); 3.37 (m, 2H); 2.99 (br. s, 2H); 2.89 (br. m, 4H); 1.96 (m, 1H); 1.48-1.38 (m, 1H); 1.29-1.21 (m, 1H); 0.96 (d, *J*= 9 Hz, 3H); 0.94 (d, *J*= 9 Hz, 3H).

[00627] **2-(R)-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one oxalate**

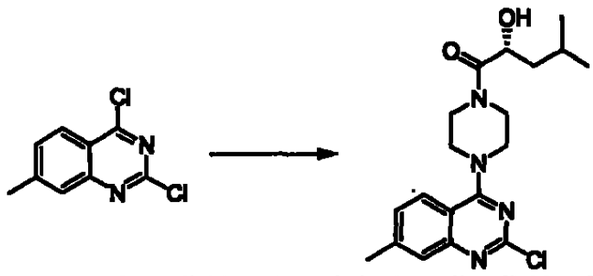
[00628]



[00629] The above product was dissolved in ethanol (250 mL). Oxalic acid dihydrate (45.76 g, 0.363 mol) was added. The thick slurry was diluted with ethanol (250 mL) and stirred at room temperature for 3 hours. The salt was filtered off, washed with ethanol (2x100 mL) and dried *in vacuo* over drying pearls. Yield: 89.0 grams (0.307 mol, 84%) of 2-(R)-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one oxalate as a white solid. ^{1}H NMR (300 MHz, D_2O): δ 4.68 (dd, *J*=3.3, 9.9 Hz, 1H); 3.95 (m, 4H); 3.35 (m, 4H); 1.80 (m, 1H); 1.59 (m, 1H); 1.41 (m, 1H); 0.96 (d, *J*= 6.5 Hz, 3H); 0.95 (d, *J*= 6.5 Hz, 3H).

[00630] **(*R*)-1-(4-(2-Chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

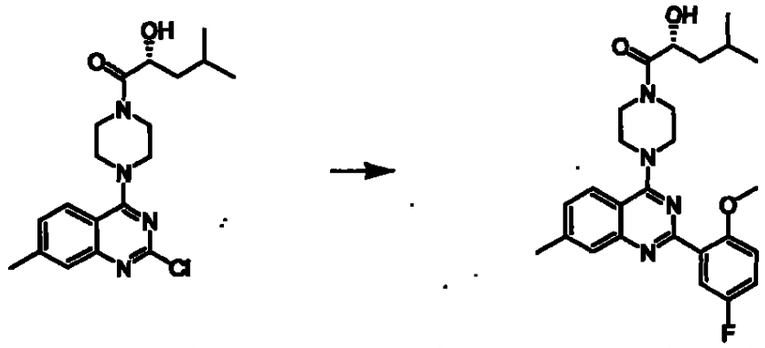
[00631]



[00632] To a solution of 2,4-dichloro-7-methylquinazoline (2.09 g, 9.83 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (2.74 mL, 19.66 mmol), followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (1.97 g, 9.83 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The mixture was then quenched with water and extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to obtain (*R*)-1-(4-(2-chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (6.78 g, 95%). *LC/MS*: *m/z* 377.5 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00633] **(*R*)-1-(4-(2-(5-Fluoro-2-methoxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00634]

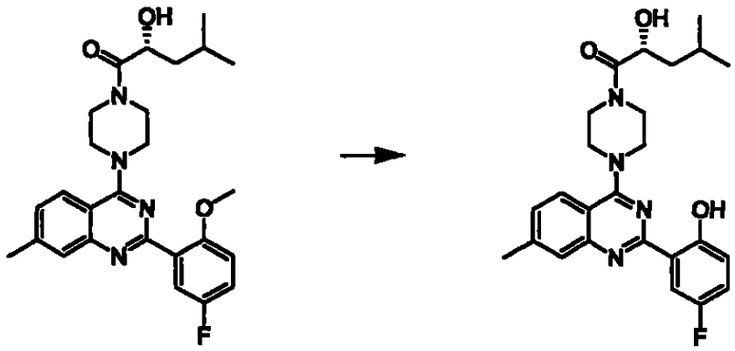


[00635] (*R*)-1-(4-(2-Chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (50 mg, 0.13 mmol), 5-fluoro-2-methoxyphenylboronic acid (27 mg, 0.16 mmol), $Pd(Ph_3P)_4$ (9.2 mg, 0.008 mmol), and K_2CO_3 (37 mg, 0.27 mmol) were placed into a microwave tube charged with a stir bar. Acetonitrile (2 mL) and H_2O (400 μL) were added, and the vessel was capped and heated at 160 °C for 12 minutes in the microwave reactor. The

reaction was partitioned between EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted once more with EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to an orange gel. The reaction was purified by silica gel chromatography using 10%–30% EtOAc in CH_2Cl_2/hexanes (2:1) to afford (*R*)-1-(4-(2-(5-fluoro-2-methoxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as a white foam (70%). LC/MS: *m/z* 467.30 $(M+H)^+$ at 2.38 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00636] (*R*)-1-(4-(2-(5-Fluoro-2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[00637]

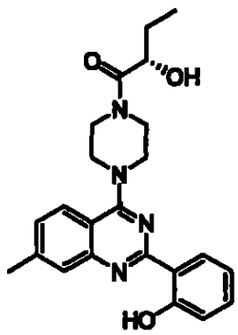


[00638] (*R*)-1-(4-(2-(5-Fluoro-2-methoxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (30 mg, 0.064 mmol) was dissolved in 1.5 mL anhydrous CH_2Cl_2. The flask was sealed with a septum, placed under an N_2 atmosphere and cooled to –78 °C, and 0.32 mL of a 1 M solution of BBr_3 in CH_2Cl_2 was added over 2 minutes. The reaction was allowed to warm to room temperature. After 5 hours, the reaction was quenched with saturated aqueous $NaHCO_3$, and partitioned between CH_2Cl_2 and water, and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated to a red oil. The reaction was purified by reverse phase HPLC to give (*R*)-1-(4-(2-(5-fluoro-2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 453.30 $(M+H)^+$ at 3.02 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00639] Example 137

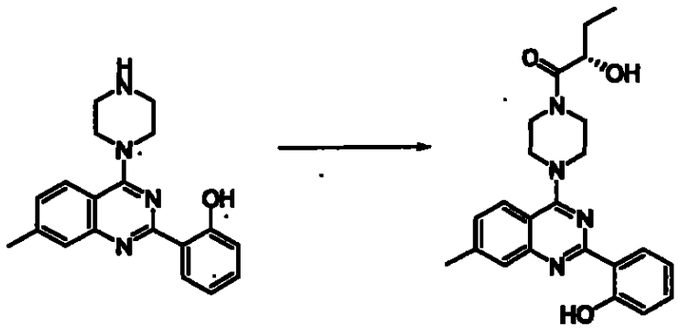
[00640] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00641]



[00642] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one

[00643]



[00644] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to (*S*)-2-hydroxybutanoic acid (29.6 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL) and a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)H_2O (0.05% TFA)) gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 407.3 $(M+H)^+$ at 2.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00645] Example 138

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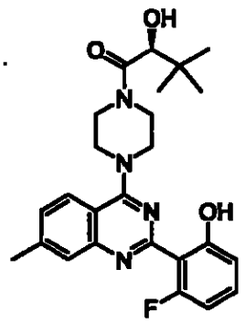
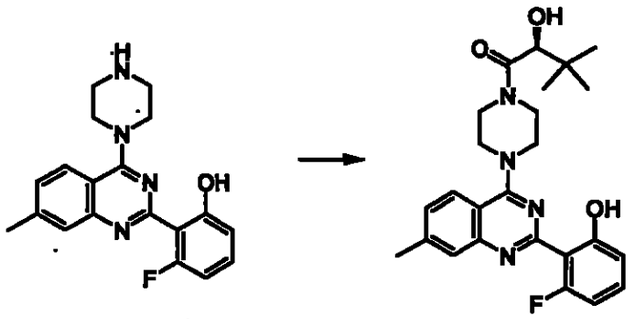
[00646] (*S*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one

[00647]



[00648] (*S*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one

[00649]

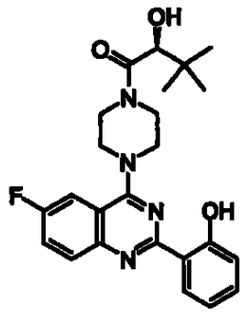


[00650] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol), (*S*)-2-hydroxy-3,3-dimethylbutanoic acid (15.24 mg, 0.12 mmol), triethylamine (25μL, 0.18 mmol), and HATU (45.6 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one as the TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00651] Example 139

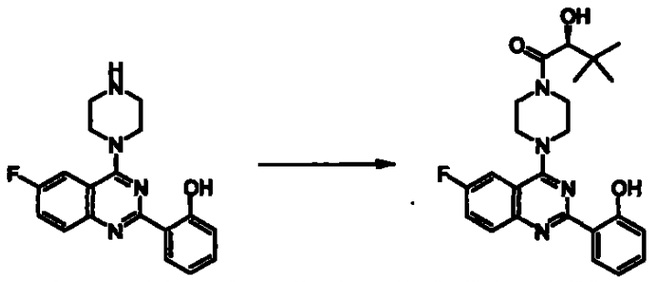
[00652] (*S*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one

[00653]



[00654] (*S*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one

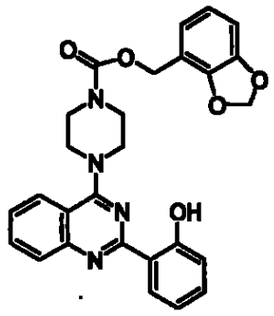
[00655]



[00656] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol), (*S*)-2-hydroxy-3,3-dimethylbutanoic acid (16 mg, 0.12 mmol), triethylamine (25 mL, 0.18 mmol), and HATU (45.6 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-3,3-dimethylbutan-1-one as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00657] Example 140

(Benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate



[00658]

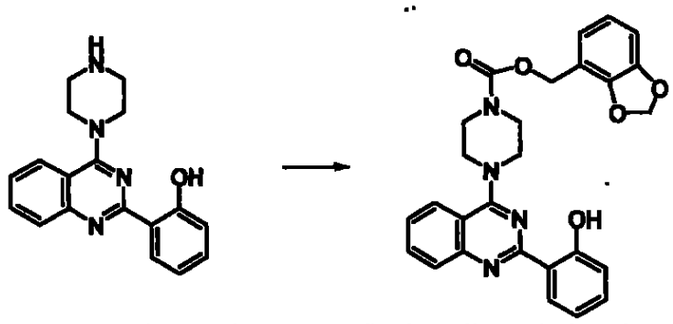
[00659] **(Benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate**

[00660]

[00661] A solution of (benzo[d][1,3]dioxol-7-yl)methanol (2.0 g, 13.1 mmol) and di(1*H*-imidazol-1-yl)methanone (4.26 g, 26.2 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was quenched with water and extracted with CH_2Cl_2, and the combined layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (2.8 g, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, J = 0.9 Hz, 1H), 7.44 (t, J = 1.4 Hz, 1H), 7.07 (dd, J = 1.6, 0.8 Hz, 1H), 6.95 (m, 2H), 6.84 (m, 1H), 6.01 (s, 2H), 5.33 (s, 2H).

[00662] **(Benzo[d][1,3]dioxol-7-yl)methyl 4-(4a,8a-dihydro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate**

[00663]



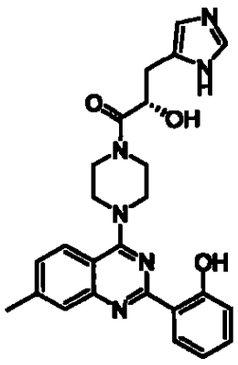
[00664] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (78 mg, 0.32 mmol), and

triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (benzo[d][1,3]dioxol-7-yl)methyl 4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 485.5 $(M+H)^+$ at 2.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00665] Example 141

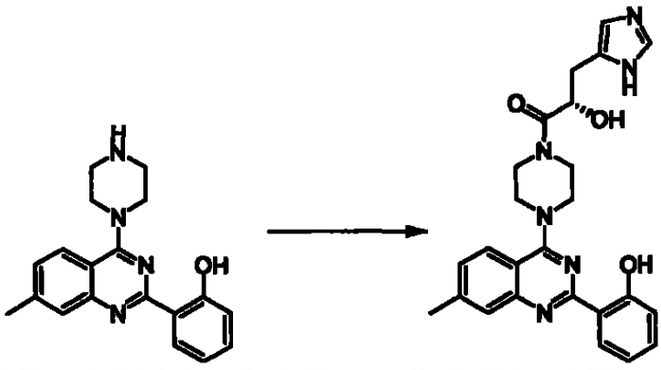
[00666] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(1*H*-imidazol-5-yl)propan-1-one

[00667]



[00668] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(1*H*-imidazol-5-yl)propan-1-one

[00669]



[00670] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (87 mg, 0.27 mmol), (*S*)-2-hydroxy-3-(1*H*-imidazol-5-yl)propanoic acid (64 mg, 0.41 mmol), triethylamine (76 μL, 0.54 mmol), and BOP (180 mg, 0.41 mmol) in 1 mL of CH_2Cl_2 were stirred at room temperature for

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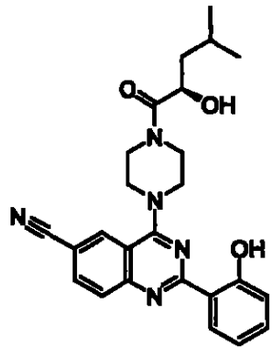
1.5 h. The reaction mixture was diluted with H_2O and CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Purification using 1–15% MeOH in CH_2Cl_2 gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(1*H*-imidazol-5-yl)propan-1-one. LC/MS: *m/z* 459.3 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00671] Example 142

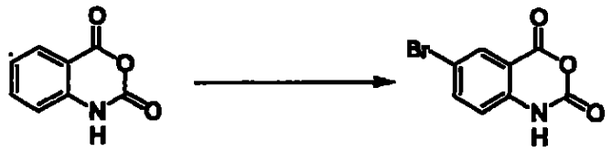
[00672] **4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile**

[00673]



[00674] **6-Bromo-1*H*-benzo[d][1,3]oxazine-2,4-dione**

[00675]



[00676] Bromine (35 mL, 660 mmol) was added dropwise to a suspension of isatoic anhydride (100 g, 610 mmol) in 1.6 L water at 50 °C. This temperature was maintained for an additional 2 hours. After cooling the solution to room temperature, the solid was filtered and washed twice with water and twice with acetone, yielding 125.6 g (85%) 6-bromo-1*H*-benzo[d][1,3]oxazine-2,4-dione as a pink solid.

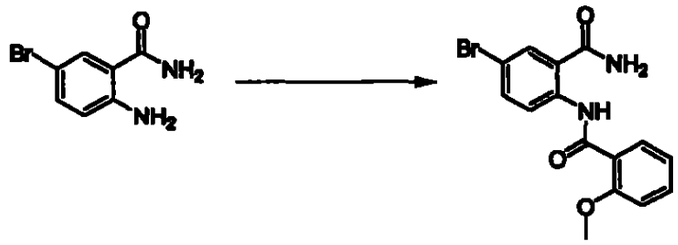
[00677] **2-Amino-5-bromo-benzamide**

[00678]

[00679] 6-Bromo-1*H*-benzo[d][1,3]oxazine-2,4-dione (56.0 g, 230 mmol) was suspended in 1 N aq. NH_4OH (600 mL, 2.6 equivalents), and the suspension was stirred 3 d at room temperature. After filtration, the collected solid was washed with water and subsequently dissolved in tetrahydrofuran. This solution was filtered, evaporated to dryness, and dried by repeated azeotropic distillation with toluene. The solid was suspended in CH_2Cl_2, filtered, and washed once CH_2Cl_2 with yielding 35.4 g (71.2%) 2-amino-5-bromo-benzamide.

[00680] **2-(*o*-Anisoyl)-amino-5-bromo-benzamide**

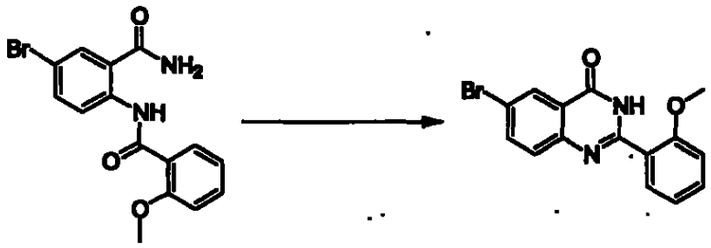
[00681]



[00682] To a solution of 2-amino-5-bromo-benzamide (29.2 g, 136 mmol) and triethylamine (25.0 mL, 173 mmol) in THF (500 mL) was added dropwise *o*-anisoyl chloride (24.0 g, 140 mmol). Stirring at room temperature was continued for 3 h, after which the formed precipitate was filtered and washed once with THF and twice with dichloromethane yielding 2-(*o*-anisoyl)-amino-5-bromo-benzamide (51.4 g, 84%) with 1 equivalent of triethylamine hydrochloride.

[00683] **6-Bromo-2-(2-methoxy-phenyl)-3*H*-quinazolin-4-one**

[00684]



[00685] 2-(*o*-Anisoyl)-amino-5-bromo-benzamide (50.8 g, 105 mmol) was suspended in 2 N aq. NaOH (500 mL) and heated to reflux until a clear solution was obtained (1.5 h). The solution was cooled to room temperature and filtered. The filtrate was acidified with conc. aq. HCl, and the precipitate formed was filtered and washed twice with 1 N aq. HCl and twice with

water. The solid was dried by repeated azeotropic distillation with toluene yielding 6-bromo-2-(2-methoxy-phenyl)-3*H*-quinazolin-4-one (31.3 g, 91%).

[00686] **6-Bromo-4-chloro-2-(2-methoxyphenyl)quinazoline**

[00687]

[00688] Method A

[00689] 6-Bromo-2-(2-methoxyphenyl)quinazolin-4(3*H*)-one (674 mg, 2.0 mmol), $POCl_3$ (624 mg, 4 mmol), and *N*, *N*-dimethylaniline (740 mg, 6.1 mmol) were dissolved in benzene (12 mL) and refluxed for 3 h. The reaction mixture was diluted with EtOAc, and the organic phase was washed with aqueous saturated $NaHCO_3$ (1x) and H_2O (2x), dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–5% EtOAc in CH_2Cl_2/hexanes (1:1) gave 6-bromo-4-chloro-2-(2-methoxyphenyl)quinazoline. LC/MS: *m/z* 348.9 $(M+H)^+$ at 3.66 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00690] Method B

[00691] 6-Bromo-2-(2-methoxyphenyl)quinazolin-4(3*H*)-one (0.31 g, 0.94 mmol), $POCl_3$ (86 μL, 0.94 mmol), and *N*, *N*-dimethylaniline (180 μL, 1.4 mmol) were refluxed in dry toluene for 3 h. Additional $POCl_3$ (0.94 mmol) was added, and the reaction was refluxed for one additional hour. The reaction mixture was diluted with EtOAc and water. The aqueous layer was made basic with $NaHCO_3$, and the layers were separated. After the organic phase was washed with water, dried over Na_2SO_4 and concentrated, purification via silica gel chromatography using 0–50% EtOAc in 1:1 hexanes:CH_2Cl_2 gave 6-bromo-4-chloro-2-(2-methoxyphenyl)quinazoline as a yellow solid (144 mg, 44%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.45–8.45 (m, 1H), 8.04–7.99 (m, 2H), 7.82 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.49–7.45 (m, 1H), 7.12–7.08 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H); LC/MS: *m/z* 350.9 $(M+H)^+$ at 3.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00692] **2-(6-Bromo-4-chloroquinazolin-2-yl)phenol**

[00693]

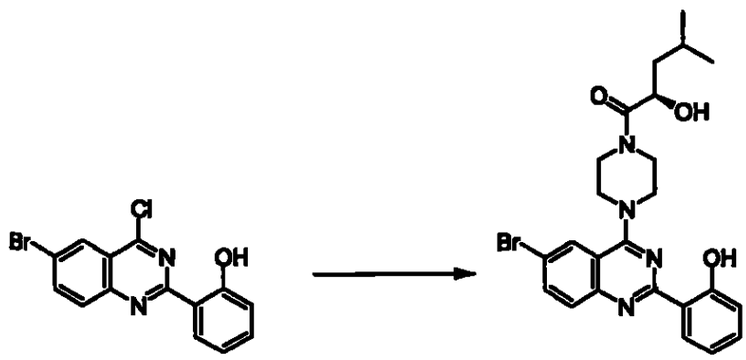
[00694] Method A

[00695] 6-Bromo-4-chloro-2-(2-methoxyphenyl)quinazoline (393 mg, 1.12 mmol) was dissolved in CH_2Cl_2 (3 mL), and the flask was flushed with N_2. After cooling the reaction mixture to –78 °C, 1 M BBr_3 in CH_2Cl_2 (3.37 mL, 3.37 mmol) was added dropwise, then the reaction was slowly warmed to room temperature and stirred for 2 h. After quenching the mixture with saturated aqueous $NaHCO_3$ (1x), it was transferred into a separatory funnel with CH_2Cl_2. The organic layer was washed with H_2O (2x), dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–5% EtOAc and CH_2Cl_2:hexanes (1:1) gave 2-(6-bromo-4-chloroquinazolin-2-yl)phenol (229 mg, 61%). LC/MS: *m/z* 335.30 $(M+H)^+$ at 4.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00696] Method B

[00697] A solution of 6-bromo-4-chloro-2-(2-methoxyphenyl)quinazoline (0.14 g, 0.4 mmol) in CH_2Cl_2 (mL) was cooled in a dry ice/acetone bath. A solution of 1.0 M BBr_3 in CH_2Cl_2 (1.2 mL, 1.2 mmol) was slowly added. The cooling bath was removed, and the reaction was stirred at room temperature for 2 h. The reaction was diluted with CH_2Cl_2 and made basic with a saturated $NaHCO_3$ solution. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated to give 6-bromo-4-chloro-2-(2-hydroxyphenyl)quinazoline (0.15 g).

[00698] **(*R*)-1-(4-(6-Bromo-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**



[00699]

[00700] Method A

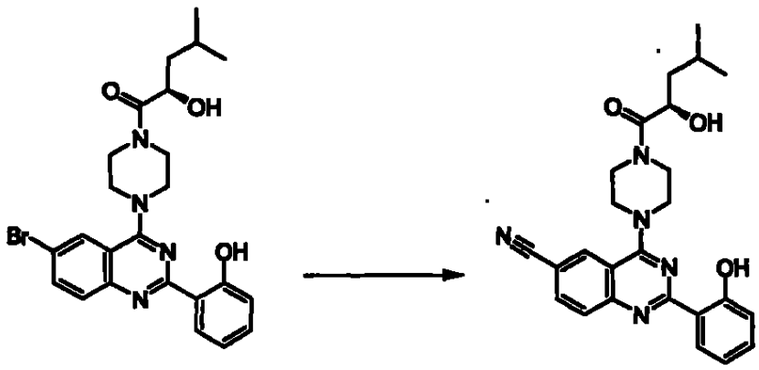
[00701] To a solution of 2-(6-bromo-4-chloroquinazolin-2-yl)phenol (228 mg, 0.68 mmol), triethylamine (129 μL, 0.92 mmol), and CH_2Cl_2 (6 mL) was added (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (185 mg, 0.92 mmol) dissolved in CH_2Cl_2 (3 mL). The flask was flushed with N_2 and stirred for 3 hours. The reaction mixture was then transferred into a separatory funnel with CH_2Cl_2, and the organic phase was washed with H_2O (2x), dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0 to 20% EtOAc and CH_2Cl_2:hexanes (1:1) gave (*R*)-1-(4-(6-bromo-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (285 mg, 84%). LC/MS: *m/z* 500.30 $(M+H)^+$ at 3.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00702] Method B

[00703] A solution of 6-bromo-4-chloro-2-(2-hydroxyphenyl)quinazoline (75 mg, 0.22 mmol), (*R*)-2-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one (60 mg, 0.3 mmol), triethylamine (42 μL, 0.3 mmol), and CH_2Cl_2 (2 mL) was stirred at room temperature overnight. After diluting with CH_2Cl_2, the reaction mixture was washed with H_2O, dried over Na_2SO_4, and concentrated. The crude material was purified by silica gel chromatography using 0–10% MeOH/CH_2Cl_2 to give (*R*)-1-{4-[6-bromo-2-(2-methoxy-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-2-hydroxy-4-methyl-pentan-1-one (40 mg, 36%). LC/MS: *m/z* 449.3 $(M+H)^+$ at 3.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00704] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile

[00705]



[00706] Method A

[00707] A mixture of (*R*)-1-{4-[6-bromo-2-(2-methoxy-phenyl)-quinazolin-4-yl]-piperazin-1-yl}-2-hydroxy-4-methyl-pentan-1-one (20 mg, 0.04 mmol), $Zn(CN)_2$ (4.7 mg, 0.04 mmol), and $Pd(PPh_3)_4$ (1.4 mg, 1.4 μmol) in DMF (0.5 mL) was heated in a microwave synthesizer at 200 °C for 15 minutes Purification via preparative HPLC gave 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile as the TFA salt. LC/MS: *m/z* 446.3 $(M+H)^+$ at 3.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00708] Method B

[00709] (*R*)-1-(4-(6-Bromo-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (188 mg, 0.38 mmol), $Zn(CN)_2$ (44 mg, 0.38 mmol), and $Pd(Ph_3)_4$ (6.5 mg, 0.0112 mmol) were dissolved in DMF (4 mL) and the reaction mixture was heated in a microwave synthesizer at 200 °C for 15 minutes EtOAc (50 mL) was added and the mixture was washed twice with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in CH_2Cl_2:hexanes (1:1) gave 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile (127 mg, 75%). LC/MS: *m/z* 446 $(M+H)^+$ at 3.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.60 (d, J = 1.5 Hz, 1H), 8.46 (dd, J = 8.4, 1.8 Hz, 1H), 8.15 (dd, J = 8.7, 1.7 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.45–7.41 (m, 1H), 6.99–6.95 (m, 2H), 4.94 (d, J = 7.0 Hz, 1H), 4.39–4.36 (m, 1H), 4.14–4.04 (m, 4H), 3.89–3.67 (m, 4H), 1.82–1.76 (m, 1H), 1.47–1.37 (m, 2H), 0.93–0.91 (m, 6H).

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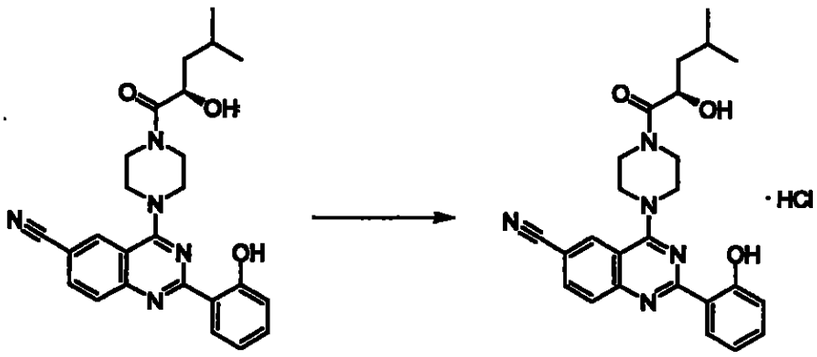
[00710] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile hydrochloride

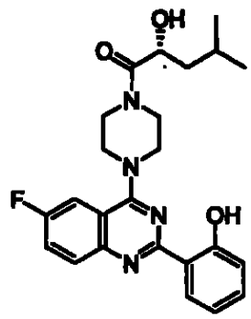
[00711]



[00712] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile (137 mg, 0.31 mmol) was dissolved in the minimum amount of CH_2Cl_2. After stirring the solution under an N_2 atmosphere for 30 minutes, 1 M HCl in ether (0.31 mL, 0.31 mmol) was added dropwise to the solution and stirred for 10 minutes. Ether was added to precipitate the hydrochloride salt of 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile, which was filtered and dried to obtain 136 mg of solid (91%). LC/MS: *m/z* 446 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.62 (s, 1H), 8.43–8.41 (m, 1H), 8.17 (dd, J = 8.7, 1.5 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.47–7.43 (m, 1H), 7.00–6.96 (m, 2H), 4.39–4.36 (m, 1H), 4.18–4.00 (m, 4H), 3.91–3.68 (m, 4H), 1.85–1.75 (m, 1H), 1.51–1.35 (m, 2H), 0.94–0.91 (m, 6H); ^{13}C NMR (100 MHz, DMSO–d6) δ 172.5, 161.7, 160.6, 135.1, 133.6, 132.4, 129.7, 126.9, 118.8, 118.4, 118.2, 117.4, 113.3, 107.3, 66.9, 48.7, 48.1, 43.5, 42.8, 41.1, 24.0, 23.4, 21.6.

[00713] Example 143

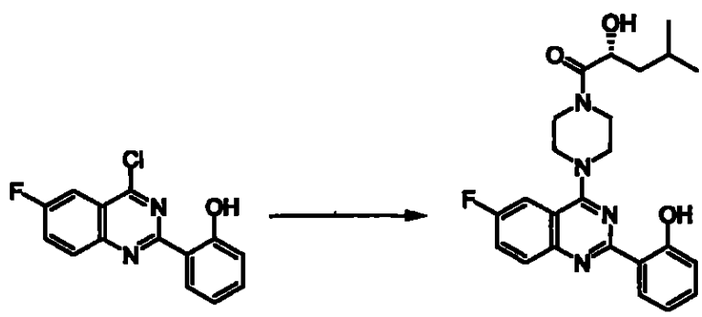
[00714] (*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one



[00715]

[00716] (*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[00717]



[00718] Method A

[00719] To a solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (25 mg, 0.09 mmol) in DMF (1 mL) was added triethylamine (25 μL, 0.18 mmol) followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one oxalate (52 mg, 0.18 mmol) at 0 °C. The reaction was stirred for 2 hours, and purification using reverse phase HPLC (10-99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.99 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00720] Method B

[00721] To a mixture of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (200 mg, 0.72 mmol) and CH_2Cl_2 (7 mL) was added (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one oxalate (275 mg, 0.95 mmol). The reaction was complete after two hours. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 mixture of CH_2Cl_2:hexanes gave (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

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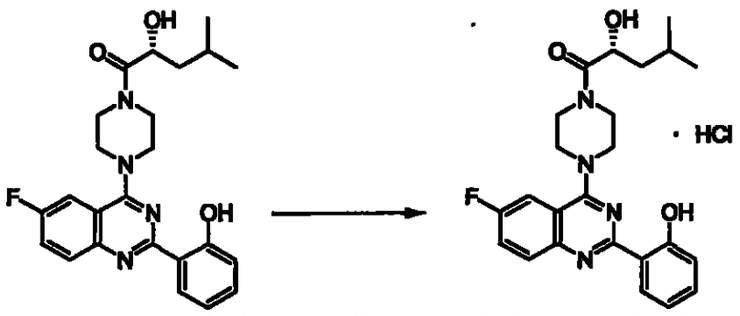
(289 mg, 91%). LC/MS: *m/z* 439.30 $(M+H)^+$ at 3.00 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.46 (m, 1H), 8.02 (m, 1H), 7.84 (m, 2H), 7.40 (m, 1H), 6.97 (m, 2H), 4.92 (d, *J* = 7.2 Hz, 1H), 4.38 (m, 1H), 3.98 (m, 4H), 3.76 (m, 4H), 1.80 (m, 1H), 1.42 (m, 2H), 0.92 (q, *J* = 3.8 Hz, 6H).

[00722] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one hydrochloride**

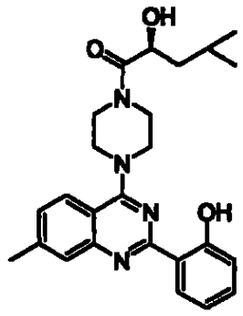
[00723]



[00724] To a solution of (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (285 mg, 0.65 mmol) in CH_2Cl_2 (2 mL) under an N_2 atmosphere was added ether (10 mL), followed by the dropwise addition of a 2 M HCl solution in ether (0.325 mL, 0.65 mmol). A precipitate was formed which was stirred for 30 min, collected by vacuum filtration, and dried to afford (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one hydrochloride (284 mg, 92%). LC/MS: *m/z* 439.30 $(M+H)^+$ at 3.00 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)): ^1H NMR (400 MHz, DMSO-d6) δ 8.32 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.02 (m, 1H), 7.92 (dd, *J* = 9.7, 2.7 Hz, 1H), 7.85 (m, 1H), 7.45 (m, 1H), 7.01 (m, 2H), 4.37 (dd, *J* = 9.2, 4.1 Hz, 1H), 4.04 (m, 4H), 3.83 (m, 4H), 1.76 (m, 1H), 1.41 (m, 2H), 0.90 (dd, *J* = 6.6, 3.7 Hz, 6H).

[00725] Example 144

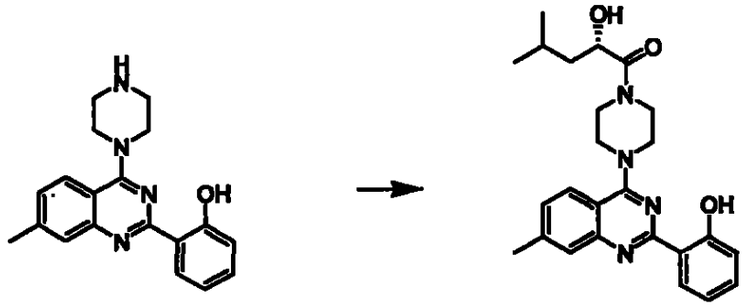
[00726] **(*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**



[00727]

[00728] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

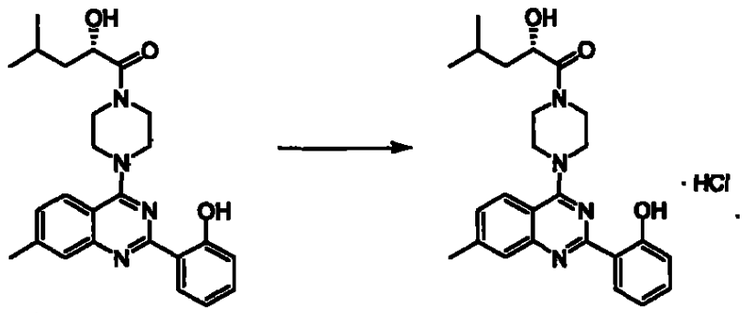
[00729]



[00730] Under an N_2 atmosphere, BOP (137 mg, 0.31 mmol) was added in a single portion to a stirring solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (100 mg, 0.31 mmol), (*S*)-2-hydroxy-4-methylpentanoic acid (41 mg, 0.31 mmol), and triethylamine (43 µL, 0.31 mmol) in DMF (0.5 ml). After stirring the mixture for 1 h at room temperature, it was partitioned between H_2O and ether. The organic phase was washed with H_2O (3x 20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 1:1 ethyl acetate / hexane gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one as a white solid. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.62 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.44 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.67 (s, 1H), 7.40–7.36 (m, 2H), 6.96-6.93 (m, 2H), 4.92 (d, *J* = 7.2 Hz, 1H) 4.41–4.36 (m, 1H), 4.06–3.67 (m, 8H), 2.51 (s, 3H), 1.85–1.73 (m, 1H), 1.49–1.35 (m, 2H), 0.93–0.91 (m, 6H).

[00731] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride

[00732]

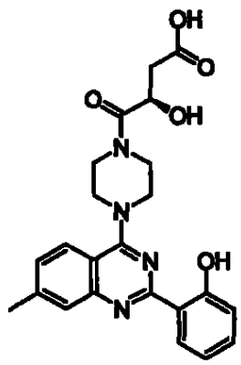


[00733] (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (90 mg, 0.20 mmol) was dissolved in 1 mL CH_2Cl_2 and treated with 1 equivalent of 2.0 M HCl in ether (100 μL, 0.20 mmol). The formed precipitate was filtered and vacuum dried to obtain (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride. *LC/MS*: *m/z* 435.5 $(M+H)^+$ at 2.62 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.27 (d, *J* = 6.8 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.50–7.45 (m, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.03–6.99 (m, 1H), 4.39–4.35 (m, 1H), 4.16–3.68 (m, 8H), 2.54 (s, 3H), 1.84–1.72 (m, 1H), 1.49–1.35 (m, 2H), 0.93 (d, *J* = 2.8 Hz, 6H).

[00734] Example 145

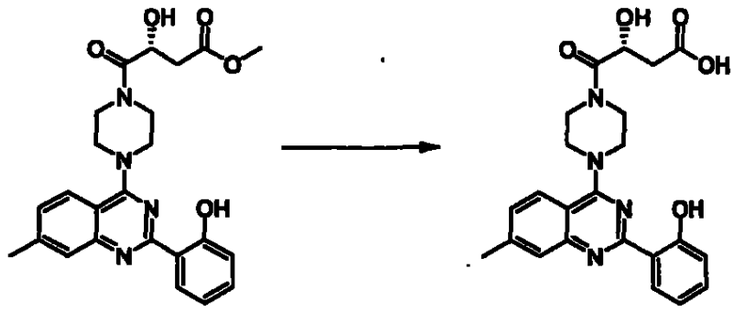
[00735] (*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoic acid

[00736]



[00737] (*R*)-3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoic acid

[00738]

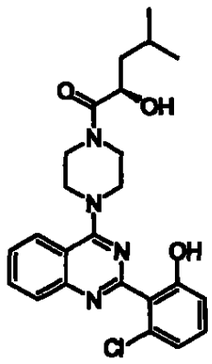


[00739] (*R*)-Methyl 3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoate (88 mg, 0.20 mmol) and $LiOH \cdot H_2O$ (33 mg, 0.78 mmol) were stirred in THF:H_2O 1:1 at room temperature for 3 h. After acidification with 1 M HCl and extraction with EtOAc, the organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The crude material was then purified via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 to obtain (*R*)-3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanoic acid (75 mg, 88%). LC/MS: *m/z* 437.3 $(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00740] Example 146

[00741] (*R*)-1-(4-(2-(2-Chloro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[00742]



[00743] 2-Amino-benzamide

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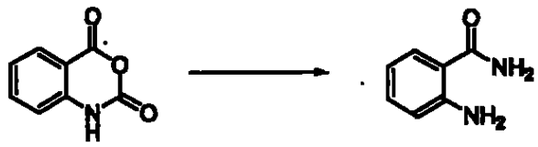
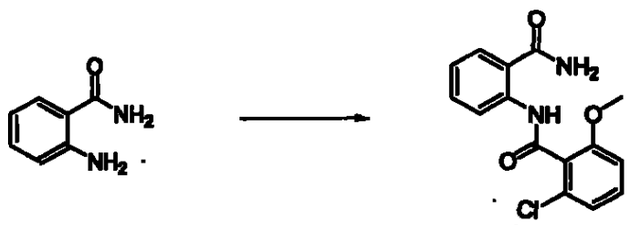
[00744]



[00745] Isatoic anhydride (40 g, 245 mmol) was suspended in 650 mL 1 N NH_4OH (2.5 equiv) and stirred at room temperature for 3 days. The precipitate was filtered and washed with water. The product was then dissolved in THF, filtered, and concentrated to dryness. The product was dried by azeotropic distillation with toluene and washed with CH_2Cl_2 to yield 10.9 g (32.7%) of 2-amino-benzamide.

[00746] **2-Chloro-*N*-(2-carboxylic acid amide phenyl)-2-methoxy-benzamide**

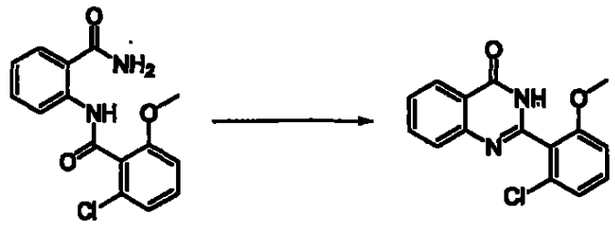
[00747]



[00748] 2-Amino-benzamide (6.9 g, 50.8 mmol) was dissolved in 50 mL of pyridine and cooled to 0 °C. 2-Chloro-6-methoxy-benzoyl chloride was added dropwise to the solution. After complete addition, the reaction was left to stir at room temperature for three days, which resulted in formation of a brown, cloudy solution. The reaction mixture was then poured into 150 mL of ice water. The precipitate was filtered and washed twice with water, twice with THF and finally twice with CH_2Cl_2 to obtain 2-chloro-*N*-(2-carboxylic acid amide phenyl)-2-methoxy-benzamide (13.3 g, 43.7 mmol, 86%).

[00749] **2-(2-Chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one**

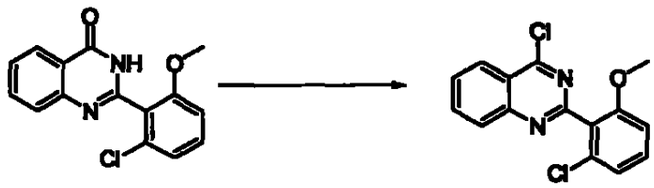
[00750]



[00751] 2-Chloro-*N*-(2-carboxylic acid amide phenyl)-2-methoxy-benzamide (13 g, 42.7 mmol) was suspended in 100 mL of a 2 N NaOH solution and heated to reflux. After refluxing for 3 hours, another 25 mL of a 2 N NaOH solution was added, and the reaction was refluxed for another hour. The mixture was cooled to room temperature and acidified with acetic acid to pH 5. The formed precipitate was collected by filtration. The product was purified over alumina using EtOAc as an eluent giving 1.7 g (5.9 mmol, 14%) of 2-(2-chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one.

[00752] 4-Chloro-2-(2-chloro-6-methoxy-phenyl)-quinazoline

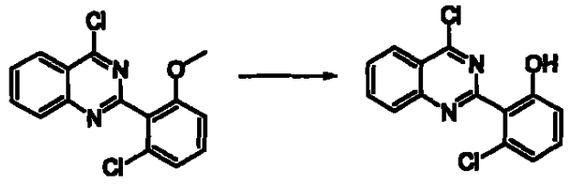
[00753]



[00754] 2-(2-Chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one (1.7 g, 5.9 mmol) was dissolved in 25 mL benzene. Then, *N,N*-dimethylaniline (1.15 mL, 9 mmol)and $POCl_3$ (1.65 mL, 17.7 mmol) were added. The reaction mixture was refluxed for 3 hours during which the yellow suspension changed to a dark red color. The mixture was cooled and diluted with 50 mL toluene. The solution was poured onto ice. Saturated aq. $NaHCO_3$ was added while stirring and cooling the mixture until the pH remained constant at 7. The layers were separated, and the aqueous layer was extracted with 100 mL toluene. The toluene layers were combined and washed with 100 mL saturated aqueous NaCl solution, 150 mL 0.5 N HCl, 150 mL 5% aq. $NaHCO_3$ and saturated aqueous NaCl solution. The toluene layer was dried over Na_2SO_4, filtered, and concentrated to dryness to yield 1.87 g impure product. The product was purified over silica gel with heptane/CH_2Cl_2 (2:1) as an eluent to yield 4-chloro-2-(2-chloro-6-methoxy-phenyl)-quinazoline (1.22 g, 64%).

[00755] 3-Chloro-2-(4-chloroquinazolin-2-yl)phenol

[00756]



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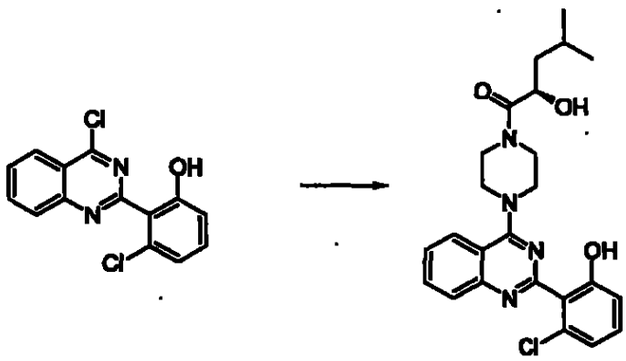
[00757] To a solution of 4-chloro-2-(2-chloro-6-methoxyphenyl)quinazoline (300 mg, 0.98 mmol) in 10 mL CH_2Cl_2 was added dropwise 5 equivalents of a 1 M BBr_3 solution in CH_2Cl_2 at –78 °C. The reaction was warmed to room temperature and was complete in 30 minutes. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution to pH 7. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4, filtered, and concentrated to obtain 3-chloro-2-(4-chloroquinazolin-2-yl)phenol. LC/MS: *m/z* 291.3 $(M+H)^+$ at 3.16 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00758] **(*R*)-1-(4-(2-(2-Chloro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00759]

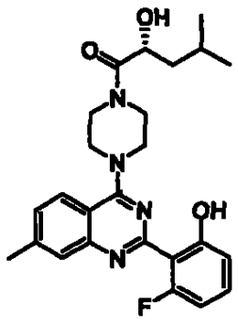


[00760] To a solution of 3-chloro-2-(4-chloroquinazolin-2-yl)phenol (42 mg, 0.14 mmol) in 2 mL CH_2Cl_2 was added triethylamine (40 µL) followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (37.5 mg, 0.187 mmol). The reaction was complete after 1 hour. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-1-(4-(2-(2-chloro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 455.5 $(M+H)^+$ at 2.45 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00761] Example 147

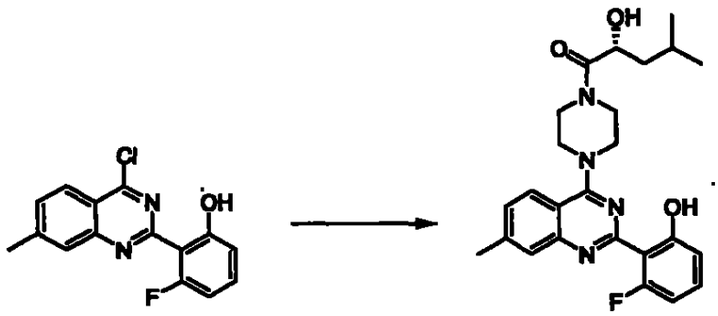
[00762] **(*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**

[00763]



[00764] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[00765]



[00766] Method A

[00767] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (50 mg, 0.174 mmol) in 1 mL DMF was added triethylamine (35.2 mg, 0.348 mmol), followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (42.1 mg, 0.21 mmol). After stirring the reaction for 1 hour, it was filtered, and purified via preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. *LC/MS*: *m/z* 453.3 (M+H)+ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00768] Method B

[00769] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (300 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) was cooled using an ice water batch. To this stirring solution was added (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (312 mg, 1.56 mmol), followed by

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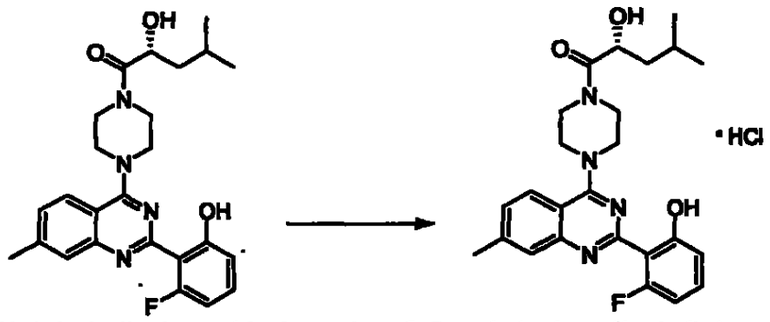
triethylamine (210 mg, 291 μL, 2.08 mmol). After letting the reaction warm to room temperature, it was stirred overnight. The mixture was partitioned between water and CH_2Cl_2 and separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to a viscous yellow oil. Purification via silica gel chromatography using 0–30% EtOAc in CH_2Cl_2/hexanes (2:1) gave (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as a bright yellow foam/solid. (413 mg, 88%). LC/MS: *m/z* 453.1 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.01 (d, *J* = 8.5 Hz, 1H), 7.68 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.37–7.32 (m, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.76–6.71 (m, 1H), 4.91 (d, *J* = 7.2 Hz, 1H), 4.40–4.35 (m, 1H), 4.02–3.65 (m, 8H), 2.52 (s, 3H), 1.82–1.73 (m, 1H), 1.47–1.34 (m, 2H), 0.91 (dd, *J* = 6.5, 4.1 Hz, 6H).

[00770] **(*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one hydrochloride**

[00771]



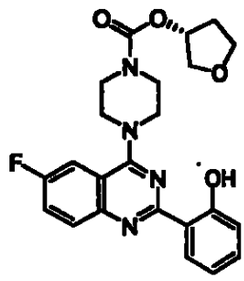
[00772] (*R*)-1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (406 mg, 0.898 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) followed by the addition of Et_2O (6 mL) under an N_2 atmosphere. A 2.0 M HCl solution in Et_2O (0.449 mL, 0.898 mmol) was added over a 2 minute period. The reaction solution changed from a clear yellow solution to a turbid white slurry. After complete addition of the HCl solution, the reaction was allowed to stir for an additional 15 minutes. The product was collected by vacuum filtration and dried under vacuum to obtain (*R*)-1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one hydrochloride as a white solid (403 mg, 92%). LC/MS: *m/z* 453.5 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.20 (d, *J* = 8.7 Hz, 1H), 7.71 (s,

1H), 7.60–7.60 (m, 1H), 7.50–7.44 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.87 (t, J = 9.1 Hz, 1H), 4.36–4.33 (m, 1H), 4.25–3.67 (m, 8H), 2.57 (s, 3H), 1.83–1.71 (m, 1H), 1.49–1.35 (m, 2H), 0.91 (d, J = 6.7 Hz, 6H).

[00773] Example 148

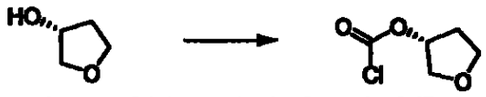
[00774] (*R*)-Tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00775]



[00776] (*R*)-Tetrahydrofuran-3-yl chloroformate

[00777]



[00778] A stirred solution of (*R*)-tetrahydrofuran-3-ol (7.9 g, 90 mmol) in anhydrous CH_2Cl_2 (50 mL) under an N_2 atmosphere was cooled in an ice bath, and a 20% solution of phosgene in toluene (134 mL, 270 mmol) was slowly added. The reaction was allowed to warm to room temperature overnight, and the solvent was removed under vacuum to afford (*R*)-tetrahydrofuran-3-yl chloroformate (12.1 g, 85%) as a clear liquid.

[00779]

[00780] (*R*)-Tetrahydrofuran -3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

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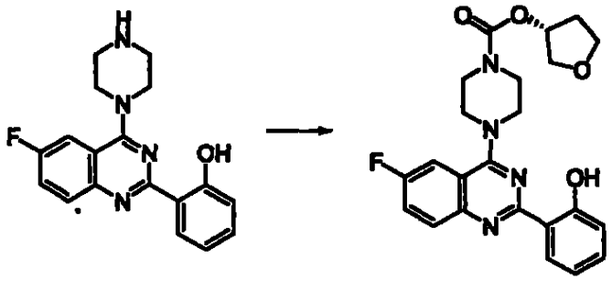


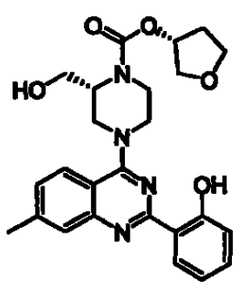
[00781]

[00782] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol), (*R*)-tetrahydrofuran-3-yl chloroformate (12 mg, 0.08 mmol), triethylamine (22 μL, 0.154 mmol) and HATU (38 mg, 0.10 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00783] Example 149

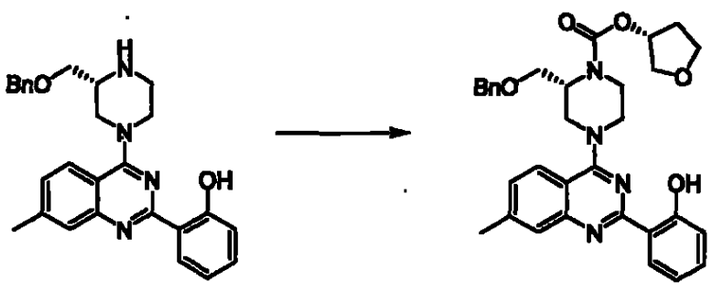
[00784] (2*R*)-(*R*)-Tetrahydrofuran-3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00785]



[00786] (2*R*)-(*R*)-Tetrahydrofuran -3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

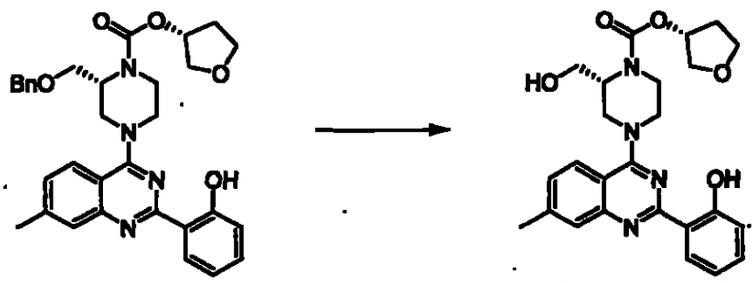
[00787]



[00788] To a solution of 2-(4-((*R*)-3-((benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol (75 mg, 0.17 mmol) in DMF (1 mL) was added triethylamine (47 μL) followed by the dropwise addition of (*R*)-tetrahydrofuran-3-yl chloroformate (25 mg, 0.17 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 455.3 $(M+H)^+$ at 2.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00789] (2*R*)-(*R*)-Tetrahydrofuran -3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00790]



[00791] To a solution of (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate TFA salt (94 mg, 0.17 mmol) in ethanol was added $Pd(OH)_2$ (78 mg), and the reaction was heated at 50 °C under an H_2 atmosphere at ambient pressure. The reaction was filtered, and purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate trifluoroacetate. LC/MS: *m/z* 465.5 $(M+H)^+$ at 2.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00792] Example 150

[00793] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

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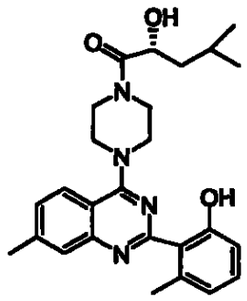
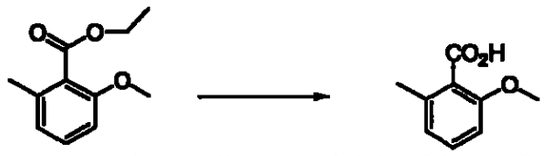
[00794]



[00795] **2-Methoxy-6-methyl-benzoic acid**

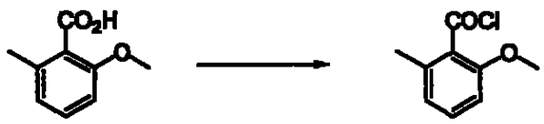
[00796]



[00797] Ethyl-2-methoxy-6-methylbenzoate (30.4 g, 0.157 mol) was added to 100 mL 3.2 M NaOH (2 equiv) and 150 mL hot EtOH. The mixture was refluxed overnight after which EtOH was removed *in vacuo*. The aqueous mixture was acidified with 5 M HCl to pH 3. CH_2Cl_2 (200 mL) was added, and the layers were separated. The water layer was extracted two times with 200 mL CH_2Cl_2, and the organic layers were combined and dried over Na_2SO_4. Filtering the Na_2SO_4 and concentrating the CH_2Cl_2 to dryness yielded 21.4 g (0.129 mol, 82.3%) of 2-methoxy-6-methyl-benzoic acid.

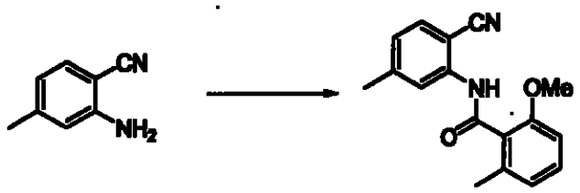
[00798] **2-Methoxy-6-methyl-benzoyl chloride**

[00799]



[00800] 2-Methoxy-6-methyl-benzoic acid (21.4 g, 0.129 mol) was refluxed for 3 hours in 230 mL thionyl chloride. Excess thionyl chloride was removed under reduced pressure. Co-evaporation of the residue with toluene gave 23.8 g of 2-methoxy-6-methyl-benzoyl chloride.

[00801] ***N*-(2-Cyano-5-methyl-phenyl)-2-methoxy-6-methyl-benzamide**

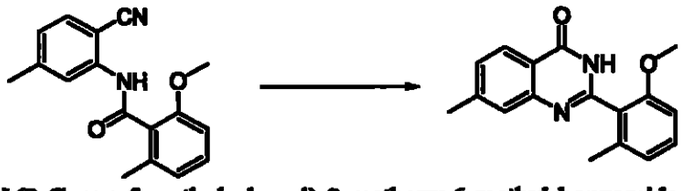


[00802]

[00803] 2-Amino-4-methyl-benzonitrile (15.4 g, 0.117 mol) was dissolved in 100 mL pyridine and cooled to 0 °C. To this mixture was added dropwise 2-methoxy-6-methylbenzoyl chloride (24 g, 0.13 mol, 1.1 equiv). During the addition the temperature did not exceed 2 °C. The reaction was stirred at room temperature for 48 hours. The mixture was poured into 400 mL ice water, and the precipitate was collected by filtration and washed with water. The crude product was dissolved in 600 mL CH_2Cl_2, and the solution was washed twice with 500 mL of a 1 N HCl solution and once with 400 mL of a saturated aq. NaCl solution. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and concentrated to dryness to yield 25.44 g (0.09 mol, 77.6%) of *N*-(2-cyano-5-methyl-phenyl)-2-methoxy-6-methyl-benzamide.

[00804] 2-(2-Methoxy-6-methyl-phenyl)-7-methyl-3*H*-quinazolin-4-one

[00805]



[00806] *N*-(2-Cyano-5-methyl-phenyl)-2-methoxy-6-methyl-benzamide (25 g, 0.09 mol) was suspended in 500 mL EtOH, and 121.3 g of 33% aq. NaOH (1 mol, 11 equiv) was added. To this was added a 35% H_2O_2 solution (50 mL, 0.58 mol), and the reaction was heated to reflux. Additional H_2O_2 was added dropwise until the reaction mixture became clear. EtOH was removed under reduced pressure, and the precipitate formed was removed by filtration. The solution was acidified with acetic acid to pH 5, and the precipitate formed was collected by filtration. The precipitate was washed twice with water and once with diethyl ether. The product was purified over alumina using EtOAc/heptane (1:1) as an eluent. Another purification was performed, over silica gel with the same eluent to yield 2-(2-methoxy-6-methyl-phenyl)-7-methyl-3*H*-quinazolin-4-one (1.61 g).

[00807] 4-Chloro-2-(2-methoxy-6-methyl-phenyl)-7-methyl-quinazoline

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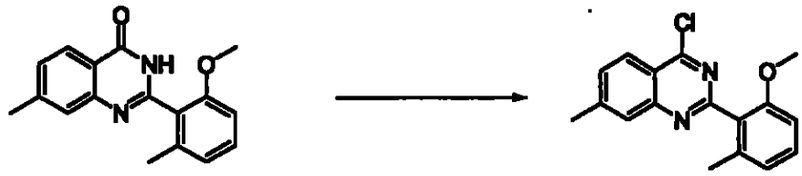
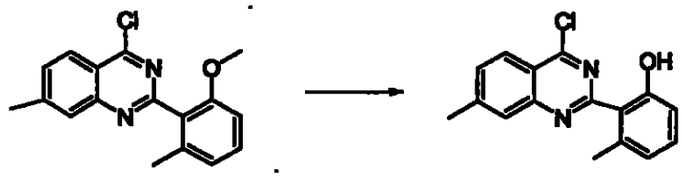
[00808]



[00809] 2-(2-Methoxy-6-methyl-phenyl)-7-methyl-3*H*-quinazolin-4-one (1.61 g, 5.74 mmol) was suspended in benzene after which was added *N,N*-dimethylaniline (1.1 mL, 8.62 mmol) and $POCl_3$ (1.61 mL, 17.27 mmol). The reaction mixture was refluxed for 3 hours during which the color changed from yellow to dark red. The reaction mixture was cooled to room temperature, diluted with 40 mL toluene and poured onto ice. Saturated aq. $NaHCO_3$ was carefully added until the pH remained constant at 7 and no more gas formed. The layers were separated, and the water layer was extracted with toluene. The organic layers were combined and washed with respectively 50 mL saturated aq. NaCl, 60 mL 0.5 N HCl , 40 mL 5% $NaHCO_3$ and 50 mL saturated aq. NaCl. The solution was dried over Na_2SO_4 and evaporated to dryness to yield 1.7 g of the impure product. The product was filtered through silica gel and washed with CH_2Cl_2:heptane (2:1) to yield of 4-chloro-2-(2-methoxy-6-methyl-phenyl)-7-methyl-quinazoline (1.22 g, 71%).

[00810] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-methylphenol

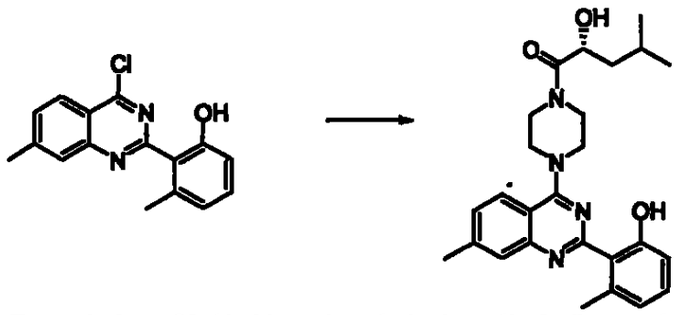
[00811]



[00812] To a solution of 4-chloro-2-(2-methoxy-6-methylphenyl)-7-methylquinazoline (669 mg, 2.24 mmol) in 7 mL CH_2Cl_2 was added dropwise 5 equivalents of a 1 M solution of BBr_3 in CH_2Cl_2 at –78 °C. The reaction was warmed to room temperature and was complete in 30 minutes. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution until the pH was neutral. The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated to obtain 2-(4-chloro-7-methylquinazolin-2-yl)-3-methylphenol. LC/MS: *m/z* 285.1 $(M+H)^+$ at 3.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00813] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00814]

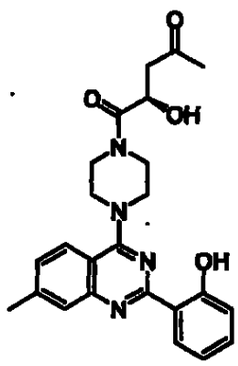


[00815] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-methylphenol (60 mg, 2.1 mmol) in 2 mL CH_2Cl_2 was added triethylamine followed by the addition of (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (54.8 mg, 2.73 mmol). The reaction was complete after 1 hour. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00816] Example 151

[00817] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentane-1,4-dione

[00818]



[00819] Methyl 2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate

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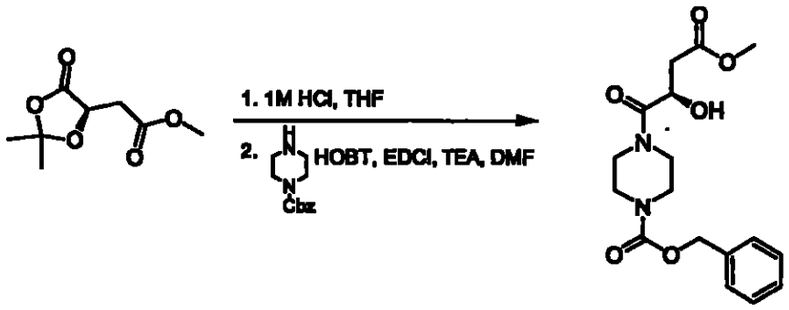
[00820]

[00821] 2-((*R*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (15.8 g, 90.9 mmol) in a 3:1 mixture of THF:MeOH (100 mL) was cooled in an ice bath. After adding 2.0 M $TMSCHN_2$ (50 mL, 100 mmol) the bath was removed, and the mixture was stirred at room temperature for 3 h. The solvent was evaporated, and the crude material was purified via silica gel chromatography using 0–50% EtOAc/hexanes to give methyl 2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate. ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (dd, J = 6.6, 3.8 Hz, 1H), 3.74 (s, 3H), 2.95 (dd, J = 17.0, 3.9 Hz, 1H), 2.81 (dd, J = 17.0, 6.6 Hz, 1H), 1.63 (s, 3H), 1.57 (s, 3H).

[00822] **4-((*R*)-2-Hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester**

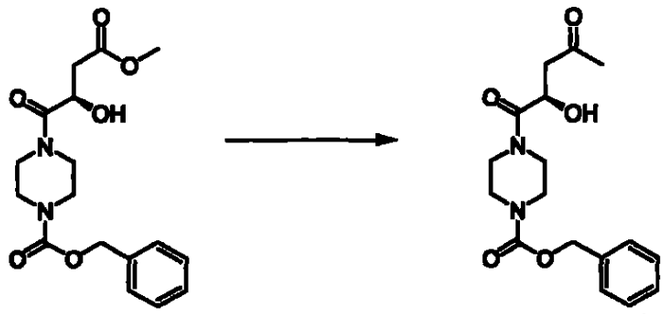
[00823]



[00824] Methyl 2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetate (17.1 g, 90.9 mmol) was stirred in a 1:1 mixture of THF:1 M HCl (200 mL) for 1 h at room temperature. After addition of NaCl to nearly saturate the aqueous layer, the mixture was extracted with EtOAc, and the extracts were dried over Na_2SO_4 and concentrated. To the resulting oil dissolved in dry DMF (500 mL) was added HOBt (13.5 g, 100 mmol) and EDCI (19.2 g, 100 mmol). After stirring for 5 min, benzyl piperazine-1-carboxylate (19.3 mL, 100 mmol) and triethylamine (13.9 mL, 100 mmol) were added to the reaction mixture, which was left stirring at room temperature overnight. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 provided a colorless oil 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (6.71 g, 21%). LC/MS: *m/z* 351.5 $(M+H)^+$ at 2.67 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00825] 4-((*R*)-2-Hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester

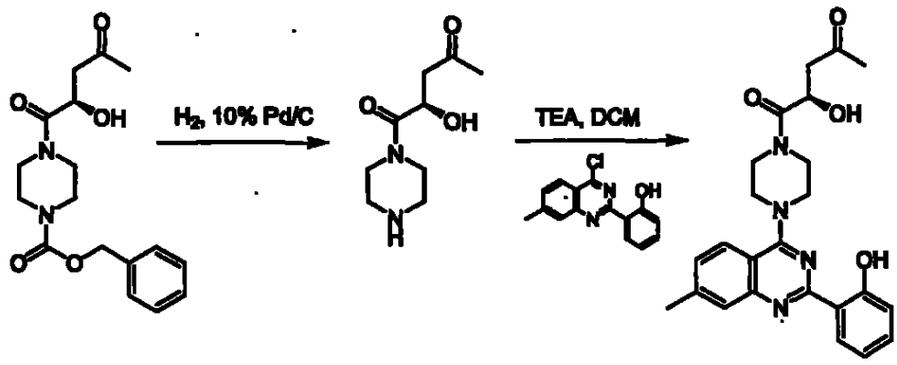
[00826] To a solution of 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (8.5 g, 24.0 mmol) in THF (240 mL) cooled in a dry ice acetone



bath, was added 1.4 M MeMgBr (61 mL, 85 mmol). The reaction was allowed to slowly warm to room temperature overnight. After quenching the mixture with saturated NH_4Cl and extracting with EtOAc, the combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave 4-((*R*)-2-hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester as a colorless oil (0.9 g, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5H), 5.15 (s, 2H), 4.79–4.74 (m, 1H), 4.00 (d, *J* = 7.8 Hz, 1H), 3.75–3.45 (m, 8H), 2.85 (dd, *J* = 16.6, 7.3 Hz, 1H), 2.63 (dd, *J* = 16.6, 3.4 Hz, 1H), 2.26 (s, 3H); LC/MS: *m/z* 335.1 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00827] (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentane-1,4-dione

[00828]



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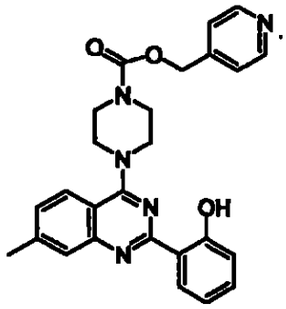
[00829] A mixture of 4-((*R*)-2-hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester (0.13 g, 0.39 mmol) and MeOH (4 mL) was stirred with 10 mg of Pd/C (10% wt Pd on carbon)under H_2 atmosphere at ambient pressure overnight. After filtration and evaporation of the solvent, the residue was taken up in CH_2Cl_2, and 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.11 g, 0.39 mmol) and triethylamine (0.11 mL, 0.78 mmol) were added. The reaction mixture was stirred at room temperature overnight, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 provided (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentane-1,4-dione as a yellow solid (91 mg, 54%). LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

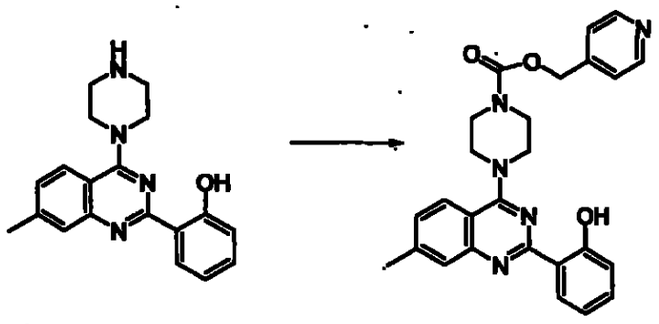
[00830] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00831]



[00832] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate.

[00833]

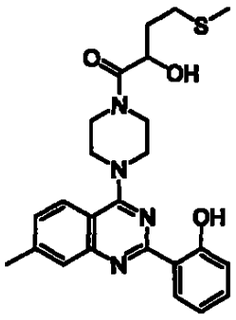


[00834] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (67 mg, 0.32 mmol), and triethylamine (44.6 μL, 0.32 mmol) in DMSO (500 μL) was heated in a microwave synthesizer at 200 °C for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 456.5 $(M+H)^+$ at 2.02 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00835] Example 153

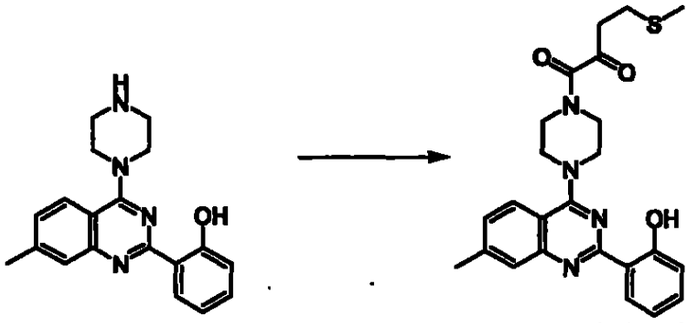
[00836] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butan-1-one

[00837]



[00838] 1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butane-1,2-dione

[00839]



[00840] A mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (200 mg, 0.63 mmol), sodium 4-methylsulfinyl-2-oxo-butyrate (160 mg, 0.94 mmol), BOP (414 mg, 0.94 mmol), and triethylamine (348 μL, 2.5 mmol) in 2.1 mL of CH_2Cl_2 was stirred at room

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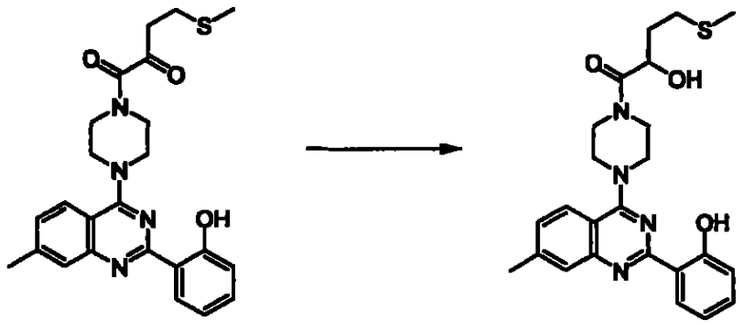
temperature for 1 h. After adding saturated $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated to give 1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butane-1,2-dione. LC/MS: *m/z* 451.2 $(M+H)^+$ at 3.10 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00841] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butan-1-one**

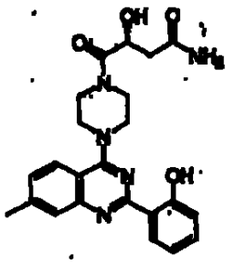
[00842]



[00843] $NaBH_4$ (34 mg, 0.88 mmol) was added to 1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butane-1,2-dione (200 mg, 0.44 mmol) in 1.5 mL of MeOH, and the reaction mixture was stirred at 0 °C for 20 minutes The reaction mixture was allowed to warm to room temperature, saturated $NaHCO_3$ was added, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Purification using preparative reverse phase HPLC with 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-(methylthio)butan-1-one as the TFA salt. (LC/MS: *m/z* 453.4 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

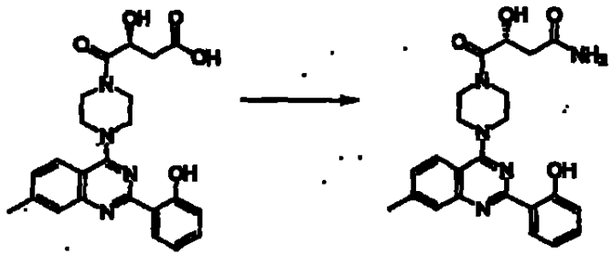
[00844] Example 154

[00845] **(*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanamide**



[00841]

[00842] (*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanamide



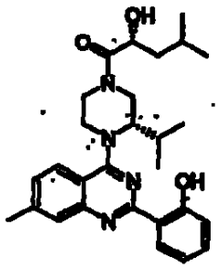
[00843]

[00844] (*R*)-3-Hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid (17 mg, 0.039 mmol) and HATU (16 mg, 0.043 mmol) were stirred in DMF (0.5 mL). After adding 0.5 M NH_3 in dioxane (0.38 mL, 0.19 mmol), the reaction mixture was stirred at room temperature for 5 h. Purification via preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanamide as the TFA salt. LC/MS: *m/z* 436.3 $(M+H)^+$ at 1.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00845] Example 155

[00846] (*R*)-2-Hydroxy-1-((*S*)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-3-isopropylpiperazin-1-yl)-4-methylpentan-1-one

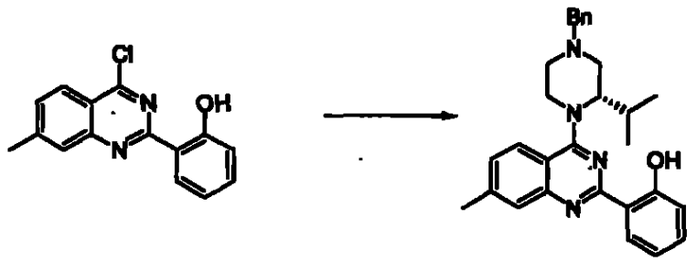
[00847] 2-(4-((*S*)-4-Benzyl-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol



[00852]

[00853] 2-(4-((*S*)-4-Benzyl-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol

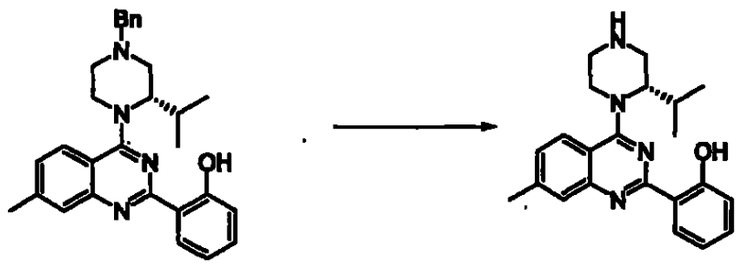
[00854]



[00855] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (200 mg, 0.74 mmol) in 10 mL DMF was added (*S*)-1-benzyl-3-isopropylpiperazine followed by the addition of triethylamine (206 μL). The reaction was heated at 85 °C for two hours. The reaction was quenched with water after cooling it to room temperature. The aqueous layer was extracted twice with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The reaction was purified via silica gel chromatography using 1:1 hexanes:CH_2Cl_2 solvent system to yield 2-(4-((*S*)-4-benzyl-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol (230 mg, 64%). LC/MS: *m/z* 453.5 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00856] 2-(4-((*S*)-2-Isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol

[00857]

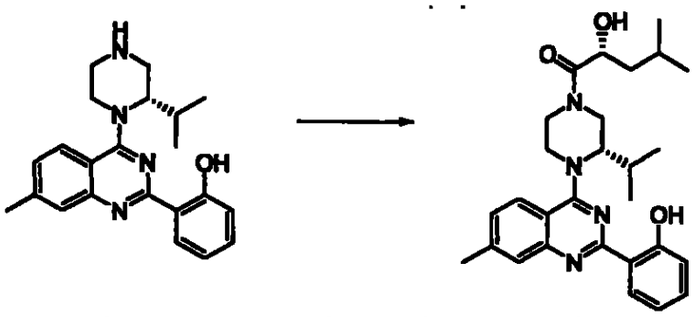


[00858] 20 mg of Pd/C was added to a round-bottom flask, and the flask was flushed with nitrogen followed by evacuation of the atmosphere under vacuum. To the flask was then added a solution of 2-(4-((*S*)-4-benzyl-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol (200 mg, 0.44 mmol) in methanol, followed by the addition of ammonium formate (32 mg, 0.88 mmol). The reaction was refluxed overnight. The reaction was filtered through a bed of Celite

to remove the catalyst. The solvent was evaporated to yield 2-(4-((*S*)-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol (126 mg). LC/MS: *m/z* 363.5 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00859] **(*R*)-2-Hydroxy-1-((*S*)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-3-isopropylpiperazin-1-yl)-4-methylpentan-1-one**

[00860]

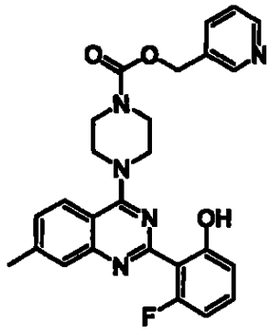


[00861] To a solution of 2-(4-((*S*)-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol (70 mg, 0.19 mmol) in DMF (0.5 mL) was added (*R*)-2-hydroxy-4-methylpentanoic acid (32.6 mg, 0.247 mmol). It was followed by the addition of triethylamine (52 μL) and a solution of HATU (94 mg) in 0.5 mL DMF at room temperature. The reaction was complete in an hour. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-((*S*)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-3-isopropylpiperazin-1-yl)-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 477.5 $(M+H)^+$ at 2.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00862] Example 156

[00863] **(Pyridin-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00864]



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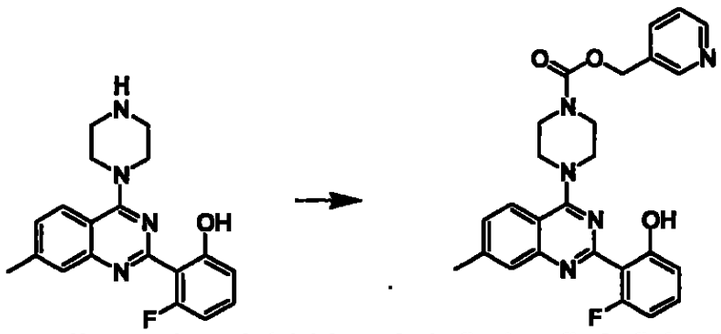
[00865] (Pyridin-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00866]

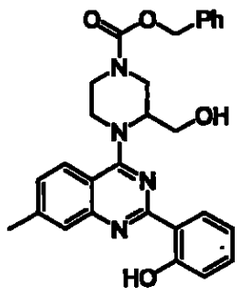


[00867] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.15 mmol), (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (53 mg, 0.26 mmol), triethylamine (30.4 mg, 0.3 mmol) and DMSO (1 mL) were stirred for 18 hours at room temperature. The reaction was purified by preparative reverse phase HPLC to give (pyridin-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 474.30 $(M+H)^+$ at 1.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00868] Example 157

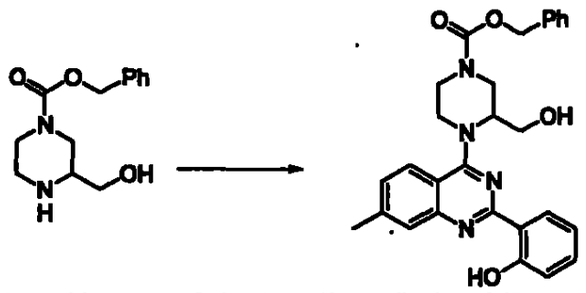
[00869] 3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester

[00870]



[00871] 3-Hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester

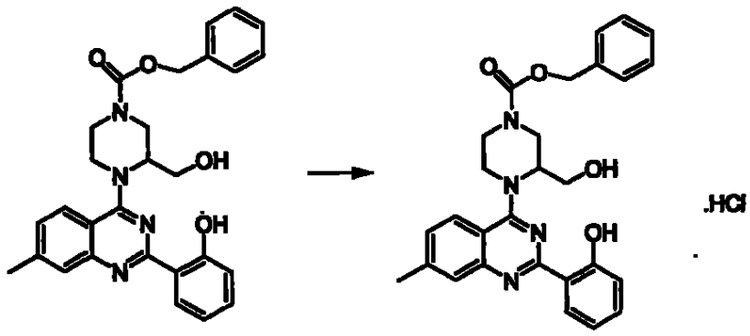
[00872]



[00873] To 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol (245 mg, 0.91 mmol) in 3.0 mL of CH_2Cl_2 was added sequentially 3-hydroxymethyl-piperazine-1-carboxylic acid benzyl ester (336.3 mg, 1.34 mmol) and triethylamine (190 mL, 1.37 mmol), and the reaction mixture was heated at 40 °C for 6 h. The reaction mixture was cooled and extracted with water (2 x 10 mL) and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to give an oil. The residue was purified by normal phase LC (20–85% EtOAc–hexanes) to give 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester (216 mg, 64% yield). LC/MS: *m/z* 485.4 (M+H)+ at 3.02 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00874] **Benzyl 3-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate hydrochloride**

[00875]



[00876] A 2.0 M HCl solution in Et_2O (212 μL, 0.42 mmol) was slowly added at room temperature to a stirring solution of 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester (206 mg, 0.42 mmol) in 500 μL of CH_2Cl_2. The reaction was stirred for 1 hour. Solvents were removed under reduced pressure, and the residue was triturated with Et_2O and filtered to give benzyl 3-(hydroxymethyl)-4-(2-(2-

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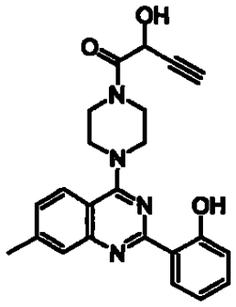
hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate hydrochloride. LC/MS: *m/z* 485.5 (M+H)+ at 3.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[00877] Example 158

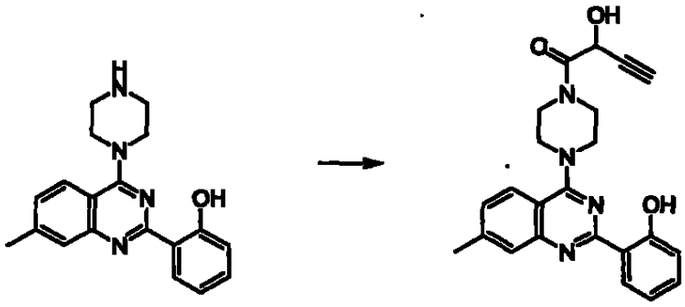
[00878] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)but-3-yn-1-one

[00879]



[00880] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)but-3-yn-1-one

[00881]

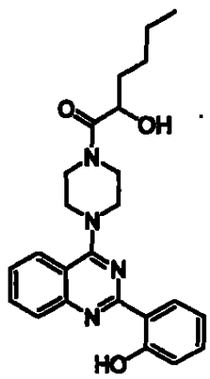


[00882] To a mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (75 mg, 0.23 mmol) in 0.78 ml CH_2Cl_2 were added successively 2-hydroxybut-3-ynoic acid (30 mg, 0.30 mmol), BOP (134 mg, 0.30 mmol), and triethylamine (36 mg, 49 µL, 0.35 mmol). The mixture was stirred at 0 °C for 30 minutes. Purification via silica gel chromatography using 0–100% ethyl acetate/hexanes gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)but-3-yn-1-one. (LC/MS: *m/z* 403.5 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00883] Example 159

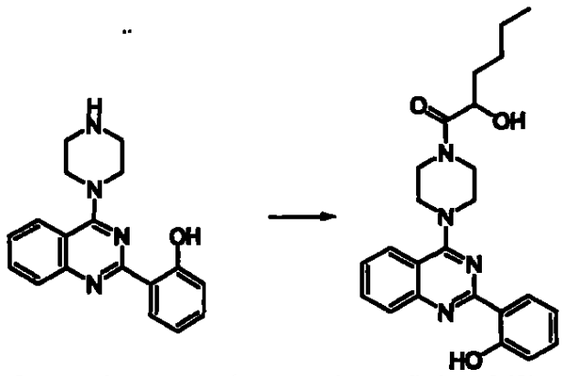
[00884] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00885]



[00886] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00887]



[00888] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-hydroxyhexanoic acid (39.3 mg, 0.297 mmol). Triethylamine (63 μL) was added at room temperature, then a solution of HATU (113 mg) in 0.5 mL DMF. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one. LC/MS: *m/z* 421.3 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00889] Example 160

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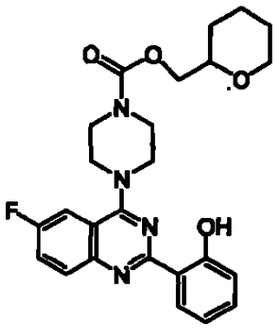
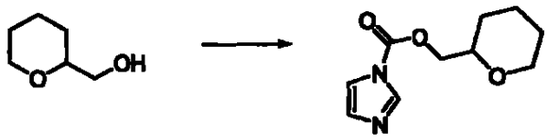
[00890] (Tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00891]



[00892] (Tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate

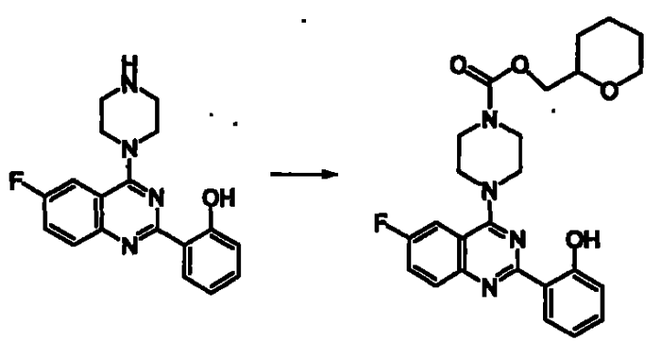
[00893]



[00894] A solution of (tetrahydro-2*H*-pyran-2-yl)methanol (1 g, 8.60 mmol) and di(1*H*-imidazol-1-yl)methanone (2.8 g, 17.2 mmol) in 17 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was quenched with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, *J* = 0.9 Hz, 1H), 7.44 (t, *J* = 1.4 Hz, 1H), 7.07 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.95 (m, 2H), 6.84 (m, 1H), 6.01 (s, 2H), 5.33 (s, 2H)

[00895] (Tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl) quinazolin-4-yl)piperazine-1-carboxylate

[00896]

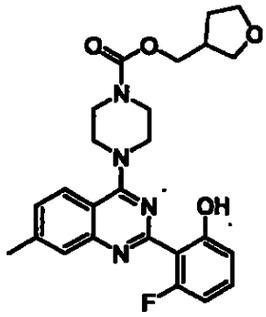


[00897] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.077 mmol), (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (48.5 mg, 0.23 mmol), triethylamine (22μL, 0.154 mmol), and HATU (38 mg, 0.10 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 467.3 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00898] Example 162

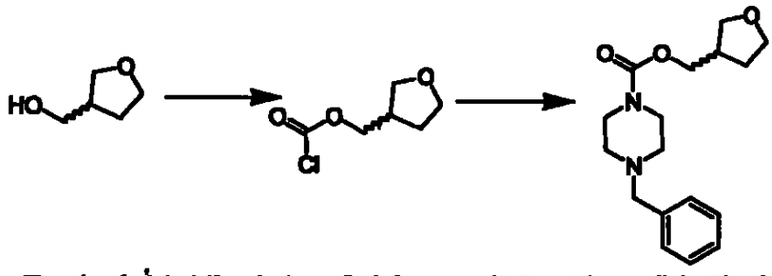
[00899] (Tetrahydrofuran-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00900]



[00901] 4-Benzyl-piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester

[00902]

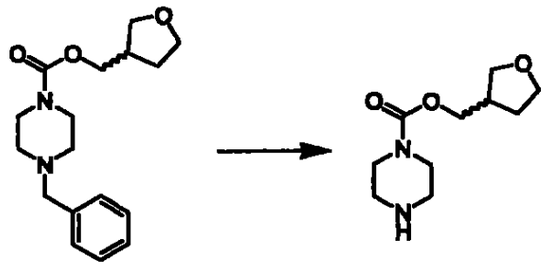


[00903] To a cooled (0 °C) solution of triphosgene (5.0 g, 17 mmol) in 50 ml dichloromethane under a nitrogen atmosphere was added dropwise a solution of tetrahydro-3-furanmethanol (5.4 g, 53 mmol) in 10 ml dichloromethane. Pyridine (4.3 ml, 53 mmol) was added dropwise, and the solution was warmed to room temperature. After 2 hours at room temperature a mixture of triethylamine (7.5 ml, 52 mmol) and *N*-benzylpiperazine (9.5 ml, 54

mmol) was added dropwise with cooling. The resulting mixture was refluxed for 1 hour. The solution was stirred at room temperature overnight under an nitrogen atmosphere. The mixture was washed with aqueous sodium bicarbonate solution (5%, 2 x 50 ml), and with a solution of saturated aqueous NaCl (50 ml). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was co-evaporated three times with toluene (50 ml) to yield 4-benzyl-piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester (13.0 g, 81%) as a brownish oil. .

[00904] **Piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester.**

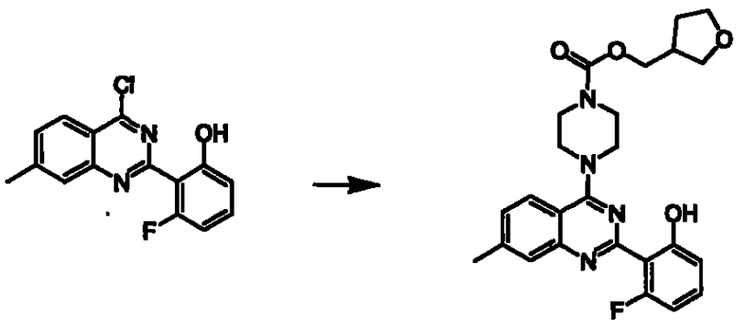
[00905]



[00906] 4-Benzyl-piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester (11.0 g) was dissolved in 100 ml ethanol. Palladium on carbon (10% Pd/C, 0.5 g) was added, and a hydrogen atmosphere was applied overnight at room temperature. The solution was filtered through Celite to remove the catalyst, and the Celite cake was rinsed with 50 ml ethanol. The combined filtrates were evaporated to dryness to yield piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester (8.0 g) as a colorless oil.

[00907] **(Tetrahydrofuran-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00908]

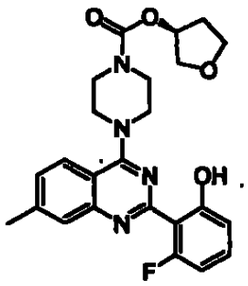


[00909] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (50 mg, 0.174 mmol) was dissolved in 1 mL DMF, followed by the addition of triethylamine (35.2 mg, 0.348 mmol). (Tetrahydrofuran-3-yl)methyl piperazine-1-carboxylate (45 mg, 0.21 mmol) was then added. After 1 hour at room temperature, the reaction was complete. It was filtered and purified by reverse phase preparative HPLC to give (tetrahydrofuran-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. *LC/MS*: *m/z* 467.3 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00910] Example 163

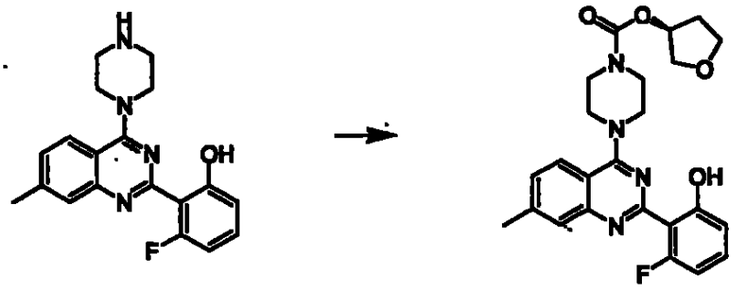
[00911] (*S*)-Tetrahydrofuran-3-yl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00912]



[00913] (*S*)-Tetrahydrofuran-3-yl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00914]



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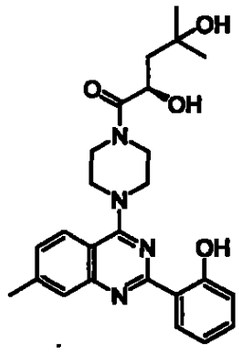
[00915] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.21 mmol) was dissolved in 1 mL anhydrous DMF under an N_2 atmosphere and cooled to 0 °C. (*S*)-Tetrahydrofuran-3-yl chloroformate (34.3 mg, 0.228 mmol) was dissolved in 150 µL anhydrous DMF and added dropwise to the reaction, followed by triethylamine (42 mg, 0.41 mmol). After 1 hour the reaction was complete, and it was filtered and purified by reverse phase HPLC to give (*S*)-tetrahydrofuran-3-yl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00916] Example164

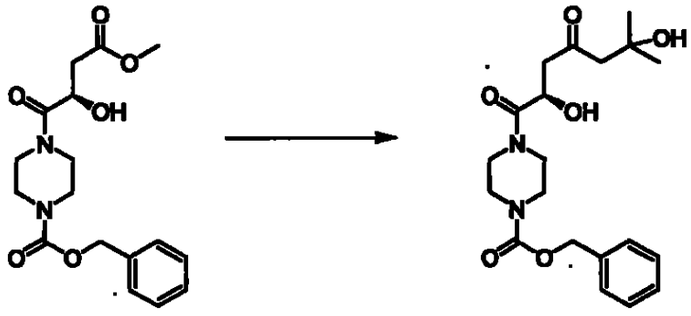
[00917] **(*R*)-2,6-Dihydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-6-methylheptane-1,4-dione**

[00918]



[00919] **4-((*R*)-2,6-Dihydroxy-6-methyl-4-oxo-heptanoyl)-piperazine-1-carboxylicacid benzyl ester**

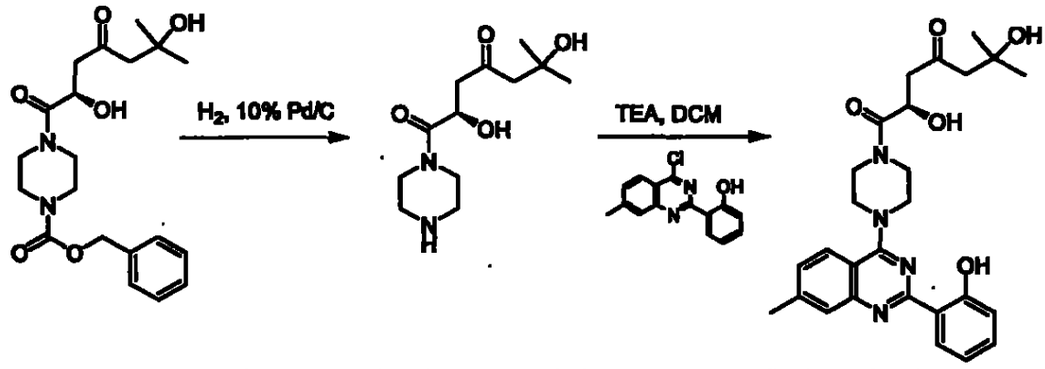
[00920]



[00921] To a solution of 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (5.26 g, 15.0 mmol) in THF (150 mL) cooled in a dry ice acetone bath was added 1.4 M MeMgBr (32 mL, 45 mmol). The reaction was allowed to slowly warm to room temperature overnight. After quenching the mixture with saturated NH_4Cl and extracting with EtOAc, the combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave 4-((*R*)-2-hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester as a colorless oil (0.79 g, 15%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 5.15 (s, 2H), 4.71–4.68 (m, 1H), 4.05 (d, J = 6.8 Hz, 1H), 3.80–3.73 (m, 1H), 3.62–3.42 (m, 6H), 3.31–3.23 (m, 1H), 1.72–1.61 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H); LC/MS: *m/z* 351.3 $(M+H)^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00922] (*R*)-2,4-Dihydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00923]



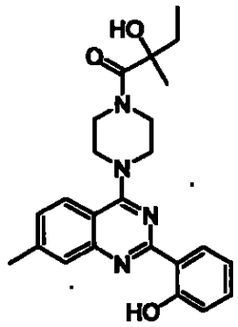
[00924] A mixture of 4-((*R*)-2,6-dihydroxy-6-methyl-4-oxo-heptanoyl)-piperazine-1-carboxylicacid benzyl ester (0.79 g, 2.20 mmol) and MeOH (25 mL) was stirred with 40 mg of Pd/C (10% wt Pd on carbon) under H_2 atmosphere at ambient pressure overnight. After filtration and evaporation of the solvent, the residue was taken up in CH_2Cl_2, and 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.61 g, 2.20 mmol) and triethylamine (0.63 mL, 4.50 mmol) were added. The reaction mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave (*R*)-2,6-dihydroxy-1-(4-(2-(2-

hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-6-methylheptane-1,4-dione as a yellow solid (372 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, J = 7.9, 1.6 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.67 (s, 1H), 7.40–7.36 (m, 1H), 7.29 (dd, J = 8.5, 1.4 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.96–6.92 (m, 1H), 4.81–4.76 (m, 1H), 4.09 (d, J = 6.8 Hz, 1H), 4.03–3.77 (m, 6H), 3.75–3.67 (m, 2H), 3.28 (s, 1H), 2.55 (s, 3H), 1.78–1.69 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 164.0, 161.3, 160.5, 150.1, 144.5, 132.7, 129.2, 127.7, 126.8, 124.4, 119.3, 118.5, 117.7, 112.7, 70.6, 66.4, 49.9, 49.0, 46.1, 44.5, 42.4, 30.6, 29.2, 21.9; LC/MS: *m/z* 451.1 $(M+H)^+$ at 2.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00925] Example 165

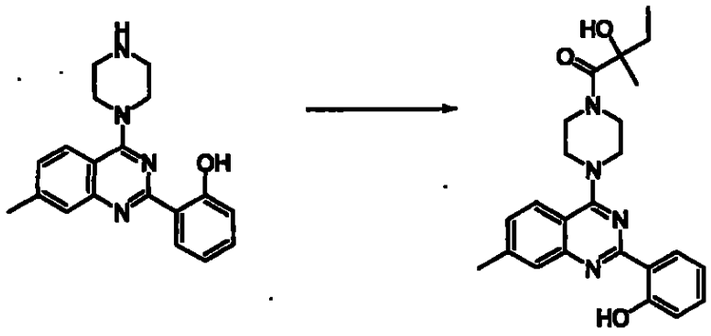
[00926] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one

[00927]



[00928] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one

[00929]

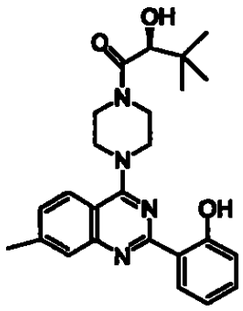


[00930] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxy-2-methylbutanoic acid (33.6 mg, 0.284 mmol). Triethylamine (61 μL) was added, followed by a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 421.3 $(M+H)^+$ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00931] Example 166

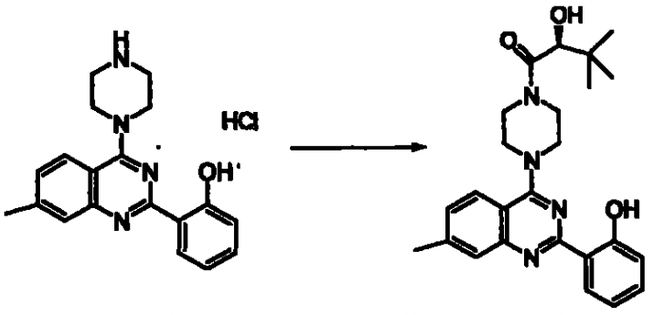
(*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3,3-dimethylbutan-1-one

[00932]



[00933] (*S*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3,3-dimethylbutan-1-one

[00934]



[00935] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol hydrochloride (30 mg, 0.09 mmol), (*S*)-2-hydroxy-3,3-dimethylbutanoic acid (16 mg, 0.12 mmol), triethylamine (37.5μL, 0.27 mmol), and HATU (45.6 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight.

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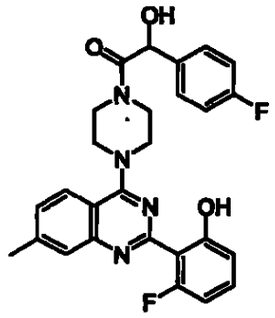
Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3,3-dimethylbutan-1-one as the TFA salt. *LC/MS*: *m/z* 434.53 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00936] Example 167

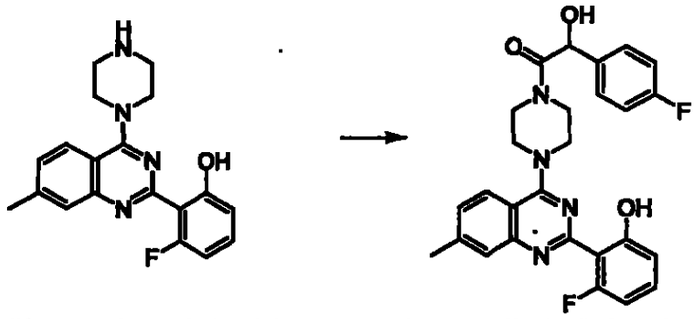
[00937] **1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-(4-fluorophenyl)-2-hydroxyethanone**

[00938]



[00939] **1-(4-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-(4-fluorophenyl)-2-hydroxyethanone**

[00940]



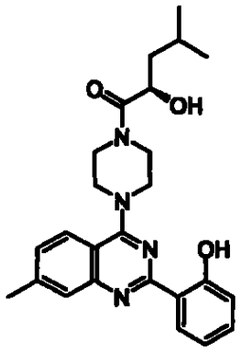
[00941] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol), 2-(4-fluorophenyl)-2-hydroxyacetic acid (19.62 mg, 0.12 mmol), triethylamine (25 μL, 0.18 mmol) and HATU (45.6 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 1-(4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-(4-fluorophenyl)-

2-hydroxyethanone as the TFA salt. LC/MS: *m/z* 491.3 $(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00942] Example 168

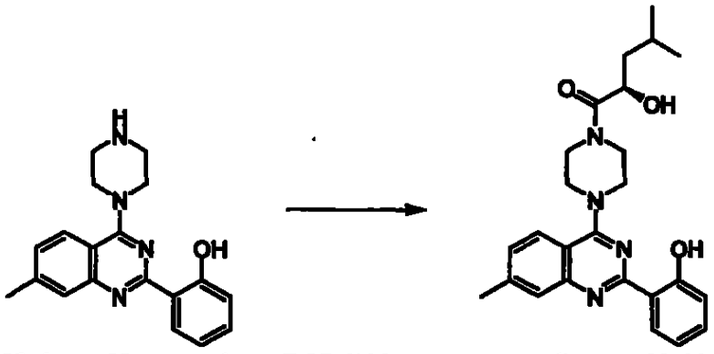
[00943] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00944]



[00945] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00946]



[00947] Under an N_2 atmosphere, BOP (138 mg, 0.31 mmol) was added in a single portion to a stirring solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (100 mg, 0.31 mmol), (*R*)-2-hydroxy-4-methylpentanoic acid (41 mg, 0.31 mmol), and triethylamine (43 µL, 0.31 mmol) in DMF (0.5 ml). After stirring the mixture for 1 h at room temperature, it was partitioned between H_2O and ether. The organic phase was washed with H_2O (3x 20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 20%

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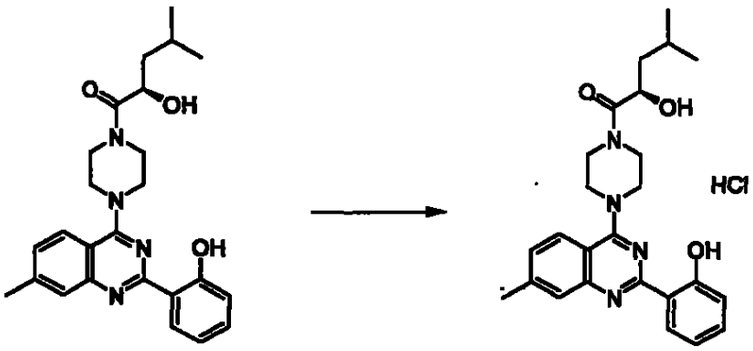
EtOAc and 80% CH_2Cl_2 gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one as a light yellow solid (89 mg, 60%). LC/MS: *m/z* 435.1 (M+H)+ at 2.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.66 (s, 1H), 7.41–7.37 (m, 1H), 7.30 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.06–7.04 (m, 1H), 6.98–6.94 (m, 1H), 4.51–4.45 (m, 1H), 4.04–3.80 (m, 6H), 3.72–3.62 (m, 3H), 2.56 (s, 3H), 2.12–1.99 (m, 1H), 1.57–1.49 (m, 1H), 1.38–1.32 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H).

[00948] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride**

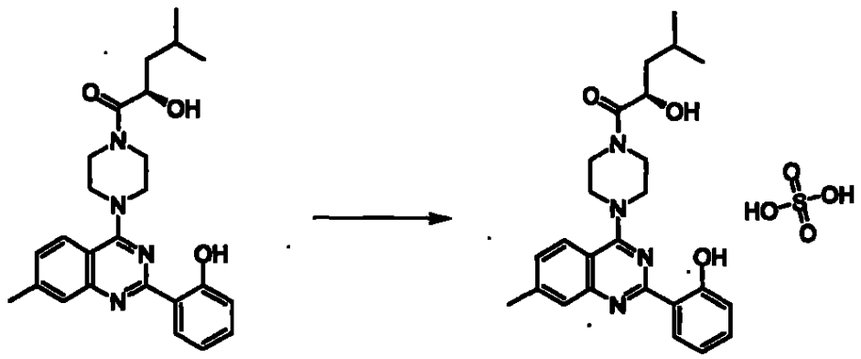
[00949]



[00950] (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (90 mg, 0.20 mmol) was dissolved in 1 mL CH_2Cl_2 and treated with 1 equivalent of 2.0 M HCl in ether (100 μL, 0.20 mmol). The formed precipitate was filtered and vacuum dried to obtain (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one hydrochloride. LC/MS: *m/z* 435.1 (M+H)+ at 2.84 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, CD_3OD) δ 8.39–8.37 (m, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.61–7.55 (m, 2H), 7.15–7.11 (m, 2H), 4.57 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.49–4.32 (m, 4H), 4.07–3.79 (m, 4H), 2.62 (s, 3H), 1.97–1.87 (m, 1H), 1.65–1.58 (m, 1H), 1.53–1.47 (m, 1H), 1.03–1.00 (m, 6H).

[00951] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one sulfate**

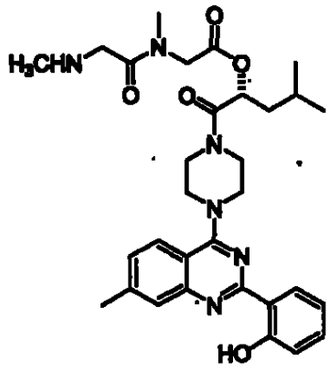
[00952]



[00953] To a stirring yellow solution of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one (200 mg, 0.46 mmol) and THF (0.9 mL) under an N_2 atmosphere was added a solution of concentrated H_2SO_4 solution (95.9%) (26 μL, 0.46 mmol) and CH_3CN (0.75 mL) in a single portion. A white precipitate formed slowly over a period of 1 h. The solid was filtered and vacuum dried to obtain (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one sulfate as a white solid (229 mg, 94%). *LC/MS*: *m/z* 435.3 (M+H)+ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.20 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.53–7.49 (m, 2H), 7.10–7.03 (m, 2H), 4.39–4.35 (m, 1H), 4.30–4.04 (m, 4H), 3.93–3.69 (m, 4H), 2.55 (s, 3H), 1.86–1.73 (m, 1H), 1.52–1.33 (m, 2H), 0.93–0.91 (m, 6H).

[00954] Example 169

[00955] (*R*)-[Methyl-(2-methylamino-acetyl)-amino]-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester



[00956]

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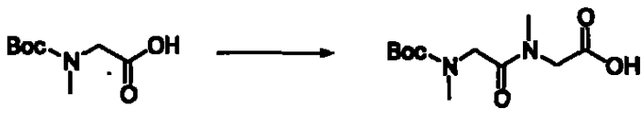
[00957] {[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid

[00958]

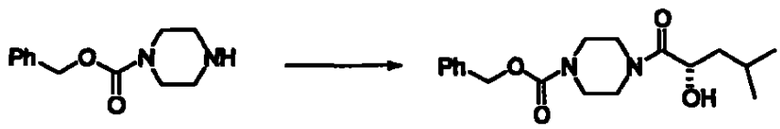


[00959] To (*tert*-butoxycarbonyl-methyl-amino)-acetic acid (2.73 g, 14.4 mmol) in 70 mL of THF was added sequentially diisopropyl ethylamine (7.5 mL, 14.4 mmol) and HBTU (5.47 g, 14.4 mmol), and the reaction mixture was stirred at room temperature for one hour. To this reaction mixture was added methylamino-acetic acid ethyl ester (2.22 g, 14.4 mmol) in one portion, and the reaction mixture was heated at 65 °C for 12 h. The reaction mixture was cooled, diluted with a solution of saturated $NaHCO_3$, and extracted with EtOAc. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid ethyl ester.

The ester was taken up in 49 mL of methanol, and to this was added a 1 *M* NaOH solution (25.1 mL, 25 mmol). The reaction mixture was heated at 65 °C for 3 h. The reaction mixture was cooled, and methanol was removed under reduced pressure. The residue was diluted with 50 mL of water and acidified with glacial acetic acid until the pH was 5. This solution was extracted with EtOAc (50 mL), and the organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give {[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid as an oil.

[00960] 4-(2(*R*)-Hydroxy-4-methyl-pentanoyl)-piperazine-1-carboxylic acid benzyl ester

[00961]

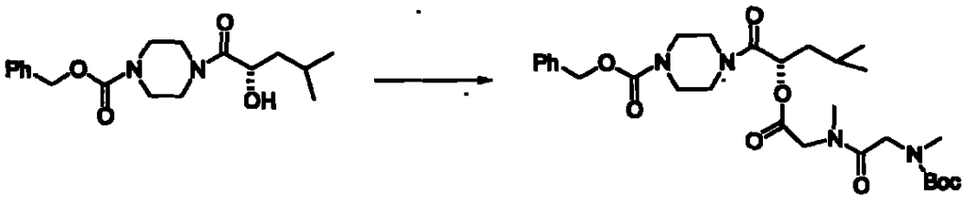


[00962] To (*R*)- 2-hydroxy-4-methyl-pentanoic acid (1.71 g, 12.9 mmol) in 48 mL of DMF was added sequentially triethylamine (4.9 mL, 35. mmol), HOBt (1.75 g, 12.9 mmol), EDCI·HCl (2.48 g, 12.9 mmol) and piperazine-1-carboxylic acid benzyl ester (2.59 g, 11.8 mmol) at room temperature. The reaction mixture was stirred for 4 h and then diluted with EtOAc (50 mL) and extracted with 50 mL of water. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue

was subjected to purification by normal phase LC using 40–85% EtOAc–hexanes to give (1.92 g, 49% yield) of 4-(2(*R*)-hydroxy-4-methyl-pentanoyl)-piperazine-1-carboxylic acid benzyl ester the desired product. LC/MS: *m/z* 335.4 $(M+H)^+$ at 2.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

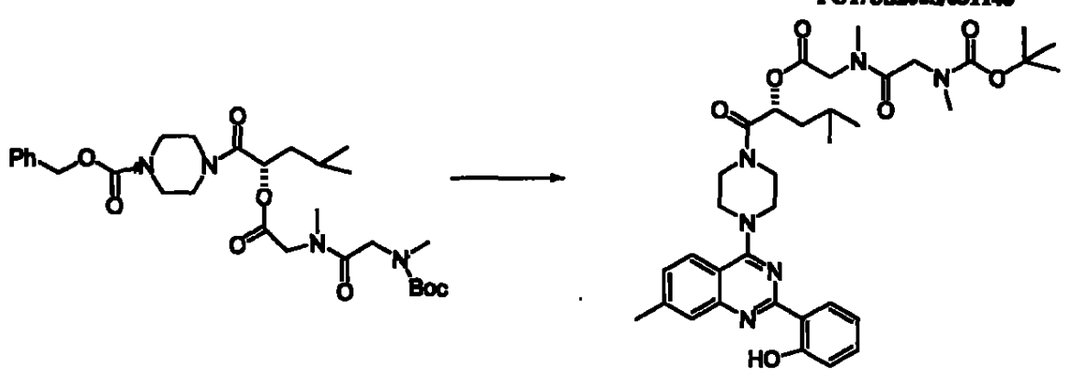
[00963] **4-[2-(2-{[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetoxy)-4-methyl-pentanoyl]-piperazine-1-carboxylic acid benzyl ester**

[00964]



[00965] To {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid (427 mg, 1.57 mmol) in 2 mL of THF was added sequentially HBTU (624 mg, 1.2 mmol), diisopropyl ethylamine (860 μL, 4.71 mmol) at room temperature. After 5 min, 4-(2-hydroxy-4-methyl-pentanoyl)-piperazine-1-carboxylic acid benzyl ester (403 mg 1.2 mmol) in 2 mL of THF was added to the reaction mixture, and the solution was heated at 65 °C for 12 h. The reaction mixture was cooled and diluted with 20 mL of CH_2Cl_2 and 10 mL of water. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was subjected to purification by normal phase LC using 30–100% EtOAc–hexanes to give 4-[2-(2-{[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetoxy)-4-methyl-pentanoyl]-piperazine-1-carboxylic acid benzyl ester (283 mg, 41% yield). LC/MS: *m/z* 577 $(M+H)^+$ at 3.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

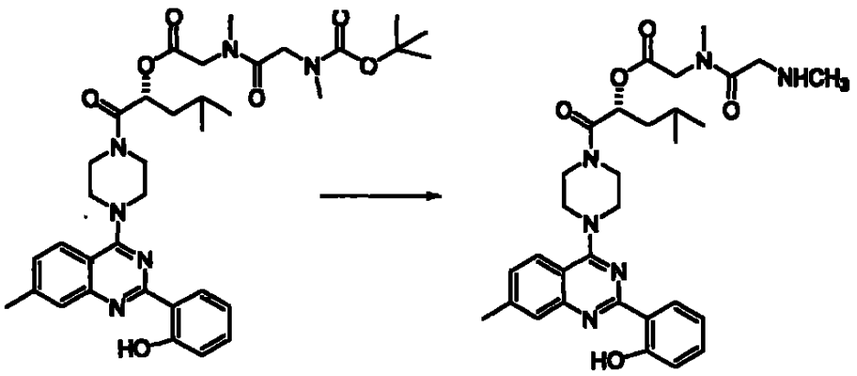
[00966] **{[2-(*tert*-Butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester.**



[00967] To 4-[2-(2-{[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetoxy)-4-methyl-pentanoyl]-piperazine-1-carboxylic acid benzyl ester (208 mg, 0.49 mmol) in 1.6 mL of methanol was added 70 mg of Pd/C (10% wt Pd on carbon). The reaction mixture was hydrogenated using a balloon of H_2 for 4 h at room temperature. The mixture was then filtered through Celite, and the solvent removed to give {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid 3-methyl-1-(piperazine-1-carbonyl)-butyl ester.

The amine was taken up in 1 mL CH_2Cl_2 and treated with 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol (53 mg, 0.19 mmol) and 49 μL of triethylamine, and stirred at room temperature for 3 h. The reaction mixture was diluted with 10 mL of CH_2Cl_2 and 10 mL of water. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester. LC/MS: *m/z* 677.4 $(M+H)^+$ at 3.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00968] [Methyl-(2-methylamino-acetyl)-amino]-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester.



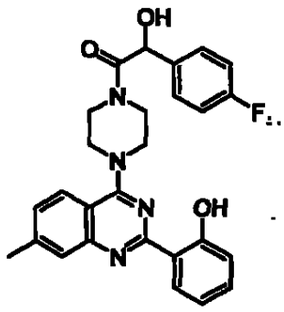
[00969]

[00970] To {[2-(*tert*-butoxycarbonyl-methyl-amino)-acetyl]-methyl-amino}-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester (42 mg, 0.062 mmol) was added 300 μL of 1.25 M HCl in methanol at room temperature, and the reaction mixture was stirred for 12 h. The solvent was removed, and the residue was purified with reverse phase *LC* using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) as eluent to give [methyl-(2-methylamino-acetyl)-amino]-acetic acid 1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carbonyl}-3-methyl-butyl ester as the TFA salt. *LC/MS*: *m/z* 577.4 (M+H)+ at 2.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00971] Example 170

[00972] **2-(4-Fluorophenyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone**

[00973]



[00974] **2-(4-Fluorophenyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone**

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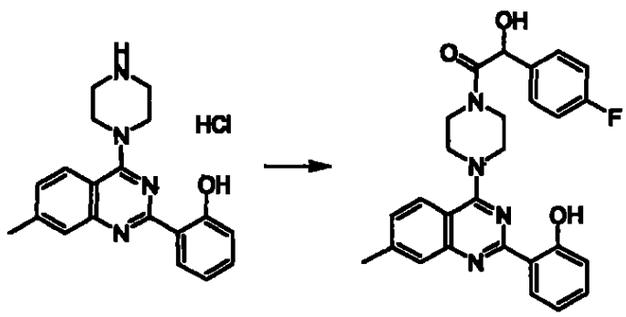
[00975]

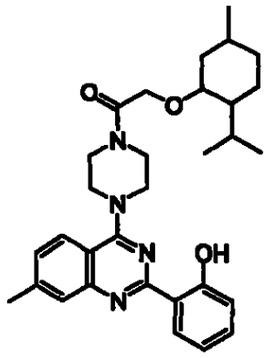


[00976] 2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol hydrochloride (prepared analogously to 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol, oxalate salt, see Example 130; 30 mg, 0.09 mmol), 2-(4-fluorophenyl)-2-hydroxyacetic acid (20 mg, 0.12 mmol), triethylamine (37.5 μL, 0.27 mmol) and HATU (45 mg, 0.12 mmol) were stirred in DMF (1 mL) overnight. Purification via preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-(4-fluorophenyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone as the TFA salt. LC/MS: *m/z* 473.1 $(M+H)^+$ at 2.63 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00977] Example 171

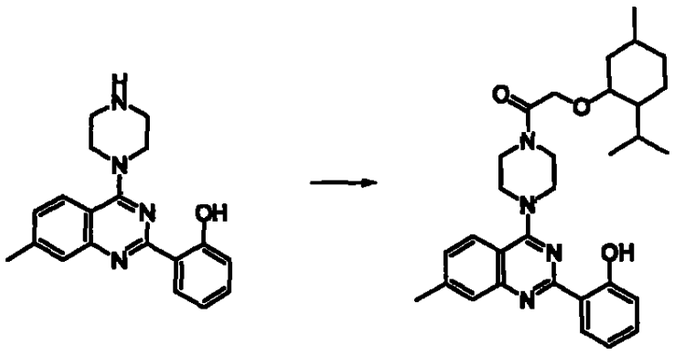
[00978] 2-(2-Isopropyl-5-methylcyclohexyloxy)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone

[00979]



[00980] 2-(2-Isopropyl-5-methylcyclohexyloxy)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone

[00981]

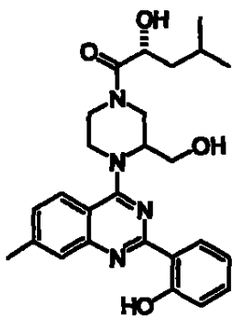


[00982] To a solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added of triethylamine (25 μL) followed by the dropwise addition of 2-(2-isopropyl-5-methylcyclohexyloxy)acetyl chloride (21 μL, 0.09 mmol) at 0 °C. The reaction was warmed to room temperature, and purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-(2-isopropyl-5-methylcyclohexyloxy)-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)ethanone as the TFA salt. LC/MS: *m/z* 517.5 $(M+H)^+$ at 3.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00983] Example 172

[00984] (*R*)-2-Hydroxy-1-{3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one

[00985]



[00986] (*R*)-2-Hydroxy-1-{3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one

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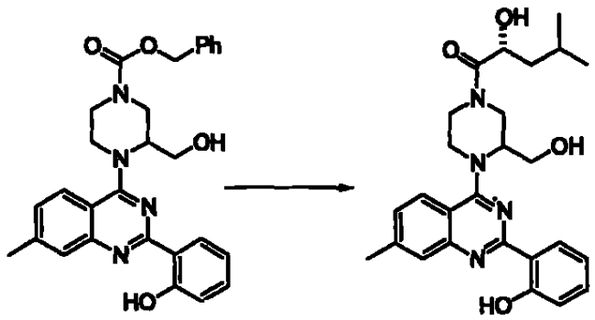
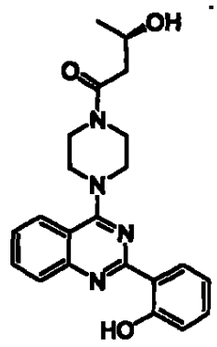
[00987]



[00988] To 3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazine-1-carboxylic acid benzyl ester (200 mg, 0.41 mmol) in 1.7 mL of methanol was added 39 mg of Pd /C (10% weight Pd on carbon). The reaction mixture was subjected to hydrogenation using a H_2 balloon for 3 h. The reaction mixture was filtered through Celite and the solvent was removed to give 2-[4-(2-hydroxymethyl-piperazin-1-yl)-7-methyl-quinazolin-2-yl]-phenol. This amine was treated with (*R*)-2-hydroxy-4-methyl-pentanoic acid (60 mg, 0.45 mmol), BOP (200 mg, 0.45 mmol) and 115 μL of triethylamine in 1.6 mL of DMF at room temperature for 12 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and 20 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to purification using 60–100% EtOAc–hexanes to give (*R*)-2-hydroxy-1-{3-hydroxymethyl-4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-methyl-pentan-1-one. LC/MS: *m/z* 465 (M+H)+ at 2.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00989] Example 173

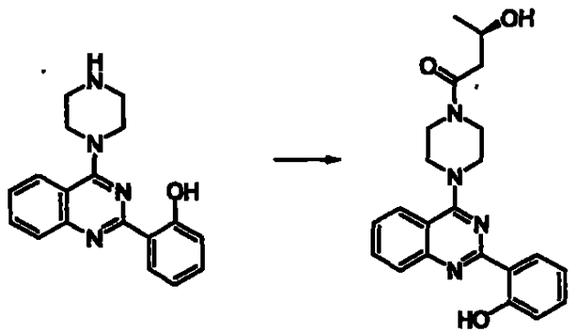
[00990] (*R*)-3-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one



[00991]

[00992] (*R*)-3-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00993]



[00994] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*R*)-3-hydroxybutanoic acid (31 mg, 0.30 mmol). Then, triethylamine (63 μL) was added, followed by a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-3-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. *LC/MS*: *m/z* 393.1 $(M+H)^+$ at 2.03 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00995] Example 174

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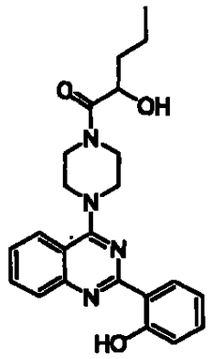
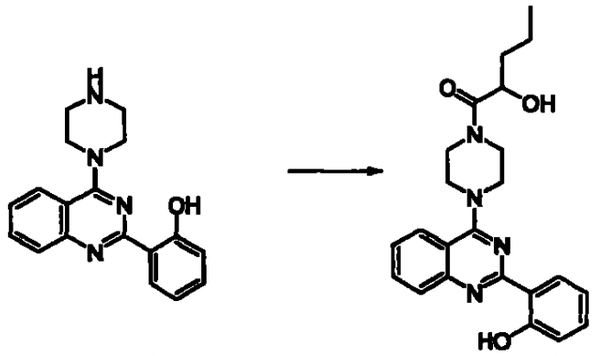
[00996] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)pentan-1-one

[00997]



[00998] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)pentan-1-one

[00999]

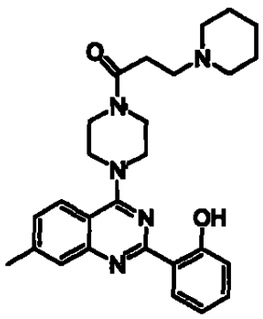


[001000] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-hydroxypentanoic acid (35 mg, 0.30 mmol). This was followed by the addition of triethylamine (63 μL) and a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.41 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001001] Example 175

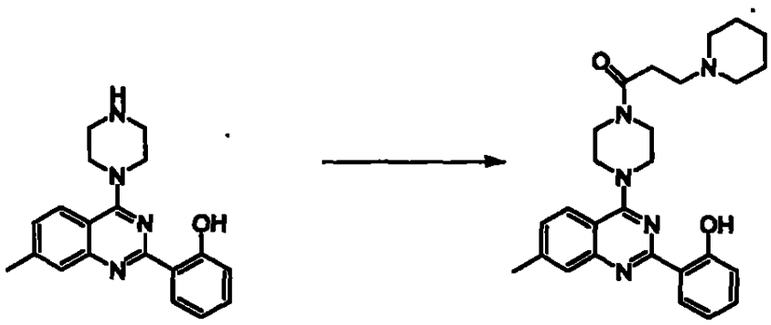
[001002] 1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(piperidin-1-yl)propan-1-one

[001003]



[001004] 1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(piperidin-1-yl)propan-1-one

[001005]

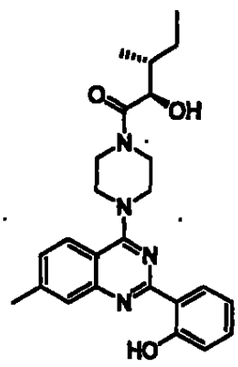


[001006] To 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (53 mg, 0.17 mmol) was added sequentially 3-(piperidin-1-yl)propanoyl chloride (33 mg, 0.19 mmol) in 28 μL of CH_2Cl_2 and triethylamine (28 μL, 0.2 mmol). The mixture was stirred at 0 °C for 20 minutes After adding H_2O and CH_2Cl_2, the phases were separated, and the organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification using preparative reverse phase HPLC with 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave 3-cyclopentyl-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. *LC/MS*: *m/z* 460.5 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001007] Example 176

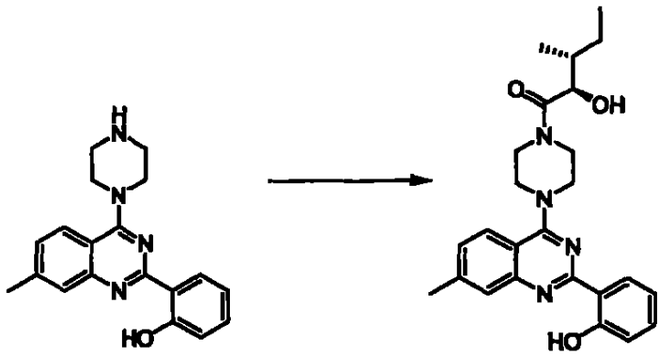
[001008] (2*R*,3*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylpentan-1-one

[001009]



[001010] (2*R*,3*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylpentan-1-one

[001011]

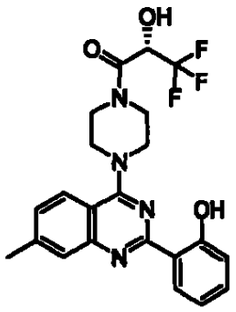


[001012] To 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (80 mg, 0.25 mmol) in 800 μL of CH_2Cl_2 was added sodium of (2*R*,3*R*)-2-hydroxy-3-methyl-pentanoate (50 mg, 0.33 mmol), BOP (144 mg, 0.33 mmol), and triethylamine (52 μL, 0.38 mmol). The reaction mixture was stirred at room temperature for 2 h. After adding H_2O and CH_2Cl_2, the layers were separated, and the organic layer was dried over Na_2SO_4 and concentrated. Purification via preparative reverse phase HPLC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave (2*R*,3*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.62 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001013] Example 177

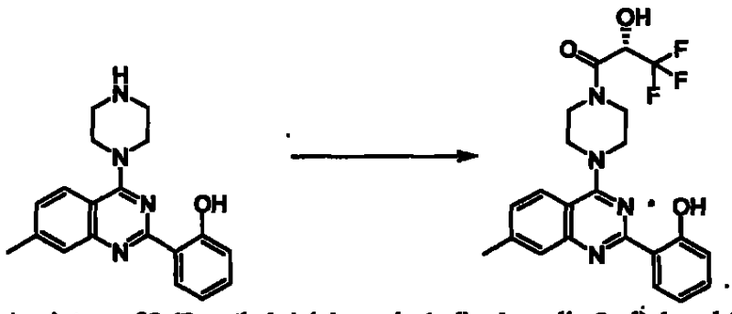
[001014] (*S*)-3,3,3-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[001015]



[001016] (*S*)-3,3,3-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[001017]



[001018] A mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (64 mg, 0.2 mmol), (*S*)-3,3,3-trifluoro-2-hydroxypropanoic acid (29 mg, 0.2 mmol), HATU (76 mg, 0.2 mmol) and triethylamine (28 μL, 0.2 mmol) in DMF (1 mL) was stirred at room temperature overnight. Purification via preparative HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-3,3,3-trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 447.1 $(M+H)^+$ at 2.53 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001019] Example 178

[001020] 2-(Trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl) quinazolin-4-yl)piperazin-1-yl)propan-1-one

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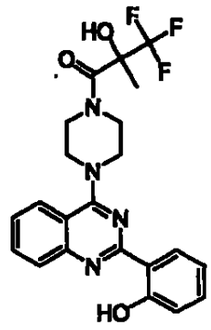
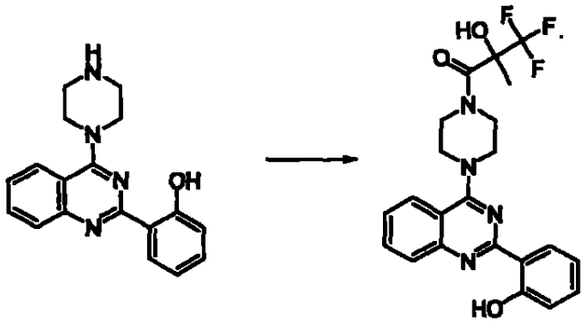
[001021]



[001022] 2-(Trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl) quinazolin-4-yl)piperazin-1-yl)propan-1-one

[001023]

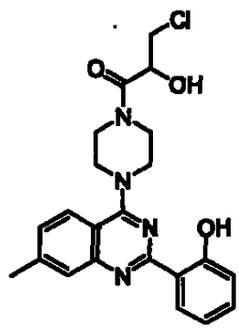


[001024] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-(trifluoromethyl)-2-hydroxypropanoic acid (47.0 mg, 0.297 mmol). Then, triethylamine (63 μL) was added, followed by a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-(trifluoromethyl)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. *LC/MS*: *m/z* 447.3 $(M+H)^+$ at 2.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001025] Example 179

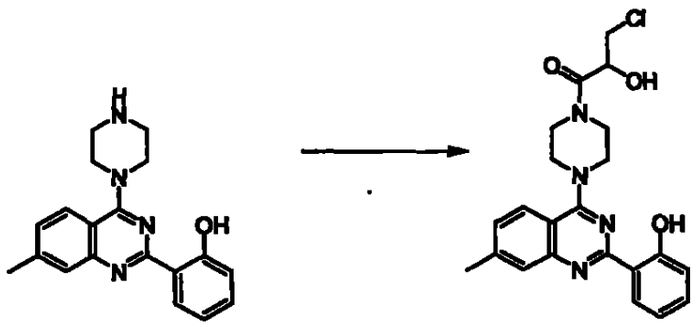
[001026] 3-Chloro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[001027]



[001028] 3-Chloro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one

[001029]

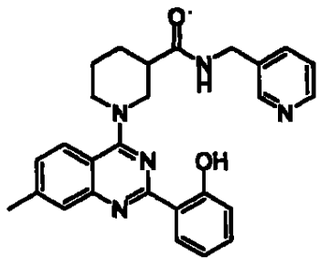


[001030] A mixture of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (121 mg, 0.38 mmol), 3-chloro-2-hydroxypropanoic acid (61 mg, 0.49 mmol), BOP (217 mg, 0.49 mmol), and triethylamine (79 μL, 0.56 mmol) in 1.2 mL of CH_2Cl_2 was stirred at room temperature for 1 h. The reaction was washed with water and the organic layer was dried over Na_2SO_4 and concentrated. Purification via preparative reverse phase HPLC using 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave 3-chloro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)propan-1-one as the TFA salt. LC/MS: *m/z* 427.2 $(M+H)^+$ at 2.59 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001031] Example 201

[001032] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)piperidine-3-carboxamide

[001033]



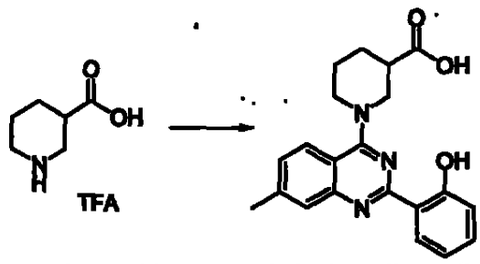
[001034] **Piperidine-3-carboxylic acid**

[001035]

[001036] To a solution of 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid (500 mg, 2.18 mmol) in CH_2Cl_2 (10 mL) was added TFA (5 ml). The reaction mixture was stirred for an hour. Excess TFA was removed under reduced pressure, and the piperidine-3-carboxylic acid was used without neutralization for the next step. LC/MS: *m/z* 1303 $(M+H)^+$ at 0.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001037] **1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid**

[001038]

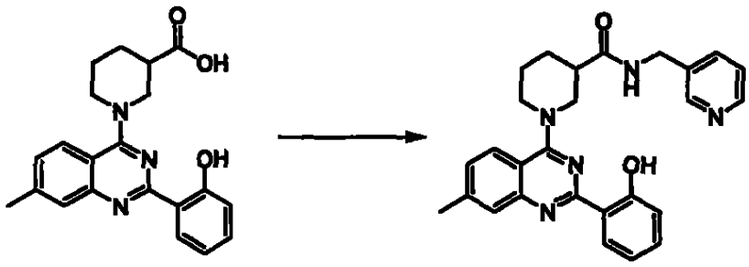


[001039] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.449 mg, 1.66 mmol) in CH_2Cl_2 was added 5 equivalents of triethylamine followed by the addition of piperidine-3-carboxylic acid as a TFA salt. The reaction was stirred for 2 hours and quenched with water. The layers were separated, and the organic extracts were dried over $MgSO_4$, filtered,

and concentrated to give 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid which was used without further purification. *LC/MS*: *m/z* 364.3 $(M+H)^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001040] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)piperidine-3-carboxamide

[001041]

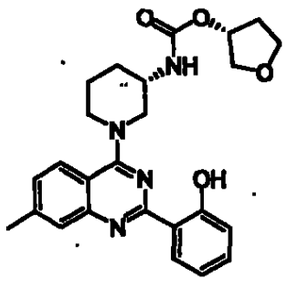


[001042] A solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid (45 mg, 0.12 mmol), (pyridin-3-yl)methanamine (14 μL, 0.136 mmol) and triethylamine (25 mg, 35 μL, 0.25 mmol) in 500 μL DMF was cooled to 0 °C, and HATU (57 mg, 0.15 mmol) was added. The reaction was warmed to room temperature, stirred overnight and purified by reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) giving 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)piperidine-3-carboxamide as the TFA salt. *LC/MS*: *m/z* 454.5 $(M+H)^+$ at 1.87 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001043] Example 203

[001044] (*R*)-Tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001045]



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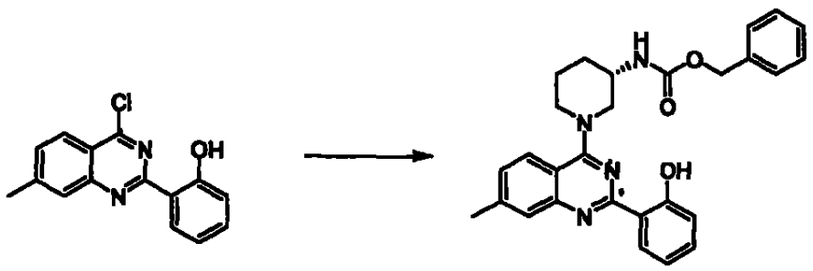
[001046] Benzyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

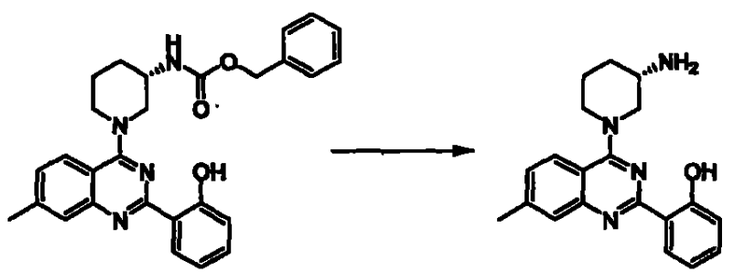
[001047]



[001048] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (1.15 g, 4.26 mmol) in CH_2Cl_2 (25 mL) at 0 °C under inert atmosphere was slowly added a solution of benzyl (*S*)-piperidin-3-ylcarbamate (1.0 g, 4.26 mmol) and triethylamine (1.18 mL, 8.52 mmol) in CH_2Cl_2 (10 mL). The reaction was allowed to warm to room temperature and was then quenched with water. The mixture was extracted with CH_2Cl_2 and the organic layers were combined, dried over $MgSO_4$, and concentrated to obtain benzyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate (2.03 g). This material was used without further purification. *LC/MS*: *m/z* 469.1 $(M+H)^+$ at 2.86 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001049] 2-(4-((*S*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001050]

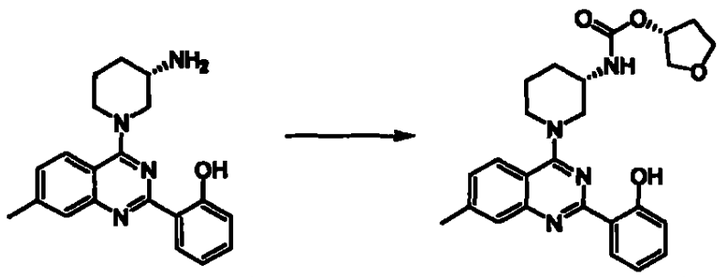


[001051] Pd/C (175 mg, 10% weight Pd on carbon) was added to a round bottom flask and the flask was flushed with N_2. To this flask was then added MeOH (10 mL). After purging the flask again with N_2, (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate (1.75 g, 3.74 mmol) dissolved in EtOAc (60 mL) and MeOH (50 mL) was added. After flushing the flask 3 times with N_2, and evacuating it under vacuum, H_2 was passed through

the vigorously stirring mixture for 4 h until hydrogenation was complete. The mixture was filtered through a pad of Celite. The filtrate was concentrated to afford 2-(4-((*S*)-3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.62 g, 50%). LC/MS: *m/z* 335.5(M+H)$^+$ at 1.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001052] (*R*)-Tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001053]

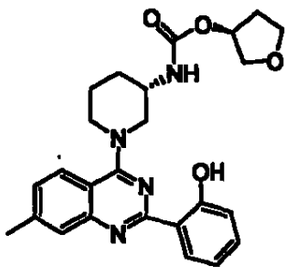


[001054] 2-(4-((*S*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol), (*R*)-tetrahydrofuran-3-yl chloroformate (22.6 mg, 0.15 mmol) and triethylamine (30 mg, 0.3 mmol) were stirred in DMF (1 mL) at 0 °C. After allowing the reaction to warm to room temperature, it was purified via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (*R*)-tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 449.3.5(M+H)$^+$ at 1.52 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001055] Example 204

[001056] (*S*)-Tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

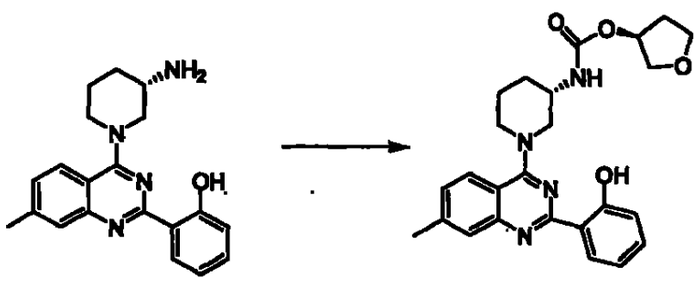
[001057]



367

[001058] (*S*)-Tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001059]

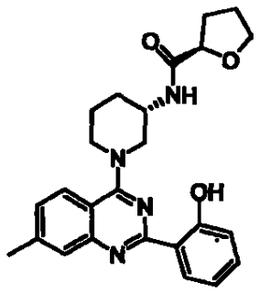


[001060] 2-(4-((*S*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol), (*S*)-tetrahydrofuran-3-yl chloroformate (22.6 mg, 0.15 mmol), and triethylamine (30 mg, 0.3 mmol) were stirred in DMF (1 mL) at 0 °C. After allowing the reaction to warm to room temperature it was purified via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (*S*)-tetrahydrofuran-3-yl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001061] Example 205

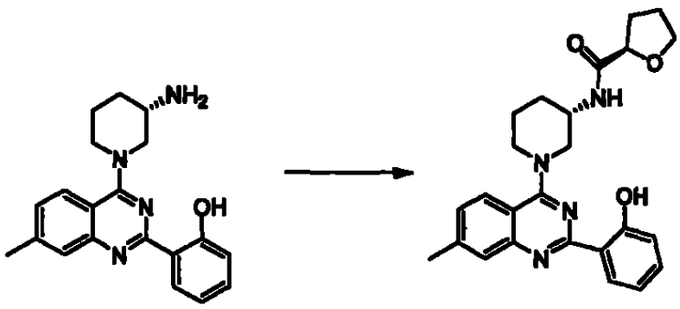
[001062] (2*R*)-Tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide

[001063]



[001064] (2*R*)-Tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide

[001065]

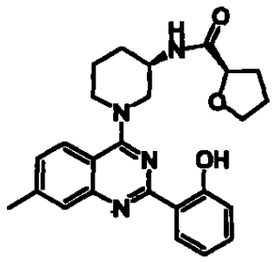


[001066] 2-(4-((*S*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol), (*R*)-tetrahydrofuran-2-carboxylic acid (22.6 mg, 0.195 mmol), triethylamine (30 mg, 0.3 mmol), and HATU (74.14 mg, 0.195 mmol) were stirred at room temperature in DMF for 1 h. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 433.3$(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001067] Example 206

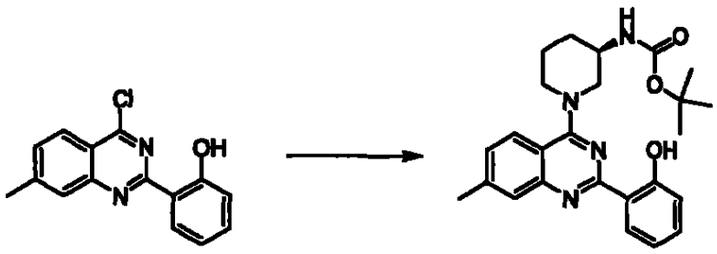
[001068] (2*R*)-Tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide

[001069]



[001070] *tert*-Butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

368

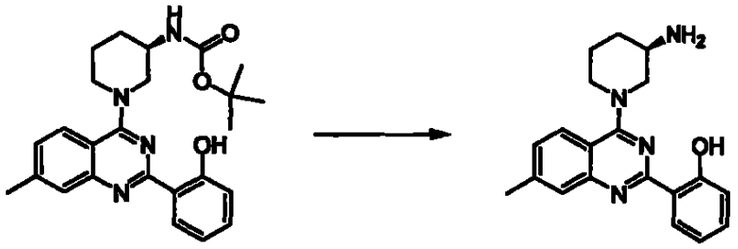


[001071]

[001072] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.5 g, 1.84 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise a solution of *tert*-butyl (*R*)-piperidin-3-ylcarbamate (0.37 g, 1.84 mmol) in CH_2Cl_2 (5 mL), then triethylamine (0.51 mL, 3.68 mmol). The mixture was allowed to warm to room temperature and was stirred for 3 h. After quenching with water, it was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated. Purification via silica gel chromatography using 5:1 CH_2Cl_2: hexanes gave *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate (0.54 g, 68%). LC/MS: *m/z* 435.5$(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001073] **2-(4-((*R*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol.**

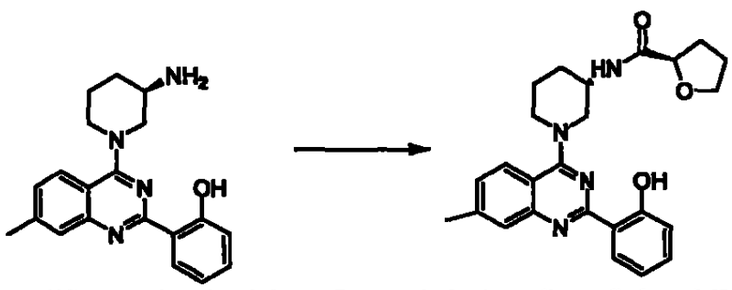
[001074]



[001075] *tert*-Butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate (0.54 g, 1.24 mmol) was dissolved in CH_2Cl_2 (15 mL) followed by the addition of TFA (8 mL). The reaction was stirred for 1.5 h, and the solvents were evaporated to an oily liquid which was diluted with CH_2Cl_2 and neutralized with a 1 M aqueous NaOH solution. The organic layer was separated, and the aqueous layer was washed two times with CH_2Cl_2. After drying the combined organic phases over $MgSO_4$, they were filtered, and concentrated to afford 2-(4-((*R*)-3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol as a solid (0.354 g, 85%). LC/MS: *m/z* 335.7$(M+H)^+$ at 1.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001076] (2*R*)-Tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide

[001077]

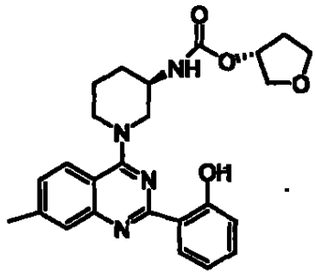


[001078] 2-(4-((*R*)-3-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol), (*R*)-tetrahydrofuran-2-carboxylic acid (22.6 mg, 0.15 mmol), triethylamine (30 mg, 0.3 mmol), and HATU (74.14 mg, 0.195 mmol) were stirred at room temperature in DMF for 1 h. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 433.3$(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001079] Example 207

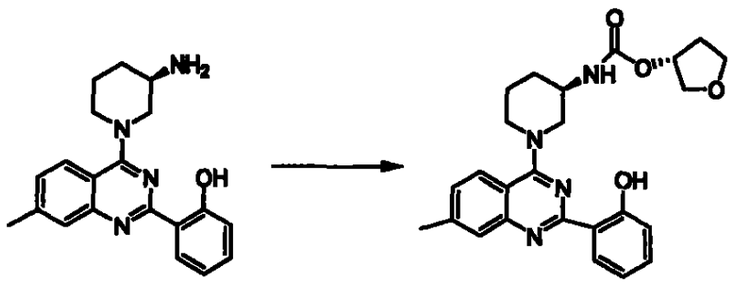
[001080] (*R*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001081]



[001082] (*R*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001083]

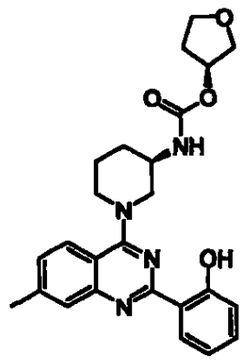


[001084] A solution of 2-(4-((*R*)-3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMF (0.5 mL) was cooled to 0 °C. Then, a solution of triethylamine (30 mg, 0.3 mmol) and (*R*)-tetrahydrofuran-3-yl chloroformate (22.6 mg, 0.15 mmol) in DMF (0.5 mL) was added dropwise. The mixture was allowed to warm to room temperature over a period of 30 min before it was purified using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*R*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 449.5$(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001085] Example 208

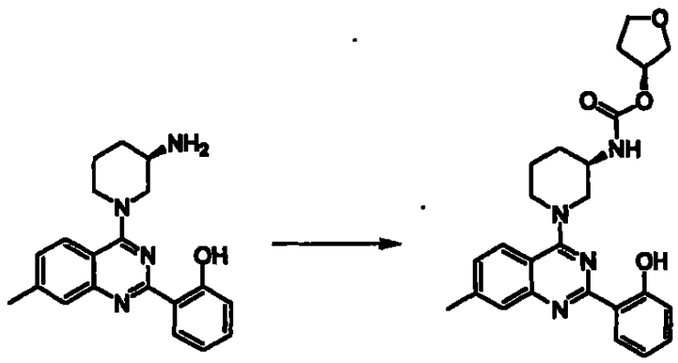
[001086] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001087]



[001088] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate

[001089]

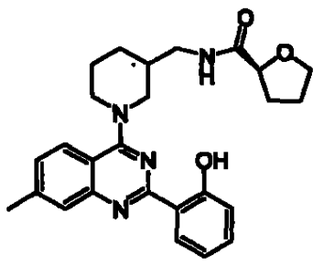


[001090] To a solution of 2-(4-((*R*)-3-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMF (0.5 mL) was cooled to 0 °C. A solution of (*S*)-tetrahydrofuran-3-yl chloroformate (22.6 mg, 0.15 mmol) in DMF (0.5 mL) was then added, followed by triethylamine (30 mg, 0.3 mmol). The mixture was allowed to warm to room temperature over a period of 30 min before it was purified using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-ylcarbamate as the TFA salt. *LC/MS: m/z* 449.5$(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

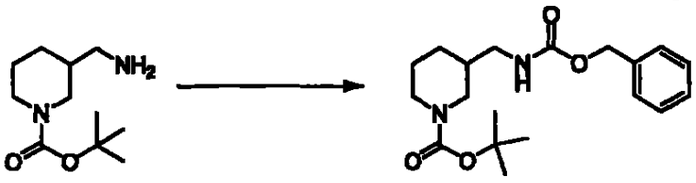
[001091] Example 209

[001092] (2*S*)-Tetrahydro-*N*-((1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)furan-2-carboxamide

[001093]



[001094] 3-(Benzyloxycarbonylamino-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester



[001095]

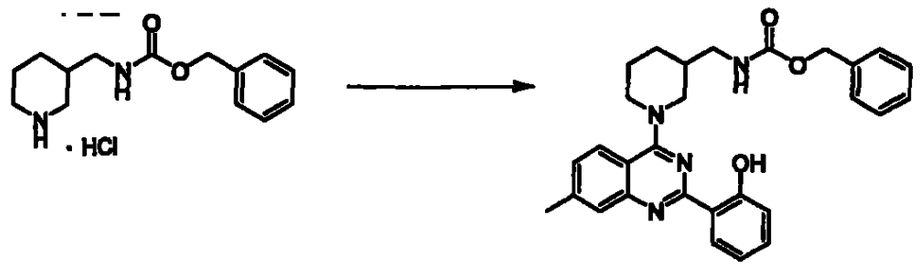
[001096] 3-Aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (3.6 g, 16.8 mmol) was dissolved in 42 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled in an ice water bath. Triethylamine (4.7 mL, 33.6 mmol) was added followed by the dropwise addition of benzyl chloroformate (3.55 mL, 25.2 mmol). After 16 hours, the reaction mixture was partitioned between CH_2Cl_2/H_2O,and separated, and the aqueous layer was extracted twice with CH_2Cl_2. All of the organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to a light yellow oil. Purification by silica gel chromatography using 97% CH_2Cl_2/3% MeOH gave the product as a clear colorless oil (55%). LC/MS: *m/z* 349.3 $(M+H)^+$ at 3.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001097] **Benzyl (piperidin-3-yl)methylcarbamate hydrochloride**

[001098]

[001099] Benzyl (1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate (3.22 g, 9.25 mmol) was treated with a 4.0 M HCl solution in dioxane (11.3 mL, 46.25 mmol). Formation of a white precipitate was observed. After 3 h, the reaction was complete. The solvent and excess HCl were removed under reduced pressure to obtain benzyl (piperidin-3-yl)methylcarbamate hydrochloride as a white solid. LC/MS: *m/z* 249.3 $(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001100] **Benzyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

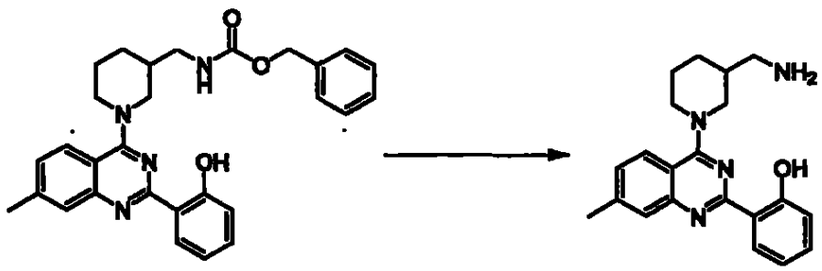


[001101]

[001102] 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (1.5 g, 5.54 mmol) was suspended in anhydrous CH_2Cl_2 (15 mL) and cooled to 0 °C under an N_2 atmosphere. A mixture of benzyl (piperidin-3-yl)methylcarbamate hydrochloride (1.73 g, 6.09 mmol) in CH_2Cl_2 (20 mL), and triethylamine (23 mL, 16.67 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature, and the reaction was complete after one hour. It was then partitioned between CH_2Cl_2/H_2O, and separated, and the organic phase was dried over Na_2SO_4, filtered, and concentrated to an orange solid. Purification by silica gel chromatography using 98% CH_2Cl_2/2% EtOAc gave benzyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as a bright yellow solid (1.75 g, 66%). LC/MS: *m/z* 483.5 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001103] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001104]



[001105] A mixture of benzyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (1.75 g, 3.63 mmol) and EtOH/EtOAc (50 mL/20 mL) was heated to obtain a homogeneous solution. After cooling to room temperature, Pd/C (175 mg, 10% wt Pd on carbon) was added and the flask was sealed with a septum. The same flask was 3 times charged with N_2 and evacuated under vacuum. The mixture was then stirred under an H_2

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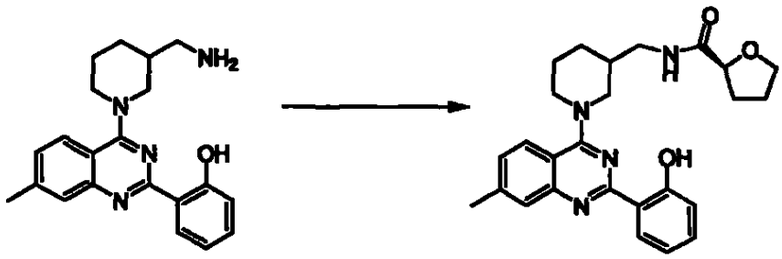
atmosphere at ambient pressure for 1 h. The product was collected by filtration through a plug of Celite, eluting with MeOH. The filtrate was concentrated to a yellow solid (1.26 g) to give 2-(4-(3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol. LC/MS: *m/z* 349.3 $(M+H)^+$ at 1.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001106] **(2*S*)-Tetrahydro-*N*-((1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)furan-2-carboxamide**

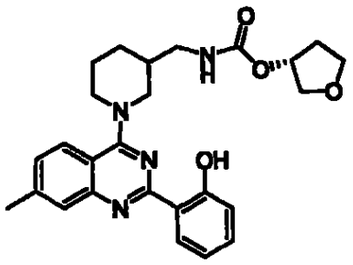
[001107]



[001108] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled in an ice water bath. To this was added (*S*)-tetrahydrofuran-2-carboxylic acid (24.0 mg, 19.8 μL, 0.2 mmol), and triethylamine (50 μL, 0.34 mmol). After 5 minutes, HATU (78.3 mg, 0.2 mmol) was added in one portion, and the reaction was allowed to warm to room temperature overnight. Purification by reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*S*)-tetrahydro-N-((1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 447.5 $(M+H)^+$ at 2.27 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001109] Example 210

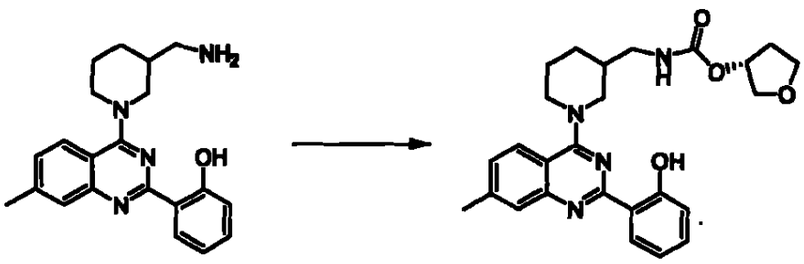
[001110] **(*R*)-Tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



[001111]

[001112] (*R*)-Tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001113]

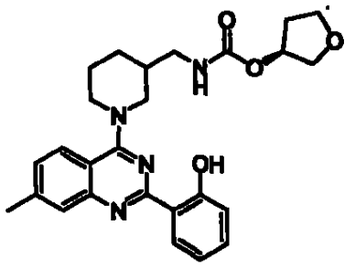


[001114] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in DMF (0.5 mL) and placed into an ice water bath. (*R*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) was dissolved in DMF (0.1 mL) and added dropwise, followed by the addition of triethylamine (50 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001115] Example 211

[001116] (*S*)-Tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

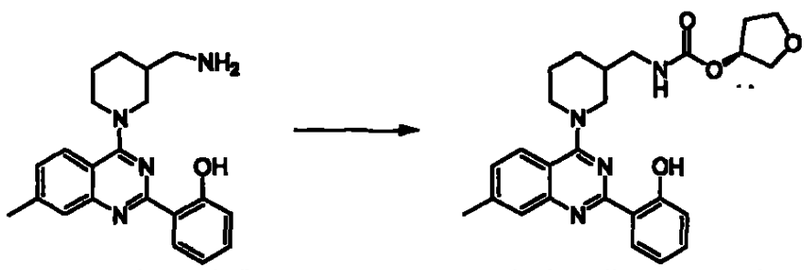
[001117]



[001118] (*S*)-Tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

372

[001119]

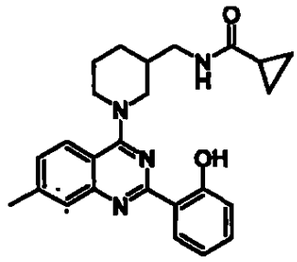


[001120] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) dissolved in *DMF* (0.5 mL) was cooled to 0 °C. (*S*)-Tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) was dissolved in DMF (0.1 mL) and added dropwise to the reaction mixture, followed by the addition of triethylamine (50 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The reaction was purified by reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*S*)-tetrahydrofuran-3-yl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

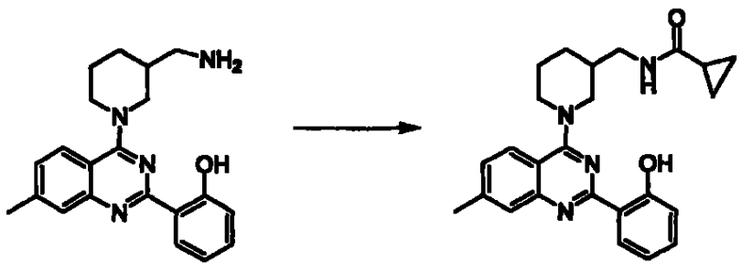
[001121] Example 212

[001122] ***N*-((1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide**

[001123]



[001124] ***N*-((1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide**



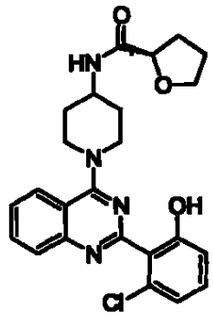
[001125]

[001126] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in DMF (0.5 mL) and cooled to 0 °C. Cyclopropanecarbonyl chloride (15.7 mg, 0.2 mmol) was dissolved in DMF (0.1 mL) and added dropwise, followed by the addition of triethylamine (50 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave *N*-((1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 417.0 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001127] Example 213

[001128] (2*R*)-*N*-(1-(2-(2-Chloro-6-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

[001129]



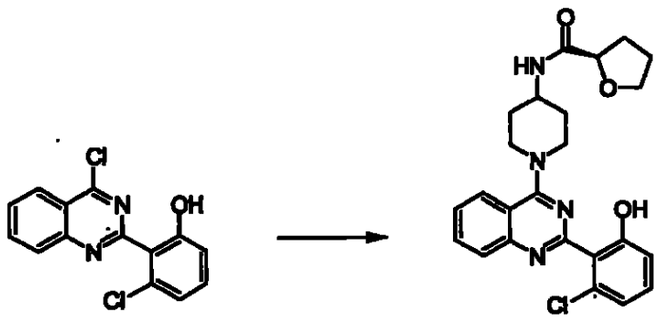
[001130] 3-Chloro-2-(4-chloroquinazolin-2-yl)phenol

[001131]

[001132] To a solution of 4-chloro-2-(2-chloro-6-methoxyphenyl)quinazoline (0.3 g, 0.98 mmol) in CH_2Cl_2 at –78 °C was added 5 equivalents of 1 M BBr_3 solution (4.9 mL, 4.9 mmol) in CH_2Cl_2. The reaction was complete after 30 minutes After allowing it to warm to room temperature, the reaction mixture was quenched with aqueous $NaHCO_3$ to pH 7, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 2:1 CH_2Cl_2:hexanes yielded 3-chloro-2-(4-chloroquinazolin-2-yl)phenol (0.17 g, 60%). LC/MS: *m/z* 291.1$(M+H)^+$ at 3.16 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001133] **(2*R*)-*N*-(1-(2-(2-Chloro-6-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide**

[001134]

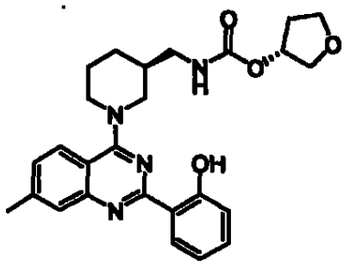


[001135] At 0 °C, to a solution of 3-chloro-2-(4-chloroquinazolin-2-yl)phenol (42 mg, 0.144 mmol) in CH_2Cl_2 was added triethylamine (80 μL, 0.58 mmol) followed by the addition of (*R*)-tetrahydro-*N*-(piperidin-4-yl)furan-2-carboxamide a oxalate. After allowing the reaction to warm to room temperature it was purified via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-*N*-(1-(2-(2-chloro-6-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide as the TFA salt. LC/MS: *m/z* 453.5$(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001136] Example 214

[001137] **(*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

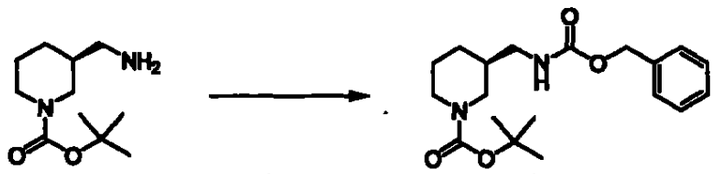
[001138]



[001139] Method 1

[001140] Benzyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate

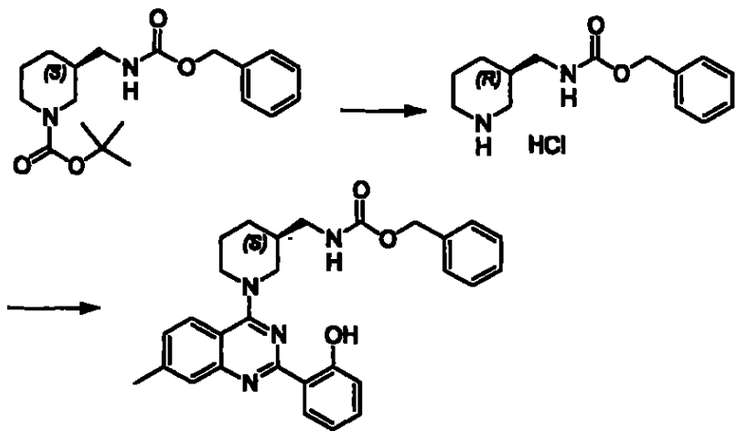
[001141]



[001142] (*S*)-*tert*-Butyl 3-(aminomethyl)piperidine-1-carboxylate (1.00 g, 4.67 mmol) was dissolved in 14 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled to 0 °C. Triethylamine (1.30 mL, 945 mg, 9.34 mmol) was added followed by the dropwise addition of benzyl chloroformate (0.99 mL, 1.20 g, 7.00 mmol). After 16 h, the reaction mixture was partitioned between H_2O and CH_2Cl_2,and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to a light yellow oil. Purification via silica gel chromatography using 97% CH_2Cl_2/3% MeOH gave benzyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate as a clear colorless oil (895 mg, 55%). LC/MS: *m/z* 349.5 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001143] Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

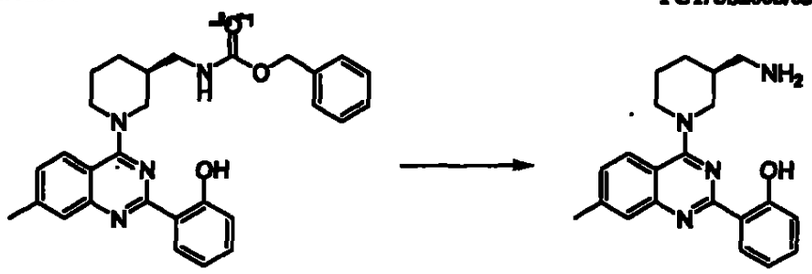
[001144]



[001145] Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (895 mg, 2.57 mmol) was treated with a 4.0 M HCl solution in dioxane (3.2 mL, 12.85 mmol). Formation of a white precipitate was observed. After 3 h, complete conversion of starting material was seen by TLC. The solvent and excess HCl were removed under reduced pressure to obtain benzyl ((*R*)-piperidin-3-yl)methylcarbamate hydrochloride as a white solid.

This solid was suspended in DMF/CH_2Cl_2 (3 mL/3 mL), followed by the addition of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (696 mg, 2.57 mmol), and triethylamine (1.8 mL, 1.3 g, 12.85 mmol). The mixture was stirred at room temperature under an N_2 atmosphere for 16 h. The reaction was then partitioned between H_2O/CH_2Cl_2, and separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography using 0–5% MeOH in CH_2Cl_2 gave benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as a thick yellow oil (610 mg, 49%). LC/MS: *m/z* 483.3 $(M+H)^+$ at 2.83 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001146] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol

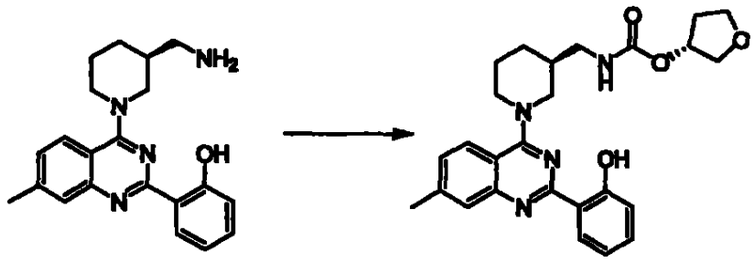


[001147]

[001148] To a mixture of benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (610 mg, 1.26 mmol) and EtOH (15 mL) in a round bottom flask was added Pd/C (61 mg, 10% wt Pd on carbon) and the flask was sealed with a septum. The atmosphere in the flask was evacuated, purged with N_2, and equipped with a balloon charged with H_2. The mixture was then stirred under an H_2 atmosphere at ambient pressure for 3 h. After filtration through a plug of Celite, using MeOH as the eluting solvent, the reaction mixture was concentrated to a yellow solid 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (441 mg). LC/MS: *m/z* 349.3 $(M+H)^+$ at 1.52 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.43–8.45 (m, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35–7.39 (m, 2H), 6.92–6.96 (m, 2H), 4.52 (d, *J* = 12.5 Hz, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 3.26–3.29 (m, 2H), 3.02–3.08 (m, 1H), 2.55–2.61 (m, 1H), 2.45–2.48 (m, 1H), 1.84–1.91 (m, 2H), 1.65–1.77 (m, 3H), 1.24–1.36 (m, 1H).

[001149] **(*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001150]



[001151] Method A

[001152] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, and (*R*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) dissolved in DMF (100 μL) was added

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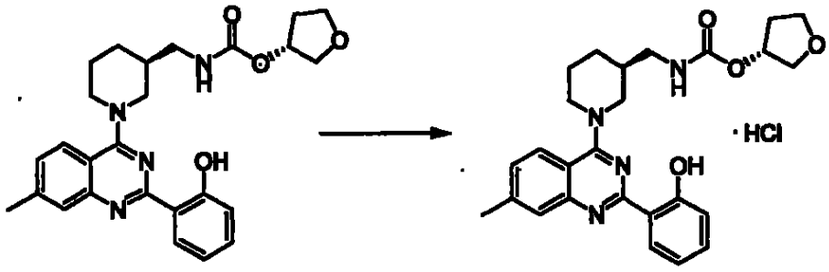
dropwise followed by triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature. The reaction was complete after two hours. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001153] Method B

[001154] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (127 mg, 0.364 mmol) was dissolved in 5 mL anhydrous DMF and cooled to 0 °C, and a solution of (*R*)-tetrahydrofuran-3-yl chloroformate (65.4 mg, 0.436 mmol) in 200 μL DMF was added dropwise followed by the addition of triethylamine (74 mg, 0.10 mL, 0.73 mmol). The reaction was allowed to warm to room temperature. The reaction was complete after two hours. The mixture was partitioned between H_2O and CH_2Cl_2, and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to a yellow solid. Purification via silica gel chromatography using 98% CH_2Cl_2/2% MeOH gave (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as an off white solid (116 mg, 69%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.41–8.43 (m, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 1H), 7.33–7.44 (m, 3H), 6.90–6.95 (m, 2H), 5.11 (dd, *J* = 6.2, 4.6 Hz, 1H), 4.38 (t, *J* = 14.5 Hz, 2H), 3.68–3.79 (m, 3H), 3.60–3.63 (m, 1H), 3.28–3.31 (m, 1H), 2.98–3.07 (m, 3H), 2.50 (s, 3H), 2.06–2.15 (m, 1H), 1.85–1.91 (m, 4H), 1.70 (d, *J* = 12.9 Hz, 1H), 1.24–1.37 (m, 1H).

[001155] (*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001156]

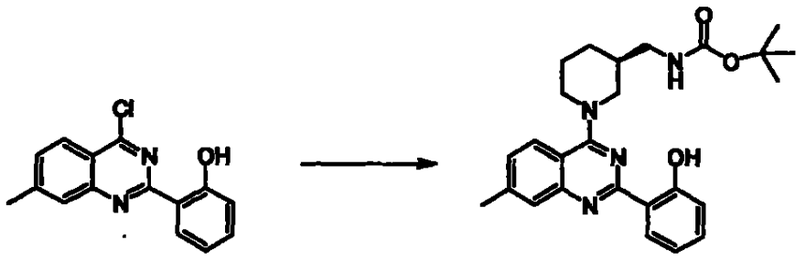


[001157] (*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (116 mg, 0.251 mmol) was suspended in 8 mL anhydrous CH_2Cl_2 and gently heated until an homogenous solution was formed. After the reaction was cooled to room temperature, a 2.0 M solution of HCl in Et_2O (0.126 mL, 0.251 mmol) was added in one portion. The reaction mixture was diluted with 25 mL Et_2O, and the product precipitated from solution. The reaction was stirred for an additional 30 minutes before the solid was filtered and dried to obtain (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride as a light yellow solid (99 mg, 70%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-*d6*) δ 8.22 (d, *J* = 7.7 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.75 (s, 1H), 7.42–7.49 (m, 3H), 6.97–7.08 (m, 2H), 5.08 (dd, *J* = 6.1, 4.6 Hz, 1H), 4.52–4.54 (m, 2H), 3.66–3.78 (m, 3H), 3.58–3.60 (m, 1H), 3.48 (t, *J* = 10.7 Hz, 1H), 3.23 (t, *J* = 11.5 Hz, 1H), 3.00 (t, *J* = 6.3 Hz, 2H), 2.53 (s, 3H), 2.05–2.14 (m, 1H), 1.80–1.91 (m, 4H), 1.72 (d, *J* = 9.0 Hz, 1H), 1.34–1.43 (m, 1H).

[001158] Method 2

[001159] *tert*-Butyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001160]

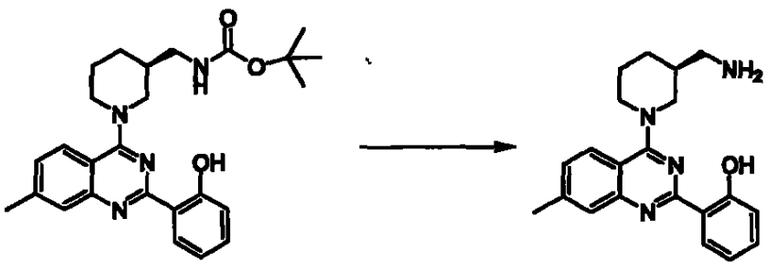


[001161] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.478 g, 1.76 mmol) in CH_2Cl_2 was added triethylamine (0.98 mL, 0.712 g, 7.04 mmol), and the mixture was cooled to 0 °C. To the reaction mixture was added *tert*-butyl ((*R*)-piperidin-3-yl)methylcarbamate oxalate (prepared analogously to 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol, oxalate salt, see Example 130; 700 mg, 2.3 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over

$MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–2% EtOAc in CH_2Cl_2 gave *tert*-butyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (700 mg, 88%). *LC/MS*: *m/z* 449.5 $(M+H)^+$ at 2.77 min · (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

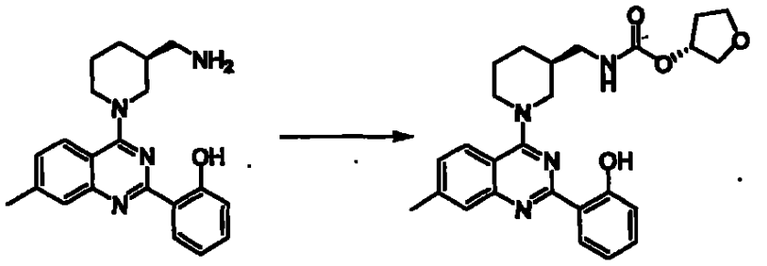
[001162] **2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol**

[001163]



[001164] To ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (700 mg, 1.56 mmol) was added 20 mL CH_2Cl_2 followed by addition of 7 mL of TFA. After the reaction was stirred for 1 hour it was neutralized with a 1.0 *M* aqueous NaOH solution. The mixture was partitioned between H_2O and CH_2Cl_2, and separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (400 mg, 74%). *LC/MS*: *m/z* 349.3 $(M+H)^+$ at 1.52 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.43–8.45 (m, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35–7.39 (m, 2H), 6.92–6.96 (m, 2H), 4.52 (d, *J* = 12.5 Hz, 1H), 4.41 (d, *J* = 13.2 Hz, 1H), 3.26–3.29 (m, 2H), 3.02–3.08 (m, 1H), 2.55–2.61 (m, 1H), 2.45–2.48 (m, 1H), 1.84–1.91 (m, 2H), 1.65–1.77 (m, 3H), 1.24–1.36 (m, 1H).

[001165] **(*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



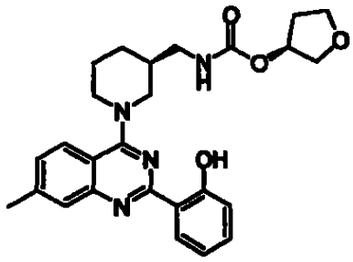
[001166]

[001167] To a solution of 2-(4-((S)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (210 mg, 0.6 mmol) in DMF at 0 °C were added (*R*)-tetrahydrofuran-3-yl chloroformate (0.09 g, 0.6 mmol) and triethylamine (167 μL, 1.2 mmol) simultaneously. Ten to fifteen minutes after addition, the reaction was complete, and quenched with water, extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (150 mg, 54%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.41–8.43 (m, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 1H), 7.33–7.44 (m, 3H), 6.90–6.95 (m, 2H), 5.11 (dd, *J* = 6.2, 4.6 Hz, 1H), 4.38 (t, *J* = 14.5 Hz, 2H), 3.68–3.79 (m, 3H), 3.60–3.63 (m, 1H), 3.28–3.31 (m, 1H), 2.98–3.07 (m, 3H), 2.50 (s, 3H), 2.06–2.15 (m, 1H), 1.85–1.91 (m, 4H), 1.70 (d, *J* = 12.9 Hz, 1H), 1.24–1.37 (m, 1H).

[001168] Example 215

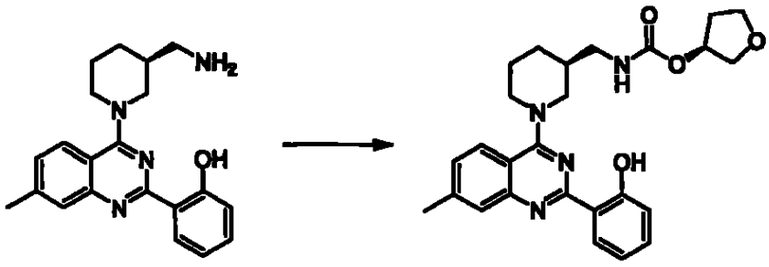
[001169] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001170]



[001171] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001172]



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[001173] Method A

[001174] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, and (*S*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) in DMF (100 μL) was added dropwise followed by triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature. The reaction was complete after two hours. Purification using preparative HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001175] Method B

[001176] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (126.8 mg, 0.364 mmol) was dissolved in 5 mL anhydrous DMF and cooled to 0 °C, and a solution of (*S*)-tetrahydrofuran-3-yl chloroformate (65.4 mg, 0.436 mmol) in 200 μl of DMF was added dropwise followed by the addition of triethylamine (74 mg, 0.102 mL, 0.728 mmol). The reaction was allowed to warm to room temperature and was complete after two hours. The mixture was partitioned between H_2O and CH_2Cl_2, separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to a yellow solid. Purification via silica gel chromatography using 98% CH_2Cl_2/2% MeOH gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as an off white solid (116 mg, 69%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).^1H NMR (400 MHz, DMSO–d6) δ 8.42 (dd, J = 8.1, 1.7 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.66 (s, 1H), 7.34–7.43 (m, 3H), 6.91–6.95 (m, 2H), 5.10–5.11 (m, 1H), 4.38 (t, J = 12.4 Hz, 2H), 3.65–3.77 (m, 4H), 2.98–3.08 (m, 3H), 2.04–2.13 (m, 1H), 1.80–1.87 (m, 4H), 1.68–1.74 (m, 1H), 1.30–1.38 (m, 1H).

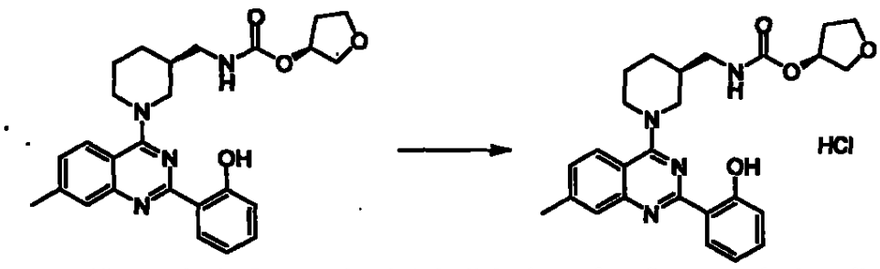
[001177] Method C

[001178] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (175 mg, 0.5 mmol) in DMF at 0 °C were added (*S*)-tetrahydrofuran-3-yl chloroformate (75 mg, 0.5 mmol) and triethylamine (137 μL, 1.0 mmol) simultaneously. Ten to fifteen minutes after addition, the reaction was complete, and it was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated. Purification via silica gel chromatography using 98% CH_2Cl_2/2% MeOH gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (150 mg, 54%). *LC/MS*: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.42 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.66 (s, 1H), 7.34–7.43 (m, 3H), 6.91–6.95 (m, 2H), 5.10–5.11 (m, 1H), 4.38 (t, *J* = 12.4 Hz, 2H), 3.65–3.77 (m, 4H), 2.98–3.08 (m, 3H), 2.04–2.13 (m, 1H), 1.80–1.87 (m, 4H), 1.68–1.74 (m, 1H), 1.30–1.38 (m, 1H).

[001179] **(*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride**

[001180]

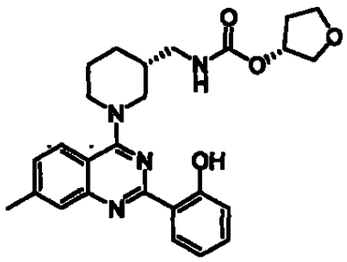


[001181] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (115 mg, 0.251 mmol) was suspended in 8 mL of anhydrous CH_2Cl_2 and gently heated until an homogenous solution was formed. After cooling to room temperature, a 2.0 M solution of HCl in Et_2O (0.126 mL, 0.251 mmol) was added in one portion. The reaction mixture was diluted with 25 mL Et_2O, and the product precipitated from the solution. The reaction was stirred for an additional 30 minutes before the solid was filtered and dried to obtain (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride (108 mg, 86%) as a light yellow solid. *LC/MS*: *m/z* 463.5$(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).^1H NMR (400 MHz, DMSO–d6) δ 8.18 (d, *J* = 6.6 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.73 (s, 1H), 7.44–7.51 (m, 2H), 7.00–7.07 (m, 2H), 5.06–5.09 (m, 1H), 4.52–4.62 (m, 2H), 3.62–3.74 (m, 4H), 3.23–3.29 (m, 1H), 3.00 (d, *J* = 6.8 Hz, 2H), 2.52 (s, 3H), 2.02–2.11 (m, 1H), 1.61–2.01 (m, 4H), 1.24–1.43 (m, 2H), 0.84–0.89 (m, 1H).

[001182] Example 216

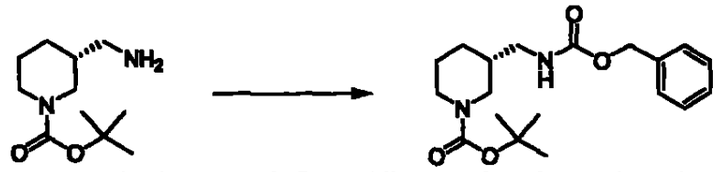
[001183] (*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001184]



[001185] Benzyl ((*R*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate

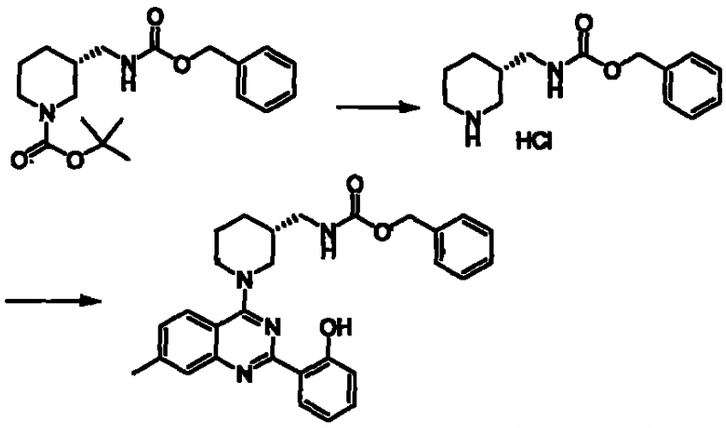
[001186]



[001187] (*R*)-*tert*-Butyl 3-(aminomethyl)piperidine-1-carboxylate (1.00 g, 4.67 mmol) was dissolved in 14 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled to 0 °C. Triethylamine (1.30 mL, 945 mg, 9.34 mmol) was added followed by the dropwise addition of benzyl chloroformate (0.99 mL, 1.20 g, 7.00 mmol). After 16 h, the reaction was complete. The mixture was partitioned between H_2O and CH_2Cl_2, and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to a light yellow oil. Purification via silica gel chromatography using 97% CH_2Cl_2/3% MeOH gave, benzyl ((*R*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate as a clear colorless oil (1.2 g, 74%). LC/MS: *m/z* 349.5 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001188] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

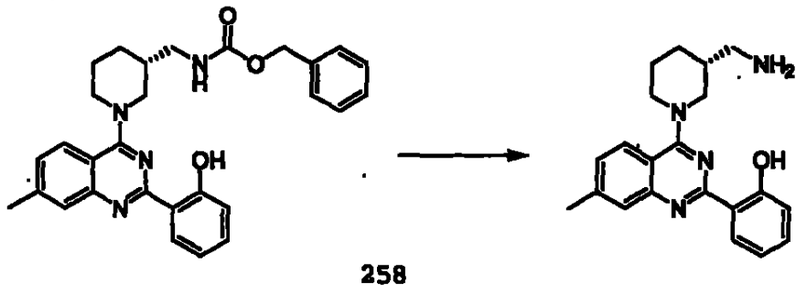
[001189]



[001190] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (1.2 g, 3.54 mmol) was treated with 4.0 M HCl solution in dioxane (4.3 mL, 17.2 mmol). Formation of a white precipitate was observed. The reaction was complete after three hours. The solvent and excess HCl were removed under reduced pressure to obtain benzyl ((*S*)-piperidin-3-yl)methylcarbamate hydrochloride as a white solid. This solid was suspended in DMF/CH_2Cl_2 (3 mL/3 mL), followed by the addition of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (958 mg, 3.54 mmol) and then triethylamine (1.8 mL, 1.3 g, 12.85 mmol). The mixture was stirred at room temperature under an N_2 atmosphere for 16 h. The reaction was then partitioned between H_2O and CH_2Cl_2, separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography using 0–5% MeOH in CH_2Cl_2 gave benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as a thick yellow oil (855 mg, 51%). LC/MS: *m/z* 483.5 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001191] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001192]



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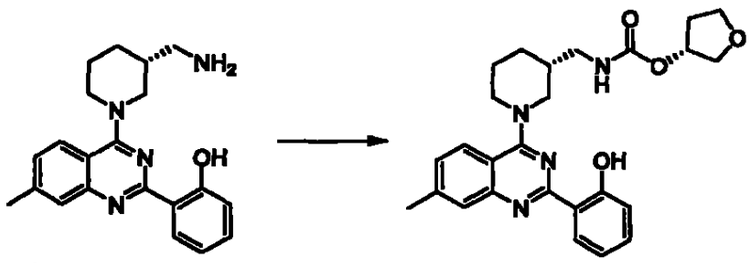
[001193] To a mixture of benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (855 mg, 1.77 mmol) and EtOH (15 mL) in a round bottom flask was added Pd/C (86 mg, 10% wt Pd on carbon) and the flask was sealed with a septum. The atmosphere in the flask was evacuated, purged with N_2, and equipped with a balloon charged with H_2. The mixture was stirred under an H_2 atmosphere at ambient pressure for 3 h. After filtration through a plug of Celite using MeOH as the eluting solvent, the reaction mixture was concentrated to 2-(4-((*R*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (625 mg) as a yellow solid. LC/MS: *m/z* 349.3 $(M+H)^+$ at 1.82 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001194] (*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001195]



[001196] Method A

[001197] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which (*R*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by the addition of triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature, and was complete after two hours. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001198] Method B

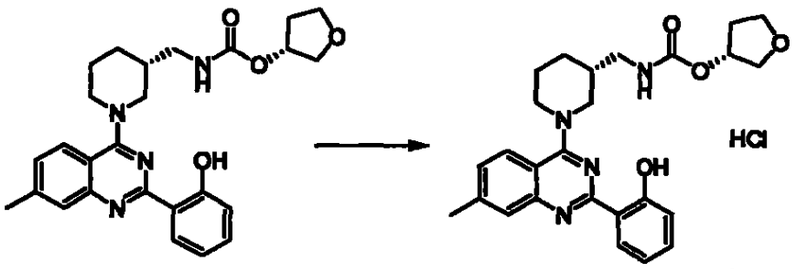
[001199] To a stirred solution of 2-(4-((*R*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (150 mg, 0.43 mmol) under an N_2 atmosphere at 0 °C was added

triethylamine (1.5 eq.) was added followed by the dropwise addition of (*R*)-tetrahydrofuran-3-yl chloroformate (65 mg, 0.43 mmol). The reaction was allowed to warm to room temperature and was stirred for 2 h. The mixture was partitioned between H_2O and CH_2Cl_2 and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 4:1 CH_2Cl_2:EtOAc afforded (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate. *LC/MS*: *m/z* 463.5$(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001200] **(*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride**

[001201]

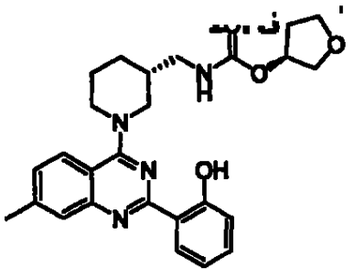
[001202] To a solution of (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-



methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (0.085 g, 0.18 mmol) in 9 mL CH_2Cl_2 was added dropwise a 2.0 M HCl solution in ether (0.09 mL, 0.18 mmol). Ether (20 mL) was then added, leading to the precipitation of (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride which was filtered and dried (85 mg, 95%). *LC/MS*: *m/z* 463.5$(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001203] Example 217

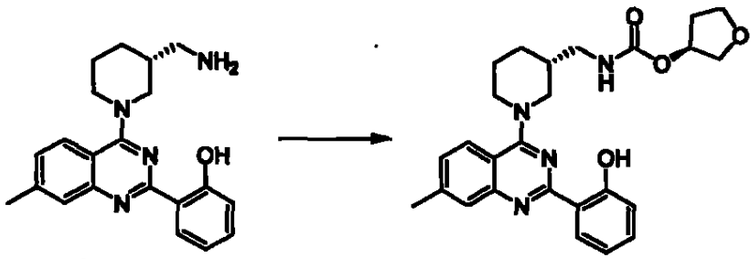
[001204] **(*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



[001205]

[001206] (*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001207]



[001208] Method A

[001209] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which (*S*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

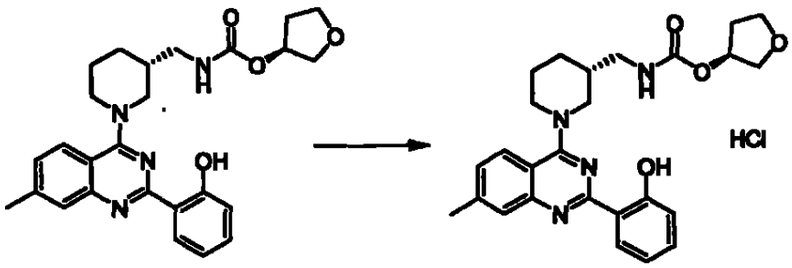
[001210] Method B

[001211] To a stirred solution of 2-(4-((*R*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (200 mg, 0.57 mmol) in DMF under an N_2 atmosphere at 0 °C was added triethylamine (115 mg, 1.14 mmol) followed by the dropwise addition of (*S*)-tetrahydrofuran-3-yl chloroformate (86 mg, 0.57 mmol). The reaction was allowed to warm to room temperature and was stirred for 2 h. The mixture was partitioned between H_2O and CH_2Cl_2 and separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were

combined, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 4:1 CH_2Cl_2:EtOAc afforded (*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate. LC/MS: *m/z* 463.5$(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001212] ((*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001213]

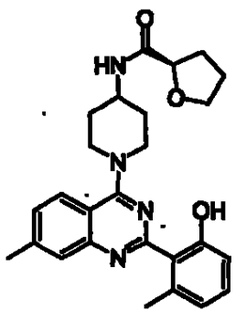


[001214] To a solution of (*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate in 12 mL CH_2Cl_2 was added dropwise 2.0 M HCl solution in ether (0.13 mL, 0.25 mmol). To the solution was then added 20 mL ether leading to the precipitation of ((*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride which was filtered and dried (116 mg, 92%). LC/MS: *m/z* 463.5$(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001215] Example 218

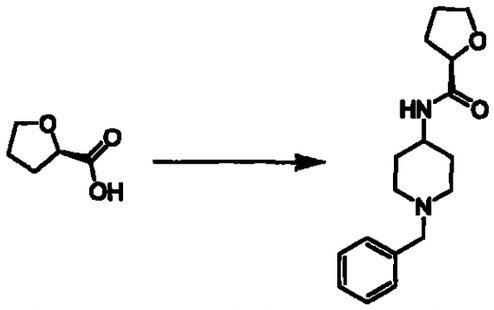
[001216] (2*R*)-Tetrahydro-*N*-(1-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)furan-2-carboxamide

[001217]



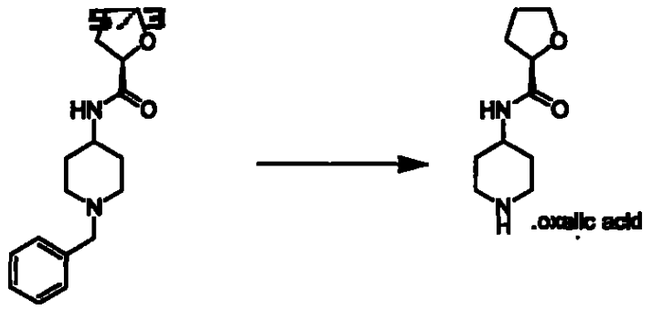
[001218] (*R*)-Tetrahydrofuran-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide

[001219]



[001220] A solution of (*R*)-tetrahydro-2-furoic acid (58.5 g, 504 mmol) and oxalyl chloride (86 mL, 1.0 mol) in 100 mL CH_2Cl_2 were refluxed for 2 hours in a flask equipped with a $CaCl_2$ guard tube. After the solution was cooled to room temperature the solvents and excess oxalyl chloride were removed by evaporation under reduced pressure. The resulting acid chloride was dissolved in 200 mL CH_2Cl_2 and added dropwise to a solution of 1-benzyl-4-amino piperidine dihydrochloride (142 g, 539 mmol) and triethylamine (240 mL, 1.7 mol) in 300 mL CH_2Cl_2 cooled in an ice bath. The resulting mixture was stirred for 2 hours at room temperature and subsequently washed twice with 300 mL portions of 5% aq. $NaHCO_3$ and 300 mL saturated aq. NaCl solution, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The solid residue was triturated with 500 mL heptanes, collected by filtration, and washed twice with 200 mL portions of heptanes. The solid was air-dried at 45 °C to yield (*R*)-tetrahydrofuran-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (128 g, 88%) as an off-white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 5H), 6.58 (ba, 1H), 4.29 (dd, *J*= 5.9, 8.4 Hz, 1H), 3.92–3.77 (m, 2H), 3.48 (s, 2H), 2.82–2.74 (m, 2H), 2.32–2.21 (m, 1H), 2.19–1.95 (m, 3H), 1.94–1.78 (m, 4H), 1.58–1.40 (m, 2H) ppm.

[001221] (*R*)-Tetrahydro-furan-2-carboxylic acid piperidin-4-ylamide as an oxalate salt

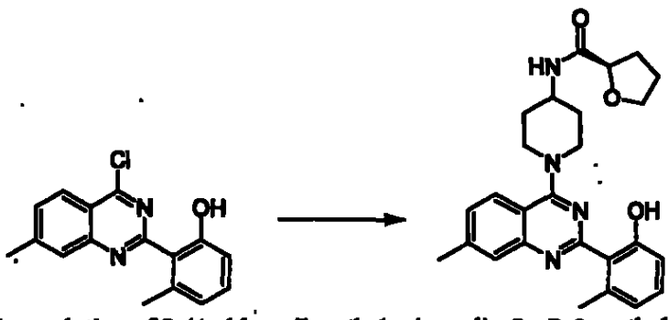


[001222]

[001223] (*R*)-Tetrahydro-furan-2-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (128 g, 444 mmol) was dissolved in 300 mL ethanol and 50 mL acetic acid. Palladium on activated carbon (5 g) was added. A hydrogen pressure of 5 bars was applied, and hydrogenation was continued until no more hydrogen was consumed (about 5 days). The suspension was filtered through Celite, and the filtrate was evaporated to dryness under reduced pressure. The residue and oxalic acid (50 g, 555 mmol) were suspended in 500 mL 2-propanol and heated to dissolve the solids. Upon cooling, the oxalate salt of *R*-tetrahydro-furan-2-carboxylic acid piperidin-4-ylamide crystallized and was collected by filtration to yield (*R*)-Tetrahydro-furan-2-carboxylic acid piperidin-4-ylamide as an oxalate salt (99.0 g, 77%) as an off-white solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.84 (d, J=7.8 Hz, 1H), 5.90 (bs, 2H), 4.18–4.14 (m, 1H), 3.89–3.67 (m, 3H), 3.25–3.20 (m, 2H), 2.94–2.71 (m, 2H), 2.13–2.00 (m, 1H), 1.56–1.58 (m, 6H) ppm.

[001224] (2*R*)-Tetrahydro-*N*-(1-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)furan-2-carboxamide

[001225]



[001226] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-methylphenol (60 mg, 2.1 mmol) in DMF (1 mL) was added triethylamine (1.17 mL, 8.4 mmol) and (*R*)-tetrahydro-*N*-(piperidin-4-yl)furan-2-carboxamide as an oxalate salt (80 mg, 2.73 mmol). This mixture was

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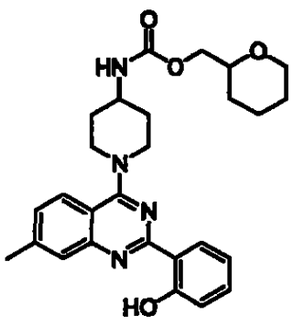
stirred for 2 h at room temperature before it was purified via reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to afford (2*R*)-tetrahydro-*N*-(1-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 447.5$(M+H)^+$ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001227] Example 219

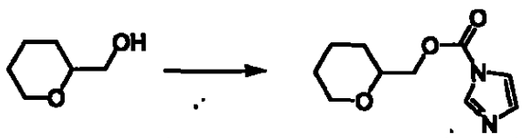
[001228] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid tetrahydro-pyran-2-ylmethyl ester

[001229]



[001230] (Tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate

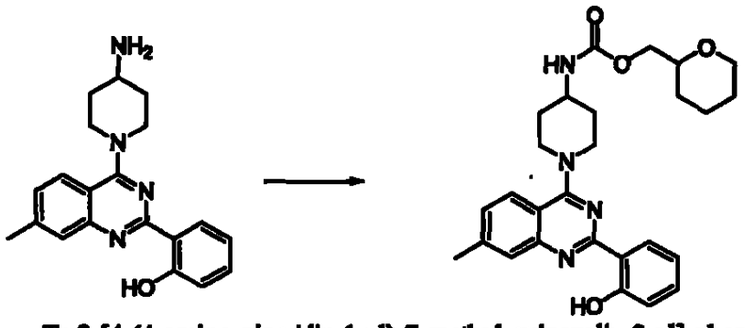
[001231]



[001232] A mixture of (tetrahydro-2*H*-pyran-2-yl)methanol (369 mg, 3.18 mmol) and di(1*H*-imidazol-1-yl)methanone (1.0 g, 6.36 mmol) in 0.3 M CH_3Cl (10 mL) was stirred at 50 °C for 3 h. After allowing the reaction to cool to room temperature, the solvent was evaporated under reduced pressure giving (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (412 mg) which was used without further purification. LC/MS: *m/z* 211.1$(M+H)^+$ at 0.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001233] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid tetrahydro-pyran-2-ylmethyl ester.

[001234]

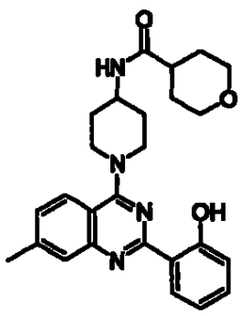


[001235] To 2-[4-(4-amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (100 mg, 0.3 mmol) in 1 mL CH_2Cl_2 was added sequentially triethylamine (62.5 µL, 0.45 mmol) and imidazole-1-carboxylic acid tetrahydro-pyran-2-ylmethyl ester(94 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 12 h and at 45 °C for 3 h. The reaction mixture was cooled and diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was purified by reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) as eluent to give the desired product {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid tetrahydro-pyran-2-ylmethyl ester as the TFA salt. LC/MS: *m/z* 477.4 (M+H)+ at 2.84 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001236] Example 220

[001237] **Tetrahydro-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2*H*-pyran-4-carboxamide**

[001238]



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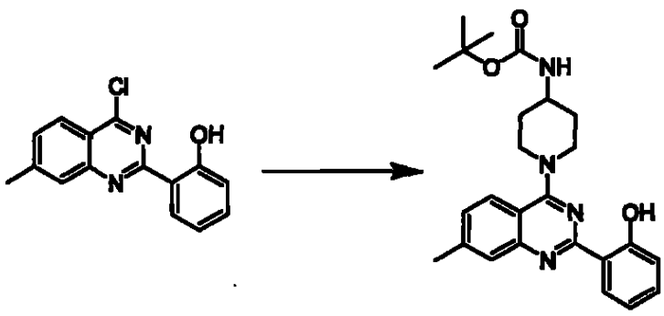
[001239] tert-butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

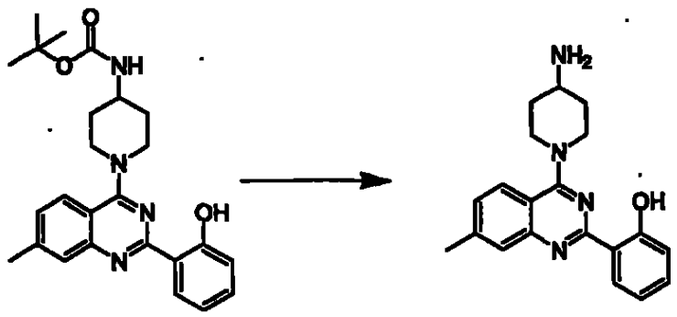
[001240]



[001241] To a cooled (0–5 °C) suspension of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (50.2 g, 186 mmol) in dichloromethane (200 mL) was slowly added a solution of *tert*-butyl piperidin-4-ylcarbamate (39.0 g, 195 mmol) and triethylamine (56 mL, 390 mmol) in dichloromethane (200 mL). The resulting mixture was stirred overnight at room temperature. Water (400 ml) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 200 mL), and the combined organic layers were dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (SiO_2, eluent: dichloromethane/heptanes 4:6–1:0). Two fractions were obtained: 38.7 g of *tert*-butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as a yellow solid, and a less pure fraction (26.1 g) that was purified by recrystallization from methanol to yield *tert*-butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate. Both fractions were combined (17.0 g, 69%).

[001242] 2-(4-(4-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol

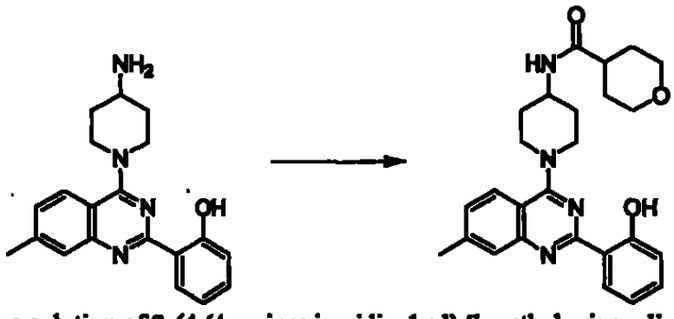
[001243]



[001244] T[illegible]-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (55.7 g, 128 mmol) was dissolved in dichloromethane (200 mL) and trifluoroacetic acid (215 ml) was slowly added (careful: immediate gas evolution!). The resulting solution was stirred overnight at room temperature under a nitrogen atmosphere and evaporated to dryness. To the residue were added equal amounts of water and dichloromethane (300 mL). The obtained emulsion was basified to pH 9 with 33% aq. NaOH. The emulsion was cleared by the addition of methanol, and the layers were separated. The aqueous layer was extracted with dichloromethane (200 mL), and the combined organic extracts were dried over sodium sulfate, filtered, and evaporated to dryness to yield crude 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol. The crude material was purified by column chromatography (SiO_2, 2% methanol in dichloromethane) to yield 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (44 g, 97%) as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8:52 (dd, *J*=2.1, 8.1 Hz, 1H), 7.77 (d, *J*=8.4 Hz, 1H), 7.62 (s, 1H), 7.37 (dt, *J*=1.5, 7.2 Hz, 1H), 7.22 (dd, *J*=1.5, 9.0 Hz, 1H), 7.04 (dd, *J*=1.2, 6.9 Hz, 1H), 6.92 (dt, *J*=1.2, 7.2 Hz, 1H), 4.49–4.39 (m, 2H), 3.34 (dt, *J*=2.4, 12.2 Hz, 2H), 3.12–3.02 (m, 1H), 2.54 (s, 3H), 2.09–2.00 (m, 2H), 1.68–1.55 (m, 2H), 1.40–1.25 (m, 2H) ppm.

[001245] **Tetrahydro-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2*H*-pyran-4-carboxamide**

[001246]



[001247] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added tetrahydro-2*H*-pyran-4-carboxylic acid (17.5 mg, 0.13 mmol) followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (44 mg, 0.117 mmol). The reaction was stirred for 16 h, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford tetrahydro-*N*-(1-(2-(2-

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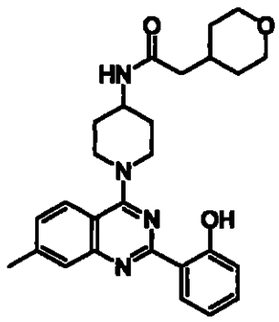
hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2*H*-pyran-4-carboxamide as the TFA salt. LC/MS: *m/z* 447.5(M+H)$^+$ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001248] Example 221

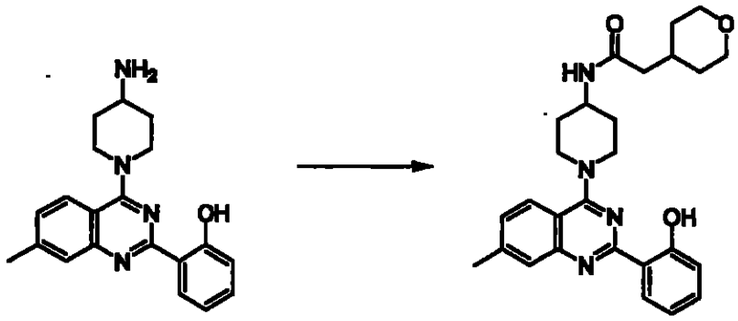
[001249] **2-(Tetrahydro-2*H*-pyran-4-yl)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide**

[001250]



[001251] **2-(Tetrahydro-2*H*-pyran-4-yl)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide**

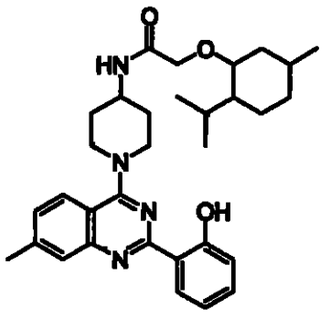
[001252]



[001253] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (13 mg, 0.09 mmol) followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (44 mg, 0.117 mmol). The reaction was stirred for 16 h, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-(tetrahydro-2*H*-pyran-4-yl)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide as the TFA salt. LC/MS: *m/z* 461.5(M+H)$^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001254] PCT/US2005/031146

[001255] 2-(2-Isopropyl-5-methylcyclohexyloxy)-*N*-(1-(2-(2-hydroxyphenyl)-7-



methylquinazolin-4-yl)piperidin-4-yl)acetamide (

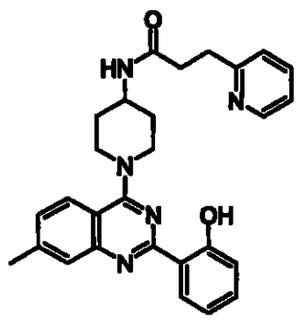
[001256] 2-(2-Isopropyl-5-methylcyclohexyloxy)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide

[001257] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) at 0 °C was added triethylamine (25 μL, 0.18 mmol) followed by the addition of 2-(2-isopropyl-5-methylcyclohexyloxy)acetyl chloride (21 mg, 0.09 mmol). The reaction was stirred for 16 h, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-(2-isopropyl-5-methylcyclohexyloxy)-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)acetamide as the TFA salt. LC/MS: *m/z* 531.3$(M+H)^+$ at 3.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001258] Example 223

[001259] *N*-(1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-3-(pyridin-2-yl)propanamide

[001260]



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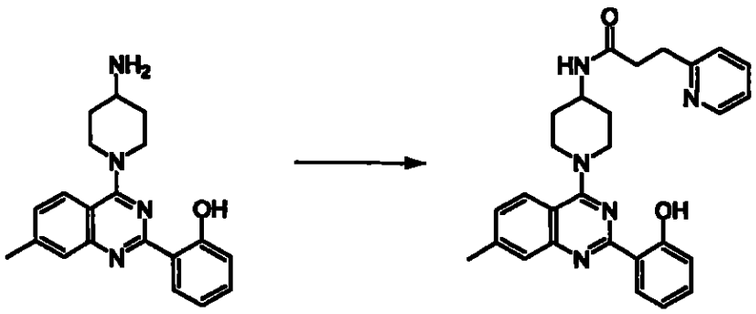
[001261] *N*-(1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-3-(pyridin-2-yl)propanamide

[001262]

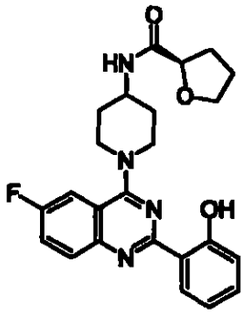


[001263] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (30 mg, 0.09 mmol) in DMF (1 mL) was added 3-(pyridin-2-yl)propanoic acid (20 mg, 0.13 mmol) followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (44 mg, 0.117 mmol). The reaction was stirred for 16 h, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford *N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-3-(pyridin-2-yl)propanamide as the TFA salt. LC/MS: *m/z* 468.3 $(M+H)^+$ at 1.86 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001264] Example 224

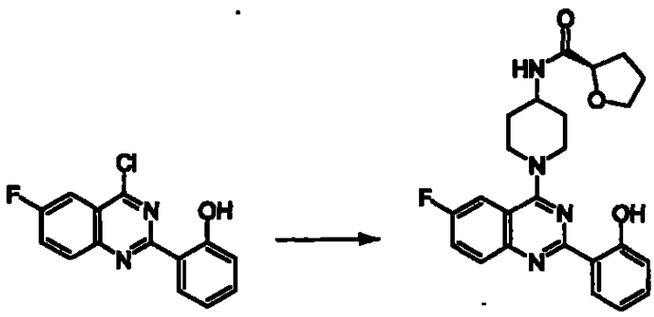
[001265] (2*R*)-*N*-(1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

[001266]



[001267] (2*R*)-*N*-(1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

[001268]

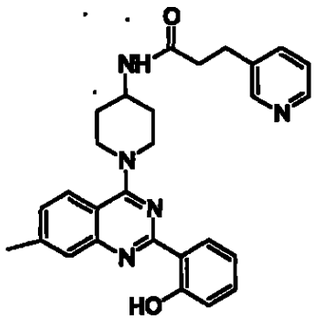


[001269] To a solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (25 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was added (*R*)-tetrahydro-*N*-(piperidin-4-yl)furan-2-carboxamide oxalate (33 mg, 0.117 mmol), followed by the addition of triethylamine (50 μL, 0.36 mmol). The reaction was stirred for 2 h before it was filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-*N*-(1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide as the TFA salt. LC/MS: *m/z* 437.1$(M+H)^+$ at 2.54 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001270] Example 225

[001271] ***N*-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-3-pyridin-3-yl-propionamide**

[001272]



[001273] ***N*-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-3-pyridin-3-yl-propionamide**

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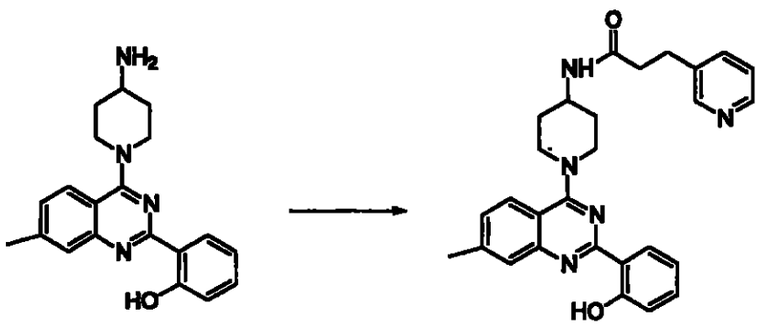
[001274]

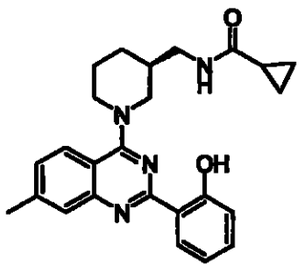


[001275] To 2-[4-(4-amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (238 mg, 0.71 mmol) in 2.4 mL of CH_2Cl_2 was added sequentially 3-pyridin-3-yl-propionic acid (118.3 mg, 0.78 mmol), triethylamine (129 μL, 0.92 mmol), and BOP (346 mg, 0.78 mmol) at room temperature. The reaction mixture was stirred for 40 min and diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oil. The residue was purified by reverse phase LC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) as eluent to give the desired product as the TFA salt. LC/MS: *m/z* 468.6 (M+H)+ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

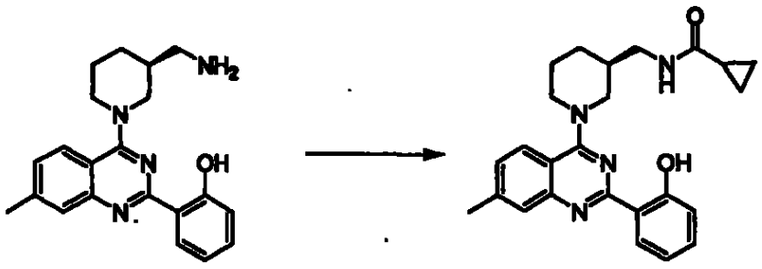
[001276] Example 226

[001277] *N*-(((*S*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide

[001278]



[001279] *N*-(((*S*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide



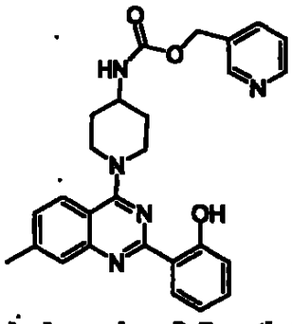
[001280]

[001281] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (35 mg, 0.10 mmol) was dissolved in DMF (1 mL). Cyclopropanecarboxylic acid (9.7 mg, 0.11 mmol) was added, followed by the addition of triethylamine (28 μL, 0.2 mmol), and the mixture was cooled in an ice water bath. HATU (42 mg, 0.11 mmol) was added in one portion, and the reaction was allowed to warm to room temperature while stirring for 16 h. The reaction mixture was filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give N-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methyl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 417.5 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001282] Example 227

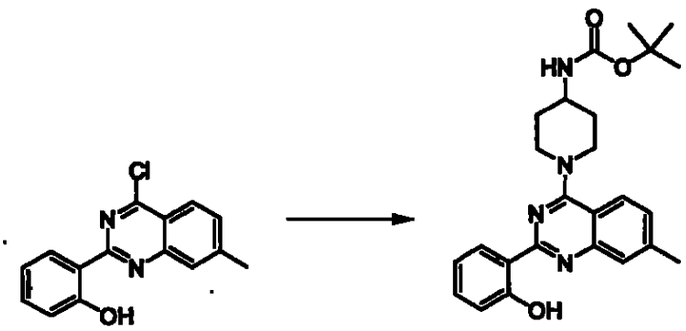
(Pyridin-3-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001283]



[001284] *tert*-Butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

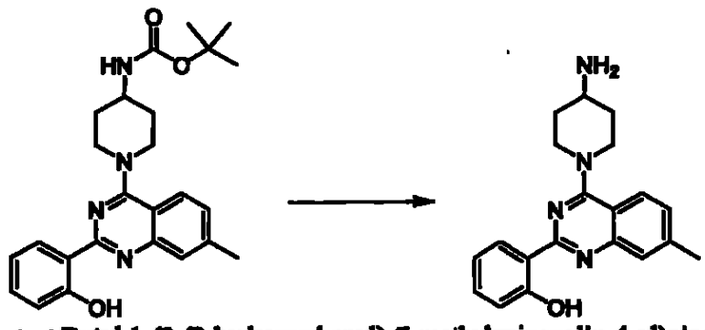
[001285]



[001286] To a suspension of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (2.0 g, 7.38 mmol) in CH_2Cl_2 (25 ml) at 0 °C under an N_2 atmosphere was added dropwise a solution of *tert*-butyl piperidin-4-ylcarbamate (1.92 g, 9.6 mmol) in CH_2Cl_2 (10 ml) and triethylamine (2.0 ml, 14.76 mmol). The reaction was stirred for 6 hours, then it was quenched with water (25 ml), and the layers were separated. The aqueous phase was extracted twice with CH_2Cl_2 (10 ml), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give *tert*-butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as a yellow solid (3.24 g, 100%). LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001287] 2-(4-(4-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001288]

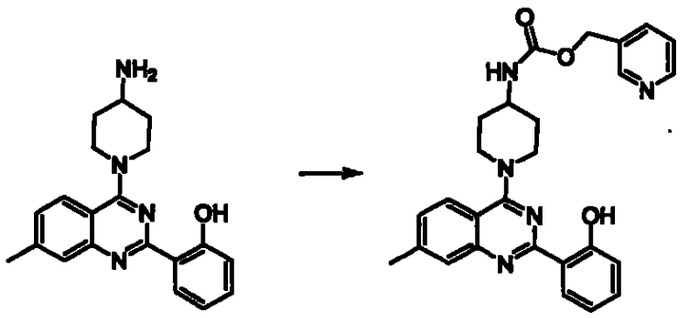


[001289] *tert*-Butyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (3.21 g, 7.39 mmol) was dissolved in CH_2Cl_2 (55 ml). TFA (50 ml) was added and the reaction was stirred for 1 hour. After evaporating the solvents *in vacuo*, the crude material was diluted with CH_2Cl_2 and neutralized with a 1 N NaOH solution. The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (30 ml). The combined organic

layer [illegible] and concentrated to give 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol as a yellow solid (2.06 g, 83%). LC/MS: *m/z* 335.3 $(M+H)^+$ at 1.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001290] (Pyridin-3-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001291]

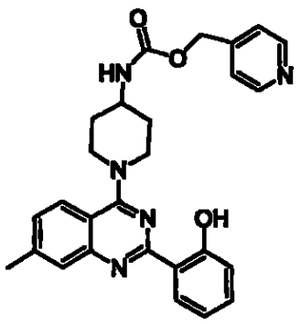


[001292] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMSO (1 mL) was added (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (53 mg, 0.263 mmol) and triethylamine (30.4 mg, 42 μL, 0.3 mmol). The reaction was stirred overnight at room temperature and then purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (pyridin-3-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as the TFA salt. LC/MS: *m/z* 470.5 $(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001293] Example 228

[001294] (Pyridin-4-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001295]



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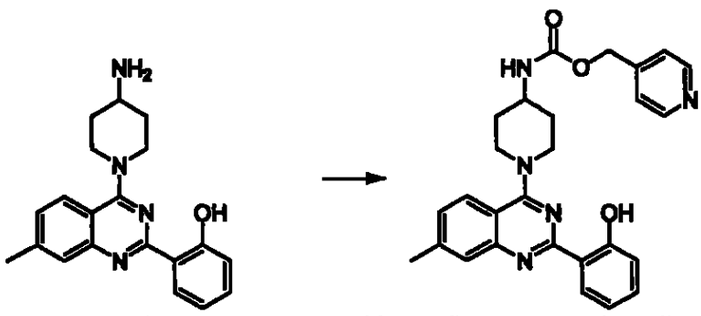
[0012[illegible]-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001297]

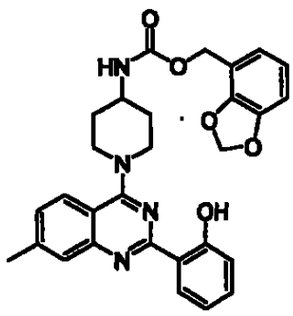


[001298] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMSO (1 mL) was added (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (53 mg, 0.263 mmol) and triethylamine (30.4 mg, 42 μL, 0.3 mmol). The reaction was stirred overnight at room temperature and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (pyridin-4-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as the TFA salt. LC/MS: *m/z* 470.5 $(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001299] Example 229

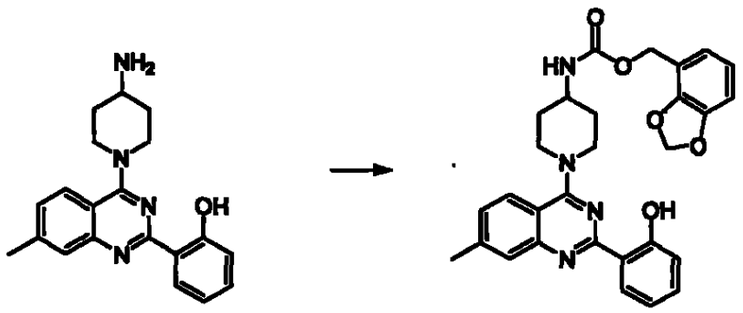
[001300] (Benzo[d][1,3]dioxol-7-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001301]



[001302] (benzo[d][1,3]dioxol-4-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

[001303]

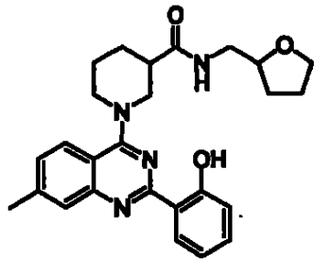


[001304] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMSO (1 mL), was added (benzo[d][1,3]dioxol-4-yl)methyl 1*H*-imidazole-1-carboxylate (65 mg, 0.263 mmol), followed by the addition of triethylamine (30.4 mg, 42 μL, 0.3 mmol). The reaction was stirred overnight at room temperature and then purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (benzo[d][1,3]dioxol-7-yl)methyl 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as the TFA salt. LC/MS: *m/z* 513.3 $(M+H)^+$ at 2.82 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001305] Example 230

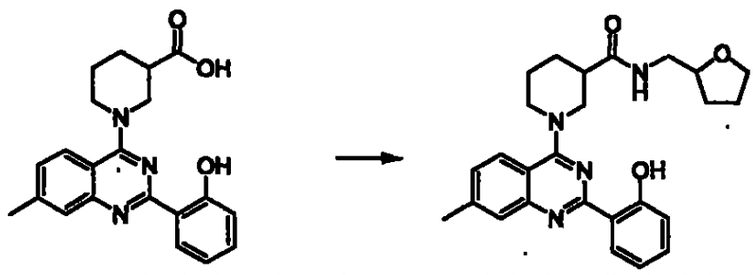
[001306] *N*-((Tetrahydrofuran-2-yl)methyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxamide

[001307]



[001308] *N*-((Tetrahydrofuran-2-yl)methyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxamide

[001309]

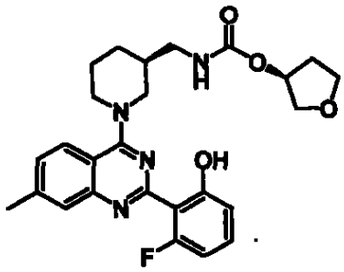


[001310] A solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxylic acid (45 mg, 0.12 mmol) in 500 μL DMF was cooled to 0 °C, and (tetrahydrofuran-2-yl)methanamine (13.2 mg, 0.13 mmol) and triethylamine (25 mg, 35 μL, 0.25 mmol) were added. After ten minutes HATU (57 mg, 0.15 mmol) was added to the reaction mixture in one portion .The reaction was allowed to warm to room temperature, stirred overnight, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) yielding *N*-((tetrahydrofuran-2-yl)methyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 447.3 $(M+H)^+$ at 2.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001311] Example 231

[001312] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001313]



[001314] *tert*-butyl piperidin-3-ylmethylcarbamate

[001315]

[001316] T / Methanolic HCl: MeOH (prepared by adding acetyl chloride (13.5 mL, 14.9 g, 0.19 mol) to 1 L of MeOH) was added to a cold solution of *tert*-butyl pyridin-3-ylmethylcarbamate (41.0 grams, 0.20 mol) in MeOH (100 mL). The solution was transferred to a Parr hydrogenation apparatus at 12 °C. PtO_2 (3 g) was added, and 12 bar pressure of H_2 was applied. After 16 hours ^1H NMR of a concentrated sample indicated the reaction to be complete. The catalyst was filtered, and conc. aq. NaOH (20 mL) was added to neutralize the HCl. The solution was concentrated to remove the bulk of the MeOH and extracted with *tert*-butyl methyl ether (4x200 mL). The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated to give the product (40.16 g, 0.187 mol, 95%) as a yellow oil that crystallized upon standing. ^1H NMR (300 MHz, $CDCl_3$): δ 4.62 (bs. s, 1H), 3.06–2.94 (m, 4H), 2.52 (dt, *J*= 12 Hz, 3Hz, 1H), 2.28 (dd, *J*= 12 Hz, 10Hz, 1H), 1.82–1.72 (m, 1H), 1.70–1.51 (m, 3H), 1.49–1.34 (m, 1H), 1.42 (s, 9H), 1.06 (dq, *J*= 12 Hz, 4Hz, 1H).

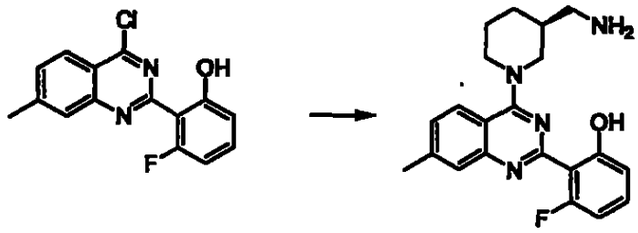
[001317] **(*R*)-*tert*-Butyl piperidin-3-ylmethylcarbamate**

[001318]

[001319] To a solution of *tert*-butyl piperidin-3-ylmethylcarbamate (162 g, 0.758 mol) in EtOH was added (+)-dianisoyltartaric acid (316 g, 0.756 mol). The suspension was heated until clear and allowed to cool to room temperature overnight. The precipitated salt was recrystallized three times from EtOH. The salt was washed with EtOH (2x200 mL) and air-dried. Residual solvent was removed *in vacuo*. The salt was taken up in *tert*-butyl methyl ether and 10% aq. NaOH. The organic layer was separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (3x200 mL). More product was extracted after addition of 30% aq. NaOH to the aqueous layer. The combined organic layers were washed with water and saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated to give (*R*)-*tert*-butyl piperidin-3-ylmethylcarbamate as a white crystalline solid (41.3 g, 0.192 mol, 25%). For ee determinations, samples of the salt were taken up in CH_2Cl_2 and 1 N aq. NaOH. The organic layer was washed with water, dried over Na_2SO_4, and filtered. A drop of 1-naphthyl isocyanate was added, and after 15 minutes a drop of morpholine was added to quench excess isocyanate. Volatiles were evaporated after another 15 minutes. The sample was dissolved in EtOH for chiral HPLC

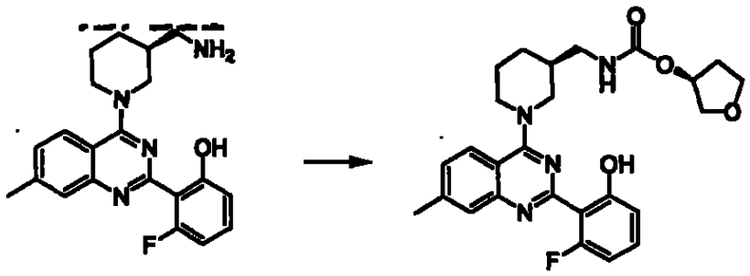
(Chiralcel OD-H, Heptane/EtOH/Et_2NH 90/10/0.2; 0.5 mL/min; Rt (*R*): 46 min, Rt (*S*): 57 min, Rt (*N*-(naphthalen-1-yl)morpholine-4-carboxamide): 64 min.

[001320] **2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol**



[001321] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (1.0 g, 3.46 mmol) was dissolved in 15 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled using an ice bath and piperidin-3-ylmethyl-carbamic acid *tert*-butyl ester/oxalic acid (1.16 g, 3.81 mmol) was added in portions, followed by triethylamine (1.05 g, 1.45 mL, 10.4 mmol). The reaction was allowed to warm to room temperature and was complete after 1.5 hour. The mixture was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted once more with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to a yellow solid. This solid was suspended in 40 mL CH_2Cl_2 and 20 mL of TFA were added. The reaction was complete after 1 hour. The solvent and the excess TFA were removed *in vacuo*, the residue was re-dissolved in CH_2Cl_2, and the pH was adjusted to 7 using an aqueous 1 M solution of NaOH. The reaction was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted once more with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to yield of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (900 mg, 71% overall yield) as a yellow solid. LC/MS: *m/z* 367.3 $(M+H)^+$ at 1.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001322] **(*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



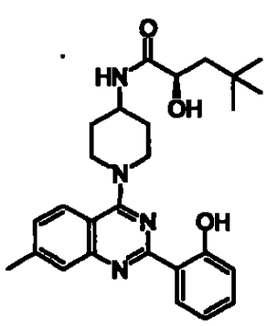
[001323]

[001324] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.11 mmol) was dissolved in anhydrous DMF (800 μL) and cooled to 0 °C, upon which (*S*)-tetrahydrofuran-3-yl chloroformate (16.3 mg, 0.12 mmol) dissolved in DMF (100 μL) was added dropwise followed by triethylamine (22 mg, 30.3 μL, 0.218 mmol). The reaction was allowed to warm to room temperature, and after 2 h the reaction was complete. The mixture was purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to yield (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 481.1 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001325] Example 232

[001326] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-4,4-dimethylpentanamide

[001327]



[001328] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-4,4-dimethylpentanamide

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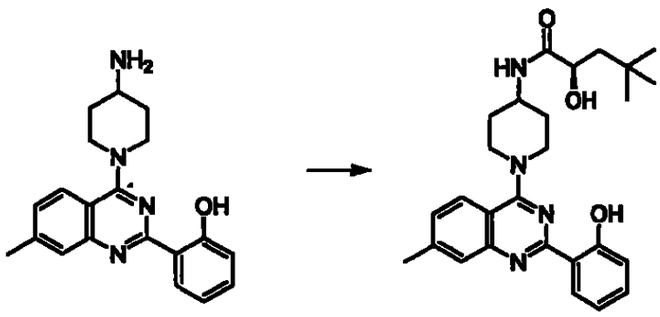
[001329]

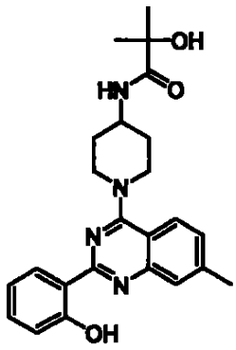


[001330] 2-(4-(4-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.15 mmol) was dissolved in DMF (1 mL) and cooled to 0 °C. (2*R*)-Hydroxy-4,4-dimethyl-pentanoic acid (26.3 mg, 0.18 mmol) was added followed by the addition of triethylamine (42 μL, 0.3 mmol). After ten minutes, HATU (68 mg, 0.18 mmol) was added in one portion. The reaction was stirred at 0 °C for 10 minutes, and then allowed to warm to room temperature. The reaction was complete after 40 minutes, then filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (2*R*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-4,4-dimethylpentanamide as the TFA salt. LC/MS: *m/z* 463.3 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001331] Example 233

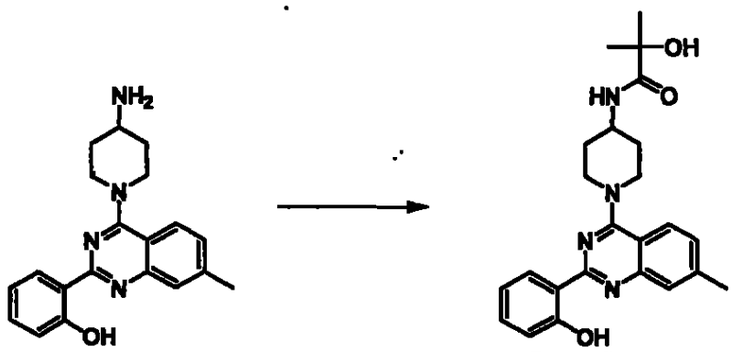
[001332] **2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide**

[001333]



[0013[illegible]] 2-Hydroxy-*N*-(1-(2-(3-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide

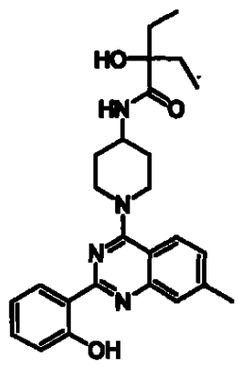
[001335]



[001336] To 2-hydroxy-2-methylpropanoic acid (28 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide as the TFA salt. LC/MS: *m/z* 421.2$(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001337] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001338]



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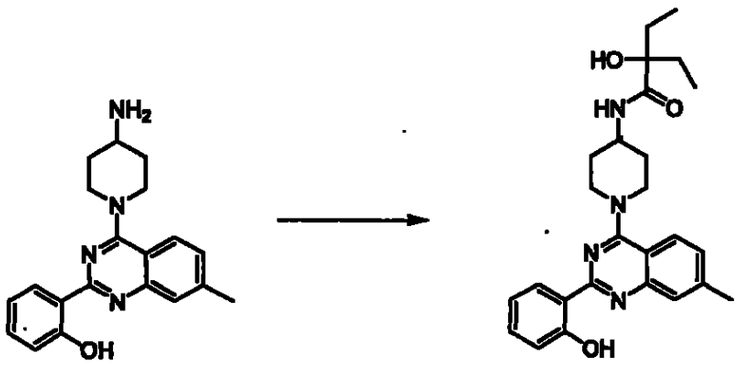
[001339] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001340]

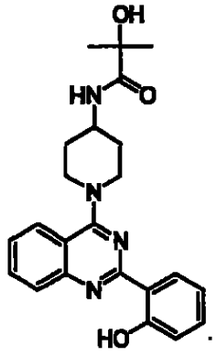


[001341] To 2-ethyl-2-hydroxybutanoic acid (36 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 449.2$(M+H)^+$ at 2.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001342] Example 235

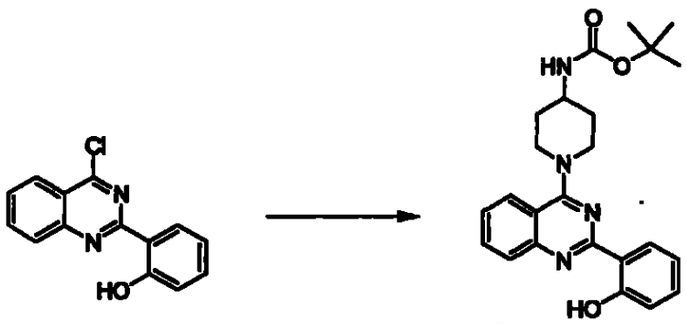
[001343] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide

[001344]



[001345] [illegible] 1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate

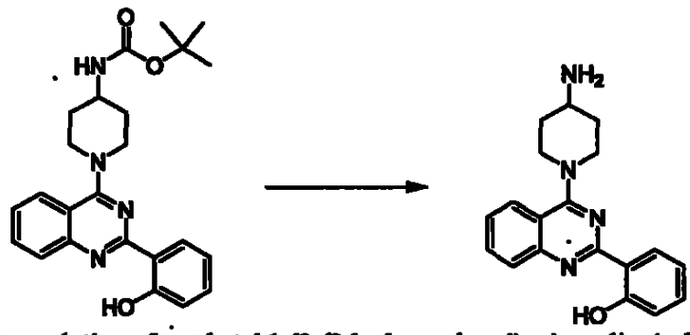
[001346]



[001347] To a suspension of 2-(4-chloroquinazolin-2-yl)phenol (2.0 g, 7.79 mmol) in CH_2Cl_2 (25 mL) at 0 °C under an N_2 atmosphere, was added dropwise *tert*-butyl piperidin-4-ylcarbamate (2.08 g, 10.13 mmol) and triethylamine (2.20 mL, 15.8 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred overnight, quenched with water and extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford *tert*-butyl 1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate (3.27 g, 100% –solvent residue). LC/MS: *m/z* 421.3$(M+H)^+$ at 2.70 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001348] 2-(4-(4-Aminopiperidin-1-yl)quinazolin-2-yl)phenol

[001349]



[001350] To a solution of *tert*-butyl 1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate (3.27 g, 8.09 mmol) in CH_2Cl_2 (75 mL) was added TFA (50 mL). The reaction was complete after 45 minutes After evaporating the solvents *in vacuo*, the crude material was diluted with CH_2Cl_2 and neutralized by adding a 1 N aqueous NaOH solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 2-(4-(4-aminopiperidin-1-

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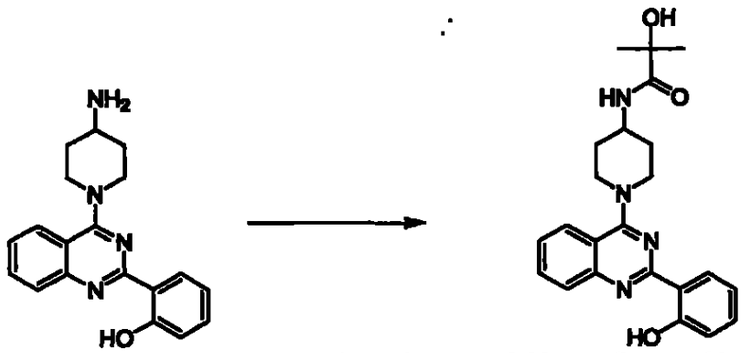
yl)quinazolin-2-yl)phenol as a solid (0.09 g, 84%). LC/MS: *m/z* 321.3$(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001351] **2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide**

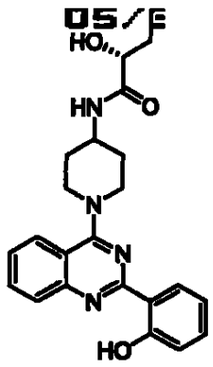
[001352]



[001353] To 2-hydroxy-2-methylpropanoic acid (27 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide as the TFA salt. LC/MS: *m/z* 407.5$(M+H)^+$ at 2.04 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001354] Example 236

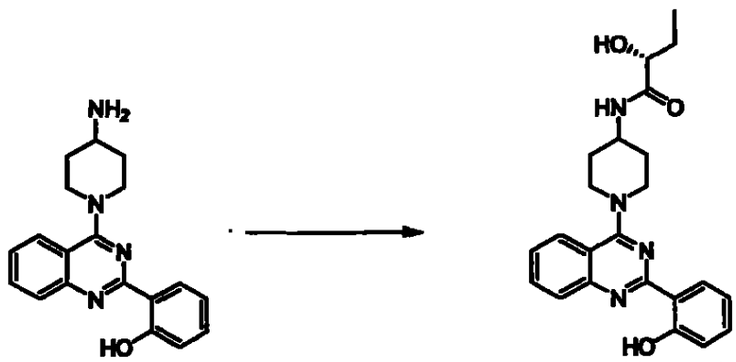
[001355] **(2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide**



[001356]

[001357] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001358]

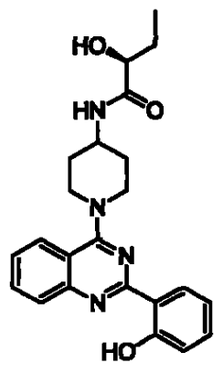


[001359] To (*R*)-2-hydroxybutanoic acid (30 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) dissolved in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 407.3$(M+H)^+$ at 2.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001360] Example 237

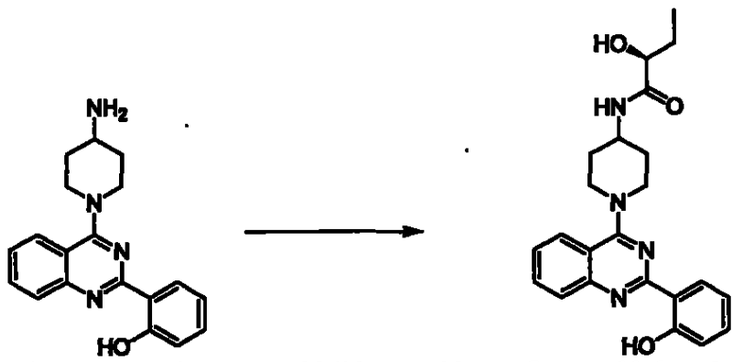
[001361] (2*S*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001362]



[001363] (2*S*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001364]

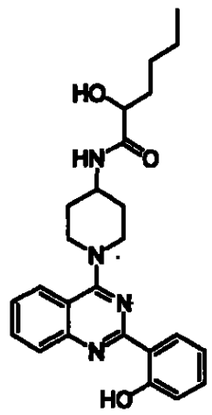


[001365] To (*S*)-2-hydroxybutanoic acid (30 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*S*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 407.3$(M+H)^+$ at 2.09 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001366] Example 238

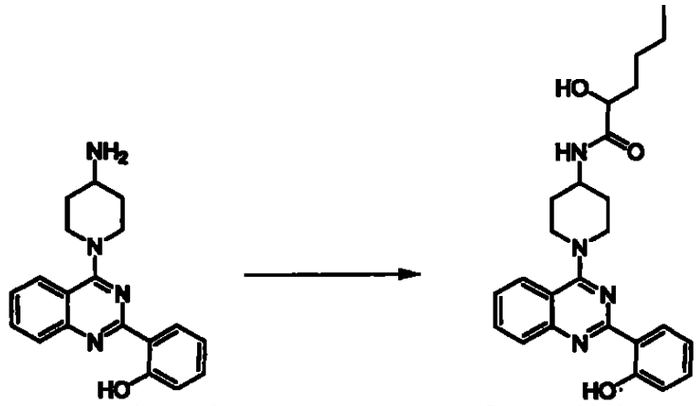
[001367] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)hexanamide

[001368]



[001369] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)hexanamide

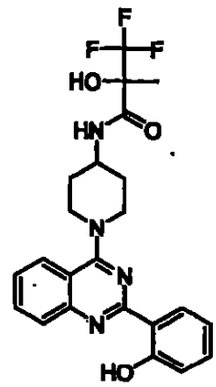
[001370]



[001371] To 2-hydroxyhexanoic acid (38 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)hexanamide as the TFA salt. LC/MS: *m/z* 435.3$(M+H)^+$ at 2.4 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

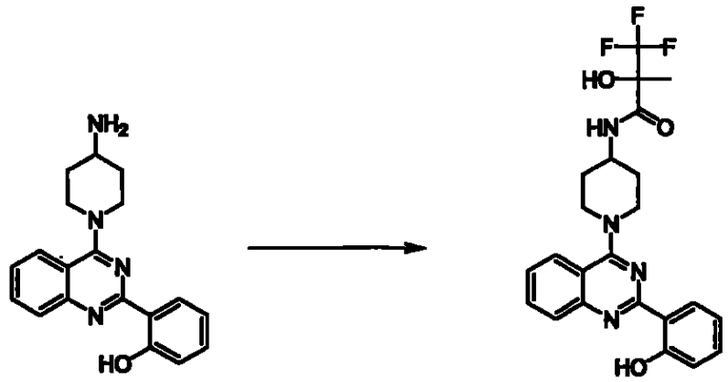
[001372] Example 239

[001373] T / 2-(Trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)propanamide



[001374] 2-(Trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)propanamide

[001375]

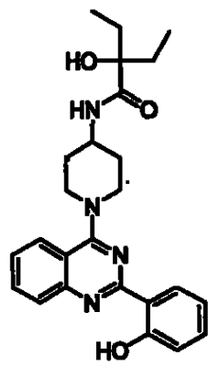


[001376] To 2-(trifluoromethyl)-2-hydroxypropanoic acid (45 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) dissolved in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-(trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)propanamide as the TFA salt. LC/MS: *m/z* 461.1$(M+H)^+$ at 2.4 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001377] Example 240

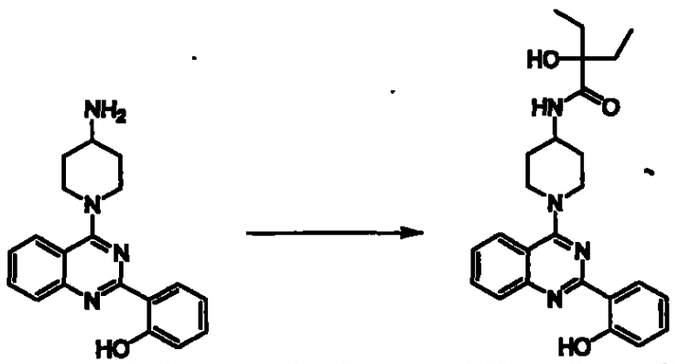
[001378] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001379]



[001380] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide

[001381]



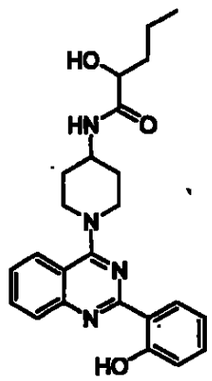
[001382] To 2-ethyl-2-hydroxybutanoic acid (38 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 435.5$(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001383] Example 241

396

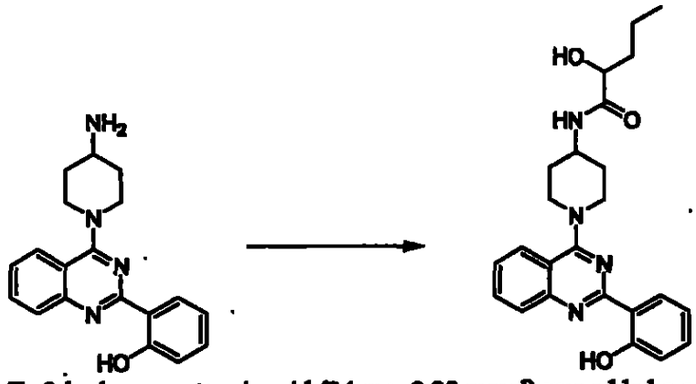
[001384] To a solution of 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)pentanamide

[001385]



[001386] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)pentanamide

[001387]

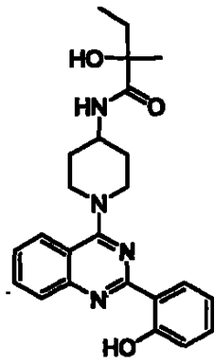


[001388] To 2-hydroxypentanoic acid (34 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)pentanamide as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001389] Example 242

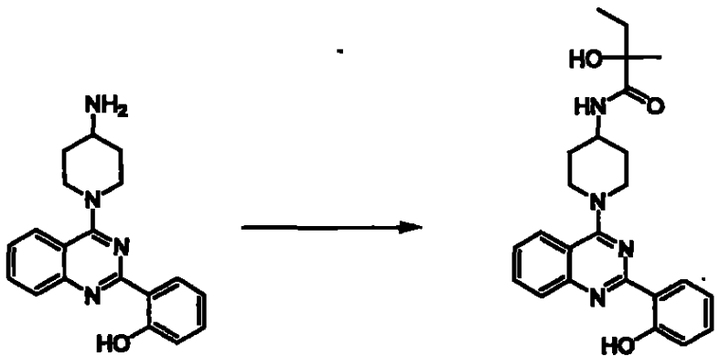
[001390] [illegible]hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide

[001391]



[001392] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide

[001393]



[001394] To 2-hydroxy-2-methylbutanoic acid (34 mg, 0.28 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)quinazolin-2-yl)phenol (0.07 g, 0.22 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.061 mL, 0.44 mmol) and a solution of HATU (0.107 g, 0.284 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide as the TFA salt. LC/MS: *m/z* 421.3$(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001395] Example 243

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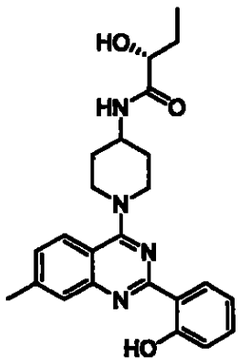
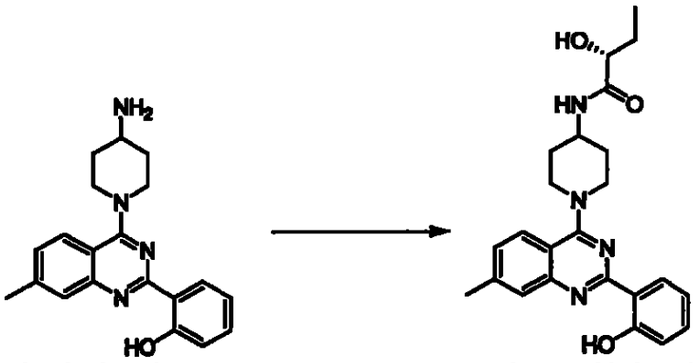
[001396] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001397]



[001398] (2*R*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001399]

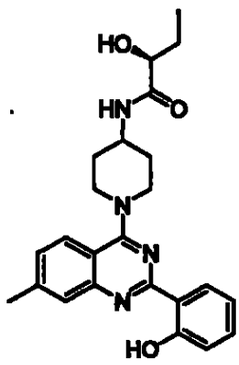


[001400] To (*R*)-2-hydroxybutanoic acid (28 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 421.3$(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001401] Example 244

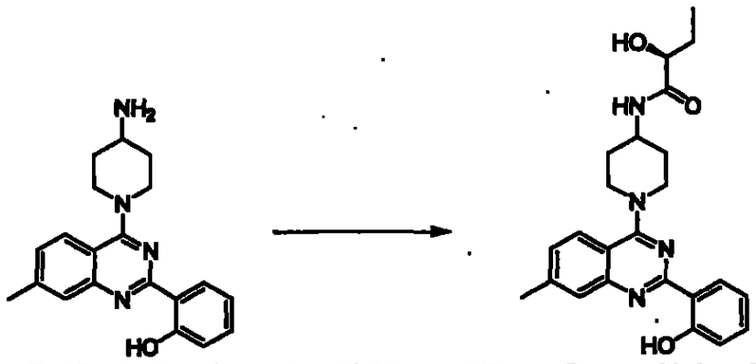
[001402] (2*S*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001403]



[001404] (2*S*)-2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001405]



[001406] To (*S*)-2-hydroxybutanoic acid (28 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, then filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*S*)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide as the TFA salt. LC/MS: *m/z* 421.3$(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001407] Example 245

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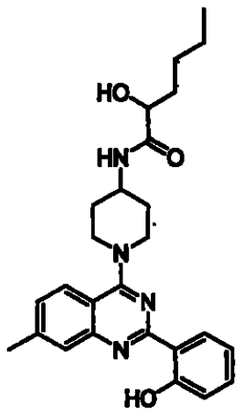
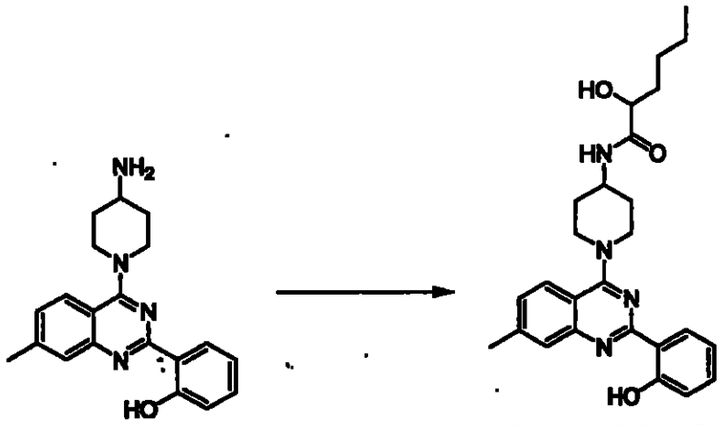
[001408] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)hexanamide

[001409]



[001410] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)hexanamide

[001411]



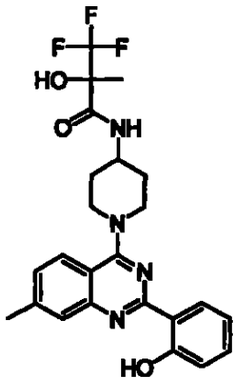
[001412] To 2-hydroxyhexanoic acid (36 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)hexanamide as the

TFA [illegible] 2.45 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001413] Example 246

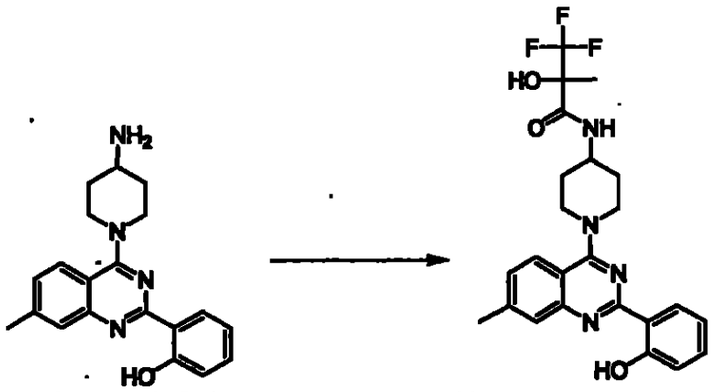
[001414] 2-(Trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)propanamide

[001415]



[001416] 2-(Trifluoromethyl)-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)propanamide

[001417]



[001418] To 2-(trifluoromethyl)-2-hydroxypropanoic acid (43 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

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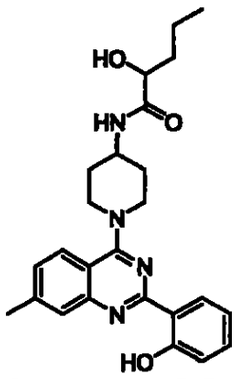
to afford 2-(trifluoromethyl)-3-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)propanamide as the TFA salt. LC/MS: *m/z* 475.1(M+H)$^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001419] Example 247

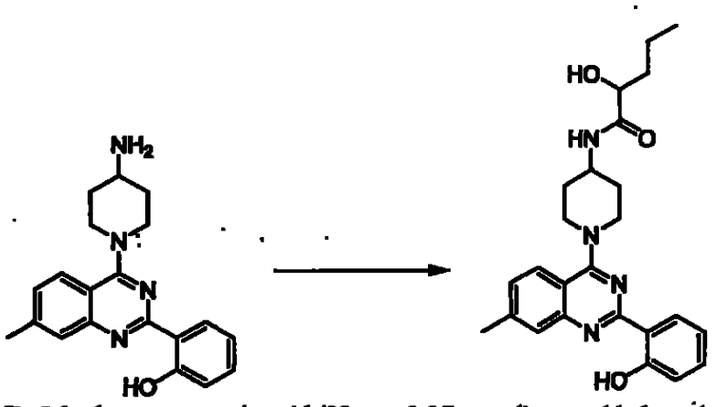
[001420] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)pentanamide

[001421]



[001422] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)pentanamide

[001423]



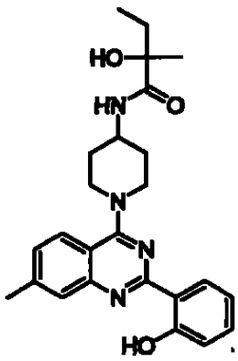
[001424] To 2-hydroxypentanoic acid (32 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified

using [illegible] CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)pentanamide as the TFA salt. LC/MS: *m/z* 435.3$(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001425] Example 248

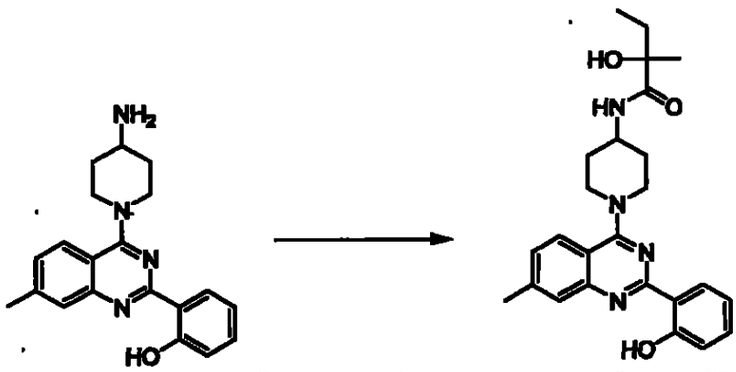
[001426] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide

[001427]



[001428] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide

[001429]



[001430] To 2-hydroxy-2-methylbutanoic acid (32 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL) followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and

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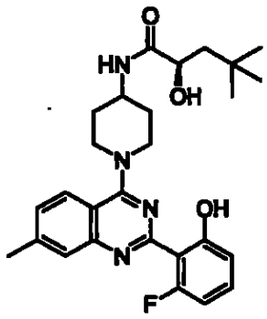
purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylbutanamide as the TFA salt. LC/MS: *m/z* 435.3$(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001431] Example 249

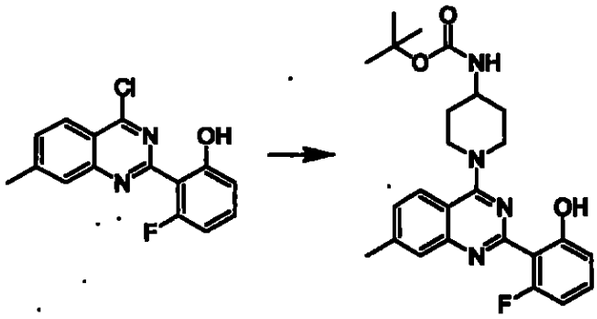
[001432] (2*R*)-*N*-(1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-hydroxy-4,4-dimethylpentanamide

[001433]



[001434] *tert*-Butyl 1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

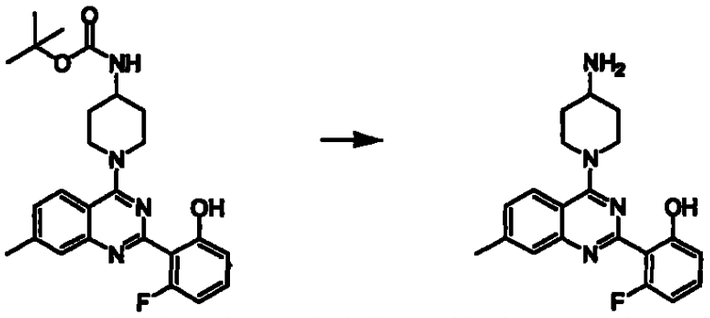
[001435]



[001436] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (700 mg, 2.42 mmol) in 10 ml CH_2Cl_2 at 0 °C was added triethylamine (0.67 mL, 4.8 mmol) followed by the addition of *tert*-butyl piperidin-4-ylcarbamate (630 mg, 3.14 mmol) under an N_2 atmosphere. The reaction was gradually warmed to room temperature and stirred overnight. The reaction mixture was then quenched with water, and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered,

and concentrated to obtain *tert*-butyl 1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (1.05 g, 96%) *LC/MS*: *m/z* 453.3$(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

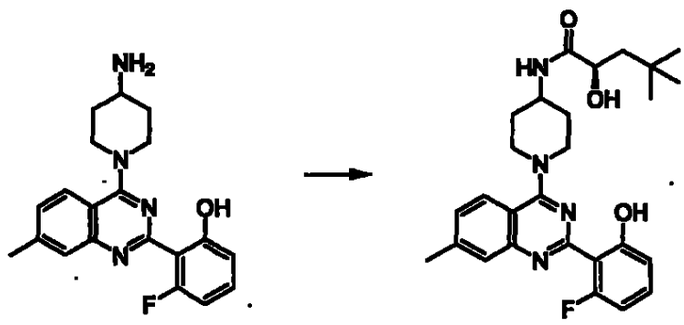
[001437] **2-(4-(4-Aminopiperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol**



[001438] To a solution of *tert*-butyl 1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (1.05 g, 2.3 mmol) in 20 ml CH_2Cl_2 was slowly added TFA (5 mL). The reaction was stirred for one hour before it was evaporated to dryness. To the residue was added CH_2Cl_2, and the reaction was neutralized using an aqueous 1 M NaOH solution. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried over MgSO4, filtered, and concentrated to obtain 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.75 g, 92%). *LC/MS*: *m/z* 353.3$(M+H)^+$ at 1.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001439] **(2*R*)-*N*-(1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-hydroxy-4,4-dimethylpentanamide**

[001440]



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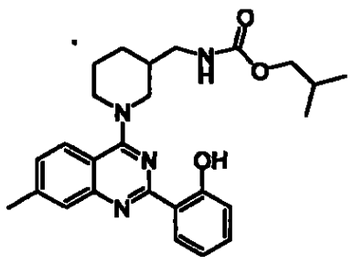
[001441] To a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (50 mg, 0.14 mmol) in 1 mL DMF at 0 °C was added (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (25 mg, 0.17 mmol), followed by the addition of triethylamine (29 mg, 0.28 mmol). HATU (65 mg, 0.17 mmol) was then added, and the reaction was stirred at 0 °C for an additional 10 minutes and then warmed to room temperature. The reaction was complete after 40 minutes, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (2*R*)-*N*-(1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-hydroxy-4,4-dimethylpentanamide as the TFA salt. LC/MS: *m/z* 481.3 $(M+H)^+$ at 2.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001442] Example 250

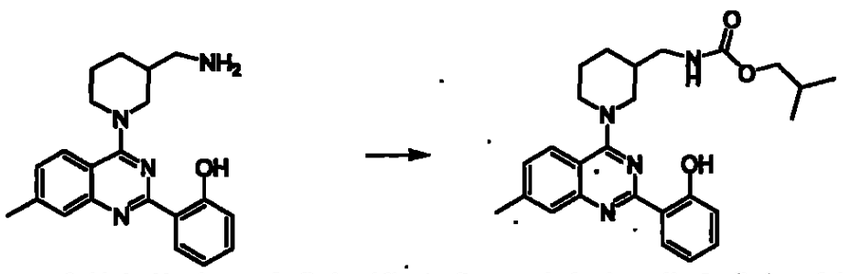
[001443] **Isobutyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001444]



[001445] **Isobutyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001446]



[001447] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which isobutyl chloroformate (27 μL, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by

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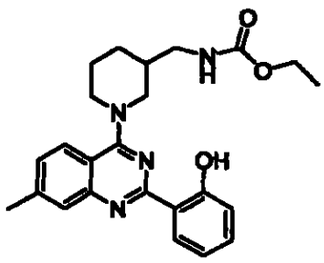
triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature, and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. *LC/MS*: *m/z* 449.5 $(M+H)^+$ at 2.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001448] Example 251

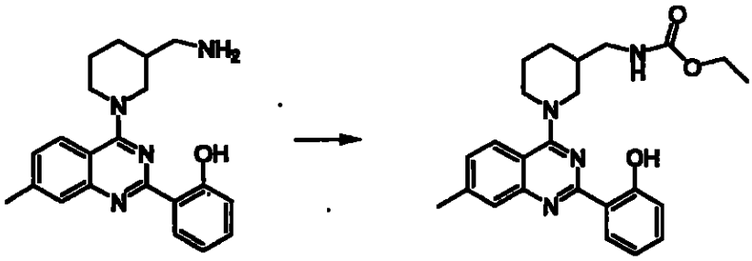
[001449] **Ethyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001450]



[001451] **Ethyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001452]



[001453] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which ethyl chloroformate (20μL, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by the addition of triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave ethyl (1-(2-(2-hydroxyphenyl)-7-

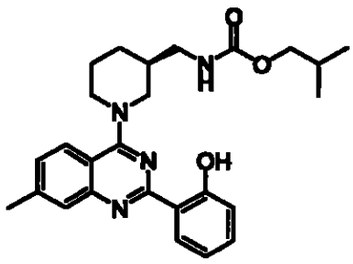
402

methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 421.0 $(M+H)^+$ at 2.48 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001454] Example 252

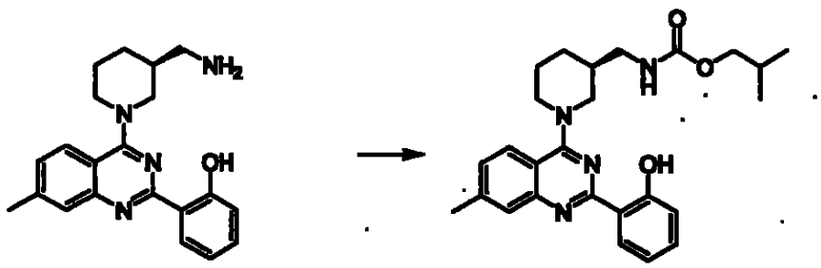
[001455] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001456]



[001457] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001458]



[001459] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which isobutyl chloroformate (27 μL, 0.2 mmol) dissolved in DMF (100 μL) was added dropwise followed by the addition of triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001460] Example 253

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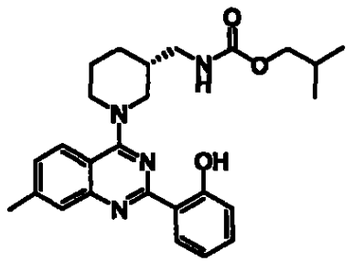
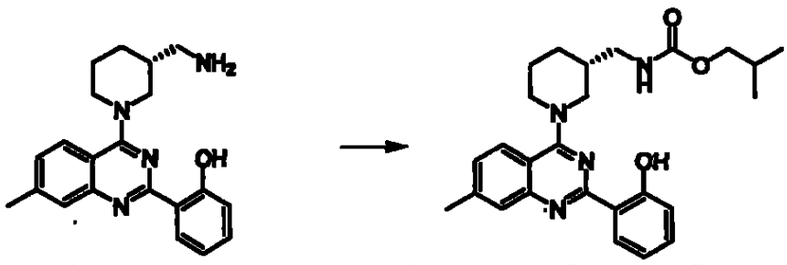
[001461] Isobutyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001462]



[001463] Isobutyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001464]



[001465] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.172 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which isobutyl chloroformate (27 μL, 0.21 mmol) dissolved in DMF (100 μL) was added dropwise followed by the addition of triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature, and it was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.78 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001466] Example 254

[001467] Ethyl((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

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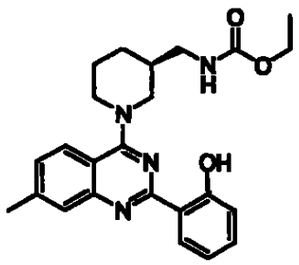
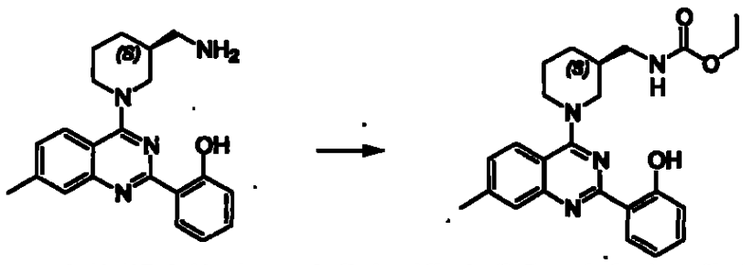
[001468]



[001469] Ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001470]

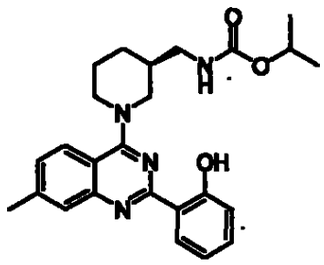


[001471] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (35 mg, 0.10 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which ethyl chloroformate (10.5 μL, 0.11 mmol) dissolved in DMF (100 μL) was added dropwise followed by triethylamine (20.2 mg, 27.8 μL, 0.2 mmol). The reaction was allowed to warm to room temperature, and it was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.50 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001472] Example 255

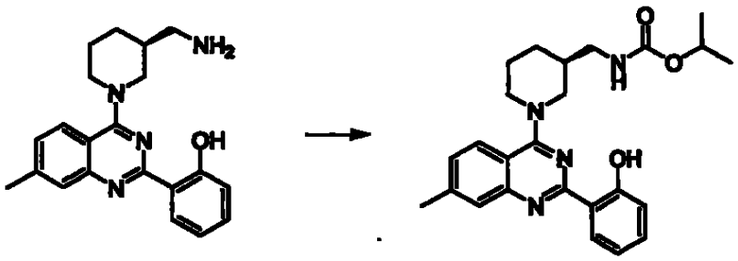
[001473] Isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001474]



[001475] Isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001476]

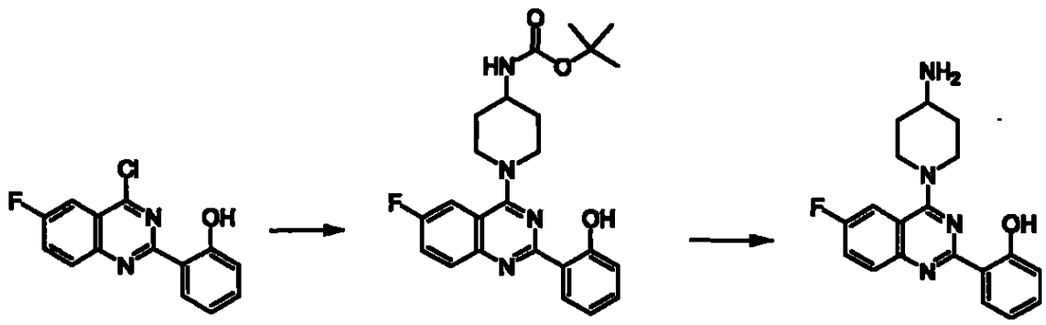


[001477] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (35 mg, 0.10 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which isopropyl chloroformate (1 M solution in toluene, 98.1 mg, 110 μL, 0.11 mmol) was dissolved in DMF (100 μL) and added dropwise, followed by triethylamine (20.2 mg, 27.8 μL, 0.2 mmol). The reaction was allowed to warm to room temperature, and it was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.61 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001478] Example 256

[001479] Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

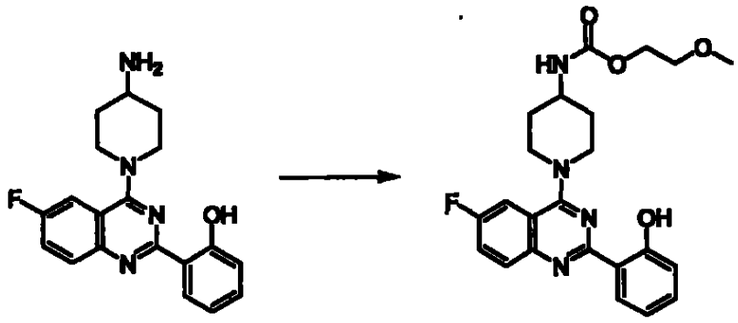
[001494]



[001495] To a stirred solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (0.20 g, 0.73 mmol) in CH_2Cl_2 (5mL) was added dropwise a solution of *tert*-butyl piperidin-4-ylcarbamate (0.19 g, 0.95 mmol) and triethylamine (203 µL, 147 mg, 1.46 mmol) in CH_2Cl_2. The reaction was stirred for 3 h and then quenched with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to obtain *tert*-butyl 1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate. The residue was dissolved in 10 mL CH_2Cl_2 and 3 mL TFA. The reaction was stirred for 2 hours and neutralized with a 1.0 M aqueous NaOH solution. The mixture was partitioned between H_2O/CH_2Cl_2 and separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to obtain 2-(4-(4-aminopiperidin-1-yl)-6-fluoroquinazolin-2-yl)phenol. LC/MS: *m/z* 339.3$(M+H)^+$ at 1.87 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001496] **2-Methoxyethyl 1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate**

[001497]

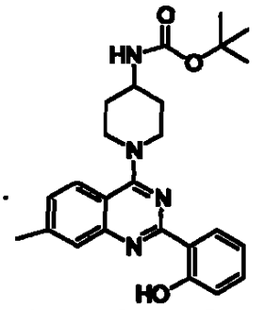


[001498] A solution of 2-(4-(4-aminopiperidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (50 mg, 0.15 mmol) in DMF (1 mL) was cooled to –40 °C (external temp). To it was added triethylamine (41 μL, 30 mg, 0.29 mmol) and a solution of 2-methoxyethyl chloroformate (17 μL, 20 mg, 0.15 mmol) in 100 μL DMF dropwise. The reaction was allowed to warm to room temperature and was stirred for 2 h. Purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl 1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperidin-4-ylcarbamate as the TFA salt. *LC/MS*: *m/z* 441.5$(M+H)^+$ at 2.6 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001499] Example 259

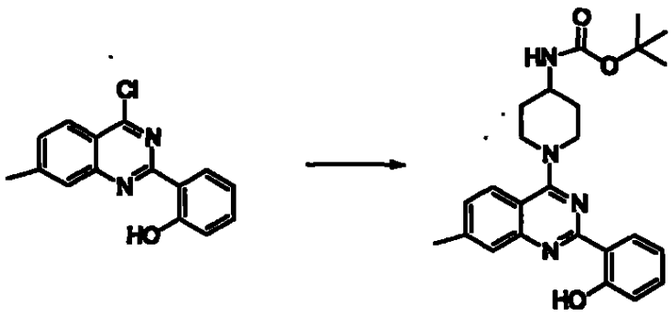
[001500] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester

[001501]



[001502] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester

[001503]



[001504] To piperidin-4-yl-carbamic acid *tert*-butyl ester (887 mg, 4.4 mmol) in 10 mL of was CH_2Cl_2 was added sequentially triethylamine (720 μL, 5.2 mmol) and 2-(4-chloro-7-methyl-

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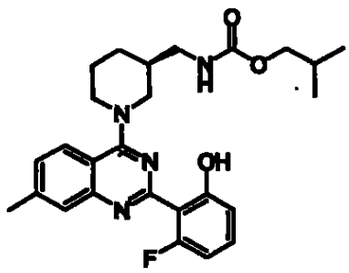
quinazolin-2-yl)-phenol (1.0 g, 3.7 mmol). The reaction mixture was stirred at room temperature for 2 h and then diluted with water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester as the TFA salt. LC/MS: *m/z* 435.2 (M+H)+ at 3.03 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001505] Example 260

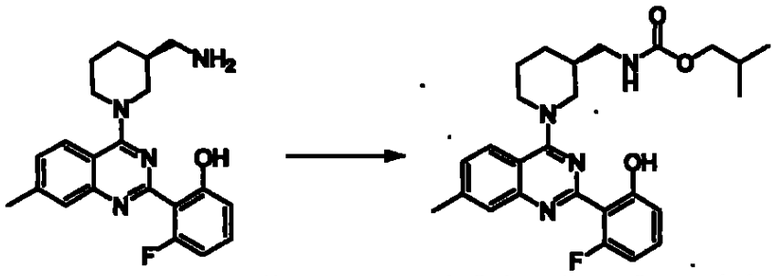
[001506] Isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001507]



[001508] Isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001509]



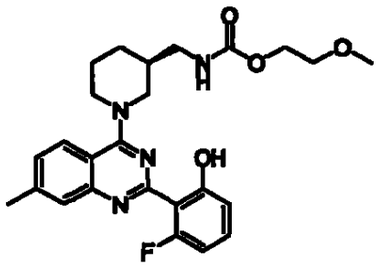
[001510] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.11 mmol) in DMF (400 μL) at 0 °C was added dropwise isobutyl chloroformate (15.7 μL, 0.12 mmol) in DMF (400 μL), followed by the addition of triethylamine

(30 μL, 0.22 mmol). The reaction was allowed to warm to room temperature and was complete after 2h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 467.1 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001511] Example 261

[001512] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

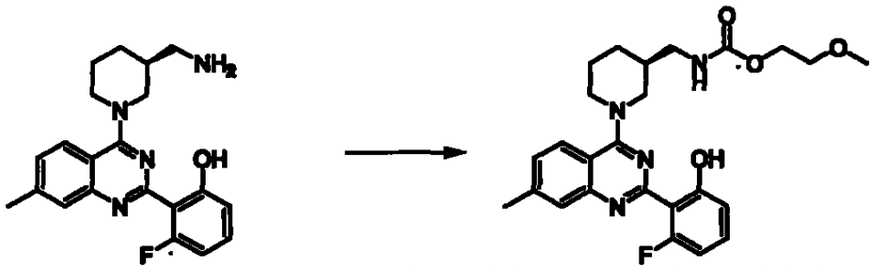
[001513]



[001514] Method A

[001515] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001516]



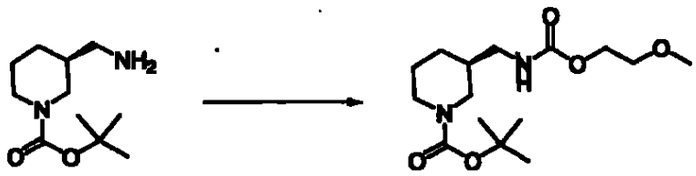
[001517] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.11 mmol) in DMF (400 μL) at 0 °C was added dropwise 2-methoxyethyl chloroformate (12.6 μL, 0.11 mmol) in DMF (400 μL), followed by the addition of triethylamine (30 μL, 0.22 mmol). The reaction was allowed to warm to room temperature and was complete after 2h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-

methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.20 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001518] Method B

[001519] 2-Methoxyethyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate

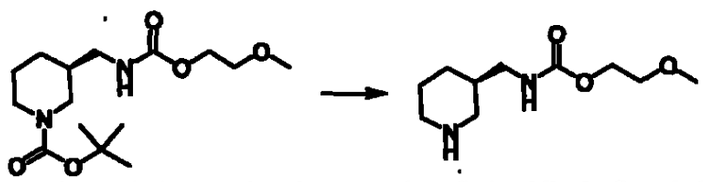
[001520]



[001521] To a solution of (*S*)-*tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (500 mg, 2.33 mmol) in CH_2Cl_2 at –10 °C was added triethylamine (650 µL, 4.66 mmol) followed by the dropwise addition of 2-methoxyethyl chloroformate (325 µL, 2.79 mmol). The reaction was warmed to room temperature and quenched with water. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, and evaporated. Purification via silica gel chromatography using 0 to 10% EtOAc in CH_2Cl_2 afforded 2-methoxyethyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate (496 mg, 67%). LC/MS: *m/z* 317.3 $(M+H)^+$ at 2.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001522] 2-Methoxyethyl ((*R*)-piperidin-3-yl)methylcarbamate

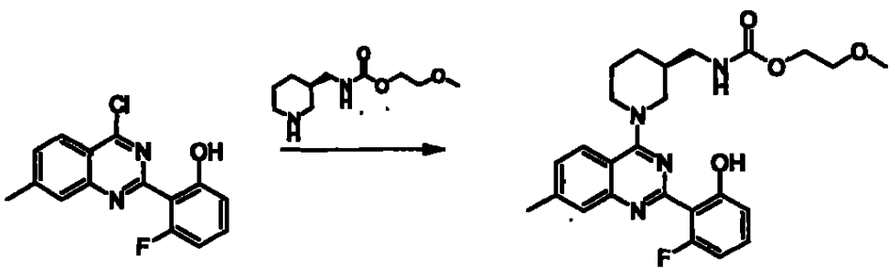
[001523]



[001524] To 2-methoxyethyl ((*S*)-1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylcarbamate (496 mg, 1.6 mmol) dissolved in 10 mL CH_2Cl_2 was added 5 mL TFA, and the reaction was stirred for 1 hour. After neutralizing the mixture with a 1 N NaOH solution it was extracted with CH_2Cl_2, and the combined organic layers were dried over MgSO4, filtered, and concentrated to give 2-methoxyethyl ((*R*)-piperidin-3-yl)methylcarbamate (300 mg, 87%) which was used without further purification. LC/MS: *m/z* 217.5 $(M+H)^+$ at 0.49 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001525] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

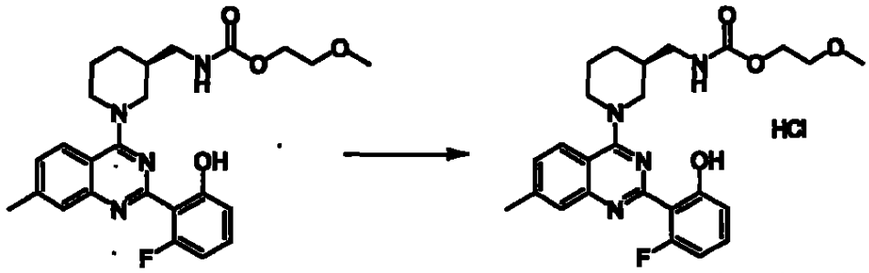
[001526]



[001527] To a solution of 2-methoxyethyl ((*R*)-piperidin-3-yl)methylcarbamate (0.24 g, 1.1 mmol) and 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (250 mg, 0.865 mmol) in CH_2Cl_2 was added triethylamine (2.41 mL, 1.73 mmol). After stirring the reaction at room temperature for 2 h, it was quenched with water and then extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0%–10% EtOAc in CH_2Cl_2 yielded 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (357 mg, 88%). LC/MS: *m/z* 469.5 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (m, 3H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.71 (m, 2H), 4.40 (d, *J* = 12.7 Hz, 2H), 4.05 (m, 2H), 3.48 (m, 2H), 3.30 (m, 1H), 3.25 (s, 3H), 3.05 (m, 3H), 1.82 (m, 3H), 1.63 (m, 1H), 1.32 (m, 1H).

[001528] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001529]



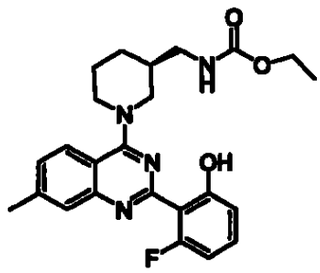
[001530] To a solution of ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (352 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) was added dropwise

a 2.0 M HCl solution in ether (0.375 mL, 0.75 mmol) under an N_2 atmosphere. It was followed by the addition of 20 mL ether which lead to the precipitation of 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride (350 mg, 92%) which was then filtered and dried. *LC/MS*: *m/z* 469.5 $(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 7.97 (d, *J* = 7.9 Hz, 1H), 7.63 (s, 1H), 7.45 (m, 3H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.82 (t, *J* = 9.5 Hz, 1H), 4.54 (s, 1H), 4.03 (d, *J* = 2.7 Hz, 2H), 3.47 (t, *J* = 4.6 Hz, 4H), 3.24 (s, 3H), 2.99 (m, 2H), 2.54 (s, 3H), 1.89 (m, 1H), 1.70 (m, 1H), 1.38 (m, 1H)

[001531] Example 262

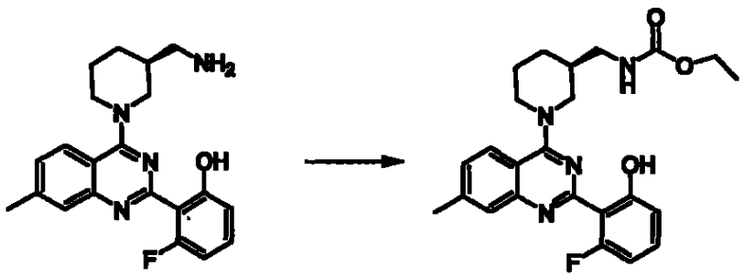
[001532] Ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001533]



[001534] Ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

[001535]



[001536] Method A

[001537] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.11 mmol) in DMF (400 μL) at 0 °C was added dropwise ethyl chloroformate (10.4 μl, 0.10 mmol) in DMF (400 μL), followed by the addition of triethylamine

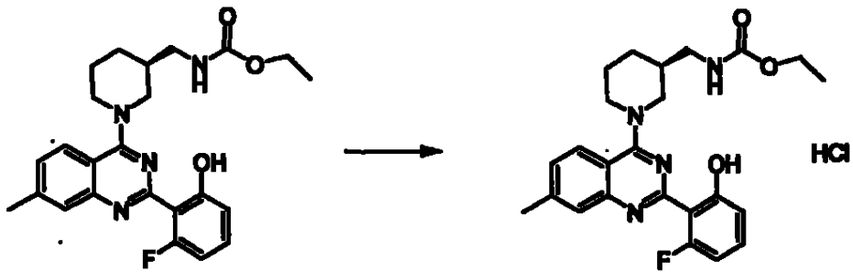
(30 μL, 0.22 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. *LC/MS: m/z* 439.5 $(M+H)^+$ at 2.31 min (*10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).*

[001538] Method B

[001539] To a stirred solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (200 mg, 0.54 mmol) in 12 mL THF was added diisopropyl ethylamine (188 μL, 1.08 mmol) at room temperature. The mixture was cooled to –60 °C, and a solution of ethyl chloroformate (52 μL, 0.54 mmol) in 0.6 mL THF was added dropwise. After allowing the reaction to warm to room temperature, the mixture was partitioned between H_2O and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted twice more with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 hexanes:CH_2Cl_2 gave ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (92 mg, 38%). *LC/MS: m/z* 439.5 $(M+H)^+$ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (m, 2H), 7.21 (m, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.70 (m, 1H), 4.40 (m, 2H), 3.98 (m, 2H), 3.27 (m, 1H), 3.05 (m, 1H), 2.97 (m, 2H), 1.84 (d, *J* = 11.0 Hz, 3H), 1.67 (d, *J* = 9.4 Hz, 1H), 1.32 (dd, *J* = 20.8, 11.3 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H)

[001540] Ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001541]



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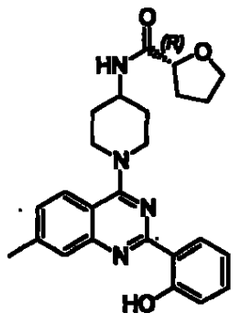
[001542] To a solution of ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (89 mg, 0.2 mmol) in 2 mL CH_2Cl_2 under an N_2 atmosphere was added ether (10 mL) followed by the dropwise addition of a 2.0 M solution of HCl in ether (0.1 mL, 0.2 mmol) which resulted in precipitation of ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride which was then filtered and dried (85 mg, 90%). *LC/MS*: *m/z* 439.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.26 (d, *J* = 8.5 Hz, 1H), 7.57 (s, 1H), 7.45 (m, 2H), 6.81 (m, 2H), 4.57 (m, 2H), 3.89 (m, 2H), 3.52 (m, 1H), 3.36 (m, 1H), 2.95 (s, 2H), 2.52 (s, 3H), 1.86 (m, 3H), 1.66 (m, 1H), 1.39 (m, 1H), 1.07 (t, *J* = 6.6 Hz, 3H).

[001543] Example 276

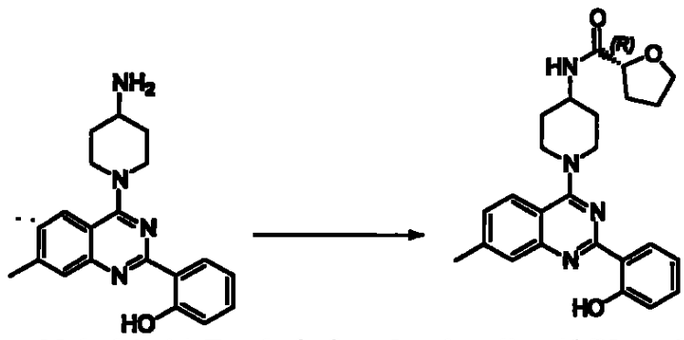
[001544] **(*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide**

[001545]



[001546] **(*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide**

[001547]



[001548] Method A: (*R*)-Tetrahydrofuran-2-carboxylic acid (23 mg, 0.20 mmol) and HATU (84 mg, 0.22 mmol) were dissolved in 0.75 mL DMF, then triethylamine (40 mg, 55 μL, 0.40 mmol) was added, followed immediately by 2-[4-(4-Amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (67 mg, 0.20 mmol). The reaction was then stirred for 30 min at room temperature, diluted with 0.75 mL 1:1 methanol / DMSO, filtered, and purified by reverse phase HPLC (2–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide as the TFA salt. LC/MS: *m/z* 433.2 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001549] Method B: (*R*)-Tetrahydrofuran-2-carboxylic acid (193 mg, 1.66 mmol) was dissolved in DMF (6 mL), followed by the addition of HATU (696 mg, 1.83 mmol). The mixture was then stirred for 15 min at room temperature under an N_2 atmosphere. The 2-[4-(4-Amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (556 mg, 1.66 mmol) was dissolved in DMF (8 mL) and added to the mixture, followed by triethylamine (336 mg, 0.463 mL, 3.32 mmol). After 30 min, theDMF was removed *in vacuo* and the crude product partitioned between water and ethyl acetate. The aqueous layer was separated, washed with ethyl acetate, and the combined organic layers dried over $MgSO_4$, filtered, and concentrated to give crude product as an orange oil. Purification via silica gel chromatography (20% ethyl acetate / 80% 1:1 CH_2Cl_2:hexane) gave pure (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide (303 mg, 42%). ^1H NMR (400 MHz, DMSO-d6) δ 8.44 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.67 (s, 1H), 7.40–7.36 (m, 2H), 6.97–6.93 (m, 2H), 4.48–4.45 (m, 2H), 4.20 (dd, *J* = 8.2, 5.3 Hz, 1H), 4.06–3.96 (m, 1H), 3.88 (dd, *J* = 14.3, 6.6 Hz, 1H), 3.74 (dd, *J* = 14.5, 6.7 Hz, 1H), 3.43–3.32 (m, 2H), 2.51 (s, 3H), 2.16–2.07 (m, 1H),

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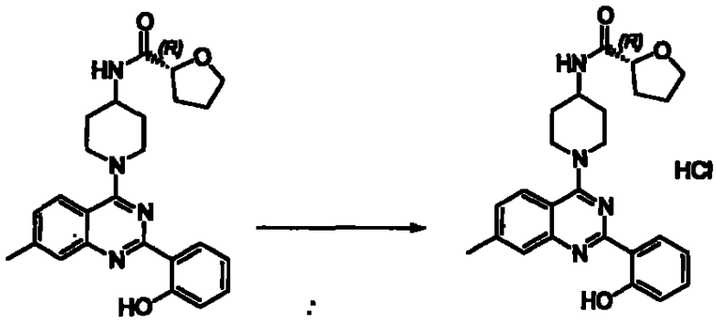
1.89–1.69 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d6) δ 171.7, 162.8, 160.7, 159.5, 149.3, 144.1, 132.5, 129.0, 127.3, 125.7, 125.4, 118.9, 118.4, 117.2, 111.9, 77.6, 68.5, 48.3, 45.5, 31.3, 31.2, 30.0, 24.9, 21.2.

[001550] (*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide hydrochloride

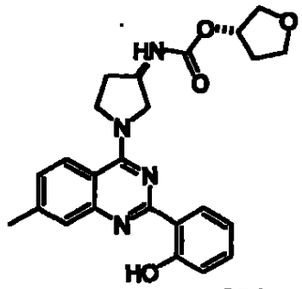


[001551] (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide (303 mg, 0.701 mmol) was dissolved in 9 mL 2:1 dry ether / dry CH_2Cl_2 and 2.0 M HCl in ether added dropwise (0.35 mL, 0.70 mmol), producing a white precipitate which was collected by filtration to give (*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide hydrochloride (268 mg, 82%). LC/MS: *m/z* 433.5 $(M+H)^+$ at 2.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^{1}H NMR (400 MHz, DMSO-d6) δ 8.20 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.80–7.79 (m, 2H), 7.51–7.47 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.05–7.01 (m, 1H), 4.66–4.63 (m, 2H), 4.21 (dd, *J* = 8.2, 5.2 Hz, 1H), 4.12–4.03 (m, 1H), 3.91–3.84 (m, 1H), 3.78–3.70 (m, 1H), 3.59 (t, *J* = 12.3 Hz, 2H), 2.54 (s, 3H), 2.16–2.05 (m, 1H), 1.97–1.94 (m, 2H), 1.89–1.72 (m, 5H).

[001552] Example 301

[001553] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001554]



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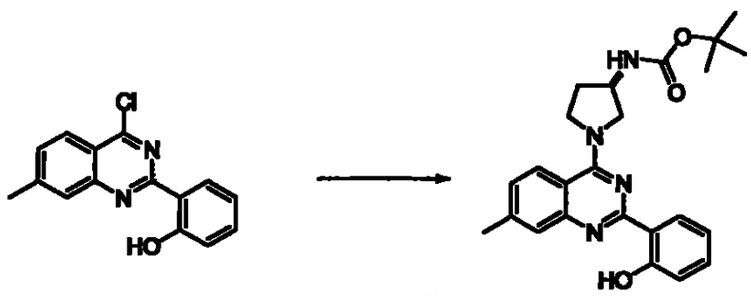
[001555] *tert*-Butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

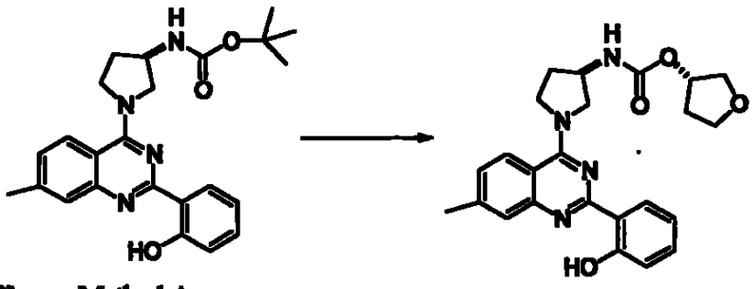
[001556]



[001557] To 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol (644 mg, 2.4 mmol) in 2.9 mL of DMF at room temperature was added sequentially (*R*)- pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (857 mg, 4.6 mmol) and triethylamine (662 μL, 4.8 mmol), and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and dried (Na_2SO_4), and the residue was purified by silica gel chromatography with 25–85% ethyl acetate/hexanes to give *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (856 mg, 86%). LC/MS: *m/z* 421 $(M+H)^+$ at 2.82 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001558] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001559]



[001560] Method A

[001561] To *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (850 mg, 2.02 mmol) was added at room temperature 4 mL of 1:1 TFA:CH_2Cl_2. The reaction mixture was stirred for 50 min, diluted with 20 mL of CH_2Cl_2, and washed with 15 mL of satd. $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4, and the

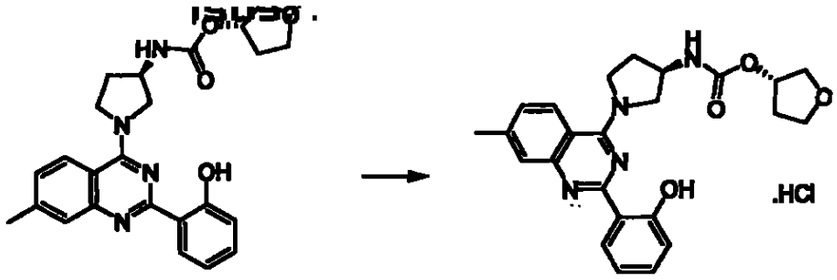
solvent was removed under reduced pressure to give (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol as an oil which was used without further purification.

To 45.9 mg (0.14 mmol) of the amine from above procedure was added 570 μL of CH_2Cl_2 and the solution was cooled to 0 °C. To this solution was added sequentially 24 μL (0.17 mmol) of triethylamine and 19.4 mg (0.13 mmol) of (*S*)- tetrahydro-furan-3-ol chloroformate. The reaction mixture was stirred at 0 °C for 45 min, diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 435 $(M+H)^+$ at 2.41 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001562] Method B

[001563] To *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (907.2 mg, 2.16 mmol) was added 4 mL of 1:1 TFA:CH_2Cl_2. The mixture was stirred at room temperature for 5 hours. The reaction was diluted with a solution of saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to give 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol. To this free amine (640 mg, 2 mmol) was added 8 ml of CH_2Cl_2 and triethylamine (335 μL, 2.4 mmol). After cooling the mixture to 0 °C, (*S*)-tetrahydrofuran-3-yl chloroformate (271 mg, 1.8 mmol) was added, and the reaction was allowed to stir for 30 minutes. Purification on silica gel using 30–100% ethyl acetate/hexanes gave (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. ^1H NMR (400 MHz, $CDCl_3$) δ 14.8 (bs, 1H), 8.34 (d, *J* = 6.4 Hz, 1H), 7.83 (d, *J* = 4.0 Hz, 1H), 7.48 (bs, 1H), 7.27 (m, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 5.21 (s, 1H), 5.06 (s, 1H), 4.37 (s, 1H), 4.15 (m, 1H), 4.02 (s, 1H), 3.97 (d, *J* = 5.6 Hz, 1H), 3.87–3.77 (m, 5H), 2.42 (s, 3H), 2.24 (t, *J* = 6.0 Hz, 1H), 2.15–2.06 (m, 1H), 1.98 (q, *J* = 9.3 Hz, 2H).

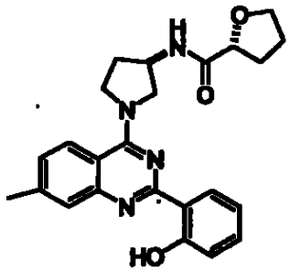
[001564] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride



[001556] A 2.0 M HCl solution in Et_2O (192 μL, 0.38 mmol) was slowly added at -20 °C to a stirring solution of (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (167 mg, 0.38 mmol) in 700 μL of CH_2Cl_2. The reaction was allowed to warm to room temperature and was stirred for 25 minutes. Solvents were removed under reduced pressure, and the residue was triturated with Et_2O and filtered to give (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride. LC/MS: *m/z* 435.2 $(M+H)^+$ at 2.41 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

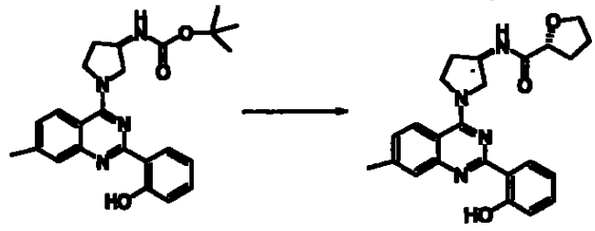
[001557] Example 302

[001558] **(*R,R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide**



[001559] **(*R, R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide.**

[001560]



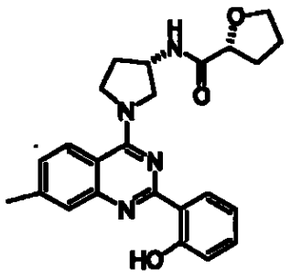
[001572] To 850 mg (2.02 mmol) of (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester was added at room temperature 4 mL of 1:1 TFA: CH_2Cl_2. The reaction mixture was stirred for 50 min and diluted with 20 mL of CH_2Cl_2 and extracted with 15 mL of satd. $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol as an oil which was used without further purification.

To 52.6 mg (0.16 mmol) of the amine from above procedure was added 600 μL of CH_2Cl_2. To this solution was added sequentially 27.4 μL (0.19 mmol) of triethylamine and 20.9 mg (0.18 mmol) of (*R*)- tetrahydro-furan-2-carboxylic acid, 24.2 mg (0.18 mmol) of HOBt, 34.6 mg (0.18 mmol) of EDCI at room temperature. The reaction mixture was stirred for 12 h, then diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*, *R*)-tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide as the TFA salt. LC/MS: *m/z* 419 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001573] Example 303

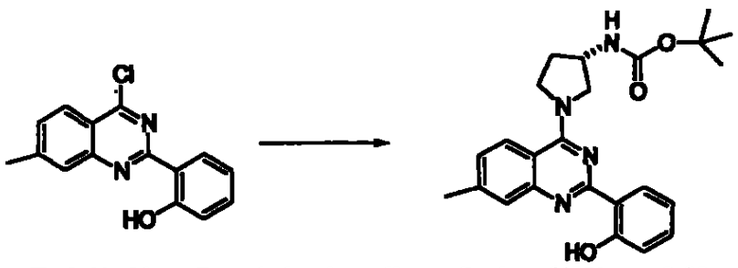
[001574] (2*R*)-Tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)furan-2-carboxamide

[001575]



[001576] (*S*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester

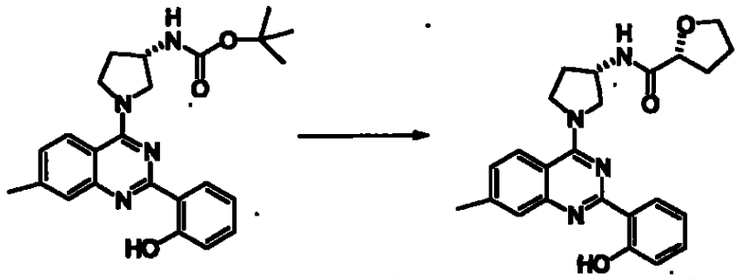
[001577]



[001578] To 2-(4-chloro-7-methyl-quinazolin-2-yl)-phenol(551 mg, 2.03 mmol) in 2.5 mL of DMF at room temperature was added sequentially (*S*)- pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (740 mg, 3.9 mmol) and triethylamine (567 μL, 4.0 mmol), and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and dried (Na_2SO_4), and the residue was purified via silica gel chromatography with 25–85% ethyl acetate/hexanes to give of (*S*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (694 mg, 81%). *LC/MS*: *m/z* 421 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001579] (2*R*)-Tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)furan-2-carboxamide

[001580]



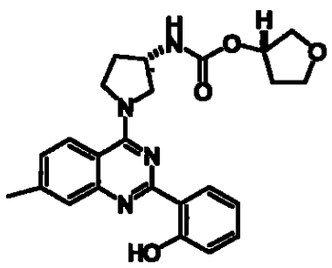
[001581] To (*S*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (690 mg, 1.64 mmol) was added at room temperature 3 mL of 1:1 TFA:CH_2Cl_2. The reaction mixture was stirred for 55 min, diluted with 20 mL of CH_2Cl_2 and washed with 15 mL of satd. $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*S*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol as an oil which was used without further purification.

[illegible] (133.3 mg, 0.42 mmol) was added 1.6 mL of CH_2Cl_2. To this solution was added sequentially triethylamine (174 μL, 1.25 mmol) and (*R*)-tetrahydro-furan-2-carboxylic acid (57.9 mg, 0.5 mmol), HOBt (67.5 mg 0.5 mmol), EDCI (95.8 mg 0.5 mmol) at room temperature. The reaction mixture was stirred for 12 h and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (2*R*)-tetrahydro-*N*-((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 419 $(M+H)^+$ at 2.34 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001582] Example 304

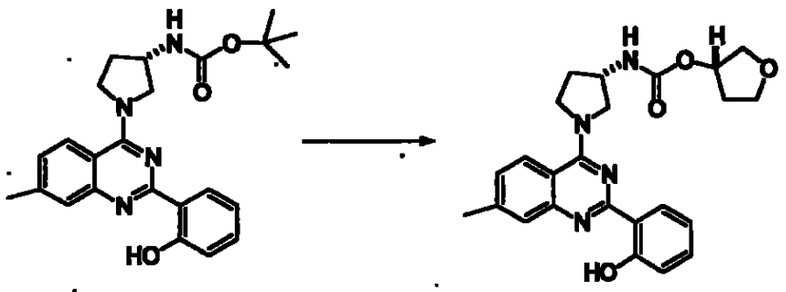
[001583] (*S*, *S*)- {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid tetrahydro-furan-3-yl ester

[001584]



[001585] (*S*, *S*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid tetrahydro-furan-3-yl ester

[001586]



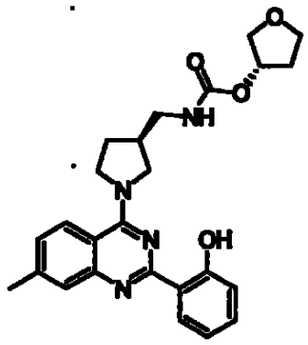
[001587] To (*S*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid *tert*-butyl ester (690 mg, 1.64 mmol) was added at room temperature, 3 mL of 1:1 TFA:CH_2Cl_2. The reaction mixture was stirred for 55 min, diluted with 20 mL of CH_2Cl_2, and washed with 15 mL of satd. $NaHCO_3$ solution. The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*S*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol as an oil which was used without further purification.

To the amine from above procedure (134.7 mg, 0.42 mmol) was added 1.6 mL of CH_2Cl_2, and the solution was cooled to 0 °C. To this solution was added sequentially triethylamine (88 µL, 0.63 mmol) and (*S*)- tetrahydro-furan-3-ol chloroformate(82.3 mg, 0.55 mmol). The reaction mixture was stirred and allowed to warm from 0 °C to room temperature over 12 h and was diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*S*, *S*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid tetrahydro-furan-3-yl ester as the TFA salt. LC/MS: *m/z* 435 $(M+H)^+$ at 2.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001588] Example 305

[001589] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

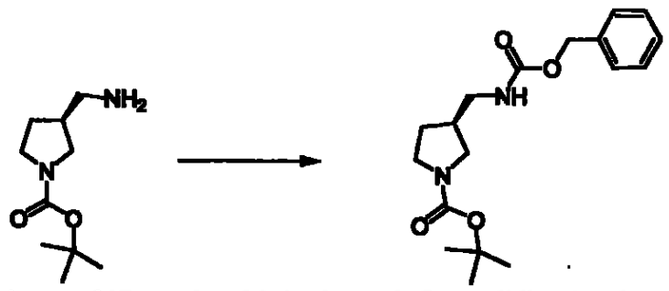
[001590]



[001591] Benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate

414

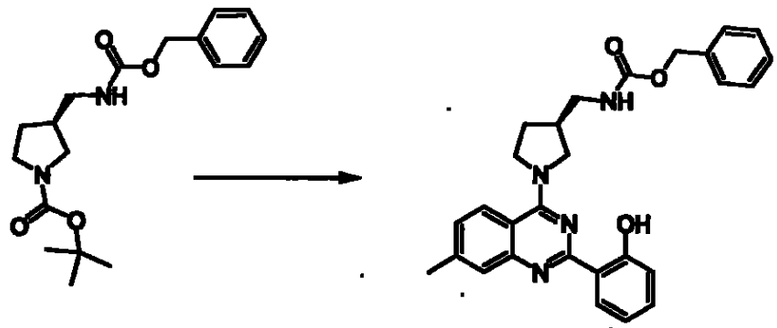
[001592]



[001593] A mixture of (*S*)-*tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (1.0 g, 5.0 mmol) and 50 mL THF was cooled in an ice bath. To this was added benzyl chloroformate (0.77 mL, 5.5 mmol), followed by triethylamine (1.39 mL, 10 mmol). After removing the ice bath, the reaction was stirred for 4 h. The mixture was poured into ice water and extracted with EtOAc. The organic extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using EtOAc in hexanes (0–40%) gave benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.29 g, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.10 (s, 2H), 4.87 (s, 1H), 3.52–2.95 (m, 6H), 2.41–2.35 (m, 1H), 2.10—1.79 (m, 2H), 1.45 (s, 9H).

[001594] **Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[001595]

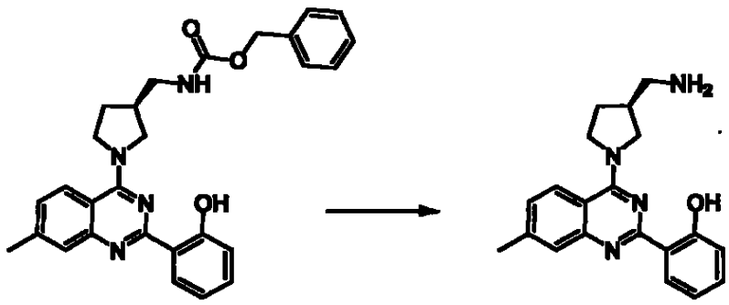


[001596] A solution of benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (0.20 g, 0.60 mmol) and 4 M HCl in dioxane (10 mL) was stirred for 3 h at room temperature. After evaporating the solvent under reduced pressure, the solid was triturated with Et_2O and dried under vacuum, then taken up in CH_2Cl_2 (10 mL). To this solution was added 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.16 g, 0.60 mmol) and triethylamine (0.25 mL, 1.8 mmol).

The reaction mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 and washed with water. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in hexanes gave benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as a colorless oil (0.19 g, 68%). *LC/MS*: *m/z* 469.1 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001597] 2-(4-((*S*)-3-(Aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol

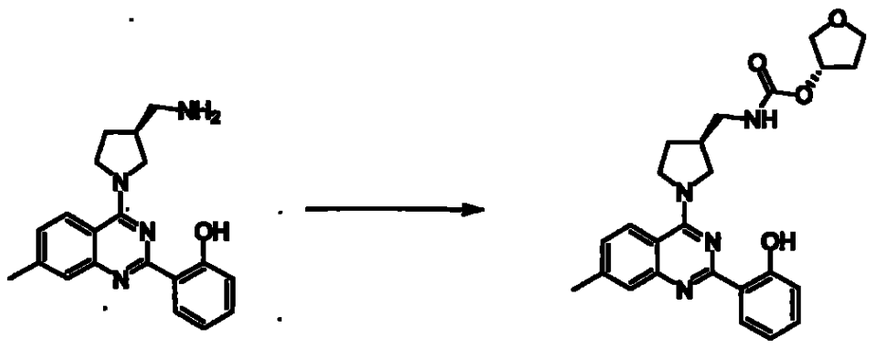
[001598]



[001599] A solution of benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.19 g, 0.41 mmol) and MeOH (5 mL) was stirred with Pd/C (20 mg, 10% weight of Pd on carbon) under an H_2 atmosphere at ambient pressure at ambient pressure overnight. Purification via silica gel chromatography using MeOH in CH_2Cl_2 (0–10%) gave 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (27 mg, 19%). *LC/MS*: *m/z* 335.5 $(M+H)^+$ at 1.28 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001600] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001601]

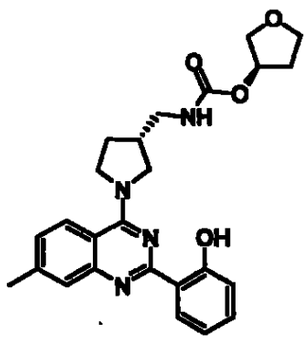


[001602] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (13 mg, 0.04 mmol) and CH_2Cl_2 (0.5 mL) was cooled in an ice bath. To this mixture was added (*S*)-tetrahydrofuran-3-yl chloroformate (6 μL, 0.04 mmol), followed by triethylamine (11 μL, 0.08 mmol). After removing the ice bath, the reaction was stirred for 3 h at room temperature. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001603] Example 306

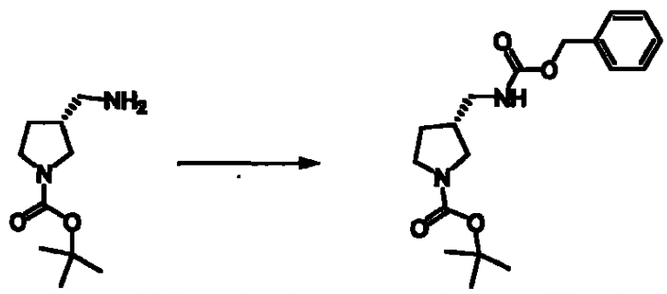
[001604] (*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001605]



[001606] Benzyl ((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate

[001607]



[001608] A solution of (*R*)-*tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (1.0 g, 5.0 mmol) and 50 mL THF was cooled in an ice bath. To this mixture was added benzyl

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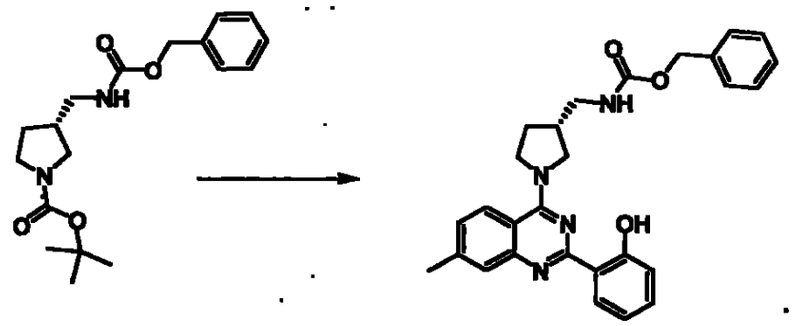
chloroformate (0.77 mL, 5.5 mmol), followed by triethylamine (1.39 mL, 10 mmol). After removing the ice bath, the reaction was stirred for 4 h. The mixture was poured into ice water and extracted with EtOAc. The organic extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using EtOAc in hexanes (0–40%) gave benzyl ((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.29 g, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.10 (s, 2H), 4.87 (s, 1H), 3.52–2.95 (m, 6H), 2.41–2.35 (m, 1H), 2.10—1.79 (m, 2H), 1.45 (s, 9H).

[001609] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

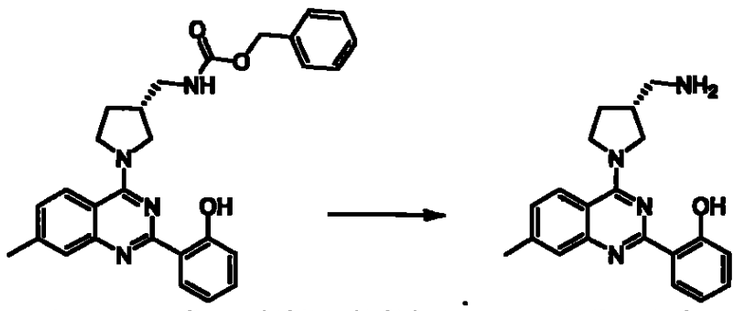
[001610]



[001611] A solution of benzyl ((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (0.20 g, 0.60 mmol) and 4 M HCl in dioxane (10 mL) was stirred for 3 h at room temperature. After evaporating the solvent under reduced pressure, the resulting solid was triturated with Et_2O and dried under vacuum, then taken up in CH_2Cl_2 (10 mL). To this solution was added 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.16 g, 0.60 mmol) and triethylamine (0.25 mL, 1.8 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 and washed with water. The CH_2Cl_2 solution was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in hexanes gave benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as a colorless oil (0.19 g, 68%). LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001612] 2-(4-((*R*)-3-(Aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol

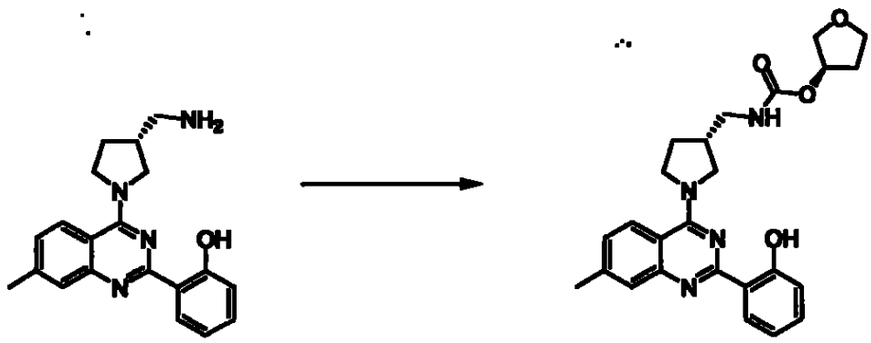
[001613]



[001614] A solution of benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.19 g, 0.41 mmol) and MeOH (5 mL) was stirred with Pd/C (20 mg, 10% weight of Pd on carbon) under an H_2 atmosphere at ambient pressure overnight. Purification via silica gel chromatography using MeOH in CH_2Cl_2 (0–10%) gave 2-(4-((*R*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (63 mg, 45%). LC/MS: *m/z* 335.7 $(M+H)^+$ at 1.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001615] (*R*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001616]



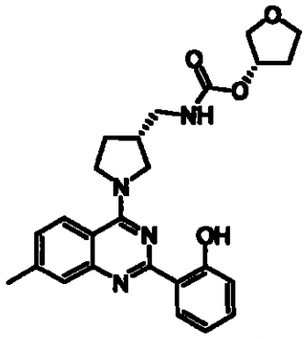
[001617] A solution of 2-(4-((*R*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (15 mg, 0.045 mmol) and CH_2Cl_2 (0.5 mL) was cooled in an ice bath. To this mixture was added (*R*)-tetrahydrofuran-3-yl chloroformate (7 μL, 0.045 mmol), followed by triethylamine (13 μL, 0.090 mmol). After removing the ice bath, the reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-

methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. *LC/MS*: *m/z* 449.3 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001618] Example 307

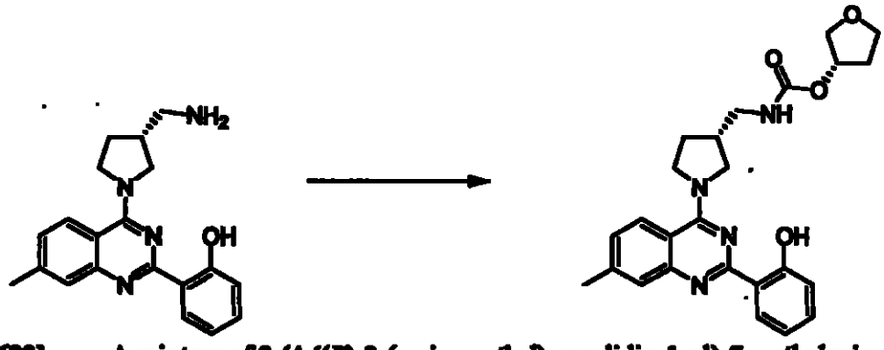
[001619] (*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001620]



[001621] (*S*)-Tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001622]



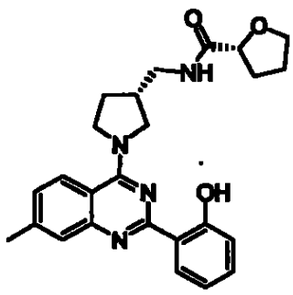
[001623] A mixture of 2-(4-((*R*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (15 mg, 0.045 mmol) and CH_2Cl_2 (0.5 mL) was cooled in an ice bath. To this was added (*S*)-tetrahydrofuran-3-yl chloroformate (7 μL, 0.045 mmol), followed by triethylamine (13 μL, 0.090 mmol). After removing the ice bath, the reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-

yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.18 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001624]. Example 308

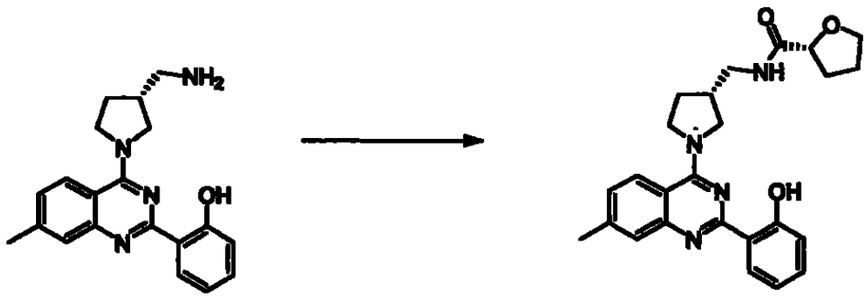
[001625] (2*R*)-Tetrahydro-*N*-(((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide

[001626]



[001627] (2*R*)-Tetrahydro-*N*-(((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide

[001628]

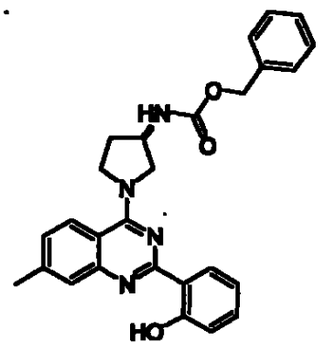


[001629] To a solution of 2-(4-((*R*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (15 mg, 0.045 mmol) and DMF (0.5 mL) was added (*R*)-tetrahydrofuran-2-carboxylic acid (6 μL, 0.062 mmol), followed by the addition of HATU (26 mg, 67 mmol) and triethylamine (13 μL, 0.090 mmol). The reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-tetrahydro-*N*-(((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide as the TFA salt. LC/MS: *m/z* 433.5 $(M+H)^+$ at 2.11 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001630] Example 309

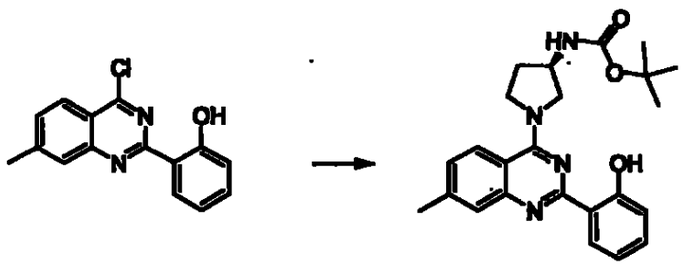
[001631] (3*R*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid benzyl ester

[001632]



[001633] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3*R*-yl}-carbamic acid *tert*-butyl ester

[001634]

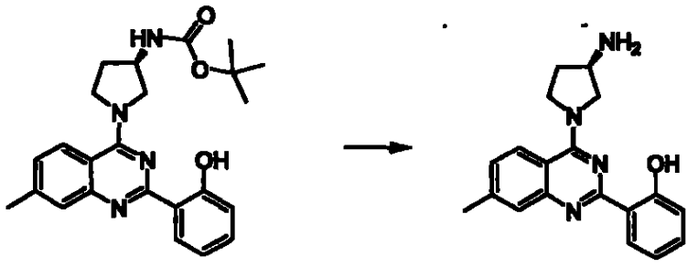


[001635] To a cooled (–15 °C) solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (43.8 g, 0.15 mol) in CH_2Cl_2 (125 mL) was added dropwise a solution of (3*R*)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine (30 g, 0.16 mol) and triethylamine (38 mL, 0.27 mol) in CH_2Cl_2 (170 mL). The addition, during which the temperature stayed below 30 °C, was completed in 20 minutes. The external cooling was removed and the reaction mixture was stirred at room temperature overnight. Water (1 L) and CH_2Cl_2 (1 L) were added. The resulting precipitate was collected by filtration, washed with water and CH_2Cl_2, and air-dried to yield 33 g of pure {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3*R*-yl}-carbamic acid *tert*-butyl ester. The filtrates were evaporated to give another batch of crude {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3*R*-yl}-carbamic acid *tert*-butyl ester which was purified by trituration with CH_2Cl_2. Total yield: 43.5 g (70%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ

8.45 (dt, J = 8 Hz, 1.7 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.57 (s, 1H), 7.37–7.31 (m, 1H), 7.18 (dd, J = 8.5 Hz, 1.7, 1H), 7.0 (dd, J = 8.3 Hz, 1.1 Hz, 1H), 6.9 (dt, J = 8.9 Hz, 1.4 Hz, 1H), 4.77 (bs, 1H), 4.40 (bs, 1H), 4.27–4.21 (m, 1H), 4.14–4.03 (m, 2H), 3.86 (dd, J = 11.8 Hz, 4.4 Hz, 1H), 2.50 (s, 3H), 2.34–2.28 (m, 1H), 2.08–2.02 (m, 1H), 1.46 (s, 9H) ppm.

[001636] 2-(4-(3*R*-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001637]

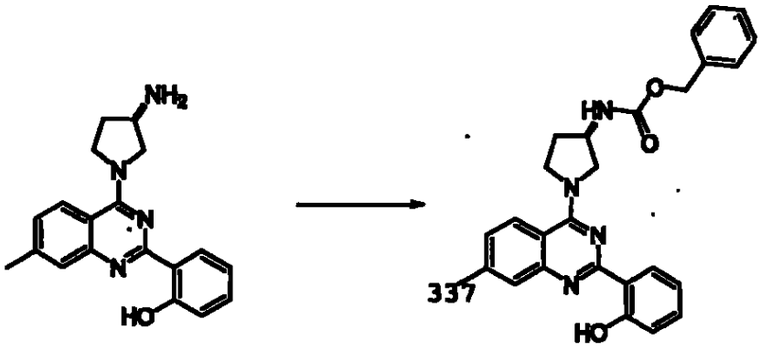


[001638] {1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3*R*-yl}-carbamic acid *tert*-butyl ester (43.5 g, 100 mmol) was stirred with CF_3CO_2H (142 mL) in CH_2Cl_2 (300 mL) at room temperature overnight. The solution was concentrated to dryness, and the residue was suspended in 10% aq. Na_2CO_3 (900 mL) and stirred for 2 hours. The suspension was filtered, and the yellow solid was washed with water several times. The product was air-dried at 45 °C to yield 2-(4-(3*R*-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (34.2 g) as a light-yellow solid. ^{1}H-NMR (300 MHz, CD_3OD): δ 8.41 (dd, J = 7.4 Hz, 1.4 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.34–7.28 (m, 1H), 7.23 (dd, J = 8.8 Hz, 1.9 Hz, 1H), 6.91–6.85 (m, 2H), 4.16–4.09 (m, 2H), 4.00–3.94 (m, 1H), 3.73–3.64 (m, 2H), 2.48 (s, 3H), 2.26–2.20 (m, 1H), 1.92–1.86 (m, 1H) ppm.

[001639] (*R*)-[1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl]-carbamic acid benzyl ester

[001640] Method A

[001641]

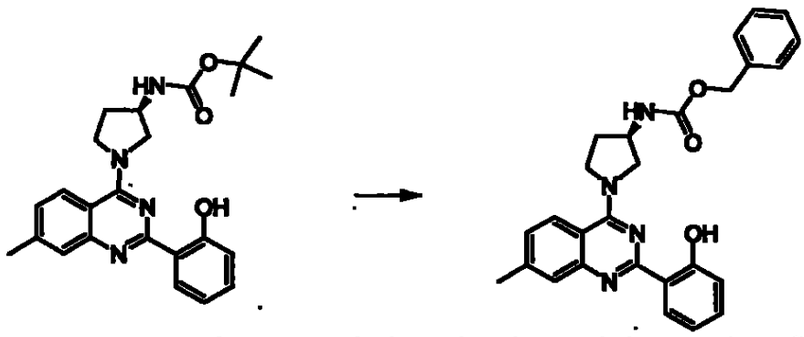


[001642] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (50.8 mg, 0.16 mmol) was added 500 μL of CH_2Cl_2 and the solution was cooled to 0 °C. To this solution was added sequentially triethylamine (33.2 μL, 0.24 mmol) and benzyl chloroformate (29.2 mg, 0.17 mmol). The reaction mixture was stirred from 0 °C to 5 °C over 45 min, then diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid benzyl ester. LC/MS: *m/z* 455.2 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001643] Method B

[001644] **Benzyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

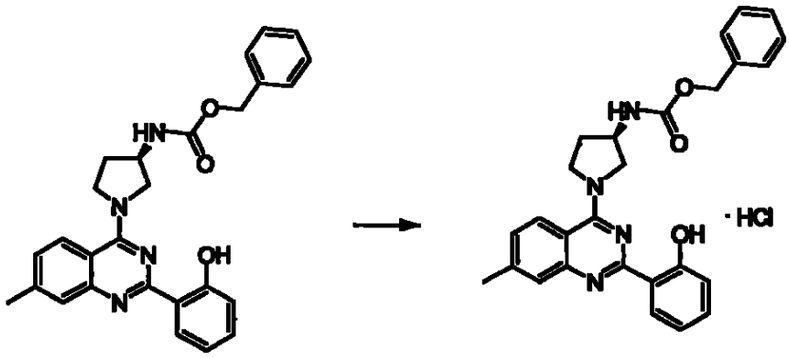
[001645]



[001646] To *tert*-butyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (398 mg, 0.94 mmol) was added 3 mL of 1:1 TFA: CH_2Cl_2. The mixture was then stirred at room temperature for 30 minutes. The reaction mixture was diluted with a solution of saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, washed with a solution of extracted 1 N NaOH, dried over Na_2SO_4 and evaporated under reduced pressure to give the intermediate amine. To this amine (300 mg, 0.94 mmol) were added 3 ml of CH_2Cl_2 and triethylamine (145 μL, 1.04 mmol). After cooling the mixture to 0 °C, benzyl chloroformate (161.6 mg, 0.94 mmol) was added, and the reaction was stirred for 30 minutes. Purification via silica gel chromatography using 20–100% ethyl acetate/hexanes gave benzyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 455.2 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001647] (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride

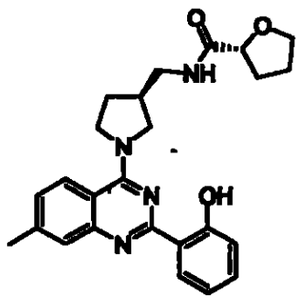
[001648]



[001649] A 2.0 M HCl solution in Et_2O (318 μL, 0.636 mmol) was slowly added to a stirring solution of benzyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (289 mg, 0.636 mmol) in 2.1 mL of CH_2Cl_2. Solvents were removed under reduced pressure and the residue was triturated with Et_2O and filtered to give benzyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride. LC/MS: *m/z* 455.2 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

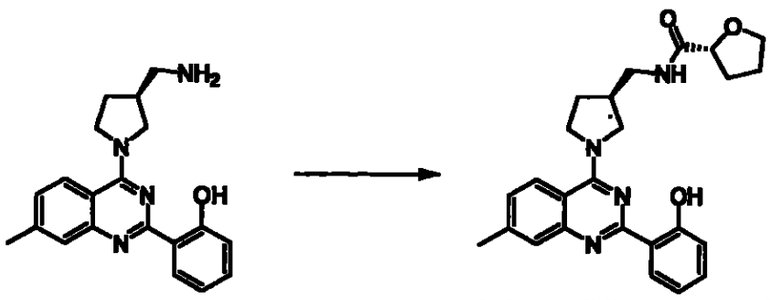
[001650] Example 310

[001651] (2*R*)-Tetrahydro-*N*-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide



[001652] (2*R*)-Tetrahydro-*N*-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide

[001653]

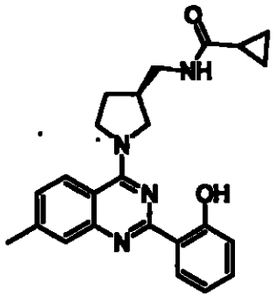


[001654] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) and DMF (0.5 mL) was added (*R*)-tetrahydrofuran-2-carboxylic acid (8.6 μL, 0.09 mmol), followed by the addition of HATU (34 mg, 0.09 mmol) and triethylamine (21 μL, 0.15 mmol). The reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-tetrahydro-*N*-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)furan-2-carboxamide as the TFA salt. *LC/MS*: *m/z* 433.5 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

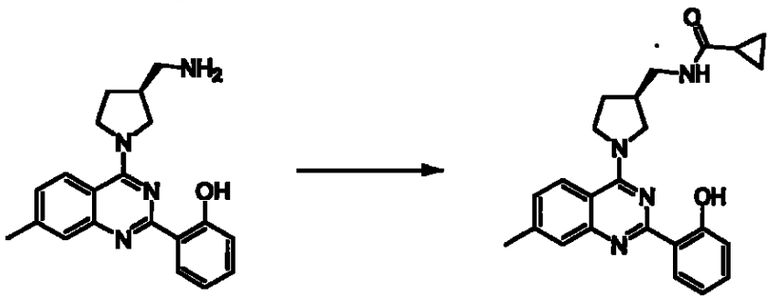
[001655] Example 311

[001656] *N*-(((*S*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide

[001657]



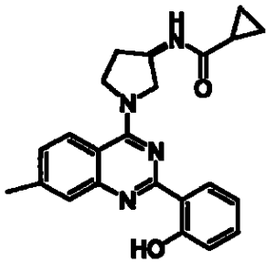
[001658] *N*-(((*S*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide



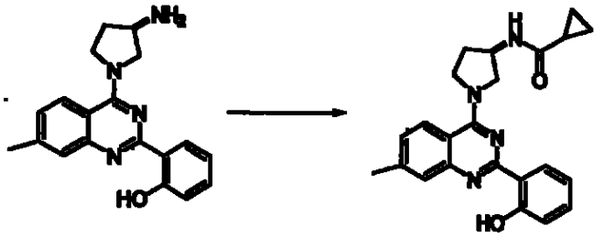
[001648] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) and CH_2Cl_2 (0.5 mL) was cooled in an ice bath. To this mixture was added cyclopropanecarbonyl chloride (7.5 μL, 82 mmol), followed by triethylamine (21 μL, 0.15 mmol). After removing the ice bath, the reaction was stirred at room temperature for 3 h. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave *N*-(((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 403.7 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001649] Example 312

[001650] (*R*)-Cyclopropanecarboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide



[001651] (*R*)-Cyclopropanecarboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide.

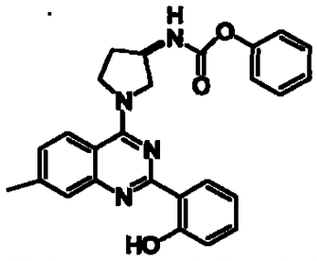


[001666] To 2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (49.3 mg, 0.15 mmol) was added 500 μL of CH_2Cl_2 and the solution was cooled to 0 °C. To this solution was added sequentially triethylamine (21.5 μL, 0.15 mmol) and cyclopropanecarbonyl chloride (16.1 mg, 0.15 mmol). The reaction mixture was stirred from 0 °C to 5 °C over 40 min and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-cyclopropanecarboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide as the TFA salt. LC/MS: *m/z* 389 $(M+H)^+$ at 2.38 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001667] Example 313

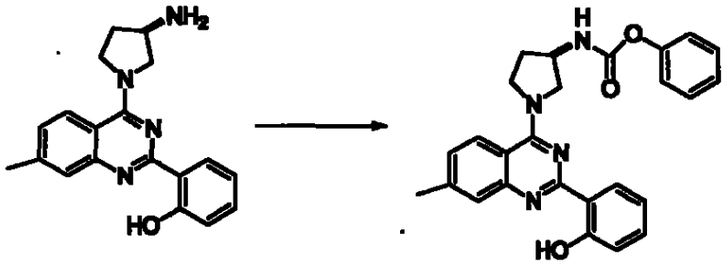
[001668] (*R*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid phenyl ester

[001669]



[001670] (*R*)-{1-[2-(2-Hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid phenyl ester.

[001671]



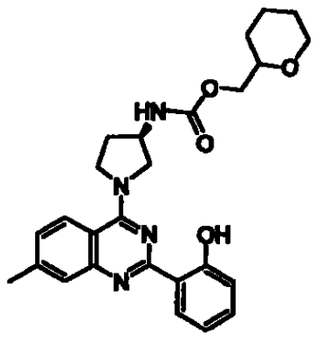
[001672] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (48 mg, 0.15 mmol) was added 500 μL of CH_2Cl_2, and the solution was cooled to 0 °C. To this solution

was added sequentially triethylamine (21 μL, 0.15 mmol) and phenyl chloroformate (22.8 mg, 0.15 mmol). The reaction mixture was stirred from 0 °C to 5 °C over 40 min, diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-carbamic acid phenyl ester as the TFA salt. LC/MS: *m/z* 441 $(M+H)^+$ at 2.78 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001673] Example 314

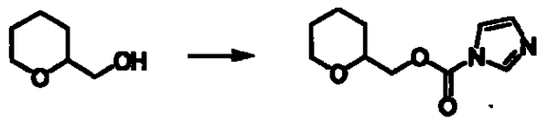
[001674] (Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001675]



[001676] (Tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate

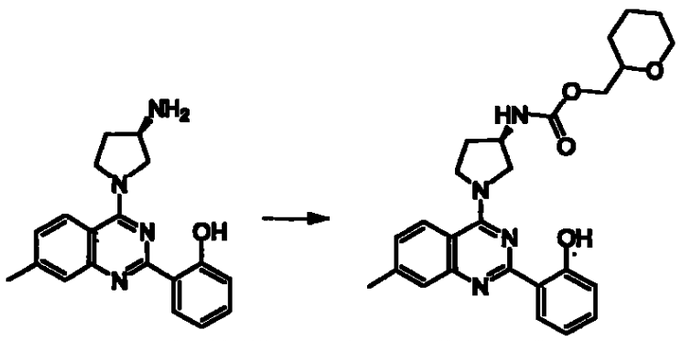
[001677]



[001678] To a mixture of (tetrahydro-2*H*-pyran-2-yl)methanol (369 mg, 3.17 mmol) and di(1*H*-imidazol-1-yl)methanone (1.03 g, 6.35 mmol) was added 10.5 mL of CH_2Cl_2. The reaction was stirred at 50 °C for 3 hours. The reaction mixture was used without further purification. LC/MS: *m/z* 211.1 $(M+H)^+$ at 0.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001679] (Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001680]

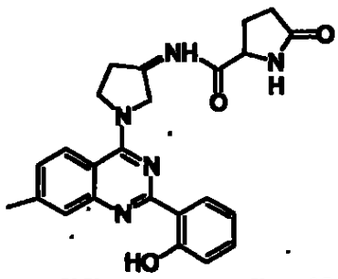


[001681] To a mixture of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (100 mg, 0.31 mmol) and (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (98 mg, 0.47 mmol) was added 1.04 mL CH_2Cl_2 and triethylamine (65 µL, 47 mg, 0.46 mmol). The mixture was stirred at room temperature overnight. An additional equivalent of (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (100 mg, 0.47 mmol) was added to the mixture, and the reaction was heated at 45 °C for 4 hours. Purification via silica gel chromatography using 10%–100% ethyl acetate/hexanes gave (tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. *LC/MS*: *m/z* 463.4 $(M+H)^+$ at 2.66 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001682] Example 315

[001683] **(*R*)-5-Oxo-pyrrolidine-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide**

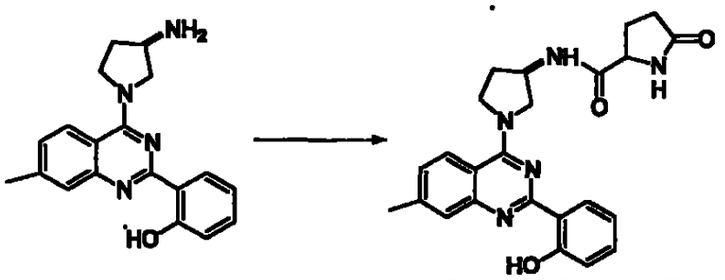
[001684]



[001685] **(*R*)-5-Oxo-pyrrolidine-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide**

422

[001686]

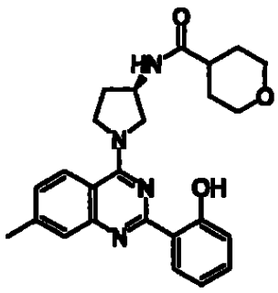


[001687] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (71 mg, 0.22 mmol) was added 890 μL of CH_2Cl_2. To this solution was added sequentially triethylamine (47 μL, 0.34 mmol) and 5-oxo-pyrrolidine-2-carboxylic acid (34.8 mg, 0.27 mmol) and BOP (119 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 2 h and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give (*R*)-5-oxo-pyrrolidine-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-amide. *LC/MS*: *m/z* 432.5 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001688] Example 316

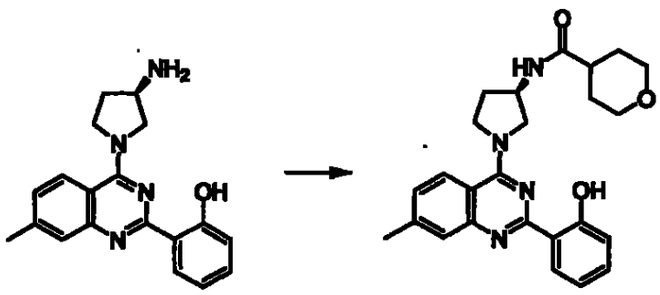
[001689] Tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2*H*-pyran-4-carboxamide

[001690]



[001691] Tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2*H*-pyran-4-carboxamide

[001692]

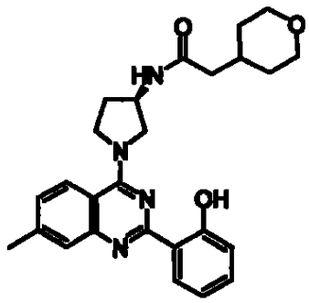


[001693] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in 1 mL of DMF was cooled to 0 °C and tetrahydro-2*H*-pyran-4-carboxylic acid (24 mg, 0.19 mmol) was added, followed by the addition of triethylamine (32 mg, 44 μL, 0.31 mmol) and HATU (71.1 mg, 0.187 mmol). The reaction was stirred at 0 °C for 10 minutes, then gradually warmed to room temperature, then filtered. Purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave tetrahydro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2*H*-pyran-4-carboxamide as the TFA salt. LC/MS: *m/z* 433.5 $(M+H)^+$ at 2.05 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001694] Example 317

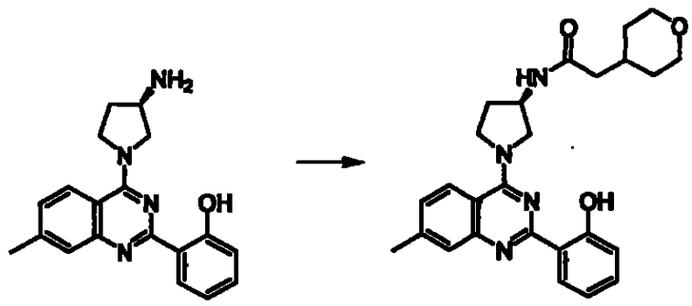
[001695] 2-(Tetrahydro-2*H*-pyran-4-yl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide

[001696]



[001697] 2-(Tetrahydro-2*H*-pyran-4-yl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide

[001698]

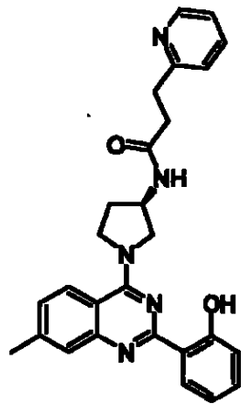


[001699] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in 1 mL of DMF cooled to 0 °C was added 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (27 mg, 0.19 mmol), followed by the addition of triethylamine (32 mg, 44 μL, 0.31 mmol) and HATU (71.1 mg, 0.187 mmol). The reaction was stirred at 0 °C for 10 minutes, then gradually warmed to room temperature. Filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 2-(tetrahydro-2*H*-pyran-4-yl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide as the TFA salt. LC/MS: *m/z* 477.3 $(M+H)^+$ at 2.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001700] Example 318

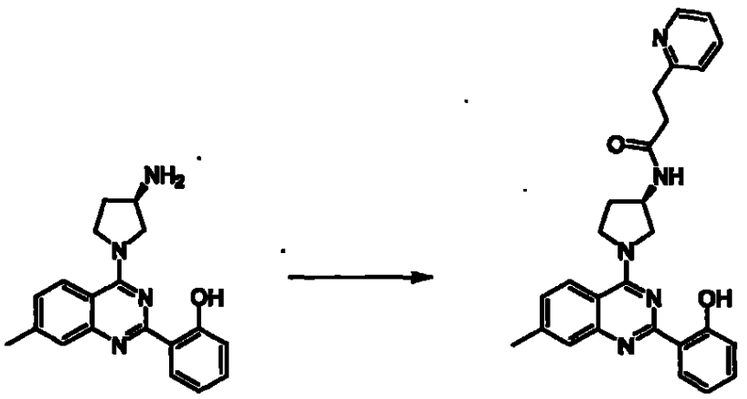
[001701] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-2-yl)propanamide

[001702]



[001703] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-2-yl)propanamide

[001704]

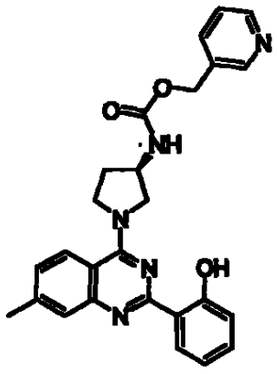


[001705] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.05 g, 0.15 mmol) in DMF (1 mL) was added 3-(pyridin-2-yl)propanoic acid (30 mg, 0.195 mmol), followed by the addition of triethylamine (42 μL, 0.30 mmol) and HATU (74 mg, 0.195 mmol). The reaction was stirred at room temperature for 2 h and then purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-2-yl)propanamide as the TFA salt. LC/MS: *m/z* 454.3 $(M+H)^+$ at 1.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001706] Example 319

[001707] (Pyridin-3-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001708]



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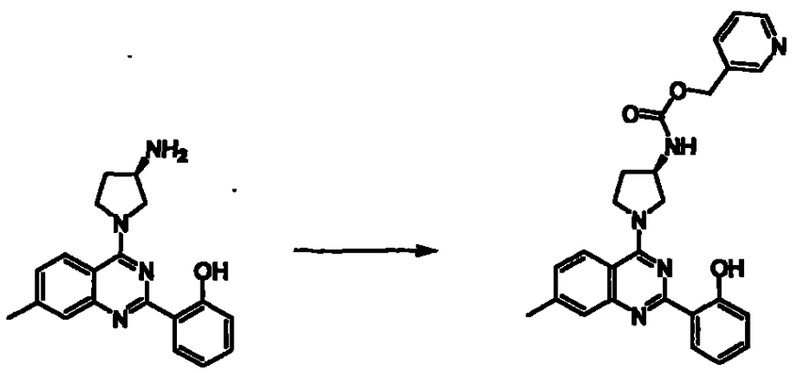
[001709] T[illegible]-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001710]

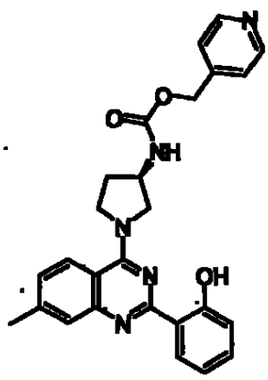


[001711] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) at room temperature was added triethylamine (43 μL, 0.31 mmol), followed by the addition of (pyridin-3-yl)methyl 1*H*-imidazole-1-carboxylate (63 mg, 0.31 mmol). The reaction was stirred at room temperature overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (pyridin-3-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 456.5 $(M+H)^+$ at 1.85 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001712] Example 320

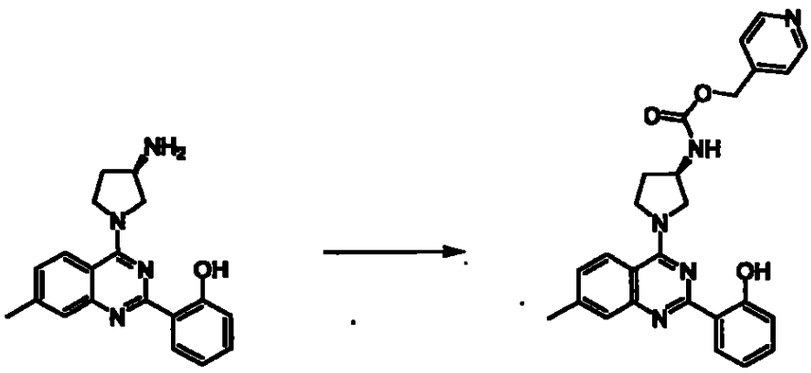
[001713] (Pyridin-4-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001714]



[001715] (Pyridin-4-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001716]

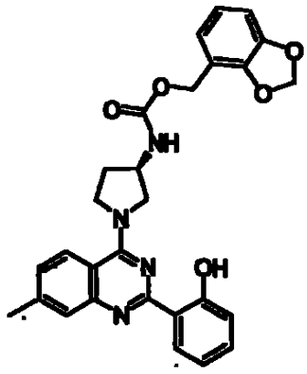


[001717] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) at room temperature was added triethylamine (43 μL, 0.31 mmol), followed by the addition of (pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate (63 mg, 0.31 mmol). The reaction was stirred at room temperature overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (pyridin-4-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 456.5 $(M+H)^+$ at 1.84 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001718] Example 321

[001719] (Benzo[d][1,3]dioxol-7-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001720]



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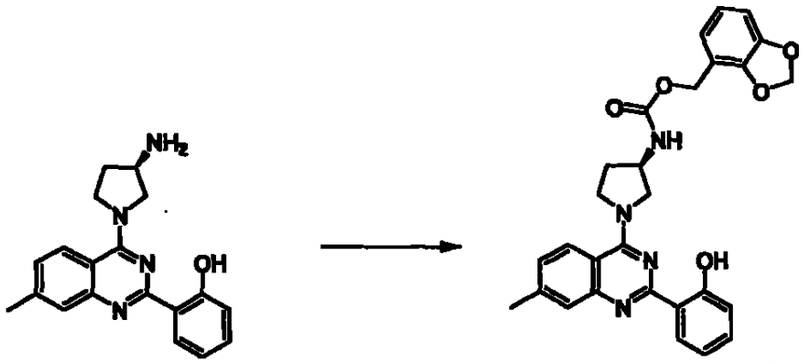
[001721] T / (benzo[d][1,3]dioxol-5-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001722]

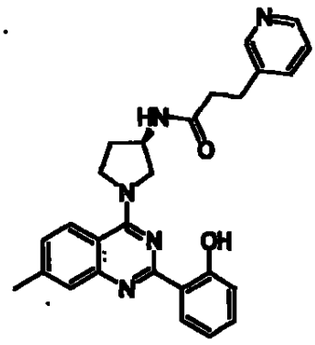


[001723] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) was added triethylamine (43 µl, 0.31 mmol), followed by the addition of (benzo[d][1,3]dioxol-4-yl)methyl 1*H*-imidazole-1-carboxylate (77 mg, 0.31 mmol). The reaction was stirred at room temperature overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (benzo[d][1,3]dioxol-7-yl)methyl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. *LC/MS*: *m/z* 499.3 $(M+H)^+$ at 2.57 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001724] Example 322

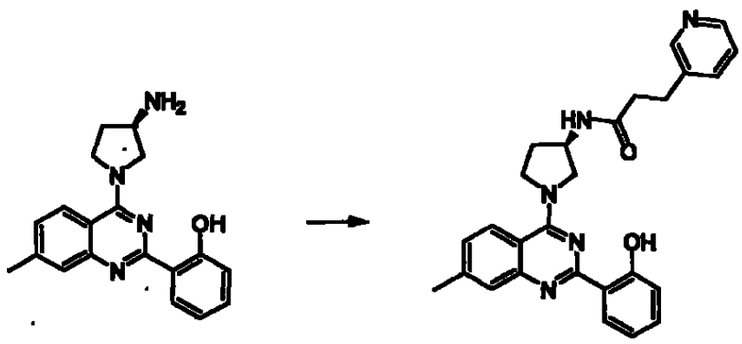
[001725] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-3-yl)propanamide

[001726]



[001727] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-3-yl)propanamide

[001728]

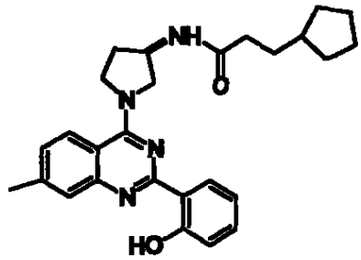


[001729] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (249 mg, 0.778 mmol) was dissolved in 2.6 mL of CH_2Cl_2. 3-(Pyridin-3-yl)propanoic acid (129 mg, 0.85 mmol) was added followed by triethylamine (102 mg, 141 μL, 1.01 mmol) and BOP (378 mg, 0.85 mmol). After stirring the reaction for 35 minutes at room temperature, it was filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(pyridin-3-yl)propanamide as the TFA salt. LC/MS: *m/z* 454.4 $(M+H)^+$ at 2.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001730] Example 323

[001731] (*R*)-3-Cyclopentyl-N-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-propionamide

[001732]



[001733] (*R*)-3-Cyclopentyl-N-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-propionamide

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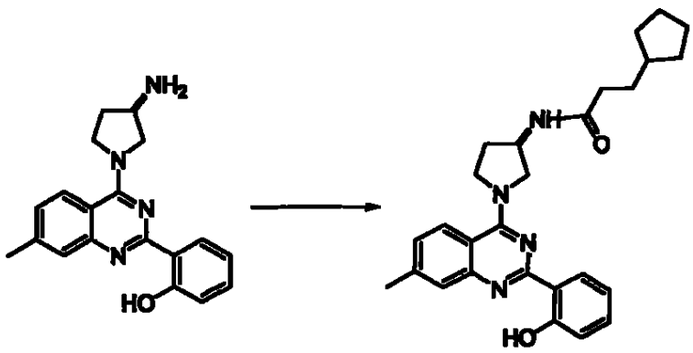
[001734]

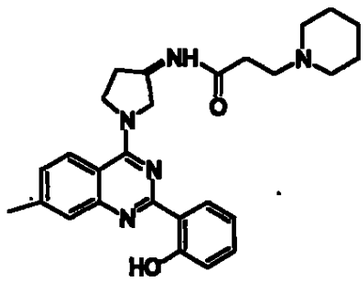


[001735] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (100 mg, 0.31 mmol) was added 1 mL of CH_2Cl_2, and the solution was cooled to 0 °C. To this solution was added sequentially triethylamine (56.6 μL, 0.41 mmol) and 3-cyclopentyl-propionyl chloride (57 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 2 h, then diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give ((*R*)-3-cyclopentyl-*N*-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-propionamide as the TFA salt. *LC/MS*: *m/z* 445.4 $(M+H)^+$ at 2.85 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001736] Example 324

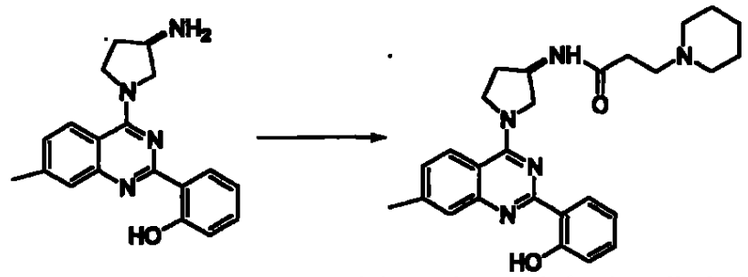
[001737] (*R*)-N-{1-[2-(2-Hydroxy-phenyl)-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide

[001738]



[001739] (*R*)-N-{1-[2-(2-Hydroxy-phenyl)-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide

[001740]

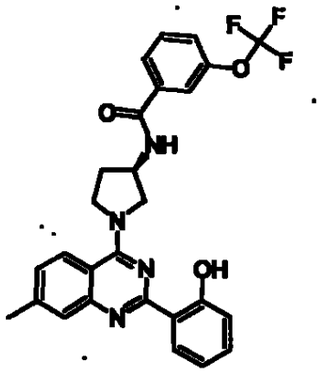


[001741] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (58.6 mg, 0.18 mmol) was added 700 μL of CH_2Cl_2. To this solution was added sequentially triethylamine (38.3 μL, 0.27 mmol), 3-piperidin-1-yl-propionic acid (37.4 mg, 0.24 mmol) and BOP (119 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 2 h and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-*N*-{1-[2-(2-hydroxy-phenyl)-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide as the TFA salt. LC/MS: *m/z* 460.4 $(M+H)^+$ at 2.1 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001742] Example 325

[001743] ***N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(trifluoromethoxy)benzamide**

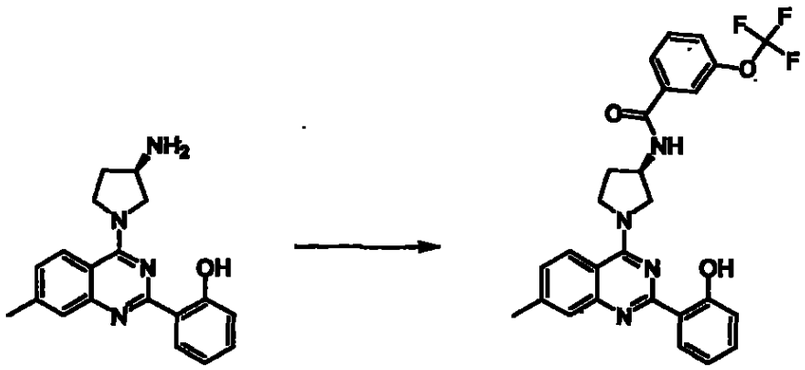
[001744]



427 426

[001745] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(trifluoromethoxy)benzamide

[001746]

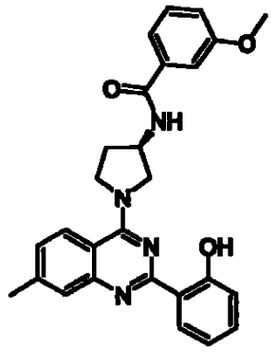


[001747] To a stirring solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (32 mg, 0.10 mmol) and DMF (1.0 mL) was added 3-(trifluoromethoxy)benzoyl chloride (19 μL, 0.10 mmol), followed by the addition of triethylamine (28 μL, 0.2 mmol). The reaction was stirred at room temperature overnight, filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(trifluoromethoxy)benzamide as the TFA salt. LC/MS: *m/z* 509.5 $(M+H)^+$ at 2.71 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001748] Example 326

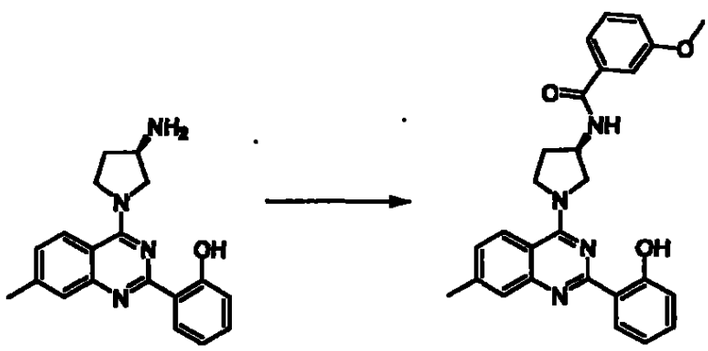
[001749] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-methoxybenzamide

[001750]



[001751] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-methoxybenzamide

[001752]

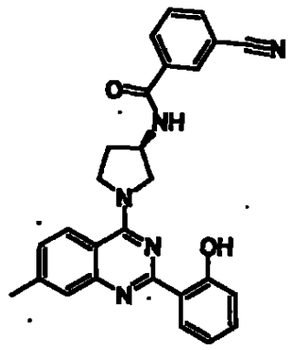


[001753] To a stirring solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (32 mg, 0.10 mmol) and DMF (1.0 mL) was added 3-methoxybenzoyl chloride (14 μL, 0.1 mmol), followed by the addition of triethylamine (28 μL, 0.2 mmol). The reaction was stirred at room temperature overnight, then filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-methoxybenzamide as the TFA salt. LC/MS: *m/z* 455.3 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001754] Example 327

[001755] 3-Cyano-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

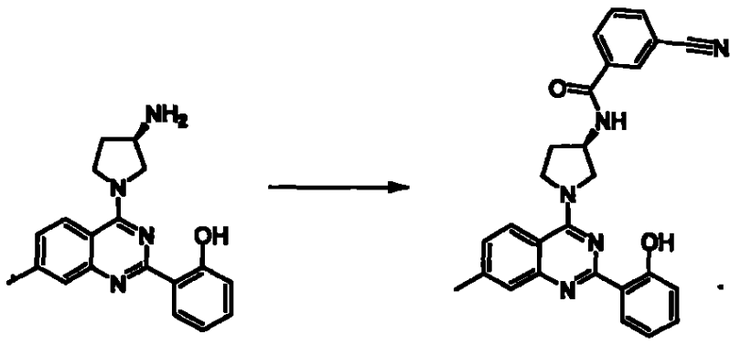
[001756]



428 427

[001757] 3-Cyano-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001758]

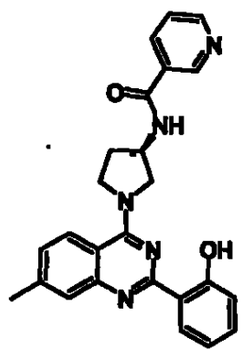


[001759] To a stirring solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (32 mg, 0.10 mmol) and DMF (1.0 mL) was added 3-cyanobenzoyl chloride (17 mg, 0.10 mmol), followed by the addition of triethylamine (28 μL, 0.20 mmol). The reaction was stirred at room temperature overnight, then filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-cyano-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 450.3 $(M+H)^+$ at 2.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001760] Example 328

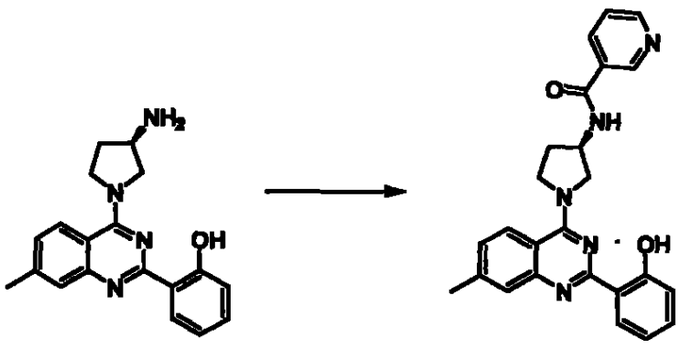
[001761] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001762]



[001763] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001764]

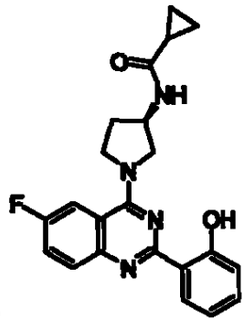


[001765] To a stirring solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (32 mg, 0.1 mmol) and DMF (1.0 mL) was added nicotinoyl chloride (18 mg, 0.1 mmol), followed by the addition of triethylamine (28 μL, 0.2 mmol). The reaction was stirred at room temperature overnight, then filtered, and purified via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide as the TFA salt. LC/MS: *m/z* 426.3 $(M+H)^+$ at 1.91 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001766] Example 329

[001767] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001768]

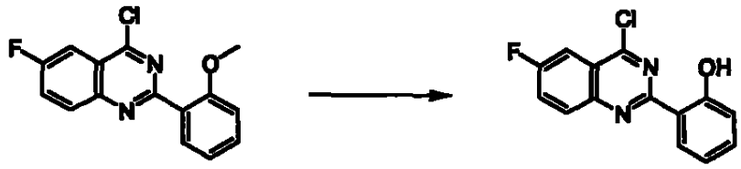


[001769] Method A

[001770] 2-(4-Chloro-6-fluoroquinazolin-2-yl)phenol

429 428

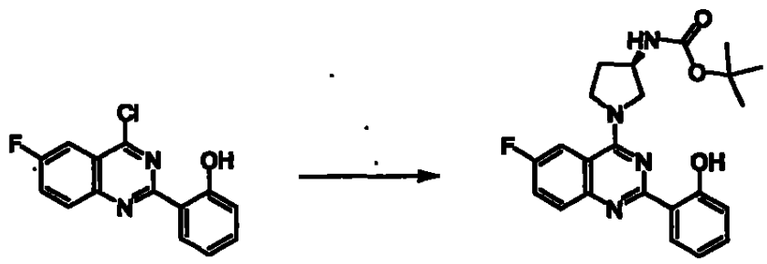
[001771]



[001772] A solution of 4-chloro-6-fluoro-2-(2-methoxyphenyl)quinazoline (3.0 g, 10.39 mmol) in CH_2Cl_2 (15 mL) was cooled to –78 °C. To it was added a 1.0 M BBr_3 solution in CH_2Cl_2 (52 mL, 52 mmol) dropwise. The reaction was allowed to warm to room temperature. It was neutralized with a saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 5–20% CH_2Cl_2/hexanes gave 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (1.68 g, 60%). LC/MS: *m/z* 275.3 $(M+H)^+$ at 3.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001773] *tert*-Butyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

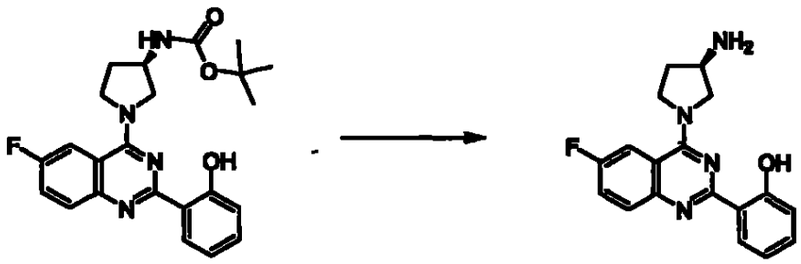
[001774]



[001775] At 0 °C under an N_2 atmosphere, a solution of *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate (264 mg, 1.42 mmol) and triethylamine (0.33 mL, 2.36 mmol) in CH_2Cl_2 was rapidly added to a stirring solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (325 mg, 1.18 mmol) in 15 mL CH_2Cl_2. The reaction mixture was stirred for 1 h before it was quenched with water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc/CH_2Cl_2 yielded *tert*-butyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 425.5 $(M+H)^+$ at 2.74 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001776] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol

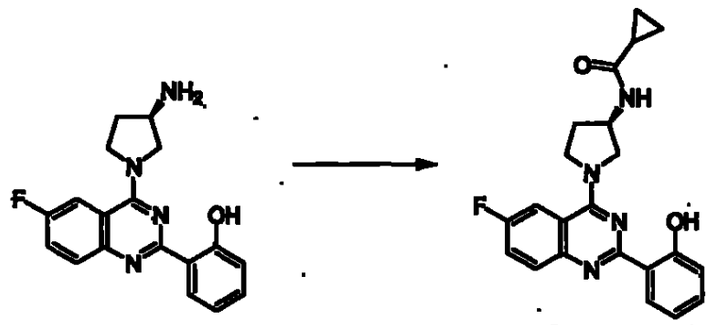
[001777]



[001778] To a solution of *tert*-butyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate (480 mg, 1.11 mmol) in CH_2Cl_2 (10 mL) was added TFA (4 mL). The reaction was stirred for an hour, diluted with 10 mL CH_2Cl_2, and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 3–20% EtOAc/CH_2Cl_2 gave 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol. LC/MS: *m/z* 325.5 $(M+H)^+$ at 1.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001779] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001780]



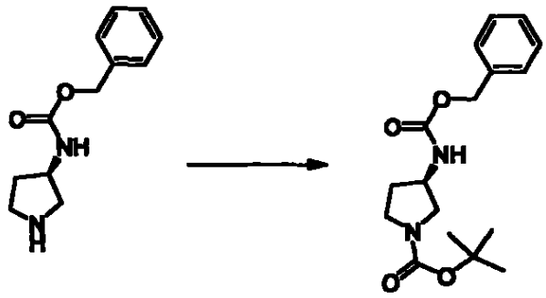
[001781] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.025 g, 0.08 mmol) in DMF (1.0 mL) was added cyclopropanecarboxylic acid (10 mg, 0.12 mmol), followed by the addition of triethylamine (22 µL, 0.16 mmol) and HATU (40 mg, 0.1 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-

fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001782] Method B

[001783] Benzyl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate

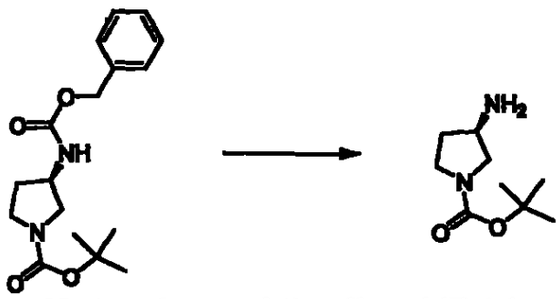
[001784]



[001785] At –10 °C, triethylamine (2.3 mL, 16.6 mmol) was added to a solution of benzyl (*R*)-pyrrolidin-3-ylcarbamate oxalate (2.0 g, 6.4 mmol) in MeOH, followed by the slow addition of Boc_2O (1.92 mL, 8.3 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was quenched with water and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in CH_2Cl_2 gave benzyl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate (1.85 g, 90%). LC/MS: *m/z* 321.3 $(M+H)^+$ at 3.01 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001786] (*R*)-*tert*-Butyl 3-aminopyrrolidine-1-carboxylate

[001787]

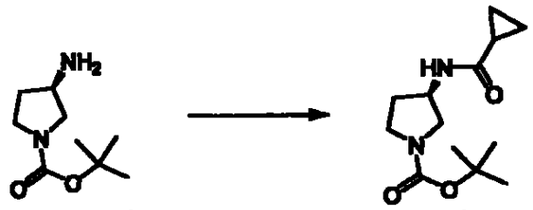


[001788] Under an N_2 atmosphere, a solution of benzyl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate (1.85 g, 5.75 mmol) in 10 mL MeOH was added to a

flask containing Pd/C (185 mg, 10% weight Pd on carbon). After evacuating the flask under vacuum and purging it twice with N_2, the reaction was stirred for 3 h under an H_2 atmosphere at ambient pressure. The reaction was filtered through a bed of Celite, and the solvent was evaporated under reduced pressure to obtain (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate which was used without further purification. LC/MS: *m/z* 187.3 $(M+H)^+$ at 1.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001789] (*R*)-*tert*-Butyl 3-(cyclopropanecarboxamido)pyrrolidine-1-carboxylate

[001790]



[001791] To a mixture of (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (500 mg, 2.68 mmol) in CH_2Cl_2 (10 mL) was added cyclopropanecarboxylic acid (276 μL, 3.48 mmol), followed by the addition of HATU (1.3 g, 3.48 mmol) and triethylamine (725 μL, 5.2 mmol). The reaction was complete after stirring for 1 h. After quenching with water, the aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified via silica gel chromatography 0–20% EtOAc/CH_2Cl_2 to afford (*R*)-*tert*-butyl 3-(cyclopropanecarboxamido)pyrrolidine-1-carboxylate (500 mg, 73%). LC/MS: *m/z* 255.3 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001792] *N*-((*R*)-Pyrrolidin-3-yl)cyclopropanecarboxamide

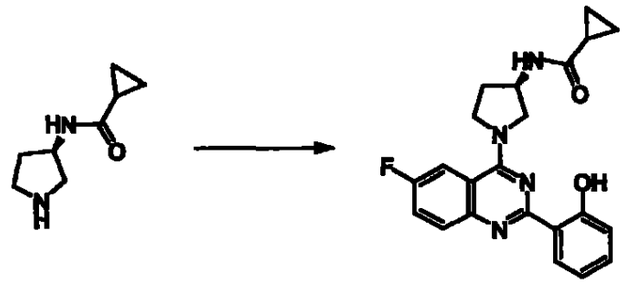
[001793]

[001794] TFA (1 mL) was added to a solution of (*R*)-*tert*-butyl 3-(cyclopropanecarboxamido)pyrrolidine-1-carboxylate (500 mg, 1.96 mmol) in 5 mL CH_2Cl_2. After stirring for 30 min, the reaction was quenched with 1M NaOH solution till neutral and

extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to yield *N*-((*R*)-pyrrolidin-3-yl)cyclopropanecarboxamide (250 mg) which was used without further purification. LC/MS: *m/z* 155.3 $(M+H)^+$ at 0.6 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

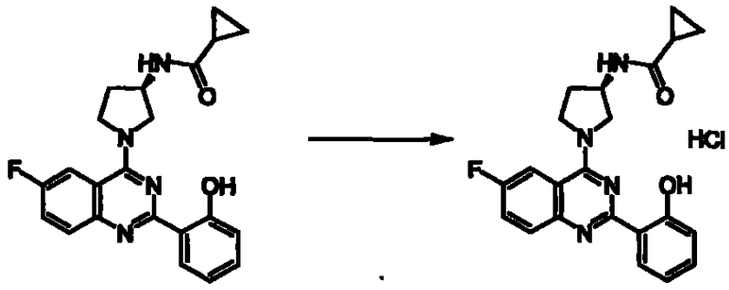
[001795] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001796]



[001797] A mixture of *N*-((*R*)-pyrrolidin-3-yl)cyclopropanecarboxamide (250 mg, 0.86 mmol), 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (250 mg, 0.86 mmol) and triethylamine (0.240 mL, 1.72 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature. The reaction was complete after one hour. The reaction was quenched with water, the aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc/CH_2Cl_2 gave *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide (230 mg, 68%). LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H-NMR (400 MHz, DMSO-d6) δ 8.42–8.46 (m, 2H), 8.03 (dd, *J* = 10.5, 2.6 Hz, 1H), 7.88–7.92 (m, 1H), 7.74–7.79 (m, 1H), 7.35–7.39 (m, 1H), 6.92–6.96 (m, 2H), 4.44–4.47 (m, 1H), 4.01–4.28 (m, 3H), 3.83–3.87 (m, 1H), 2.20–2.28 (m, 1H), 1.99–2.06 (m, 1H), 1.51–1.57 (m, 1H), 0.63–0.73 (m, 4H).

[001798] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide hydrochloride



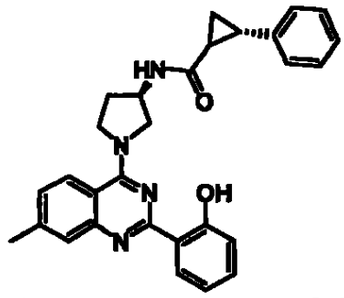
[001799]

[001800] To a solution of *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide (225 mg, 0.57 mmol) in 5 mL CH_2Cl_2 was added a 2 M HCl solution in ether (0.28 mL, 0.57 mmol), which resulted in the precipitation of a solid. After the addition of 20 mL ether, the reaction mixture was stirred for 1 h. The solvents were evaporated under reduced pressure to afford *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide hydrochloride (225 mg, 91%). LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.23 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 10.6 Hz, 1H), 7.91–7.94 (m, 1H), 7.79–7.83 (m, 1H), 7.44–7.48 (m, 1H), 7.00–7.03 (m, 2H), 4.44 (t, *J* = 4.9 Hz, 1H), 4.09–4.23 (m, 3H), 3.87–3.90 (m, 1H), 2.25–2.34 (m, 1H), 2.02–2.09 (m, 1H), 1.49–1.55 (m, 1H), 0.68–0.71 (m, 4H).

[001801] Example 330

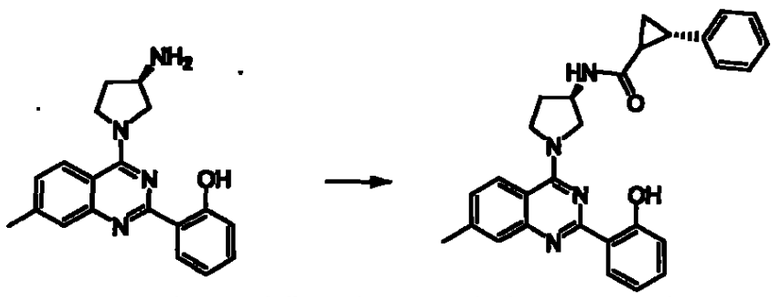
[001802] (2*S*)-*N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-phenylcyclopropanecarboxamide

[001803]



[001804] (2*S*)-*N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-phenylcyclopropanecarboxamide

[001805]

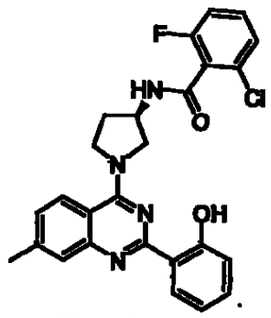


[001806] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. (2*R*)-2-Phenylcyclopropanecarbonyl chloride (31 mg, 0.17 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (2*S*)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-phenylcyclopropanecarboxamide as the TFA salt. LC/MS (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)), LC/MS: *m/z* 465.4 $(M+H)^+$ at 2.88 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001807] Example 331

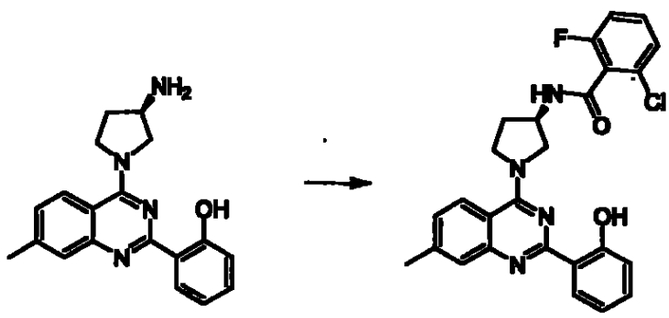
[001808] 2-Chloro-6-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001809]



[001810] 2-Chloro-6-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001811]

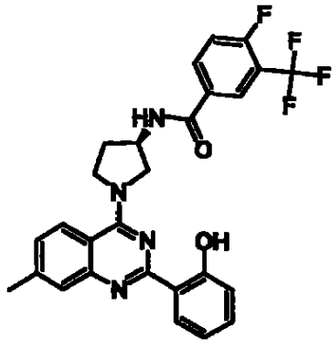


[001812] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-Chloro-6-fluorobenzoyl chloride (36 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 2-chloro-6-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 477.3 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001813] Example 332

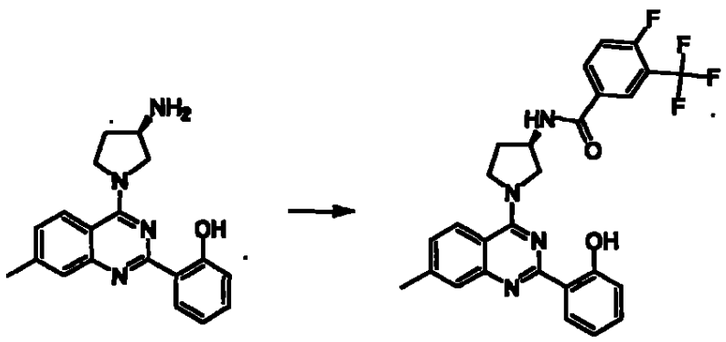
[001814] 4-Fluoro-3-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001815]



[001816] 4-Fluoro-3-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001817]

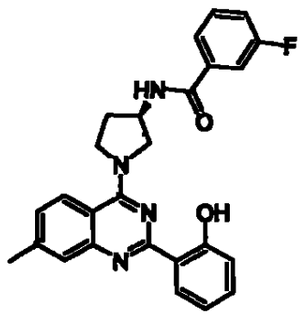


[001818] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 4-Fluoro-3-(trifluoromethyl)benzoyl chloride (42 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 4-fluoro-3-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 511.5 $(M+H)^+$ at 3.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001819] Example 333

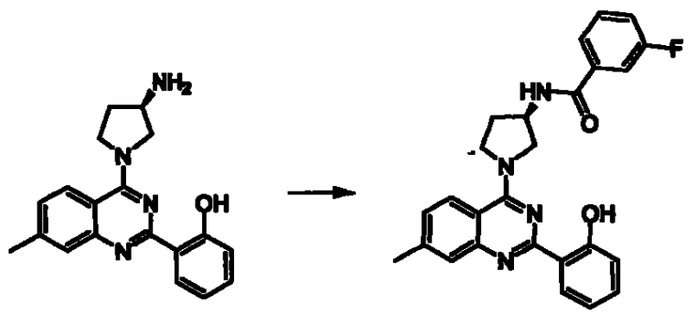
[001820] 3-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001821]



[001822] 3-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001823]

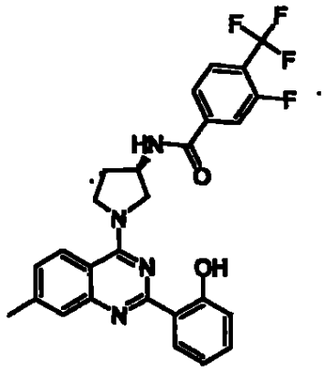


[001824] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 3-Fluorobenzoyl chloride (30 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 443.5 $(M+H)^+$ at 2.83 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001825] Example 334

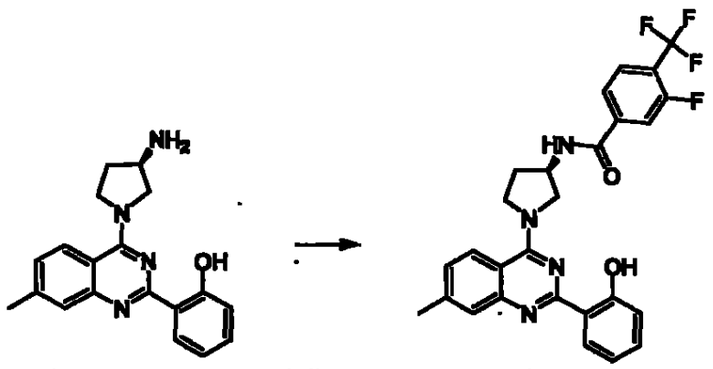
[001826] 3-Fluoro-4-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001827]



[001828] 3-Fluoro-4-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001829]

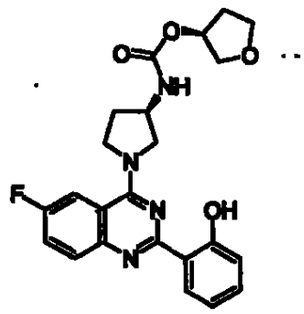


[001830] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 3-Fluoro-4-(trifluoromethyl)benzoyl chloride (42 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-fluoro-4-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 511.5 $(M+H)^+$ at 3.1 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001831] Example 335

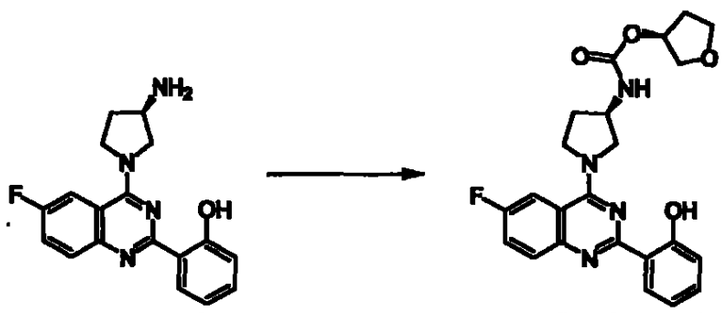
[001832] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001833]



[001834] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001835]

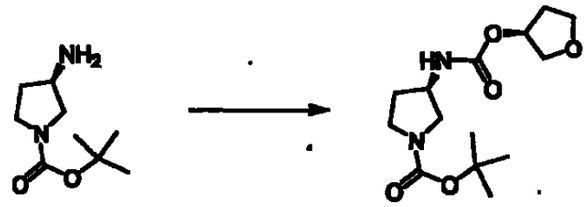


[001836] A solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.092 mmol) in DMF (1.0 mL) was cooled to –40 °C. To this mixture was added triethylamine (26 μL, 0.184 mmol), followed by the addition of (*S*)-tetrahydrofuran-3-yl chloroformate (0.014 g, 0.092 mmol). After allowing the reaction to warm to room temperature the mixture was filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*S*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001837] Method B

[001838] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate

[001839]

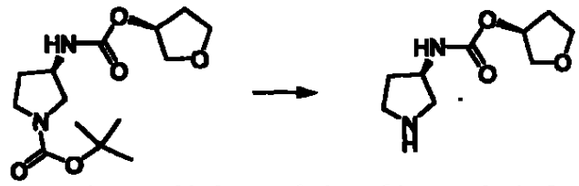


[001840] To a solution of (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (500 mg, 2.6 mmol) in 5 mL CH_2Cl_2 was added triethylamine (0.73 mL, 5.2 mmol), and the reaction was cooled to –20 °C. (*S*)-tetrahydrofuran-3-yl chloroformate (525 mg, 3.48 mmol) was added in portions over a period of 10 minutes to the above reaction mixture. After allowing the reaction to warm to room temperature, it was quenched with water and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford (*S*)-

tetrahydrofuran-3-yl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate. Purification via silica gel chromatography using 0–20% EtOAc in CH_2Cl_2 gave (*S*)-tetrahydrofuran-3-yl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate (490 mg, 63%). *LC/MS*: *m/z* 301.3 $(M+H)^+$ at 2.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001841] **(*S*)-Tetrahydrofuran-3-yl (*R*)-pyrrolidin-3-ylcarbamate**

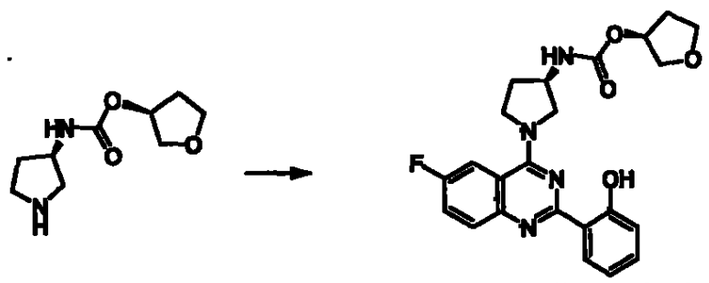
[001842]



[001843] TFA (1 mL) was added to a solution of (*S*)-tetrahydrofuran-3-yl (*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ylcarbamate (490 mg, 1.63 mmol) in 5 mL CH_2Cl_2. After stirring for 30 min, the reaction was quenched with NaOH and extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated to yield (*S*)-tetrahydrofuran-3-yl (*R*)-pyrrolidin-3-ylcarbamate (230 mg) which was used without further purification. *LC/MS*: *m/z* 201.3 $(M+H)^+$ at 0.59 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001844] **(*S*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate**

[001845]

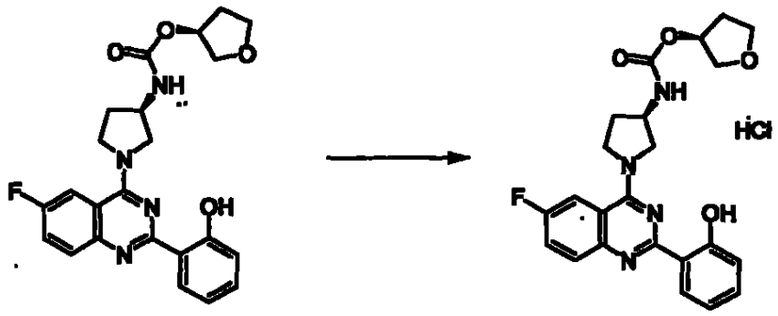


[001846] A mixture of (*S*)-tetrahydrofuran-3-yl (*R*)-pyrrolidin-3-ylcarbamate (225 mg, 1.12 mmol), 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (250 mg, 0.86 mmol), and triethylamine (0.240 mL, 1.72 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature. The reaction was complete in one hour. The reaction was quenched with water, the aqueous layer was extracted twice with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and

concentrated. Purification via silica gel chromatography using 0–10% EtOAc/CH_2Cl_2 gave (*S*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate (250 mg, 66%). LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.43 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.99 (d, *J* = 2.6 Hz, 1H), 7.87–7.91 (m, 1H), 7.74–7.79 (m, 1H), 7.70 (d, *J* = 6.2 Hz, 1H), 7.35–7.39 (m, 1H), 6.91–6.96 (m, 2H), 5.15 (s, 1H), 4.21–4.25 (m, 2H), 4.12–4.14 (m, 1H), 4.01–4.06 (m, 1H), 3.87–3.89 (m, 1H), 3.65–3.78 (m, 4H), 2.02–2.26 (m, 3H), 1.82–1.89 (m, 1H).

[001847] **(*S*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride**

[001848]

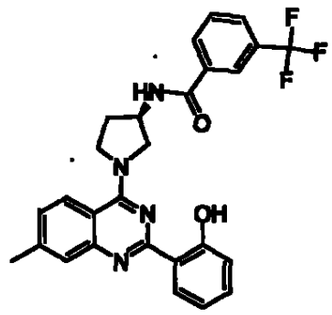


[001849] To a mixture of (*S*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate (250 mg, 0.57 mmol) and CH_2Cl_2 (25 mL) was added a 2.0 M HCl solution in ether (0.285 mL, 0.57 mmol). After the addition of ether (40 mL), the reaction was stirred for 1 h. The resulting solid was filtered and dried to afford (*S*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.18 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.00 (d, *J* = 9.6 Hz, 1H), 7.90–7.94 (m, 1H), 7.78–7.83 (m, 1H), 7.45–7.49 (m, 1H), 7.00–7.03 (m, 2H), 5.10 (s, 1H), 4.09–4.25 (m, 4H), 3.90–3.92 (m, 1H), 3.62–3.75 (m, 4H), 2.22–2.27 (m, 1H), 2.03–2.14 (m, 2H), 1.83–1.91 (m, 1H).

[001850] Example 336

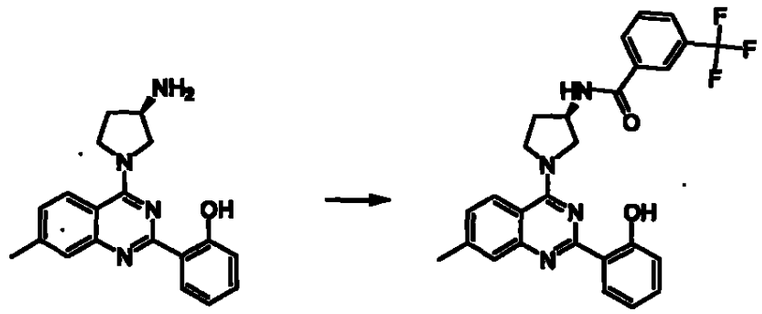
[001851] **3-(Trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide**

[001852]



[001853] 3-(Trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001854]

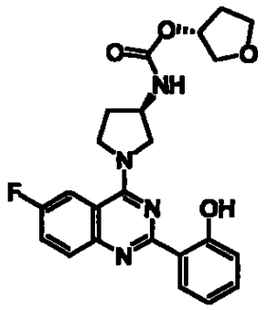


[001855] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (130 mg, 0.406 mmol) was dissolved in 0.7 mL anhydrous CH_2Cl_2 and cooled to 0 °C. 3-(Trifluoromethyl)benzoyl chloride (42 mg, 0.18 mmol) dissolved in 0.7 mL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (53 mg, 74 µL, 0.52 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 493.5 $(M+H)^+$ at 3.03 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001856] Example 337

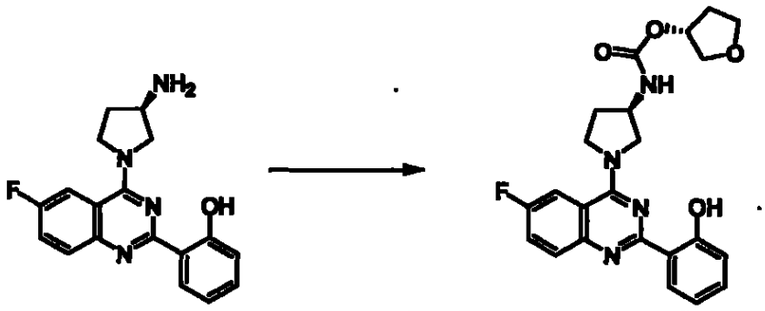
[001857] (*R*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001858]



[001859] (*R*)-Tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001860]



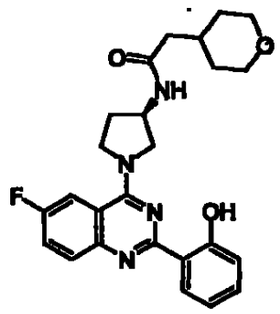
To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.092 mmol) in DMF (1.0 mL) was cooled to –40 °C, triethylamine (26 μL, 0.184 mmol) was added, followed by the addition of (*R*)-tetrahydrofuran-3-yl chloroformate (0.014 g, 0.092 mmol). After warming to room temperature, the mixture was filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain (*R*)-tetrahydrofuran-3-yl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001861] Example 338

[001862] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)acetamide

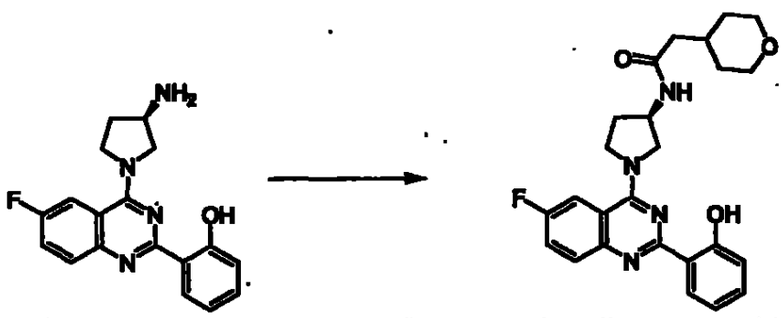
437 436

[001863]



[001864] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)acetamide

[001865]

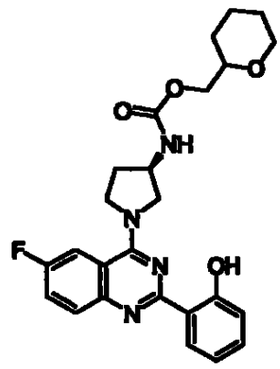


To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.092 mmol) in DMF (1.0 mL) was added 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (0.017 g, 0.12 mmol), followed by the addition of triethylamine (25.6 μL, 0.184 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(tetrahydro-2*H*-pyran-4-yl)acetamide as the TFA salt. LC/MS: *m/z* 451.5 $(M+H)^+$ at 2.15 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001866] Example 339

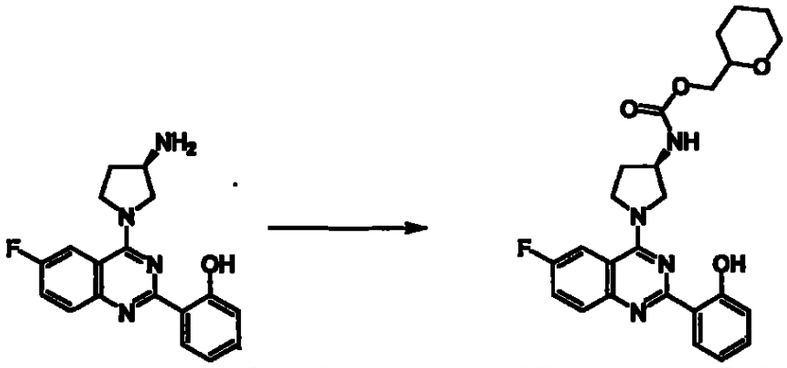
[001867] (Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001868]



[001869] (Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001870]



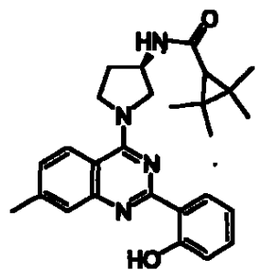
[001871] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) at room temperature was added triethylamine (43 μL, 0.31 mmol), followed by the addition of (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (39 mg, 0.13 mmol). The reaction was stirred at room temperature overnight, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 467.3 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001872] Example 340

[001873] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2,2,3,3-tetramethylcyclopropanecarboxamide

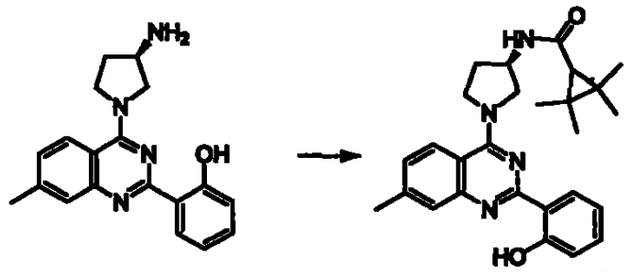
438 437

[001874]



[001875] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2,2,3,3-tetramethylcyclopropanecarboxamide

[001876]

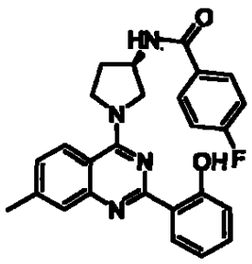


[001877] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.156 mmol) was dissolved in 0.52 mL of anhydrous CH_2Cl_2. 2,2,3,3-Tetramethylcyclopropanecarboxylic acid (26.63 mg, 0.18 mmol) was added, followed by triethylamine (22.14 mg, 30.49 μL, 0.22 mmol) and BOP (82.93 mg, 0.18 mmol). After stirring the mixture for 30 minutes at room temperature, it was filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2,2,3,3-tetramethylcyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 445.4 $(M+H)^+$ at 2.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001878] Example 341

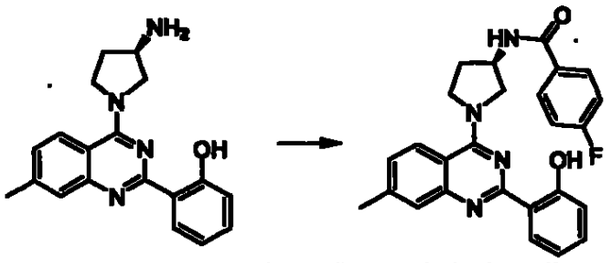
[001879] 4-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001880]



[001881] 4-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

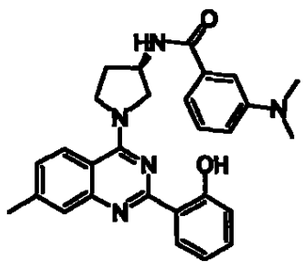
[001882]



[001883] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 4-Fluorobenzoyl chloride (25 mg, 0.15 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (19 mg, 26 μL, 0.18 mmol). The reaction was stirred for 15 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 4-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 443.4 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001884] Example 342

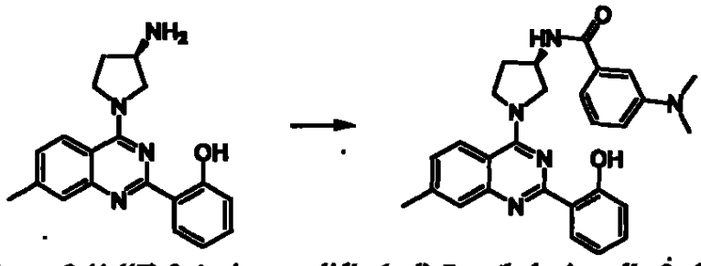
[001885] 3-(Dimethylamino)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide



[001886]

[001887] 3-(Dimethylamino)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

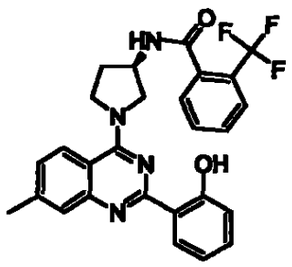
[001888]



[001889] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 3-(Dimethylamino)benzoyl chloride hydrochloride (34 mg, 0.15 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (32 mg, 44 μL, 0.31 mmol). The reaction was stirred for 1.5 hour at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 3-(dimethylamino)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 468.4 $(M+H)^+$ at 2.39 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001890] Example 343

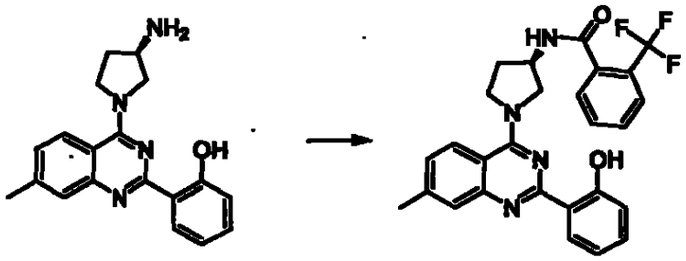
[001891] 2-(Trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide



[001892]

[001893] 2-(Trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

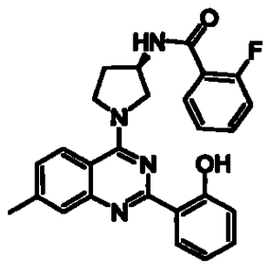
[001894]



[001895] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-(Trifluoromethyl)benzoyl chloride (39 mg, 0.18 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 20 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 2-(trifluoromethyl)-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 493.4 $(M+H)^+$ at 2.76 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001896] Example 344

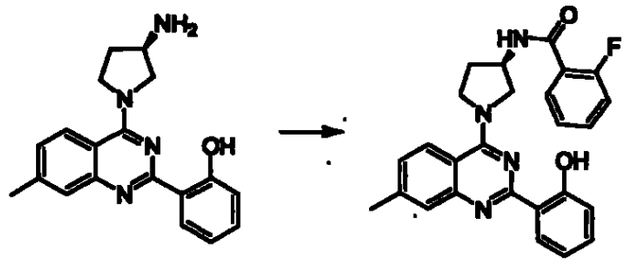
[001897] 2-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide



[001898]

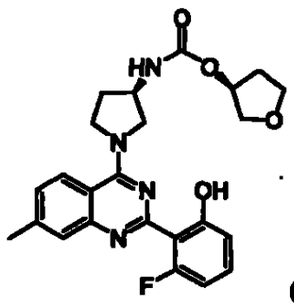
[001899] 2-Fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide

[001900]



[001901] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50.6 mg, 0.158 mmol) was dissolved in 260 μL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-Fluorobenzoyl chloride (27 mg, 0.17 mmol) dissolved in 260 μL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (21 mg, 28 μL, 0.20 mmol). The reaction was stirred for 15 minutes at 0 °C and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 2-fluoro-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)benzamide as the TFA salt. LC/MS: *m/z* 443.4 $(M+H)^+$ at 2.69 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001902] Example 345

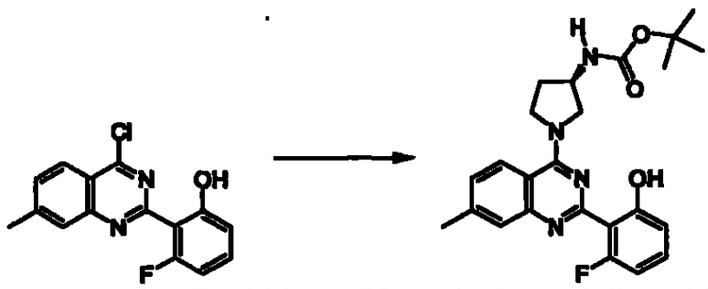


[001903] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001904]

[001905] *tert*-Butyl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

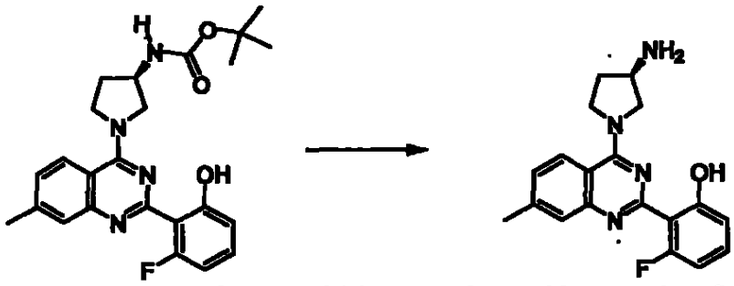
[001906]



[001907] A solution of *tert*-butyl (*R*)-pyrrolidin-3-ylcarbamate (368 mg, 1.97 mmol) and triethylamine (0.46 mL, 3.28 mmol) in CH_2Cl_2 was rapidly added to a stirring solution of 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (475 mg, 1.65 mmol) in 15 mL CH_2Cl_2 at 0 °C under an N_2 atmosphere. The reaction was stirred for 1 h before it was quenched with water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc/CH_2Cl_2 yielded *tert*-butyl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001908] 2-(4-((*R*)-3-Aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol

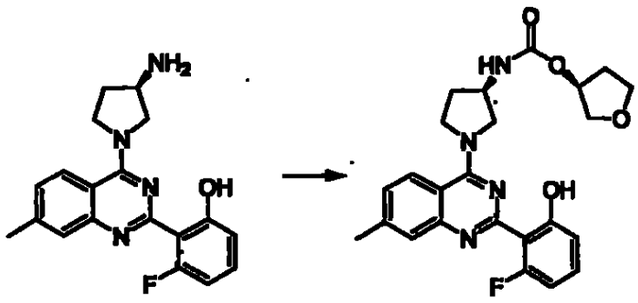
[001909]



[001910] To a solution of *tert*-butyl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (500 mg, 1.14 mmol) in CH_2Cl_2 (15 mL) was added TFA (5 mL). The mixture was stirred for 1 h and then neutralized with a 1 M NaOH solution, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 3–20% EtOAc/CH_2Cl_2 gave 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol. LC/MS: *m/z* 339.5 $(M+H)^+$ at 0.56 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001911] **(*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

[001912]



[001913] Method A

[001914] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.12 mmol) in 800 μL of anhydrous DMF cooled to 0 °C was added (*S*)-tetrahydrofuran-3-yl chloroformate (20 mg, 19 μL, 0.13 mmol) dropwise, followed by the addition of triethylamine (24 mg, 33 μL, 0.23 mmol). The reaction was warmed to room temperature and stirred overnight, and the product purified via reverse phase HPLC (10%–99%

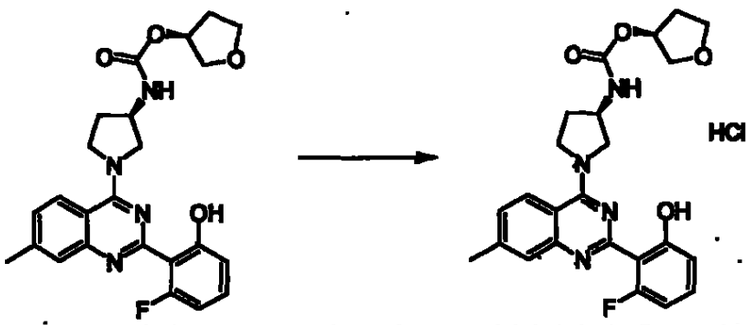
CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.05 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001915] Method B

[001916] At room temperature, *N*-ethyl-*N*-isopropylpropan-2-amine (155 mL, 0.88 mmol) was added to a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (150 mg, 0.40 mmol) in THF. The mixture was cooled in an ice bath, and (*S*)-tetrahydrofuran-3-yl chloroformate (63 mg, 0.42 mmol) was added slowly over a period of 10 minutes. After warming to room temperature, the reaction was quenched with water and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in CH_2Cl_2/hexanes (1:1) gave (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (160 mg, 84%). LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.18 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 6.3 Hz, 1H), 7.58 (s, 1H), 7.29–7.38 (m, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.67–6.72 (m, 1H), 5.14 (s, 1H), 4.23–4.24 (m, 1H), 3.99–4.13 (m, 3H), 3.64–3.85 (m, 5H), 2.50 (s, 3H), , 2.07–2.22 (m, 2H), 2.00–2.03 (m, 1H), 1.85–1.90 (m, 1H).

[001917] (*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride

[001918]



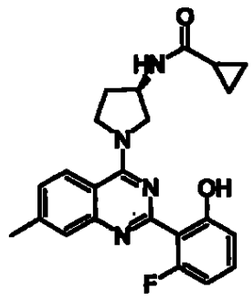
[001919] To a solution of (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate (160 mg, 0.35 mmol) in 2 mL CH_2Cl_2 was added 2 M HCL solution in ether (0.176 mL, 0.35 mmol) resulting in precipitation of a solid. After the addition of 10 mL ether, the reaction was stirred for 30 minutes, filtered and the

resulting solid was dried to obtain (*S*)-tetrahydrofuran-3-yl (*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate hydrochloride (130 mg, 76%).). LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.29 (s, 1H), 7.57 (s, 2H), 7.43–7.49 (m, 1H), 6.83–6.89 (m, 2H), 5.08 (s, 1H), 4.23–4.42 (m, 4H), 3.62–3.73 (m, 5H), 2.24–2.34 (m, 1H), 2.04–2.11 (m, 2H), 1.86–1.92 (m, 1H).

[001920] Example 346

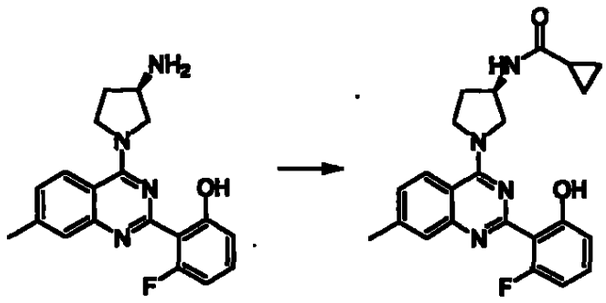
[001921] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001922]



[001923] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide

[001924]



[001925] Method A

[001926] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (40 mg, 0.12 mmol) in 800 μL of anhydrous DMF at 0 °C was added cyclopropanecarboxylic acid (11 mg, 0.13 mmol), followed by the addition of triethylamine (24

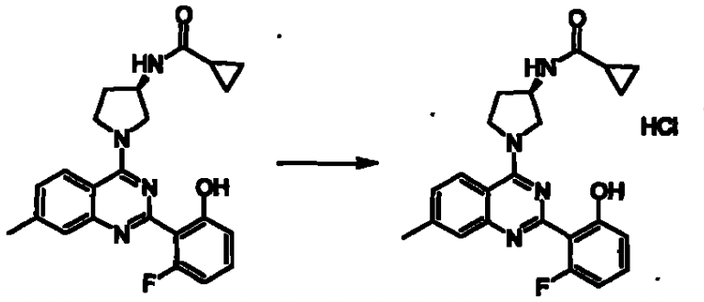
mg, 33 μL, 0.24 mmol) and HATU (60 mg, 0.16 mmol). The mixture was allowed to warm to room temperature and was stirred overnight. Filtration and purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.2 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001927] Method B

To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (100 mg, 0.295 mmol) in 10 mL DMF, at –20 °C, was added cyclopropanecarboxylic acid (23 μL, 0.30 mmol), followed by the addition of triethylamine (82 μL, 0.59 mmol) and a solution of HATU (124 mg, 0.32 mmol) in 4 mL DMF. The mixture was warmed to room temperature and stirred for 1 h. Cold water was added to the reaction mixture which resulted in the formation of a precipitate which was collected by filtration and dissolved in CH_2Cl_2. The solution was then dried over $MgSO_4$, filtered, and concentrated to afford *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide (80 mg, 66%) LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.08 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001928] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide hydrochloride

[001929]



[001930] A 2 M HCl solution in ether (0.16 mL, 0.32 mmol) was added to a solution of *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide (133 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) under an N_2 atmosphere. Additional ether was then added (15 mL) and the reaction mixture was stirred for an hour. The formed precipitate was then filtered and dried to afford *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-

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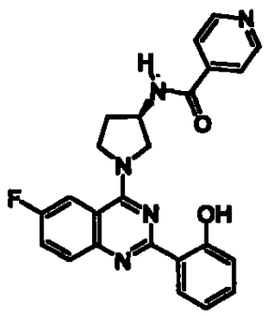
7-methylquinazolin-4-yl)pyrrolidin-3-yl)cyclopropanecarboxamide hydrochloride (135 mg, 95%). LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.07 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.32 (d, *J* = 7.6 Hz, 1H), 7.56–7.58 (m, 2H), 7.43–7.49 (m, 1H), 6.83–6.88 (m, 2H), 3.94–4.41 (m, 5H), 2.52 (s, 3H), 2.25–2.36 (m, 1H), 1.91–2.13 (m, 1H), 1.47–1.54 (m, 1H), 0.63–0.69 (m, 4H)

[001931] Example 347

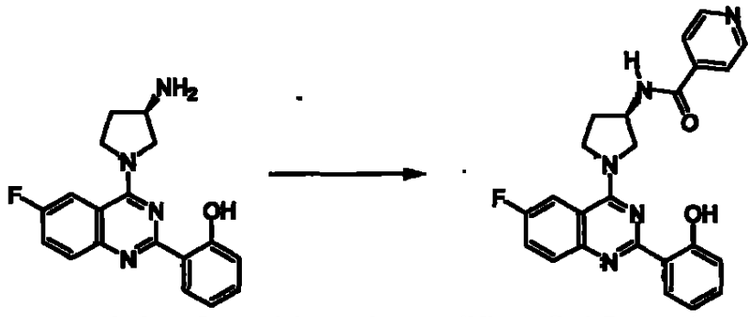
[001932] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001933]



[001934] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001935]



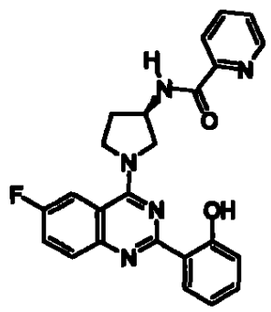
[001936] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added isonicotinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-

hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide as the TFA salt. LC/MS: *m/z* 430.5 $(M+H)^+$ at 1.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001937] Example 348

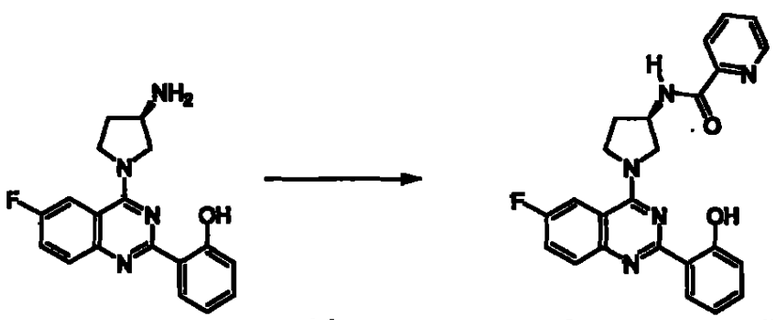
[001938] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001939]



[001940] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001941]



[001942] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added picolinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)picolinamide as the TFA salt. LC/MS: *m/z* 430.5 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001943] Example 349

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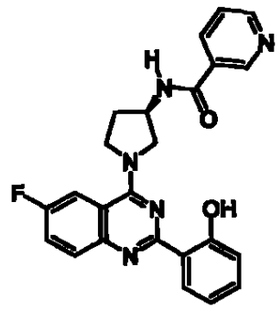
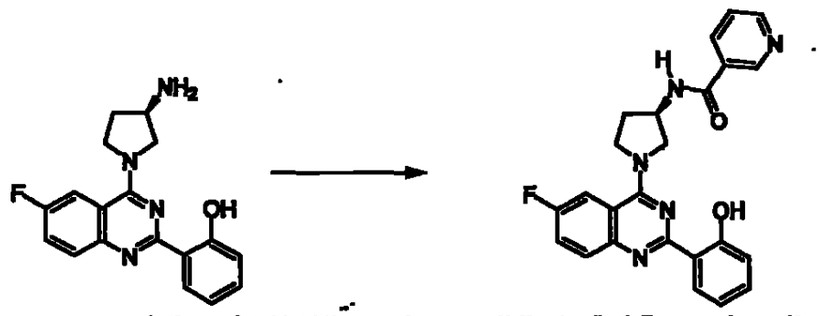
[001944] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001945]



[001946] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001947]

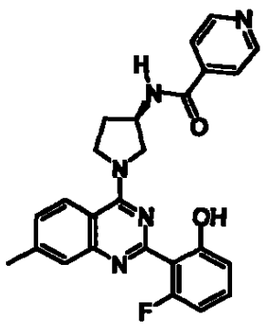


[001948] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added nicotinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)nicotinamide as the TFA salt. LC/MS: *m/z* 430.5 $(M+H)^+$ at 1.98 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001949] Example 350

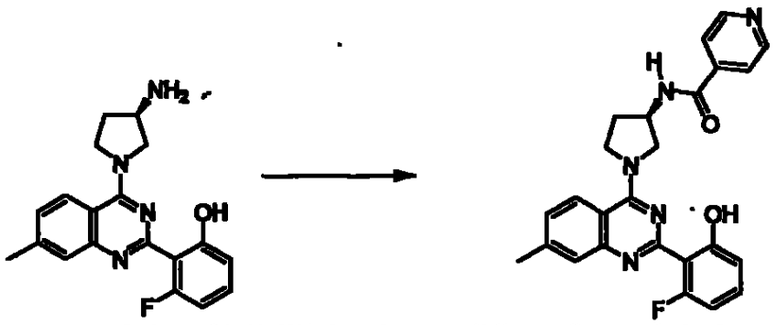
[001950] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001951]



[001952] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001953]

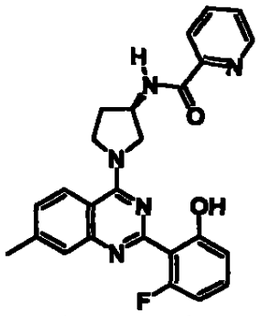


[001954] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) in DMF (0.5 mL) was added isonicotinic acid (0.014 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide as the TFA salt. LC/MS: *m/z* 444.5 $(M+H)^+$ at 1.85 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001955] Example 351

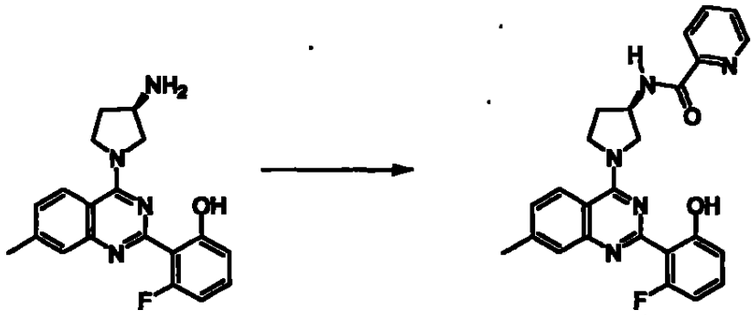
[001956] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001957]



[001958] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001959]

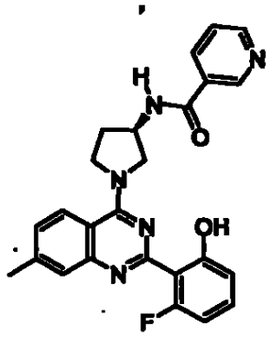


[001960] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added picolinic acid (0.014 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide as the TFA salt. LC/MS: *m/z* 444.5 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001961] Example 352

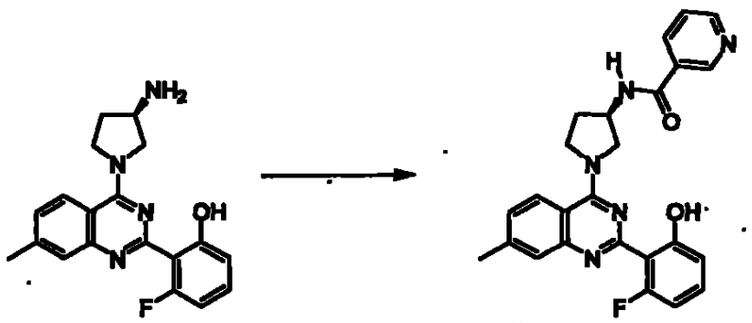
[001962] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001963]



[001964] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide

[001965]



[001966] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added nicotinic acid (0.014 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)nicotinamide as the TFA salt. LC/MS: *m/z* 444.5 $(M+H)^+$ at 1.89 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001967] Example 353

[001968] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

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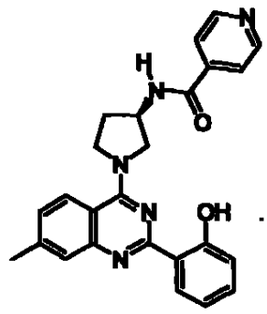
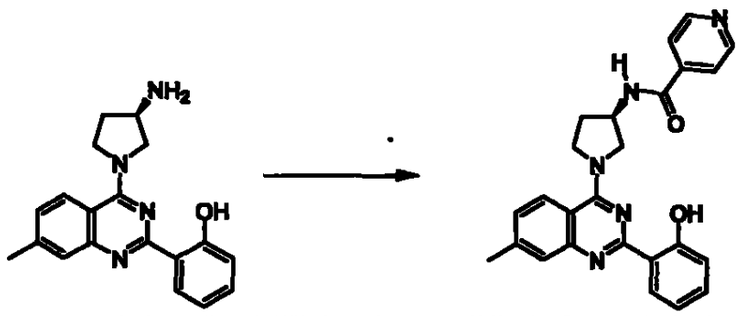
[001969]



[001970] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide

[001971]

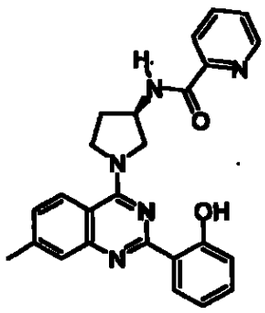


[001972] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added isonicotinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)isonicotinamide as the TFA salt. LC/MS: *m/z* 426.1 $(M+H)^+$ at 1.93 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001973] Example 354

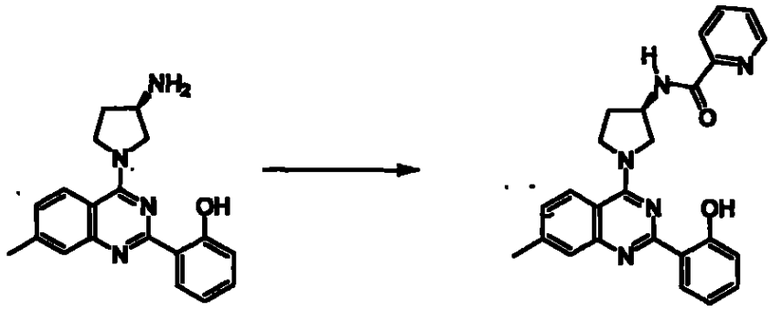
[001974] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001975]



[001976] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide

[001977]



[001978] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added picolinic acid (0.015 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)picolinamide as the TFA salt. LC/MS: *m/z* 426.1 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001979] Example 355

[001980] (*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

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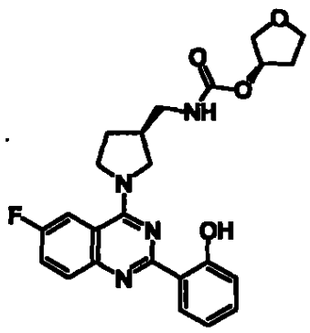
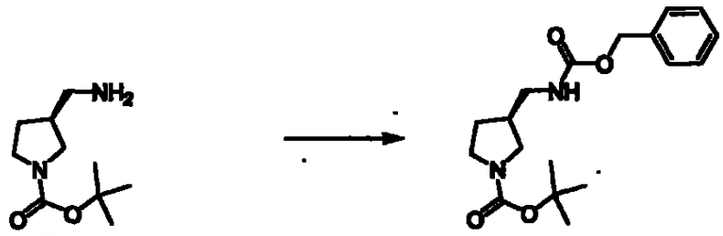
[001981]



[001982] Benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate

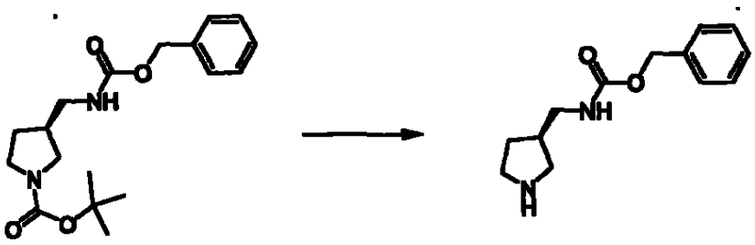
[001983]



[001984] To a stirring solution of (*S*)-*tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (1.5 g, 7.5 mmol) in 25 mL CH_2Cl_2 was added triethylamine (2.1 mL, 15 mmol) at 0 °C, followed by the dropwise addition of benzyl chloroformate (1.58 mL, 11.2 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was quenched with water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 3% MeOH in CH_2Cl_2 gave benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.5 g, 60%). LC/MS: *m/z*: 335.5 $(M+H)^+$ at 3.01 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001985] Benzyl ((*R*)-pyrrolidin-3-yl)methylcarbamate

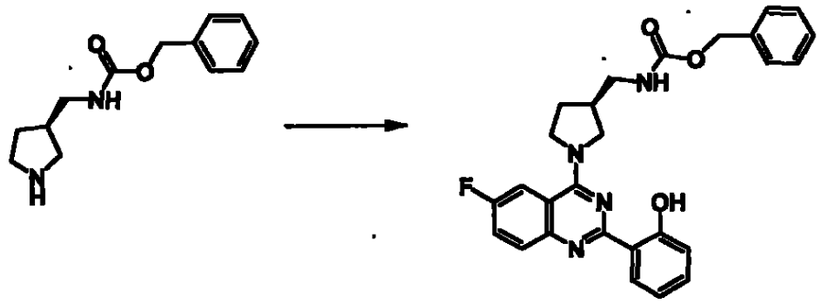
[001986]



[001987] To a stirred solution of ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.5 g, 4.48 mmol) in CH_2Cl_2 (20 mL) was slowly added TFA (5 mL). The reaction was stirred for 2 h. After removing the solvents under reduced pressure, the mixture was neutralized with a 1 M NaOH solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford benzyl ((*R*)-pyrrolidin-3-yl)methylcarbamate (800 mg, 76%). LC/MS: *m/z* 335.3 $(M+H)^+$ at 1.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

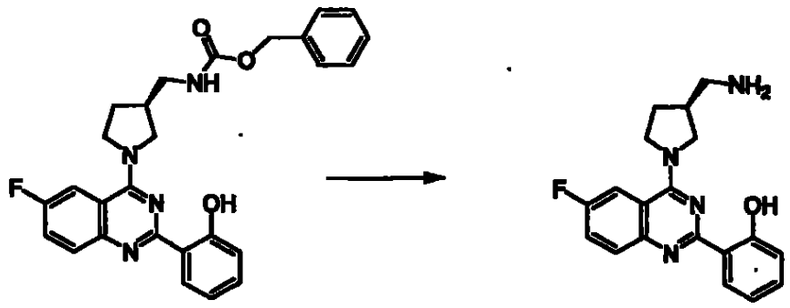
[001988] Benzyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001989]



[001990] A solution of triethylamine (507 μL, 3.64 mmol) and benzyl ((*R*)-pyrrolidin-3-yl)methylcarbamate (0.47 g, 2 mmol) in CH_2Cl_2 was added dropwise to a solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (0.5 g, 1.82 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred at room temperature for 3 h. After quenching the reaction with water, the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 5–10% EtOAc in CH_2Cl_2 yielded benzyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate. LC/MS: *m/z* 473.1 $(M+H)^+$ at 2.91 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001991] 2-(4-((*S*)-3-(Aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol

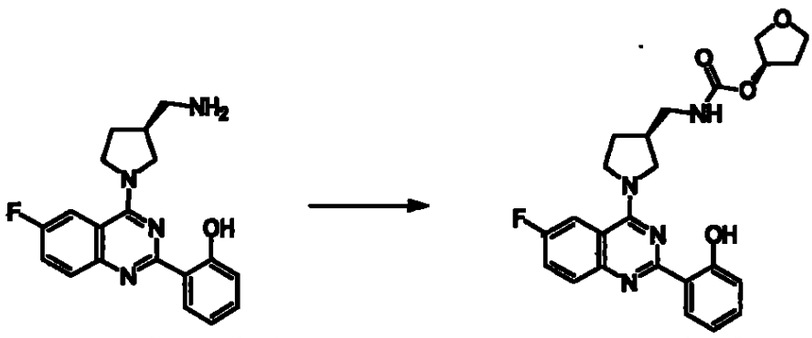


[001992]

[001993] Under an N_2 atmosphere, a mixture of benzyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.770 g, 1.6 mmol) and MeOH (5 mL) was added to Pd/C (77 mg, 10 % weight Pd on carbon) weighed into a 100 mL flask. After the atmosphere in the flask was evacuated and purged with N_2 three times, the reaction mixture was vigorously stirred under an H_2 atmosphere at ambient pressure overnight and then filtered through a pad of Celite, concentrated, and dried to obtain 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.45 g, 81%). *LC/MS*: *m/z* 459.5 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001994] **(*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[001995]



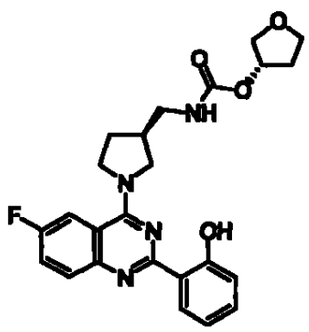
[001996] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol) and (*R*)-tetrahydrofuran-3-yl chloroformate (13 mg, 0.09 mmol). The reaction was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (*R*)-tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the

TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001997] Example 356

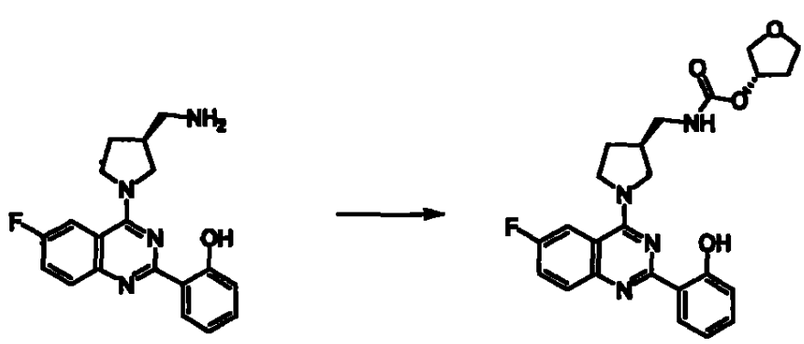
[001998] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[001999]



[002000] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate.

[002001]



[002002] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol) and (*S*)-tetrahydrofuran-3-yl chloroformate (13 mg, 0.09 mmol). The reaction was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the

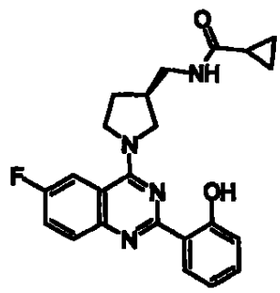
449

TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002003] Example 357

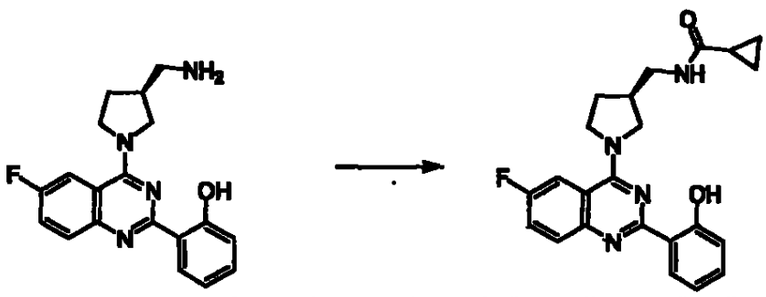
[002004] *N*-(((*S*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide

[002005]



[002006] *N*-(((*S*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide

[002007]

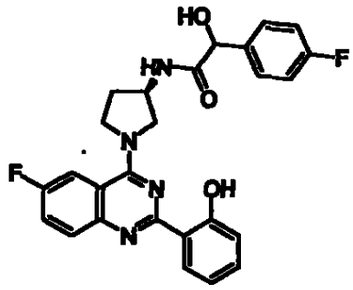


[002008] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) and cyclopropanecarboxylic acid (10 mg, 0.12 mmol) in DMF (1.0 mL) was added triethylamine (25 μL, 0.18 mmol) followed by the addition of HATU (45 mg, 0.117 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-(((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methyl)cyclopropanecarboxamide as the TFA salt. LC/MS: *m/z* 407.3 $(M+H)^+$ at 2.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002009] Example 358

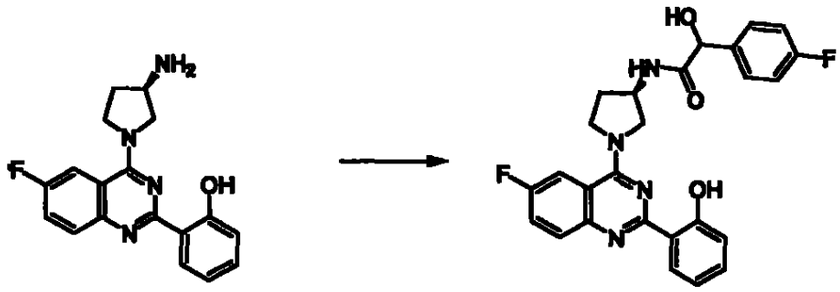
[002010] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[002011]



[002012] *N*-((*R*)-1-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[002013]

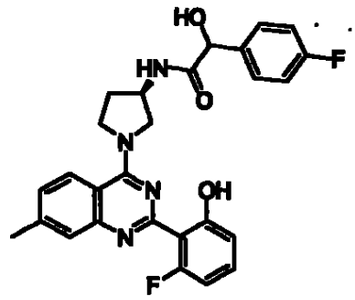


[002014] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added 2-(4-fluorophenyl)-2-hydroxyacetic acid (20 mg, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide as the TFA salt. LC/MS: *m/z* 477.3 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002015] Example 359

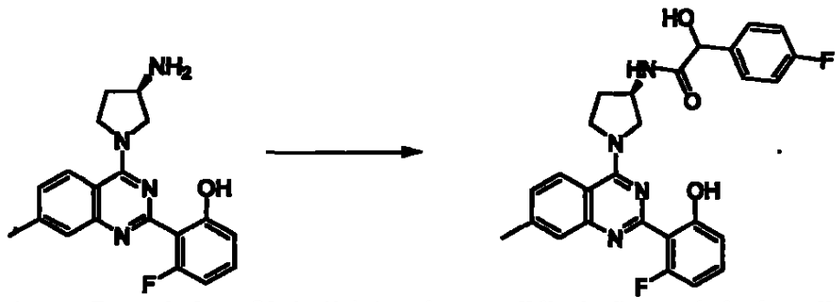
[002016] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[002017]



[002018] *N*-((*R*)-1-(2-(2-Fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[002019]

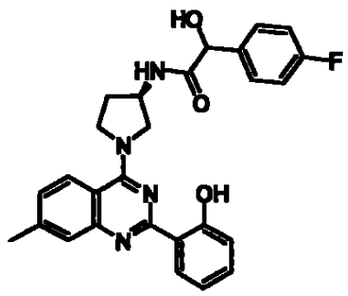


[002020] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added 2-(4-fluorophenyl)-2-hydroxyacetic acid (0.020 g, 0.12 mmol), followed by the addition of triethylamine (25.6 μL, 0.184 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain *N*-((*R*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2-(4-fluorophenyl)-2-hydroxyacetamide as the TFA salt. LC/MS: *m/z* 4491.3 $(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002021] Example 360

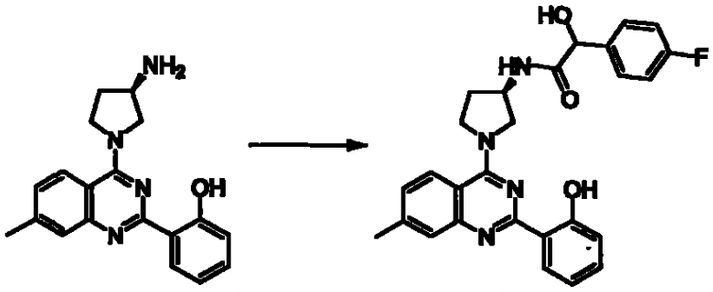
[002022] 2-(4-Fluorophenyl)-2-hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide

[002023]



[002024] 2-(4-Fluorophenyl)-2-hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide

[002025]



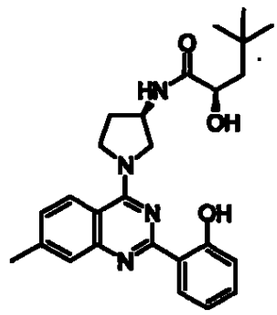
[002026] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) was added 2-(4-fluorophenyl)-2-hydroxyacetic acid (0.02 g, 0.12 mmol), followed by the addition of triethylamine (25 μL, 0.18 mmol) and HATU (0.045 g, 0.12 mmol). The reaction was stirred at room temperature for 2 h, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to obtain 2-(4-fluorophenyl)-2-hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)acetamide as the TFA salt. *LC/MS*: *m/z* 473.1 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002027] Example 361

[002028] (2*R*)-2-Hydroxy-*N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-4,4-dimethylpentanamide

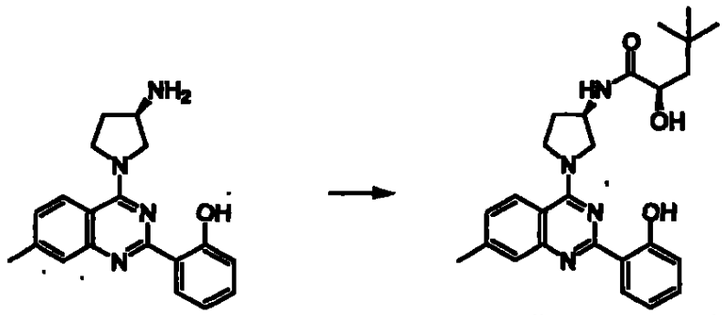
449
451

[002029]



[002030] (2*R*)-2-Hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-4,4-dimethylpentanamide

[002031]

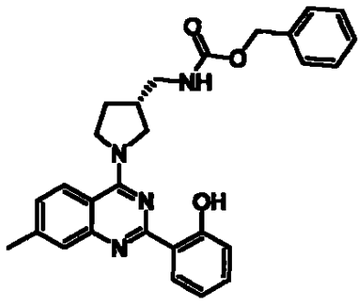


[002032] To a stirred solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in 1 mL of DMF cooled at 0 °C was added (*R*)-2-hydroxy-4,4-dimethylpentanoic acid (27.3 mg, 0.187 mmol), followed by the addition of triethylamine (32 mg, 44 μL, 0.31 mmol), then HATU (71.1 mg, 0.187 mmol). The reaction was stirred at 0 °C for 10 minutes, warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (2*R*)-2-hydroxy-*N*-((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-4,4-dimethylpentanamide as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.4 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002033] Example 362

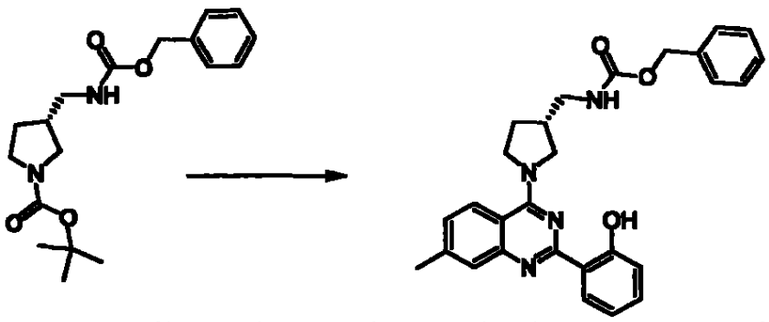
[002034] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002035]



[002036] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002037]

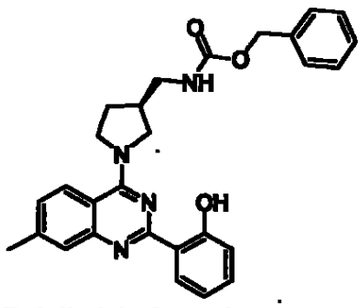


[002038] A mixture of benzyl ((*R*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (0.20 g, 0.60 mmol) and 4 M HCl (10 mL) in dioxane was stirred at room temperature for 3 h. After evaporating the solvent under reduced pressure, the solid was triturated with Et_2O, dried under vacuum, and taken up in CH_2Cl_2 (10 mL). 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (0.16 g, 0.60 mmol) was added to this solution, followed by the addition of triethylamine (0.25 mL, 1.8 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 and washed with water. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in hexanes gave benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as a colorless oil (0.19 g, 68% yield). LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002039] Example 363

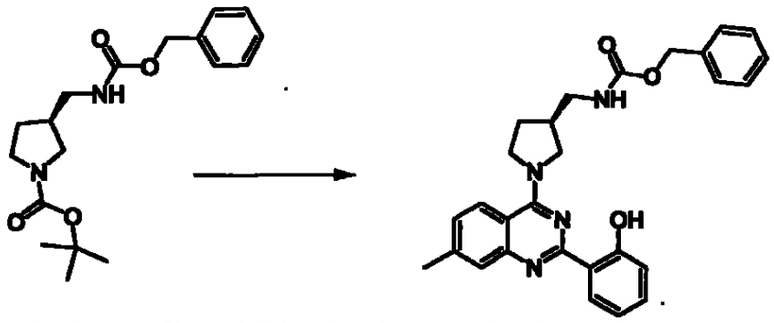
[002040] Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002041]



[002042] Benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002043]

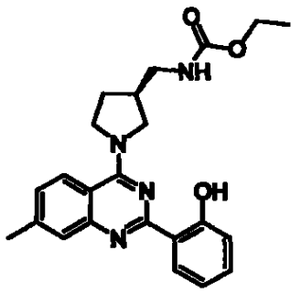


[002044] A mixture of benzyl ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (0.20 g, 0.60 mmol) and 4 M HCl in dioxane (10 mL) was stirred for 3 h at room temperature. After evaporating the solvent under reduced pressure, the solid was triturated with Et_2O, dried under vacuum, and taken up in CH_2Cl_2 (10 mL). 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (0.16 g, 0.60 mmol) was added to this solution, followed by the addition of triethylamine (0.25 mL, 1.8 mmol). The reaction mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2 and washed with water. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in hexanes gave benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as a colorless oil (0.19 g, 68% yield). LC/MS: *m/z* 469.1 $(M+H)^+$ at 2.58 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002045] Example 364

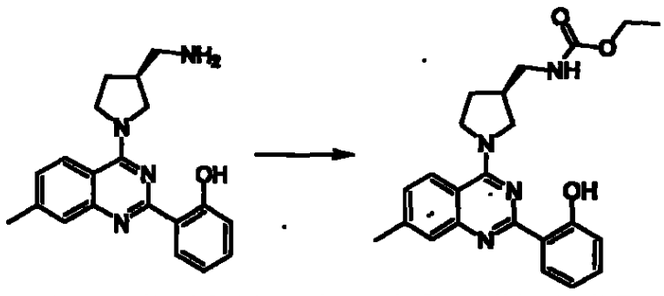
[002046] Ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002047]



[002048] Ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002049]

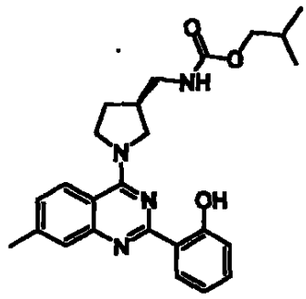


[002050] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) in CH_2Cl_2 (1.0 mL) was cooled in an ice bath. To this mixture was added ethyl chloroformate (7.8 μL, 0.082 mmol), followed by triethylamine (21 μL, 0.15 mmol). After removing the ice bath, the reaction was stirred for 3 h at room temperature. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave ethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 407.1 $(M+H)^+$ at 2.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002051] Example 365

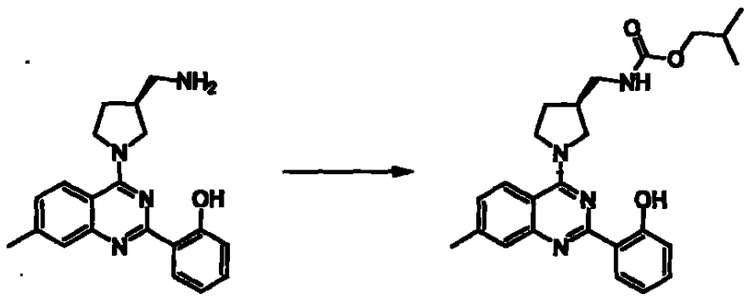
[002052] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002053]



[002054] Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002055]



[002056] Method A

[002057] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) in CH_2Cl_2 (1.0 mL) was cooled in an ice bath. To this mixture was added isobutyl chloroformate (11 μL, 0.082 mmol), followed by the addition of triethylamine (21 μL, 0.15 mmol). After removing the ice bath, the reaction was stirred for 3 h at room temperature. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.55 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

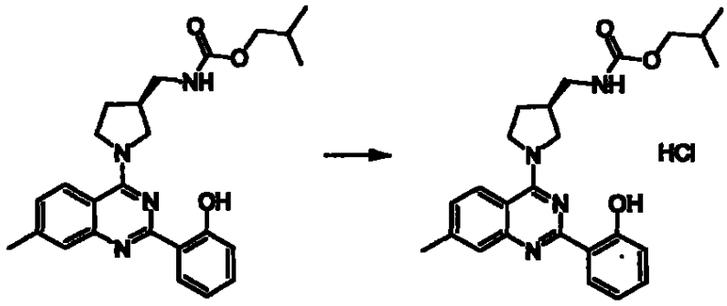
[002058] Method B

[002059] A mixture of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (200 mg, 0.6 mmol), THF (6.0 mL), and CH_2Cl_2 was stirred under an N_2 atmosphere. Triethylamine (0.166 mL, 1.2 mmol) was added, and the reaction was cooled in an ice bath. To

this was added 1 M isobutyl chloroformate solution (78 μL in 600 μL THF, 0.6 mmol). After allowing the reaction mixture to warm to room temperature, CH_2Cl_2 was added, and the organic solution washed twice with water, then dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–20% EtOAc in CH_2Cl_2/hexanes (1:1) gave isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (183 mg, 70%). LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.63 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). LC/MS: *m/z* 435 $(M+H)^+$ at 2.63 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.43 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.22 (d, *J* = 8.7 Hz, 1H), 7.58 (s, 1H), 7.42–7.31 (m, 3H), 6.93–6.89 (m, 2H), 4.17–3.91 (m, 3H), 3.80–3.69 (m, 3H), 3.34–3.30 (m, 1H), 3.21–3.07 (m, 2H), 2.49 (s, 3H), 2.16–2.08 (m, 1H), 1.88–1.74 (m, 2H), 0.88 (d, *J* = 6.7 Hz, 6H).

[002060] **Isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride**

[002061]



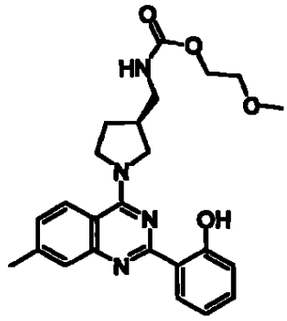
[002062] A solution of isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (183 mg, 0.42 mmol) in CH_2Cl_2 (1.5 mL) was stirred under an N_2 atmosphere. A 1.0 M HCl solution in ether (0.42 ml, 0.42 mmol) was added dropwise to this solution. After 10 minutes, 5 mL ether was added, and a precipitate formed which was filtered and dried to obtain isobutyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (169 mg, 85%). LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.64 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.24 (d, *J* = 6.8 Hz, 1H), 7.80 (s, 1H), 7.53–7.45 (m, 2H), 7.41–7.38 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 7.05–7.02 (m, 1H), 4.36–3.85 (m, 5H), 3.77–3.70

(m, 2H), 3.22–3.08 (m, 2H), 2.54 (s, 3H), 2.18–2.13 (m, 1H), 1.87–1.77 (m, 2H), 0.87 (d, J = 6.7 Hz, 6H).

[002063] Example 366

[002064] 2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002065]



[002066] 2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002067] Method A

[002068] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (25 mg, 0.075 mmol) in anhydrous CH_2Cl_2 was cooled in an ice bath. Then 2-methoxyethyl chloroformate (8.6 μL, 0.075 mmol) was added, followed by the addition of triethylamine (16 μL, 0.11 mmol). After removing the ice bath, the reaction was stirred at room temperature for 4 h. Water and saturated aqueous $NaHCO_3$ solution were added, and the reaction mixture was stirred at room temperature overnight. After separation of the aqueous and organic layers, the organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification via preparative reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)), *m/z*: M+1 *obs* = 437.3; t_R = 2.18 minutes

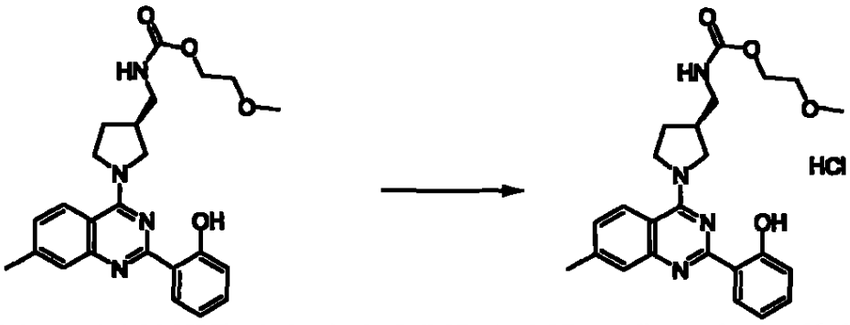
[002069] Method B

[002070] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.12 g, 0.35 mmol) and triethylamine (98 μL, 0.7 mmol) in anhydrous DMF (4.0 mL) was cooled in an ice bath. 2-Methoxyethyl chloroformate (40 mL, 0.35 mmol) was added, and

the ice bath was removed. The solution was stirred at room temperature overnight. Purification via silica gel chromatography using 0–10% MeOH in CH_2Cl_2 gave 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.12 g, 80%). LC/MS: *m/z* 437.5 $(M+H)^+$ at 2.20 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002071] **2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride**

[002072]



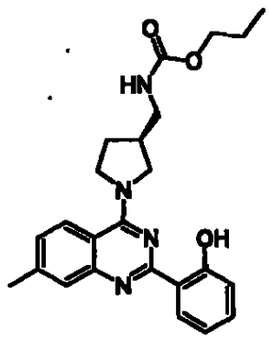
[002073] A 1.0 M HCl solution in Et_2O (0.27 mL, 0.27 mmol) was slowly added to a stirring solution of 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.12 g, 0.27 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 30 minutes at room temperature, then Et_2O was slowly added to the solution until a precipitate formed. After stirring for 1 h, the solid was filtered and washed with Et_2O to obtain 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (0.10 g, 77%). LC/MS: *m/z* 437.1 $(M+H)^+$ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.24 (d, *J* = 7.3 Hz, 1H), 7.77 (s, 1H), 7.52–7.48 (m, 3H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.05–7.02 (m, 1H), 4.22–4.12 (m, 2H), 4.08–4.05 (m, 3H), 3.87–3.83 (m, 1H), 2H), 3.24 (s, 3H), 3.23–3.12 (m, 2H), 2.54 (s, 3H), 2.55–2.52 (m, 1H), 2.17–2.13 (m, 1H), 1.84–1.77 (m, 1H).

[002074] Example 367

[002075] **Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

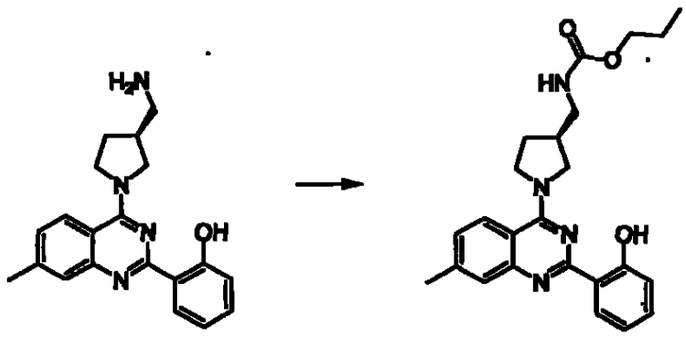
455 453

[002076]



[002077] Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002078]



[002079] Method A

[002080] Propyl chloroformate (12 mg, 0.10 mmol) and triethylamine (30 mg, 42 μL, 0.30 mmol) were added to 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (33 mg, 0.10 mmol) in 1 mL anhydrous DMF. The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.43 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

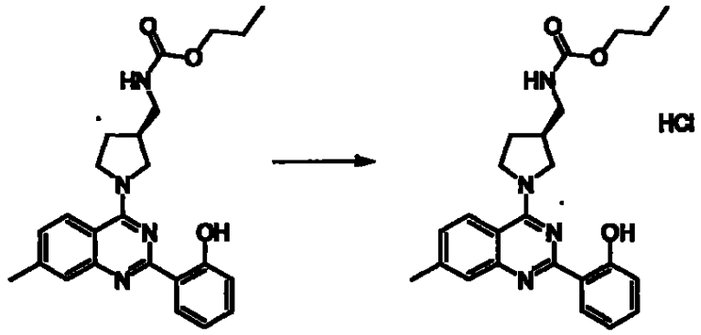
[002081] Method B

[002082] A solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (301 mg, 0.9 mmol) in CH_2Cl_2 (10 ml) was stirred under an N_2 atmosphere. Triethylamine (0.25 mL, 1.8 mmol) was added, and the solution was cooled to –30 °C. A 1 M

propyl chloroformate solution (0.1 mL in 0.9 mL CH_2Cl_2, 0.9 mmol) was added, and the reaction mixture was allowed to warm to room temperature over a period of 30 minutes. After adding CH_2Cl_2 to the reaction mixture, it was washed 2 times with water, before it was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–20% EtOAc in CH_2Cl_2 gave propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (236 mg, 62%). LC/MS: *m/z* 421 $(M+H)^+$ at 2.54 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.43 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.21 (d, *J* = 8.7 Hz, 1H), 7.58 (s, 1H), 7.39–7.31 (m, 3H), 6.93–6.89 (m, 2H), 4.09–3.86 (m, 6H), 3.78–3.73 (m, 1H), 3.21–3.09 (m, 2H), 2.49 (s, 3H), 2.15–2.09 (m, 1H), 1.83–1.74 (m, 1H), 1.62–1.48 (m, 2H), 0.89–0.86 (m, 3H).

[002083] Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride

[002084]



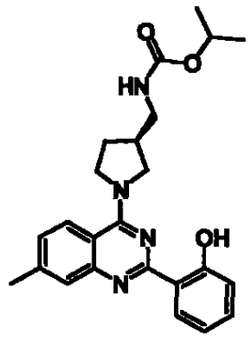
[002085] A solution of propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (232 mg, 0.552 mmol) in CH_2Cl_2 (2 mL) was stirred under an N_2 atmosphere. A 2.0 M HCl solution in ether (0.276 mL, 0.552 mmol) was added dropwise to this solution. After 10 minutes, ether (8 mL) was added until a precipitate formed, which was filtered and dried to obtain propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (223 mg, 88%). LC/MS: *m/z* 421 $(M+H)^+$ at 2.54 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.24 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.82 (s, 1H), 7.54–7.49 (m, 2H), 7.41–7.37 (m, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.06–7.02 (m, 1H), 4.29–3.78 (m, 7H), 3.24–3.08

(m, 2H), 2.54 (s, 3H), 2.18–2.12 (m, 1H), 1.84–1.79 (m, 1H), 1.59–1.50 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H).

[002086] Example 368

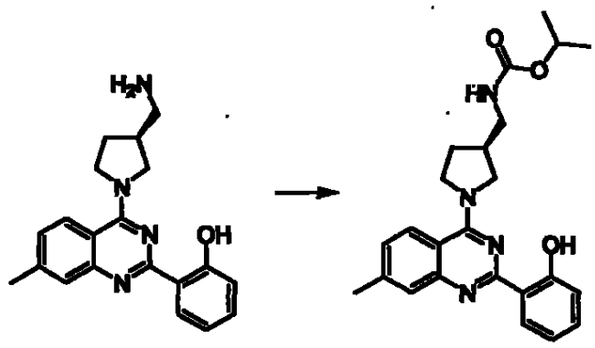
[002087] Isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002088]



[002089] Isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002090]



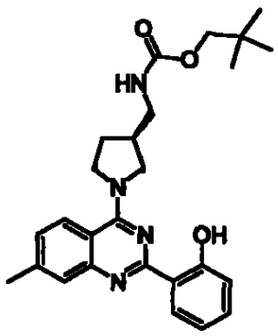
[002091] Isopropyl chloroformate (12 mg, 0.10 mmol) and triethylamine (30 mg, 42 µL, 0.30 mmol) were added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (33 mg, 0.10 mmol) in 1 mL anhydrous DMF. The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give isopropyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-

methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 421.1 $(M+H)^+$ at 2.42 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002092] Example 369

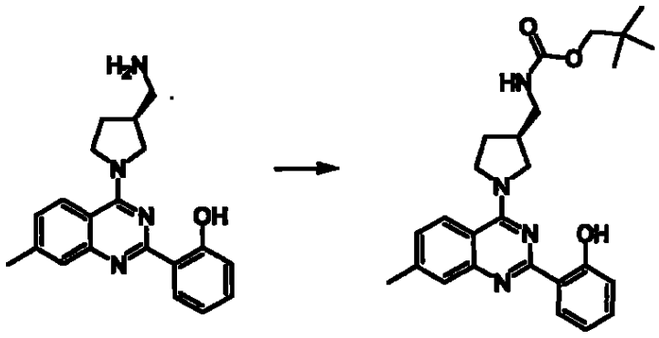
[002093] Neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002094]



[002095] Neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002096]



[002097] Method A

[002098] Neopentyl chloroformate (15 mg, 0.10 mmol) and triethylamine (30 mg, 42 μL, 0.30 mmol) were added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (33 mg, 0.10 mmol) in 1 mL anhydrous DMF. The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-

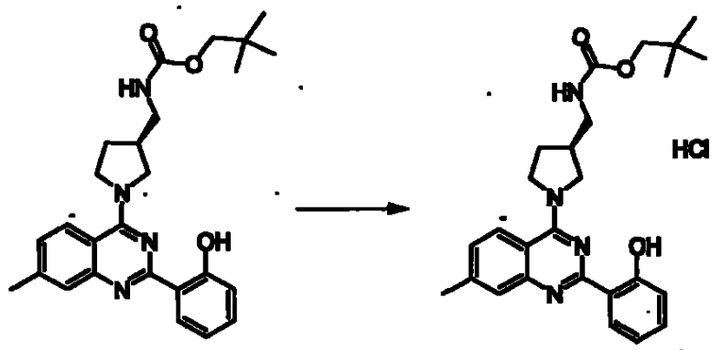
methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.3 $(M+H)^+$ at 2.67 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002099] Method B

[002100] A mixture of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (200 mg, 0.6 mmol), THF (6.0 mL), and DMF (1 mL) was stirred under an N_2 atmosphere. Triethylamine (0.166 mL, 1.2 mmol) was added, and the reaction was cooled in an ice bath. To this was added 1 M neopentyl chloroformate solution (89 μL in 600 μL THF, 0.6 mmol). After allowing the reaction mixture to warm to room temperature over a period of 30 minutes, CH_2Cl_2 was added to the reaction mixture, and it was washed once with water before it was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–20% EtOAc in CH_2Cl_2/hexanes (1:1) gave neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (222 mg, 94%). LC/MS: *m/z* 449 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, acetic acid-d4) δ 8.42 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.20 (d, *J* = 8.7 Hz, 1H), 7.57 (s, 1H), 7.40–7.29 (m, 3H), 6.92–6.89 (m, 2H), 4.11–3.92 (m, 3H), 3.78–3.61 (m, 3H), 3.33–3.28 (m, 1H), 3.23–3.10 (m, 2H), 2.49 (s, 3H), 2.16–2.08 (m, 1H), 1.83–1.75 (m, 1H), 0.89 (s, 9H).

[002101] **Neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride**

[002102]



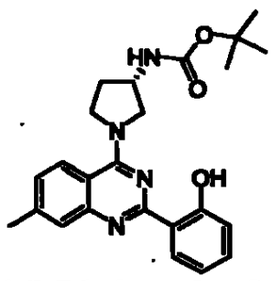
[002103] A solution of neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (215 mg, 0.48 mmol) in CH_2Cl_2 (2 ml) was stirred under an N_2 atmosphere. A 1.0 M HCl solution in ether (0.48 ml, 0.48 mmol) was added dropwise to this solution. After 10 minutes, ether (8 ml) was added until a precipitate formed, which was filtered

and dried to obtain neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (214 mg, 92%). LC/MS: *m/z* 449 $(M+H)^+$ at 2.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.31 (d, *J* = 8.7 Hz, 1H)1H), 7.85 (s, 1H), 7.54–7.49 (m, 2H), 7.47–7.45 (m, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.05–7.02 (m, 1H), 4.33–3.74 (m, 5H), 3.70–3.64 (m, 2H), 3.19–3.16 (m, 2H), 2.53 (s, 3H), 2.18–2.13 (m, 1H), 1.87–1.81 (m, 1H), 0.88 (s, 9H).

[002104] Example 370

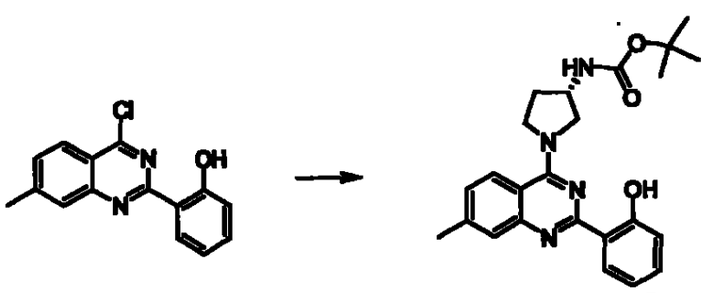
[002105] *tert*-Butyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[002106]



[002107] *tert*-Butyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate

[002108]



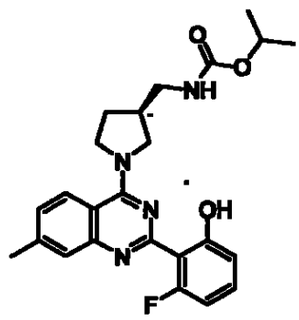
[002109] *tert*-Butyl (*S*)-pyrrolidin-3-ylcarbamate (245 mg, 1.31 mmol) was dissolved in 1.8 mL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (300 mg, 1.1 mmol) dissolved in 1.8 mL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (134 mg, 184 μL, 1.32 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. Purification via silica gel chromatography using

10–100% ethyl acetate/hexanes gave *tert*-butyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate. LC/MS: *m/z* 421.0 $(M+H)^+$ at 2.84 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002110] Example 371

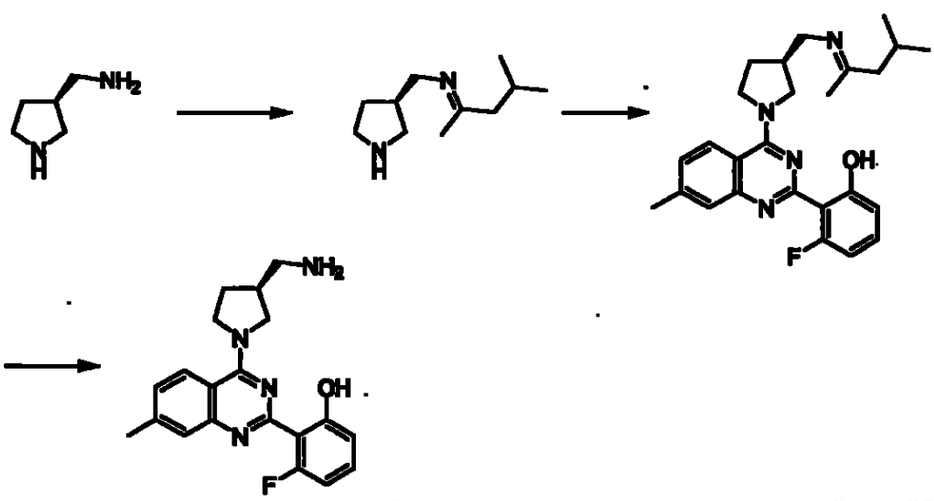
[002111] Isopropyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002112]



[002113] 2-(4-((*S*)-3-(Aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol

[002114]

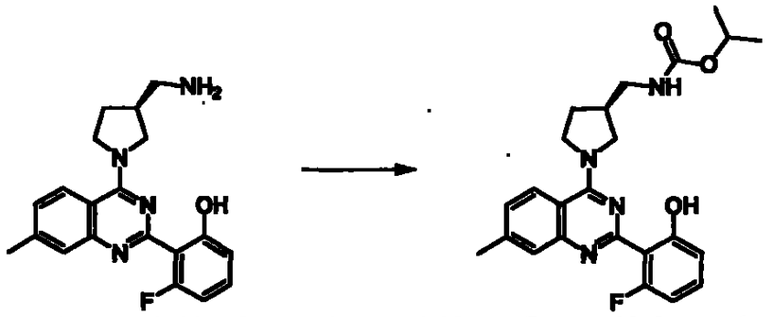


[002115] A mixture of ((*S*)-pyrrolidin-3-yl)methanamine (0.6 g, 6.0 mmol), Na_2CO_3 (2.2 g, 21 mmol) and methyl isobutyl ketone (12 mL, 6.0 mmol) under an N_2 atmosphere was refluxed overnight using a Dean Stark apparatus. After allowing the reaction to cool to room temperature,

2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (1.73 g, 5.99 mmol) was added, and the mixture was stirred overnight at room temperature under an N_2 atmosphere. The reaction was then quenched with water. The aqueous layer was extracted twice with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to obtain a crude material containing 2-(4-((*S*)-3-((*E*)-(4-methylpentan-2-ylideneamino)methyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol which was then hydrolyzed by heating at 50 °C in 80 mL of a water/isopropanol mixture (1:1) for 6 hours. The reaction was cooled to room temperature, and the aqueous layer was extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 5–20% MeOH and CH_2Cl_2 afforded 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (400 mg, 19% after 3 steps). LC/MS: *m/z* 353.1 $(M+H)^+$ at 1.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002116] Isopropyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002117]

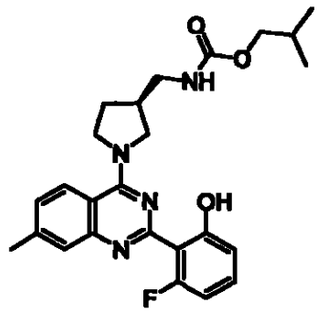


[002118] Isopropyl chloroformate (10 mg, 0.09 mmol) was added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) and triethylamine (25 mL, 0.18 mmol) in DMF (0.6 mL) at –78 °C (external temperature). The reaction mixture was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford isopropyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002119] Example 372

[002120] Isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002121]



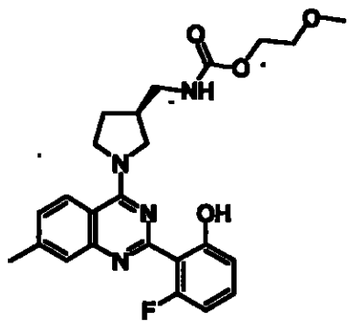
[002122] Isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002123] Isobutyl chloroformate (12 mg, 0.09 mmol) was added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) and triethylamine (25 mL, 0.18 mmol) in DMF (0.6 mL) at –70 °C (external temperature). The reaction mixture was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford isobutyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 453.5 $(M+H)^+$ at 2.46 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002124] Example 373

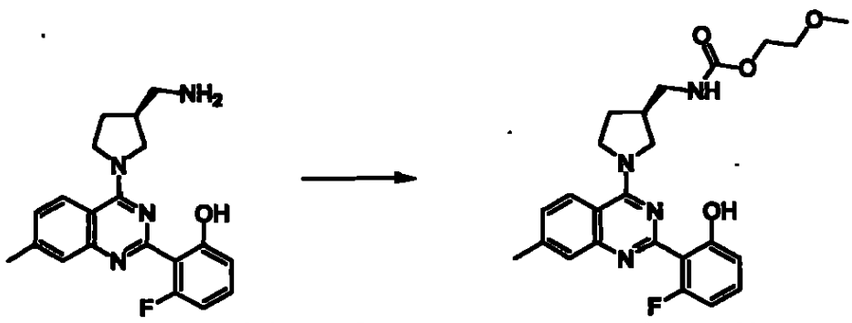
[002125] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002126]



[002127] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002128]

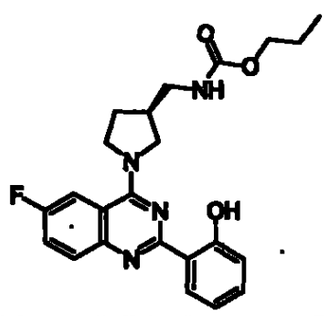


[002129] 2-Methoxyethyl chloroformate (12 mg, 0.09 mmol) was added to a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (0.03 g, 0.09 mmol) and triethylamine (25 mL, 0.18 mmol) in DMF (0.6 mL) at –78 °C. The reaction mixture was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. *LC/MS*: *m/z* 455.5 $(M+H)^+$ at 2.11 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002130] Example 374

[002131] Propyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

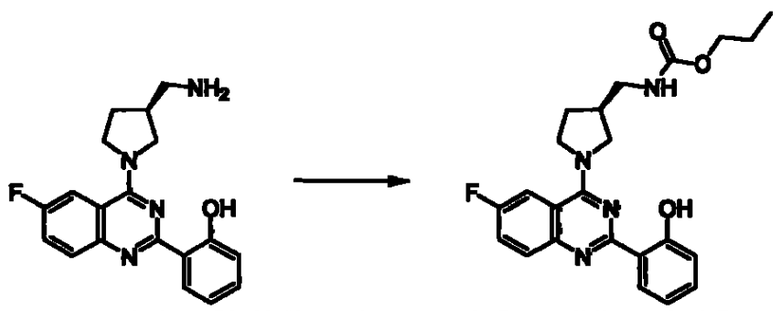
[002132]



[002133] Propyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

460 488

[002134]

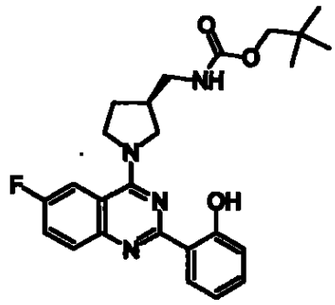


[002135] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol), followed by the addition of propyl chloroformate (11 mg, 0.09 mmol). The reaction was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford propyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 425.3 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002136] Example 375

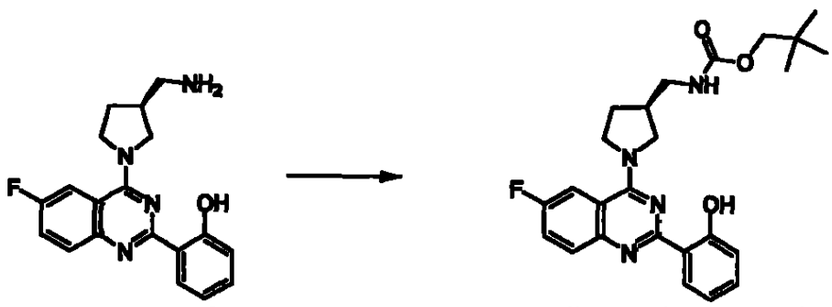
[002137] Neopentyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002138]



[002139] Neopentyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002140]

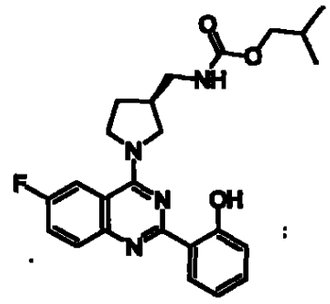


[002141] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol), followed by the addition of neopentyl chloroformate (13 mg, 0.09 mmol). The reaction was warmed to room temperature, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford neopentyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 453.5 $(M+H)^+$ at 2.88 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002142] Example 376

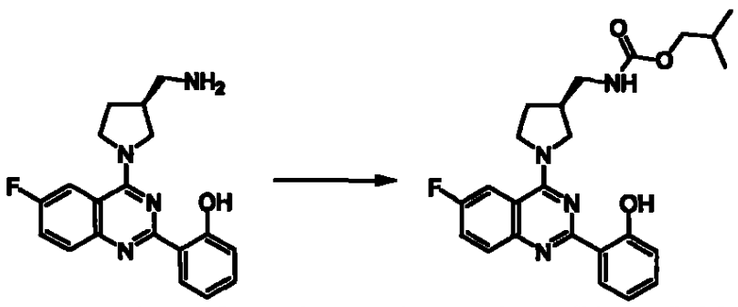
[002143] Isobutyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002144]



[002145] Isobutyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002146]

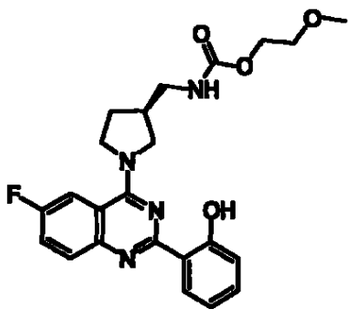


[002147] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol), followed by the addition of isobutyl chloroformate (12 mg, 0.09 mmol). The reaction was warmed to room temperature, and filtered and purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.76 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002148] Example 377

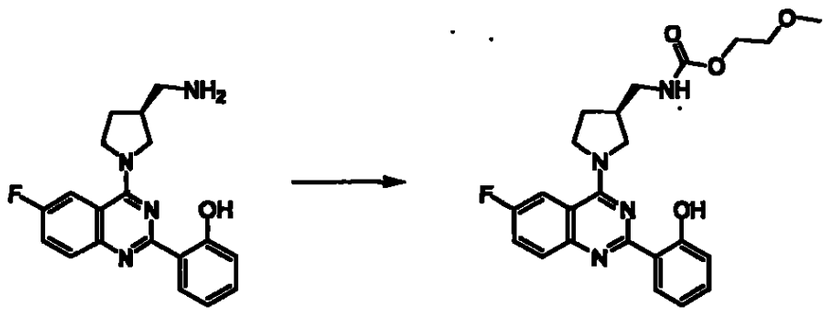
[002149] 2-Methoxyethyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002150]



[002151] 2-Methoxyethyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate

[002152]

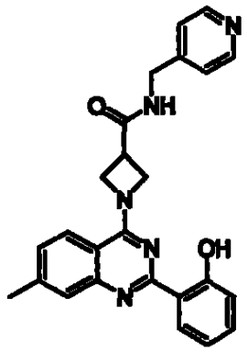


[002153] To a solution of 2-(4-((*S*)-3-(aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol (0.03 g, 0.09 mmol) in DMF (1.0 mL) at –60 °C (external temperature) was added triethylamine (25 mL, 0.18 mmol), followed by the addition of 2-methoxyethyl chloroformate (12 mg, 0.09 mmol). The reaction was warmed to room temperature, and filtered and purification via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ((*S*)-1-(6-fluoro-2- (2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 441.5 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002154] Example 401

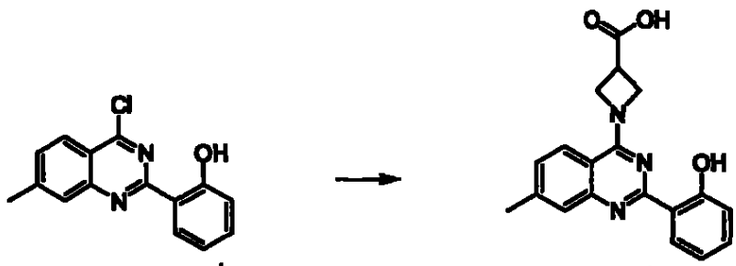
[002155] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-4-yl)methyl)azetidine-3-carboxamide

[002156]



[002157] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid

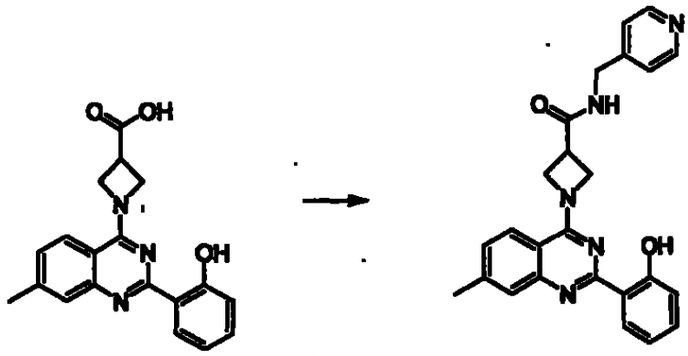
[002158]



[002159] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (2.84 g, 10.5 mmol) and azetidine-3-carboxylic acid (1.06 g, 10.5 mmol) in DMF (100 mL) was added triethylamine (3.18 g, 4.39 mL, 31.5 mmol). The reaction was stirred at room temperature overnight then diluted with H_2O (400 mL). The pH of the solution was adjusted to 3–4 by addition of an aqueous 1 M HCl solution. The white precipitate then obtained was filtered, washed with H_2O, and purified by silica gel chromatography using 0–15% MeOH–CH_2Cl_2 giving 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid. *LC/MS*: *m/z* 336.3 $(M+H)^+$ at 1.97 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002160] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-4-yl)methyl)azetidine-3-carboxamide

[002161]



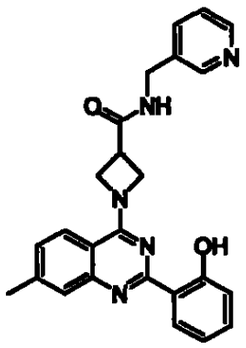
[002162] To a solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid (34 mg, 0.1 mmol) and HATU (57 mg, 0.15 mmol) in DMF (1 mL) was added (pyridin-4-yl)methanamine (32 mg, 30μL, 0.30 mmol). The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) giving 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-

((pyridin-4-yl)methyl)azetidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 426.3 $(M+H)^+$ at 1.72 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002163] Example 402

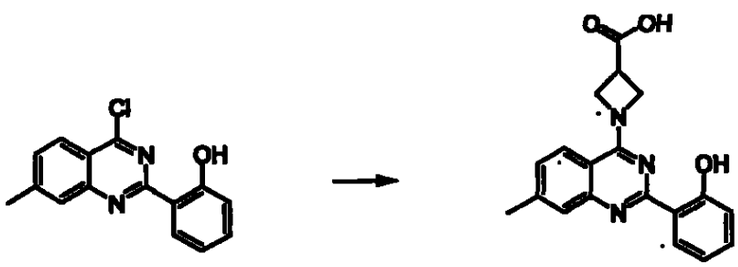
[002164] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)azetidine-3-carboxamide

[002165]



[002166] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid

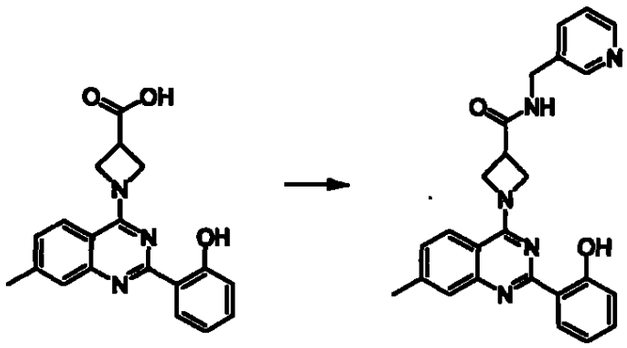
[002167]



[002168] To a solution of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (2.84 g, 10.5 mmol) and azetidine-3-carboxylic acid (1.06 g, 10.5 mmol) in DMF (100 mL) was added triethylamine (3.18 g, 4.39 mL, 31.5 mmol). The reaction was stirred at room temperature overnight then diluted with H_2O (400 mL). The pH of the solution was adjusted to 3–4 by addition of an aqueous 1 M HCl solution. The white precipitate then obtained was filtered, washed with H_2O, and purified by silica gel chromatography using 0–15% MeOH–CH_2Cl_2 giving 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid. LC/MS: *m/z* 336.3 $(M+H)^+$ at 1.97 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002169] 1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)azetidine-3-carboxamide

[002170]

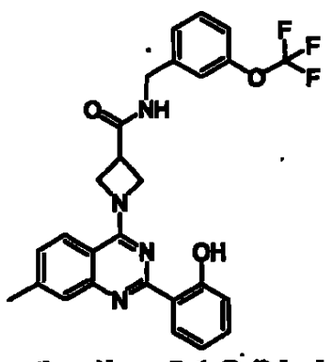


[002171] To a solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid (34 mg, 0.1 mmol) and HATU (57 mg, 0.15 mmol) in DMF (1 mL) was added (pyridin-3-yl)methanamine (32 mg, 30μL, 0.30 mmol). The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-*N*-((pyridin-3-yl)methyl)azetidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 426.3 $(M+H)^+$ at 1.72 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002172] Example 403

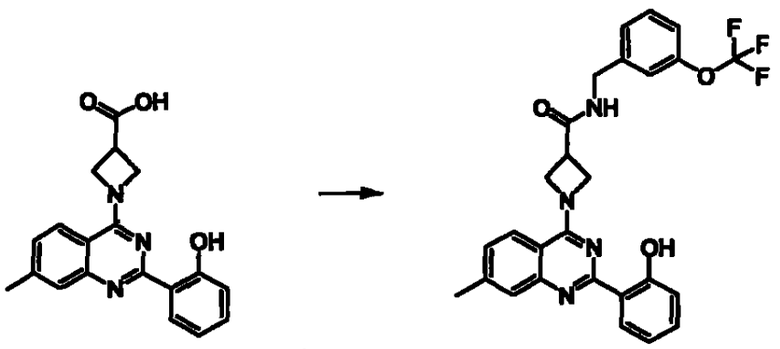
[002173] *N*-(3-(Trifluoromethoxy)benzyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxamide

[002174]



[002175] *N*-(3-(Trifluoromethoxy)benzyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxamide

[002176]

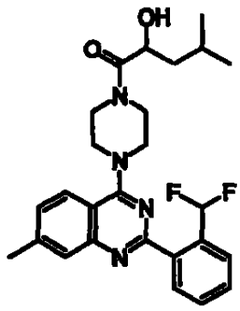


[002177] To a solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid (34 mg, 0.10 mmol) and HATU (57 mg, 0.15 mmol) in DMF (1 mL) was added (3-(trifluoromethoxy)phenyl)methanamine (57 μL, 0.30 mmol). The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-(3-(trifluoromethoxy)benzyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 509.3 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

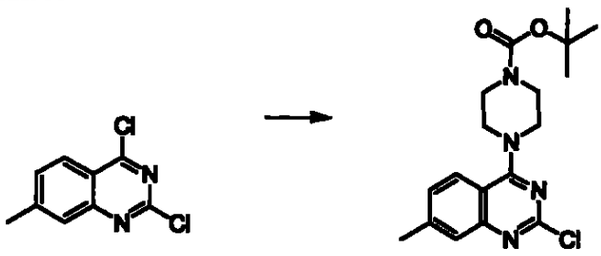
[002178] Example 501

[002179] 1-(4-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[002180]



[002181] *tert*-Butyl 4-(2-chloro-7-methylquinazolin-4-yl)piperazine-1-carboxylate

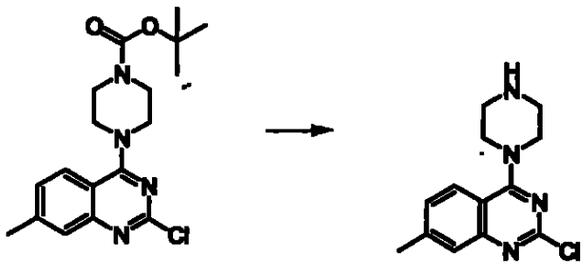


[002182]

[002183] A solution of 2,4-dichloro-7-methylquinazoline (0.43 g, 2.0 mmol), *tert*-butyl piperazine-1-carboxylate (0.37 g, 2.0 mmol), and triethylamine (0.56 mL, 4.0 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature overnight. The solution was washed with water, dried over Na_2SO_4, and evaporated to give *tert*-butyl 4-(2-chloro-7-methylquinazolin-4-yl)piperazine-1-carboxylate (0.72 g, 99%). LC/MS: *m/z* 363.1 $(M+H)^+$ at 3.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

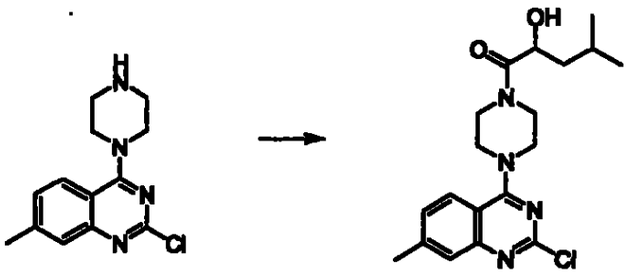
[002184] **2-chloro-7-methyl-4-(piperazin-1-yl)quinazoline dihydrochloride**

[002185]



[002186] *tert*-Butyl 4-(2-chloro-7-methylquinazolin-4-yl)piperazine-1-carboxylate (0.72 g, 2.0 mmol) in 4 M HCl in dioxane (10 mL) was stirred at room temperature for five hours. The solvent was evaporated to give 2-chloro-7-methyl-4-(piperazin-1-yl)quinazoline dihydrochloride (0.67 g, 100%). LC/MS: *m/z* 263.3 $(M+H)^+$ at 1.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002187] **1-(4-(2-Chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one**



[002188]

[002189] A solution of 2-chloro-7-methyl-4-(piperazin-1-yl)quinazoline dihydrochloride (127 mg, 0.38 mmol), 2-hydroxy-4-methylpentanoic acid (55 mg, 0.42 mmol), HATU (158 mg, 0.42 mmol), and triethylamine (163 μL, 1.2 mmol) in DMF (4 mL) was stirred at room temperature for four hours. The reaction was diluted with water and was extracted with EtOAc. The combined extracts were washed with saturated aqueous NaCl and water, dried over Na_2SO_4, and evaporated. Purification via silica gel chromatography using 0–50% EtOAc in hexanes gave 1-(4-(2-chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (23 mg, 16%). LC/MS: *m/z* 377.3 $(M+H)^+$ at 2.71 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

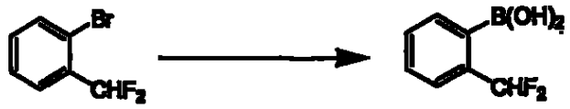
[002190] 1-Bromo-2-(difluoromethyl)benzene

[002191]

[002192] A mixture of 2-bromo benzaldehyde (27.1 g, 0.15 mol) and (diethylamino)sulfur trifluoride (52 g, 0.32 mol) in anhydrous benzene (250 mL) was heated to reflux overnight under an N_2 atmosphere. The mixture was treated with $NaHCO_3$ (sat. aq.) and CH_2Cl_2, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with water and saturated aq. NaCl. Removal of the solvent gave 1-bromo-2-difluoromethylbenzene (16 g, 52%). ^1H NMR($CDCl_3$): δ 7.68 (d, 1H, J = 7.6), 7.62 (d, 1 H, J = 7.6), 7.43 (t, 1 H, J = 7.6), 7.34 (t, 1 H, J = 7.6), 7.06–6.79 (t, 1 H, J = 55.2).

[002193] 2-(Difluoromethyl)phenylboronic acid

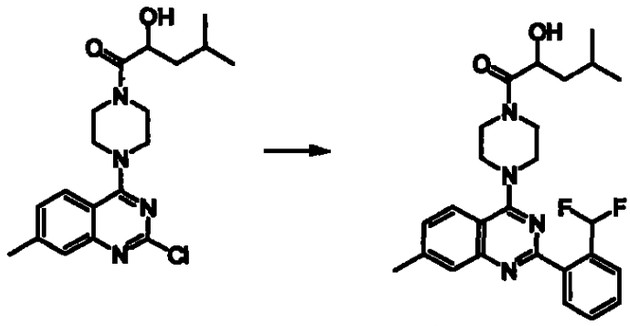
[002194]



[002195] To a solution of 1-bromo-2-difluoromethylbenzene (16 g, 0.077 mol) in THF (300 mL) was added *n*-BuLi (2.5 M, 46 mL, 0.12 mol) dropwise at –78 °C. After one hour, trimethyl borate (16 g, 0.15 mol) was added dropwise. The mixture was warmed to room temperature slowly overnight, and then the mixture was treated with water and ethyl acetate. The organic layer was extracted with a 10% aqueous NaOH solution. The aqueous solution was acidified with dilute aq. HCl and extracted with ethyl acetate. Removal of the solvent gave 2-(difluoromethyl)phenylboronic (0.7 g, 5.3%). ^{1}H NMR($CDCl_3$): δ 8.28 (d, 1 H, *J* = 7.2), 7.86 (d, 1H, *J* = 7.2), 7.58–7.79 (m, 1 H), 7.73 (t, 1 H, *J* = 7.2), 7.65 (t, 1 H).

[002196] 1-(4-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[002197]

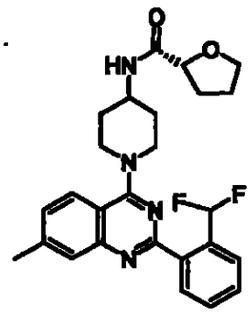


[002198] A mixture of 1-(4-(2-chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (23 mg, 61 μmol), 2-(difluoromethyl)phenylboronic acid (13 mg, 73 μmol), $Pd(dppf)Cl_2$ (3 mg, 3.7 μmol), and K_2CO_3 (17 mg, 122 μmol) in DMF (1 mL) and H_2O (0.5 mL) was heated in a sealed microwave vial at 170 °C for 6 minutes. After filtration and evaporation of the solvents, the mixture was purified using preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 1-(4-(2-(2-(difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 469.3 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002199] Example 502

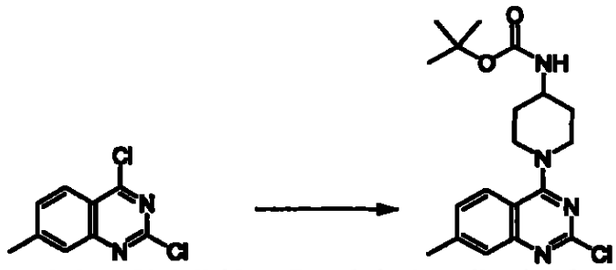
[002200] (2*R*)-*N*-(1-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

[002201]



[002202] *tert*-Butyl 1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate

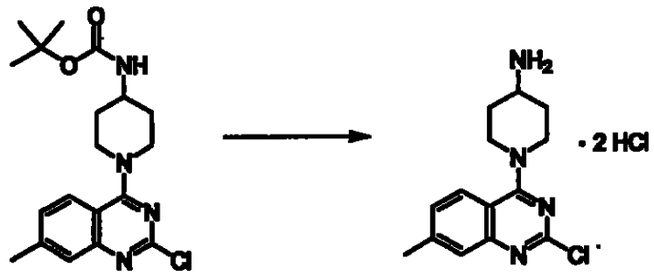
[002203]



[002204] To a solution of 2,4-dichloro-7-methylquinazoline (1.06 g, 5.0 mmol) in CH_2Cl_2 (20 mL) cooled in an ice bath under an N_2 atmosphere was added *tert*-butyl piperidin-4-ylcarbamate (1.0 g, 5.0 mmol) dissolved in CH_2Cl_2 (30 mL). To this was added triethylamine (1.4 mL, 10.0 mmol), and the reaction was allowed to warm to room temperature. After stirring for 1 h, the solution was washed with water and dried over Na_2SO_4. The solvents were evaporated to obtain *tert*-butyl 1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate as a yellow solid (1.6 g, 85%). LC/MS: *m/z* 377.5 $(M+H)^+$ at 2.96 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002205] 1-(2-Chloro-7-methylquinazolin-4-yl)piperidin-4-amine dihydrochloride

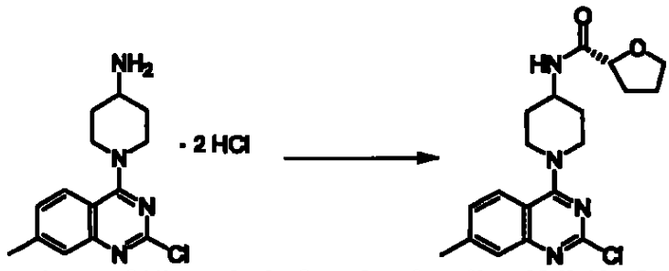
[002206]



[002207] Under an N_2 atmosphere, a 4 M HCl solution in dioxane (50 mL) was added to *tert*-butyl 1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-ylcarbamate (1.06 g, 2.82 mmol), and the mixture was stirred for 3 h. After evaporating the solvents, the resulting solid was taken up in CH_2Cl_2 and EtOAc and concentrated to yield 1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-amine dihydrochloride as a pale pink powder (985 mg, 100%). LC/MS: *m/z* 277.3 $(M+H)^+$ at 1.57 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002208] (*R*)-*N*-(1-(2-Chloro-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

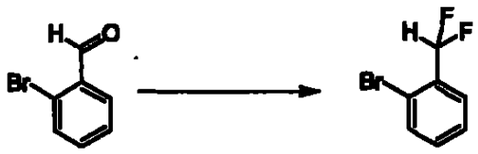
[002209]



[002210] To a mixture of (*R*)-tetrahydrofuran-2-carboxylic acid (0.13 mL, 1.58 mmol) in CH_2Cl_2 (2 mL) was added HATU (0.5 g, 1.58 mmol). After adding triethylamine (0.74 mL, 5.28 mmol), the solution was stirred for 30 min. 1-(2-Chloro-7-methylquinazolin-4-yl)piperidin-4-amine dihydrochloride (460 mg, 1.32 mmol) was added and the reaction was stirred overnight. The yellow, cloudy solution was washed 4 times with H_2O, and the aqueous layer was re-extracted with CH_2Cl_2. After concentrating the combined organic phases, purification via silica gel chromatography using 0–100% EtOAc in hexanes provided (*R*)-*N*-(1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide (0.17 g, 33%). LC/MS: *m/z* 475.3 $(M+H)^+$ at 2.20 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002211] 1-Bromo-2-difluoromethyl-benzene

[002212]

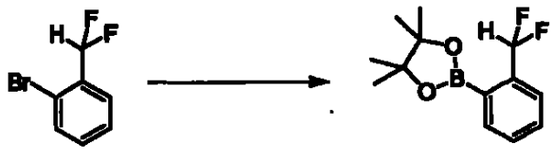


[002213] A solution of 2-bromobenzaldehyde (55.5 g, 300 mmol) and (diethylamino)sulfur trifluoride (75.0 g, 467 mmol) in 250 ml dichloromethane was refluxed under a nitrogen

atmosphere overnight. The cooled solution was poured into 0.5 L aqueous 15% $NaHCO_3$ and stirred until no more CO_2 was produced. The layers were separated, and the aqueous layer was extracted with 250 ml dichloromethane. The combined organic layers were washed with 250 ml 5% aq. $NaHCO_3$ and saturated aq. NaCl, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The crude material was purified by vacuum distillation, and the fraction boiling at 62–63 °C at 12 mbar was collected, yielding 1-bromo-2-difluoromethyl-benzene (42.6 g, 69%) as a light-yellow oil.

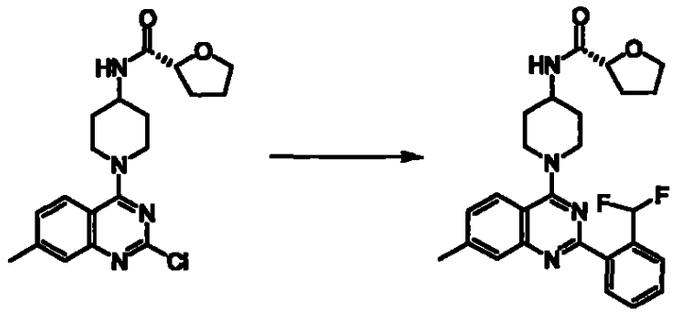
[002214] 2-(2-Difluoromethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

[002215]



[002216] To a solution of 1-bromo-2-difluoromethyl-benzene (19.8 g, 95.7 mmol) in dry THF (200 ml) at –78 °C under a nitrogen atmosphere was added 2.5 M *n*-BuLi in hexanes (42 ml, 105 mmol) slowly. After completion of the addition, the resulting dark solution was stirred for an additional hour at –78 °C. Subsequently, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25 ml, 123 mmol) was added, and the solution was slowly warmed to room temperature. After stirring overnight at room temperature under a nitrogen atmosphere the solution was poured into 400 ml water. Ethyl acetate (300 ml) was added and the layers were separated. The aqueous layer was extracted twice with ethyl acetate (150 ml and 50 ml respectively), and the combined organic layers were washed with water, dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The resulting brown oil (21 g) was purified by bulb-to-bulb-distillation at $3x10^{-3}$ mbar at 90–95 °C to yield 2-(2-difluoromethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (14.4 g, 59%) as a slightly yellow oil.

[002217] (2*R*)-*N*-(1-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

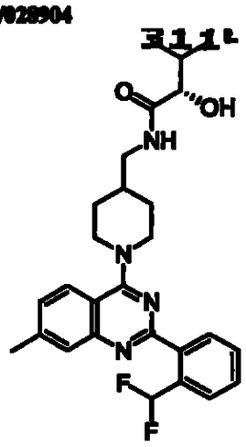


[002218]

[002219] To a mixture of (*R*)-*N*-(1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide (65.2 mg, 0.17 mmol), 2-(2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.09 mL, 0.35 mmol), $Pd(dppf)Cl_2$ (17.1 mg, 0.02 mmol), and K_2CO_3 (48.1 mg, 0.35 mmol) was added DMF (3.3 mL), and the reaction was heated in a microwave synthesizer at 170 °C for 6 min. Since LC/MS showed that reaction was not complete, another 2 equivalents of 2-(2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.09 mL, 0.38 mmol) were added, and the reaction was heated to 170 °C in a microwave synthesizer for 6 minutes The solution was diluted with EtOAc and washed with H_2O. The aqueous fraction was re-extracted with EtOAc and the organic layers were combined, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in CH_2Cl_2/hexanes (1:1) gave (2*R*)-*N*-(1-(2-(2-(difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide (38 mg, 47%). LC/MS: *m/z* 467.3 $(M+H)^+$ at 2.20 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002220] Example 503

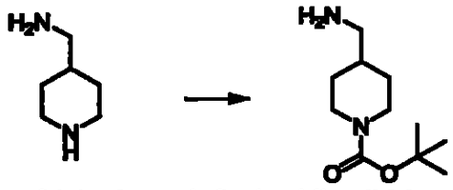
[002221] (2*S*)-*N*-((1-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide



[002222]

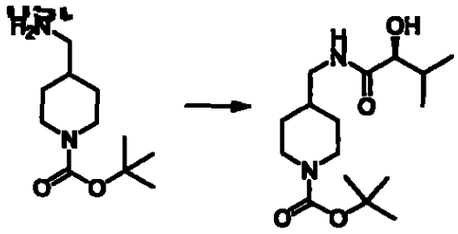
[002223] *tert*-Butyl 4-(aminomethyl)piperidine-1-carboxylate

[002224]



[002225] A solution of 4-(aminomethyl)-piperidine (25.3 g, 222 mmol) and benzaldehyde (23.5 g, 222 mmol) in 250 mL toluene was refluxed overnight under a nitrogen atmosphere in a flask equipped with a Dean-Stark trap. The solution was cooled to 0–5 °C in an ice bath, and Boc_2O (53.2 g, 244 mmol) was added in one portion. The ice bath was removed, and stirring at room temperature was continued for 6 hours. The mixture was evaporated to dryness under reduced pressure, and the residue was stirred overnight with potassium bisulphate in water (33.2 g $KHSO_4$ in 244 mL water). The solution was extracted twice with 200 ml portions of diethyl ether and was made alkaline with 50 ml 30% aqueous sodium hydroxide solution. After saturation of the solution with sodium chloride, it was extracted with dichloromethane (1x 150 ml, 2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness, yielding *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (41.8 g, 88%) as an orange oil.

[002226] 4-[((*S*)-2-Hydroxy-3-methyl-butyrylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester

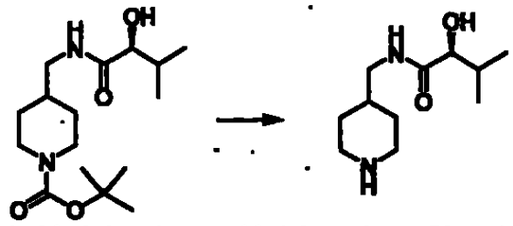


[002227]

[002228] HOBt (23.5 g, 174 mmol) and EDCI·HCl (33.5 g, 174 mmol) were added to a mixture of *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (37.3 g, 174 mmol), (*S*)-(+)-2-hydroxy-3-methyl-butanoic acid (20.6 g, 174 mmol), and triethylamine (50 mL, 349 mmol) in a mixture of dichloromethane (500 mL) and DMF (250 mL) cooled in an ice bath. The reaction was stirred overnight at room temperature. An additional portion of EDCI·HCl (5 g) and triethylamine (4 mL) were added, and stirring was continued for another 4 hours. The mixture was diluted to 1 L by the addition of dichloromethane and was washed with 500 mL portions of water, 1 N HCl solution, 5% aq. $NaHCO_3$ solution, water, and saturated aqueous NaCl solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure yielding 52 g of the crude product. This crude material was stirred with 200 mL diisopropyl ether, and the solid was collected by filtration and washed twice with 100 mL portions of diisopropyl ether to yield to 33 g (64%) of 4-[((*S*)-2-hydroxy-3-methyl-butyrylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester.

[002229] (*S*)-2-Hydroxy-3-methyl-*N*-piperidin-4-ylmethyl-butyramide

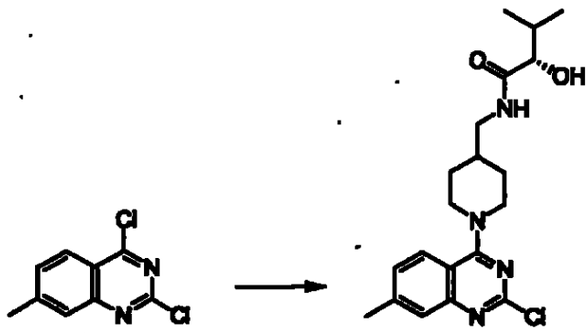
[002230]



[002231] Acetyl chloride (30 mL) was added dropwise to 500 mL methanol cooled in an ice bath, and after completion of the addition the solution was stirred at room temperature for 30 minutes. 4-[((*S*)-2-hydroxy-3-methyl-butyrylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester (33 g) in 150 mL methanol was added, and stirring was continued for 2 hours at room temperature. The solution was evaporated to dryness to yield to 26.6 g of (*S*)-2-hydroxy-3-methyl-*N*-piperidin-4-ylmethyl-butyramide hydrochloride as a white solid.

[002232] (*S*)-*N*-((1-(2-Chloro-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide

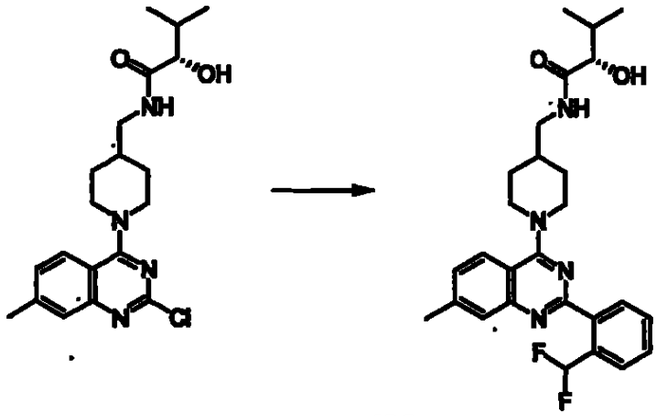
[002233]



[002234] A solution of 2,4-dichloro-7-methylquinazoline (1.07 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was cooled in an ice bath. (*S*)-2-Hydroxy-3-methyl-N-((piperidin-4-yl)methyl)butanamide hydrochloride (1.25 g, 5.0 mmol) suspended in 30 mL of CH_2Cl_2 was added in portions, followed by the addition of triethylamine (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and was stirred for 1.5 h. After washing the mixture 4 times with H_2O, the aqueous portion was re-extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and dried under vacuum to obtain (*S*)-*N*-((1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide as a yellow solid (1.83 g, 94%). LC/MS: *m/z* 391.3 $(M+H)^+$ at 2.32 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002235] (2*S*)-*N*-((1-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide

[002236]



[002237] To a solution of (*S*)-*N*-((1-(2-chloro-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide (200 mg, 0.51 mmol), 2-(2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (195 μL, 0.77 mmol), and K_2CO_3 (142 mg, 1.02 mmol) in a DMF:H_2O mixture (4:1) was added Pd(dppf)Cl_2 (25.3 mg, 0.03 mmol). The reaction mixture was heated in a microwave synthesizer at 170 °C for 6 minutes The reaction was diluted with EtOAc and washed with 30 mL saturated aqueous NaCl solution. The organic portion was 3 times washed with H_2O, and the combined aqueous layers were re-extracted 3 times with EtOAc. All combined organic portions were then dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–70% EtOAc in CH_2Cl_2:hexanes (1:1) yielded 177 mg (71%) of (2*S*)-*N*-((1-(2-(2-(difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)methyl)-2-hydroxy-3-methylbutanamide which crystallized as a white solid after freezing it for 1 h. LC/MS: *m/z* 483.3 $(M+H)^+$ at 2.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002238] Table 3 below recites analytical data for exemplary compounds of the present invention.

Table 3

101	449.3	2.79
102	421	2.48
103	499.3	2.97
104	464.5	2.03
105	447.1	2.32
106	465.5	2.47
107	442.5	1.97
108	407.5	2.21
109	393.1	2.04
110	461.1	2.56
111	453.5	3.21
112	461.3	2.49
113	421.1	2.76
114	474.3	1.19
115	421.3	2.51
116	442.5	1.96
117	439.5	2.79
118	393.3	2.22
119	465.2	2.5

120	435.3	2.65
121	393.3	2.21
122	435.3	2.56
123	465.3	2.5
124	407.5	2.29
125	453.4	2.79
126	471.2	2.93
127	445.5	3.32
128	451.5	2.82
129	407.5	2.31
130	469.3	2.87
131	469.4	2.88
132	466.5	2.04
133	454.3	1.94
134	421.1	2.46
135	467.1	2.59
136	453.3	3.02
137	407.3	2.28
138	453.3	2.43

139	439.5	2.95
140	485.5	2.94
141	459.3	2.13
142	448.3	3.17
143	439.5	2.99
144	436.3	2.9
145	437.3	2.04
146	455.5	2.45
147	453.3	2.4
148	439.5	2.8
149	485.5	2.23
150	449.3	2.22
151	435.5	2.13
152	468.5	2.02
153	453.4	2.73
154	436.3	1.94
155	477.5	2.96
156	474.3	1.19
157	485.4	3.02

Cmpd No.	LC-MS M+1	LC-RT min
158	403.5	2.34
159	421.3	2.6
160	467.3	3.13
162	467.3	2.33
163	453.3	2.25
164	451.3	2.18
165	421.3	2.4
166	434.53	2.61
167	491.3	2.46
168	435.3	2.91
169	577.4	2.5
170	473.1	2.63
171	517.5	3.49
172	465	2.77
173	393.1	2.03
174	407.5	2.41
175	480.5	2.33
176	435.5	2.62
177	447.1	2.53
178	447.3	2.5
179	427.2	2.59
180	435.2	2.66
181	435.3	2.69
182	435.3	2.5
183	435.3	2.5
184	449.3	2.5
185	449.3	2.56
201	464.5	1.87
203	449.3	2.34
204	449.3	2.33
205	433.3	2.33
206	433.5	2.34
207	449.5	2.34
208	449.5	2.33
209	447.5	2.27
210	463.5	2.34
211	463.5	2.34
212	417	2.3
213	453.5	1.96
214	463.5	2.32
215	463.5	2.36
216	463.5	2.35
217	463.5	2.35
218	447.5	2.02

Cmpd No.	LC-MS M+1	LC-RT min
219	477.4	2.84
220	447.5	2.19
221	461.5	2.22
222	531.3	3.08
223	468.3	1.86
224	437.1	2.54
225	488.6	2.19
226	417.5	2.3
227	470.5	1.98
228	470.5	1.98
229	513.3	2.82
230	447.3	2.21
231	481.1	2.17
232	463.3	2.58
233	421.2	2.17
234	449.2	2.42
235	407.5	2.04
236	407.3	2.08
237	407.5	2.09
238	435.3	2.4
239	461.1	2.4
240	435.5	2.29
241	421.1	2.24
242	421.3	2.18
243	421.3	2.18
244	421.3	2.18
245	449.3	2.45
246	475.1	2.46
247	435.3	2.31
248	435.3	2.24
249	481.3	2.42
250	449.5	2.77
251	421	2.48
252	449.3	2.8
253	449.5	2.78
254	421.1	2.5
255	435.5	2.61
256	435.5	2.61
257	451.1	2.34
258	441.5	2.6
259	435.2	3.03
260	467.1	2.66
261	469.1	2.2
262	439.3	2.31

Cmpd No.	LC-MS M+1	LC-RT min
264	435.1	2.6
265	449.3	2.72
266	449.2	2.55
267	449.3	2.58
268	449.1	2.54
269	449.5	2.57
270	435.2	2.88
271	447.2	2.46
272	449.2	2.57
273	449.2	2.57
274	463.4	2.42
275	463.4	2.43
276	433.2	2.33
277	433.2	2.32
278	449.2	2.85
279	435.4	2.61
301	435	2.41
302	419	2.35
303	419	2.34
304	435	2.39
305	449.3	2.18
306	449.3	2.16
307	449.3	2.18
308	433.5	2.11
309	455.2	2.81
310	433.5	2.13
311	403.7	2.17
312	389.2	2.38
313	441	2.78
314	463.4	2.66
315	432.5	2.24
316	433.5	2.05
317	447.3	2.07
318	454.3	1.79
319	458.5	1.85
320	456.5	1.84
321	499.3	2.57
322	454.4	2.08
323	445.4	2.85
324	460.4	2.1
325	509.5	2.71
326	455.3	2.43
327	450.3	2.39
328	428.3	1.91

Cmpd No.	LC-MS M+1	LC-RT min
329	393.3	2.23
330	485.4	2.68
331	477.3	2.81
332	511.5	3.07
333	443.5	2.63
334	511.5	3.1
335	439.5	2.25
336	493.5	3.03
337	439.5	2.25
338	451.5	2.15
339	467.3	2.5
340	445.4	2.95
341	443.4	2.73
342	468.4	2.39
343	493.4	2.76
344	443.3	2.69
345	453.3	2.05
346	407.5	2.2
347	430.5	1.95
348	430.5	2.43
349	430.5	1.98
350	444.5	1.85
351	444.5	2.24
352	444.5	1.89
353	426.1	1.93
354	426.1	2.33
355	453.3	2.29
356	453.3	2.29

Cmpd No.	LC-MS M+1	LC-RT min
357	407.3	2.26
358	477.3	2.6
359	491.3	2.24
360	473.1	2.32
361	449.3	2.4
362	469.1	2.58
363	469.1	2.58
364	407.7	2.3
365	435.3	2.57
366	437.3	2.18
367	421.1	2.44
368	421.1	2.43
369	449.3	2.67
370	421	2.84
371	439.5	2.31
372	453.5	2.46
373	455.5	2.11
374	425.3	2.31
375	453.5	2.88
376	439.5	2.76
377	441.5	2.3
401	426.3	1.72
402	426.3	1.72
403	509.3	2.73
404	393.2	1.95
405	421.2	2.29
406	421.2	2.2
407	435.4	2.23

Cmpd No.	LC-MS M+1	LC-RT min
408	435.4	2.16
409	421.2	2.15
410	421.1	2.4
411	435.2	2.24
412	405.2	2.09
413	435.4	2.16
414	435.2	2.17
415	449.2	2.25
416	435.3	2.25
417	419.4	2.06
418	421.2	2.57
419	423.2	2.15
420	407.2	2.42
501	467.3	2.14
502	469.3	2.44
503	483.3	2.24
504	455.4	2.91
505	367.9	2.79
506	339.9	2.38
507	469.3	2.97
508	441.3	2.54
509	455.5	2.13
510	469.5	2.37
511	471.3	2.28
512	467.3	2.14
513	483.3	2.25
514	483.3	2.24

[002239] Methods:

[002240] (A) Micromass MUX LCT 4 channel LC/MS, Waters 60F pump, Gilson 215 4 probe autosampler, Gilson 849 injection module, 1.5 mL/min/column flow rate, 10-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 columns (50 x 4.60 mm), Waters MUX UV-2488 UV detector, Cedex 75 ELSD detectors.

[002241] (B) PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 10-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.

[002242] (C) PESciex API-150-EX LC/MS, Shimadzu LC-8A pumps, Gilson 215 autosampler, Gilson 819 injection module, 3.0 mL/min flow rate, 40-99% CH_3CN (0.035 % TFA) / H_2O (0.05 % TFA) gradient, Phenomenex Luna 5u C18 column (50 x 4.60 mm), Shimadzu SPD-10A UV/Vis detector, Cedex 75 ELSD detector.

[002243] ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUNDS

[002244] A) Optical methods for assaying NaV inhibition properties of compounds:

[002245] Compounds of the invention are useful as antagonists of voltage-gated sodium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the NaV of interest were placed into microtiter plates. After an incubation period, the cells were stained with fluorescent dyes sensitive to the transmembrane potential. The test compounds were added to the microtiter plate. The cells were stimulated with either a chemical or electrical means to evoke a NaV dependent membrane potential change from unblocked channels, which was detected and measured with trans-membrane potential-sensitive dyes. Antagonists were detected as a decreased membrane potential response to the stimulus. The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR®) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today 4(9): 431-439).

[002246] B) VIPR® optical membrane potential assay method with chemical stimulation

[002247] Cell Handling and Dye Loading

[002248] 24 hours before the assay on VIPR, CHO cells endogenously expressing a NaV1.2 type voltage-gated NaV are seeded in 96-well poly-lysine coated plates at 60,000 cells per well. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

1) On the day of the assay, medium is aspirated and cells are washed twice with 225 µL of Bath Solution #2 (BS#2).
2) A 15 uM CC2-DMPE solution is prepared by mixing 5 mM coumarin stock solution with 10% Pluronic 127 1:1 and then dissolving the mix in the appropriate volume of BS#2.
3) After bath solution is removed from the 96-well plates, the cells are loaded with 80 µL of the CC2-DMPE solution. Plates are incubated in the dark for 30 minutes at room temperature.
4) While the cells are being stained with coumarin, a 15 µL oxonol solution in BS#2 is prepared. In addition to $DiSBAC_2(3)$, this solution should contain 0.75 mM ABSC1 and 30 µL veratridine (prepared from 10 mM EtOH stock, Sigma #V-5754).
5) After 30 minutes, CC2-DMPE is removed and the cells are washed twice with 225 µL of BS#2. As before, the residual volume should be 40 µL.
6) Upon removing the bath, the cells are loaded with 80 µL of the $DiSBAC_2(3)$ solution, after which test compound, dissolved in DMSO, is added to achieve the desired test concentration to each well from the drug addition plate and mixed thoroughly. The volume in the well should be roughly 121 µL. The cells are then incubated for 20-30 minutes.
7) Once the incubation is complete, the cells are ready to be assayed on VIPR® with a sodium addback protocol. 120 µL of Bath solution #1 is added to stimulate the NaV dependent depolarization. 200 µL tetracaine was used as an antagonist positive control for block of the NaV channel.

[002249] Analysis of VIPR® Data:

[002250] Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

$$(\text{intensity}_{460\,nm} - \text{background}_{460\,nm})$$

$R(t) = \frac{\text{(intensity}_{580\text{ nm}} - \text{background}_{580\text{ nm}})}{\text{(intensity}_{490\text{ nm}} - \text{background}_{490\text{ nm}})}$

[002251] The data is further reduced by calculating the initial (R_i) and final (R_f) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus $R = R_f/R_i$ is then calculated. For the Na^+ addback analysis time windows, baseline is 2-7 sec and final response is sampled at 15-24 sec.

[002252] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative (N) and positive (P) controls are calculated as above. The compound antagonist activity A is defined as:

$A = \frac{R-P}{N-P} * 100$. where R is the ratio response of the test compound

Solutions [mM]

Bath Solution #1: NaCl 160, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.4 with NaOH

Bath Solution #2 TMA-Cl 160, $CaCl_2$ 0.1, $MgCl_2$ 1, HEPES 10, pH 7.4 with KOH (final K concentration ~ 5 mM)

CC2-DMPE: prepared as a 5 mM stock solution in DMSO and stored at -20°C

$DiSBAC_2(3)$: prepared as a 12 mM stock in DMSO and stored at -20°C

ABSC1: prepared as a 200 mM stock in distilled H_2O and stored at room temperature

[002253] Cell Culture

[002254] CHO cells are grown in DMEM (Dulbecco's Modified Eagle Medium; GibcoBRL #10569-010) supplemented with 10% FBS (Fetal Bovine Serum, qualified; GibcoBRL #16140-071) and 1% Pen-Strep (Penicillin-Streptomycin; GibcoBRL #15140-122). Cells are grown in

vented cap flasks, in 90% humidity and 10% CO_2, to 100% confluence. They are usually split by trypsinization 1:10 or 1:20, depending on scheduling needs, and grown for 2-3 days before the next split.

[002255] C) VIPR® optical membrane potential assay method with electrical stimulation

[002256] The following is an example of how NaV1.3 inhibition activity is measured using the optical membrane potential method#2. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.-

[002257] HEK293 cells stably expressing NaV1.3 are plated into 96-well microtiter plates. After an appropriate incubation period, the cells are stained with the voltage sensitive dyes CC2-DMPE/DiSBAC2(3) as follows.

[002258] *Reagents:*

100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

10 mM $DiSBAC_2(3)$ (Aurora #00-100-010) in dry DMSO

10 mM CC2-DMPE (Aurora #00-100-008) in dry DMSO

200 mM ABSC1 in H_20

Hank's Balanced Salt Solution (Hyclone #SH30268.02) supplemented with 10 mM HEPES (Gibco #15630-080)

[002259] *Loading protocol:*

[002260] 2X CC2-DMPE = 20 μM CC2-DMPE: 10 mM CC2-DMPE is vortexed with an equivalent volume of 10% pluronic, followed by vortexing in required amount of HBSS containing 10 mM HEPES. Each cell plate will require 5 mL of 2X CC2-DMPE. 50 μL of 2X CC2-DMPE is to wells containing washed cells, resulting in a 10 μM final staining concentration. The cells are stained for 30 minutes in the dark at RT.

[002261] 2X $DISBAC_2(3)$ with ABSC1 = 6μM $DISBAC_2(3)$ and 1 mM ABSC1: The required amount of 10 mM $DISBAC_2(3)$ is added to a 50 ml conical tube and mixed with 1 μL 10% pluronic for each mL of solution to be made and vortexed together. Then HBSS/HEPES is added to make up 2X solution. Finally, the ABSC1 is added .

[002262] The 2X $DiSBAC_2(3)$ solution can be used to solvate compound plates. Note that compound plates are made at 2X drug concentration. Wash stained plate again, leaving residual

volume of 50 µL. Add 50 µl well of the 2X DiSBAC$_2$(3) w/ ABSC1. Stain for 30 minutes in the dark at RT.

[002263] The electrical stimulation instrument and methods of use are described in ION Channel Assay Methods PCT/US01/21652, herein incorporated by reference. The instrument comprises a microtiter plate handler, an optical system for exciting the coumarin dye while simultaneously recording the coumarin and oxonol emissions, a waveform generator, a current- or voltage-controlled amplifier, and a device for inserting electrodes in well. Under integrated computer control, this instrument passes user-programmed electrical stimulus protocols to cells within the wells of the microtiter plate.

[002264] Reagents

[002265] Assay buffer #1

140 mM NaCl, 4.5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 10 mM glucose, pH 7.40, 330 mOsm

Pluronic stock (1000X): 100 mg/mL pluronic 127 in dry DMSO
Oxonol stock (3333X): 10 mM DiSBAC$_2$(3) in dry DMSO
Coumarin stock (1000X): 10 mM CC2-DMPE in dry DMSO
ABSC1 stock (400X): 200 mM ABSC1 in water

[002266] Assay Protocol

1. Insert or use electrodes into each well to be assayed.
2. Use the current-controlled amplifier to deliver stimulation wave pulses for 3 s. Two seconds of pre-stimulus recording are performed to obtain the un-stimulated intensities. Five seconds of post-stimulation recording are performed to examine the relaxation to the resting state.

[002267] Data Analysis

[002268] Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which

there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

$$R(t) = \frac{(\text{intensity}_{460\,nm} - \text{background}_{460\,nm})}{(\text{intensity}_{580\,nm} - \text{background}_{580\,nm})}$$

[002269] The data is further reduced by calculating the initial (R_I) and final (R_F) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus $R = R_F/R_I$ is then calculated.

[002270] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative (N) and positive (P) controls are calculated as above. The compound antagonist activity A is defined as:

$A = \frac{R-P}{N-P} * 100$. where R is the ratio response of the test compound.

[002271] ELECTROPHYSIOLOGY ASSAYS FOR NaV ACTIVITY AND INHIBITION OF TEST COMPOUNDS

[002272] Patch clamp electrophysiology was used to assess the efficacy and selectivity of sodium channel blockers in dorsal root ganglion neurons. Rat neurons were isolated from the dorsal root ganglions and maintained in culture for 2 to 10 days in the presence of NGF (50 ng/ml) (culture media consisted of NeurobasalA supplemented with B27, glutamine and antibiotics). Small diameter neurons (nociceptors, 8-12 μm in diameter) have been visually identified and probed with fine tip glass electrodes connected to an amplifier (Axon Instruments). The "voltage clamp" mode has been used to assess the compound's IC50 holding the cells at – 60 mV. In addition, the "current clamp" mode has been employed to test the efficacy of the compounds in blocking action potential generation in response to current injections. The results of these experiments have contributed to the definition of the efficacy profile of the compounds.

[002273] VOLTAGE-CLAMP assay in DRG neurons

[002274] TTX-resistant sodium currents were recorded from DRG somata using the whole-cell variation of the patch clamp technique. Recordings were made at room temperature (~22° C) with thick walled borosilicate glass electrodes (WPI; resistance 3-4 MΩ) using an Axopatch 200B amplifier (Axon Instruments). After establishing the whole-cell configuration, approximately 15 minutes were allowed for the pipette solution to equilibrate within the cell before beginning recording. Currents were lowpass filtered between 2-5 kHz and digitally sampled at 10 kHz. Series resistance was compensated 60-70% and was monitored continuously throughout the experiment. The liquid junction potential (-7 mV) between the intracellular pipette solution and the external recording solution was not accounted for in the data analysis. Test solutions were applied to the cells with a gravity driven fast perfusion system (SF-77; Warner Instruments).

[002275] Dose-response relationships were determined in voltage clamp mode by repeatedly depolarizing the cell from the experiment specific holding potential to a test potential of +10mV once every 60 seconds. Blocking effects were allowed to plateau before proceeding to the next test concentration.

[002276] Solutions

[002277] Intracellular solution (in mM): Cs-F (130), NaCl (10), $MgCl_2$ (1), EGTA (1.5), $CaCl_2$ (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[002278] Extracellular solution (in mM): NaCl (138), $CaCl_2$ (1.26), KCl (5.33), KH_2PO_4 (0.44), $MgCl_2$ (0.5), $MgSO_4$ (0.41), $NaHCO_3$ (4), Na_2HPO_4 (0.3), glucose (5.6), HEPES (10), CdCl2 (0.4), NiCl2 (0.1), TTX (0.25×10^{-3}).

[002279] CURRENT-CLAMP assay for NaV channel inhibition activity of compounds

[002280] Cells were current-clamped in whole-cell configuration with a Multiplamp 700A amplifier (Axon Inst). Borosilicate pipettes (4-5 MOhm) were filled with (in mM):150 K-gluconate, 10 NaCl, 0.1 EGTA, 10 Hepes, 2 $MgCl_2$, (buffered to pH 7.34 with KOH). Cells were bathed in (in mM): 140 NaCl, 3 KCl, 1 MgCl , 1 CaCl , and 10 Hepes). Pipette potential was zeroed before seal formation; liquid junction potentials were not corrected during acquisition. Recordings were made at room temperature.

[002281] Following these procedures, representative compounds of the present invention were found to possess desired voltage gated sodium channel activity and selectivity.

[002282] ASSAYS FOR DETECTING AND MEASURING L-Type CaV 1.2 INHIBITION PROPERTIES OF COMPOUNDS

[002283] A) Optical methods for assaying CaV inhibition properties of compounds:

[002284] Compounds of the invention are useful as antagonists of voltage-gated calcium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the CaV of interest were placed into microtiter plates. After an incubation period, the cells were stained with fluorescent dyes sensitive to the transmembrane potential. The test compounds were added to the microtiter plate. The cells were stimulated with electrical means to evoke a CaV dependent membrane potential change from unblocked channels, which was detected and measured with trans-membrane potential-sensitive dyes. Antagonists were detected as a decreased membrane potential response to the stimulus. The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR®) (See, Gonzalez, J. E., K. Oades, et al. (1999) "Cell-based assays and instrumentation for screening ion-channel targets" Drug Discov Today 4(9): 431-439).

[002285] VIPR® optical membrane potential assay method with electrical stimulation

Positive Control (100% Block)

The positive control for this assay was 125uM mibefradil, achieved by adding 25uL of 250uM solution to the assay plates containing 25uL of assay buffer. Each assay plate included positive control wells.

Negative Control (No Block)

The negative (baseline) control for this assay was DMSO. This was achieved by adding 25uL of 1% DMSO (in assay buffer) to the assay plates containing 25uL of assay buffer. Each assay plate included negative control wells.

Background Subtraction

Fluorescence background from plastic in assay plates (or from the assay buffer) was assessed by running a cell-free plate through the HVIPR under the same optical configuration. The average background values for each row and each wavelength were subtracted in MOD3 prior to ratio change and activity calculations.

Reagents

Assay Buffers:

Bath Y (Prepared by Vertex Lab Support)

140mM TMA-Cl

4.5mM KCl

1mM $MgCl_2$

10mM HEPES, pH7.4

10mM glucose

Osmolarity = 295mOsm (280-310 acceptable range)

500mM $BaCl_2$ (Sigma #B0750), in H_2O

100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

10mM $DiSBAC_2(3)$ (Aurora #00-100-010) in dry DMSO

10mM CC2-DMPE (Aurora #00-100-008) in dry DMSO

200mM Acid Yellow 17 (Aurora #VABSC) in H_2O

Assay Volume

50uL

DMSO Conc in Assay

0.5% (1uL of 75% DMSO/25% water, dilution factor of 160)

Incubation Time of Compounds

20-25 minutes

Instrumentation

This screen was conducted on the Allegro™ system. The system is diagrammed below: The Allegro™ is equipped with a compound plate storage unit (stacker). The stacker holds a set of trays (each tray holds 12 compound plates). The libraries were received from Compound Management, as pre-spotted (1uL/well of compound and controls) intermediate plates in 384-well format, as a 1.6mM stock solution in 75% DMSO/25% de-ionized H_2O. The plates are diluted in 80uL oxonol dye solution to create a 2X stock. Three EVIPR readers are integrated to the Allegro system by a Mitsubishi robotic arm. Only one EVIPR was used per run.

Instrumentation Settings

Optical:

Read Frequency: 10Hz

Excitation Wavelength: 400nm

Emission Wavelengths: 460nm and 560nm

Electrical Stimulation:

Pulse Width: 11.1ms

Stimulation Current: 0.8 amps

Stimulation Frequency: 90Hz

Pre-stimulation time: 2 s

Stimulation time: 3 s

Post-stimulation time: 1 s

Waveform: Biphasic Square Wave

Plate Washer Settings:

Settings for ELx405 washer will leave a residual volume of 25uL.

Plate Type: 384

# of cycles: 3

Soak/shake: No

Dispense: dispense volume 100

	dispense flow rate	1
	dispense height	80
	horizontal disp pos	-20
	horiz y disp pos	-5
Aspirate:	aspirate height	48
	horizontal aspr pos	-18
	horiz y asp pos	-5
	aspiration rate	0
	aspiration delay	0
	final asp delay	500

Assay Procedure

Procedure run on HTS Allegro™:

1. **Carousel:** Assay plates (Cell plates) loaded into carousel module #1 (CO_2 = 5%, ambient temperature and Rh)
2. **Barrier:** Assay plates retrieved from carousel and passed through environmental barrier (The remaining steps are conducted at room temperature and ambient CO_2)
3. **Washer:** Assay plates washed with Bath Y on Biotek ELx405.
4. **MultiReagent Dispenser (MRD):** 25uL of CC2-DMPE (and equal volume Pluronic) in Bath Y added to each well to make 10uM.
5. **Barrier:** Assay plates passed through barrier.
6. **Carousel:** 30-minute incubation at room temperature.
7. **Barrier:** Assay plates passed through barrier.
8. **Washer:** Assay plates washed with Bath Y on Biotek ELx405
9. **High Density Transfer Station:**
    a. 80uL oxonol dye loading solution (4uM DiSBAC2(3), 1mM VABSC and 30mM $BaCl_2$ in BathY) added to compound plates (pre-spotted with 1uL compound) using a MultiDrop (offline)

b. Plates mixed (3 times 20uL) on CyBiWell (offline). Plates loaded onto compound tray.

c. Compound tray retrieved from compound tray stacker and compound plate barcodes read.

d. Assay plate barcode read and moved to SciClone deck

e. 25uL compound plus oxonol aspirated from compound plate on SciClone deck and transferred to assay plate.

i. Final assay volume = 50uL

ii. Final compound concentration = 10uM

f. SciClone tips washed in DMSO and 5% ethanol in water to remove external carry-over.

10. **Carousel:** Assay plates incubated for 20 minutes at RT

11. **Barrier:** Assay plates passed through final barrier

12. **Mitsubishi Robotic Arm:** Retrieves assay plate from barrier output, delivers cell plates to EVIPR 384-1, and sends command to initiate EVIPR run.

Assay Window

Assay window criteria:

Passing plates ≤0.5, rejected plates > 0.5

$$Assay\ Window = \frac{3(SD_{Platestack} + SD_{Baseline})}{(AVE_{Baseline} - AVE_{Platestack})} = 1 - Z'$$

Data Reduction

The EVIPR files were reduced to decrease the amount of data pumped into the database. Two "windows" of interest were filtered out of each EVIPR file. Each window is a slice of the response measured in each well. The first window is measured before stimulation. The second

PCT/US2005/031146
window samples the peak of the response. The ratio of the two is used to determine the response size.

Data Analysis

Once the data were collected on the VIPR, they were archived and uploaded, in reduced form, to Mod3. Once in Mod3, each individual assay plate was QC'ed (looking for acceptable window and dynamic range).

[002286] **HERG Assay**

[002287] hERG-inhibition was assayed in a Chinese Hamster Lung cell line (CHL) stably transduced with the structural gene for hERG. Cells express high numbers of hERG channels resulting in 500pA to 1.5nA of hERG outward K^+ currents. The method used a planar patch instrument (IonWorks HT, Molecular Devices) that allowed medium-throughput electrophysiology measurements in 384-well format. The potency of hERG inhibition was measured at 1.1μM, 3.3μM, 10μM, and 30μM of the compound studied. The compound was added from a 3x aqueous addition buffer.

[002288] The compounds of the present invention exhibit a desirably low activity against hERG.

[002289] **CYP-450 Isozyme assay**

[002290] Compound preparation:

1. The desired compound was plated (2mM in 75% DMSO/25% H_2O) with a Piezo Sample Distribution Robot (PSDR™) at 8nL per well.
2. The compound was centrifuged briefly at approximately 1000rpm to shift the compound drop to the bottom of the well.
3. PVP 10K (excipient, 0.2% in 75% DMSO/25% H_2O) was plated with a PSDR™ at 100nL per well.
4. The compound and PVP 10K were centrifuged briefly at approximately 1000rpm to ensure an adequate mix of compound and excipient.
5. The dry-down of the plates was initiated using house vacuum for at least 3 hours.
6. The plates were transferred to a high vacuum (50millitorr) apparatus and the dry-down process was continued for at least 15 hours.

[002291] The following assay protocol was employed for a desired CYP-450 isozyme (CYP3A4, CYP2C9, CYP1A2, CYP2C19, or CYP2D6).

[002292] **Assay Protocol**

All reagents below were added using a Flying Reagent Dispenser (FRD™).

1. 800 nL of dH_2O was added to the 100% activity control, compound, and background control wells.
2. 800 nL of the appropriate control drug (3A4:clotrimazole, 2C9:miconazole, 1A2:ticlopidine, 2C19:lansoprazole, or 2D6:propanolol; 10uM final dissolved in dH_2O) was added to the drug control wells.
3. 200 nL of 500mM K^+ Phosphate buffer (pH 8.4)was added to the 100% activity control, drug control, and compound wells.
4. 600 nL of Control Insect Baculosomes (PanVera P2315) in 500mM K^+ Phosphate Buffer (pH 8.4) was added to the background control wells. The calculation for this reagent was based on the protein concentration of the 100% activity control wells.
5. The plate was scanned for compound fluorescence using a NanoPlate™ Fluorescence Plate Reader (NPR™).
6. 200 nL of $NADP^+$ (Sigma, 100 μM final) and substrate in 100mM K^+ Phosphate buffer (50mM K^+ Phosphate buffer for 2C9 and 2C19) was added to all wells. Fluorogenic substrate (3A4:5 μM Vivid™ 3A4 Red, 2C9:1μM Vivid™ 2C9 Green, 1A2:2μM Vivid™ 1A2 Blue, 2C19:10μM Vivid™ 2C19 Blue, and 2D6: 10μM Vivid™ 2D6 Blue) was added at a final concentration corresponding to the K_m of the substrate for its pertinent CYP450 isozyme.
7. 400 nL of the desired CYP450 isozyme and recycling buffer (3.3mM glucose-6-phosphate, 0.4units/ml glucose-6-phosphate dehydrogenase, 100mM $MgCl_2$, and 0.00025% Antifoam 289; reagents obtained from Sigma) in 100mM K^+ Phosphate Buffer (50mM K^+ Phosphate buffer for 2C9 and 2C19) were added to the 100% activity control, drug control, and compound wells. The desired isozyme was added to obtain the following final concentrations of the desired isozyme: 5nM CYP3A4, 10nM CYP2C9, 5nM CYP1A2, 5nM CYP2C19, or 20nM CYP2D6.
8. The plate was incubated for 60 minutes at room temperature.

9. The plate was scanned for solution fluorescence using a NanoPlate™ Fluorescence Plate Reader (NPR™).

10. The NPR™ data was converted into a format compatible with importation into a data visualizer and complete the analysis of data acquired.

[002293] The compounds of the present invention exhibit a desirably low activity against one or more of the CYP450 isozymes.

[002294] The activity of selected compounds of the present invention against NaV 1.8 channel is shown below in Table 4. In Table 4, the symbols have the following meaning:

"+++" means < 2 μM; "++" means between 2 μM and 10 μM; and "+" means > 10μM.

[002295] Table 4

101	+++	137	++	175	+	228	+	285	+
102	++	138	+	176	+	229	+	286	++
103	+	139	++	177	++	230	++	287	+
104	+	140	+	178	+	231	++	288	+
105	++	141	+	179	+	232	++	289	+
106	+	142	++	180	++	233	+	270	++
107	++	143	++	181	+	234	+	271	+
108	++	144	++	182	++	235	++	272	++
109	++	145	+	183	++	236	+	273	++
110	+	146	+	184	++	237	+	274	++
111	+	147	++	185	++	238	+	275	++
112	+	148	++	201	++	239	+	276	++
113	++	149	+	203	+	240	+	277	++
114	++	150	+	204	+	241	+	278	+
115	+	151	+	205	+	242	++	279	++
116	++	152	+	206	++	243	+	301	++
117	++	153	++	207	+++	244	+	302	+
118	++	154	+	208	+++	245	+	303	++
119	+	155	+	210	++	246	+	304	+
120	++	156	++	211	+	247	+	305	++
121	++	157	++	212	+	248	++	306	+
122	++	158	+	213	+	249	++	307	+
123	+	159	++	214	+	250	+++	308	+
124	+	160	+	215	+	251	++	309	+++
125	+	162	++	216	+	252	+	310	++
126	+	163	++	217	+	253	+	311	+++
127	+++	164	+	218	++	254	++	312	++
128	++	165	++	219	+++	255	+	314	++
129	+	166	+	220	+	256	++	315	+
130	+	167	+	221	+	257	++	316	+
131	+	168	++	222	+	258	+++	317	++
132	++	169	+	223	+	259	+++	318	+
133	++	170	+	224	+	260	+++	319	++
134	++	172	+	225	+	261	++	320	++
135	+++	173	+	226	+	262	++	321	+
136	+	174	++	227	+	264	+	322	+

Cmpd #	IC50
323	+
324	+
325	+
326	+
327	+
328	+
329	++
335	++
337	++
338	+
339	++
340	+++
342	+
345	++
346	++
347	+

Cmpd #	IC50
348	+
349	+
350	+
351	++
352	+
353	+
354	++
355	+
356	+
357	+
358	+
359	+
360	+
361	++
362	+
363	++

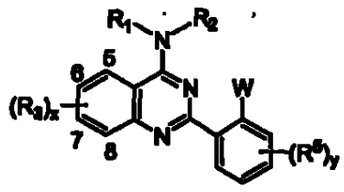
Cmpd #	IC50
364	+++
365	+++
366	++
367	+++
368	++
369	+++
370	+++
371	+++
372	+++
373	++
374	+
375	+
376	+
377	++
401	+
402	+

Cmpd #	IC50
403	+
404	+
405	+
406	+
407	+
408	+
409	+
410	+
411	++
412	+
413	++
414	++
415	++
416	+
417	+
418	++

Cmpd #	IC50
419	++
420	+++
501	++
502	++
503	++
504	++
505	++
506	++
507	++
508	++
509	+
510	++
511	++
512	++
513	+
514	++

CLAIMS

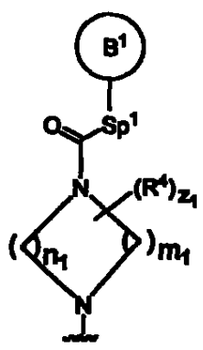
1. A compound of formula I:



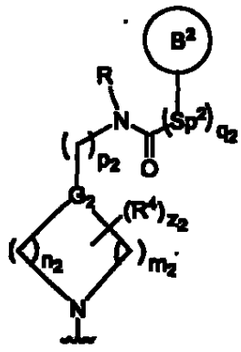
I;

or a pharmaceutically acceptable salt or derivative thereof, wherein:

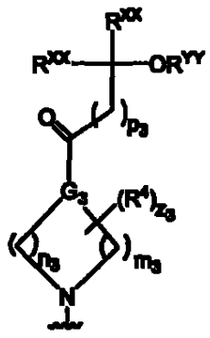
R^1 and R^2, taken together with the nitrogen atom, form a substituted ring selected from:



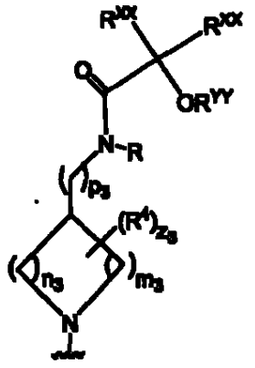
(A)



(B)

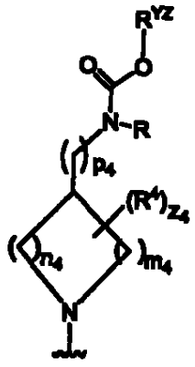


(C)



(D)

or



(E);

wherein, in ring (A):

each of m_1 and n_1 is independently 0-3, provided that m_1+n_1 is 2-6;

wherein w_1 is 0-4;

Sp^1 is –O-, -S-, -NR'-, or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO_2-, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, -SO_2-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-, provided that Sp^1 is attached to the carbonyl group through an atom other than carbon;

ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w_1 independent occurrences of -R^{11}, wherein w_1 is 0-4;

wherein, in ring (B):

G_2 is -N-, or CH;

each of m_2 and n_2 is independently 0-3, provided that $m_2 + n_2$ is 2-6;

p_2 is 0-2; provided that when G_2 is N, then p_2 is not 0;

q_2 is 0 or 1;

z_2 is 0-4;

Sp^2 is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO_2-, -OCO-, -NR'CO_2-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, -SO_2-, -NR'-, -SO_2NR'-, NR'SO_2-, or -NR'SO_2NR'-;

ring B^2 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of –R^{12}, wherein w_2 is 0-4;

wherein, in ring (C) or ring (D):

G_3 is -N-, -CH-NH-, or -CH-CH_2-NH-;

each of m_3 and n_3 is independently 0-3, provided that m_3+n_3 is 2-6;

p_3 is 0-2;

z_3 is 0-4;

each R^{XX} is hydrogen, C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently

selected from nitrogen, oxygen, or sulfur; wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3;

provided that both R^{XX} are not simultaneously hydrogen;

R^{YY} is hydrogen, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or $-PO(R')_2$;

wherein, in ring (E):

each of m_4 and n_4 is independently 0-3, provided that $m_4 + n_4$ is 2-6;

p_4 is 1-2;

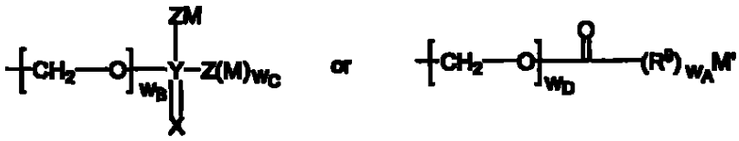
z_4 is 0-4;

R^{YZ} is C_1-C_6 aliphatic group, optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3;

x and y, each, is independently 0-4;

W is OR^{XY};

R^{XY} is hydrogen or a group selected from:



wherein:

each of w_A, w_B, w_C, and w_D is independently 0 or 1;

each M is independently selected from hydrogen, Li, Na, K, Mg, Ca, Ba, $-N(R^7)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^7$, $-R^7$, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, $-CO_2R^7$, $-C(O)-N(R^7)_2$, $S(O)_2-N(R^7)_2$, $N(R^7)-C(O)-R^7$, $C(O)R^7$, $-S(O)_n-R^7$, OCF_3, $-S(O)_n-R^6$, $N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$, or $-NO_2$;

n is 0-2;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^7)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a

substituent selected from oxo, $-OR^7$, $-R^7$, $-N(R^7)_2$, $N(R^7)_3$, $-R'OH$, $-CN$, $-CO_2R'$, $-C(O)-N(R^7)_2$, $-S(O)_2-N(R^7)_2$, $-N(R^7)-C(O)-R^7$, $-C(O)R^7$, $-S(O)_2-R^7$, $-OCF_3$, $-S(O)_2-R^6$, $-N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$, or $-NO_2$;

Z is $-CH_2-$, $-O-$, $-S-$, $-N(R^7)_2-$; or,

when M is absent, then Z is hydrogen, =O, or =S;

Y is P or S, wherein when Y is S, then Z is not S;

X is O or S;

each R^7 is independently selected from hydrogen, or C_1-C_4 aliphatic, optionally substituted with up to two Q_1;

each Q_1 is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatom or heteroatom group selected from O, N, NH, S, SO, or SO_2; wherein Q_1 is optionally substituted with up to three substituents selected from oxo, -OH, $-O(C_1-C_4$ aliphatic), $-C_1-C_4$ aliphatic, $-NH_2$, $NH(C_1-C_4$ aliphatic), $-N(C_1-C_4$ aliphatic$)_2$, $-N(C_1-C_4$ aliphatic$)-C(O)-C_1-C_4$ aliphatic, $-(C_1-C_4$ aliphatic$)-OH$, -CN, $-CO_2H$, $-CO_2(C_1-C_4$ aliphatic), $-C(O)-NH_2$, $-C(O)-NH(C_1-C_4$ aliphatic), $-C(O)-N(C_1-C_4$ aliphatic$)_2$, halo or $-CF_3$;

R^6 is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, $S(O)_n$ or $N(R^7)$; and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from OH, C_1-C_4 alkyl, $O-C_1-C_4$ alkyl or $O-C(O)-C_1-C_4$ alkyl;

R^9 is $C(R^7)_2$, O or $N(R^7)$;

each occurrence of R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4, and R^5 is independently $Q-R^X$; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by –NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, -OP(O)(OR)-, or -POR-; and each occurrence of R^X is independently selected from -R', halogen, =O, =NR', $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -NR'COR', $-NR'CON(R')_2$, $-NR'CO_2R'$, -COR', $-CO_2R'$, -OCOR', $-CON(R')_2$, $-OCON(R')_2$, -

SOR', $-SO_2R'$, $-SO_2N(R')_2$, $-NR'SO_2R'$, $-NR'SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, or $-OPO(R')_2$; and

each occurrence of R is independently hydrogen or C_{1-6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally *substituted* 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

2. The compound according to claim 1, wherein W is OH.

3. The compound according to claim 1, wherein x is 1 and R^3 is present at the 6- or 7-position of the quinazoline ring.

4. The compound according to claim 3, wherein R^3 is selected from -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(cyclopropyl), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$, or -CN.

5. The compound according to claim 4, wherein x is 1 and R^3 is at the 7-position of the quinazoline ring and is $-CH_3$.

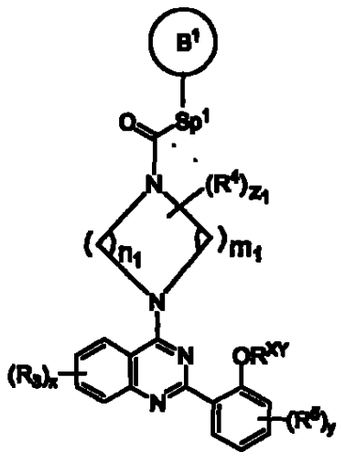
6. The compound according to claim 1, wherein y is 0.

7. The compound according to claim 1, wherein y is 1, and R^5 is halo.

8. The compound according to claim 7, wherein R^5 is halo at the 6-position.

9. The compound according to claim 1, wherein z_1, z_2, z_3, and z_4 each is 0.

10. The compound according to claim 1, wherein said compound has formula I-A:



I-A.

11. The compound according to claim 10, wherein Sp^1 is -O-, -O-CH_2-, -S-, or -NH-, or -NH-CH_2-.

12. The compound according to claim 10, wherein each of m_1 and n_1 is 2.

13. The compound according to claim 10, wherein ring B^1 is a 5-6 membered, saturated, monocyclic heterocyclic ring having having 1-2 heteroatoms selected from O, S, or N, wherein ring B^1 is optionally substituted with w independent occurrences of $-R^{11}$, wherein w_1 is 0-4.

14. The compound according to claim 13, wherein ring B1 is tetrahydrofuranyl, tetrahydro-[2*H*]-pyranyl, pyridyl, or phenyl.

15. The compound according to claim 10, wherein Sp^1 is a bond, O, or –O-CH_2-; R is hydrogen; and n_1 and m_1 are both simultaneously 2.

16. The compound according to claim 10, wherein:

n_1 and m_1 each is 2;

R^{XY} is hydrogen;

y is 0 or 1 and R^5 is fluoro;

x is 1 and R^3 is Me at 7-position or fluoro at 6-position;

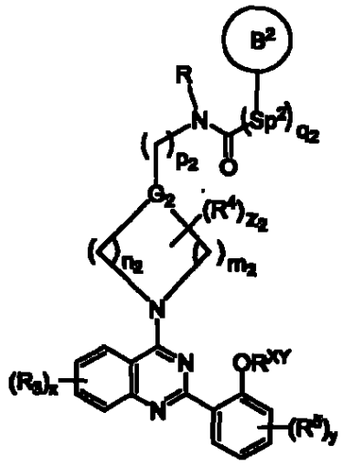
z_1 is 0;

Sp^1 is $-O-CH_2-$;

w_1 is 0; and

ring B^1 is tetrahydrofuran-3-yl, phenyl, pyridine-3-yl, pyridine-4-yl, or tetrahydro[2H]-pyran-4-yl.

17. The compound according to claim 1, wherein said compound has formula I-B:



I-B.

18. The compound according to claim 17, wherein G_2 is CH and p_2 is 1 or 2.

19. The compound according to claim 17, wherein m_2 and n_2 each is 1 or 2.

20. The compound according to claim 17, wherein m_2 is 1 and n_2 each is 2.

21. The compound according to claim 17, wherein n_2 is 1, and m_2 is 3.

22. The compound according to claim 17, wherein Sp^2 is -O- or $-O-CH_2-$.

23. The compound according to claim 17, wherein ring B^2 is a 5-6 membered, saturated, monocyclic heterocyclic ring having having 1-2 heteroatoms selected from O, S, or N, wherein ring B^2 is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4.

24. The compound according to claim 23, wherein ring B^2 is tetrahydrofuranyl, tetrahydro[2*H*]pyranyl, or pyridyl.

25. The compound according to claim 17, wherein

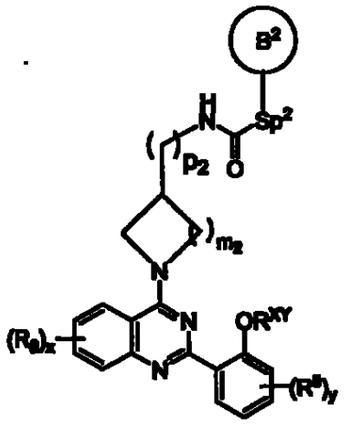
Sp^2 is a bond, O, or $-O-CH_2-$;

p_2 is 1;

R is hydrogen; and

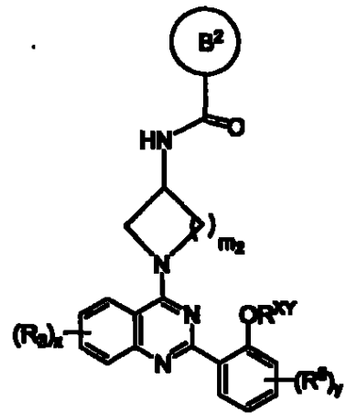
n_2 is 1 and m_2 is 2 or 3.

26. The compound according to claim 17, wherein said compound has formula I-B-i or formula I-B-ii:



I-B-i

or



I-B-ii;

wherein:

m_2 is 2 or 3; and

Sp^2 is –O- or -O-CH_2.

27. The compound of formula I-B-I according to claim 26, wherein:

p_2 is 1;

m_2 is 3;

Sp^2 is -O-;

y is 0 or 1, and R^5 is fluoro;

x is 1 and R^3 is 7-Me; and

ring B^2 is tetrahydrofuranyl.

28. The compound of formula I-B-I according to claim 26, wherein:

p_2 is 0 or 1;

m_2 is 2;

Sp^2 is -O- or -O-CH_2-;

y is 0;

x is 1 and R^3 is 7-Me; and

ring B^2 is tetrahydrofuranyl, tetrahydro[2H]pyranyl, pyridyl, or phenyl.

29. The compound of formula I-B-II according to claim 26, wherein:

p_2 is 0;

m_2 is 2;

Sp^2 is a bond;

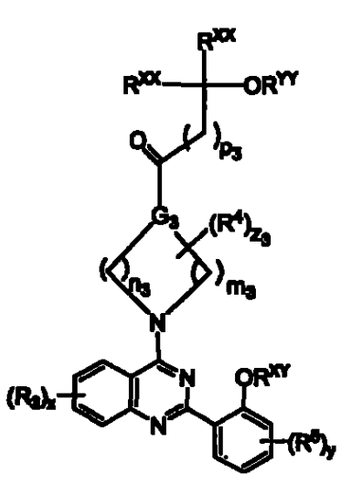
y is 0 or 1, and R^5 is fluoro;

x is 1 and R^3 is 7-Me or 6-F; and

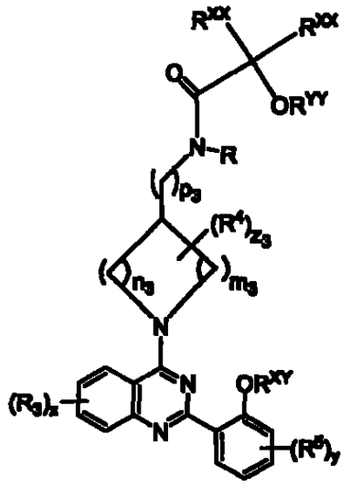
ring B^2 is cyclopropyl optionally substituted with C1-C4 alkyl, or pyridyl.

30. The compound of formula I-B-I or formula I-B-II according to claim 17, wherein R^{XY} is hydrogen.

31. The compound according to claim 1, wherein said compound has formula I-C or formula I-D:



I-C



I-D.

32. The compound according to claim 31, wherein one R^{XX} is hydrogen and the other R^{XX} is not hydrogen.

33. The compound according to claim 31, wherein one R^{XX} is hydrogen and the other R^{XX} is C1-C6 alkyl optionally substituted with halo.

34. The compound according to claim 31, wherein both R^{XX} are simultaneously C1-C6 alkyl.

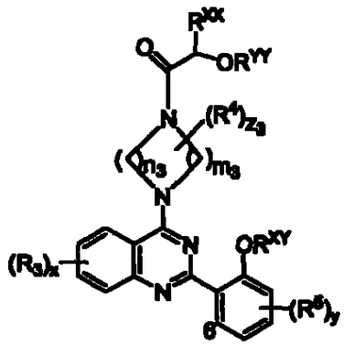
35. The compound according to claims 33 or 34, wherein said alkyl is selected from methyl, ethyl, isopropyl, *n*-propyl, *n*-butyl, *sec*-butyl, or *t*-butyl.

36. The compound according to claim 31, wherein p_3 is 0.

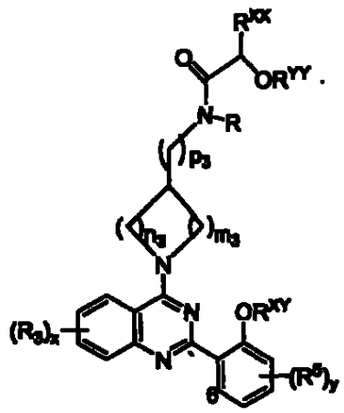
37. The compound according to claim 31, wherein m_3 and n_3 each is 2.

38. The compound according to claim 31, wherein R^{YY} is hydrogen.

39. The compound according to claim 31, wherein said compound has formula I-C-1 or formula I-D-1:



I-C-1



I-D-1

40. The compound according to claim 39, wherein R^{XX} is C1-C6 alkyl.

41. The compound according to claim 39, wherein x is 1, and R^3 is C1-C4 alkyl at the 7-position.

42. The compound according to claim 39, wherein x is 1 and R^3 is F, CN, or CF_3 at the 6-position.

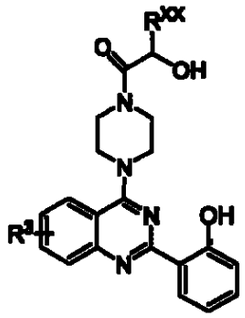
43. The compound according to claim 39, wherein R^{XX} is methyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, or *t*-butyl.

44. The compound according to claim 41, wherein R^3 is methyl, *n* -propyl, isopropyl, *n* -butyl, *sec*-butyl, or *t*-butyl.

45. The compound according to claim 39, wherein R^{XY} is hydrogen, and y is 0.

46. The compound according to claim 39, wherein R^{XY} is hydrogen, y is 1 and R^5 is 6-F.

47. The compound according to claim 31, wherein said compound has formula I-C-ii:

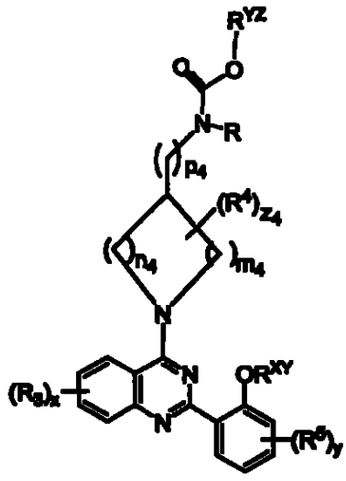


I-C-ii.

48. The compound according to claim 47, wherein R^3 is methyl at the 7-position of the quinazoline ring.

49. The compound according to claim 47, wherein R^{XX} is $CH_2C(O)OH$ or $CH_2C(O)NH_2$.

50. The compound according to claim 1, wherein said compound has formula I-E:



I-E.

51. The compound according to claim 50, wherein p_4 is 1.

52. The compound according to claim 50, wherein m_4 and n_4 each is 2.

53. The compound according to claim 50, wherein n_4 is 1, m_4 is 3, z_4 is 0, p_4 is 1, y is 0 or 1, and x is 1.

54. The compound according to claim 50, wherein n_4 is 1, m_4 is 2, z_4 is 0, p_4 is 1, y is 0 or 1, and x is 1.

55. The compound according to claim 50, wherein n_4 is 1, m_4 is 3, z_4 is 0, p_4 is 1, y is 0 or 1, x is 1, and R and R^{XY} both are hydrogen.

56. The compound according to claim 50, wherein n_4 is 1, m_4 is 2, z_4 is 0, p_4 is 1, y is 0 or 1, x is 1, and R and R^{XY} both are hydrogen.

57. The compound according to claim 50, wherein R^{YZ} is C1-C4 alkyl group optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3.

58. The compound according to claim 50, wherein:

n_4 is 1 and m_4 is 3;

p_4 is 1;

z_4 is 0;

R^{YZ} is C1-C6 alkyl, wherein up to two $-CH_2-$ groups therein is optionally replaced by -O-;

y is 0 or 1, and R^5 is 6-fluoro; and

x is 1 and R^3 is C1-C4 alkyl.

59. The compound according to claim 50, wherein:

n_4 is 1 and m_4 is 2;

p_4 is 1;

z_4 is 0;

R^{YZ} is C1-C6 alkyl, wherein up to two $-CH_2-$ groups therein is optionally replaced by -O-;

y is 0 or 1, and R^5 is 6-fluoro; and

x is 1 and R^3 is C1-C4 alkyl.

60. The compound according to claim 50, wherein:

n_4 is 1 and m_4 is 3;

p_4 is 1;

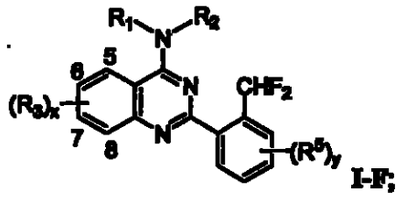
z_4 is 0;

R^{YZ} is benzyl;

y is 0 or 1, and R^5 is 6-fluoro; and

x is 1 and R^3 is C1-C4 alkyl.

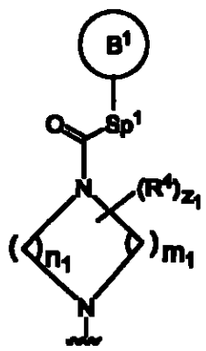
61. A compound according having formula I-F:



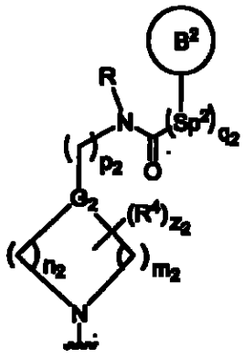
I-F;

wherein:

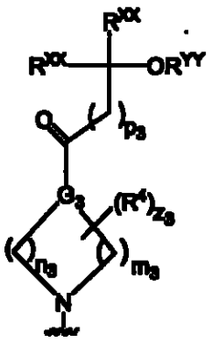
R^1 and R^2, taken together with the nitrogen atom, form a substituted ring selected from:



(A)

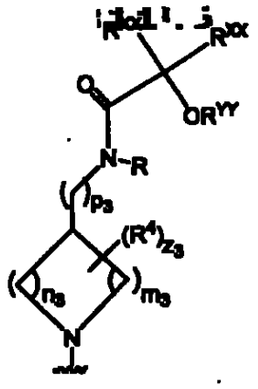


(B)

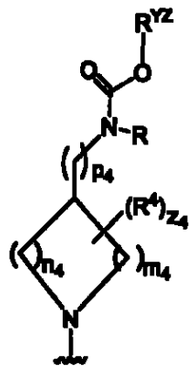


(C)

486 985



(D) or



(E);

wherein, in ring (A):

each of m_1 and n_1 is independently 0-3, provided that m_1+n_1 is 2-6;

z_1 is 0-4;

Sp^1 is –O-, -S-, -NR'-, or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$, provided that Sp^1 is attached to the carbonyl group through an atom other than carbon;

ring B^1 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B^2 is optionally substituted with w_1 independent occurrences of $-R^{11}$, wherein w_1 is 0-4;

wherein, in ring (B):

G_2 is -N-, or CH;

each of m_2 and n_2 is independently 0-3, provided that $m_2 + n_2$ is 2-6;

p_2 is 0-2; provided that when G_2 is N, then p_2 is not 0;

q_2 is 0 or 1;

z_2 is 0-4;

Sp^2 is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, –CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$, or $-NR'SO_2NR'-$;

ring B is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of $-R^{12}$, wherein w_2 is 0-4;

wherein, in ring (C) or ring (D):

G_3 is -N-, -CH-NH-, or -CH-CH_2-NH-;

each of m_3 and n_3 is independently 0-3, provided that m_3+n_3 is 2-6;

p_3 is 0-2;

z_3 is 0-4;

each R^{XX} is hydrogen, C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R^{XX} is optionally substituted with w_3 independent occurrences of $-R^{13}$, wherein w_3 is 0-3;

provided that both R^{XX} are not simultaneously hydrogen;

R^{YY} is hydrogen, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$, or $-PO(R')_2$;

wherein, in ring (E):

each of m_4 and n_4 is independently 0-3, provided that $m_4 + n_4$ is 2-6;

p_4 is 1-2;

z_4 is 0-4;

R^{YZ} is C_1-C_6 aliphatic group, optionally substituted with w_4 independent occurrences of $-R^{14}$, wherein w_4 is 0-3;

x and y, each, is independently 0-4;

each occurrence of R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4, and R^5 is independently $Q-R^X$; wherein Q is a bond or is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by $-NR-$, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, -OP(O)(OR)-, or -POR-; and each occurrence of R^X is independently selected from -R', halogen, =O, =NR', $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -NR'COR', $-NR'CON(R')_2$, $-NR'CO_2R'$, -COR', $-CO_2R'$, -OCOR', $-CON(R')_2$, $-OCON(R')_2$, -

$SO_2N(R')_2$, $-NR'SO_2R'$, $-NR'SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, or $-OPO(R')_2$; and

each occurrence of R is independently hydrogen or C_{1-6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R'; are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

62. The compound according to claim 1, wherein said compound is selected from Table 2.

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

64. A method for treating or lessening the severity of a disease, disorder, or condition selected from acute, chronic, neuropathic, or inflammatory pain, arthritis, migrane, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain, said method comprising the step of administering to said patient an effective amount of a composition according to claim 62.

65. The method according to claim 63, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated sodium channels.

66. The method according to claim 64, wherein the disease, condition, or disorder is acute, chronic, neuropathic, or inflammatory pain.

67. The method according to claim 64, wherein the disease, condition, or disorder is radicular pain, sciatica, back pain, head pain, or neck pain.

68. The method according to claim 64, wherein the disease, condition, or disorder is severe or intractable pain, acute pain, postsurgical pain, back pain, or cancer pain.

69. The method according to claim 64, wherein said disease is selected from femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, including, abdominal; pancreatic; IBS pain; chronic headache pain; migraine; tension headache, including, cluster headaches; chronic neuropathic pain, including, post-herpetic neuralgia; diabetic neuropathy; HIV- associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phantom pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac Pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, including, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); or prostatitis.

488 485

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/031146

A. CLASSIFICATION OF SUBJECT MATTER
C07D239/94 C07D401/04 C07D401/12 C07D401/14 C07D403/04
C07D403/12 C07D403/14 C07D405/12 C07D405/14 A61P9/06
A61P25/00 A61K31/498

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/32632 A (ELI LILLY AND COMPANY; AMBLER, SAMANTHA, JAYNE; BAKER, STEPHEN, RICHAR) 10 May 2001 (2001-05-10) page 19 - page 29; claims 1-32; table I	1,61,63, 64
P,X	WO 2004/078733 A (VERTEX PHARMACEUTICALS INCORPORATED; GONZALES, JESUS, E., III; WILSON,) 16 September 2004 (2004-09-16) cited in the application claims 1-249	1-69

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2006	09/02/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Negido, B

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/031146

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. [X] Claims Nos.: 64-69
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 64-69 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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 an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/031146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0132632 A	10-05-2001	AU 1071301 A	14-05-2001
		EP 1230225 A2	14-08-2002
WO 2004078733 A	16-09-2004	AU 2004217891 A1	16-09-2004
		CA 2517844 A1	16-09-2004
		EP 1608632 A1	28-12-2005

PATENT COOPERATION TREATY

PCT

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
VPI/04-129WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/031146	31/08/2005	02/09/2004
Applicant		
VERTEX PHARMACEUTICALS INCORPORATED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [X] Certain claims were found unsearchable (See Box II).

3. [ ] Unity of invention is lacking (see Box III).

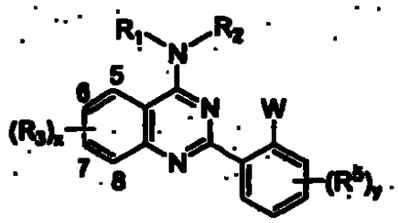
4. With regard to the title,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to compounds useful as inhibitors of voltage-gated sodium channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.



I:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/031146 492

A. CLASSIFICATION OF SUBJECT MATTER
C07D239/94 C07D401/04 C07D401/12 C07D401/14 C07D403/04
C07D403/12 C07D403/14 C07D405/12 C07D405/14 A61P9/06
A61P25/00 A61K31/498

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/32632 A (ELI LILLY AND COMPANY; AMBLER, SAMANTHA, JAYNE; BAKER, STEPHEN, RICHAR) 10 May 2001 (2001-05-10) page 19 - page 29; claims 1-32; table I	1,61,63, 64
P,X	WO 2004/078733 A (VERTEX PHARMACEUTICALS INCORPORATED; GONZALES, JESUS, E., III; WILSON,) 16 September 2004 (2004-09-16) cited in the application claims 1-249	1-69

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2006	09/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Megido, B

4

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/031146

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. [X] Claims Nos.: 64-69
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 64-69 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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 allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/031146

494

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0132632 A	10-05-2001	AU 1071301 A	14-05-2001
		EP 1230225 A2	14-08-2002
WO 2004078733 A	16-09-2004	AU 2004217891 A1	16-09-2004
		CA 2517844 A1	16-09-2004
		EP 1608632 A1	28-12-2005

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/031146	31.08.2005	02.09.2004

International Patent Classification (IPC) or both national classification and IPC
C07D239/94, C07D401/04, C07D401/12, C07D401/14, C07D403/04, C07D403/12, C07D403/14, C07D405/12,

Applicant
VERTEX PHARMACEUTICALS INCORPORATED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Megido, B Telephone No. +31 70 340-8523

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

-496 ~~498~~

WRITTEN PINI N OF THE INTERNATI NAL SEARCHING AUTHORITY

International application No.
PCT/US2005/031146

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

497 499

WRITTEN PINION F THE INTERNATIONAL SEARCHING AUTH RITY

International application No.
PCT/US2005/031146

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. 64-69

because:

☒ the said international application, or the said claims Nos. 64-69 (with respect to industrial application) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

498 495

WRITTEN PINION OF THE INTERNATIONAL SEARCHING AUTH RITY

International application No.
PCT/US2005/031146

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-69
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-69
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-63
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

Claims 64-69 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67(1)(IV) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

1 Novelty (Article 33(2) PCT)

1.1 Reference is made to the following document:

D1: WO 01/32632 A (ELI LILLY AND COMPANY; AMBLER, SAMANTHA, JAYNE; BAKER, STEPHEN, RICHAR) 10 May 2001 (2001-05-10)

1.2 The subject-matter of the claims 1-69 of the present application is new in the sense of Article 33(2) PCT and meets the criteria of Article 33(1) PCT, because the substitution of the quinazoline core with the ring systems **A-E** *directly* attached at the 4 position (according to general formulas I and I-F of the present application) is different over the prior art.

1.3 In the prior art document D1, which is considered to represent the most relevant state of the art, this 4 position is substituted with a *different* ring system attached to the quinazoline core *via* an *heteroatom*.

2 Inventive Step (Article 33(3) PCT)

2.1 The subject-matter of claims 1-69 of the present application is considered to involve an inventive step in the sense of Article 33(3) PCT and to meet the criteria of Article 33(1) PCT.

2.2 Document D1, which is considered to represent the most relevant state of the art, discloses (the references in parentheses applying to this document):

4-substituted quinazoline derivates according to general formula I (pages 4-29,

table I and claims 1-32) with activity as ion channel modulators through its capacity to influence the *metabotropic* receptor mGluR1, which is involved in changes in the function of ion channels (page 1, line 13 to page 2, line 26).

2.3 From this, the subject-matter of independent claim 1 differs in that:
In the case of the present application, the quinazoline core is substituted with th cited ring systems **A-E** directly attached at the 4 position.
In the case of the closest prior art document D1, the 4 position is substituted with a different ring system attached to the core quinazoline structure *via* an heteroatom (O or N).

2.4 The problem to be solved by the present invention may be regarded as:
The provision of alternative quinazoline derivatives with activity as ion channel modulators.

2.5 The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
Starting from the teaching of closest prior art document D1, for a person skilled in the art it would not be obvious to modify the substitution pattern of the core structure of quinazoline in the way disclosed in the present application to come to a solution to the proposed problem.

2.6 Therefore, the subject-matter of claim 1 of the present application and its dependent claims 2-60,62 is considered to be the result of an inventive activity.

2.7 The subject-matter of independent claim 61 refers to compounds according to general formula I-F. This compounds share the inventive feature of compounds according to general formula I disclosed in claim 1 of the present application and are considered to be the result of an inventive activity.

2.8 The subject-matter of independent claim 63 refers to pharmaceutical compositions based in the inventive compounds disclosed in claim 1 of the present application.

2.9 The subject-matter of independent claim 64 and its dependent claims 65-69 refers to

methods of treatment based in the inventive compounds disclosed in claim 1 of the present application.

2.10 Therefore, the subject-matter of claims 1-69 meets the criteria of Article 33(1) PCT, because this subject-matter is considered to involve an inventive step in the sense of Article 33(3) PCT.

Re Item VIII.

1 Content, form and clarity of the claims (Article 6 and Rule 6 PCT)

1.1 In claim 1 of the present application the term "derivative" is used (page 459, line 2) and associated to the compounds according to general formula I.

1.2 This Authority considers that for a person skilled in the art will be not clear how and where in the molecule, derivatives could be made.

1.3 In fact, the subject-matter claimed is written as a result to be achieved, which is not allowable.

1.4 Furthermore, derivatives of compounds according to general formula I may well represent a completely separate invention from that is disclosed in the present application.

1.5 Claim 61 of the present application is formulated in an unclear way. It states "A compound according having formula I-F". The actual formulation is misleading and points to a dependent nature of the claim (the wording "according..."). This is in disagreement with the actual content of the claim in view of the general formula I from claim 1.

1.6 In this procedure the following, more logical option was considered:
that the claim 61 is an independent claim and that it should be read as "A compound according to formula I-F" or the equivalent wording "A compound having formula I-F".

1.7 The wording of this claim 61 should be redrafted to avoid this unclarity.

503 SPD

PATENTS

IN THE INTERNATIONAL BUREAU OF WIPO

Applicant: Vertex Pharmaceuticals Incorporated
Serial No.: PCT/US2005/031146
Filed: 31 August 2005
Title: QUINAZOLINES USEFUL AS MODULATORS OF ION CHANNELS
Atty. Docket: VPI/04-129 WO

INTERNATIONAL BUREAU OF WIPO
34, CHEMIN DES COLUMBETTES
1211 GENEVA 20, SWITZERLAND
FACSIMILE NO.: 41 22 740 14 35

ATTENTION: Yoshiko Kuwahara

ARTICLE 34 AMENDMENT

Applicant hereby requests consideration of the specification amendments presented herein pursuant to PCT Article 34. Applicant provides herewith marked-up replacement pages 91, 92, 97, 107, 114, 116, 118, 122, 124, 129, 130, 132, 133, 135, 136, 149, 150-152, 167, 173, 174, 181, 182, 187, 188, 195, 198, 205, 206, 209, 210, 211, 226, 249, 253, 255, 256, 258, 281, 284, 304, 316, 318, 320, 321, 353, 354, 376, 396, 410, 416, 428, 431, and 437 with deletions indicated by strikethrough lines with bracketing and additions indicated by underlining. The page numbers in each replacement page correspond to the page numbers in the PCT International Publication No. WO 2006/028904, Corrected Version, published March 16, 2006.

The amendments either correct inadvertent errors in the compound names, structural depiction or numbering, or remove the inadvertent recitation of incorrect analytical data. The amendments are further limited to the "Examples" section of the specification beginning at page 90 and ending at page 458. The specific amendments are discussed in further detail below.

Applicant has amended paragraph [00226] at page 91, to delete the inadvertent recitation of the incorrect ^{13}C NMR spectral data.

Applicant has amended paragraph [00229] at page 92 to delete the inadvertent recitation of the incorrect ^{1}H NMR spectral data and the LC/MS data.

509 501

Applicant has amended paragraphs [00251] and [00253] at page 97, to recite in each case the correct compound name.

Applicant has amended paragraph [00313] at page 107 to recite the term "TFA salt" to clarify the compound intended.

Applicant has amended paragraph [00355] at page 114 to delete the inadvertent recitation of the term "aminobenzamide" before the term "2-amino-5-fluorobenzamide" to clarify the compound intended.

Applicant has amended paragraph [00363] at page 116 to recite the correct compound name.

Applicant has amended paragraph [00372] at page 118 to recite "0.255 ml" in place of "2.55ml" the correct an inadvertent stoichiometry error.

Applicant has amended paragraph [00397] at page 122, to recite the correct chemical reagent name.

Applicant has amended paragraph [00409] at page 124 to delete the inadvertent recitation of the incorrect ^{1}H NMR spectral data.

Applicant has amended paragraphs [00439] and [00441] at page 129 to draw the correct (R) stereochemical bond in place of the (S) stereochemical bond in the depicted compound to correct an inadvertent error.

Applicant has amended paragraph [00443] at page 130 to recite numerals "393.30" in place of "421.30" and to recite numerals "2.22" in place of "2.51" to correct an inadvertent recitation of the incorrect LC/MS analytical data.

Applicant has deleted paragraphs [00461] to [00466] at pages 132-133 to correct the inadvertent double recitation of an experimental for compound 118.

Applicant has amended paragraphs [00479] at page 135 and paragraphs [00481] and [00482] at page 136 to insert the stereochemical term "(R)" before the compound name to correct inadvertent errors. Applicant has also amended paragraph [00479] at page135 to recite the correct compound name.

Applicant has amended paragraph [00554] at page 149 to recite the term "TFA salt" after the compound name to clarify the compound intended.

Applicant has moved the chemical scheme from the top of page 150 to beneath paragraph [00560] on page 150 to correct an inadvertent error. Applicant has also amended page 150 to remove the paragraph number "[00557]" so that paragraph [00556] and [00557] are now joined as a single paragraph. Applicant has also amended paragraph [00559] at page150 to recite the correct compound name.

505 805

Applicant has amended paragraphs [00570], [00572], [00574], [00576], and [00578] at pages 151-152 to recite the correct compound names.

Applicant has amended paragraph [00662] at page 167 to recite the correct compound name.

Applicant has amended paragraph [00703] at page 173 to delete the inadvertent recitation of the incorrect LC/MS data and to recite the correct compound name.

Applicant has amended paragraph [00707] at page 174 to recite the correct compound name.

Applicant has amended paragraphs [00746] and [00748] at page 181 to recite the correct compound name.

Applicant has amended paragraph [00751] at page 182 to recite the correct compound name.

Applicant has amended paragraph [00782] at page 187 to delete the inadvertent recitation of the phrase "and HATU (38 mg, 0.10 mmol)".

Applicant has amended paragraph [00788] at page 188 to delete the inadvertent recitation of the incorrect LC/MS data.

Applicant has inserted the caption "Example 152" between paragraphs [00829] and [00830] at page 195 to correct an inadvertent error.

Applicant has deleted paragraph [00788] at page 198 to remove a superfluous compound name.

Applicant has amended paragraph [00894] at page 205 to delete the inadvertent recitation of the incorrect ^{1}H NMR spectral data.

Applicant has amended paragraph [00897] at page 206 to delete the inadvertent recitation of the phrase "and HATU (38 mg, 0.10 mmol)".

Applicant has amended paragraphs [00915], [00917], and [00919] at page 209 to recite the correct compound names. Applicant has also amended the side chain moiety in the chemical scheme depicted in paragraph [00920] to correct an inadvertent error.

Applicant has amended paragraphs [00921] and [00924] at page 210 to recite the correct compound names. Applicant has also amended the side chain moiety in the chemical scheme depicted in paragraph [00923] to correct an inadvertent error.

Applicant has amended paragraph [00924] at page 211 to recite the correct compound name.

506 505

Applicant has amended paragraph [001006] at page 226 to recite the correct compound name and to recite the term "bis" before the phrase "TFA salt" to clarify the salt intended.

Applicant has amended paragraph [001145] at page 249 to recite the correct compound name.

Applicant has amended paragraph [001164] at page 253 to recite the correct compound name and to delete the inadvertent recitation of the incorrect ^{1}H NMR spectral data.

Applicant has amended paragraph [001176] at page 255 and paragraph [001178] at page 256 to delete the inadvertent recitation of the incorrect ^{1}H NMR spectral data.

Applicant has amended paragraph [001190] at page 258 to recite the correct compound name.

Applicant has amended paragraph [001321] at page 281 to insert the stereochemical term "(S)" before the compound name to clarify the stereochemistry intended.

Applicant has inserted the caption "Example 234" between paragraphs [001336] and [001337] at page 284 to correct an inadvertent error.

Applicant has amended paragraph [001447] at page 304 to delete the stereochemical term "(R)" before the compound name to clarify that no stereochemical preference was intended.

Applicant has amended paragraph [001527] at page 316 to delete the inadvertent recitation of the incorrect ^{1}H NMR spectral data.

Applicant has amended paragraph [001539] at page 318 to delete the inadvertent recitation of the incorrect ^{1}H NMR spectral data.

Applicant has amended paragraph [001549] at page 320 to recite the correct compound name.

Applicant has amended paragraph [001551] at page 321 to recite the correct compound name.

Applicant has amended paragraphs [001736], [001739], and [00741] at pages 353-354 to recite the correct compound name.

Applicant has amended paragraph [001871] at page 376 to recite the correct compound name.

Applicant has amended paragraph [001987] at page 396 to recite numerals "235.3" in place of "335.3" to correct an inadvertent recitation of the incorrect LC/MS analytical data.

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Applicant has amended paragraphs [002073] and [002104] at pages 410 and 416, respectively, to delete the inadvertent recitation of the incorrect ^{1}H NMR spectral data.

Applicant has amended paragraph [002178] at page 428 to recite the caption "Example 502" in place of "Example 501" to correct an inadvertent error.

Applicant has amended paragraph [002199] at page 431 to recite the caption "Example 501" in place of "Example 502" to correct an inadvertent error.

Applicant has amended paragraph [002229] at page 437 to recite the term "hydrochloride" after the compound name to clarify the compound intended and to correct an inadvertent error. Applicant has also amended the structure in paragraph [002230] to depict the HCl salt to clarify the structure intended and to correct an inadvertent error.

Applicant respectfully submits that the foregoing amendments rectify inadvertent errors in the specification that would have been obvious to one of skill in the art. Support for these amendments is either found throughout the specification as filed.

Applicant respectfully submits that no new matter is presented with this amendment.

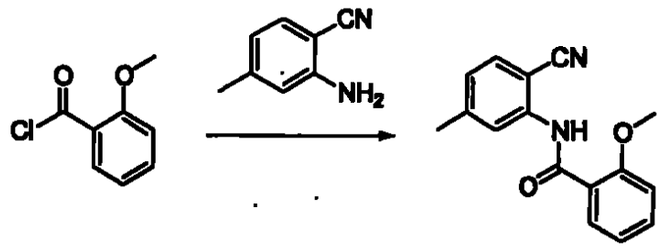
Applicant would like to thank the Examiner for consideration of these amendments.

Respectfully submitted,

Michael C. Badia (Reg. No. 51,424)
Agent for Applicants
c/o Vertex Pharmaceutical Incorporated
130 Waverly Street
Cambridge, Massachusetts 02139
United States of America
Main: (617) 444-6100
Direct: (617) 444-6467
Fax: (617) 444-6483
Customer No. 27916
Dated: January 22, 2007

[00224] *N*-(2-Cyano-5-methyl-phenyl)-2-methoxy-benzamide

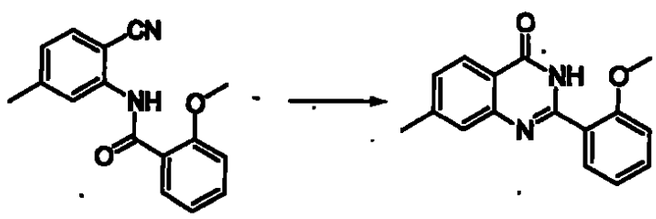
[00225]



[00226] To a stirred solution of 4-methyl-2-aminobenzonitrile (100 g, 0.75 mol) in 800 mL CH_2Cl_2 was added triethylamine (77.4 g, 0.76 mol) and dimethylaminopyridine (4.62 g, 0.037 mol). The solution was cooled to 0–5 °C, and *o*-anisoyl chloride (129 g, 0.75 mol) was added over 1 h while maintaining the reaction temperature at 0–5 °C. The reaction was then stirred at 30–40 °C for 3 h. Water (400 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (600 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to yield a solid residue, to which 800 mL hexane were added. The slurry was stirred and filtered to give *N*-(2-cyano-5-methyl-phenyl)-2-methoxy-benzamide as a yellow powder (180 g, 90%). mp 147–149 °C. ^{1}H NMR ($CDCl_3$) δ 2.429 (s, 3H), 4.2 (s, 3H), 6.8–7.2 (m, 3H), 7.4–7.6 (m, 2H), 8.2–8.4 (d, 1H), 8.6 (s, 1H), 10.8 (bs, 1H); ~~[^{13}C NMR ($CDCl_3$) δ 22.68, 55.7, 99, 111.27, 116.7, 120.3, 121.1, 124.15, 131.7, 132.25, 133.67, 141.32, 141.1, 157.2, 163.]~~ M/z (obs., $[m+H]^+$) = 268.

[00227] 2-(2-Methoxyphenyl)-7-methyl-3*H*-quinazolin-4-one

[00228]



[00229] To a mechanically stirred suspension of *N*-(2-cyano-5-methylphenyl)-2-methoxybenzamide (180 g, 0.67 mol) in 1.8 L ethanol under an N_2 atmosphere was added 6 N sodium hydroxide solution (310 g in 1.25 L water). To the above mixture, 30% hydrogen peroxide (350 mL, 3.64 mol) was slowly added. The solution was then slowly heated to 80 °C

and maintained at this temperature for 4 h. The reaction mixture was concentrated under reduced pressure to remove ethanol, giving a suspension which was quenched with ice cold water (1.8 L) and acidified with acetic acid to pH 5–6 to give a solid residue. The solid was filtered and washed with water, then dissolved in 5.5 L CH_2Cl_2 and washed with water (2x18 L). The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure to give a light yellow solid (100 g, 54%). mp165–170 °C. ~~[^{1}H NMR ($CDCl_3$) δ 2.429 (s, 3H), 4.2 (s,3), 6.8–7.2 (m, 3H), 7.4–7.6 (m, 2H), 8.2–8.4 (d, 1H), 8.6 (s, 1H), 10.8 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 21.68, 55.6, 111.3, 118.2, 119.6, 121.1, 125.7, 127.14, 127.64, 130.96, 132.56, 144.9, 149.06, 150.42, 157.25, 161.52. M/z (obs., $[m+H]^+$) = 268.]~~

[00230] **4-Chloro-2-(2-methoxy-phenyl)-7-methyl-quinazoline**

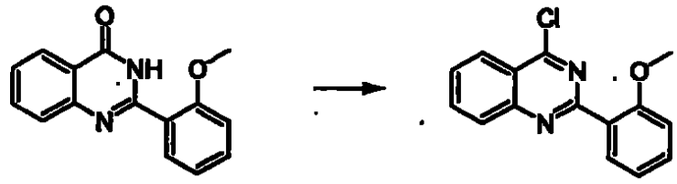
[00231]

[00232] To a mechanically stirred suspension of 2-(2-methoxyphenyl)-7-methyl-3*H*-quinazolin-4-one (100 g, 0.37 mol) in 1 L toluene was added diisopropyl ethylamine (100 mL), followed by phosphorus oxychloride (69 g, 0.45 mol). The reaction was then heated to 80 °C for 4 h. The reaction mixture was distilled under reduced pressure to remove toluene, and the resulting residue was dissolved in 2.2 L CH_2Cl_2. Ice water was added, and the pH was adjusted to 8–9 with saturated aqueous sodium bicarbonate solution while maintaining the temperature below 20 °C. The resulting organic layer was separated and the aqueous solution extracted with CH_2Cl_2, then the combined the organic layers were dried over sodium sulfate and distilled under reduced pressure. The crude product was dissolved 2:1 CH_2Cl_2/hexane, and the solution was passed through silica gel (2.5 kg, 60–120 mesh), followed by washing the silica bed with 2:1 CH_2Cl_2/hexane until the product eluted. The pure fractions were collected and combined, and the solvent was removed under reduced pressure. Hexane (500 mL) was added, and the mixture was stirred and filtered to give 4-chloro-2-(2-methoxy-phenyl)-7-methyl-quinazoline as a white to off-white solid (77 g, 72%). mp 161–164 °C. ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3H), 3.9 (s, 3H), 6.9–7.2 (m, 2H), 7.4–7.6 (m, 2H), 7.7–8 (d, 2H), 8.2 (d,1H); ^{13}C NMR ($CDCl_3$) δ 22.23, 56.06, 112.2, 120.26, 120.69, 125.34, 127.94, 130.45, 131.08, 131.08. M/z (obs., $[m+H]^+$) = 285.

resulting residue was filtered and washed with water. The resulting solid was then suspended in 600 mL of 5% aq. NaOH solution and boiled for one hour. The reaction was allowed to cool to room temperature, and it was neutralized with acetic acid, upon which 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one was precipitated. The product was collected by filtration, washed with water, and dried overnight *in vacuo* to yield 27 g (73%) of pure 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one. LC/MS: *m/z* 253.0 $(M+H)^+$ at 3.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (DMSO) δ 3.86 (s, 3H), δ 7.09 (t, 1H), δ 7.18 (d, 1H), δ 7.53 (m, 2H), δ 7.70 (m, 2H), δ 7.80 (m, 1H), δ 8.14 (d, 1H), δ 12.11 (s, 1H); ^{13}C NMR (DMSO) δ 55.75, δ 111.86, δ 120.89, δ 120.97, δ 122.74, δ 125.75, δ 126.45, δ 127.26, δ 130.41, δ 132.13, δ 134.32, δ 148.97, δ 152.48, δ 157.12, δ 161.35

[00251] ~~[4-Chloro-3,4-dihydro-2-(2-methoxyphenyl)quinazoline]~~ 4-chloro-2-(2-methoxyphenyl) quinazoline

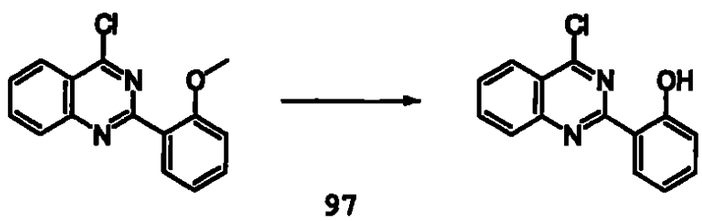
[00252]



[00253] A suspension of 2-(2-methoxyphenyl)quinazolin-4(3*H*)-one (567 g, 2.1 mol) in phosphoryl chloride (2 L, 21 mol) and a catalytic amount of *N,N*-dimethyl aniline was brought to reflux. The reaction started immediately with the evolution of gas (HCl) upon the addition of *N,N*-dimethyl aniline. After the production of gas had ceased the mixture was cooled to room temperature. The excess $POCl_3$ was evaporated. The resulting dark solution was cooled to room temperature and slowly poured on ice and water, while maintaining the temperature below 5 °C. The cold suspension was extracted with dichloromethane. The extract was dried over sodium sulfate and filtered, and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (silica gel, CH_2Cl_2). Yield: 189 g (33%) of [~~4-chloro-3,4-dihydro-2-(2-methoxyphenyl)quinazoline~~ 4-chloro-2-(2-methoxyphenyl) quinazoline] ^1H-NMR (300 MHz, Me_2SO-d_6): δ 3.85 (s, 3 H), 7.15 (t, 1 H), 7.25 (d, 1 H), 7.60 (t, 2 H), 7.70 (d, 1 H), 7.8 (d, 1 H), 7.9 (t, 1 H), 8.2 (d, 1 H).

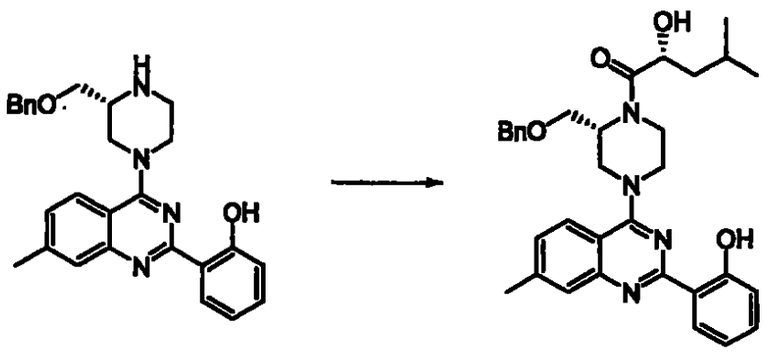
[00254] 2-(4-Chloroquinazolin-2-yl)phenol

[00255]



[00308] (*R*)-1-((*R*)-2-((Benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

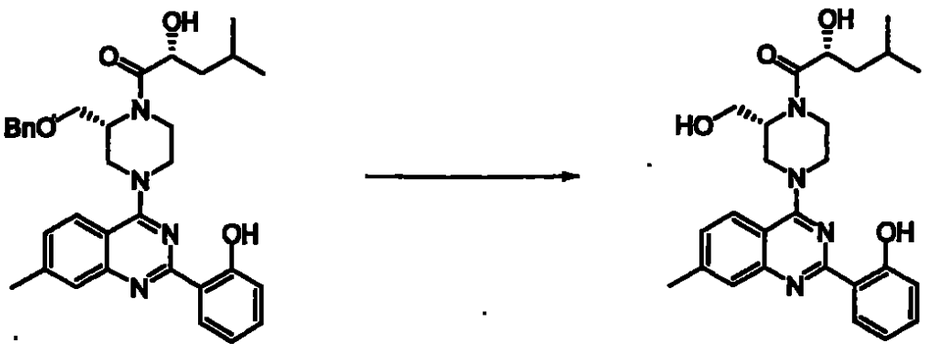
[00309]



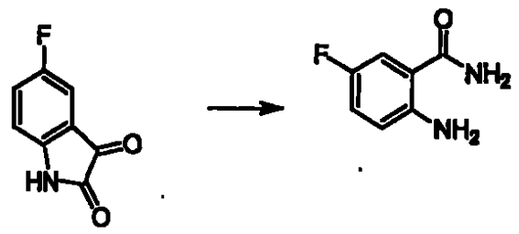
[00310] To a solution of 2-(4-((*R*)-3-((benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol (100 mg, 0.22 mmol) in DMF (1 mL) was added (*R*)-2-hydroxy-4-methylpentanoic acid (30 mg, 0.22 mmol) followed by the addition of triethylamine (61 μL), then HATU (109 mg) at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-1-((*R*)-2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 555.7 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00311] (*R*)-2-Hydroxy-1-((*R*)-2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one

[00312]



[00313] To a solution of (*R*)-1-((*R*)-2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one trifluoroacetate (29.6 mg, 0.053 mmol) in ethanol was added $Pd(OH)_2$ (188 mg), and the reaction was heated at 50 °C

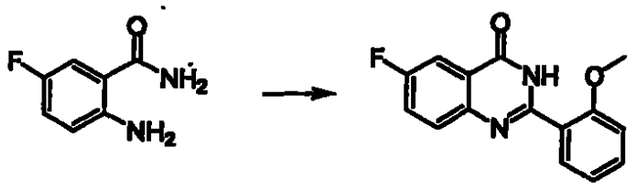


[00351]

[00352] 5-Fluoro-1*H*-indole-2,3-dione (35.3 g, 213 mmol) was heated in acetic acid (300 mL), 1 mL concentrated sulfuric acid, and 22 mL 35% aq. hydrogen peroxide at 70 °C. The solution was kept at that temperature one and a half hours during which time a solid formed in the reaction mixture. After cooling to room temperature this solid was collected by filtration and was washed three times with water. The wet solid was suspended in 150 mL water, and 40 mL of a 25% aq. ammonia solution was added. This mixture was stirred at room temperature 3 days. The formed solid was collected by filtration and was washed twice with water. The solid was dried by azeotropic distillation with toluene (3 x 100 mL) to yield 2-amino-5-fluorobenzamide (9.5 g). The combined filtrates were extracted with ethyl acetate (2x100 mL). The combined extracts were dried over sodium sulfate, filtered, and evaporated to dryness to yield 2-amino-5-fluorobenzamide (3.5 g) as an off-white solid. Both fractions were combined for use in the next reaction step.

[00353] **6-Fluoro-2-(2-methoxyphenyl)-3*H*-quinazolin-4-one**

[00354]

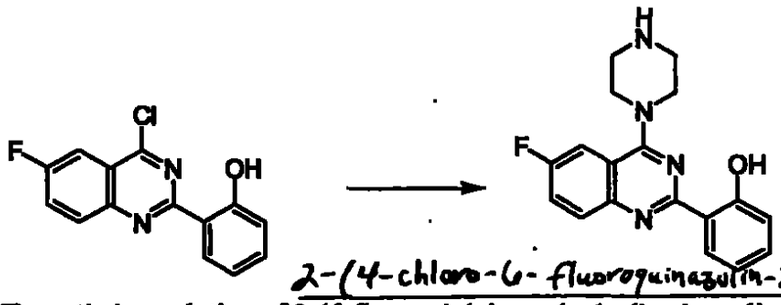


[00355] *o*-Anisoyl chloride (15.7 g, 92 mmol) was added dropwise to a solution of ~~2-aminobenzamide~~ 2-amino-5-fluorobenzamide (13.0 g, 84 mmol) and triethylamine (16 mL, 110 mmol) in tetrahydrofuran (100 mL) cooled in an ice bath. Immediately a precipitate started forming. Stirring of the solution was continued for 5 hours at room temperature. The formed precipitate was collected by filtration and was washed twice with diethyl ether and dried at 50 °C *in vacuo*. The dried solid was suspended in 2 N aqueous sodium hydroxide solution (250 mL) and heated at reflux until a clear solution was obtained (3 hours). The reaction mixture was cooled to room temperature and filtered. The filtrate was acidified to pH<1 with concentrated aqueous HCl. The formed precipitate was collected by filtration and washed twice with water,

and concentrated. Purification via silica gel chromatography using 5–20% CH_2Cl_2 in hexanes gave 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (1.61 g, 57%). LC/MS: *m/z* 275.1 $(M+H)^+$ at 3.8 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00361] **2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol**

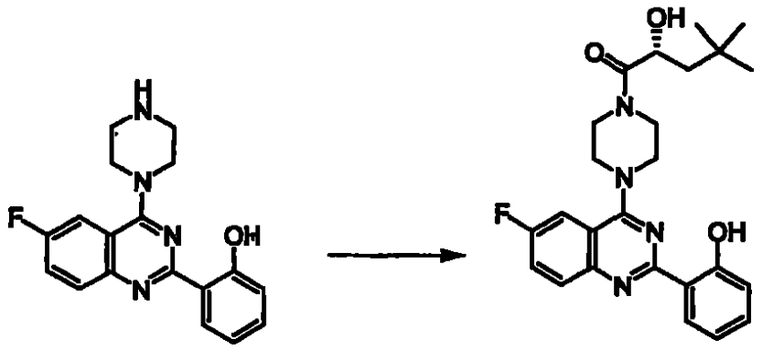
[00362]



2-(4-chloro-6-fluoroquinazolin-2-yl)phenol

[00363] To a stirring solution of ~~2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol~~ (500 mg, 1.82 mmol) in CH_2Cl_2 (20 mL) at 0 °C, under an N_2 atmosphere was rapidly added a solution of piperazine (0.263 g, 7.28 mmol) and triethylamine (0.35 mL, 2.55 mmol) in CH_2Cl_2. The mixture was stirred for 1 h and then quenched with H_2O, extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–5% MeOH in CH_2Cl_2 gave 2-(6-fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (400 mg, 68%). LC/MS: *m/z* 325.5 $(M+H)^+$ at 2.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.42 (m, 1H), 7.97 (m, 1H), 7.78 (m, 2H), 7.39 (m, 1H), 6.95 (m, 2H), 3.83 (t, J = 4.9 Hz, 4H), 2.92 (t, J = 4.9 Hz, 4H).

[00364] **(*R*)-1-(4-(6-Fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one**



[00365]

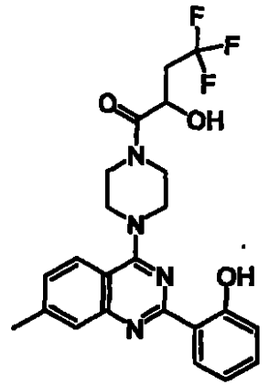
[00366] Method A

under an inert atmosphere was added dropwise a 2 M HCl solution in ether ~~(2.55~~ 0.255 mL, 0.51 mmol). To it was then added ether (15 mL) which resulted in formation of a precipitate that was allowed to stir for an hour. The product was collected by vacuum filtration and dried to afford (*R*)-1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4,4-dimethylpentan-1-one hydrochloride (230 mg, 92%). LCMS: *m/z* 453.5 $(M+H)^+$ at 3.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.40 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.04 (m, 1H), 7.88 (m, 2H), 7.43 (m, 1H), 6.99 (m, 2H), 4.45 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.02 (m, 4H), 3.79 (m, 4H), 1.56 (m, 1H), 1.42 (m, 1H), 0.97 (s, 9H).

[00373] Example 112

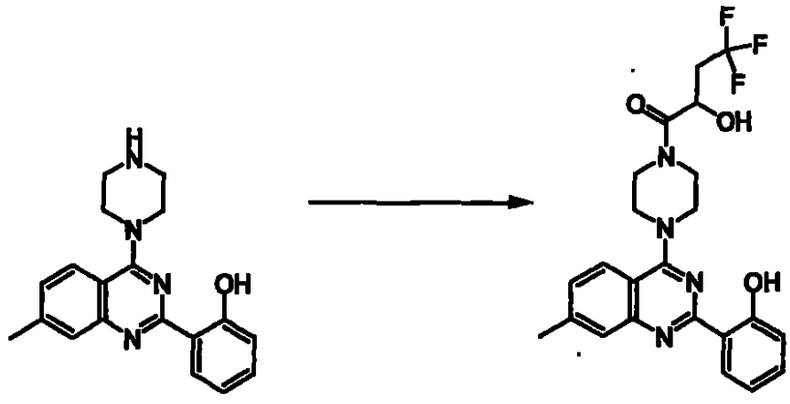
[00374] **4,4,4-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one**

[00375]



[00376] **4,4,4-Trifluoro-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)butan-1-one**

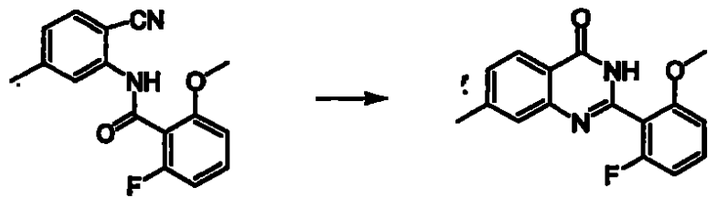
[00377]



[00397] 6-Fluoro-2-anisoic acid (110 g, 0.70 mol) was added in portions over 15 minutes to a mixture of thionyl chloride (230 ml, 3.2 mol), toluene (200 mL), and DMF (1 mL). The resulting mixture was stirred overnight at room temperature. The solution was evaporated to dryness and added dropwise to an ice-bath cooled solution of 2-amino-4-methylbenzonitrile (92.5 g, 0.70 mol) in pyridine (200 mL). The dropping funnel was rinsed with a minimal amount of acetonitrile. The resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere and was subsequently poured into 2 L ice water. The resulting slurry was stirred vigorously for 1 hour. The formed solid was collected by filtration and was washed twice with water. The filter cake was dissolved in 2 L dichloromethane, and this solution was washed with 1 N aq. HCl (400 mL) and with saturated aq. NaCl (400 mL), dried over sodium sulfate, filtered, and evaporated to dryness to give *N*-(2-cyano-5-methylphenyl)-2-fluoro-6-methoxybenzamide (186 g, 93%) as a brownish solid. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 9.09 (s, 1H), 8.58 (s, 1H), 7.59–7.42 (m, 2H), 7.09–7.02 (m, 1H), 6.94–6.83 (m, 2H), 4.11 (s, 3H), 2.57 (s, 3H) ppm.

[00398] **2-(2-Fluoro-6-methoxy-phenyl)-7-methyl-3*H*-quinazolin-4-one**

[00399]

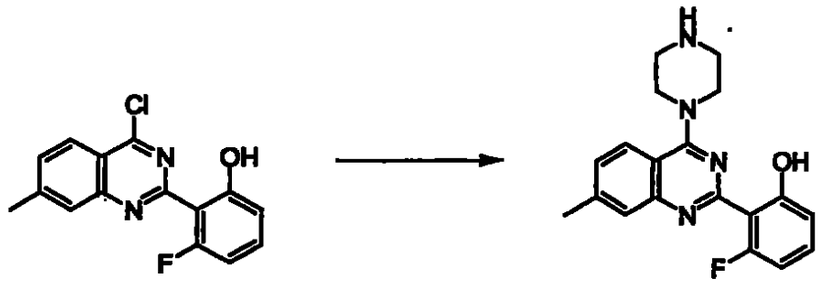


[00400] To a suspension of *N*-(2-cyano-5-methylphenyl)-2-fluoro-6-methoxybenzamide (31.5 g, 111 mmol) in ethanol (626 mL) was added 6 M aqueous NaOH solution (205 mL). After 10 minutes, 30% aqueous H_2O_2 (60 mL) was added, forming a slurry. The reaction was heated to reflux for 18 h and cooled to room temperature. NaOH (22.2 g, 0.56 mol) and 30% aqueous H_2O_2 (26 mL) were added, and the reaction was heated to reflux for six hours. The reaction cooled to room temperature, 30% aqueous H_2O_2 (45 mL) was added, and the reaction was heated to reflux for 18 h. The reaction was cooled to room temperature, NaOH (10 g, 0.25 mol) and 30% aqueous H_2O_2 (70 mL) were added, and the reaction was heated to reflux for six hours. The reaction was cooled to room temperature and poured over ice (800 mL). The pH was adjusted to 3–4 by addition of conc. HCl solution, and the precipitated off-white solid was filtered and washed with water (3 x 40 mL). The solid was dried under vacuum to provide 2-(2-fluoro-6-methoxy-phenyl)-7-methyl-3*H*-quinazolin-4-one (28 g, 89%).

pH 7. After partitioning between CH_2Cl_2 and H_2O, the mixture was separated and the aqueous layer was twice extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to a brown solid. Purification via silica gel chromatography using 75% CH_2Cl_2/ 25% hexanes gave 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol as a yellow solid (4.37 g, 66%). LC/MS: *m/z* 289.1 $(M+H)^+$ at 3.71 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 7.60 (dd, J = 8.6, 1.5 Hz, 1H), 7.42–7.36 (m, 1H), 6.86–6.82 (m, 2H), 3.81 (s, 3H), 2.64 (s, 3H)

[00407] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol

[00408]



[00409] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (4.37 g, 15.14 mmol) was suspended in CH_2Cl_2 (65 mL) under an N_2 atmosphere and placed into an ice water bath. To this solution was added a solution of piperazine (4.00 g, 45.42 mmol) and triethylamine (4.2 mL, 30.28 mmol) in CH_2Cl_2 (15 mL) in one portion. After stirring the reaction for 30 minutes, it was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted twice more with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated to a bright yellow solid which was purified via silica gel chromatography using a 95%/5% mixture of CH_2Cl_2/MeOH to afford 3-fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (4.32 g, 85%) as a bright yellow solid. LC/MS: *m/z* 339.3 $(M+H)^+$ at 1.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ~~[^1H NMR (400 MHz, DMSO-d6) δ 7.92 (d, J = 8.5 Hz, 1H), 7.63 (s, 1H), 7.39–7.30 (m, 2H), 6.78 (d, J = 8.3 Hz, 1H), 6.74–6.69 (m, 1H), 3.83 (t, J = 4.8 Hz, 4H), 2.88 (t, J = 4.9 Hz, 4H).]~~

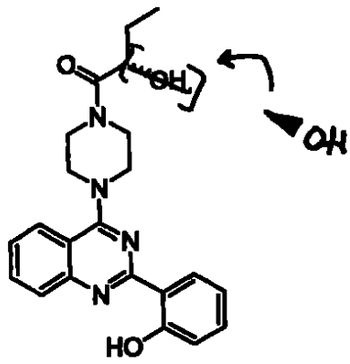
[00410] (Pyridin-4-yl)methyl 1*H*-imidazole-1-carboxylate

reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.79 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00437] Example 118

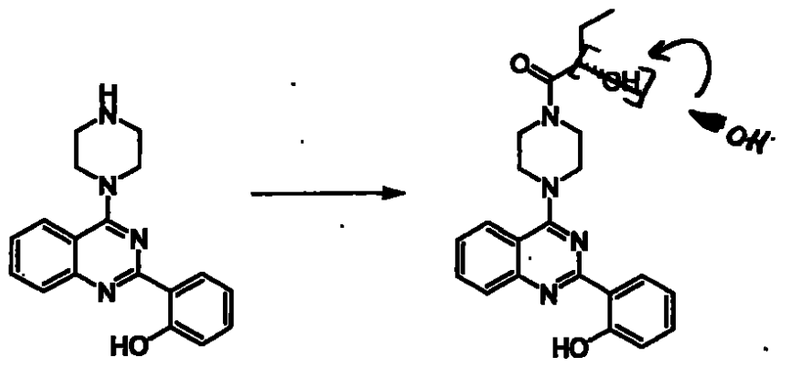
[00438] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00439]



[00440] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00441]



[00442] Method A

[00443] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*R*)-2-hydroxybutanoic acid (31 mg, 0.297 mmol), followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-(4-(2-(2-

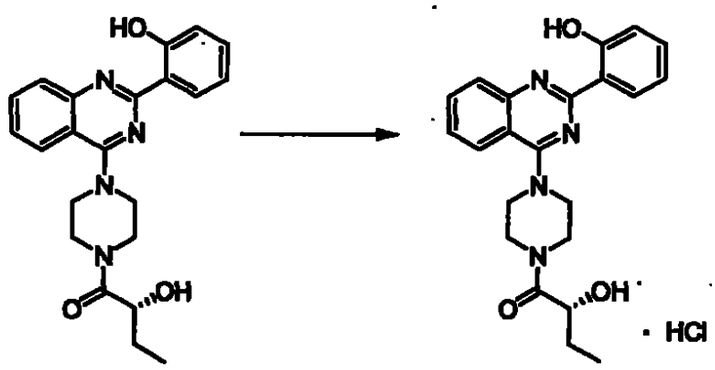
hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* ~~421.30~~ 393.30 $(M+H)^+$ at ~~2.51~~ 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00444] Method B

[00445] To a solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (250 mg, 0.82 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (227 μL, 1.63 mmol) followed by the addition of (*R*)-2-hydroxybutanoic acid (110 mg, 1.06 mmol) and HATU (380 mg, 1.00 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with H_2O. The aqueous layer was extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 CH_2Cl_2:hexanes gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one (280 mg, 88%). LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.47 (m, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.89 (m, 2H), 7.57 (m, 1H), 7.40 (m, 1H), 6.96 (m, 2H), 4.92 (d, *J* = 7.1 Hz, 1H), 3.88 (m, 8H), 1.67 (m, 1H), 1.51 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H).

[00446] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride**

[00447]



[00448] To a solution of (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one (280 mg, 0.71 mmol) in CH_2Cl_2 under an N_2 atmosphere was added a 2 M HCl solution in ether (0.355 mL, 0.71 mmol), followed by the addition of ether which resulted in the formation of precipitate which was stirred for an hour and then filtered and dried to afford (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one hydrochloride (272 mg, 90%). LC/MS: *m/z* 393.1 $(M+H)^+$ at 2.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO–d6) δ 8.27 (dd, *J* = 7.9, 1.6 Hz,

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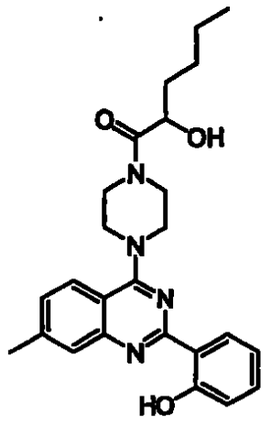
[00455] Example 120

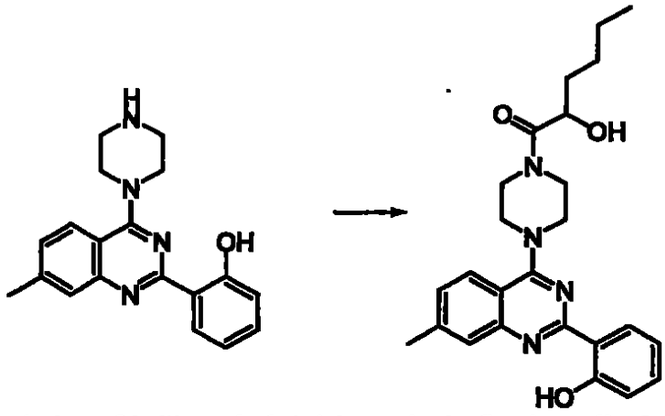
[00456] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00457]



[00458] 2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one

[00459]



[00460] A solution of 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.22 mmol) in DMF (0.5 mL) was added to 2-hydroxyhexanoic acid (37.5 mg, 0.284 mmol). It was followed by the addition of triethylamine (61 μL), then a solution of HATU (108 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)hexan-1-one as the TFA salt. LC/MS: *m/z* 435.3 $(M+H)^+$ at 2.65 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00461] ~~Example 121~~

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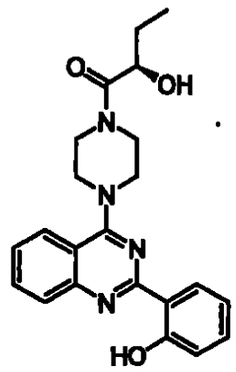
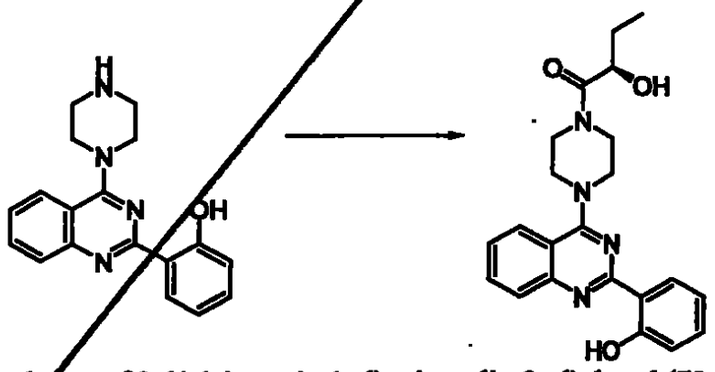
~~[00462] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one~~

[00463]



[00464] (*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one

[00465]



[00466] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to (*R*)-2-hydroxybutanoic acid (31 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL), then a solution of HATU (113 mg) in 0.5 mL DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)butan-1-one as the TFA salt. LC/MS: *m/z* 393.3 $(M+H)^+$ at 2.21 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00467] Example 122

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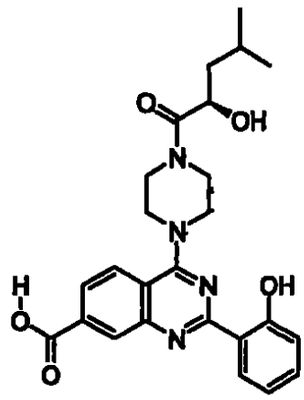
[00475]



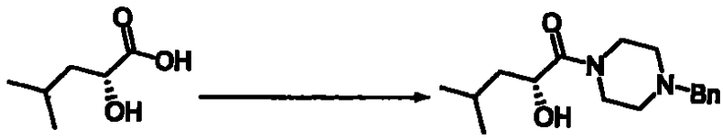
[00476] (*R*)-α-hydroxyisocaproic acid

[00477]

[00478] To a cooled solution (0–5 °C) of D-leucine (200 g, 1.5 mol) in sulfuric acid (3 L, 1 M) was added dropwise a solution of sodium nitrite (240 g, 3.5 mol) in water (1 L) while maintaining the temperature between 0–5 °C. The reaction mixture was stirred at room temperature overnight. The solution was saturated with sodium chloride and extracted with *tert*-butyl methyl ether (3x). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. (*R*)-α-hydroxyisocaproic acid was isolated as a white solid in a yield of 67% (132 g).

[00479] (*R*)-1-(4-Benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one

[00480]



[00481] To a cooled solution (0–5 °C) of (*R*)-α-hydroxyisocaproic acid (64.5 g, 0.5 mol), 1-benzylpiperazine (88 g, 0.5 mol) and triethylamine (71 ml, 0.5 mol) in CH_2Cl_2 (850 ml) was added in portions HOBt (68 g, 0.5 mol) and EDCI·HCl (96 g, 0.5 mol). The reaction mixture was stirred at room temperature overnight. The organic layer was washed with water (3x) and once with brine, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo*. Crude

(R)-1-(4-benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one ~~1-(4-benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one~~ (132 g, 91%) was used in the next step without further purification

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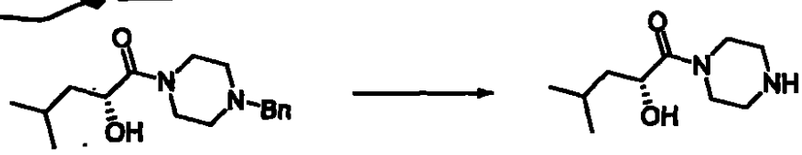
[00481] (R) 2-Hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one



[00482] To a solution of 1-(4-benzyl-piperazin-1-yl)-2-hydroxy-4-methyl-pentan-1-one (132 g) in methanol (1 L) was added Pd/C (20 g,10% weight Pd on carbon). The reaction mixture was stirred at room temperature overnight under an atmosphere of hydrogen. The reaction mixture was filtered through Celite, and the solvent was removed *in vacuo*. (R)-2-Hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one was obtained as an oil (68 g, 74%).

[00483] 1,2,3,4-Tetrahydro-2,4-dioxoquinazoline-7-carboxylic acid

[00484] To a stirring mixture of dimethyl 2-aminobenzene-1,4-dioate (10.5 g, 50 mmol) and AcOH (3.4 mL, 60 mmol) in H_2O (200 mL) was added KOCN (8.1 g, 100 mmol). The reaction mixture was heated at 100 °C for 3 h. After cooling in an ice bath, NaOH (24 g, 600 mmol) was slowly added to the mixture and stirred for another 3 h at room temperature. Acidification with concentrated HCl resulted in formation of a yellow solid which was filtered, washed with water and dried under vacuum (8.3 g). NMR data showed that the solid consisted of a 3:1 mixture of the desired 1,2,3,4-tetrahydro-2,4-dioxoquinazoline-7-carboxylic acid and a side product. This mixture was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.98 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.67 (dd, J = 8.2, 1.4 Hz, 1H).

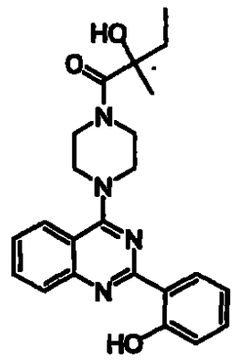
[00485] 2,4-Dichloroquinazoline-7-carboxylic acid

[00554] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.077 mmol), 2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (14.3 mg, 0.10 mmol), triethylamine (22μL, 0.154 mmol), and HATU (38 mg, 0.10 mmol) were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 1-(4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanone. LC/MS: *m/z* 451.5 $(M+H)^+$ at 2.60 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00555] Example 129

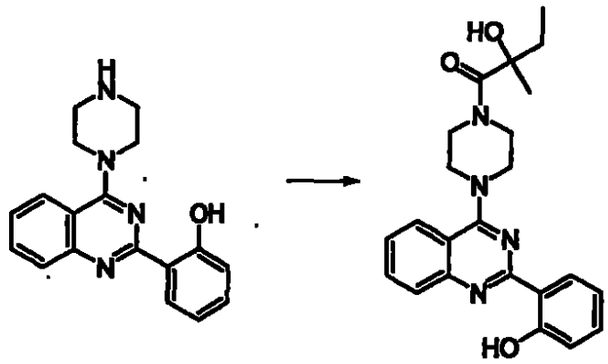
[00556] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one**

[00557]



[00558] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one**

[00559]



[00560] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (70 mg, 0.23 mmol) in DMF (0.5 mL) was added to 2-hydroxy-2-methylbutanoic acid (39.3 mg, 0.297 mmol). It was followed by the addition of triethylamine (63 μL) and a solution of HATU (113 mg) in 0.5 mL

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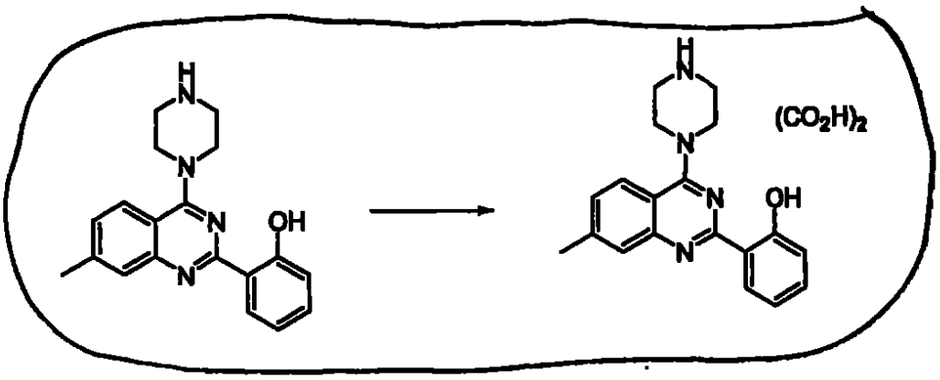
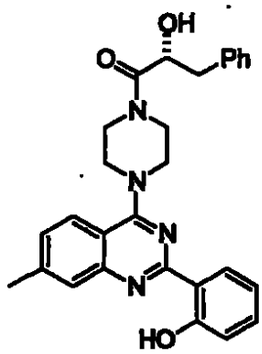


~~[00557]~~ ← DMF at room temperature. The reaction was stirred overnight. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-hydroxy-1-(4-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one as the TFA salt. LC/MS: *m/z* 407.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00558] Example 130

[00559] (*R*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}~~[2-phenyl-ethanone]~~

3-phenylpropan-1-one

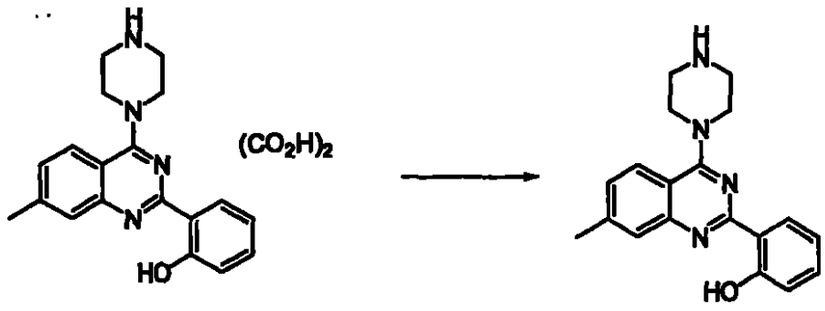


[00560] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol, oxalate salt

[00561] To 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (30.6 g, 95.4 mmol) in 900 mL CH_2Cl_2 was added oxalic acid (9.45 g, 105 mmol, 1.1 eq.) dissolved in 36 mL of methanol. The resulting cloudy solution was stirred for 3h and the resulting solid was filtered, washed with hexanes, and dried to give 29.3 g (75 %) the oxalate salt of 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol. LC/MS: *m/z* 321.2 $(M+H)^+$ at 2.36 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00562] 2-(7-Methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol

525

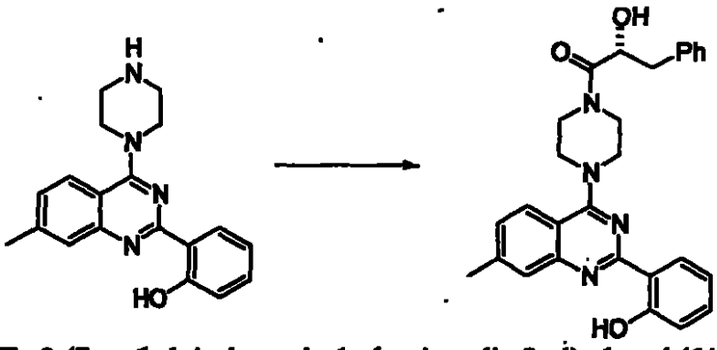


[00568]

[00569] To the oxalate salt of 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (1.32 g, 3.2 mmol) in 10 mL of CH_2Cl_2 was added triethylamine (2.2 mL, 16.0 mmol) at room temperature. The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with 10 mL of water, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol as an oil which was used without further purification.

[00570] (*R*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-~~2-phenyl-ethanone~~

[00571] 3-phenylpropan-1-one



[00572] To 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (64 mg, 0.19 mmol) in 600 µL of CH_2Cl_2 was added sequentially 3-(*R*)-phenyl lactic acid (35 mg, 0.21 mmol), BOP (93 mg, 0.21 mmol), and triethylamine (27.7 µL, 0.2 mmol) at room temperature. The reaction mixture was stirred for 1.5 h, diluted with 10 mL of methylene chloride, and washed with water (2 x 10 mL). The solvent was removed under reduced pressure to give an oil which was purified by normal phase LC (35%–100% EtOAc/ hexanes) to give (*R*)-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-~~2-phenyl-ethanone.~~ 3-phenylpropan-1-one LC/MS: *m/z* 469.3 $(M+H)^+$ at 2.87 min (10%–99%·CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00573] Example 131

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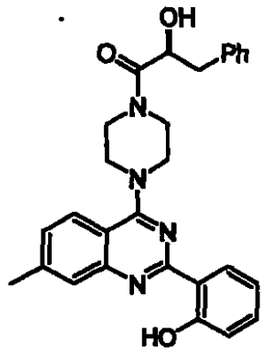
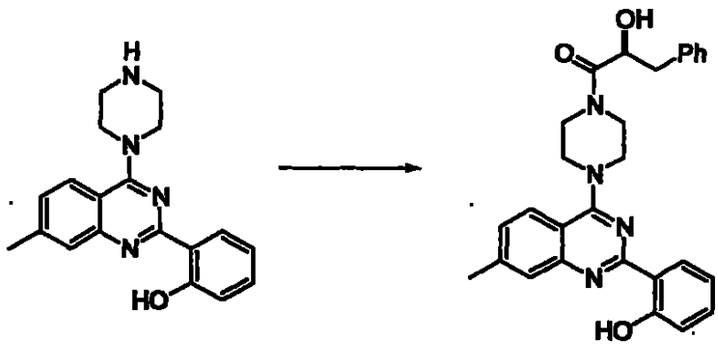
[00574] (*S*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-~~2-phenyl-ethanone~~

[00575] 3 phenylpropan-1-one



[00576] (*S*)-2-Hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-~~2-phenyl-ethanone~~

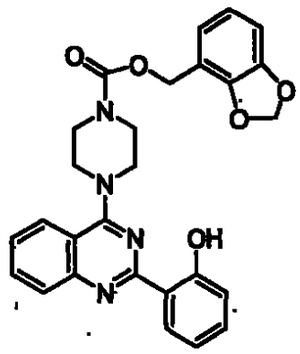
[00577] 3 phenylpropan-1-one



[00578] To 2-(7-methyl-4-piperazin-1-yl-quinazolin-2-yl)-phenol (79.9 mg, 0.25 mmol) in 800 μL of CH_2Cl_2 was added sequentially 3-~~(R)~~(S)-phenyl lactic acid(41.4 mg, 0.25 mmol), BOP(110 mg, 0.25 mmol), triethylamine (34.7 μL, 0.25 mmol) at room temperature. The reaction mixture was stirred for 1.5 h, diluted with 10 mL of methylene chloride, and washed with water (2 x 10 mL). The solvent was removed under reduced pressure to give an oil which was purified by normal phase LC (35%-100% EtOAc/hexanes) to give (*S*)-2-hydroxy-1-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-~~2-phenyl-ethanone~~ 3-phenylpropan-1-one. LC/MS: *m/z* 469.4 $(M+H)^+$ at 2.88 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00579] Example 132

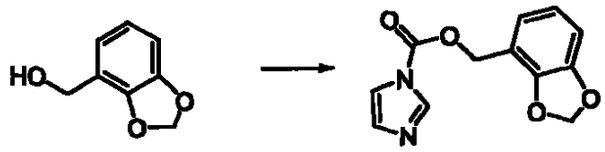
527 524



[00658]

[00659] (Benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate

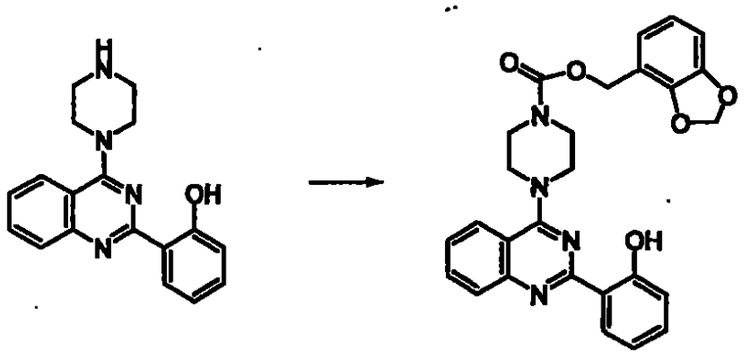
[00660]



[00661] A solution of (benzo[d][1,3]dioxol-7-yl)methanol (2.0 g, 13.1 mmol) and di(1*H*-imidazol-1-yl)methanone (4.26 g, 26.2 mmol) in 20 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was quenched with water and extracted with CH_2Cl_2, and the combined layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 10–70% EtOAc in CH_2Cl_2 gave (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (2.8 g, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, J = 0.9 Hz, 1H), 7.44 (t, J = 1.4 Hz, 1H), 7.07 (dd, J = 1.6, 0.8 Hz, 1H), 6.95 (m, 2H), 6.84 (m, 1H), 6.01 (s, 2H), 5.33 (s, 2H).

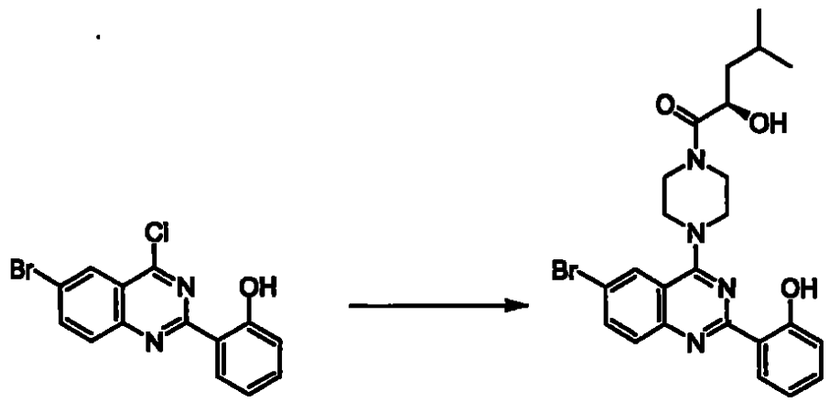
[00662] (Benzo[d][1,3]dioxol-7-yl)methyl ~~4-(4a,8a-dihydro-2-(2-~~ 1-(2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00663]



[00664] A solution of 2-(4-(piperazin-1-yl)quinazolin-2-yl)phenol (50 mg, 0.16 mmol), (benzo[d][1,3]dioxol-7-yl)methyl 1*H*-imidazole-1-carboxylate (78 mg, 0.32 mmol), and

528 655



[00699]

[00700] Method A

[00701] To a solution of 2-(6-bromo-4-chloroquinazolin-2-yl)phenol (228 mg, 0.68 mmol), triethylamine (129 μL, 0.92 mmol), and CH_2Cl_2 (6 mL) was added (*R*)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (185 mg, 0.92 mmol) dissolved in CH_2Cl_2 (3 mL). The flask was flushed with N_2 and stirred for 3 hours. The reaction mixture was then transferred into a separatory funnel with CH_2Cl_2, and the organic phase was washed with H_2O (2x), dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0 to 20% EtOAc and CH_2Cl_2:hexanes (1:1) gave (*R*)-1-(4-(6-bromo-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (285 mg, 84%). LC/MS: *m/z* 500.30 $(M+H)^+$ at 3.29 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

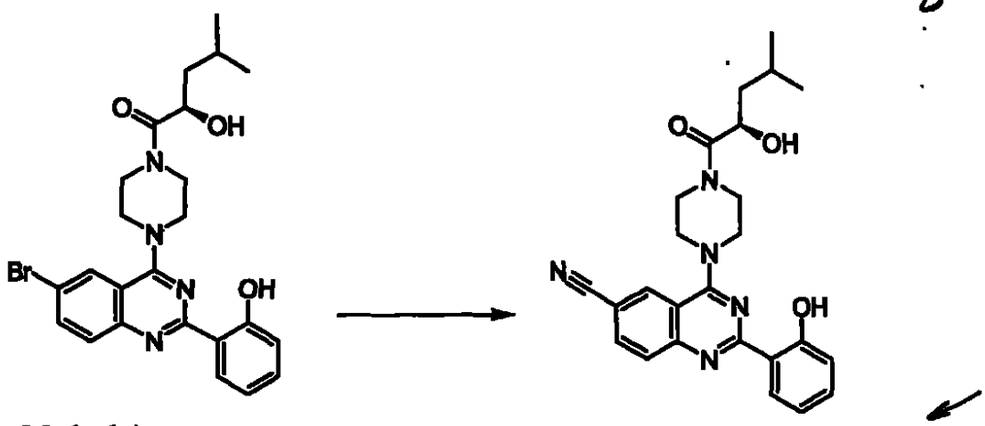
[00702] Method B

[00703] A solution of 6-bromo-4-chloro-2-(2-hydroxyphenyl)quinazoline (75 mg, 0.22 mmol), (*R*)-2-hydroxy-4-methyl-1-piperazin-1-yl-pentan-1-one (60 mg, 0.3 mmol), triethylamine (42 μL, 0.3 mmol), and CH_2Cl_2 (2 mL) was stirred at room temperature overnight. After diluting with CH_2Cl_2, the reaction mixture was washed with H_2O, dried over Na_2SO_4, and concentrated. The crude material was purified by silica gel chromatography using 0–10% MeOH/CH_2Cl_2 to give (*R*)-1-{4-[6-bromo-2-(2-~~methoxy-phenyl~~ hydroxyphenyl)-quinazolin-4-yl]-piperazin-1-yl}-2-hydroxy-4-methyl-pentan-1-one (40 mg, 36%). ~~[LC/MS: *m/z* 449.3 $(M+H)^+$ at 3.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).]~~

[00704] 4-[4-((*R*)-2-Hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile

529 530

[00705]



[00706] Method A

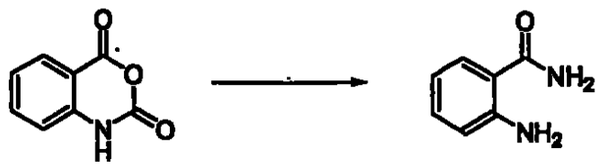
[00707] A mixture of (*R*)-1-{4-[6-bromo-2-(2-~~methoxy-phenyl~~hydroxyphenyl)-quinazolin-4-yl]-piperazin-1-yl}-2-hydroxy-4-methyl-pentan-1-one (20 mg, 0.04 mmol), $Zn(CN)_2$ (4.7 mg, 0.04 mmol), and $Pd(PPh_3)_4$ (1.4 mg, 1.4 μmol) in DMF (0.5 mL) was heated in a microwave synthesizer at 200 °C for 15 minutes Purification via preparative HPLC gave 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile as the TFA salt. LC/MS: *m/z* 446.3 $(M+H)^+$ at 3.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00708] Method B

[00709] (*R*)-1-(4-(6-Bromo-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (188 mg, 0.38 mmol), $Zn(CN)_2$ (44 mg, 0.38 mmol), and $Pd(Ph_3)_4$ (6.5 mg, 0.0112 mmol) were dissolved in DMF (4 mL) and the reaction mixture was heated in a microwave synthesizer at 200 °C for 15 minutes EtOAc (50 mL) was added and the mixture was washed twice with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–40% EtOAc in CH_2Cl_2:hexanes (1:1) gave 4-[4-((*R*)-2-hydroxy-4-methyl-pentanoyl)-piperazin-1-yl]-2-(2-hydroxy-phenyl)-quinazoline-6-carbonitrile (127 mg, 75%). LC/MS: *m/z* 446 $(M+H)^+$ at 3.24 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^1H NMR (400 MHz, DMSO-d6) δ 8.60 (d, $J = 1.5$ Hz, 1H), 8.46 (dd, $J = 8.4$, 1.8 Hz, 1H), 8.15 (dd, $J = 8.7$, 1.7 Hz, 1H), 8.00 (d, $J = 8.7$ Hz, 1H), 7.45–7.41 (m, 1H), 6.99–6.95 (m, 2H), 4.94 (d, $J = 7.0$ Hz, 1H), 4.39–4.36 (m, 1H), 4.14–4.04 (m, 4H), 3.89–3.67 (m, 4H), 1.82–1.76 (m, 1H), 1.47–1.37 (m, 2H), 0.93–0.91 (m, 6H).

530 522

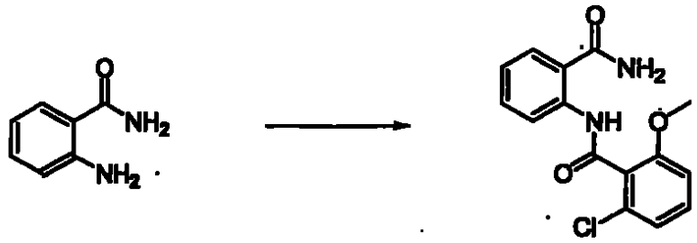
[00744]



[00745] Isatoic anhydride (40 g, 245 mmol) was suspended in 650 mL 1 N NH_4OH (2.5 equiv) and stirred at room temperature for 3 days. The precipitate was filtered and washed with water. The product was then dissolved in THF, filtered, and concentrated to dryness. The product was dried by azeotropic distillation with toluene and washed with CH_2Cl_2 to yield 10.9 g (32.7%) of 2-amino-benzamide.

[00746] ~~[2-Chloro-*N*-(2-carboxylic acid amide-phenyl)-2-methoxy-benzamide.]~~

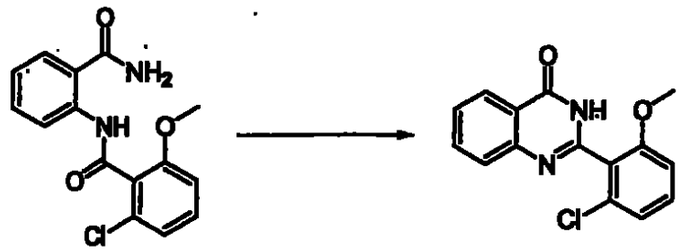
[00747] *N*-(2-carbamoylphenyl)-2-chloro-6-methoxybenzamide



[00748] 2-Amino-benzamide (6.9 g, 50.8 mmol) was dissolved in 50 mL of pyridine and cooled to 0 °C. 2-Chloro-6-methoxy-benzoyl chloride was added dropwise to the solution. After complete addition, the reaction was left to stir at room temperature for three days, which resulted in formation of a brown, cloudy solution. The reaction mixture was then poured into 150 mL of ice water. The precipitate was filtered and washed twice with water, twice with THF and finally twice with CH_2Cl_2 to obtain ~~[2-chloro-*N*-(2-carboxylic acid amide-phenyl)-2-methoxy-benzamide]~~ (13.3 g, 43.7 mmol, 86%). *N*-(2-carbamoylphenyl)-2-chloro-6-methoxybenzamide

[00749] **2-(2-Chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one**

[00750]



N-(2-carbamoylphenyl)-2-chloro-6-methoxybenzamide

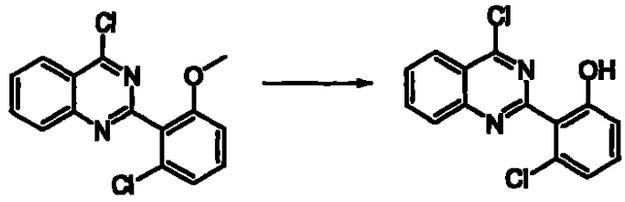
[00751] ~~2-Chloro-*N*-(2-carboxylic acid amide-phenyl)-2-methoxy-benzamide~~ (13 g, 42.7 mmol) was suspended in 100 mL of a 2 N NaOH solution and heated to reflux. After refluxing for 3 hours, another 25 mL of a 2 N NaOH solution was added, and the reaction was refluxed for another hour. The mixture was cooled to room temperature and acidified with acetic acid to pH 5. The formed precipitate was collected by filtration. The product was purified over alumina using EtOAc as an eluent giving 1.7 g (5.9 mmol, 14%) of 2-(2-chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one.

[00752] **4-Chloro-2-(2-chloro-6-methoxy-phenyl)-quinazoline**

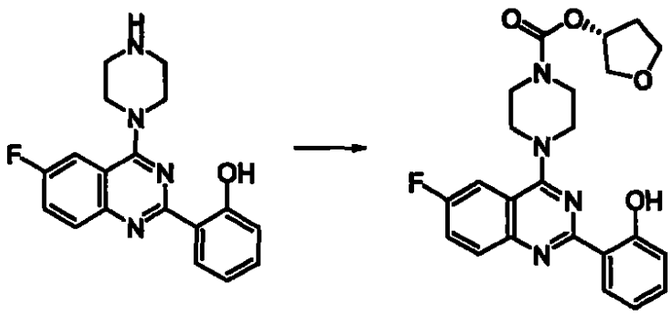
[00753]

[00754] 2-(2-Chloro-6-methoxy-phenyl)-3*H*-quinazolin-4-one (1.7 g, 5.9 mmol) was dissolved in 25 mL benzene. Then, *N,N*-dimethylaniline (1.15 mL, 9 mmol)and $POCl_3$ (1.65 mL, 17.7 mmol) were added. The reaction mixture was refluxed for 3 hours during which the yellow suspension changed to a dark red color. The mixture was cooled and diluted with 50 mL toluene. The solution was poured onto ice. Saturated aq. $NaHCO_3$ was added while stirring and cooling the mixture until the pH remained constant at 7. The layers were separated, and the aqueous layer was extracted with 100 mL toluene. The toluene layers were combined and washed with 100 mL saturated aqueous NaCl solution, 150 mL 0.5 N HCl, 150 mL 5% aq. $NaHCO_3$ and saturated aqueous NaCl solution. The toluene layer was dried over Na_2SO_4, filtered, and concentrated to dryness to yield 1.87 g impure product. The product was purified over silica gel with heptane/CH_2Cl_2 (2:1) as an eluent to yield 4-chloro-2-(2-chloro-6-methoxy-phenyl)-quinazoline (1.22 g, 64%).

[00755] **3-Chloro-2-(4-chloroquinazolin-2-yl)phenol**



[00756]



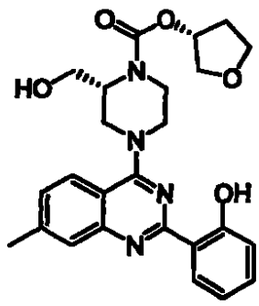
[00781]

[00782] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.08 mmol), (*R*)-tetrahydrofuran-3-yl chloroformate (12 mg, 0.08 mmol), triethylamine (22 μL, 0.154 mmol) ~~and HATU (38 mg, 0.10 mmol)~~ were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-tetrahydrofuran-3-yl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.80 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00783] Example 149

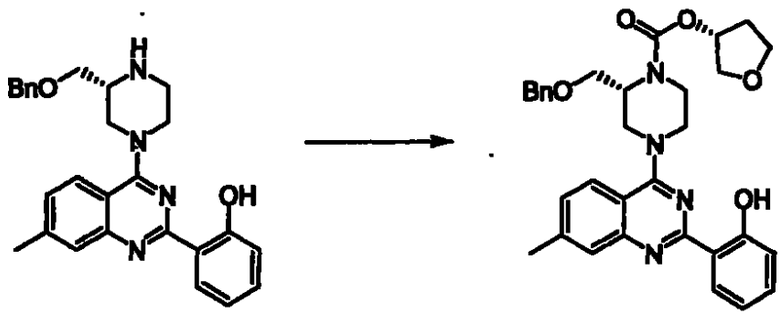
[00784] **(2*R*)-(*R*)-Tetrahydrofuran-3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00785]



[00786] **(2*R*)-(*R*)-Tetrahydrofuran -3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

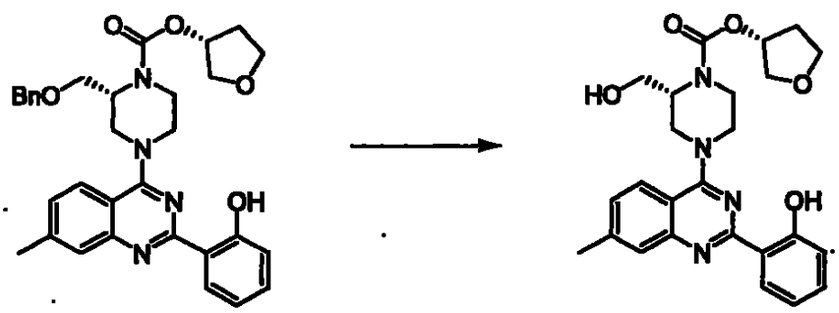
[00787]



[00788] To a solution of 2-(4-((*R*)-3-((benzyloxy)methyl)piperazin-1-yl)-7-methylquinazolin-2-yl)phenol (75 mg, 0.17 mmol) in DMF (1 mL) was added triethylamine (47 μL) followed by the dropwise addition of (*R*)-tetrahydrofuran-3-yl chloroformate (25 mg, 0.17 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 10 minutes. Purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. ~~[LC/MS: *m/z* 455.3 $(M+H)^+$ at 2.95 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).]~~

[00789] **(2*R*)-(*R*)-Tetrahydrofuran -3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate**

[00790]



[00791] To a solution of (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-((benzyloxy)methyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate TFA salt (94 mg, 0.17 mmol) in ethanol was added $Pd(OH)_2$ (78 mg), and the reaction was heated at 50 °C under an H_2 atmosphere at ambient pressure. The reaction was filtered, and purification using reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (2*R*)-(*R*)-tetrahydrofuran-3-yl 2-(hydroxymethyl)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate trifluoroacetate. LC/MS: *m/z* 465.5 $(M+H)^+$ at 2.23 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

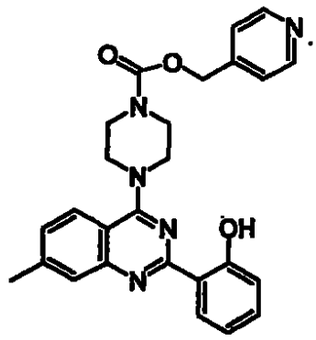
[00792] Example 150

[00793] **(*R*)-2-Hydroxy-1-(4-(2-(2-hydroxy-6-methylphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

[00829] A mixture of 4-((*R*)-2-hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester (0.13 g, 0.39 mmol) and MeOH (4 mL) was stirred with 10 mg of Pd/C (10% wt Pd on carbon)under H_2 atmosphere at ambient preasure overnight. After filtration and evaporation of the solvent, the residue was taken up in CH_2Cl_2, and 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.11 g, 0.39 mmol) and triethylamine (0.11 mL, 0.78 mmol) were added. The reaction mixture was stirred at room temperature overnight, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 provided (*R*)-2-hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)pentane-1,4-dione as a yellow solid (91 mg, 54%). LC/MS: *m/z* 435.5 $(M+H)^+$ at 2.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

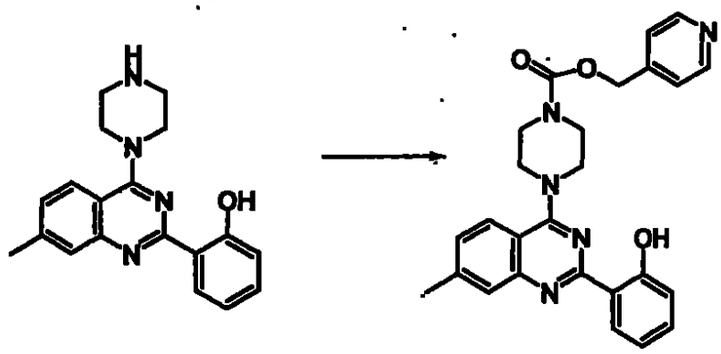
[00830] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00831]

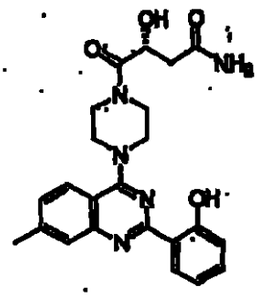


[00832] (Pyridin-4-yl)methyl 4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate.

[00833]

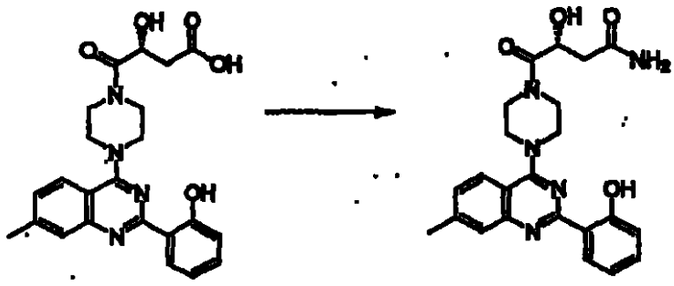


535



[00841]

[00842] (*R*)-3-Hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanamide



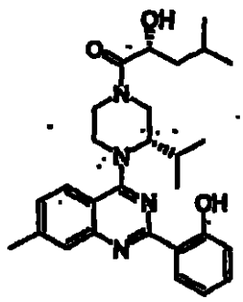
[00843]

[00844] (*R*)-3-Hydroxy-4-{4-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperazin-1-yl}-4-oxo-butyric acid (17 mg, 0.039 mmol) and HATU (16 mg, 0.043 mmol) were stirred in DMF (0.5 mL). After adding 0.5 M NH_3 in dioxane (0.38 mL, 0.19 mmol), the reaction mixture was stirred at room temperature for 5 h. Purification via preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*R*)-3-hydroxy-4-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-oxobutanamide as the TFA salt. LC/MS: *m/z* 436.3 $(M+H)^+$ at 1.94 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00845] Example 155

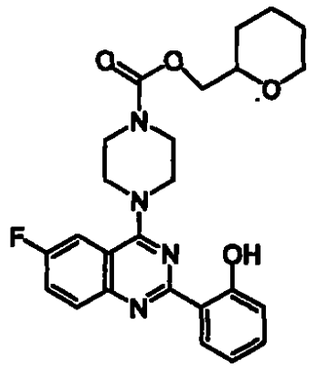
[00846] (*R*)-2-Hydroxy-1-((*S*)-4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)-3-isopropylpiperazin-1-yl)-4-methylpentan-1-one

~~[00847] 2-(4-((*S*)-4-Benzyl-2-isopropylpiperazin-1-yl)-7-methylquinazolin-2-yl)phenol~~



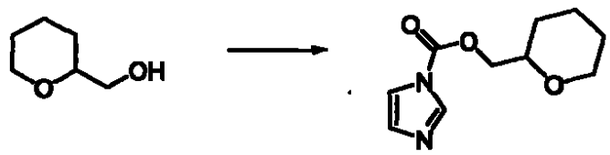
[00890] (Tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate

[00891]



[00892] (Tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate

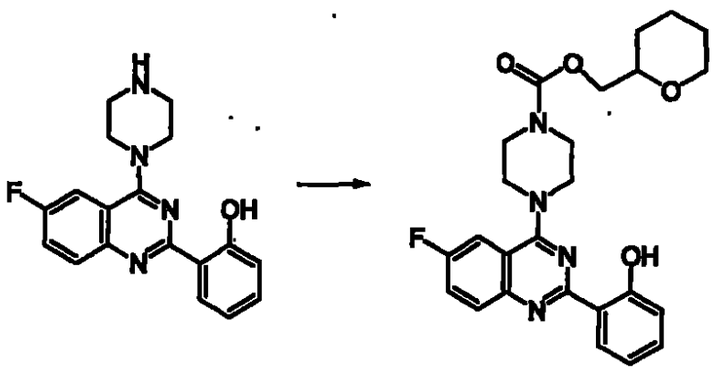
[00893]



[00894] A solution of (tetrahydro-2*H*-pyran-2-yl)methanol (1 g, 8.60 mmol) and di(1*H*-imidazol-1-yl)methanone (2.8 g, 17.2 mmol) in 17 mL CH_2Cl_2 was heated overnight at 50 °C The reaction was quenched with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. ~~[^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, J = 0.9 Hz, 1H), 7.44 (t, J = 1.4 Hz, 1H), 7.07 (dd, J = 1.6, 0.8 Hz, 1H), 6.95 (m, 2H), 6.84 (m, 1H), 6.01 (s, 2H), 5.33 (s, 2H)]~~

[00895] (Tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl) quinazolin-4-yl)piperazine-1-carboxylate

[00896]

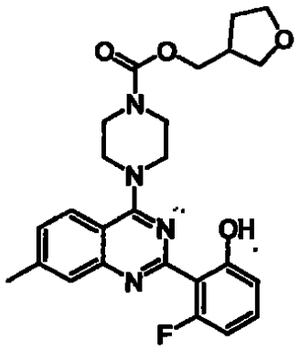


[00897] 2-(6-Fluoro-4-(piperazin-1-yl)quinazolin-2-yl)phenol (25 mg, 0.077 mmol), (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (48.5 mg, 0.23 mmol), triethylamine (22μL, 0.154 mmol), ~~and HATU (38 mg, 0.10 mmol)~~ were stirred in DMF (1 mL) overnight. Purification via reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (tetrahydro-2*H*-pyran-2-yl)methyl 4-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 467.3 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00898] Example 162

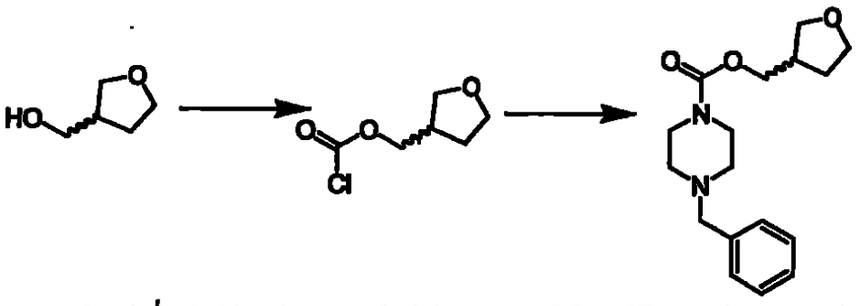
[00899] (Tetrahydrofuran-3-yl)methyl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate

[00900]



[00901] 4-Benzyl-piperazine-1-carboxylic acid tetrahydro-furan-3-ylmethyl ester

[00902]



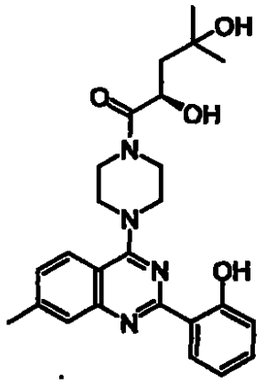
[00903] To a cooled (0 °C) solution of triphosgene (5.0 g, 17 mmol) in 50 ml dichloromethane under a nitrogen atmosphere was added dropwise a solution of tetrahydro-3-furanmethanol (5.4 g, 53 mmol) in 10 ml dichloromethane. Pyridine (4.3 ml, 53 mmol) was added dropwise, and the solution was warmed to room temperature. After 2 hours at room temperature a mixture of triethylamine (7.5 ml, 52 mmol) and *N*-benzylpiperazine (9.5 ml, 54

[00915] 3-Fluoro-2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol ~~2-(7-Methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol~~ (70 mg, 0.21 mmol) was dissolved in 1 mL anhydrous DMF under an N_2 atmosphere and cooled to 0 °C. (*S*)-Tetrahydrofuran-3-yl chloroformate (34.3 mg, 0.228 mmol) was dissolved in 150 µL anhydrous DMF and added dropwise to the reaction, followed by triethylamine (42 mg, 0.41 mmol). After 1 hour the reaction was complete, and it was filtered and purified by reverse phase HPLC to give (*S*)-tetrahydrofuran-3-yl 4-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazine-1-carboxylate as the TFA salt. LC/MS: *m/z* 453.3 $(M+H)^+$ at 2.25 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00916] Example164

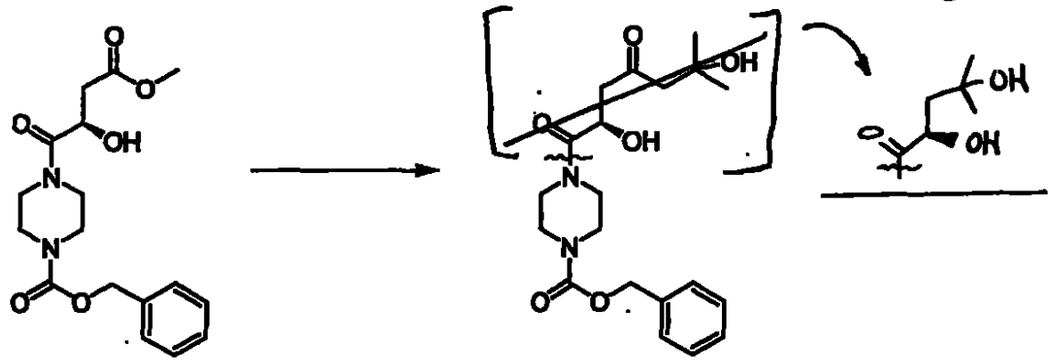
[00917] -2,4- (*R*)-~~2,6-~~Dihydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)~~6-methylheptane-1,4-dione~~

[00918] 4-methylpentan-1-one



[00919] ~~4-((*R*)-2,6-Dihydroxy-6-methyl-4-oxo-heptanoyl)-piperazine-1-carboxylicacid benzyl ester~~ (*R*)-Benzyl-4-(2-hydroxy-4-methoxy-4-oxobutanoyl)piperazine-1-carboxylate

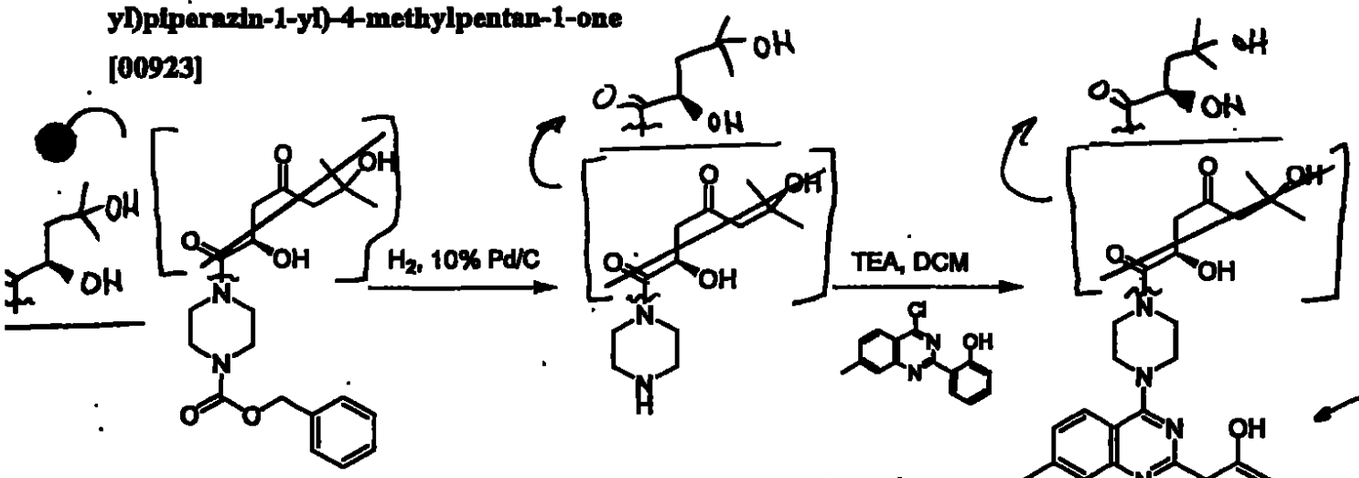
[00920]



[00921] To a solution of 4-((*R*)-2-hydroxy-3-methoxycarbonyl-propionyl)-piperazine-1-carboxylic acid benzyl ester (5.26 g, 15.0 mmol) in THF (150 mL) cooled in a dry ice acetone bath was added 1.4 M MeMgBr (32 mL, 45 mmol). The reaction was allowed to slowly warm to room temperature overnight. After quenching the mixture with saturated NH_4Cl and extracting with EtOAc, the combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave 4-((*R*)-2-hydroxy-4-oxo-pentanoyl)-piperazine-1-carboxylic acid benzyl ester as a colorless oil (0.79 g, 15%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 5.15 (s, 2H), 4.71–4.68 (m, 1H), 4.05 (d, J = 6.8 Hz, 1H), 3.80–3.73 (m, 1H), 3.62–3.42 (m, 6H), 3.31–3.23 (m, 1H), 1.72–1.61 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H); *LC/MS*: *m/z* 351.3 $(M+H)^+$ at 2.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00922] **(*R*)-2,4-Dihydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-4-methylpentan-1-one**

[00923]



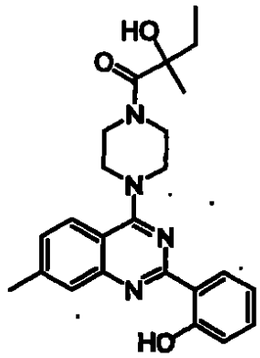
[00924] A mixture of 4-((*R*)-2,6-dihydroxy-6-methyl-4-oxo-heptanoyl)-piperazine-1-carboxylic acid benzyl ester (0.79 g, 2.20 mmol) and MeOH (25 mL) was stirred with 40 mg of Pd/C (10% wt Pd on carbon) under H_2 atmosphere at ambient pressure overnight. After filtration and evaporation of the solvent, the residue was taken up in CH_2Cl_2, and 2-(4-chloro-7-methylquinazolin-2-yl)phenol (0.61 g, 2.20 mmol) and triethylamine (0.63 mL, 4.50 mmol) were added. The reaction mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography using 0–10% MeOH/CH_2Cl_2 gave (*R*)-2,6-dihydroxy-1-(4-(2-(2-

hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-6-methylheptane-1,4-dione as a yellow solid (372 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, J = 7.9, 1.6 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.67 (s, 1H), 7.40–7.36 (m, 1H), 7.29 (dd, J = 8.5, 1.4 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.96–6.92 (m, 1H), 4.81–4.76 (m, 1H), 4.09 (d, J = 6.8 Hz, 1H), 4.03–3.77 (m, 6H), 3.75–3.67 (m, 2H), 3.28 (s, 1H), 2.55 (s, 3H), 1.78–1.69 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 164.0, 161.3, 160.5, 150.1, 144.5, 132.7, 129.2, 127.7, 126.8, 124.4, 119.3, 118.5, 117.7, 112.7, 70.6, 66.4, 49.9, 49.0, 46.1, 44.5, 42.4, 30.6, 29.2, 21.9; LC/MS: *m/z* 451.1 $(M+H)^+$ at 2.12 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[00925] Example 165

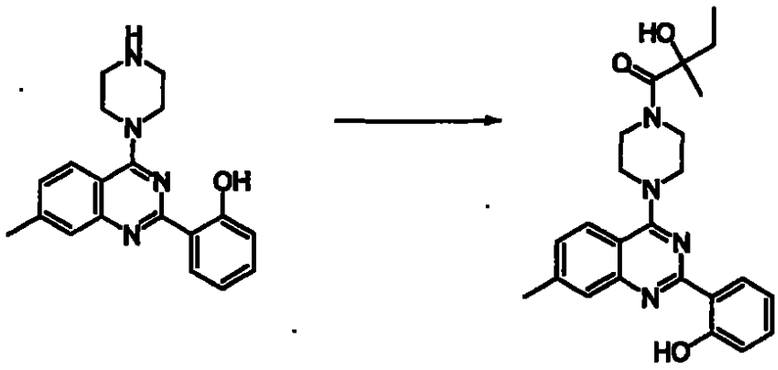
[00926] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one**

[00927]



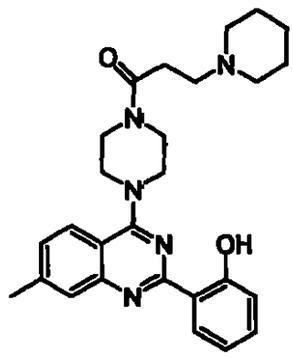
[00928] **2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-methylbutan-1-one**

[00929]



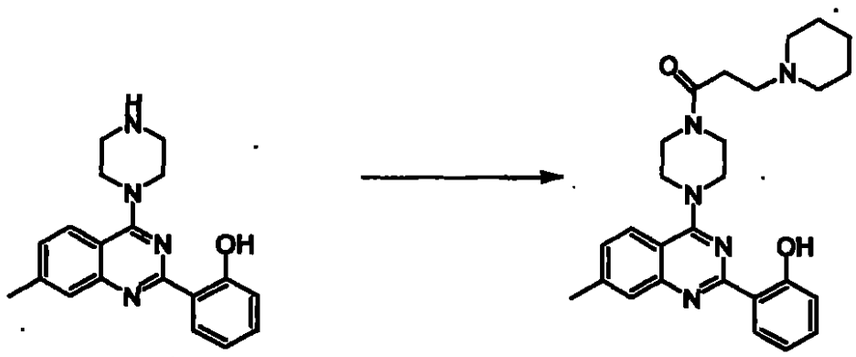
[001002] 1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(piperidin-1-yl)propan-1-one

[001003]



[001004] 1-(4-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(piperidin-1-yl)propan-1-one

[001005]



[001006] To 2-(7-methyl-4-(piperazin-1-yl)quinazolin-2-yl)phenol (53 mg, 0.17 mmol) was added sequentially 3-(piperidin-1-yl)propanoyl chloride (33 mg, 0.19 mmol) in 28 μL of CH_2Cl_2 and triethylamine (28 μL, 0.2 mmol). The mixture was stirred at 0 °C for 20 minutes After adding H_2O and CH_2Cl_2, the phases were separated, and the organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification using preparative reverse phase HPLC with 10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) gave 1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-(piperidin-1-yl)propan-1-one bis as the TFA salt. LC/MS: *m/z* 460.5 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001007] Example 176

[001008] (2*R*,3*R*)-2-Hydroxy-1-(4-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-3-methylpentan-1-one

[001144]

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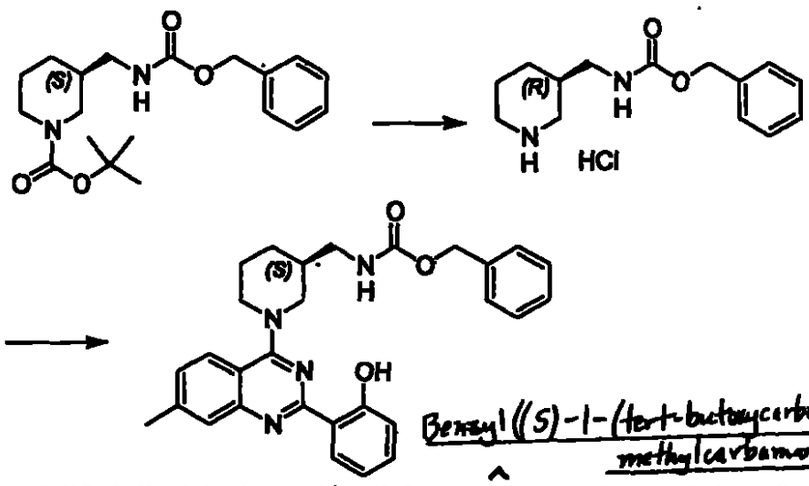


Benzyl ((S)-1-(tert-butoxycarbonyl)piperidin-3-yl) methylcarbamate

[001145] [Benzyl ((S)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate] (895 mg, 2.57 mmol) was treated with a 4.0 M HCl solution in dioxane (3.2 mL, 12.85 mmol). Formation of a white precipitate was observed. After 3 h, complete conversion of starting material was seen by TLC. The solvent and excess HCl were removed under reduced pressure to obtain benzyl ((*R*)-piperidin-3-yl)methylcarbamate hydrochloride as a white solid.

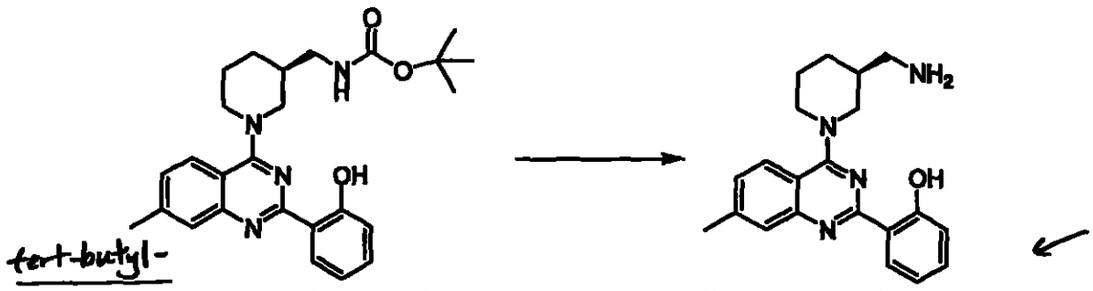
This solid was suspended in DMF/CH_2Cl_2 (3 mL/3 mL), followed by the addition of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (696 mg, 2.57 mmol), and triethylamine (1.8 mL, 1.3 g, 12.85 mmol). The mixture was stirred at room temperature under an N_2 atmosphere for 16 h. The reaction was then partitioned between H_2O/CH_2Cl_2, and separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography using 0–5% MeOH in CH_2Cl_2 gave benzyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as a thick yellow oil (610 mg, 49%). LC/MS: *m/z* 483.3 $(M+H)^+$ at 2.83 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001146] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol

$MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0–2% EtOAc in CH_2Cl_2 gave *tert*-butyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (700 mg, 88%). LC/MS: *m/z* 449.5 $(M+H)^+$ at 2.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

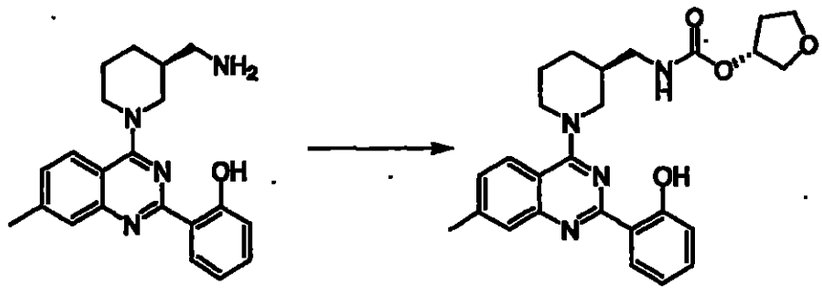
[001162] **2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol**

[001163]



[001164] To ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (700 mg, 1.56 mmol) was added 20 mL CH_2Cl_2 followed by addition of 7 mL of TFA. After the reaction was stirred for 1 hour it was neutralized with a1.0 M aqueous NaOH solution. The mixture was partitioned between H_2O and CH_2Cl_2, and separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (400 mg, 74%). LC/MS: *m/z* 349.3 $(M+H)^+$ at 1.52 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ~~^{1}H NMR (400 MHz, DMSO-d6) δ 8.43–8.45 (m, 1H), 7.95 (d, *J*=8.5 Hz, 1H), 7.64 (s, 1H), 7.35–7.39 (m, 2H), 6.92–6.96 (m, 2H), 4.52 (d, *J*=12.5 Hz, 1H), 4.41 (d, *J*=13.2 Hz, 1H), 3.26–3.29 (m, 2H), 3.02–3.08 (m, 1H), 2.55–2.61 (m, 1H), 2.45–2.48 (m, 1H), 1.84–1.91 (m, 2H), 1.65–1.77 (m, 3H), 1.24–1.36 (m, 1H).~~

[001165] **(*R*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**



[001166]

[001173] Method A

[001174] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, and (*S*)-tetrahydrofuran-3-yl chloroformate (31 mg, 0.2 mmol) in DMF (100 μL) was added dropwise followed by triethylamine (35 mg, 48 μL, 0.34 mmol). The reaction was allowed to warm to room temperature. The reaction was complete after two hours. Purification using preparative HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001175] Method B

[001176] 2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (126.8 mg, 0.364 mmol) was dissolved in 5 mL anhydrous DMF and cooled to 0 °C, and a solution of (*S*)-tetrahydrofuran-3-yl chloroformate (65.4 mg, 0.436 mmol) in 200 μl of DMF was added dropwise followed by the addition of triethylamine (74 mg, 0.102 mL, 0.728 mmol). The reaction was allowed to warm to room temperature and was complete after two hours. The mixture was partitioned between H_2O and CH_2Cl_2, separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to a yellow solid. Purification via silica gel chromatography using 98% CH_2Cl_2/2% MeOH gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as an off white solid (116 mg, 69%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) [~~^{1}H NMR (400 MHz, DMSO-d6) δ 8.42 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.66 (s, 1H), 7.34–7.49 (m, 3H), 6.91–6.95 (m, 2H), 5.10–5.11 (m, 1H), 4.38 (t, *J* = 12.4 Hz, 2H), 3.65–3.77 (m, 4H), 2.98–3.08 (m, 3H), 2.04–2.13 (m, 1H), 1.80–1.87 (m, 4H), 1.68–1.74 (m, 1H), 1.30–1.38 (m, 1H).~~]

[001177] Method C

[001178] To a solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (175 mg, 0.5 mmol) in DMF at 0 °C were added (*S*)-tetrahydrofuran-3-yl chloroformate (75 mg, 0.5 mmol) and triethylamine (137 μL, 1.0 mmol) simultaneously. Ten to fifteen minutes after addition, the reaction was complete, and it was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and

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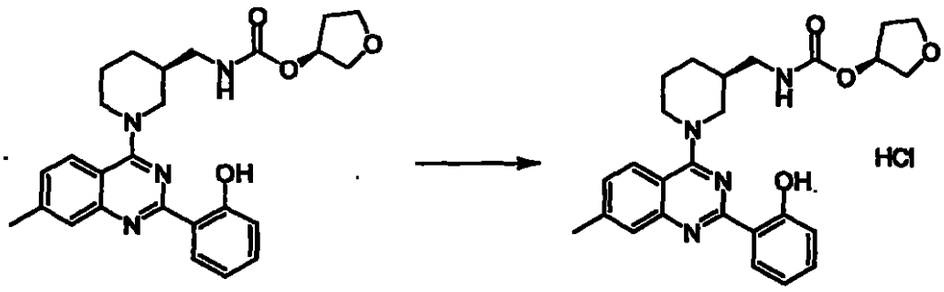
concentrated. Purification via silica gel chromatography using 98% CH_2Cl_2/2% MeOH gave (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (150 mg, 54%). LC/MS: *m/z* 463.5 $(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). [^{1}H NMR (400 MHz, DMSO-d6) δ 8.42 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.66 (s, 1H), 7.34–7.43 (m, 3H), 6.91–6.95 (m, 2H), 5.10–5.11 (m, 1H), 4.38 (t, *J* = 12.4 Hz, 2H), 3.65–3.77 (m, 4H), 2.98–3.08 (m, 3H), 2.04–2.13 (m, 1H), 1.80–1.87 (m, 4H), 1.68–1.74 (m, 1H), 1.30–1.38 (m, 1H).]

[001179] **(*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride**

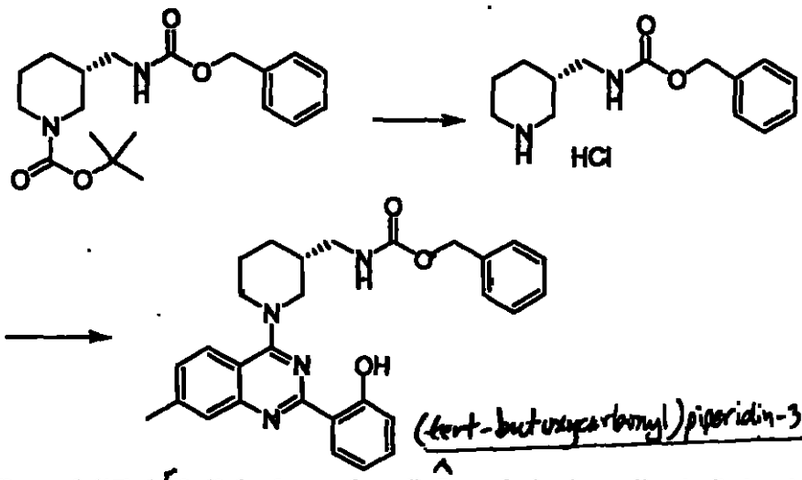
[001180]



[001181] (*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (115 mg, 0.251 mmol) was suspended in 8 mL of anhydrous CH_2Cl_2 and gently heated until an homogenous solution was formed. After cooling to room temperature, a 2.0 M solution of HCl in Et_2O (0.126 mL, 0.251 mmol) was added in one portion. The reaction mixture was diluted with 25 mL Et_2O, and the product precipitated from the solution. The reaction was stirred for an additional 30 minutes before the solid was filtered and dried to obtain (*S*)-tetrahydrofuran-3-yl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride (108 mg, 86%) as a light yellow solid. LC/MS: *m/z* 463.5$(M+H)^+$ at 2.37 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).^{1}H NMR (400 MHz, DMSO–d6) δ 8:18 (d, *J* = 6.6 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.73 (s, 1H), 7.44–7.51 (m, 2H), 7.00–7.07 (m, 2H), 5.06–5.09 (m, 1H), 4.52–4.62 (m, 2H), 3.62–3.74 (m, 4H), 3.23–3.29 (m, 1H), 3.00 (d, *J* = 6.8 Hz, 2H), 2.52 (s, 3H), 2.02–2.11 (m, 1H), 1.61–2.01 (m, 4H), 1.24–1.43 (m, 2H), 0.84–0.89 (m, 1H).

[001182] Example 216

[001189]

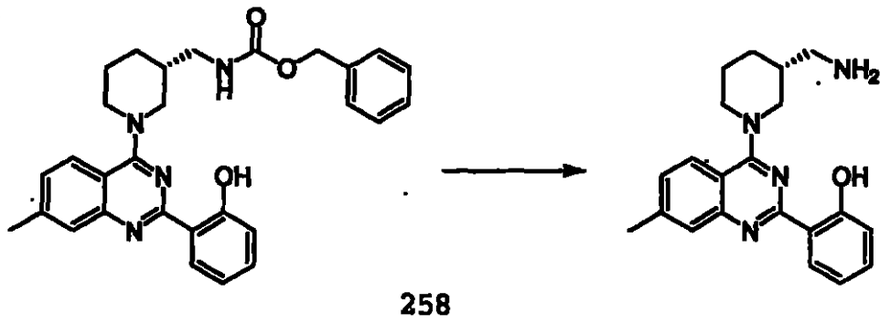


(tert-butoxycarbonyl)piperidin-3-yl) methylcarbamate

[001190] Benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (1.2 g, 3.54 mmol) was treated with 4.0 M HCl solution in dioxane (4.3 mL, 17.2 mmol). Formation of a white precipitate was observed. The reaction was complete after three hours. The solvent and excess HCl were removed under reduced pressure to obtain benzyl ((*S*)-piperidin-3-yl)methylcarbamate hydrochloride as a white solid. This solid was suspended in DMF/CH_2Cl_2 (3 mL/3 mL), followed by the addition of 2-(4-chloro-7-methylquinazolin-2-yl)phenol (958 mg, 3.54 mmol) and then triethylamine (1.8 mL, 1.3 g, 12.85 mmol). The mixture was stirred at room temperature under an N_2 atmosphere for 16 h. The reaction was then partitioned between H_2O and CH_2Cl_2, separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography using 0–5% *MeOH* in CH_2Cl_2 gave benzyl ((*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as a thick yellow oil (855 mg, 51%). LC/MS: *m/z* 483.5 $(M+H)^+$ at 2.81 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

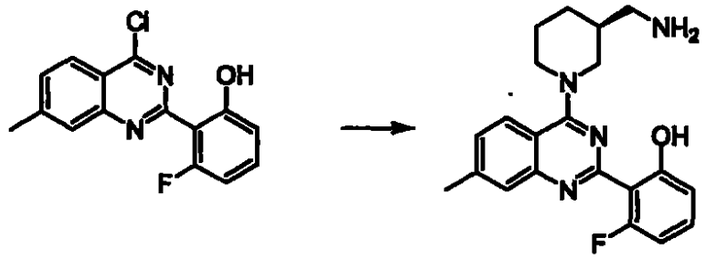
[001191] 2-(4-((*R*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol

[001192]



(Chiralpak AD-H, 5 μm, 4.6 mm x 250 mm/90/10/0.2; 0.5 mL/min; Rt (*R*): 46 min, Rt (*S*): 57 min, Rt (*N*-(naphthalen-1-yl)morpholine-4-carboxamide): 64 min.

[001320] **2-(4-((*S*)-3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol**

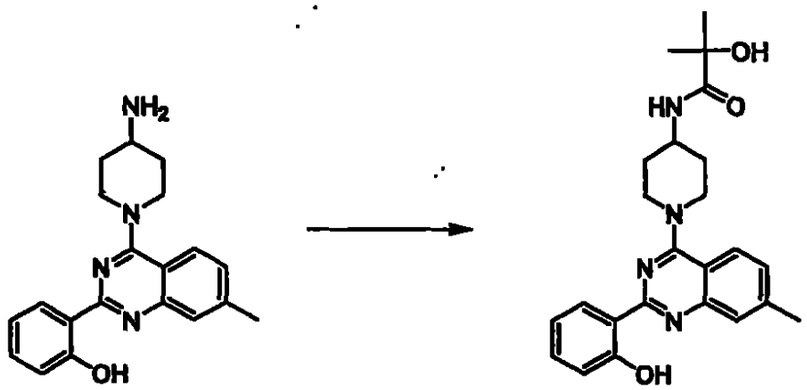


[001321] 2-(4-Chloro-7-methylquinazolin-2-yl)-3-fluorophenol (1.0 g, 3.46 mmol) was dissolved in 15 mL anhydrous CH_2Cl_2 under an N_2 atmosphere and cooled using an ice bath and (*S*)-piperidin-3-ylmethyl-carbamic acid *tert*-butyl ester/oxalic acid (1.16 g, 3.81 mmol) was added in portions, followed by triethylamine (1.05 g, 1.45 mL, 10.4 mmol). The reaction was allowed to warm to room temperature and was complete after 1.5 hour. The mixture was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted once more with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to a yellow solid. This solid was suspended in 40 mL CH_2Cl_2 and 20 mL of TFA were added. The reaction was complete after 1 hour. The solvent and the excess TFA were removed *in vacuo*, the residue was re-dissolved in CH_2Cl_2, and the pH was adjusted to 7 using an aqueous 1 M solution of NaOH. The reaction was partitioned between CH_2Cl_2 and H_2O and separated, and the aqueous layer was extracted once more with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated to yield of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (900 mg, 71% overall yield) as a yellow solid. LC/MS: *m/z* 367.3 $(M+H)^+$ at 1.35 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001322] **(*S*)-Tetrahydrofuran-3-yl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001334] 2-Hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide

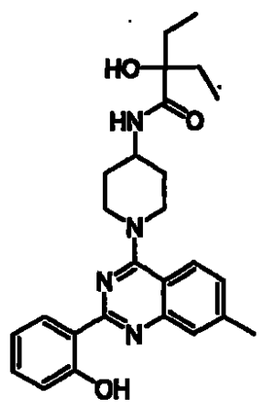
[001335]



[001336] To 2-hydroxy-2-methylpropanoic acid (28 mg, 0.27 mmol) was added a solution of 2-(4-(4-aminopiperidin-1-yl)-7-methylquinazolin-2-yl)phenol (0.07 g, 0.21 mmol) in DMF (0.5 mL), followed by the addition of triethylamine (0.058 mL, 0.42 mmol) and a solution of HATU (0.103 g, 0.273 mmol) in DMF (0.5 mL). The reaction was stirred overnight, filtered, and purified using reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford 2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-2-methylpropanamide as the TFA salt. *LC/MS*: *m/z* 421.2$(M+H)^+$ at 2.17 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA))

[001337] 2-Ethyl-2-hydroxy-*N*-(1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)butanamide

[001338]



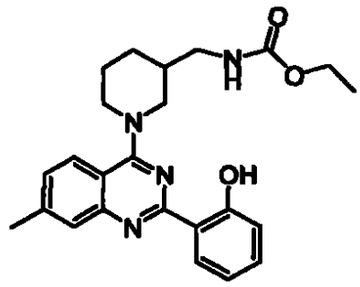
PCT/US05/31146

triethylamine (35 mg, 48 µL, 0.34 mmol). The reaction was allowed to warm to room temperature, and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave isobutyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 449.5 $(M+H)^+$ at 2.77 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001448] Example 251

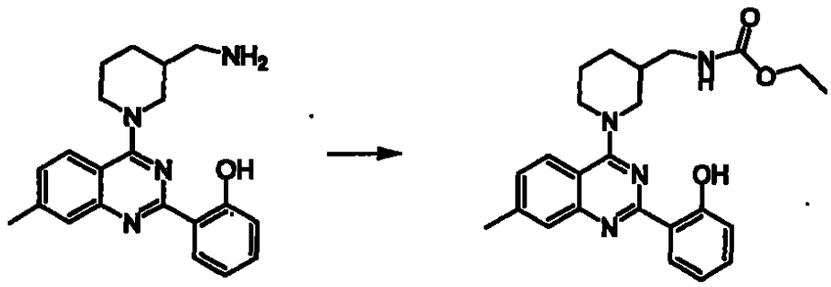
[001449] **Ethyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

[001450]



[001451] **Ethyl (1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate**

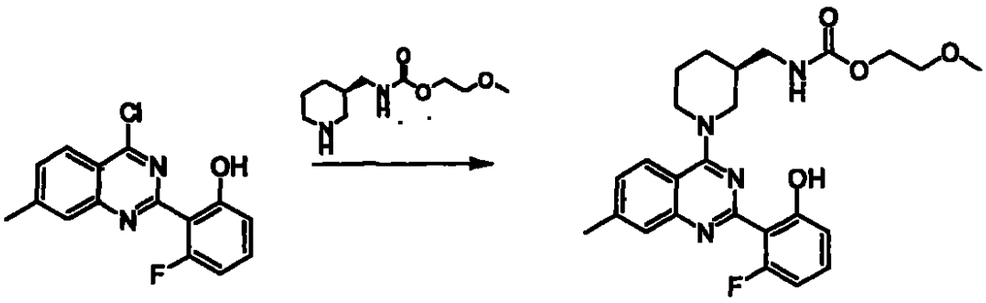
[001452]



[001453] 2-(4-(3-(Aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)phenol (60 mg, 0.17 mmol) was dissolved in anhydrous DMF (1 mL) and cooled to 0 °C, upon which ethyl chloroformate (20µL, 0.2 mmol) dissolved in DMF (100 µL) was added dropwise followed by the addition of triethylamine (35 mg, 48 µL, 0.34 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave ethyl (1-(2-(2-hydroxyphenyl)-7-

[001525] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate

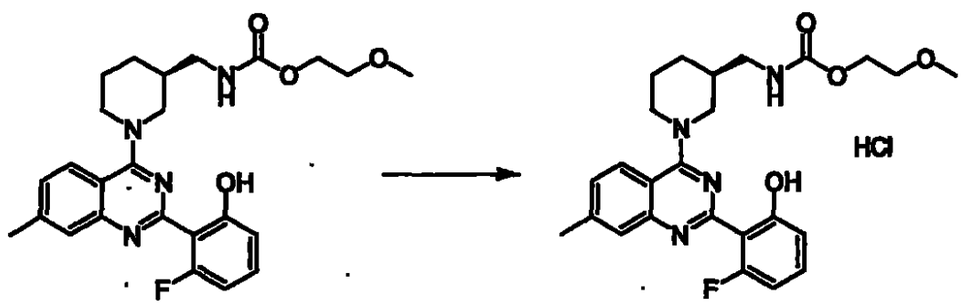
[001526]



[001527] To a solution of 2-methoxyethyl ((*R*)-piperidin-3-yl)methylcarbamate (0.24 g, 1.1 mmol) and 2-(4-chloro-7-methylquinazolin-2-yl)-3-fluorophenol (250 mg, 0.865 mmol) in CH_2Cl_2 was added triethylamine (2.41 mL, 1.73 mmol). After stirring the reaction at room temperature for 2 h, it was quenched with water and then extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 0%–10% EtOAc in CH_2Cl_2 yielded 2-methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (357 mg, 88%). LC/MS: *m/z* 469.5 $(M+H)^+$ at 2.30 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ~~^{1}H NMR (400 MHz; DMSO-d6) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.35 (m, 3H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.71 (m, 2H), 4.40 (d, *J* = 12.7 Hz, 2H), 4.05 (m, 2H), 3.48 (m, 2H), 3.30 (m, 1H), 3.25 (s, 3H), 3.05 (m, 3H), 1.82 (m, 3H), 1.63 (m, 1H), 1.32 (m, 1H).~~

[001528] 2-Methoxyethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001529]



[001530] To a solution of ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (352 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) was added dropwise

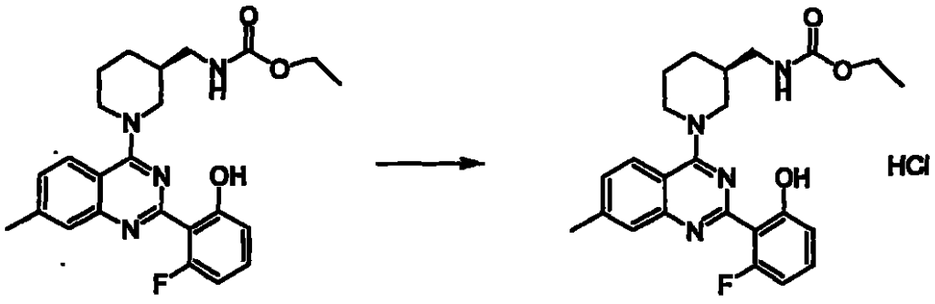
(30 μL, 0.22 mmol). The reaction was allowed to warm to room temperature and was complete after 2 h. Purification by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) gave 2-methoxyethyl ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate as the TFA salt. LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.31 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001538] Method B

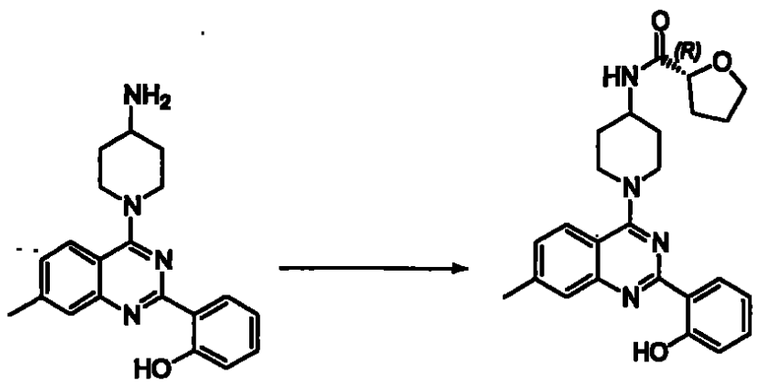
[001539] To a stirred solution of 2-(4-((*S*)-3-(aminomethyl)piperidin-1-yl)-7-methylquinazolin-2-yl)-3-fluorophenol (200 mg, 0.54 mmol) in 12 mL THF was added diisopropyl ethylamine (188 μL, 1.08 mmol) at room temperature. The mixture was cooled to –60 °C, and a solution of ethyl chloroformate (52 μL, 0.54 mmol) in 0.6 mL THF was added dropwise. After allowing the reaction to warm to room temperature, the mixture was partitioned between H_2O and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted twice more with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography using 0–10% EtOAc in 50:50 hexanes:CH_2Cl_2 gave ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate (92 mg, 38%). LC/MS: *m/z* 439.5 $(M+H)^+$ at 2.40 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)): ~~[^{1}H NMR (400 MHz, DMSO-d6) δ 7.87 (d, *J*= 8.5 Hz, 1H), 7.64 (s, 1H), 7.34 (m, 2H), 7.21 (m, 1H), 6.78 (d, *J*= 8.3 Hz, 1H), 6.70 (m, 1H), 4.40 (m, 2H), 3.98 (m, 2H), 3.27 (m, 1H), 3.05 (m, 1H), 2.97 (m, 2H), 1.84 (d, *J*= 11.0 Hz, 3H), 1.67 (d, *J*= 9.4 Hz, 1H), 1.32 (dd, *J*= 20.8, 11.3 Hz, 1H), 1.16 (t, *J*= 7.1 Hz, 3H)]~~

[001540] Ethyl ((*S*)-1-(2-(2-fluoro-6-hydroxyphenyl)-7-methylquinazolin-4-yl)piperidin-3-yl)methylcarbamate hydrochloride

[001541]



552

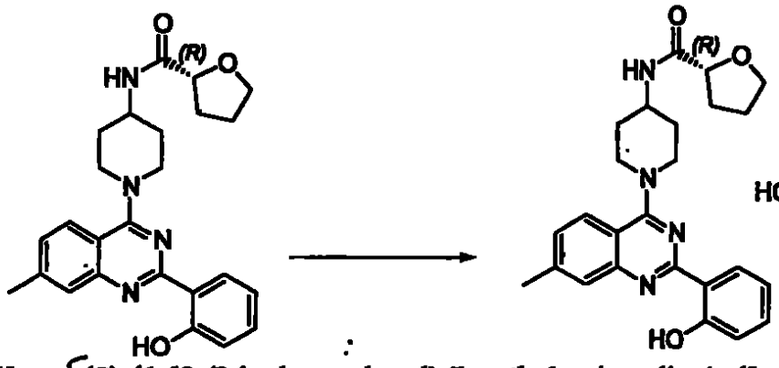


[001548] Method A: (*R*)-Tetrahydrofuran-2-carboxylic acid (23 mg, 0.20 mmol) and HATU (84 mg, 0.22 mmol) were dissolved in 0.75 mL DMF, then triethylamine (40 mg, 55 μL, 0.40 mmol) was added, followed immediately by 2-[4-(4-Amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (67 mg, 0.20 mmol). The reaction was then stirred for 30 min at room temperature, diluted with 0.75 mL 1:1 methanol / DMSO, filtered, and purified by reverse phase HPLC (2–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give (*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide as the TFA salt. LC/MS: *m/z* 433.2 $(M+H)^+$ at 2.33 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001549] Method B: (*R*)-Tetrahydrofuran-2-carboxylic acid (193 mg, 1.66 mmol) was dissolved in DMF (6 mL), followed by the addition of HATU (696 mg, 1.83 mmol). The mixture was then stirred for 15 min at room temperature under an N_2 atmosphere. The 2-[4-(4-Amino-piperidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (556 mg, 1.66 mmol) was dissolved in DMF (8 mL) and added to the mixture, followed by triethylamine (336 mg, 0.463 mL, 3.32 mmol). After 30 min, theDMF was removed *in vacuo* and the crude product partitioned between water and ethyl acetate. The aqueous layer was separated, washed with ethyl acetate, and the combined organic layers dried over $MgSO_4$, filtered, and concentrated to give crude product as an orange oil. Purification via silica gel chromatography (20% ethyl acetate / 80% 1:1 CH_2Cl_2:hexane) gave pure ~~(*R*)-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide~~ (*R*)-tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide (303 mg, 42%). ^1H NMR (400 MHz, DMSO-d6) δ 8.44 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.67 (s, 1H), 7.40–7.36 (m, 2H), 6.97–6.93 (m, 2H), 4.48–4.45 (m, 2H), 4.20 (dd, *J* = 8.2, 5.3 Hz, 1H); 4.06–3.96 (m, 1H), 3.88 (dd, *J* = 14.3, 6.6 Hz, 1H), 3.74 (dd, *J* = 14.5, 6.7 Hz, 1H), 3.43–3.32 (m, 2H), 2.51 (s, 3H), 2.16–2.07 (m, 1H),

1.89–1.69 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d6) δ 171.7, 162.8, 160.7, 159.5, 149.3, 144.1, 132.5, 129.0, 127.3, 125.7, 125.4, 118.9, 118.4, 117.2, 111.9, 77.6, 68.5, 48.3, 45.5, 31.3, 31.2, 30.0, 24.9, 21.2.

[001550] **(*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide hydrochloride**

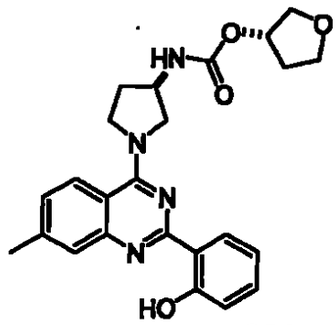


[001551] ~~(*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide~~ (303 mg, 0.701 mmol) was dissolved in 9 mL 2:1 dry ether / dry CH_2Cl_2 and 2.0 M HCl in ether added dropwise (0.35 mL, 0.70 mmol), producing a white precipitate which was collected by filtration to give (*R*)-Tetrahydro-furan-2-carboxylic acid {1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-piperidin-4-yl}-amide hydrochloride (268 mg, 82%). *LC/MS*: *m/z* 433.5 $(M+H)^+$ at 2.26 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ^{1}H NMR (400 MHz, DMSO-d6) δ 8.20 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.80–7.79 (m, 2H), 7.51–7.47 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.05–7.01 (m, 1H), 4.66–4.63 (m, 2H), 4.21 (dd, *J* = 8.2, 5.2 Hz, 1H), 4.12–4.03 (m, 1H), 3.91–3.84 (m, 1H), 3.78–3.70 (m, 1H), 3.59 (t, *J* = 12.3 Hz, 2H), 2.54 (s, 3H), 2.16–2.05 (m, 1H), 1.97–1.94 (m, 2H), 1.89–1.72 (m, 5H).

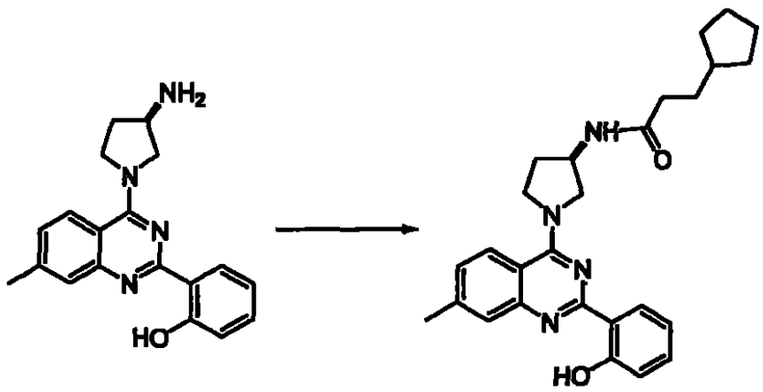
[001552] Example 301

[001553] **(*S*)-Tetrahydrofuran-3-yl (*R*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

[001554]



[001734]

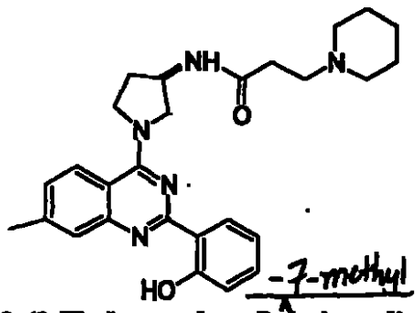


[001735] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (100 mg, 0.31 mmol) was added 1 mL of CH_2Cl_2, and the solution was cooled to 0 °C. To this solution was added sequentially triethylamine (56.6 µL, 0.41 mmol) and 3-cyclopentyl-propionyl chloride (57 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 2 h, then diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give ((*R*)-3-cyclopentyl-*N*-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-propionamide as the TFA salt. LC/MS: *m/z* 445.4 $(M+H)^+$ at 2.85 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001736] Example 324

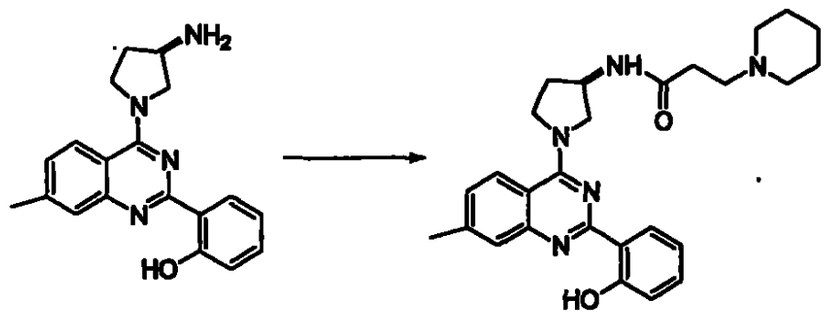
[001737] **(*R*)-N-{1-[2-(2-Hydroxy-phenyl)-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide**

[001738]



[001739] **(*R*)-N-{1-[2-(2-Hydroxy-phenyl)-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide**

[001740]

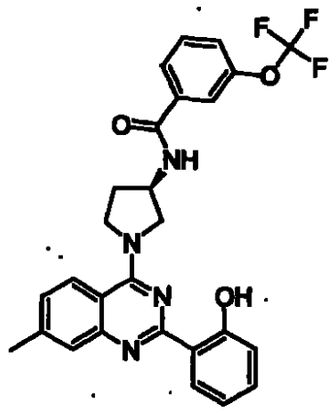


[001741] To (*R*)-2-[4-(3-amino-pyrrolidin-1-yl)-7-methyl-quinazolin-2-yl]-phenol (58.6 mg, 0.18 mmol) was added 700 μL of CH_2Cl_2. To this solution was added sequentially triethylamine (38.3 μL, 0.27 mmol), 3-piperidin-1-yl-propionic acid (37.4 mg, 0.24 mmol) and BOP (119 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 2 h and diluted with water and CH_2Cl_2 (10 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via preparative reverse phase HPLC using 10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA) to give (*R*)-*N*-{1-[2-(2-hydroxy-phenyl)-7-methyl-quinazolin-4-yl]-pyrrolidin-3-yl}-3-piperidin-1-yl-propionamide as the TFA salt. LC/MS: *m/z* 460.4 $(M+H)^+$ at 2.1 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

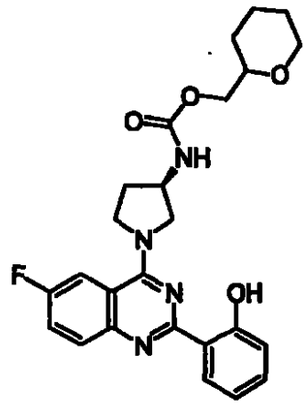
[001742] Example 325

[001743] ***N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-3-(trifluoromethoxy)benzamide**

[001744]

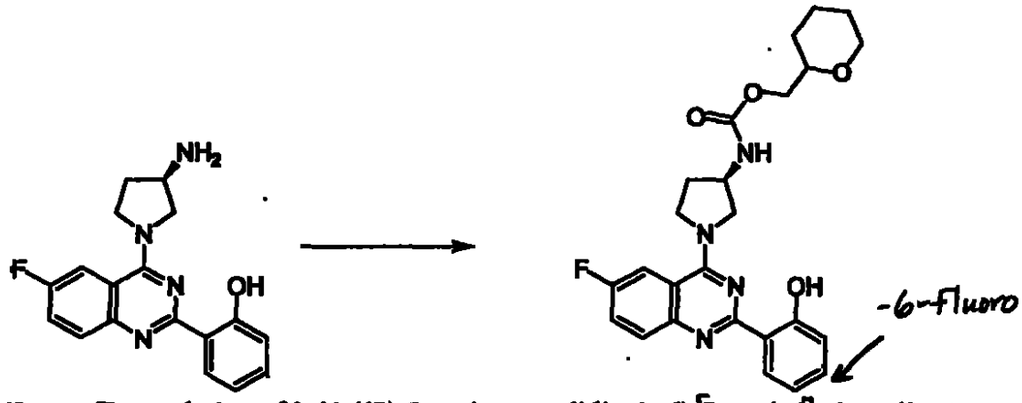


[001868]



[001869] (Tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate

[001870]



[001871] To a solution of 2-(4-((*R*)-3-aminopyrrolidin-1-yl)-7-methylquinazolin-2-yl)phenol (50 mg, 0.16 mmol) in DMSO (0.5 mL) at room temperature was added triethylamine (43 μL, 0.31 mmol), followed by the addition of (tetrahydro-2*H*-pyran-2-yl)methyl 1*H*-imidazole-1-carboxylate (39 mg, 0.13 mmol). The reaction was stirred at room temperature overnight, filtered, and purified via reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to afford (tetrahydro-2*H*-pyran-2-yl)methyl (*R*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-ylcarbamate as the TFA salt. LC/MS: *m/z* 467.3 $(M+H)^+$ at 3.13 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001872] Example 340

[001873] *N*-((*R*)-1-(2-(2-Hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)-2,2,3,3-tetramethylcyclopropanecarboxamide

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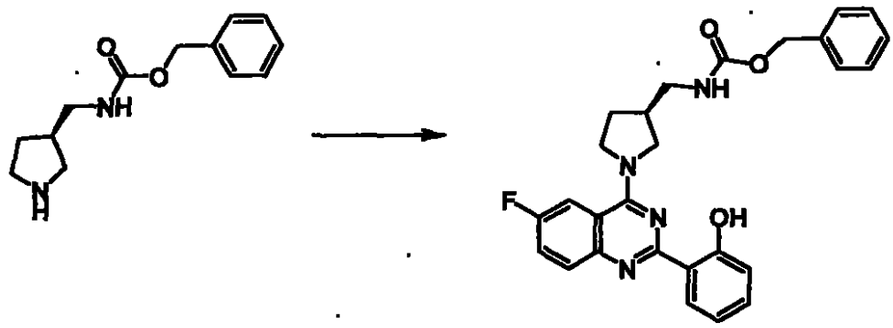
[001987] To a stirred solution of ((*S*)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)methylcarbamate (1.5 g, 4.48 mmol) in CH_2Cl_2 (20 mL) was slowly added TFA (5 mL). The reaction was stirred for 2 h. After removing the solvents under reduced pressure, the mixture was neutralized with a 1 M NaOH solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford benzyl ((*R*)-pyrrolidin-3-yl)methylcarbamate (800 mg, 76%). LC/MS: *m/z* ~~335.3~~ 235.3 $(M+H)^+$ at 1.22 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001988] **Benzyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

[001989]



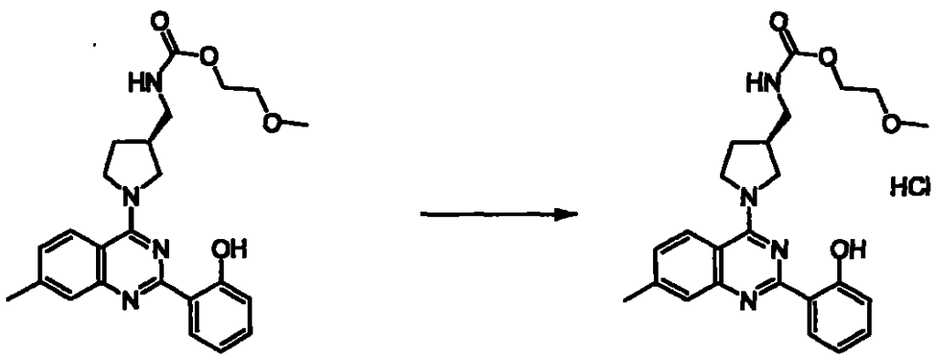
[001990] A solution of triethylamine (507 μL, 3.64 mmol) and benzyl ((*R*)-pyrrolidin-3-yl)methylcarbamate (0.47 g, 2 mmol) in CH_2Cl_2 was added dropwise to a solution of 2-(4-chloro-6-fluoroquinazolin-2-yl)phenol (0.5 g, 1.82 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred at room temperature for 3 h. After quenching the reaction with water, the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography using 5–10% EtOAc in CH_2Cl_2 yielded benzyl ((*S*)-1-(6-fluoro-2-(2-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate. LC/MS: *m/z* 473.1 $(M+H)^+$ at 2.91 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[001991] **2-(4-((*S*)-3-(Aminomethyl)pyrrolidin-1-yl)-6-fluoroquinazolin-2-yl)phenol**

the ice bath was removed. The solution was stirred at room temperature overnight. Purification via silica gel chromatography using 0–10% MeOH in CH_2Cl_2 gave 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.12 g, 80%). LC/MS: *m/z* 437.5 $(M+H)^+$ at 2.20 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002071] **2-Methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride**

[002072]



[002073] A 1.0 M HCl solution in Et_2O (0.27 mL, 0.27 mmol) was slowly added to a stirring solution of 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate (0.12 g, 0.27 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 30 minutes at room temperature, then Et_2O was slowly added to the solution until a precipitate formed. After stirring for 1 h, the solid was filtered and washed with Et_2O to obtain 2-methoxyethyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (0.10 g, 77%). LC/MS: *m/z* 437.1 $(M+H)^+$ at 2.19 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ~~[^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.24 (d, *J* = 7.3 Hz, 1H), 7.77 (s, 1H), 7.52–7.48 (m, 3H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.05–7.02 (m, 1H), 4.22–4.12 (m, 2H), 4.08–4.05 (m, 3H), 3.87–3.83 (m, 1H), 2H), 3.24 (s, 3H), 3.23–3.12 (m, 2H), 2.54 (s, 3H), 2.55–2.52 (m, 1H), 2.17–2.13 (m, 1H), 1.84–1.77 (m, 1H).]~~

[002074] Example 367

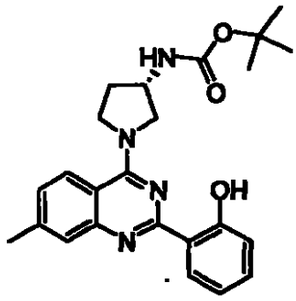
[002075] **Propyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate**

and dried to obtain neopentyl ((*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-yl)methylcarbamate hydrochloride (214 mg, 92%). LC/MS: *m/z* 449 $(M+H)^+$ at 2.75 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)). ~~[^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (d, *J* = 8.7 Hz, 1H)1H), 7.85 (s, 1H), 7.54–7.49 (m, 2H), 7.47–7.45 (m, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.05–7.02 (m, 1H), 4.33–3.74 (m, 5H), 3.70–3.64 (m, 2H), 3.19–3.16 (m, 2H), 2.53 (s, 3H), 2.18–2.13 (m, 1H), 1.87–1.81 (m, 1H), 0.88 (s, 9H).]~~

[002104] Example 370

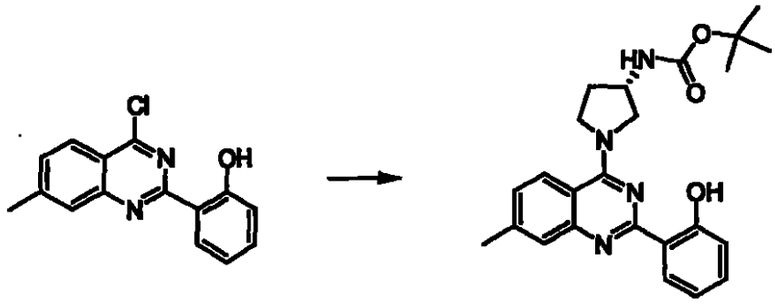
[002105] ***tert*-Butyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

[002106]



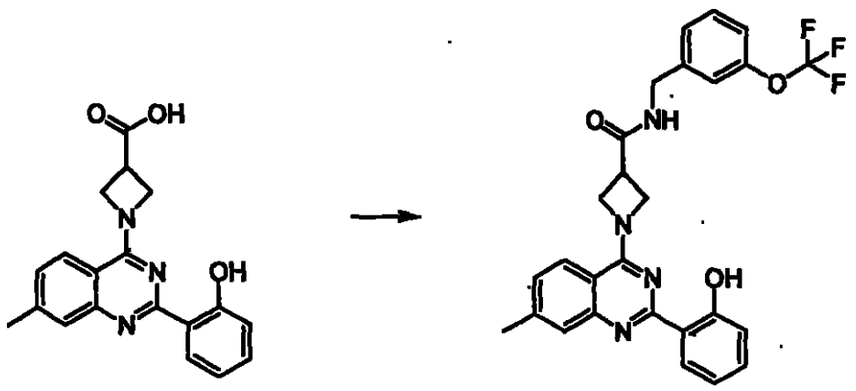
[002107] ***tert*-Butyl (*S*)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)pyrrolidin-3-ylcarbamate**

[002108]



[002109] *tert*-Butyl (*S*)-pyrrolidin-3-ylcarbamate (245 mg, 1.31 mmol) was dissolved in 1.8 mL of anhydrous CH_2Cl_2 and cooled to 0 °C. 2-(4-Chloro-7-methylquinazolin-2-yl)phenol (300 mg, 1.1 mmol) dissolved in 1.8 mL of anhydrous CH_2Cl_2 was added dropwise to the mixture followed by triethylamine (134 mg, 184 μL, 1.32 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. Purification via silica gel chromatography using

[002176]

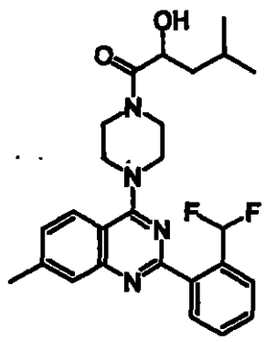


[002177] To a solution of 1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxylic acid (34 mg, 0.10 mmol) and HATU (57 mg, 0.15 mmol) in DMF (1 mL) was added (3-(trifluoromethoxy)phenyl)methanamine (57 μL, 0.30 mmol). The reaction was stirred at room temperature overnight, filtered, and purified by reverse phase HPLC (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give *N*-(3-(trifluoromethoxy)benzyl)-1-(2-(2-hydroxyphenyl)-7-methylquinazolin-4-yl)azetidine-3-carboxamide as the TFA salt. LC/MS: *m/z* 509.3 $(M+H)^+$ at 2.73 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002178] ~~Example 501~~ Example 502

[002179] 1-(4-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[002180]



[002181] *tert*-Butyl 4-(2-chloro-7-methylquinazolin-4-yl)piperazine-1-carboxylate

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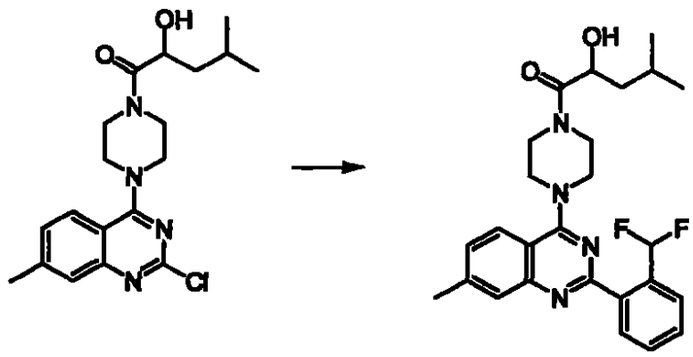
[002195] To a solution of 1-bromo-2-difluoromethylbenzene (16 g, 0.077 mol) in THF (300 mL) was added *n*-BuLi (2.5 M, 46 mL, 0.12 mol) dropwise at –78 °C. After one hour, trimethyl borate (16 g, 0.15 mol) was added dropwise. The mixture was warmed to room temperature slowly overnight, and then the mixture was treated with water and ethyl acetate. The organic layer was extracted with a 10% aqueous NaOH solution. The aqueous solution was acidified with dilute aq. HCl and extracted with ethyl acetate. Removal of the solvent gave 2-(difluoromethyl)phenylboronic (0.7 g, 5.3%). ^{1}H NMR($CDCl_3$): δ 8.28 (d, 1 H, J = 7.2), 7.86 (d, 1H, J = 7.2), 7.58–7.79 (m, 1 H), 7.73 (t, 1 H, J = 7.2), 7.65 (t, 1 H).

[002196] 1-(4-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one

[002197]



[002198] A mixture of 1-(4-(2-chloro-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (23 mg, 61 μmol), 2-(difluoromethyl)phenylboronic acid (13 mg, 73 μmol), $Pd(dppf)Cl_2$ (3 mg, 3.7 μmol), and K_2CO_3 (17 mg, 122 μmol) in DMF (1 mL) and H_2O (0.5 mL) was heated in a sealed microwave vial at 170 °C for 6 minutes. After filtration and evaporation of the solvents, the mixture was purified using preparative reverse phase HPLC (10–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)) to give 1-(4-(2-(2-(difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one as the TFA salt. LC/MS: *m/z* 469.3 $(M+H)^+$ at 2.44 min (10%–99% CH_3CN (0.035% TFA)/H_2O (0.05% TFA)).

[002199] ~~Example 502~~ Example 501

[002200] (2*R*)-*N*-(1-(2-(2-(Difluoromethyl)phenyl)-7-methylquinazolin-4-yl)piperidin-4-yl)-tetrahydrofuran-2-carboxamide

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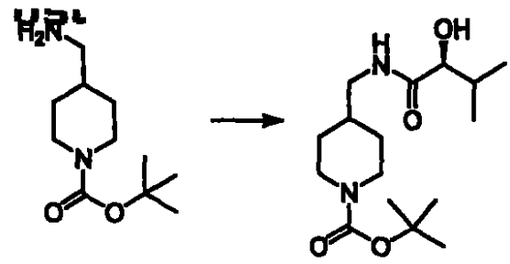
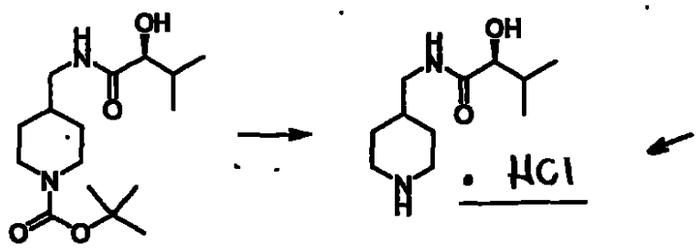


[002227]

[002228] HOBt (23.5 g, 174 mmol) and EDCI·HCl (33.5 g, 174 mmol) were added to a mixture of *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (37.3 g, 174 mmol), (*S*)-(+)-2-hydroxy-3-methyl-butanoic acid (20.6 g, 174 mmol), and triethylamine (50 mL, 349 mmol) in a mixture of dichloromethane (500 mL) and DMF (250 mL) cooled in an ice bath. The reaction was stirred overnight at room temperature. An additional portion of EDCI·HCl (5 g) and triethylamine (4 mL) were added, and stirring was continued for another 4 hours. The mixture was diluted to 1 L by the addition of dichloromethane and was washed with 500 mL portions of water, 1 N HCl solution, 5% aq. $NaHCO_3$ solution, water, and saturated aqueous NaCl solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure yielding 52 g of the crude product. This crude material was stirred with 200 mL diisopropyl ether, and the solid was collected by filtration and washed twice with 100 mL portions of diisopropyl ether to yield to 33 g (64%) of 4-[((*S*)-2-hydroxy-3-methyl-butyrylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester.

[002229] (*S*)-2-Hydroxy-3-methyl-*N*-piperidin-4-ylmethyl-butyramide hydrochloride

[002230]



[002231] Acetyl chloride (30 mL) was added dropwise to 500 mL methanol cooled in an ice bath, and after completion of the addition the solution was stirred at room temperature for 30 minutes. 4-[((*S*)-2-hydroxy-3-methyl-butyrylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester (33 g) in 150 mL methanol was added, and stirring was continued for 2 hours at room temperature. The solution was evaporated to dryness to yield to 26.6 g of (*S*)-2-hydroxy-3-methyl-*N*-piperidin-4-ylmethyl-butyramide hydrochloride as a white solid.

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VPI/04-129 WO

QUINAZOLINAS ÚTILES COMO MODULADORES DE CANALES IÓNICOS

REFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

[0001] La presente solicitud reivindica el beneficio según 35 U.S.C. § 119 a la solicitud de patente provisoria de los Estados Unidos serie N.° 60/607.150, presentada el 2 de septiembre de 2004, solicitud de patente provisoria de los Estados Unidos serie N.° 60/607.037, presentada el 2 de septiembre de 2004, solicitud de patente provisoria de los Estados Unidos serie N.° 60/607.033, presentada el 2 de septiembre de 2004, solicitud de patente provisoria de los Estados Unidos serie N.° 60/607.036, presentada el 2 de septiembre de 2004 y solicitud de patente provisoria de los Estados Unidos serie N.° 60/607.245, presentada el 2 de septiembre de 2004, la totalidad del contenido de cada una de las anteriores solicitudes se incorpora a la presente como referencia.

CAMPO TÉCNICO DE LA INVENCIÓN

[0002] La presente invención se refiere a compuestos de utilidad como inhibidores de canales iónicos. La invención también provee composiciones farmacéuticamente aceptables que

comprenden los compuestos de la invención y métodos para usar las composiciones en el tratamiento de diversos trastornos.

ANTECEDENTES DE LA INVENCIÓN

[0003] Los canales de Na son centrales en la generación de potenciales de acción en todas las células excitables, por ejemplo neuronas y miocitos. Juegan papeles clave en tejidos excitables que incluyen el encéfalo, los músculos lisos del tracto gastrointestinal, el músculo esquelético, el sistema nervioso periférico, la médula espinal y las vías aéreas. Como tales, juegan papeles clave en diversos estados patológicos tales como epilepsia (véase, Moulard, B. y D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents 12(1): 85-91)), dolor (Véase, Waxman, S. G., S. Dib-Hajj, y otro (1999) "Sodium channels and pain" Proc Natl Acad Sci U S A 96(14): 7635-9 y Waxman, S. G., T. R. Cummins, y otro (2000) "Voltage-gated sodium channels and the molecular pathogenesis of pain: a review" J Rehabil Res Dev 37(5): 517-28), miotonia (Véase, Meola, G. y V. Sansone (2000) "Therapy in miotonic disorders and in muscle channelopaties" Neurol Sci 21(5): S953-61 y Mankodi, A. y C. A. Thornton (2002) "Miotonic syndromes" Curr Opin Neurol 15(5): 545-52), ataxia (Véase, Meisler, M. H., J. A. Kearney, y otro (2002) "Mutations of voltage-gated sodium channels in movement disorders and

epilepsy" Novartis Found Simp 241: 72-81), esclerosis múltiple (Véase, Black, J. A., S. Dib-Hajj, y otro (2000) "Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of mice with experimental allergic encephalomyelitis and humans with multiple sclerosis" Proc Natl Acad Sci U S A 97(21): 11598-602 y Renganatan, M., M. Gelderblom, y otro (2003) "Expression of Na(v)1,8 sodium channels perturbs the firing patterns of cerebellar purkinje cells" Brain Res 959(2): 235-42), intestino irritable (Véase, Su, X., R. E. Wachtel, y otro (1999) "Capsaicin sensitivity and voltage-gated sodium currents in colon sensory neurons from rat dorsal root ganglia" Am J Phisiol 277(6 Pt 1): G1180-8 y Laird, J. M., V. Souslova, y otro (2002) "Deficits in visceral pain and referred hiperalgesia in Nav1.8 (SNS/PN3)-null mice" J Neurosci 22(19): 8352-6), incontinencia urinaria y dolor visceral (Véase, Yoshimura, N., S. Seki, y otro (2001) "The involvement of the tetrodotoxin-resistant sodium channel Na(v)1,8 (PN3/SNS) in a rat model of visceral pain" J Neurosci 21(21): 8690-6), además de una disposición de disfunciones psiquiátricas tales como ansiedad y depresión (Véase, Hurley, S. C. (2002) "Lamotrigine update and its use in mood disorders" Ann Pharmacother 36(5): 860-73).

[0004] Los canales de Na regulados por voltaje comprenden una familia de genes que consiste en 9 subtipos diferentes

(NaV1.1-NaV1.9). Estos subtipos muestran localización específica de tejido y diferencias funcionales (Véase, Goldin, A. L. (2001) "Resurgence de sodium channel research" Annu Rev Physiol **63**: 871-94). Tres miembros de la familia de genes (NaV1.8, 1.9, 1.5) son resistentes a bloqueos mediante el bien conocido bloqueador de canales de Na TTX, que demuestra una especificidad de subtipo dentro de esta familia de genes. El análisis mutacional ha identificado el glutamato 387 como residuo crítico para la fijación de TTX (Véase, Noda, M., H. Suzuki, y otro (1989) "A single point mutation confers tetrodotoxin and saxitoxin insensitivity on the sodium channel II" FEBS Lett **259**(1): 213-6).

[0005] En general, los canales de sodio regulados por voltaje v(NaV) son responsables de iniciar el rápido ascenso de los potenciales de acción en el tejido excitable del sistema nervioso, por lo cual se transmiten las señales eléctricas que componen y codifican las sensaciones dolorosas normales y aberrantes. Los antagonistas de canales de NaV pueden atenuar estas señales de dolor y son útiles para tratar diversas condiciones dolorosas, incluso, sin limitaciones, dolor agudo, crónico, inflamatorio y neuropático. Los antagonistas de NaV conocidos, tales como TTX, lidocaína (Véase Mao, J. y L. L. Chen (2000) "Systemic lidocaine for neuropatic pain relief" Pain **87**(1): 7-17.) bupivacaína, fenitoína (Véase, Jensen, T.

S. (2002) "Anticonvulsants in neuropatic pain: rationale and clinical evidence" Eur J Pain 6 (Suppl A): 61-8), lamotrigina (Véase, Rozen, T. D. (2001) "Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia" Headache 41 Suppl 1: S25-32 y Jensen, T. S. (2002) "Anticonvulsants in neuropatic pain: rationale and clinical evidence" Eur J Pain 6 (Suppl A): 61-8.) y carbamazepina (Véase, Backonja, M. M. (2002) "Use of anticonvulsants for treatment of neuropatic pain" Neurology 59(5 Suppl 2): S14-7), demostraron ser útiles para atenuar el dolor el humanos y modelos animales.

[0006] La hiperalgesia (extrema sensibilidad a algo doloroso) que se desarrolla en presencia de lesión tisular o inflamación refleja, al menos en parte, un aumento de la excitabilidad de las neuronas aferentes primarias de alto umbral que inervan el sitio de la lesión. La activación de los canales de sodio regulados por voltaje es esencial para la generación y la propagación de los potenciales de acción de las neuronas. Hay un cuerpo creciente de evidencias que indican que la modulación de las corriente de NaV es un mecanismo endógeno usado para controlar la excitabilidad neuronal (Véase, Goldin, A. L. (2001) "Resurgence of sodium channel research" Annu Rev Physiol 63: 871-94.). Se encuentran varios canales de sodio regulados por voltaje diferenciados desde los puntos de vista

cinético y farmacológico en las neuronas del ganglio de la raíz dorsal (DRG). La corriente resistente a TTX es insensible a concentraciones micromolares de tetrodotoxinas y muestra lenta cinética de activación e inactivación y un umbral de activación más despolarizado cuando se compara con otros canales de sodio regulados por voltaje. Las corrientes de sodio resistentes a TTX están restringidas principalmente a una subpoblación de neuronas sensitivas que probablemente intervienen en la nocicepción. Específicamente, las corrientes de sodio resistentes a TTX se expresan casi exclusivamente en neuronas que tienen pequeño diámetro de cuerpo celular; y dan origen a axones de pequeño diámetro de conducción lenta y que responden a capsaicina. Un gran cuerpo de evidencias experimentales demuestra que los canales de sodio resistentes a TTX se expresan en las fibras C y son importantes en la transmisión de información nociceptiva a la médula espinal.

[0007] La administración intratecal de oligo-desoxinucleótidos antisentido dirigidos a una región singular del canal de sodio resistente a TTX (NaV1.8) dio por resultado una significativa reducción de la hiperaglesia inducida por PGE_2 (Véase, Khasar, S. G., M. S. Gold, y otro (1998) "A tetrodotoxin-resistant sodium current mediates inflammatory pain in the rat" Neurosci Lett 256(1): 17-20). Más recientemente, Word y colaboradores generaron una línea de ratón knockout que carece de NaV1.8

funcional. La mutación tiene efecto analgésico en pruebas que evalúan la respuesta del animal al agente inflamatorio carragenano (Véase, Akopian, A. N., V. Souslova, y otro (1999) "The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways" Nat Neurosci 2(6): 541-8.). Además, se observó déficit en la mecanorrecepción y la termorrecepción en estos animales. La analgesia demostrada por mutantes knockout para Navl.8 concuerda con observaciones sobre el papel de corrientes resistentes a TTX en la nocicepción.

[0008] Los experimentos inmunohistoquímicos, de hibridación in-situ y de electrofisiología in-vitro han demostrado todos que el canal de sodio NaV1.8 se ubica selectivamente en las neuronas sensitivas pequeñas del ganglio de la raíz dorsal y el ganglio trigémino (Véase Akopian, A. N., L. Sivilotti, y otro (1996) "A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons" Nature 379(6562): 257-62.). El papel primario de estas neuronas es la detección y la transmisión de estímulos nociceptivos. La evidencia antisentido e inmunohistoquímica también avala el papel de NaV1.8 en el dolor neuropático (Véase, Lai, J., M. S. Gold, y otro (2002) "Inhibition of neuropatic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8" Pain 95(1-2): 143-52 y Lai, J., J. C. Hunter, y otro

(2000) "Blockade of neuropatic pain by antisense targeting of tetrodotoxin- resistant sodium channels in sensory neurons" Methods Enzymol 314: 201-13.). La proteína NaV1.8 se regula hacia arriba a lo largo de las fibras C no lesionadas adyacentes a la lesión del nervio. El tratamiento antisentido previene la redistribución de NaV1.8 a lo largo del nervio y revierte el dolor neuropático. En conjunto, el knockout génico y los datos antisentido avalan el papel de NaV1.8 en la detección y la transmisión del dolor inflamatorio y neuropático.

|0009| En la actualidad se usan o se analizan varios bloqueadores de canal de Na en la clínica para tratar epilepsia (Véase Moulard, B. y D. Bertrand (2002) "Epilepsy and sodium channel blockers" Expert Opin. Ther. Patents 12(1): 85-91.); dolor agudo (Véase, Wiffen, P., S. Collins, y otro (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev 3), crónico (Véase, Wiffen, P., S. Collins, y otro (2000) "Anticonvulsant drugs for acute and chronic pain" Cochrane Database Syst Rev 3 y Guai, D. R. (2001) "Adjunctive agents in the management of chronic pain" Pharmacoterapy 21(9): 1070-81), inflamatorio (Véase Gold, M. S. (1999) "Tetrodotoxin-resistant Na+ currents and inflammatory hiperalgesia". Proc Natl Acad Sci U S A 96(14): 7645-9) y neuropático (Véase Strichartz, G. R., Z. Zhou, y

otro (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropatic pain" Novartis Found Symp **241**: 189-201 y Sandner-Kiesling, A., G. Rumpold Seitlinger, y otro (2002) "Lamotrigine monotherapy for control of neuralgia after nerve section" Acta Anaestesiol Scand **46**(10): 1261-4); arritmias cardiacas (Véase, An, R. H., R. Bangalore, y otro (1996) "Lidocaine block of LQT-3 mutant human Na+ channels" Circ Res **79**(1): 103-8 y Wang, D. W., K. Yazawa, y otro (1997) "Pharmacological targeting of long QT mutant sodium channels" J Clin Invest **99**(7): 1714-20); neuroprotección (Véase, Taylor, C. P. y L. S. Narasimhan (1997) "Sodium channels and therapy of central nervous system diseases" Adv Pharmacol **39**: 47-98) y como anestésico (Véase, Strichartz, G. R., Z. Zhou, y otro (2002) "Therapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropatic pain". Novartis Found Symp **241**: 189-201).

[0010] Se han desarrollado diversos modelos animales con importancia clínica para el estudio de moduladores de canales de sodio para numerosas indicaciones diferentes de dolor, por ejemplo, dolor crónico maligno, véase, Kohase, H., y otro, Acta Anaesthesiol Scand. 2004; 48(3):382-3; dolor por cáncer de fémur (véase, Kohase, H., y otro, Acta Anaesthesiol Scand. 2004; 48(3):382-3); dolor óseo crónico no maligno (véase,

Ciocon, J. O. y otro, J Am Geriatr Soc. 1994; 42(6):593-6); artritis reumatoide (véase, Calvino, B. y otro, Behav Brain Res. 1987; 24(1):11-29); osteoartritis (véase, Guzman, R. E., y otro, Toxicol Pathol. 2003; 31(6):619-24); estenosis espinal (véase, Takenobu, Y. y otro, J Neurosci Methods. 2001; 104(2):191-8); dolor lumbar neuropático (véase, Hines, R., y otro, Pain Med. 2002; 3(4):361-5; Massie, J. B., y otro, J Neurosci Methods. 2004; 137(2):283-9; dolor lumbar neuropático (véase, Hines, R., y otro, Pain Med. 2002; 3(4):361-5; Massie, J. B., y otro, J Neurosci Metods. 2004; 137(2):283-9); síndrome de dolor miofascial (véase, Dalpiaz & Dodds, J Pain Palliat Care Pharmacoter. 2002; 16(1):99-104; Sluka KA y otro, Muscle Nerve. 2001; 24(1):37-46); fibromialgia (véase, Bennet & Tai, Int J Clin Pharmacol Res. 1995;15(3):115-9); dolor de articulación temporomandibular (véase, Ime H, Ren K, Brain Res Mol Brain Res. 1999; 67(1):87-97); dolor visceral crónico, incluso abdominal (véase, Al-Chaer, E. D., y otro, Gastroenterology. 2000; 119(5):1276-85); dolor pelviano/perineal (véase, Wesselmann y otro, Neurosci Lett. 1998; 246(2):73-6); pancreático (véase, Vera-Portocarrero, L. B., y otro, Anesthesiology. 2003; 98(2):474-84); dolor IBS (véase, Verne, G. N., y otro, Pain. 2003; 105(1-2):223-30; La JH y otro, World Gastroenterol. 2003; 9(12):2791-5); dolor con cefalea crónica (véase, Willimas & Stark, Cefalalgia. 2003;

23(10):963-71); migraña (véase, Yamamura, H., y otro, J Neurophysiol. 1999; 81(2):479-93); cefalea por tensión, incluso cefaleas acuminadas (véase, Costa, A., y otro, Cefalalgia. 2000; 20(2):85-91); dolor neuropático crónico, incluso neuralgia post-herpética (véase, Attal, N., y otro, Neurology. 2004; 62(2):218-25; Kim & Chung 1992, Pain 50:355); neuropatía diabética (véase, Beidoun A y otro, Clin J Pain. 2004; 20(3):174-8; Courteix, C., y otro, Pain. 1993; 53(1):81-8); neuropatía asociada a HIV (véase, Portegies & Rosenberg, Ned Tijdsch Geneeskd. 2001; 145(15):731-5; Joseph EK y otro, Pain. 2004; 107(1-2):147-58; Oh, S. B., y otro, J Neurosci. 2001; 21(14):5027-35); neuralgia del trigémino (véase, Sato, J., y otro, Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004; 97(1):18-22; Imamura Y y otro, Exp Brain Res. 1997; 116(1):97-103);

neuropatía de Charcot-Marie Toot (véase, Sereda, M., y otro, Neuron. 1996; 16(5):1049-60);

neuropatías sensitivas hereditarias (véase, Lee, M. J., y otro, Hum Mol Genet. 2003; 12(15):1917-25); lesión de nervios periféricos (véase, Attal, N., y otro, Neurology. 2004; 62(2):218-25; Kim & Chung 1992, Pain 50:355; Bennett & Xie, 1988, Pain 33:87; Decostered, I. & Woolf, C. J., 2000, Pain 87:149; Shir, Y. & Seltzer, Z. 1990; Neurosci Lett 115:62); neuromas dolorosos (véase, Nahabedian & Johnson, Ann Plast

Surg. 2001; 46(1):15-22; Devor & Raber, Behav Neural Biol. 1983; 37(2):276-83); descargas extópicas proximales y distales (véase, Liu, X. y otro, Brain Res. 2001; 900(1):119-27); radiculopatías (véase, Devers & Galer, (véase, Clin J Pain. 2000; 16(3):205-8; Haiashi N y otro, Spine. 1998; 23(8):877-85); dolor neuropático inducido por quimioterapia (véase, Aley, K. O., y otro, Neuroscience. 1996; 73(1):259-65); dolor neuropático inducido por radioterapia;

dolor post-mastectomía (véase, Devers & Galer, Clin J Pain. 2000; 16(3):205-8); dolor central (Cahana, A., y otro, Anest Analg. 2004; 98(6):1581-4), lesión de la médula espinal (véase, Hains, B. C., y otro, Exp Neurol. 2000; 164(2):426-37); dolor posterior a accidente cerebrovascular; dolor talámico (véase, LaBuda, C. J., y otro, Neurosci Lett. 2000; 290(1):79-83); síndrome de dolor regional complejo (véase, Wallace, M. S., y otro, Anesthesiology. 2000; 92(1):75-83; Xantos D y otro, J Pain. 2004; 5(3 Suppl 2):S1); dolor fantasma (véase, Weber, W. E., Ned Tijdsch Geneeskd. 2001; 145(17):813-7; Levitt & Heiback, Pain. 1981; 10(1):67-73); dolor intratable (véase, Yokoyama, M., y otro, Can J Anaest. 2002; 49(8):810-3); dolor agudo, dolor agudo post-operatorio (véase, Koppert, W., y otro, Anest Analg. 2004; 98(4):1050-5; Brennan, T. J., y otro, Pain. 1996; 64(3):493-501); dolor musculoesquelético agudo; dolor articular (véase, Gotoh, S., y

otro, Ann Rheum Dis. 1993; 52(11):817-22); dolor lumbar mecánico (véase, Kehl, L. J., y otro, Pain. 2000; 85(3):333-43); dolor de cuello; tendinitis; dolor por lesión/ejercicio (véase, Sesay, M., y otro, Can J Anaest. 2002; 49(2):137-43); dolor visceral agudo, incluso dolor abdominal; pielonefritis; apendicitis; colecistitis; obstrucción intestinal; hernias; etc. (véase, Giambernardino, M. A., y otro, Pain. 1995; 61(3):459-69); dolor torácico, incluso dolor cardiaco (véase, Vergona, R. A., y otro, Life Sci. 1984; 35(18):1877-84); dolor pelviano, dolor por cólico renal, dolor obstétrico agudo, incluso dolor de parto (véase, Segal, S., y otro, Anest Analg. 1998; 87(4):864-9); dolor por corte de cesárea; dolor inflamatorio agudo, por quemadura y por traumatismo; dolor intermitente agudo, incluso endometriosis (véase, Cason, A. M., y otro, Horm Behav. 2003; 44(2):123-31);

dolor agudo por herpes zoster; anemia de células falciformes; pancreatitis aguda (véase, Toma, H; Gastroenterology. 2000; 119(5):1373-81); dolor sistémico; dolor orofacial, incluso dolor por sinusitis, dolor dental (véase, Nusstein, J., y otro, J Endod. 1998; 24(7):487-91; Chidiac, J. J., y otro, Eur J Pain. 2002; 6(1):55-67); multiple sclerosis (MS) pain (see, Sakurai & Kanazawa, J Neurol Sci. 1999; 162(2):162-8); dolor de depresión (véase, Greene B, Curr Med Res Opin. 2003; 19(4):272-7); dolor por lepra; dolor por enfermedad de Behcet;

adiposis dolorosa (véase, Devillers & Oranje, Clin Exp Dermatol. 1999; 24(3):240-1); dolor flebítico; dolor por Guillain-Barre; piernas dolorosas y dedos móviles de los pies; síndrome de Haglund; dolor por eritromelalgia (véase, Legroux-Crespel, E., y otro, Ann Dermatol Venereol. 2003; 130(4):429-33); dolor por enfermedad de Fabry (véase, Germain, D. P., J Soc Biol. 2002;196(2):183-90); enfermedad vesical y urogenital, incluso, incontinencia urinaria (véase, Berggren, T., y otro, J Urol. 1993; 150(5 Pt 1):1540-3); vejiga hiperactiva (véase, Chuang, Y. C., y otro, Urology. 2003; 61(3):664-70); síndrome de vejiga dolorosa (véase, Yoshimura, N., y otro, J Neurosci. 2001; 21(21):8690-6); cistitis intersticial (IC) (véase, Giannakopoulos& Campilomatos, Arch Ital Urol Nefrol Androl. 1992; 64(4):337-9; Boucher, M., y otro, J Urol. 2000; 164(1):203-8); y prostatitis (véase, Maiersak, J. S., Int Surg. 1998; 83(4):347-9; Keit, I. M., y otro, J Urol. 2001; 166(1):323-8).

[0011] Lamentablemente, tal como se describió antes, la eficacia de los bloqueadores de canales de sodio y los bloqueadores de calcio actualmente usados para los estados patológicos antes descritos se ha visto en gran medida limitada por ciertos efectos secundarios. Estos efectos secundarios incluyen diversas alteraciones del SNC, por ejemplo visión borrosa, mareos, náuseas y sedación, además de

otras patologías con mayor potencial de poner en peligro la vida, tales como arritmias cardíacas e insuficiencia cardiaca. Dichos efectos secundarios indeseables se pueden evitar con un bloqueador de canales de Na que exhiba cierto grado de selectividad en su actividad contra un subtipo de canal de Na. No obstante, los bloqueadores de canales de Na que se encuentran en la actualidad en el mercado carecen de dicha selectividad. Quizás debido a esta falta de selectividad molecular, los fármacos actualmente en el mercado exhiben bloqueo dependiente del uso y generalmente tienen mayor afinidad en los potenciales despolarizados que resultan de la dirección preferencial de las neuronas que se descargan activamente, que se cree son un factor clave en la ventana terapéutica de los fármacos bloqueadores de canales de Na existentes. Si bien cada fármaco tiene su propio perfil terapéutico singular, los actuales bloqueadores de canales de Na generalmente se asocian a efectos secundarios del sistema nervioso central (SNC) y cardiovasculares (CV), incluso cambios de la presión arterial, que a menudo están limitados por la dosis. Mareos, sedación, náuseas, ataxia y confusión son algunos de los efectos secundarios específicos observados para fenitoína™, mexiletina™ y lidocaína™.

[0012] También hay una necesidad de desarrollar bloqueadores de los canales de Na con mínima o ninguna actividad

inhibitoria contra el canal hERG. hERG (gen relacionado con éter a-go-go humano) codifica un canal de iones potasio (canal hERG) que interviene en la repolarización cardiaca. Véase, por ejemplo, Pearlstein, R., R. Vaz, y otro (2003). "Understanding the Structure-Activity Relationship of the Human Ether-a-go-go-Related Gene Cardiac K(+) Channel. A Model for Bad Behavior." J Med Chem **46**(11): 2017-22. La interacción con el canal hERG es un indicador de posible toxicidad cardiaca. El bloqueo hERG aumenta la probabilidad de prolongación y dispersión del intervalo QT cardiaco. Un subgrupo de compuestos que prolongan el intervalo QT puede causar fibrilación ventricular e insuficiencia cardiaca. Belardinelli, L., C. Antzelevitch y M.A. Vos (2003). "Assessing predictors of drug-induced torsade de pointes". Trends Pharmacol Sci. **24** (12): 619-25; Al-Khatib, S. M., N. M. LaPointe, y otro (2003). "What clinicians should know about the QT interval." Jama **289**(16): 2120-7; http://www.fenichel.net/pages/site map.htm.

[0013] También hay una necesidad de desarrollar bloqueadores de canales de Na que tienen mínima o ninguna actividad inhibidora contra la familia de enzima citocromo P450. Dentro de esta familia, se cree que la isoforma CYP 3A4 es la principal isoforma presente en el hígado y el intestino delgado. Otras isoformas clave incluyen CYP 2D6, CYP $2C_9$ y CYP

875

579

1A2. Véase, por ejemplo, la patente de los Estados Unidos N° 6.514.687, cuyas descripciones se incorporan en la presente por referencia. Un bloqueador de canales de Na que inhibe uno o más de las isoformas puede causar efectos secundarios indeseables o puede causar interacciones indeseables entre fármacos cuando se administra con otro fármaco que interactúa con dicha isoforma. Véase, por ejemplo, Davit, B., y otro (1999), "FDA Evaluations Using In Vitro Metabolism to Predict and Interpret In Vivo Metabolic Drug-Drug Interactions: Impact on Labeling", J. Clin. Pharmacol., 39: 899-910; "Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, Dept. of Healt and Human Services, U.S.F.D.A (http://www.fda.gov/cder/guidance.htm).

[0014] También hay una necesidad de desarrollar bloqueadores de canales de Na que exhiban selectividad contra cierto subtipo de canal de Na. De particular utilidad son los compuestos que tienen una actividad deseable baja contra NaV 1.2.

[0015] También hay una necesidad de desarrollar bloqueadores de canales de Na que tienen actividad deseable baja contra canales de calcio de tipo L 1,2. Los canales de calcio CaV1.2 tienen abundante expresión en músculo liso y estriado, especialmente en corazón, encéfalo y células endocrinas. El bloqueo de estos canales puede tener utilidad terapéutica,

pero también pueden dar por resultado significativos efectos secundarios. Las preocupaciones más significativas son deterioro de la contractilidad cardiaca (es decir, un efecto inotrópico negativo) y enlentecimiento de la conducción eléctrica en las regiones marcapasos del corazón. Véase, por ejemplo, Kizer, J. R., y otro, "Epidemiologic Review of the Calcium Channel Blocker Drugs", Arch. Intern Med. 2001; 161: 1145-1158.

[0016] También hay una necesidad de bloqueadores de canales de Na que tengan baja actividad deseable contra los canales de potasio 1,5 ("Kv1.5"; también conocido como KCNA5). Kv1.5 se encuentra sobre todo en células auriculares humanas, pero también en el cerebro. Véase, por ejemplo, Gutman, G. A., y otro, "Compendium of Voltage-Gated Ion Channels: Potassium Channels", Pharmacol. Rev., 55: 583-585 (2003). El bloqueo no deseado de Kv1.5 podría producir convulsiones o ataxia.

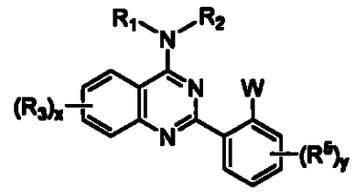
[0017] También hay una necesidad de desarrollar bloqueadores de canales de Na con propiedades farmacocinéticas y/o farmacodinámicas mejoradas y, en consecuencia, son más adecuadas para la administración *in vivo* con fines terapéuticos. Dichas propiedades incluyen solubilidad acuosa, biodisponibilidad, cinética de depuración, etc. Véase, por ejemplo, Shargel, L., Yu, A., Ed's "Applied Biopharmaceutics & Pharmacokinetics", 4t Ed., McGraw-Hill, Nueva York, 1999;

Yacobi, A., Skelly, J.P., Shah, V.P., Benet, L.Z., Ed's. "Integration of Pharmacokinetics, Pharmacodynamics and Toxicokinetics in Rational Drug Development", Plenum Press, Nueva York, 1993; Lee, J.S., Obach, R.S., Fisher, M.B., Ed's. "Drug Metabolizing Enzymes Citochrome P450 and Other Enzymes in Drug Discovery and Development", Marcel Dekker, Nueva York, 2003; Birkett, D.J. "Pharmacokinetics Made Easy", McGraw-Hill Australia, Roseville, Australia, 2002; Katzung, B.G. "Basic & Clinical Pharmacology", McGraw-Hill, Nueva York, 2001; Welling, P.G., Tse, F.L.S., Ed's. "Pharmacokinetics", Marcel Dekker, Nueva York, 1988; Thomas, G. "Medicinal Chemistry An Introduction", Wiley & Sons, Nueva York, 2000; y Gennaro, A. R., y otro, "Remington: The Science and Practice of Pharmacy", 20th Ed., Lippincott, Williams, & Wilkins (2003).

[0018] El bloqueador de canales de Na que cumpla con una o más de las anteriores necesidades no cubiertas sería un mejoramiento muy deseado respecto de los bloqueadores de canales de Na comercializados en la actualidad y sería de gran beneficio para los pacientes que necesiten de un tratamiento con ellos.

SÍNTESIS DE LA INVENCIÓN

[0019] La presente invención provee compuestos de fórmula I:



I;

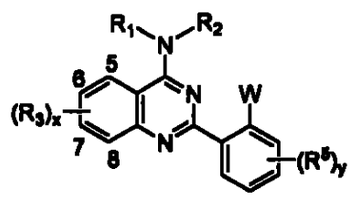
o una de sus sales o derivados farmacéuticamente aceptables.

[0020] Estos compuestos y composiciones farmacéuticamente aceptables son de utilidad para tratar o tratar o reducir la gravedad de enfermedades, trastornos o condiciones patológicas seleccionados, pero sin limitación, de dolor agudo, crónico, neuropático o inflamatorio, artritis, migraña, cefaleas acuminadas, neuralgia de trigémino, neuralgia herpética, neuralgias generales, epilepsia o condiciones epilépticas, trastornos neurodegenerativos, trastornos psiquiátricos tales como ansiedad y depresión, miotonía, arritmia, trastornos del movimiento, trastornos neuroendocrinos, ataxia, esclerosis múltiple, síndrome de intestino irritable, incontinencia, dolor visceral, dolor de osteoartritis, neuralgia posherpética, neuropatía diabética, dolor radicular, ciático, dolor de espalda, dolor de cabeza o cuello, dolor severo o intratable, dolor nociceptivo, dolor intenso, dolor posquirúrgico o dolor por cáncer.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0021] *I. General Descripción de los compuestos de la invención:*

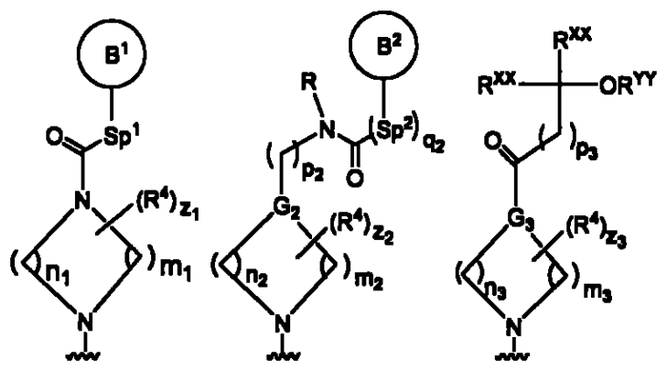
[0022] La presente invención provee un compuesto de la fórmula I:



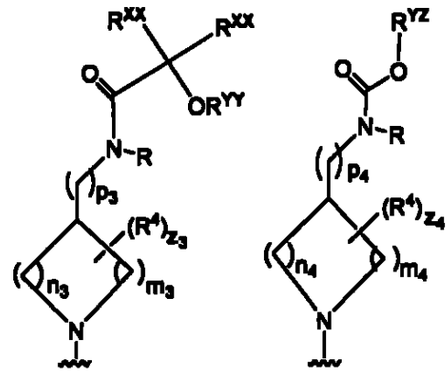
I;

o una de sus sales o derivados farmacéuticamente aceptables, en donde:

R^1 y R^2, junto con el átomo de nitrógeno, forman un anillo sustituido seleccionado de:



(A) (B) (C)



(D) o (E);

en donde, en el anillo (A):

cada uno de m_1 y n_1 es, de modo independiente, 0-3, con la condición de que m_1+n_1 sea 2-6;

z_1 es 0-4;

Sp^1 es -O-, -S-, -NR'- o un ligador de alquilideno C_1-C_6, en donde hasta dos unidades de metileno están opcional e independientemente reemplazadas por -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$ o $-NR'SO_2NR'-$, con la condición de que Sp^1 esté unido al grupo carbonilo a través de un átomo distinto del carbono;

anillo B^1 es un anillo heterocíclico monocíclico, saturado, parcialmente insaturado o aromático de 4-8 miembros que tiene 1-4 heteroátomos seleccionados de O, S o N, en donde el anillo

B^1 está opcionalmente sustituido con w_1 apariciones independientes de $-R^{11}$, en donde w_1 es 0-4;

en donde, en el anillo (B):

G_2 es -N- o CH;

cada uno de m_2 y n_2 es, de modo independiente, 0-3, con la condición de que $m_2 + n_2$ sea 2-6;

p_2 es 0-2; con la condición de que cuando G_2 es N, p_2 no sea 0;

q_2 es 0 ó 1;

z_2 es 0-4;

Sp^2 es un enlace o un ligador de alquilideno C_1-C_6, en donde hasta dos unidades de metileno están opcional e independientemente reemplazadas por -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$ o $-NR'SO_2NR'-$;

anillo B^2 es un anillo heterocíclico monocíclico, saturado, parcialmente insaturado o aromático de 4-8 miembros que tiene 1-4 heteroátomos seleccionados de O, S o N, en donde el anillo B está opcionalmente sustituido con w apariciones independientes de $-R^{12}$, en donde w_2 es 0-4;

en donde, en el anillo (C) o anillo (D):

G_3 es -N-, -CH-NH- o $-CH-CH_2-NH-$;

cada uno de m_3 y n_3 es, de modo independiente, 0-3, con la condición de que m_3+n_3 sea 2-6;

p_3 es 0-2;

z_3 es 0-4;

cada R^{xx} es hidrógeno, grupo alifático C_1-6, un anillo monocíclico saturado, parcialmente insaturado o totalmente insaturado de 3-8-miembros que tiene 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillos bicíclicos saturados, parcialmente insaturados o totalmente insaturados de 8-12 miembros que tiene 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre; en donde R^{xx} está opcionalmente sustituido con w_3 apariciones independientes de $-R^{13}$, en donde w_3 es 0-3;

con la condición de que ambos R^{xx} no sean de forma simultánea hidrógeno;

R^{yy} es hidrógeno, $-COR'$, $-CO_2R'$, $-CON(R')_2$, $-SOR'$, $-SO_2R'$, $-SO_2N(R')_2$, $-COCOR'$, $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$ o $-PO(R')$;

en donde, en el anillo (E):

cada uno de m_4 y n_4 es, de modo independiente, 0-3, con la condición de que $m_4 + n_4$ sea 2-6;

p_4 es 1-2;

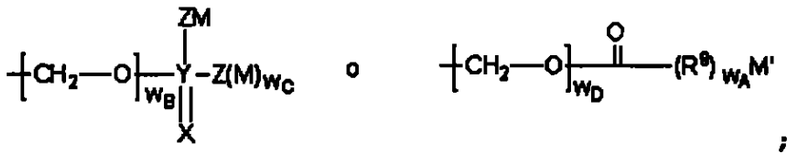
z_4 es 0-4;

R^yZ es grupo alifático C_1-C_6, opcionalmente sustituido con w_4 apariciones independientes de $-R^{14}$, en donde w_4 es 0-3;

x e y, es cada uno, de modo independiente, 0-4;

W es OR^{XY};

R^{XY} es hidrógeno o un grupo seleccionado de:



;

en donde:

cada uno de w_A, w_B, wC y w_D es, de modo independiente, 0 ó 1;

cada M está seleccionado, de modo independiente, de hidrógeno, Li, Na, K, Mg, Ca, Ba, $-N(R^7)_4$, alquilo C_1-C_12, alquenilo C_2-C_12 o $-R^6$; en donde 1 a 4 radicales $-CH_2$ del grupo alquilo o alquenilo, distinto de $-CH_2$ que está unido a Z, está opcionalmente reemplazado por un grupo de heteroátomo seleccionado de O, S, S(O), $S(O_2)$ o $N(R^7)$; y en donde cualquier hidrógeno en dicho alquilo, alquenilo o R^6 está opcionalmente reemplazado con un sustituyente seleccionado de oxo, $-OR^7$, $-R^7$, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, $-CO_2R^7$, $-C(O)-N(R^7)_2$, $S(O)_2-N(R^7)_2$, $N(R^7)-C(O)-R^7$, $C(O)R^7$, $-S(O)_n-R^7$, OCF_3, $-S(O)_n-R^6$, $N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$ o $-NO_2$;

n es 0-2;

M' es H, alquilo C_1-C_12, alquenilo C_2-C_12 o $-R^6$; en donde 1 a 4 radicales $-CH_2$ del grupo alquilo o alquenilo está opcionalmente reemplazado por un grupo de heteroátomo seleccionado de O, S, S(O), $S(O_2)$ o $N(R^7)$; y en donde cualquier

hidrógeno en dicho alquilo, alquenilo o R^6 está opcionalmente reemplazado con un sustituyente seleccionado de oxo, $-O\ R^7$, $-R^7$, $-N(R^7)_2$, $N(R^7)_3$, $-\ R^7OH$, $-CN$, $-CO_2\ R^7$, $-C(O)-N(R^7)_2$, $-S(O)_2-N(R^7)_2$, $-N(R^7)-C(O)-\ R^7$, $-C(O)\ R^7$, $-S(O)_n-\ R^7$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$ o $-NO_2$;

Z es $-CH_2-$, $-O-$, $-S-$, $-N(R^7)_2-$; o

cuando M está ausente, Z es hidrógeno, =O o =S;

Y es P o S, en donde cuando Y es S, Z no es S;

X es O o S;

cada R^7 está seleccionado, de modo independiente, de hidrógeno o alifático C_1-C_4, opcionalmente sustituido con hasta dos Q_1;

cada Q_1 está seleccionado, de modo independiente, de un sistema de anillos carbocíclicos saturados, parcialmente saturados o insaturados de 3-7 miembros; o un anillo heterocíclico saturado, parcialmente saturado o insaturado de 5-7 miembros que contiene uno o varios heteroátomos o grupos de heteroátomos seleccionados de O, N, NH, S, SO o SO_2; en donde Q_1 está opcionalmente sustituido con hasta tres sustituyentes seleccionados de oxo, -OH, -O(alifático C_1-C_4), -alifático C_1-C_4, $-NH_2$, NH(alifático C_1-C_4), -N(alifático C_1-C_4)$_2$, -N(alifático C_1-C_4)-C(O)-alifático C_1-C_4, -(alifático C_1-C_4)-OH, -CN, $-CO_2H$, $-CO_2$(alifático C_1-C_4), $-C(O)-NH_2$, -C(O)-NH(alifático C_1-C_4), -C(O)-N(alifático C_1-C_4)$_2$, halo o $-CF_3$;

R^6 es un sistema de anillos carbocíclicos o heterocíclicos saturados, parcialmente saturados o insaturados de 5-6 miembros o un sistema de anillos bicíclicos saturados, parcialmente saturados o insaturados de 8-10 miembros; en donde cualquiera de dichos sistemas de anillos heterocíclicos contiene uno o varios heteroátomos seleccionados de O, N, S, $S(O)_n$ o $N(R^7)$; y en donde cualquiera de dichos sistemas de anillos contiene opcionalmente 1 a 4 sustituyentes independientemente seleccionados de OH, alquilo C_1-C_4, O-alquilo C_1-C_4 u O-C(O)-alquilo C_1-C_4;

R^9 es $C(R^7)_2$, O o $N(R^7)$;

cada aparición de R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4 y R^5 es, de modo independiente, $Q-R^X$; en donde Q es un enlace o es una cadena de alquilideno C_1-C_6 en donde hasta dos unidades de metileno no adyacentes de Q están opcional e independientemente reemplazadas por -NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, -OP(O)(OR)- o -POR-; y cada aparición de R^X está seleccionada, de modo independiente, de -R', halógeno, =O, =NR', $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -NR'COR', $-NR'CON(R')_2$, $-NR'CO_2R'$, -COR', $-CO_2R'$, -OCOR', $-CON(R')_2$, $-OCON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, $-NR'SO_2R'$, $-NR'SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$ u $-OPO(R')_2$; y

cada aparición de R es, de modo independiente, hidrógeno o grupo alifático C_1-6 que tiene hasta tres sustituyentes; y cada aparición de R′ es, de modo independiente, hidrógeno o grupo alifático C_1-6, un anillo monocíclico saturado, parcialmente insaturado o totalmente insaturado de 3-8-miembros que tiene 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillos bicíclicos saturados, parcialmente insaturados o totalmente insaturados de 8-12 miembros que tiene 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde R' tiene hasta cuatro sustituyentes; o R y R′, dos apariciones de R o dos apariciones de R′, se toman junto con los átomos a los que están unidos para formar un anillo monocíclico o bicíclico opcionalmente sustituido de 3-12 miembros saturado, parcialmente insaturado o totalmente insaturado que tiene 0-4 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre.

[0023] *2. Los compuestos y las definiciones:*

[0024] Los compuestos de esta invención incluyen los descritos en general con anterioridad y que se ilustran además con las clases, subclases y especies descritas en la presente. Tal como se usa en la presente, se deben aplicar las siguientes

definiciones, salvo que se indique otra cosa. A los fines de esta invención, los elementos químicos se identifican de acuerdo con la Tabla Periódica de Elementos, versión CAS y el Handbook of Chemistry and Physics, 75th Ed. Adicionalmente, los principios generales de la química orgánica se describen en "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999 y "March's Advanced Organic Chemistry", 5th Ed., Smith, M.B. y March, J., eds. John Wiley & Sons, New York: 2001, cuyos contenidos totales se incorporan en la presente por referencia.

[0025] Tal como se describe en la presente, los compuestos de la invención pueden estar opcionalmente sustituidos con uno o varios sustituyentes, tal como se ilustra en general con anterioridad o como se ejemplifica por medio de clases, subclases y especies particulares de la invención. Se apreciará que la frase "opcionalmente sustituido" se usa de modo indistinto con la frase "sustituido o no sustituido". En general, el término "sustituido", ya sea que esté precedido por el término "opcional" o no, se refiere al reemplazo de uno o varios radicales hidrógeno en una estructura dada con el radical de un sustituyente especificado. Salvo que se indique otra cosa, un grupo opcionalmente sustituido puede tener un sustituyente en cada posición sustituible del grupo y cuando más de una posición en una estructura dada puede estar

sustituida con más de un sustituyente seleccionado de un grupo especificado, el sustituyente puede ser igual o diferente en cada posición. Las combinaciones de sustituyentes comprendidas por esta invención son preferentemente aquellas que resultan en la formación de compuestos estables o químicamente viables. El término "estable", tal como se usa en la presente, se refiere a compuestos que no están sustancialmente alterados cuando se someten a condiciones para permitir su producción, detección y, con preferencia, su recuperación, purificación y uso para uno o varios de los fines revelados en la presente. En algunas formas de realización, un compuesto estable o químicamente viable es uno que no se altera sustancialmente cuando se mantiene a una temperatura de 40°C o menos, en ausencia de humedad u otras condiciones químicamente reactivas, durante al menos una semana.

[0026] El término "alifático" o "grupo alifático", tal como se usa en la presente, significa una cadena lineal (es decir, no ramificada) o cadena hidrocarbonada ramificada sustituida o no sustituida que está completamente saturada o que contiene una o varias unidades de instauración o un hidrocarburo monocíclico o bicíclico que está completamente saturado o que contiene una o varias unidades de insaturación, pero que no es aromático (también referido en la presente como "carbociclo" "cicloalifático" o "cicloalquilo"), que tiene un único punto

de unión con el resto de la molécula. Salvo que se especifique otra cosa, los grupos alifáticos contienen 1-20 alifático átomos de carbono. En algunas formas de realización, los grupos alifáticos contienen 1-10 alifático átomos de carbono. En otras formas de realización, los grupos alifáticos contienen 1-8 alifático átomos de carbono. En otras formas más de realización, los grupos alifáticos contienen 1-6 alifático átomos de carbono y en otras formas de realización los grupos alifáticos contienen 1-4 alifático átomos de carbono. En algunas formas de realización, "cicloalifático" (o "carbociclo" o "cicloalquilo") se refiere a hidrocarburo monocíclico C_3-C_8 o hidrocarburo bicíclico C_8-C_{12} que está completamente saturado o que contiene una o varias unidades de insaturación, pero que no es aromático, que tiene un único punto de unión con el resto de la molécula en donde todo anillo individual en dicho sistema de anillos bicíclicos tiene 3-7 miembros. Los grupos alifáticos apropiados incluyen, pero sin limitación, grupos lineal o ramificado, alquilo, alquenilo, alquinilo sustituidos o no sustituidos y sus híbridos tales como (cicloalquil)alquilo, (cicloalquenil)alquilo o (cicloalquil)alquenilo.

[0027] El término "heteroalifático", tal como se usa en la presente, significa grupo alifáticos en donde uno o dos átomos de carbono se reemplazan independientemente por uno o más de

oxígeno, azufre, nitrógeno, fósforo o silicio. Los grupos heteroalifáticos pueden ser sustituidos o no sustituidos, ramificados o no ramificados, cíclicos o acíclicos e incluyen grupos "heterociclo", "heterociclilo", "heterocicloalifático" o "heterocíclico".

[0028] El término "heterociclo", "heterociclilo", "heterocicloalifático" o "heterocíclico" tal como se usa en la presente significa sistemas de anillos no aromáticos, monocíclicos, bicíclicos o tricíclicos en donde uno o más miembros del anillo son un heteroátomo seleccionado independientemente. En algunas formas de realización, el grupo "heterociclo", "heterociclilo", "heterocicloalifático" o "heterocíclico" tiene 3 a 14 miembros del anillo en donde uno o varios miembros del anillo es un heteroátomo seleccionado, de modo independiente, de oxígeno, azufre, nitrógeno o fósforo y cada anillo en el sistema contiene 3 a 7 miembros del anillo.

[0029] El término "heteroátomo" significa uno o varios de oxígeno, azufre, nitrógeno, fósforo o silicio (incluso cualquier forma oxidada de nitrógeno, azufre, fósforo o silicio; la forma cuaternaria de cualquier nitrógeno básico o un nitrógeno sustituible de un anillo heterocíclico, por ejemplo, N (como en 3,4-dihidro-2*H*-pirrolilo), NH (como en pirrolidinilo) o NR^+ (como en pirrolidinilo N-sustituido)).

[0030] El término "insaturado", tal como se usa en la presente, significa que un resto tiene una o varias unidades de insaturación.

[0031] El término "alcoxi" o "tioalquilo", tal como se usa en la presente, se refiere a un grupo alquilo, como se definió con anterioridad, unido a la cadena de carbonos principal a través de un átomo de oxígeno ("alcoxi") o azufre ("tioalquilo").

[0032] Los términos "haloalquilo", "haloalquenilo" y "haloalcoxi" significan alquilo, alquenilo o alcoxi, según el caso, sustituido con uno o varios átomos de halógeno. El término "halógeno" significa F, Cl, Br o I.

[0033] El término "arilo" usado solo o como parte de un resto más grande que en "aralquilo", "aralcoxi" o "ariloxialquilo", se refiere a sistemas de anillos monocíclicos, bicíclicos y tricíclicos que tienen un total de 5 a 14 miembros del anillo, en donde al menos un anillo en el sistema es aromático y en donde cada anillo en el sistema contiene 3 a 7 miembros del anillo. El término "arilo" se puede usar indistintamente con el término "anillo arilo". El término "arilo" también se refiere a sistemas de anillos heteroarilos tal como se define a continuación.

[0034] El término "heteroarilo", usado solo o como parte de un resto más grande que en "heteroaralquilo" o

"heteroarilalcoxi", se refiere a sistemas de anillos monocíclicos, bicíclicos y tricíclicos que tienen un total de 5 a 14 miembros del anillo, en donde al menos un anillo en el sistema es aromático, al menos un anillo en el sistema contiene uno o varios heteroátomos y en donde cada anillo en el sistema contiene 3 a 7 miembros del anillo. El término "heteroarilo" se puede usar indistintamente con el término "anillo heteroarilo" o el término "heteroaromático".

[0035] Un grupo arilo (incluyendo aralquilo, aralcoxi, ariloxialquilo y similares) o heteroarilo (incluyendo heteroaralquilo y heteroarilalcoxi y similares) puede contener uno o varios sustituyentes y en consecuencia puede ser "opcionalmente sustituido". A menos que se defina de otro modo con anterioridad y en la presente, los sustituyentes adecuados en el átomo de carbono insaturado de un grupo arilo o heteroarilo generalmente se seleccionan de halógeno; $-R^{\circ}$; $-OR^{\circ}$; $-SR^{\circ}$; fenilo (Ph) opcionalmente sustituido con R°; $-O(Ph)$ opcionalmente sustituido con R°; $-(CH_2)_{1-2}(Ph)$, opcionalmente sustituido con R°; $-CH=CH(Ph)$, opcionalmente sustituido con R°; $-NO_2$; $-CN$; $-N(R^{\circ})_2$; $-NR^{\circ}C(O)R^{\circ}$; $-NR^{\circ}C(S)R^{\circ}$; $-NR^{\circ}C(O)N(R^{\circ})_2$; $-NR^{\circ}C(S)N(R^{\circ})_2$; $-NR^{\circ}CO_2R^{\circ}$; $-NR^{\circ}NR^{\circ}C(O)R^{\circ}$; $-NR^{\circ}NR^{\circ}C(O)N(R^{\circ})_2$; $-NR^{\circ}NR^{\circ}CO_2R^{\circ}$; $-C(O)C(O)R^{\circ}$; $-C(O)CH_2C(O)R^{\circ}$; $-CO_2R^{\circ}$; $-C(O)R^{\circ}$; $-C(S)R^{\circ}$; $-C(O)N(R^{\circ})_2$; $-C(S)N(R^{\circ})_2$; $-OC(O)N(R^{\circ})_2$; $-OC(O)R^{\circ}$; -

$C(O)N(OR^\circ)$ R°; $-C(NOR^\circ)$ R°; $-S(O)_2R^\circ$; $-S(O)_3R^\circ$; $-SO_2N(R^\circ)_2$; $-S(O)R^\circ$; $-NR^\circSO_2N(R^\circ)_2$; $-NR^\circSO_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(=NH)-N(R^\circ)_2$; $-P(O)_2R^\circ$; $-PO(R^\circ)_2$; $-OPO(R^\circ)_2$; $-(CH_2)_{0-2}NHC(O)R^\circ$; fenilo (Ph) opcionalmente sustituido con R°; -O(Ph) opcionalmente sustituido con R°; $-(CH_2)_{1-2}(Ph)$, opcionalmente sustituido con R°; o -CH=CH(Ph), opcionalmente sustituido con R°; en donde cada aparición independiente de R° está seleccionada de hidrógeno, alifático C_{1-6} opcionalmente sustituido, un anillo no sustituido de 5-6 miembros heteroarilo o heterocíclico, fenilo, -O(Ph) o $-CH_2(Ph)$, o, con independencia de la definición anterior, dos apariciones independientes de R°, en el mismo sustituyente o en sustituyentes diferentes, junto con los átomos a los que cada grupo R° está unido, para formar un anillo monocíclico o biciclico opcionalmente sustituido de 3-12 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-4 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre.

[0036] Los sustituyentes opcionales en el grupo alifático de R° están seleccionados de NH_2, NH(alifático C_{1-4}), N(alifático $C_{1-4})_2$, halógeno, alifático C_{1-4}, OH, O(alifático C_{1-4}), NO_2, CN, CO_2H, CO_2(alifático C_{1-4}), O(haloalifático C_{1-4}) o haloalifático C_{1-4}, en donde cada uno de los grupos alifáticos C_{1-4} anteriores de R° no está sustituido.

[0037] Un grupo alifático o heteroalifático o un anillo heterocíclico no aromático pueden contener uno o varios sustituyentes y en consecuencia pueden estar "opcionalmente sustituidos". A menos que se defina de otro modo con anterioridad y en la presente, sustituyentes adecuados en el carbono saturado de un grupo alifático o heteroalifático o de un anillo heterocíclico no aromático se seleccionan de aquellos enumerados con anterioridad para el carbono insaturado de un grupo arilo o heteroarilo y adicionalmente incluyen los siguientes: =O, =S, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2$(alquilo), $=NNHSO_2$(alquil) o $=NR^*$, donde cada R^* está seleccionado, de modo independiente, de hidrógeno o un C_{1-6} grupo alifático opcionalmente sustituido.

[0038] A menos que se defina de otro modo con anterioridad y en la presente, los sustituyentes opcionales en el nitrógeno de un anillo heterocíclico no aromático se seleccionan generalmente de $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^{+1})_2$, $-C(=NH)-N(R^+)_2$ o $-NR^+SO_2R^+$; en donde R^+ es hidrógeno, un alifático C_1-6 opcionalmente sustituido, fenilo opcionalmente sustituido, -O(Ph) opcionalmente sustituido, opcionalmente sustituido $-CH_2$(Ph), opcionalmente sustituido $-(CH_2)_{1-2}$(Ph); -CH=CH(Ph) opcionalmente sustituido; o un anillo heteroarilo o heterocíclico no sustituido de 5-6 miembros que tiene uno a

cuatro heteroátomos seleccionados, de modo independiente, de oxígeno, nitrógeno o azufre, o, con independencia de la definición anterior, dos apariciones independientes de R^+, en el mismo sustituyente o en sustituyentes diferentes, junto con los átomos a los que cada grupo R^+ está unido, forman un anillo monocíclico o bicíclico de 3-12 miembros saturado, parcialmente insaturado o totalmente insaturado, opcionalmente sustituido, con 0-4 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre.

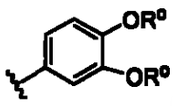
[0039] Los sustituyentes opcionales en el grupo alifático o el anillo fenilo de R^+ están seleccionados de $-NH_2$, -NH(alifático C_{1-4}), -N(alifático C_{1-4})$_2$, halógeno, alifático C_{1-4}, -OH, -O(alifático C_{1-4}), $-NO_2$, -CN, $-CO_2H$, $-CO_2$(alifático C_{1-4}), -O(halo alifático C_{1-4}) o halo(alifático C_{1-4}), en donde cada uno de los grupos alifáticos C_{1-4} anteriores de R^+ no está sustituido.

[0040] El término "cadena de alquilideno" se refiere a una cadena carbonada lineal o ramificada que puede estar totalmente saturada o tener una o más unidades de instauración y tiene dos puntos de fijación al resto de la molécula.

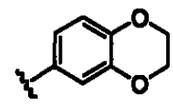
[0041] Tal como se detalló con anterioridad, en algunas formas de realización, dos apariciones independientes de R° (o R^+, R, R' o cualquier otra variable definida de forma similar en la presente), se toman juntos con el(os) átomo(s) a los que están

unidos para formar un anillo monocíclico o bicíclico de 3-12 miembros saturado, parcialmente insaturado o totalmente insaturado opcionalmente sustituido, con 0-4 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre.

[0042] Los anillos de ejemplo que se forman cuando dos apariciones independientes de R° (o R^+, R, R' o cualquier otra variable definida de forma similar en la presente), que junto con los átomos a los que cada grupo variable está unido incluyen, pero sin limitación los siguientes: a) dos apariciones independientes de R° (o R^+, R, R' o cualquier otra variable definida de forma similar en la presente) que están unidas al mismo átomo y se toman juntas con ese átomo para formar un anillo, por ejemplo, $N(R^\circ)_2$, donde ambas apariciones de R° se toman juntas con el átomo de nitrógeno para formar un grupo piperidin-1-ilo, piperazin-1-ilo o morfolin-4-ilo; y b) dos apariciones independientes de R° (o R^+, R, R' o cualquier otra variable definida de forma similar en la presente) que están unidas a diferentes átomos y se toman juntas con los dos de esos átomos para formar un anillo, por ejemplo, donde un grupo fenilo está sustituido con dos apariciones de OR°



, estas dos apariciones de R° se toman juntas con los átomos de oxígeno a los que están unidos para formar un anillo

fusionado de 6 miembros que contiene oxígeno:  . Se apreciará que una variedad de otros anillos se puede formar cuando dos apariciones independientes de R^o (o R^+, R, R' o cualquier otra variable definida de forma similar en la presente) se une junto con los átomos a los que cada grupo variable y que los ejemplos detallados con anterioridad no pretenden ser limitativos.

A menos que se establezca otra cosa, las estructuras representadas en la presente también incluyen todas las formas isoméricas de la estructura (por ejemplo, enantiomérica, diastereomérica y geométrica (o conformacional)); por ejemplo, las configuraciones R y S para cada centro asimétrico, isómeros (Z) y (E) de enlace doble e isómeros (Z) y (E) conformacionales. En consecuencia, los isómeros estereoquímicos individuales así como las mezclas enantioméricas, diastereoméricas y geométricas (o conformacionales) de los presentes compuestos están dentro del alcance de la invención. A menos que se establezca otra cosa, todas las formas tautoméricas de los compuestos de la invención están dentro del alcance de la invención. Adicionalmente, salvo que se establezca otra cosa, las estructuras representadas en la presente también incluyen compuestos que difieren sólo en la presencia de uno o varios

átomos isotópicamente enriquecidos. Por ejemplo, los compuestos que tienen las presentes estructuras excepto en el reemplazo de hidrógeno por deuterio o tritio o el reemplazo de un carbono por un carbono enriquecido con ^{13}C o ^{14}C están dentro del alcance de esta invención. Estos compuestos son de utilidad, por ejemplo, como herramientas analíticas o sondas en pruebas biológicas.

[0043] *3. Descripción de los ejemplos de compuestos:*

[0044] En una forma de realización, R es hidrógeno o R es alifático C_1-C_6. los ejemplos de R incluyen alquilo C_1-C_6, por ejemplo, metilo, etilo, propilo o butilo.

[0045] En una forma de realización, R' es hidrógeno.

[0046] En una forma de realización, R' es un grupo alifático C_1-C_8, opcionalmente sustituido con hasta 3 sustituyentes seleccionados de halo, CN, CF_3, CHF_2, OCF_3 o $OCHF_2$, en donde hasta dos unidades metileno de dicho alifático C_1-C_8 están opcionalmente reemplazadas con -CO-, -CONH(alquilo C_1-C_4)-, -CO_2-, -OCO-, -N(alquilo C_1-C_4)CO_2-, -O-, -N(alquil C_1-C_4)CON(alquilo C_1-C_4)-, -OCON(alquilo C_1-C_4)-, -N(alquil C_1-C_4)CO-, -S-, -N(alquilo C_1-C_4)-, -SO_2N(alquilo C_1-C_4)-, N(alquil C_1-C_4)SO_2- o -N(alquil C_1-C_4)SO_2N(alquilo C_1-C_4)-.

[0047] En una forma de realización, R' es un anillo monocíclico de 3-8 miembros saturado, parcialmente insaturado

o totalmente insaturado anillo con 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde R' está opcionalmente sustituido con hasta 3 sustituyentes seleccionados de halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$ o alquilo C_1-C_6, en donde hasta dos unidades de metileno de dicho alquilo C_1-C_6 está opcionalmente reemplazado con -CO-, -CONH(alquilo C_1-C_4)-, $-CO_2-$, -OCO-, -N(alquil C_1-C_4)CO_2-, -O-, -N(alquil C_1-C_4)CON(alquilo C_1-C_4)-, -OCON(alquilo C_1-C_4)-, -N(alquil C_1-C_4)CO-, -S-, -N(alquilo C_1-C_4)-, $-SO_2$N(alquilo C_1-C_4)-, N(alquil C_1-C_4)SO_2- o -N(alquil C_1-C_4)SO_2N(alquilo C_1-C_4)-.

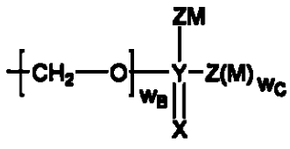
[0048] En una forma de realización, R' es un sistema bicíclico de 8-12 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre; en donde R' está opcionalmente sustituido con hasta 3 sustituyentes seleccionado de halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$ o alquilo C_1-C_6, en donde hasta dos unidades de metileno de dicho alquilo C_1-C_6 está opcionalmente reemplazado con -CO-, -CONH(alquilo C_1-C_4)-, $-CO_2-$, -OCO-, -N(alquil C_1-C_4)CO_2-, -O-, -N(alquil C_1-C_4)CON(alquilo C_1-C_4)-, -OCON(alquilo C_1-C_4)-, -N(alquil C_1-C_4)CO-, -S-, -N(alquilo C_1-C_4)-, $-SO_2$N(alquilo C_1-C_4)-, N(alquil C_1-C_4)SO_2- o -N(alquil C_1-C_4)SO_2N(alquilo C_1-C_4)-.

[0049] En una forma de realización, dos apariciones de R' se toman juntos con el(os) átomo(s) a los que están unidos para

formar un anillo monociclico o bicíclico opcionalmente sustituido de 3-12 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-4 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde R' está opcionalmente sustituido con hasta 3 sustituyentes seleccionado de halo, CN, CF_3, CHF_2, OCF_3, $OCHF_2$ o alquilo C_1-C_6, en donde hasta dos unidades metileno de dichos alquilo C_1-C_6 está opcionalmente reemplazadas con -CO-, -CONH(alquil C_1-C_4)-, $-CO_2-$, -OCO-, -N(alquil C_1-C_4)CO_2-, -O-, -N(alquil C_1-C_4)CON(alquilo C_1-C_4)-, -OCON(alquilo C_1-C_4)-, -N(alquil C_1-C_4)CO-, -S-, -N(alquilo C_1-C_4)-, $-SO_2N$(alquilo C_1-C_4)-, N(alquil C_1-C_4)SO_2- o -N(alquil C_1-C_4)SO_2N(alquilo C_1-C_4)-.

[0050] En otra forma de realización, W es OH.

[0051] En aun otra forma de realización, R^{XY} es:



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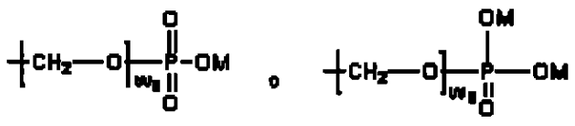
[0052] En cierta forma de realización, Y es P y X es O.

[0053] En otra forma de realización, cada Z es -O-.

[0054] En otra forma de realización más, R^{XY} está seleccionado de:



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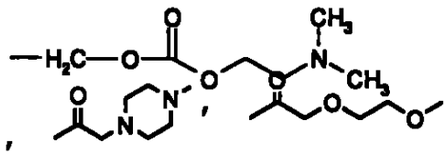
[0055] En otra forma de realización más, R^{xy} está seleccionado de: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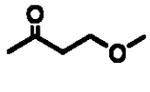
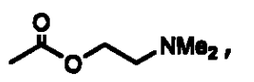
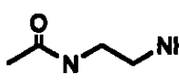
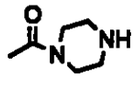
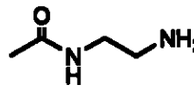
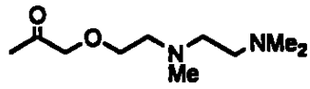
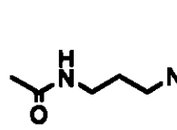
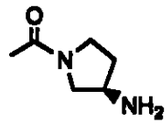
, 
, -(L)-lisina, $-PO_3Na_2$,


, 
, -(L)-tirosina, 
, $-PO_3Mg$,

$-PO_3(NH_4)_2$, $-CH_2-OPO_3Na_2$, 
, -(L)-serina,

$-SO_3Na_2$, 
, $-SO_3Mg$, $-SO_3(NH_4)_2$,

$-CH_2-OSO_3Na_2$, $-CH_2-OSO_3(NH_4)_2$, 
, 
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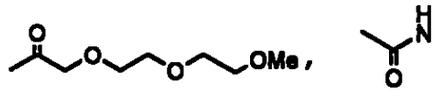
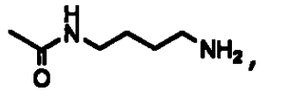
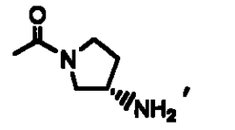
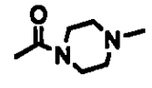

, 
, 
, 
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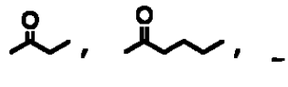
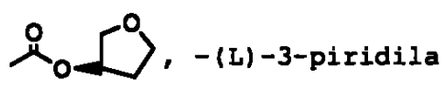
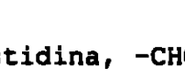
acetilo, 
,
, -(L)-valina, -ácido (L)-glutámico, -ácido (L)-aspártico, -ácido (L)-γ-t-butil-aspártico,


, -(L)-3-piridilalanina, -(L)-histidina, -CHO, 
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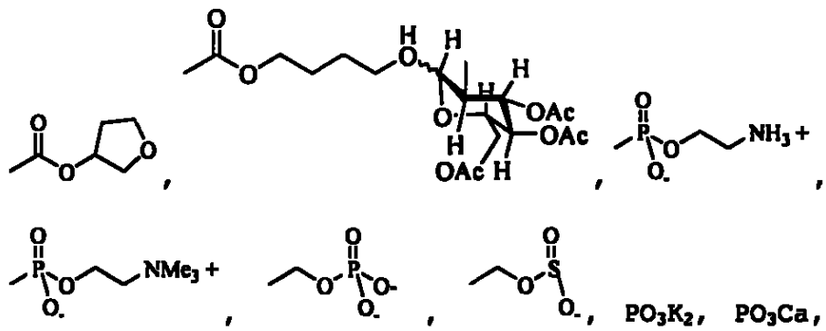
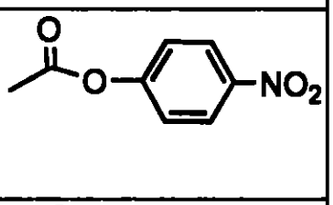
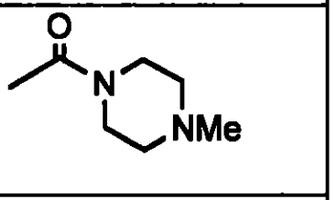
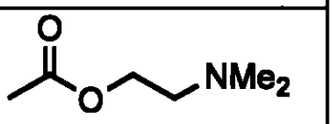
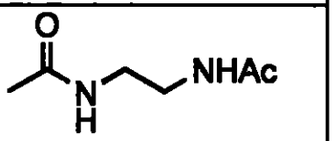
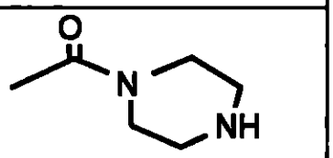
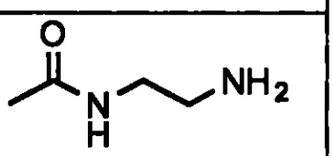
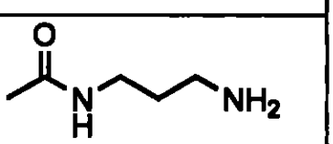
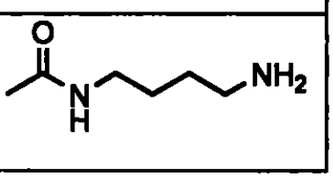
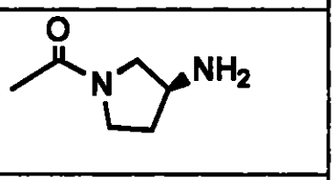
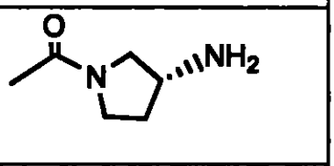
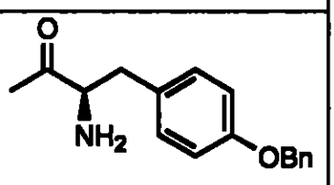
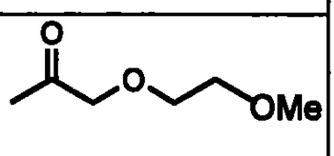
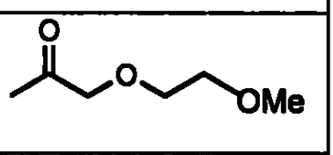
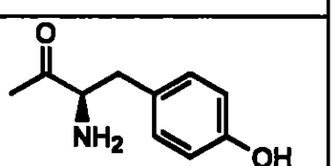
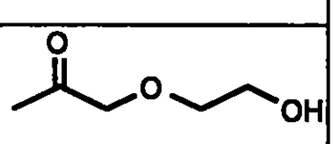
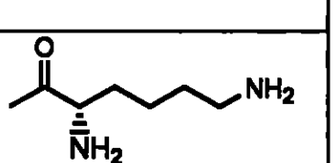
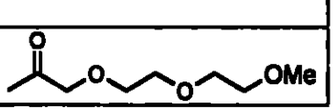


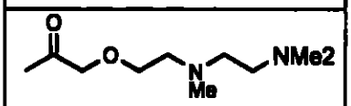
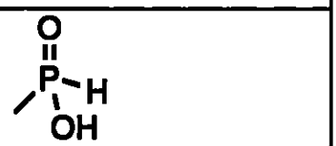
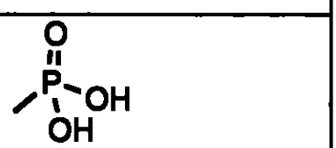
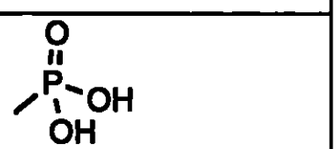
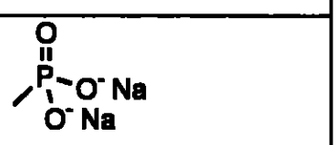
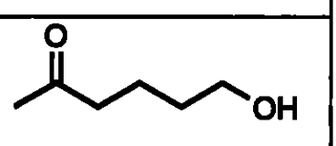
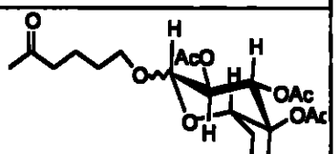
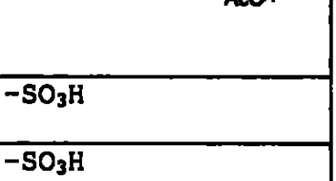
espermina, PO_3-

(espermidina)$_2$ o PO_3-(meglamina)$_2$.

[0056] En otra forma de realización más, R^{XY} está seleccionado de:

R^{XY}









R^{XY}










R^{XY}








$-SO_3H$
$-SO_3H$

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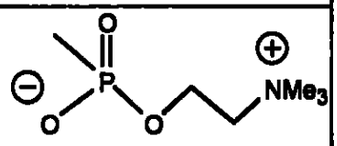
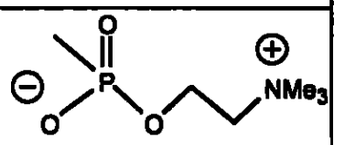
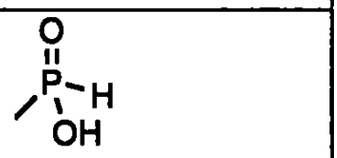
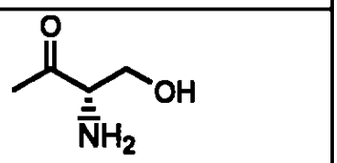
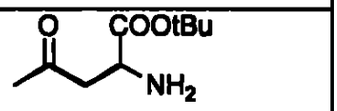
R^{XY}




PO_3K_2
PO_3Ca
PO_3Mg


[0057] En una forma de realización, x es 0-2 o x es 1 ó 2 o, x es 1.

[0058] En una forma de realización, R^3 está presente en la posición 6 o 7 del anillo de quinazolina.

[0059] En otra forma de realización, R^3 es seleccionado de halo, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$ o un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6, arilo, heteroarilo, cicloalifático, heterocicloalifático, arilalquilo C_1-C_6, heteroarilalquilo C_1-C_6, cicloalifáticoalquilo C_1-C_6 o heterocicloalifáticoalquilo C_1-C_6.

[0060] En una forma de realización, R^3 es independientemente Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, $-COOH$, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, $-CONH$(ciclopropilo), $-CONHCH_3$, $-CONHCH_2CH_3$ o un grupo opcionalmente sustituido seleccionado de -piperidinilo, piperizinilo, morfolino, fenilo, feniloxi, bencilo o benciloxi.

[0061] En otra forma de realización, cada grupo R^3 es independientemente halógeno, CN, alquilo C_1-C_6, OR', $N(R')_2$, $CON(R')_2$ o $NRCOR'$ opcionalmente sustituido.

[0062] En una forma de realización, x es 1 ó 2 y cada grupo R^3 es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN.

[0063] En otra forma de realización más, x es 1 y R^3 es un anillo quinazolina en la posición 6 y está seleccionada de -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN.

[0064] En otra forma de realización más, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$.

[0065] En una forma de realización, R^3 es un anillo quinazolina en la posición 6 y es $-CON(R')_2$ o NRCOR'.

[0066] En otra forma de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y está seleccionado de -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN.

[0067] En otra forma de realización más, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$. o, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es $-CON(R')_2$ o NRCOR'.

[0068] En una forma de realización, y es 0-4 y R^5 es independientemente halógeno, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, -OR', $-CH_2OR'$, -SR', $-CH_2SR'$, - -NRCOR', $-CON(R')_2$, $-S(O)_2N(R')_2$, -OCOR', -COR', $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, -

$P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$ o un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6, arilo, heteroarilo, cicloalifático, heterocicloalifático, arilalquilo C_1-C_6, heteroarilalquilo C_1-C_6, cicloalifáticoalquilo C_1-C_6 o heterocicloalifáticoalquilo C_1-C_6.

[0069] En otra forma de realización, R^5 es independientemente Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-ilo, $OCOCH(CH_3)_2$, OCO(ciclopentilo), $-COCH_3$, fenoxi opcionalmente sustituido o benciloxi opcionalmente sustituido.

[0070] En ciertas formas de realización, cada uno de z_1, z_2, z_3 o z_4 es independientemente 0-2. En otras formas de realización, cada uno de z_1, z_2, z_3 o z_4 es 0 y el anillo no está sustituido. Los grupos R^4 preferidos, cuando están presentes, con cada uno independientemente halógeno, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$ o un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6, arilo, heteroarilo, cicloalifático, heterocicloalifático, arilalquilo C_1-C_6, heteroarilalquilo C_1-C_6, cicloalifáticoalquilo C_1-C_6 o heterocicloalifáticoalquilo C_1-C_6. Otros ejemplos de grupos R^4 son Cl, Br, F, CF_3, CH_3, $-CH_2CH_3$, CN, -COOH, $-N(CH_3)_2$, $-N(Et)_2$, -

$N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, $-OH$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2(CH_2)_3CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)NHCH_2CH(CH_3)_2$, $-NHCOOCH_3$, $-C(O)C(CH_3)_3$, $-COO(CH_2)_2CH_3$, $-C(O)NHCH(CH_3)_2$, $-C(O)CH_2CH_3$ o un grupo opcionalmente sustituido seleccionado de piperidinilo, piperizinilo, morfolino, alcoxi C_{1-4}, fenilo, feniloxi, bencilo, benciloxi, $-CH_2$ciclohexilo, piridilo, $-CH_2$piridilo o $-CH_2$tiazolilo.

[0071] En ciertas formas de realización, x es 0-2. En otras formas de realización, x es 1 ó 2. En otras formas más de realización x es 1 y R^3 está sustituido a la posición 6 o 7 del anillo quinazolina. Cuando el anillo quinazolina está sustituido (x es 1-4), los grupos R^3 son halógeno, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$ o un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6, arilo, heteroarilo, cicloalifático, heterocicloalifático, arilalquilo C_1-C_6, heteroarilalquilo C_1-C_6, cicloalifáticoalquilo C_1-C_6 o heterocicloalifáticoalquilo C_1-C_6. En otras formas más de realización, cada aparición de R^3 es independientemente Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, $-COOH$, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, $-CONH$(ciclopropilo), $-CONHCH_3$, $-CONHCH_2CH_3$ o un grupo

opcionalmente sustituido seleccionado de piperidinilo, piperizinilo, morfolino, fenilo, feniloxi, bencilo o benciloxi. En otras formas más de realización, x es 1 ó 2 y cada grupo R^3 es independientemente halógeno, CN, alquilo C_1-C_6 opcionalmente sustituido, OR', $N(R')_2$, $CON(R')_2$ o NRCOR'. En aun otras formas de realización, x es 1 ó 2 y cada grupo R^3 es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN. En otras formas más de realización, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN. En aun otras formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN. En otras formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$. En otras formas más de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$. En otras formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es $-CON(R')_2$ o NRCOR'. En aun otras formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es $-CON(R')_2$ o NRCOR'.

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[0072] En algunas formas de realización, y es 0-4 y el grupo R^5, cuando está presente, es cada uno independientemente halógeno, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-NRCOR'$, $-CON(R')_2$, $-S(O)_2N(R')_2$, $-OCOR'$, $-COR'$, $-CO_2R'$, $-OCON(R')_2$, $-NR'SO_2R'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$, $-OPO(R')_2$ o un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6, arilo, heteroarilo, cicloalifático, heterocicloalifático, arilalquilo C_1-C_6, heteroarilalquilo C_1-C_6, cicloalifáticoalquilo C_1-C_6 o heterocicloalifáticoalquilo C_1-C_6.

[0073] En aun otras formas de realización, y es 0-4 y cada aparición de R^5 es independientemente Cl, Br, F, CF_3, Me, Et, CN, -COOH, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2NHC(CH_3)_2$, $-OCOC(CH_3)_3$, $-OCOCH_2C(CH_3)_3$, $-O(CH_2)_2N(CH_3)_2$, 4-CH_3-piperazin-1-ilo, $OCOCH(CH_3)_2$, OCO(ciclopentilo), $-COCH_3$, opcionalmente sustituido fenoxi o opcionalmente sustituido benciloxi.

[0074] En otra forma de realización más, cada uno de z_1, z_2, z_3 o z_4 es 0-4 y los grupos R^4, cuando están presentes, son cada uno independientemente halógeno, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$ o un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6,

arilo, heteroarilo, cicloalifático, heterocicloalifático, arilalquilo C_1-C_6, heteroarilalquilo C_1-C_6, cicloalifáticoalquilo C_1-C_6 o heterocicloalifáticoalquilo C_1-C_6.

[0075] En otras formas más de realización, cada uno de z_1, z_2, z_3 o z_4 es 0-4 y los grupos R^4 son cada uno independientemente Cl, Br, F, CF_3, CH_3, $-CH_2CH_3$, CN, -COOH, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, -OH, $-CH_2OH$, $-NHCOCH_3$, $-SO_2NH_2$, $-SO_2(CH_2)_3CH_3$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)_2$, $-SO_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)NHCH_2CH(CH_3)_2$, $-NHCOOCH_3$, $-C(O)C(CH_3)_3$, $-COO(CH_2)_2CH_3$, $-C(O)NHCH(CH_3)_2$, $-C(O)CH_2CH_3$ o un grupo opcionalmente sustituido seleccionado de -piperidinilo, piperizinilo, morfolino, alcoxi C_{1-4}, fenilo, feniloxi, bencilo, benciloxi, $-CH_2$ciclohexilo, piridilo, $-CH_2$piridilo o $-CH_2$tiazolilo.

[0076] Para los compuestos descritos directamente con anterioridad, en algunas formas de realización, x es 0-4 y los grupos R^3, cuando están presentes, son cada uno independientemente halógeno, CN, NO_2, $-N(R')_2$, $-CH_2N(R')_2$, $-OR'$, $-CH_2OR'$, $-SR'$, $-CH_2SR'$, $-COOR'$, $-NRCOR'$, $-CON(R')_2$, $-OCON(R')_2$, COR', $-NHCOOR'$, $-SO_2R'$, $-SO_2N(R')_2$ o un grupo opcionalmente sustituido seleccionado de alifático C_1-C_6, arilo, heteroarilo, cicloalifático, heterocicloalifático, arilalquilo C_1-C_6, heteroarilalquilo C_1-C_6, cicloalifáticoalquilo C_1-C_6 o heterocicloalifáticoalquilo C_1-C_6.

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[0077] En aun otras formas de realización, x es 1 ó 2 y cada aparición de R^3 es independientemente Cl, Br, F, CF_3, $-OCF_3$, Me, Et, CN, $-COOH$, $-NH_2$, $-N(CH_3)_2$, $-N(Et)_2$, $-N(iPr)_2$, $-O(CH_2)_2OCH_3$, $-CONH_2$, $-COOCH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OH$, $-NHCOCH_3$, $-NHCOCH(CH_3)_2$, $-SO_2NH_2$, -CONH(ciclopropilo), $-CONHCH_3$, $-CONHCH_2CH_3$ o un grupo opcionalmente sustituido seleccionado de -piperidinilo, piperizinilo, morfolino, fenilo, feniloxi, bencilo o benciloxi.

[0078] En otras formas más de realización, x es 1 ó 2 y cada grupo R^3 es independientemente halógeno, CN, opcionalmente sustituido C_1-C_6alquilo, OR', $N(R')_2$, $CON(R')_2$ o NRCOR'.

[0079] En aun otra formas de realización, x es 1 ó 2 y cada grupo R^3 es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN.

[0080] En otras formas más de realización, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN.

[0081] En aun otra formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN.

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[0082] En otras formas más de realización, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$.

[0083] En aun otra formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$.

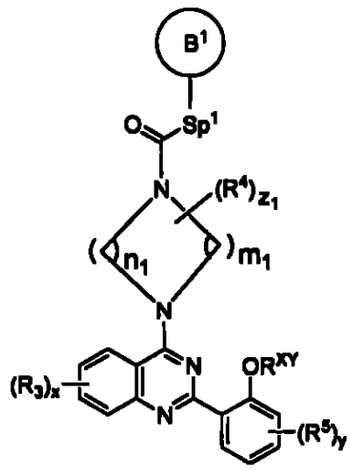
[0084] En otras formas más de realización, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es $-CON(R')_2$ o NRCOR'.

[0085] En aun otra formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$.

[0086] En aun otra formas de realización para los compuestos antes descritos directamente, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN. En otras formas más de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN. En aun otra formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$. En otras formas más de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-OCH_3$ u $-OCH_2CH_3$. En aun otra formas de

realización, x es 1 y R^3 es un anillo quinazolina en la posición 6 y es $-CON(R')_2$ o $NRCOR'$. En aun otra formas de realización, x es 1 y R^3 es un anillo quinazolina en la posición 7 y es $-CON(R')_2$ o $NRCOR'$.

[0087] En una forma de realización, la presente invención provee compuestos de fórmula **I-A**:



I-A;

en donde x, y, n_1, m_1, z_1, R^{XY}, R^4, R^5, Sp^1 y anillo B^1 son tal como se definió con anterioridad.

[0088] En una forma de realización, Sp^1 está seleccionada de -O-, -S- o -NR'-. o, Sp^1 es -O- o, Sp^1 es $-O-CH_2-$. En otra forma de realización, Sp^1 es -NR'- o, Sp^1 es -NH- o, Sp^1 es $-NH-CH_2-$.

[0089] En una forma de realización, cada uno de m_1 y n_1 es 1. En otra forma de realización, cada uno de m_1 y n_1 es 2.

[0090] En una forma de realización, anillo B^1 es un anillo heterocíclico monocíclico de 4-8 miembros, saturado,

parcialmente insaturado o aromático, con 1-4 heteroátomos seleccionados de O, S o N, en donde anillo B^1 está opcionalmente sustituido con w apariciones independientes de -R^{11}, en donde w_1 es 0-4.

|0091| En otra forma de realización, anillo B^1 es un anillo heterocíclico monocíclico de 4-8 miembros, saturado, con 1-4 heteroátomos seleccionados de O, S o N, en donde anillo B^1 está opcionalmente sustituido con w apariciones independientes de -R^{11}, en donde w_1 es 0-4.

|0092| En otra forma de realización más, anillo B^1 es un anillo heterocíclico monocíclico de 5-6 miembros, saturado, con 1-2 heteroátomos seleccionados de O, S o N, en donde anillo B^1 está opcionalmente sustituido con w apariciones independientes de -R^{11}, en donde w_1 es 0-4.

|0093| En una forma de realización, w_1 es 0.

|0094| En otra forma de realización, anillo B^1 es tetrahidrofuranilo.

|0095| En otra forma de realización más, Sp^1 es en enlace, O u -O-CH_2-; R es hidrógeno; y n_1 y m_1 son ambos simultáneamente 1 ó 2.

|0096| En una forma de realización, R es hidrógeno o R es alquilo C_1-C_6. Los R preferidos incluyen metilo, etilo, propilo o butilo.

|0097| En otra forma de realización, z_1 es 0.

[0098] De acuerdo con otra forma de realización, el anillo B^1 es tetrahidrofuranilo, tetrahidro-[*2H*]-piranilo, piridilo o fenilo.

[0099] De acuerdo con aun otra forma de realización, Sp^1 es un enlace, -O-, $-O-CH_2-$ o $-NH-CH_2$.

[00100] En una forma de realización:

n_1 y m_1 cada uno es 2;

R^{x1} es hidrógeno;

y es 0 ó 1 y R^5 es flúor;

x es 1 y R^3 es Me en una posición 7 o flúor en una posición 6;

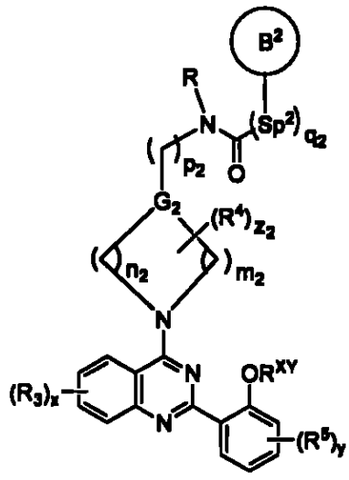
z_1 es 0;

Sp^1 es $-O-CH_2-$;

w_1 es 0; y

el anillo B^1 es tetrahidrofuran-3-ilo, fenilo, piridin-3-ilo, piridin-4-ilo o tetrahidro[2H]-piran-4-ilo.

[00101] De acuerdo con otra forma de realización, la presente invención provee compuestos de fórmula I-B:



I-B;

en donde x, y, n_2, m_2, z_2, q_2, R, Sp^2, anillo B^2, R^{XY}, R^3, R^4 y R^5 son como se definió con anterioridad.

[00102] En una forma de realización, G_2 es N o G_2 es CH.

[00103] En una forma de realización, p_2 es 0 o p_2 es 1 o, p_2 es 2.

[00104] En otra forma de realización, q_2 es 0 o q_2 es 1.

[00105] En una forma de realización, p_2 es 1 y q_2 es 1.

[00106] En otra forma de realización, G_2 es CH, p_2 es 0 y q_2 es 1.

[00107] En una forma de realización, m_2 y n_2 cada uno es 1 o m_2 y n_2 cada uno es 2 o n_2 es 1 y m_2 es 2 o n_2 es 1 y m_2 es 3.

[00108] En otra forma de realización, Sp^2 está seleccionada de -O-, -S- o -NR'-. En una forma de realización, Sp^2 es -O- o Sp^2 es -NR'- o Sp^2 es -NH-.

[00109] En una forma de realización, anillo B^2 es un anillo heterocíclico monocíclico de 4-8 miembros, saturado, parcialmente insaturado o aromático con 1-4 heteroátomos seleccionados de O, S o N, en donde anillo B es opcionalmente sustituido con w apariciones independientes de $-R^{12}$, en donde w_2 es 0-4.

[00110] En otra forma de realización, anillo B^2 es un anillo heterocíclico monocíclico de 4-8 miembros, saturado con 1-4 heteroátomos seleccionados de O, S o N, en donde anillo B^2 está opcionalmente sustituido con w apariciones independientes de $-R^{12}$, en donde w_2 es 0-4.

[00111] En otra forma de realización más, el anillo B^2 es anillo heterocíclico monocíclico de 5-6 miembros, saturado, con 1-2 heteroátomos seleccionados de O, S o N, en donde el anillo B^2 está opcionalmente sustituido con w apariciones independientes de $-R^{12}$, en donde w_2 es 0-4.

[00112] En una forma de realización, w_2 es 0.

[00113] De acuerdo con aun otra forma de realización, Sp^2 es un enlace, -O- u $-O-CH_2-$.

[00114] En otra forma de realización, anillo B^2 es tetrahidrofuranilo, tetrahidro[2*H*]piranilo o piridilo.

[00115] En otra forma de realización más,

i) Sp^2 es un enlace, O u $-O-CH_2-$;

ii) p_2 es 1;

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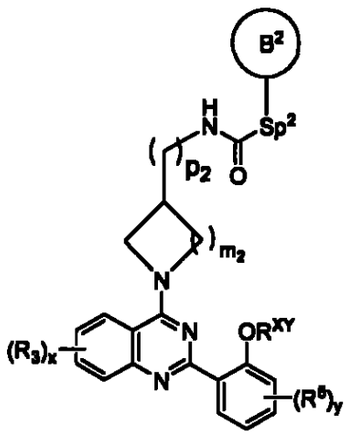
iii) R es hidrógeno; y

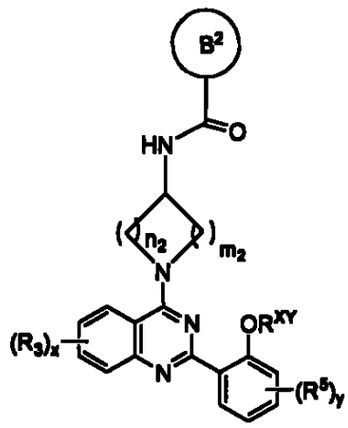
iv) n_2 es 1 y m_2 es 2 o 3.

[00116] En una forma de realización, R es hidrógeno o R es alquilo C_1-C_6. Los R preferidos incluyen metilo, etilo, propilo o butilo.

[00117] En una forma de realización, los compuestos de fórmula I-B tienen la fórmula I-B-i o la fórmula I-B-ii:



I-B-i



I-B-ii.

[00118] En una forma de realización de fórmula I-B-i:

i) p_2 es 1;

ii) m_2 es 3;

iii) Sp^2 es -O-;

iv) y es 0 ó 1 y R^5 es flúor;

v) x es 1 y R^3 es 7-Me; y

vi) anillo B^2 es tetrahidrofuranilo.

[00119] En otra forma de realización de fórmula I-B-i:

i) p_2 es 0 ó 1;

ii) m_2 es 1 ó 2, de preferencia 2;

iii) Sp^2 es -O- u $-O-CH_2-$;

iv) y es 0;

v) x es 1 y R^3 es 7-Me; y

vi) anillo B^2 es tetrahidrofuranilo, tetrahidro[2H]piranilo, piridilo o fenilo.

[00120] En una forma de realización de fórmula **I-B-ii**:

(i) n_2 es 1, m_2 es 1 ó 2, de preferencia 2;

(ii) y es 0 ó 1 y R^5 es flúor;

(iii) x es 1 y R^3 es 7-Me o 6-F; y

(iv) anillo B^2 es ciclopropilo opcionalmente sustituido con alquil C_1-C_4 o piridilo.

[00121] En una forma de realización de fórmula **I-B-ii**:

(i) n_2 y m_2 son ambos 2;

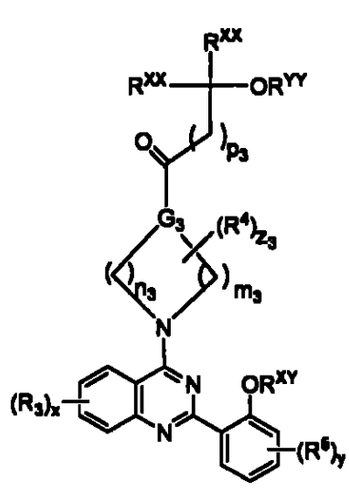
(ii) y es 0;

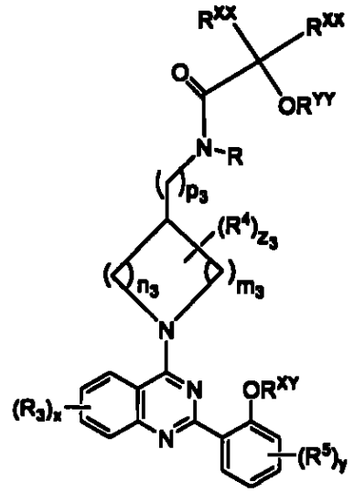
(iii) x es 1 y R^3 es alquilo C_1-C_4 en la posición 7; y

(iv) anillo B^2 es tetrahidrofuranilo opcionalmente sustituido.

[00122] En una forma de realización de fórmula **I-B-i** o fórmula **I-B-ii**, R^{XY} es hidrógeno.

[00123] De acuerdo con una forma de realización, la presente invención provee compuestos de fórmula **I-C** o fórmula **I-D**:





I-CI-D;

en donde x, y, n_3, m_3, z_3, p_3, R^{XX}, R^{YY}, R^{XY}, R^3, R^4 y R^5 son tal como se definió con anterioridad.

[00124] En una forma de realización de la presente invención, un R^{XX} es hidrógeno y el otro R^{XX} no es hidrógeno.

[00125] En otra forma de realización de la presente invención, ambos R^{XX} no son hidrógeno.

[00126] En otra forma de realización, un R^{XX} es hidrógeno y el otro R^{XX} es alquilo C_1-C_6 opcionalmente sustituido con halo o ambos R^{XX} son simultáneamente alquilo C_1-C_6. Los ejemplos de alquilo incluyen metilo, etilo, isopropilo, *n*-propilo, *n*-butilo, *sec*-butilo o *t*-butilo.

[00127] En una forma de realización de la presente invención, p_3 es 0 o p_3 es 1 o p_3 es 2.

[00128] En una forma de realización de la presente invención, m_3 y n_3 cada uno es 1 o m_3 y n_3 cada uno es 2 o m_3 y n_3 cada uno es 3.

[00129] En una forma de realización de la presente invención, R^{xx} es grupo alifático C_{1-6}, en donde R^{xx} es opcionalmente sustituido con w apariciones independientes de $-R^{13}$, en donde w_3 es 0-3 o R^{xx} es grupo alquilo C_1-C_6 opcionalmente sustituido con w_3 apariciones independientes de $-R^{13}$, en donde w_3 es 0-3.

[00130] En una forma de realización de la presente invención, R^{xx} es grupo alquilo C_1-C_6.

[00131] En otra forma de realización de la presente invención, R^{xx} es un anillo monocíclico de 3-8-miembros saturado, parcialmente insaturado o totalmente insaturado anillo con 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillo bicíclico de 8-12 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde R^{xx} es opcionalmente sustituido con w_3 apariciones independientes de $-R^{13}$, en donde w_3 es 0-3.

[00132] En otra forma de realización, R^{xx} es un anillo monocíclico de 3-8-miembros saturado, parcialmente insaturado o totalmente insaturado con 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde

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R^{XX} es opcionalmente sustituido con w apariciones independientes de $-R^{13}$, en donde w_3 es 0-3.

[00133] En otra forma de realización, R^{XX} es un sistema de anillo bicíclico de 8-12 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde R^{XX} es opcionalmente sustituido con w_3 apariciones independientes de $-R^{13}$, en donde w_3 es 0-3.

[00134] En otra forma de realización, R^{YY} es hidrógeno, -COR', -CO_2R', -CON(R')$_2$, -SOR', -SO_2R', -SO_2N(R')$_2$, -COCOR', -$COCH_2COR'$, -P(O)(OR')$_2$, -$P(O)_2$OR' o -PO(R').

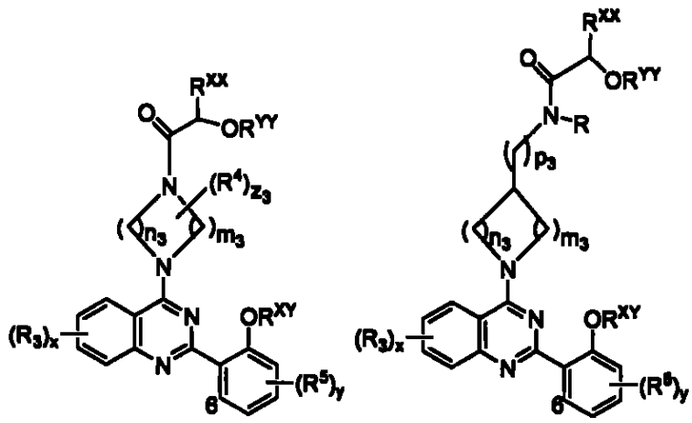
[00135] O R^{YY} es hidrógeno.

[00136] En otra forma de realización, R^{YY} es -COR', -CO_2R', -CON(R')$_2$, -SOR', -SO_2R', -SO_2N(R')$_2$, -COCOR', -$COCH_2COR'$, -P(O)(OR')$_2$, -$P(O)_2$OR' o -PO(R').

[00137] En otra forma de realización, R^{YY} es R^{XY}.

[00138] En una forma de realización, R es hidrógeno o R es alquilo C_1-C_6. Los R preferidos incluyen metilo, etilo, propilo o butilo.

[00139] En una forma de realización, la presente invención provee un compuesto de la fórmula I-C-i o fórmula I-D-i:



I-C-iI-D-i;

en donde x, y, n_3, m_3, z_3, p_3, R^{XX}, R^{YY}, R^{XY}, R^3, R^4 y R^5 son tal como se definió con anterioridad.

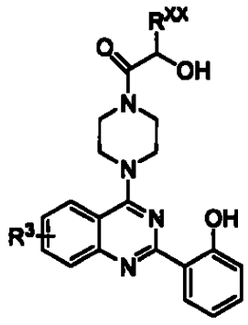
[00140] En una forma de realización de I-C-i o I-D-i, R^{XX} es alquilo C_1-C_6. En otra forma de realización, x es 1 y R^3 es alquilo C_1-C_4 en la posición 7 o x es 1 y R^3 es F, CN o CF_3 en la posición 6.

[00141] En una forma de realización, R^{XX} es metilo, *n*-propilo, isopropilo, *n*-butilo, *sec*-butilo o *t*-butilo.

[00142] En una forma de realización, R^3 es alquilo C_1-C_6 o R^3 es metilo, *n* -propilo, isopropilo, *n* -butilo, *sec*-butilo o *t*-butilo.

[00143] En una forma de realización de I-C-i o I-D-i, R^{XY} es hidrógeno e y es 0 o R^{XY} es hidrógeno, y es 1 y R^5 es 6-F.

[00144] En otra forma de realización, la presente invención provee un compuesto de la fórmula I-C-ii:



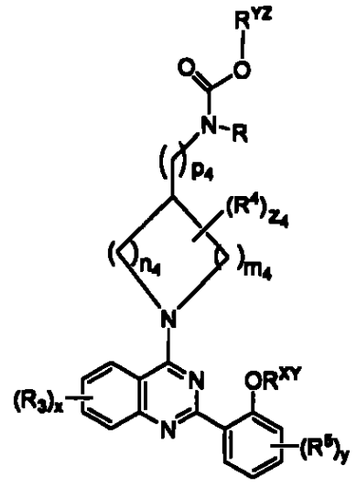
I-C-ii;

en donde R^3 y R^{XX} son tal como se definió con anterioridad.

[00145] En otra forma de realización, R^3 es metilo en la posición 6 o 7 del anillo quinazolina.

[00146] En otra forma de realización de fórmula I-C-ii, R^{XX} es $CH_2C(O)OH$ o $CH_2C(O)NH_2$.

[00147] De acuerdo con una forma de realización, la presente invención provee un compuesto de la fórmula I-E:



I-E;

en donde x, y, n_4, m_4, z_4, p_4, R^{YZ}, R^{XY}, R^3, R^4 y R^5 son tal como se definió con anterioridad.

[00148] En una forma de realización, p_4 es 1 o p_4 es 2.

[00149] En una forma de realización, m_4 y n_4 cada uno es 1 o m_4 y n_4 cada uno es 2 o m_4 y n_4 cada uno es 3. En una forma de realización, n_4 es 1 y m_4 es 3. En otra forma de realización, n_4 es 1 y m_4 es 2.

[00150] En una forma de realización, n_4 es 1, m_4 es 3, z_4 es 0, p_4 es 1, y es 0 ó 1 y x es 1.

[00151] En otra forma de realización, n_4 es 1, m_4 es 2, z_4 es 0, p_4 es 1, y es 0 ó 1 y x es 1.

[00152] En una forma de realización, n_4 es 1, m_4 es 3, z_4 es 0, p_4 es 1, y es 0 ó 1, x es 1 y R y R^{XY} son ambos hidrógeno.

[00153] En otra forma de realización, n_4 es 1, m_4 es 2, z_4 es 0, p_4 es 1, y es 0 ó 1, x es 1 y R y R^{XY} son ambos hidrógeno.

[00154] En una forma de realización, R^{YZ} es alquilo C_1-C_6, opcionalmente sustituido con w_4 apariciones independientes de -R^{14}, en donde w_4 es 0-3. En otra forma de realización, R^{YZ} es grupo alquilo C_1-C_4 opcionalmente sustituido con w_4 apariciones independientes de -R^{14}, en donde w_4 es 0-3 o R^Y e un grupo alquilo C_1-C_6.

[00155] En una forma de realización, R es hidrógeno o R es alquilo C_1-C_6. Los R preferidos incluyen metilo, etilo, propilo o butilo.

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[00156] En otra forma de realización:

(i) n_4 es 1 y m_4 es 3;

(ii) p_4 es 1;

(iii) z_4 es 0;

(iv) R^{YZ} es alquilo C_1-C_6, en donde hasta dos grupos -CH_2- están opcionalmente reemplazados por -O-;

(v) y es 0 ó 1 y R^5 es 6-flúor; y

(vi) x es 1 y R^3 es alquilo C_1-C_4.

[00157] En otra forma de realización:

(i) n_4 es 1 y m_4 es 2;

(ii) p_4 es 1;

(iii) z_4 es 0;

(iv) R^{YZ} es alquilo C_1-C_6, en donde hasta dos de los grupos -CH_2- está opcionalmente reemplazada por -O-;

(v) y es 0 ó 1 y R^5 es 6-flúor; y

(vi) x es 1 y R^3 es alquilo C_1-C_4.

[00158] En otra forma de realización:

(i) n_4 es 1 y m_4 es 3;

(ii) p_4 es 1;

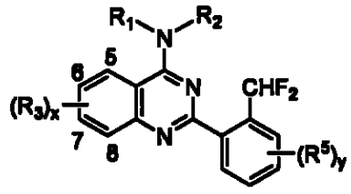
(iii) z_4 es 0;

(iv) R^{YZ} es bencilo;

(v) y es 0 ó 1 y R^5 es 6-flúor; y

(vi) x es 1 y R^3 es alquilo C_1-C_4.

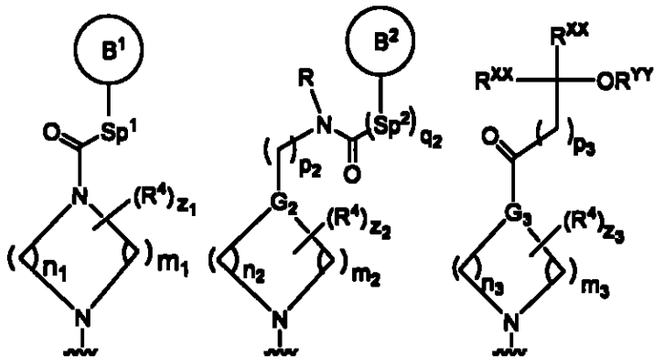
|00159| En otra forma de realización, la presente invención provee compuestos de fórmula I-F:



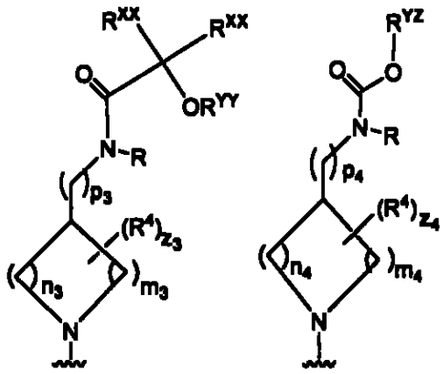
I-F;

en donde:

R^1 y R^2, tomados juntos con el átomo de nitrógeno, forman un anillo sustituido seleccionado de:



(A) (B) (C)



(D) o (E);

en donde, en anillo (A):

cada uno de m_1 y n_1 es independientemente 0-3, con la condición de que m_1+n_1 sea 2-6;

z_1 es 0-4;

Sp^1 es -O-, -S-, -NR'- o un ligador alquilideno C_1-C_6, en donde hasta dos unidades metileno se reemplazan opcionalmente e independientemente por -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$ o $-NR'SO_2NR'-$, dio que Sp^1 se adosa al grupo carbonilo a través de un átomo distinto del carbono;

El anillo B^1 es un anillo heterocíclico monocíclico de 4-8 miembros, saturado, parcialmente insaturado o aromático, con 1-4 heteroátomos seleccionados de O, S o N, en donde anillo B^1 está opcionalmente sustituido con w_1 apariciones independientes de $-R^{11}$, en donde w_1 es 0-4;

en donde, en anillo (B):

G_2 es -N- o CH;

Cada uno de m_2 y n_2 es independientemente 0-3, con la condición de que $m_2 + n_2$ sea 2-6;

p_2 es 0-2; con la condición de que cuando G_2 es N, p_2 no sea 0;

q_2 es 0 ó 1;

z_2 es 0-4;

Sp^2 es un enlace o un ligador alquilideno C_1-C_6, en donde hasta dos unidades metileno son opcional e independientemente reemplazados por -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$ o $-NR'SO_2NR'-$;

el anillo B^2 es un anillo heterociclico monociclico de 4-8 miembros, saturado, parcialmente insaturado o aromático, con 1-4 heteroátomos seleccionados de O, S o N, en donde anillo B es opcionalmente sustituido con w apariciones independientes de $-R^{12}$, en donde w_2 es 0-4;

en donde, en anillo (C) o anillo (D):

G_3 es -N-, -CH-NH- o $-CH-CH_2-NH-$;

Cada uno de m_3 y n_3 es independientemente 0-3, con la condición de que m_3+n_3 sea 2-6;

p_3 es 0-2;

z_3 es 0-4;

cada R^{xx} es hidrógeno, grupo alifático C_{1-6}, un anillo monocíclico de 3-8 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillo biciclico de 8-12 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-5 heteroátomos seleccionados, de modo independiente, de

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nitrógeno, oxígeno o azufre; en donde R^{XX} es opcionalmente sustituido con w_3 apariciones independientes de $-R^{13}$, en donde w_3 es 0-3;

con la condición de que ambos R^{XX} no sean simultáneamente hidrógeno;

R^{YY} es hidrógeno, $-COR'$, $-CO_2R'$, $-CON(R')_2$, $-SOR'$, $-SO_2R'$, $-SO_2N(R')_2$, $-COCOR'$, $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$ o $-PO(R')$;

en donde, en el anillo (E):

cada uno de m_4 y n_4 es independientemente 0-3, con la condición de que $m_4 + n_4$ sea 2-6;

p_4 es 1-2;

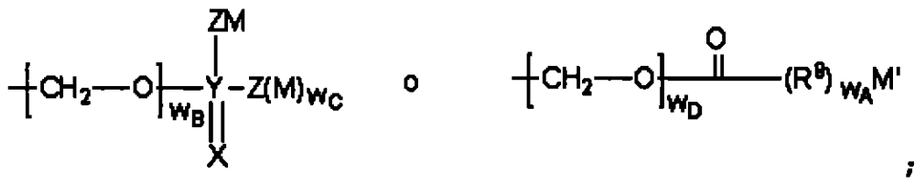
z_4 es 0-4;

R^{YZ} es grupo alifático C_1-C_6, opcionalmente sustituido con w_4 apariciones independientes de $-R^{14}$, en donde w_4 es 0-3;

x y i, cada uno, es independientemente 0-4;

W es OR^{XY};

R^{XY} es hidrógeno o un grupo seleccionado de:



;

en donde:

cada uno de w_A, w_B, wC y w_D es independientemente 0 ó 1;

cada M está seleccionado, de modo independiente, de hidrógeno, Li, Na, K, Mg, Ca, Ba, $-N(R^7)_4$, alquilo C_1-C_{12}-, alquenilo C_2-C_{12}-o $-R^6$; en donde 1 a 4 radicales $-CH_2$ del grupo alquilo o alquenilo, distintos de $-CH_2$ unidos a Z, están opcionalmente reemplazados por un grupo de heteroátomos seleccionado de O, S, S(O), $S(O_2)$ o $N(R^7)$; y en donde cualquier hidrógeno en dicho alquilo, alquenilo o R^6 está opcionalmente reemplazado con un sustituyente seleccionado de oxo, $-OR^7$, - R^7, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, $-CO_2$ R^7, $-C(O)-N(R^7)_2$, $S(O)_2-N(R^7)_2$, $N(R^7)-C(O)-$ R^7, C(O) R^7, $-S(O)_n-$ R^7, OCF_3, $-S(O)_n-R^6$, $N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$ o $-NO_2$;

n es 0-2;

M' es H, alquilo C_1-C_{12}-, alquenilo C_2-C_{12}- o $-R^6$; en donde 1 a 4 radicales $-CH_2$ del grupo alquilo o alquenilo está opcionalmente reemplazado por un grupo heteroátomo seleccionado de O, S, S(O), $S(O_2)$ o $N(R^7)$; y en donde cualquier hidrógeno de dicho alquilo, alquenilo o R^6 está opcionalmente reemplazado con un sustituyente seleccionado de oxo, -O R^7, - R^7, $-N(R^7)_2$, $N(R^7)_3$, - R^7OH, -CN, $-CO_2$ R^7, $-C(O)-N(R^7)_2$, $-S(O)_2-N(R^7)_2$, $-N(R^7)-C(O)-$ R^7, $-C(O)$ R^7, $-S(O)_n-$ R^7, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$ o $-NO_2$;

Z es $-CH_2-$, -O-, -S-, $-N(R^7)_2-$; o,

cuando M está ausente, luego Z es hidrógeno, =O o =S;

Y es P o S, en donde cuando Y es S, luego Z no es S;

X es O o S;

cada R^7 está seleccionado, de modo independiente, de hidrógeno o alifático C_1-C_4, opcionalmente sustituido con hasta dos Q_1;

cada Q_1 está seleccionado, de modo independiente, de un sistema de anillo carbocíclico de 3-7 miembros saturado, parcialmente saturado o insaturado; o un anillo heterocíclico de 5-7 miembros saturado, parcialmente saturado o insaturado que contiene uno o más heteroátomos o grupos heteroátomos seleccionados de O, N, NH, S, SO o SO_2; en donde Q_1 está opcionalmente sustituido con hasta tres sustituyentes seleccionados de oxo, -OH, -O(alifático C_1-C_4), -alifático C_1-C_4, $-NH_2$, NH(alifático C_1-C_4), -N(alifático C_1-C_4)$_2$, -N(alifático C_1-C_4)-C(O)- alifático C_1-C_4, -(alifático C_1-C_4)-OH, -CN, $-CO_2H$, $-CO_2$(alifático C_1-C_4), $-C(O)-NH_2$, -C(O)-NH(alifático C_1-C_4), -C(O)-N(alifático C_1-C_4)$_2$, halo o $-CF_3$;

R^6 es un anillo carbocíclico o heterocíclico de 5-6 miembros saturado, parcialmente saturado o insaturado o un sistema de anillo bicíclico de 8-10 miembros saturado, parcialmente saturado o insaturado; en donde cualquiera de dichos sistemas de anillos heterocíclicos contiene uno o varios heteroátomos seleccionados de O, N, S, $S(O)_n$ o $N(R^7)$; y en donde cualquiera de dichos sistemas de anillo opcionalmente contienen 1 a 4 sustituyentes independientemente seleccionados de OH, alquilo C_1-C_4, O-alquilo C_1-C_4 o O-C(O)-alquilo C_1-C_4;

R^9 es $C(R^7)_2$, O o $N(R^7)$;

Cada aparición de R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4 y R^5 es independientemente $Q-R^X$; en donde Q es un enlace o es una cadena alquilideno C_1-C_6 en donde hasta dos unidades metileno no adyacentes de Q son reemplazados opcionalmente e independientemente por -NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, -OP(O)(OR)- o -POR-; y cada aparición de R^X es seleccionado independientemente de -R', halógeno, =O, =NR', $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -NR'COR', $-NR'CON(R')_2$, $-NR'CO_2R'$, -COR', $-CO_2R'$, -OCOR', $-CON(R')_2$, $-OCON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, $-NR'SO_2R'$, $-NR'SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$ u $-OPO(R')_2$; y

cada aparición de R es independientemente hidrógeno o C_{1-6} grupo alifático con hasta tres sustituyentes; y cada aparición de R' es independientemente hidrógeno o grupo alifático C_{1-6}, un anillo monocíclico de 3-8 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillo bicíclico de 8-12 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde R' tiene hasta cuatro

sustituyentes; o R y R', dos apariciones de R o dos apariciones de R', se toman juntas con el(os) átomo(s) a los que están unidos para formar un anillo monocíclico o bicíclico opcionalmente sustituido de 3-12 miembros saturado, parcialmente insaturado o totalmente insaturado con 0-4 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxigeno o azufre.

[00160] En compuestos de fórmula **I-F**, los ejemplos de formas de realización de n_1, m_1, n_2, m_2, n_3, m_3, n_4, m_4, x, y, z_1, z_2, z_3, z_4, q_2, p_3, p_4, R^{XY}, R^{XX}, R^{YY}, R^{YZ}, R^3, R^4, R^5, R^{11}, R^{12}, R^{13}, R^{14}, R, Sp^1, Sp^2, anillo B^1, anillo B^2, etc., son tal como se definió con anterioridad para los compuestos de fórmula **I-A** a través de fórmula **I-E**.

[00161] En una forma de realización, la presente invención provee los compuestos mostrados a continuación en **Tabla 2**.

Tabla 2

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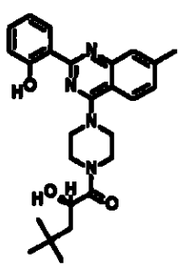	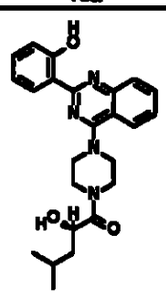	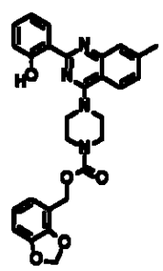
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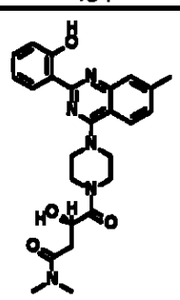	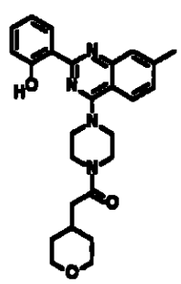	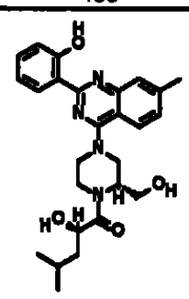
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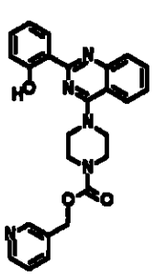	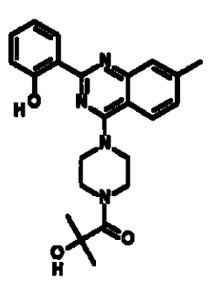	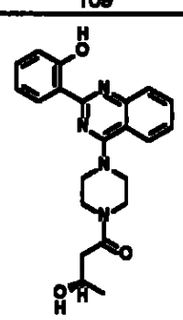
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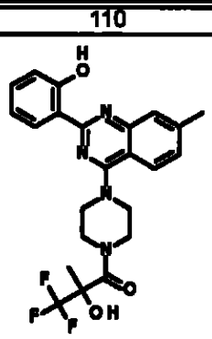	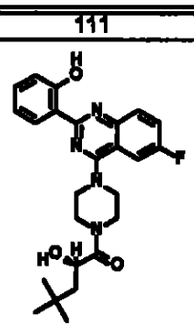	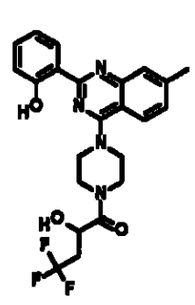

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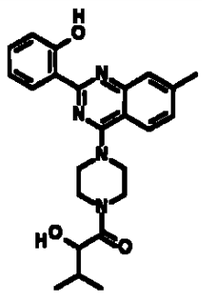	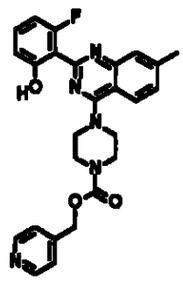	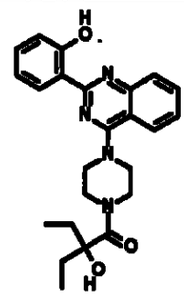
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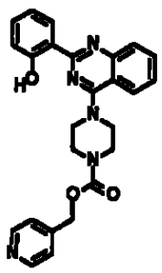	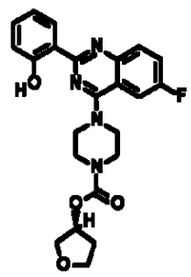	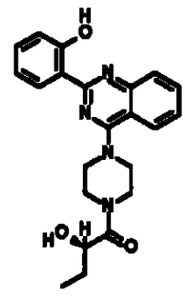
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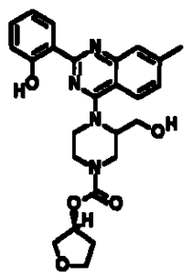	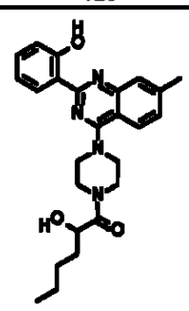	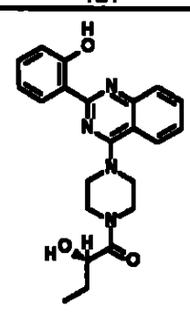
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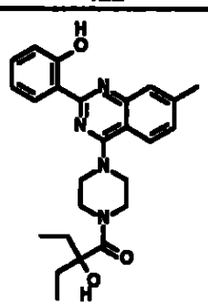	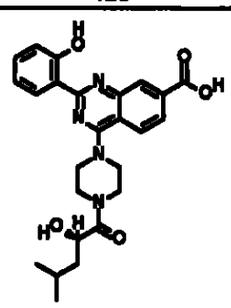	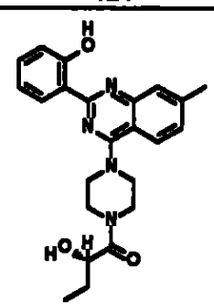

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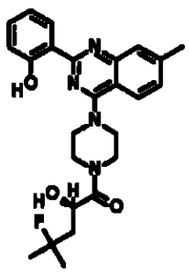	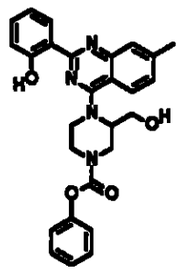	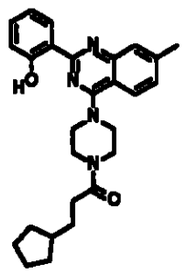
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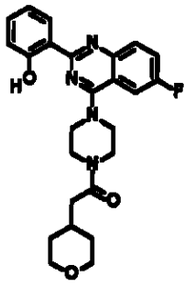	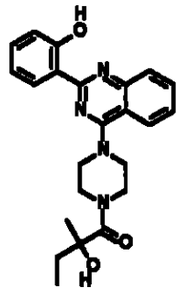	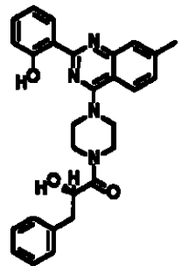
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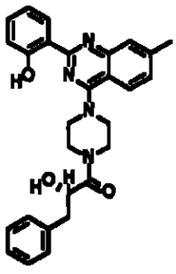	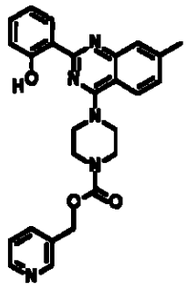	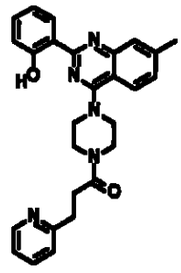
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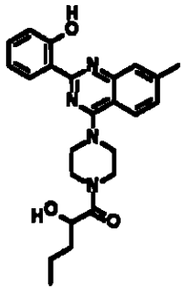	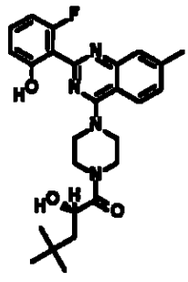	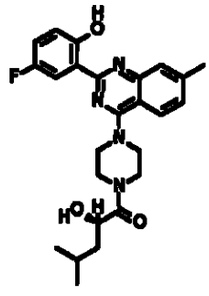

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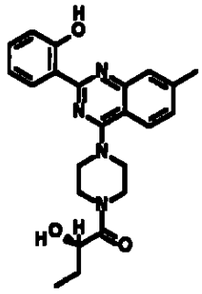	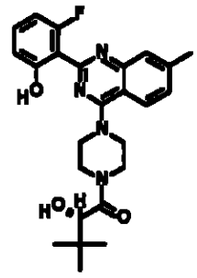	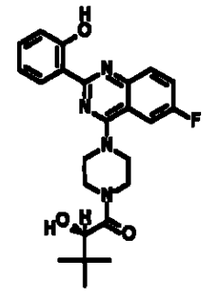
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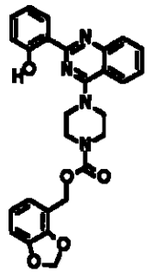	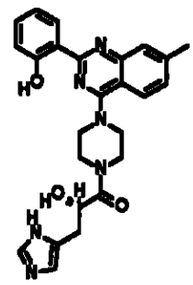	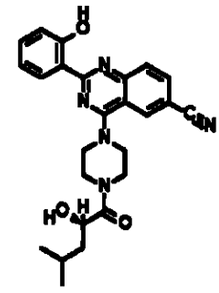
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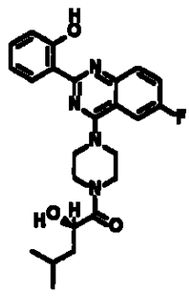	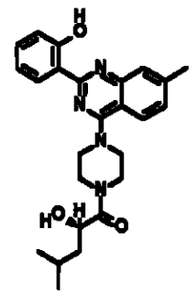	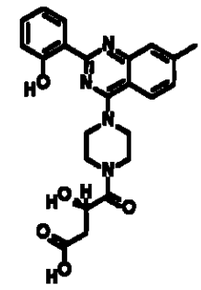
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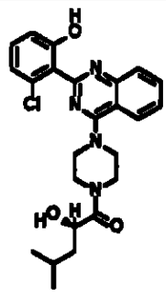	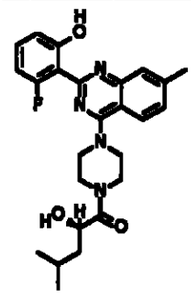	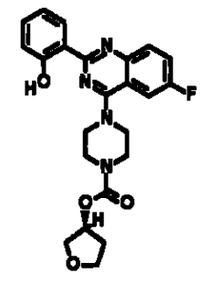

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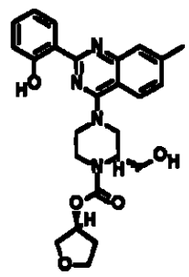	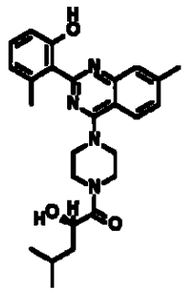	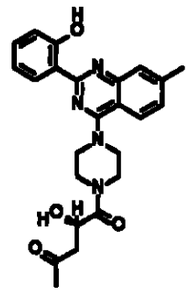
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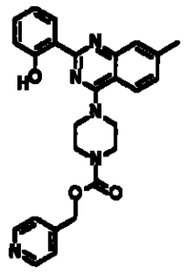	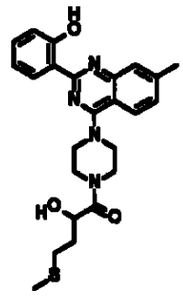	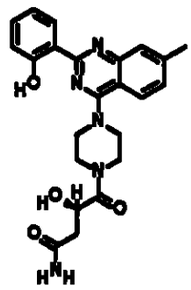
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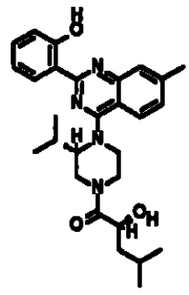	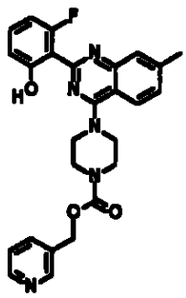	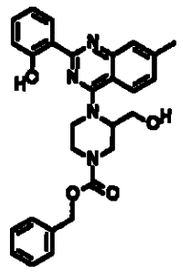
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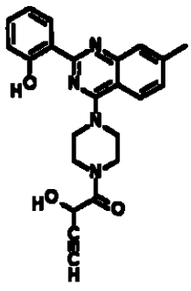	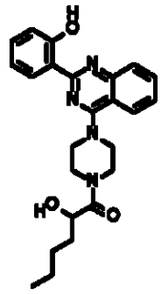	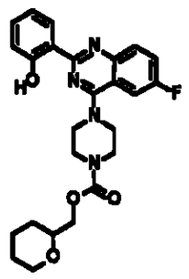

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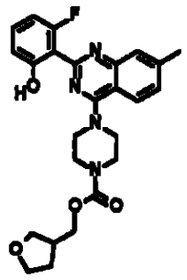	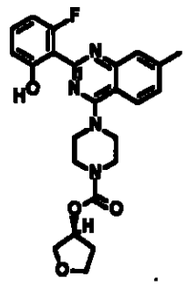	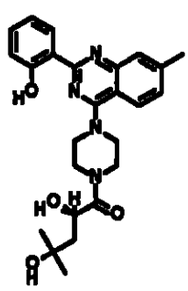
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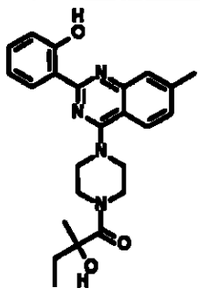	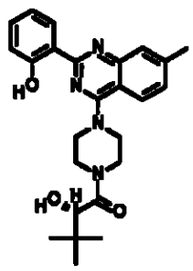	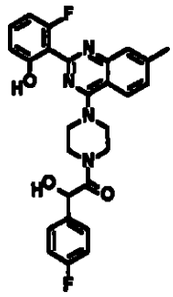
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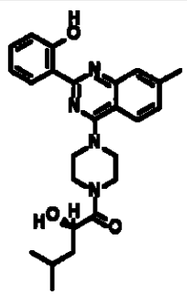	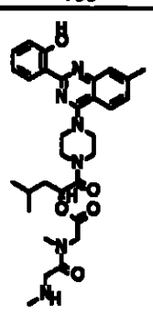	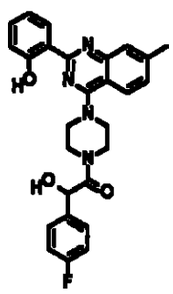
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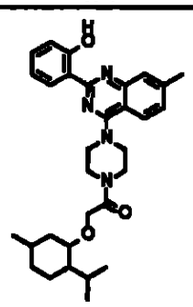	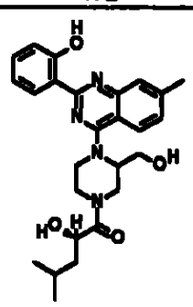	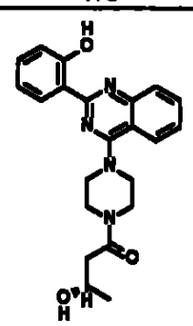

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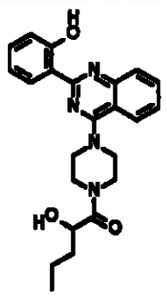	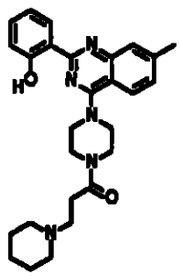	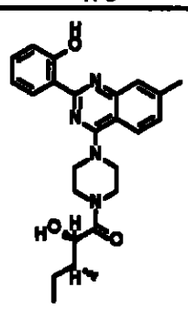
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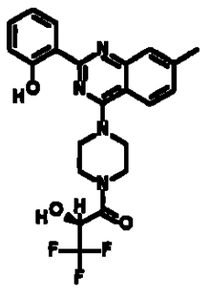	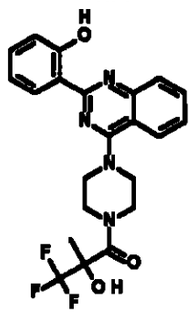	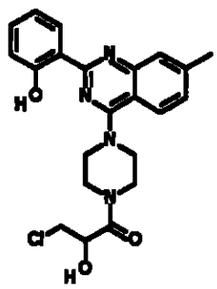
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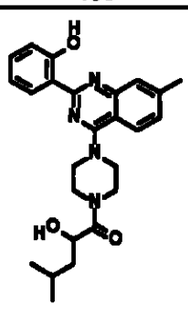	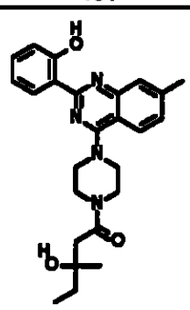	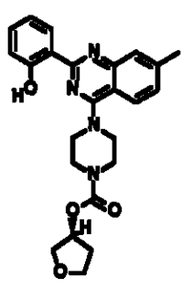
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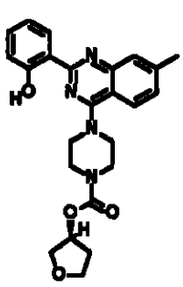	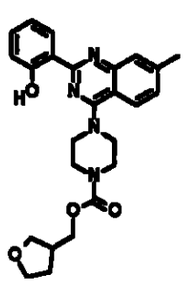	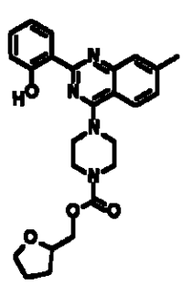

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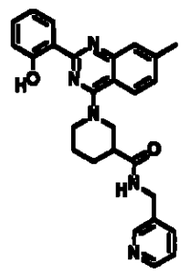	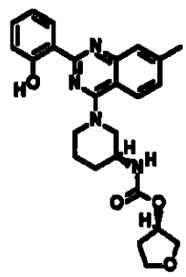	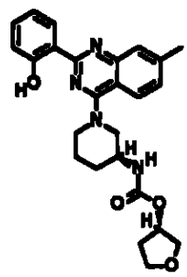
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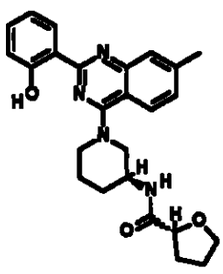	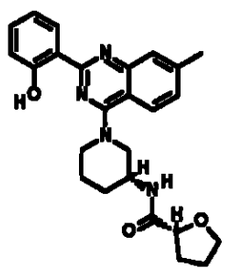	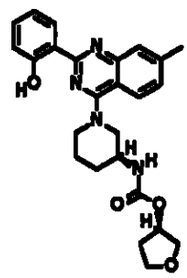
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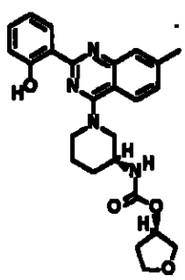	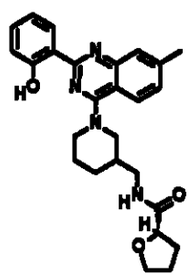	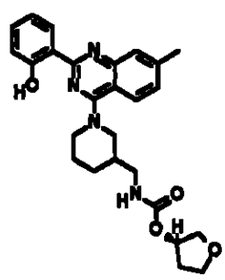
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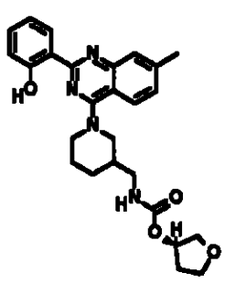	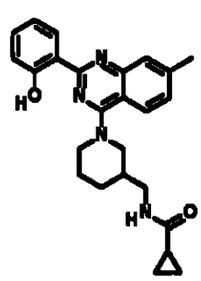	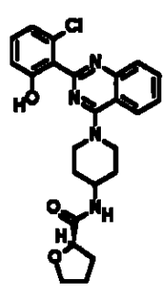

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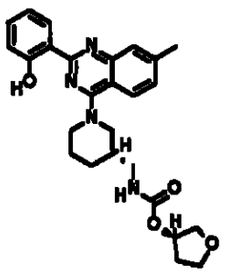	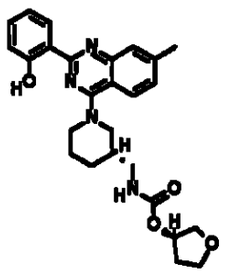	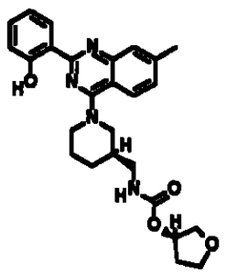
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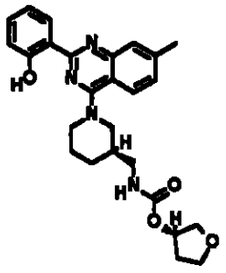	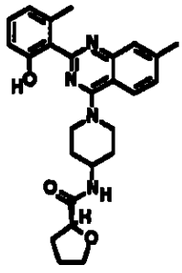	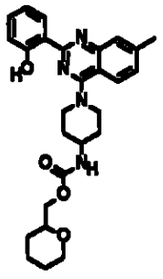
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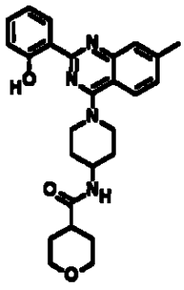	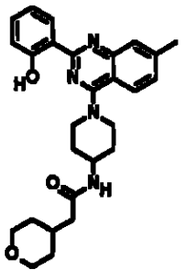	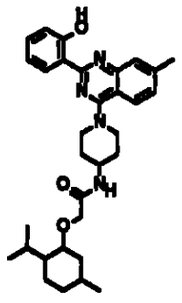
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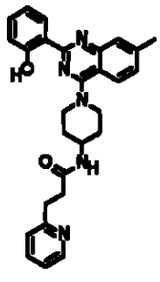	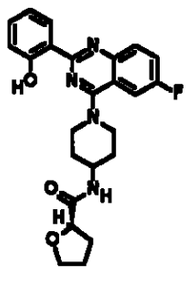	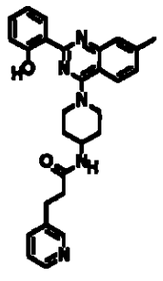

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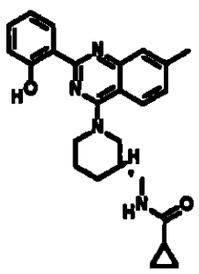	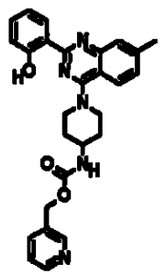	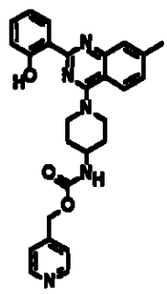
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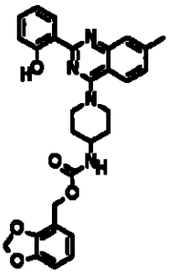	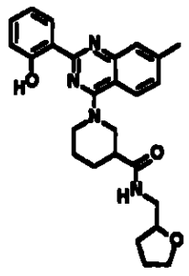	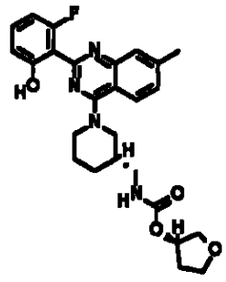
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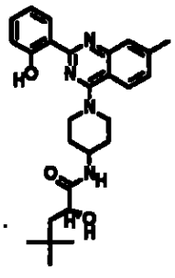	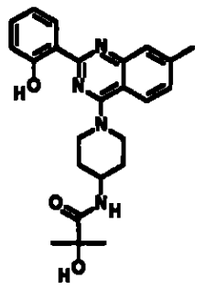	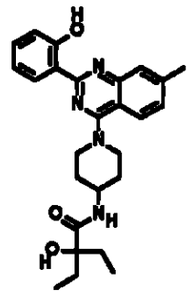
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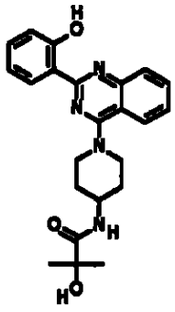	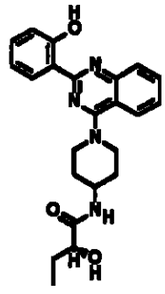	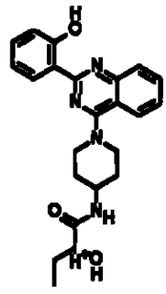

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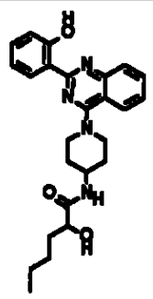	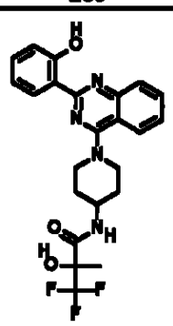	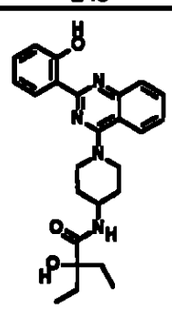
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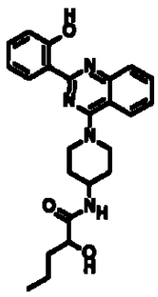	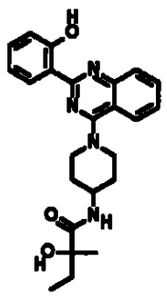	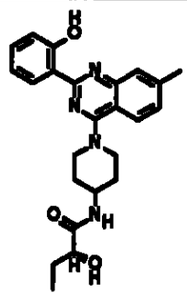
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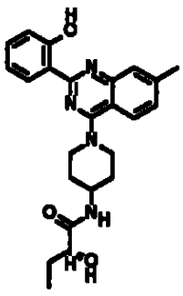	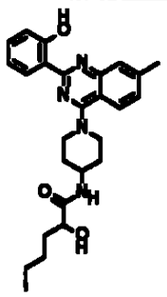	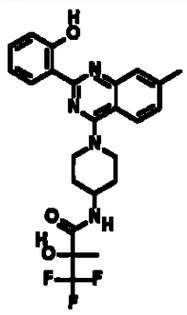
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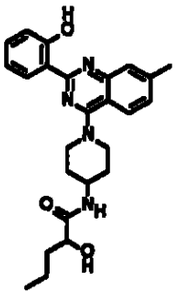	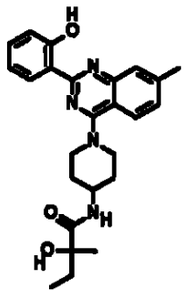	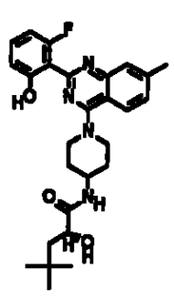

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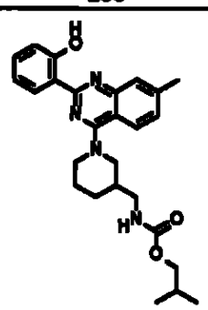	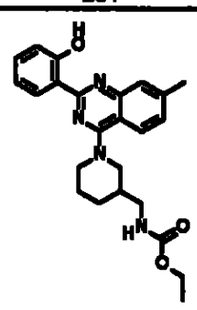	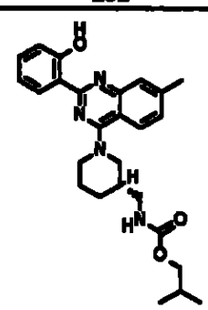
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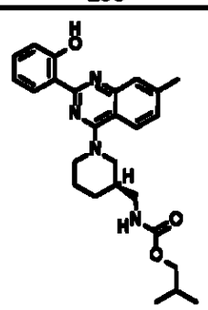	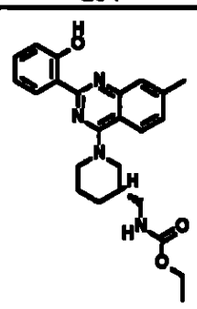	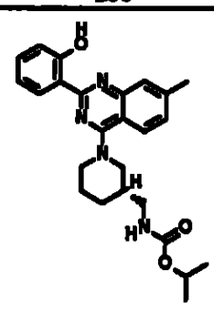
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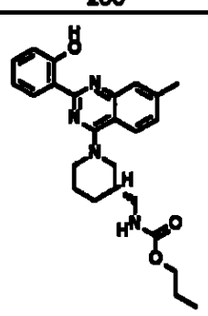	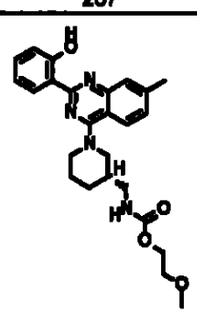	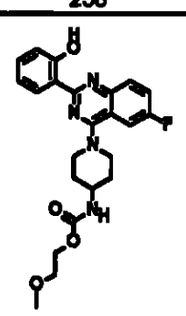
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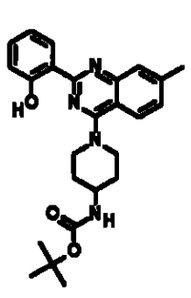	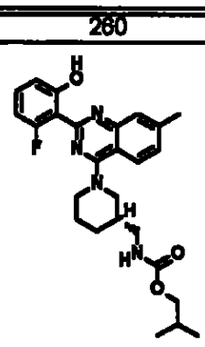	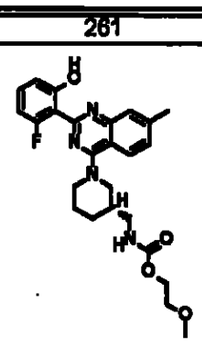

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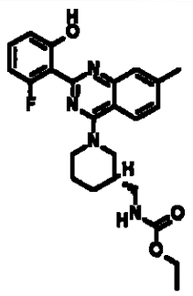	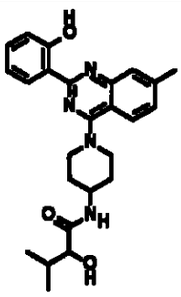	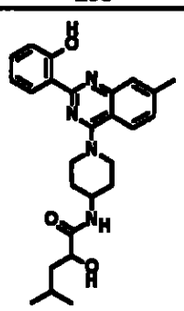
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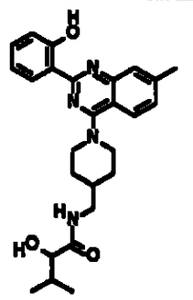	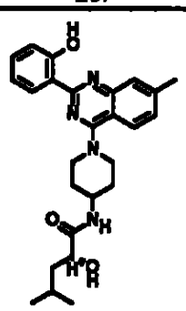	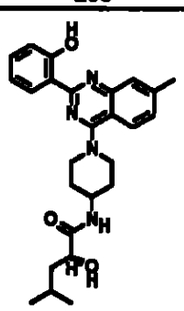
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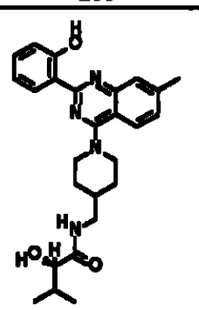	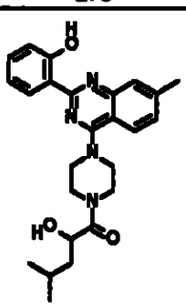	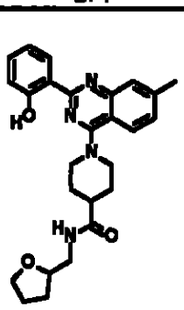
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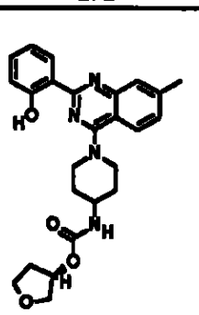	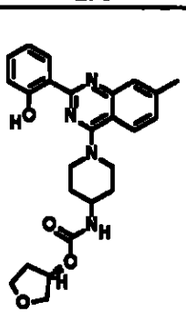	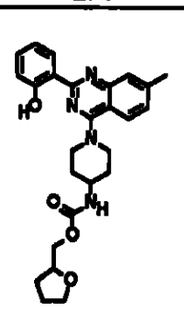

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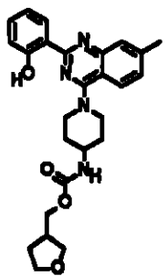	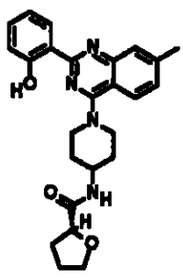	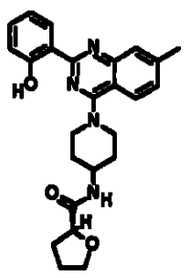
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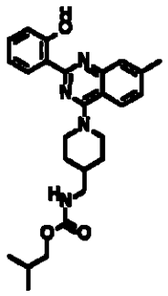	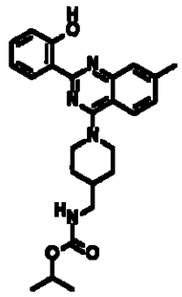	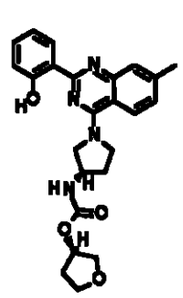
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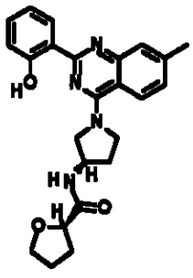	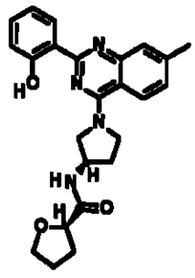	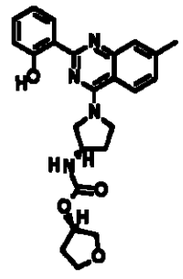
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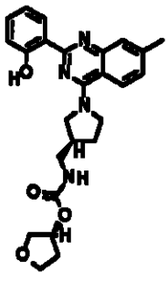	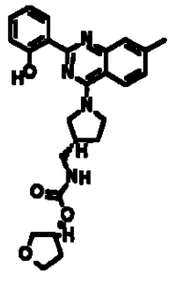	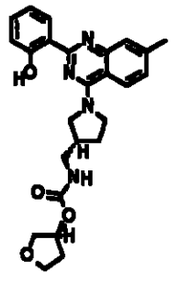

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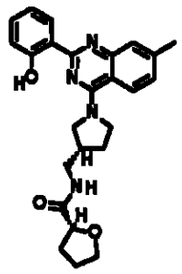	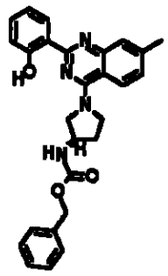	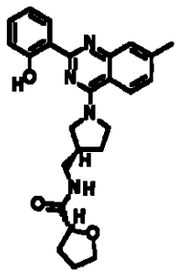
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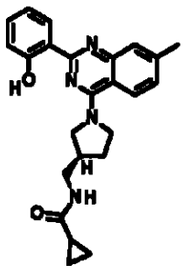	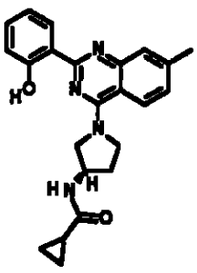	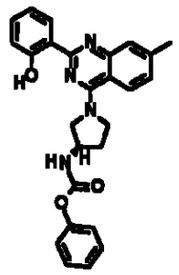
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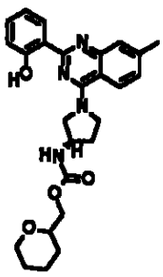	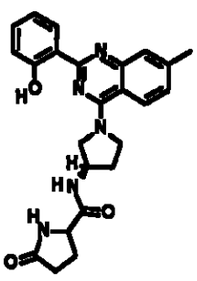	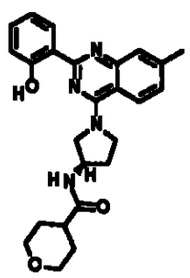
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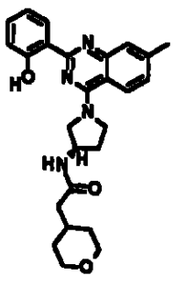	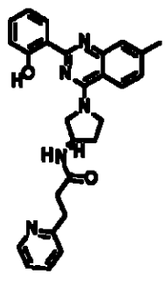	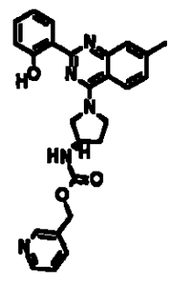

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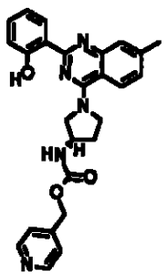	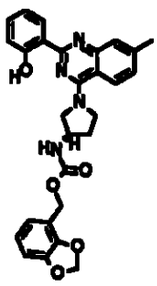	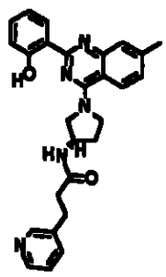
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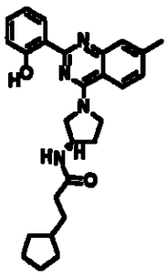	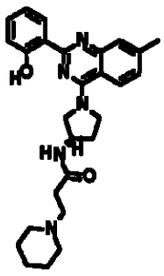	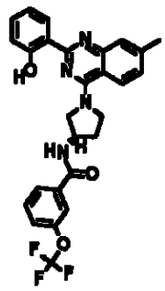
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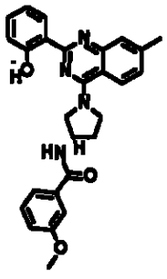	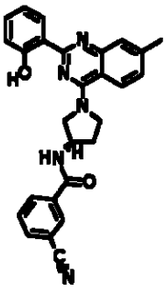	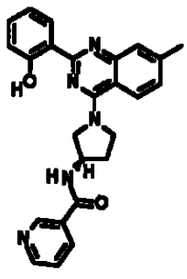
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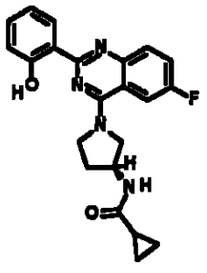	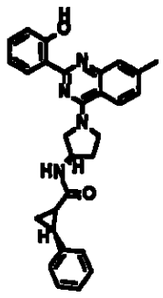	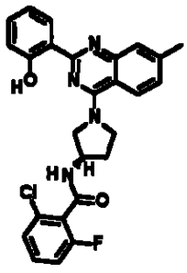

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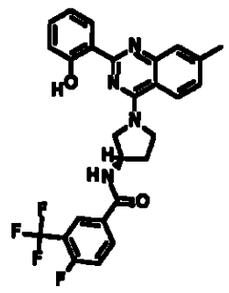	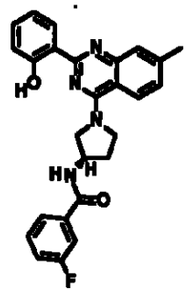	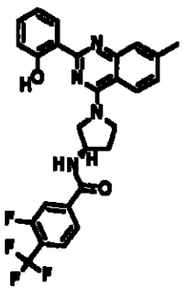
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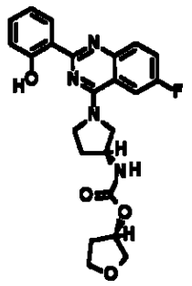	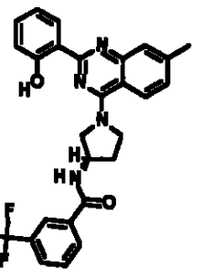	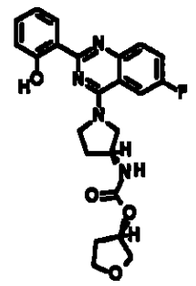
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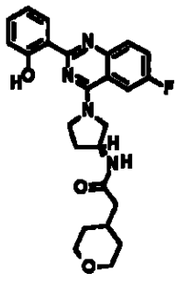	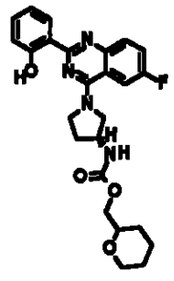	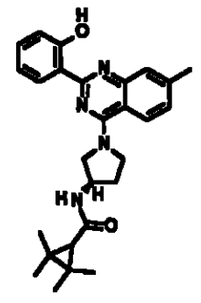
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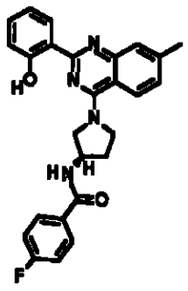	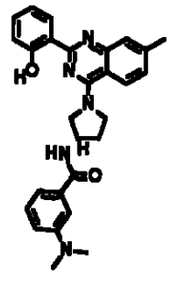	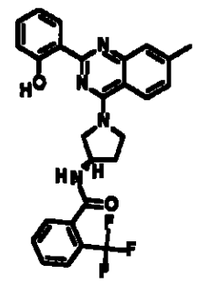

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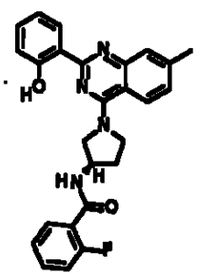	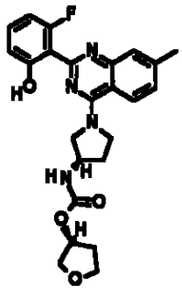	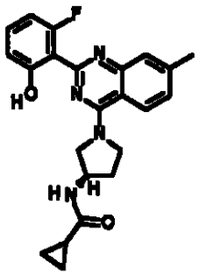
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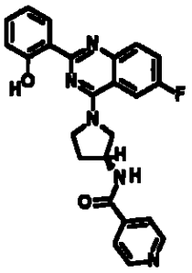	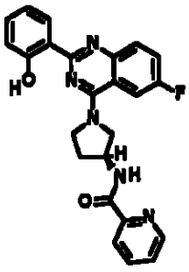	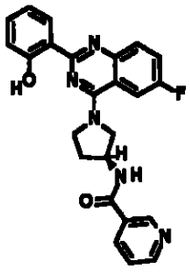
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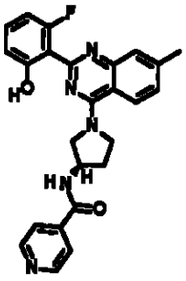	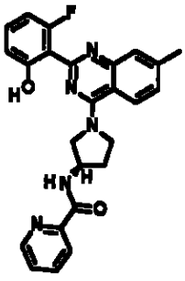	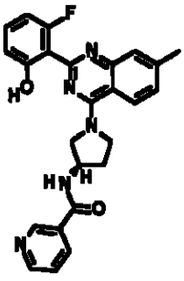
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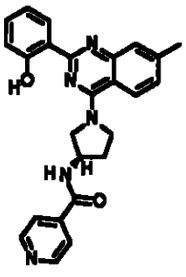	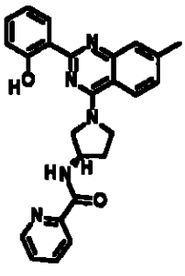	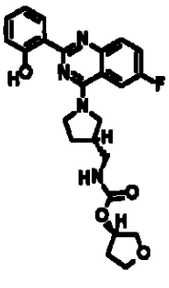

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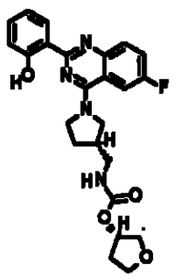	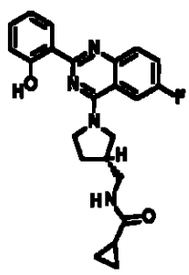	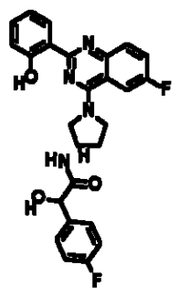
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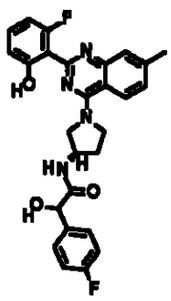	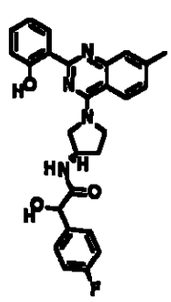	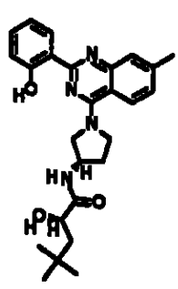
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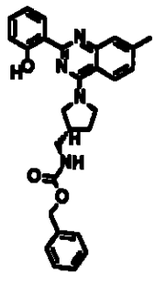	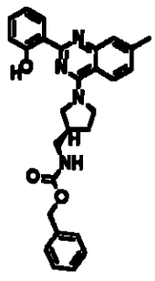	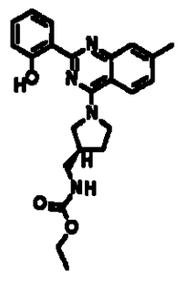
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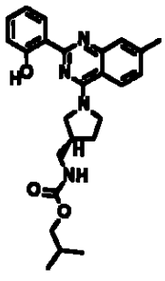	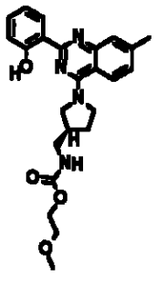	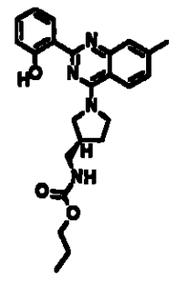

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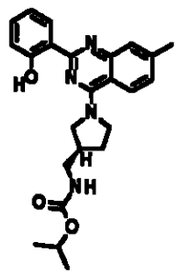	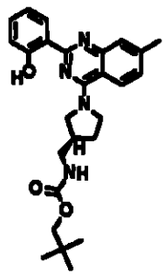	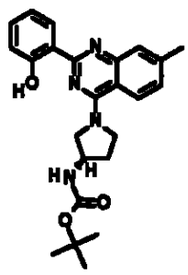
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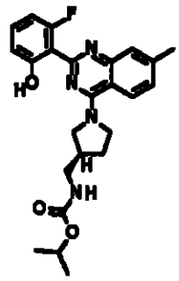	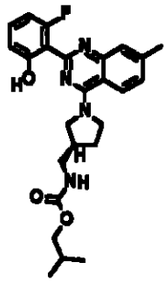	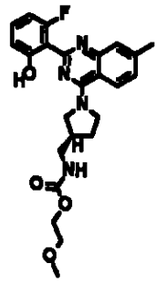
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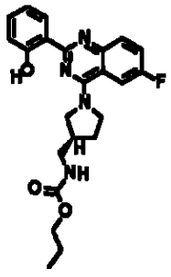	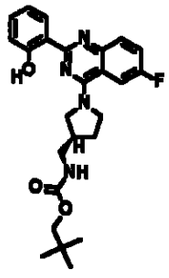	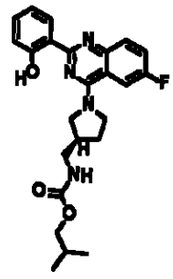
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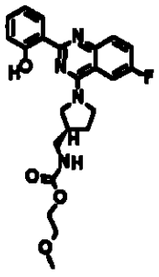	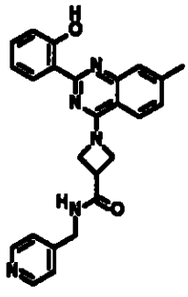	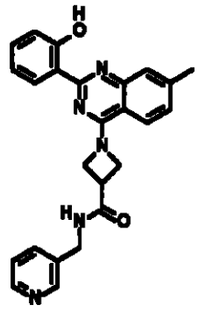

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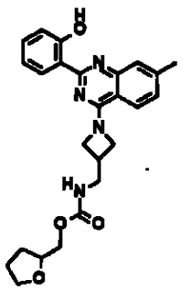	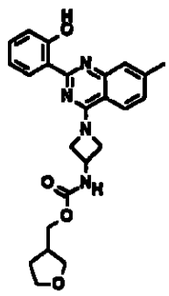	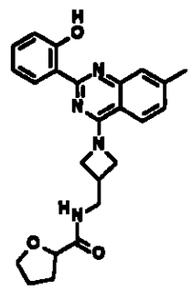
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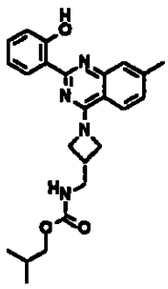	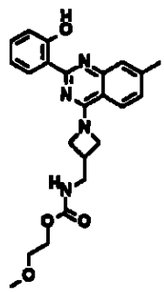	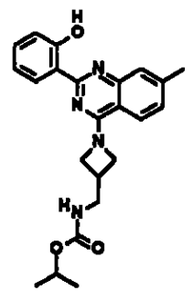

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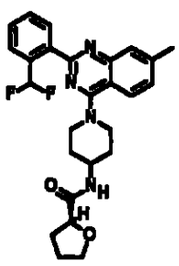	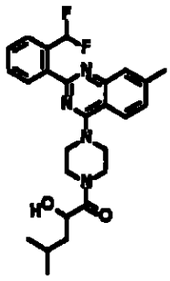	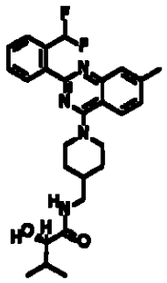
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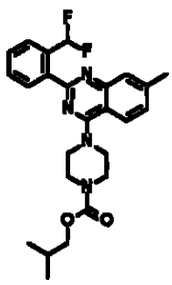	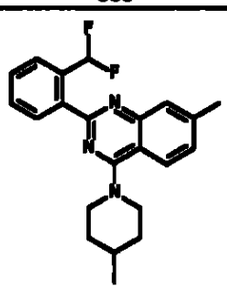	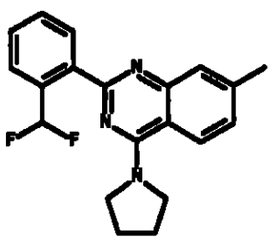
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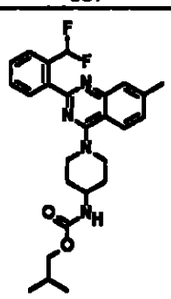	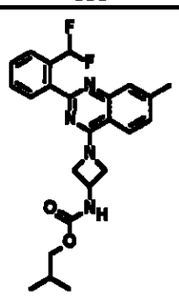	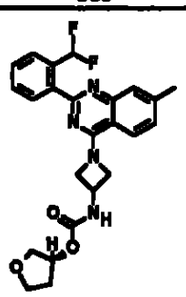
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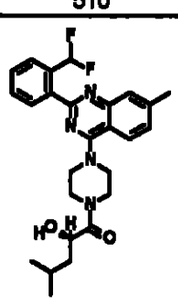	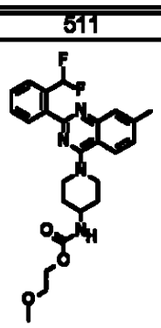	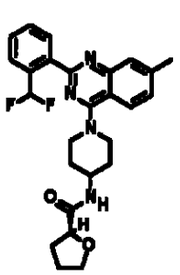

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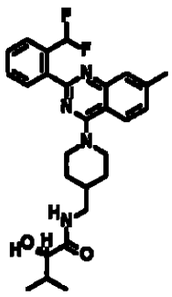	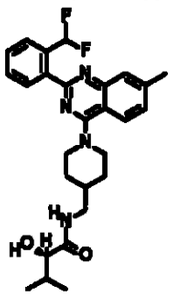

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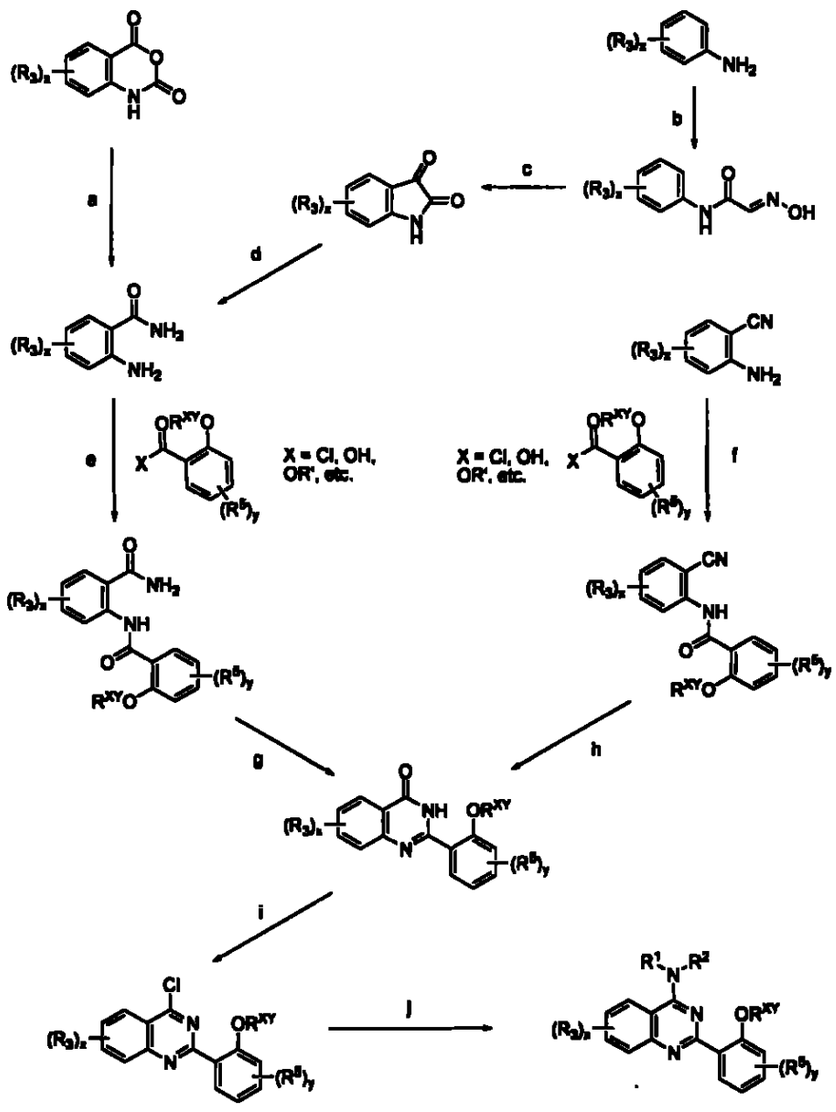
[00162] *4. General Synthetic Methodology:*

[00163] *4. Procedimientos generales de síntesis:*

[00164] En general, los compuestos de esta invención se pueden preparar por medio de métodos conocidos por los especialistas en el arte para la preparación de compuestos análogos, tal como se ilustra por lose esquemas siguientes generales y los ejemplos de preparación siguientes.

[00165] Esquema A: preparaciones general por 4-cloroquinazolinas



[00166] Condiciones: a) NH_4OH ac.; b) hidrato de cloral, HCl, Na_2SO_4, $HONH_2$*HCl c) H_2SO_4; d) ácido acético, H_2SO_4, H_2O_2 ac.; e) Et_3N, THF; f) Et_3N, DMAP, CH_2Cl_2; g) NaOH ac.; h) NaOH ac., H_2O_2 ac. i) $POCl_3$, N,N-dimetilanilina, benceno; j) R^1R^2NH, Et_3N, CH_2Cl_2

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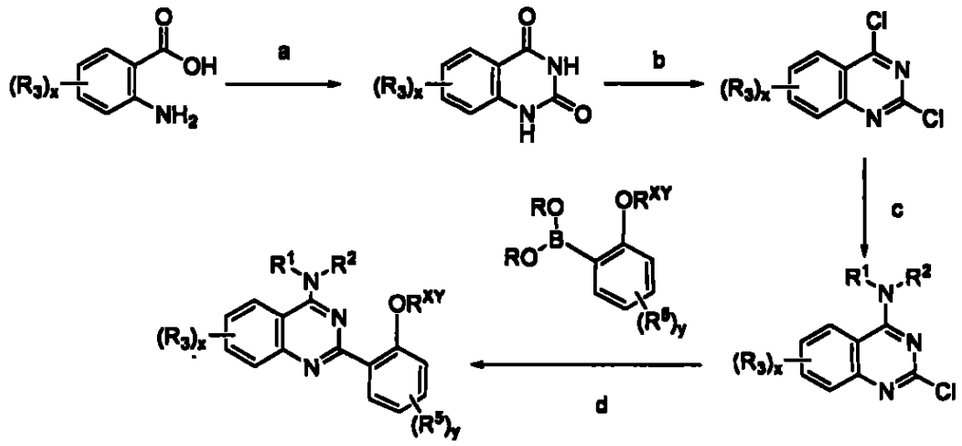
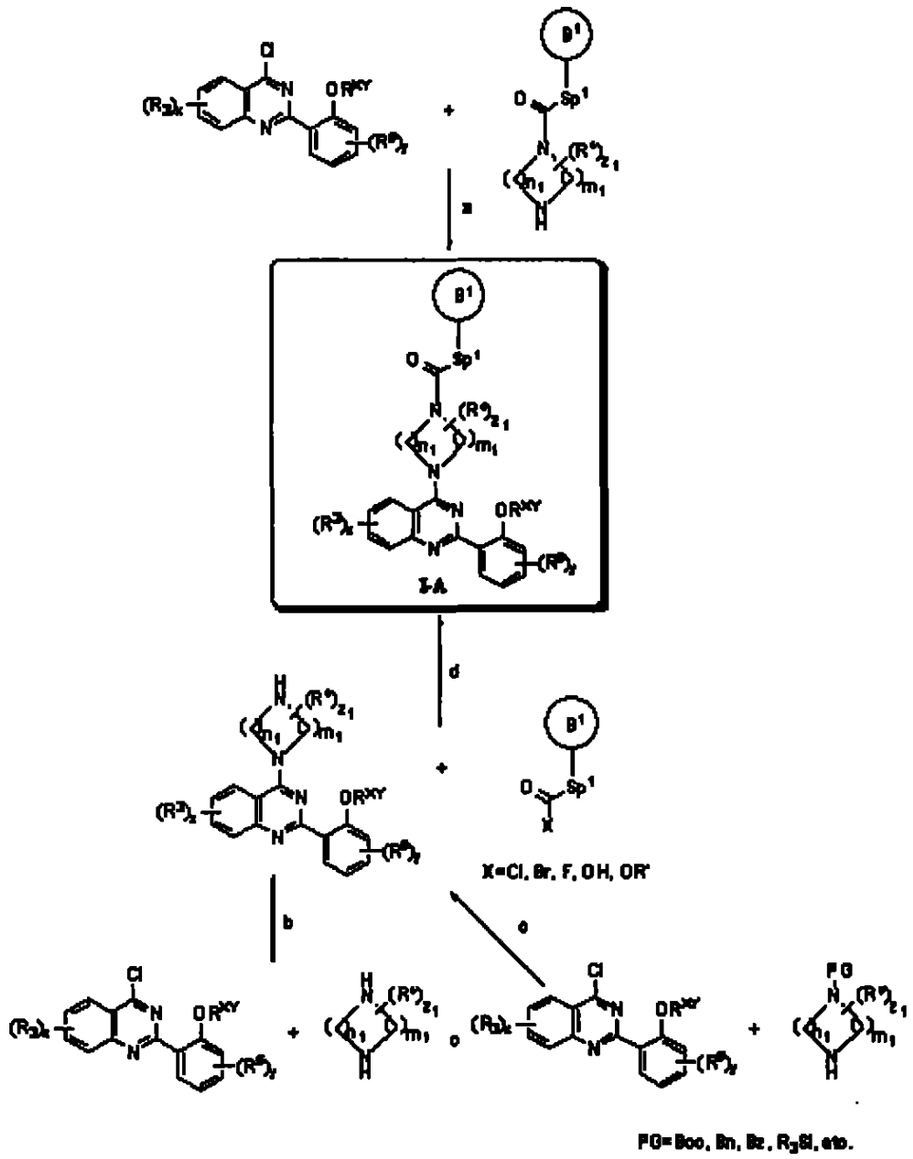
[00167] Esquema B: preparaciones generales por 2,4-dicloroquinazolinas



[00168] Condiciones: a) AcOH, KOCN; b) $POCl_3$; c) Et_3N, DCM, R^1R^2NH; d) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, H_2O

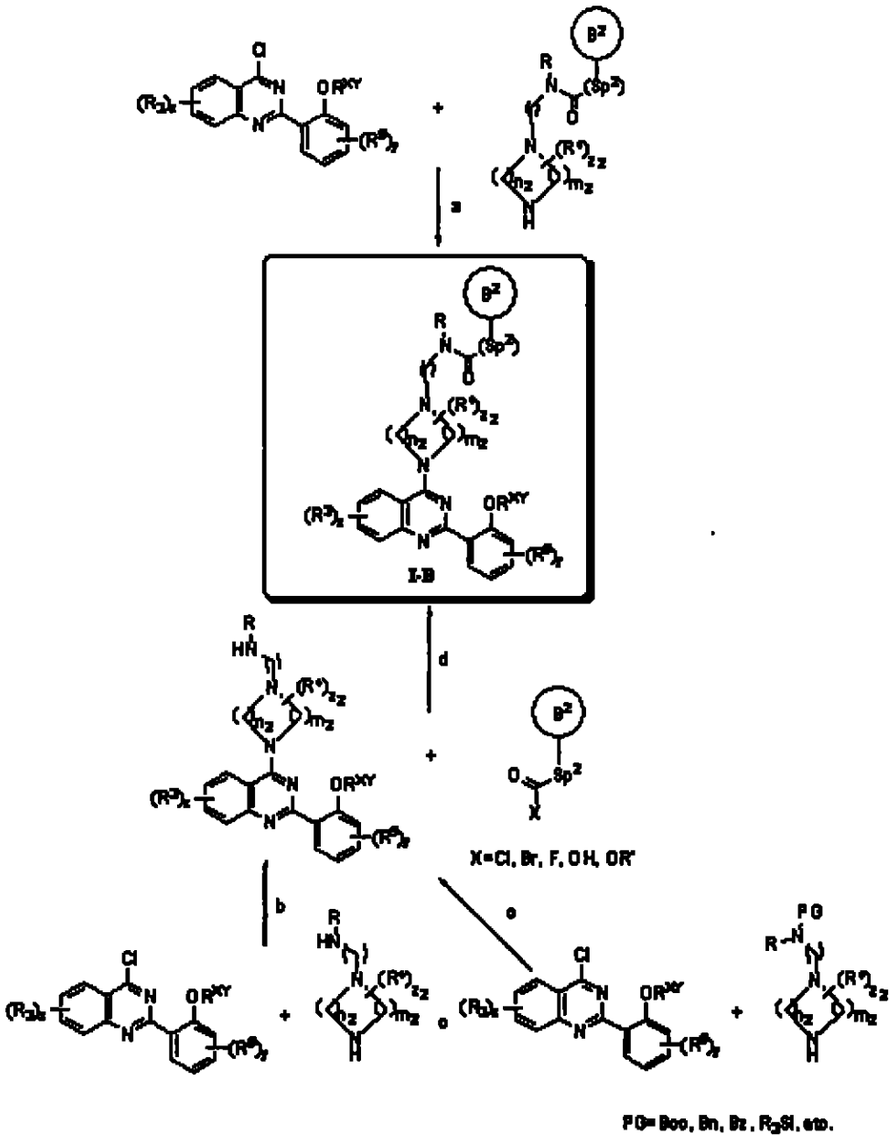
[00169] Esquema I-A para la fórmula I-A:



[00170] Condiciones: a) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; b) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; c) i. DCM o THF, trietilamina, 0 °C hasta temperatura ambiente, ii. Desprotección: 1:1 TFA / DCM, ta,

para Boc; H_2, Pd / C durante Bn; NaOH para Bz, TBAF para R3Si, etc.; d) Para haluros ácidos, DCM o THF, trietilamina; para ácidos carboxílico, EDC, HOBt, trietilamina, DMF; para X=OR', THF o DMF, calor.

[00171] Esquema I-B para compuestos de fórmula I-B:



[00172] Condiciones: a) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; b) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; c) i. DCM o THF, trietilamina, 0 °C hasta

temperatura ambiente, ii. Desprotección: 1:1 TFA / DCM, ta, para Boc; H_2, Pd / C durante Bn; NaOH para Bz, TBAF para R3Si, etc.; d) Para haluros ácidos, DCM o THF, trietilamina; para ácidos carboxílicos, EDC, HOBt, trietilamina, DMF; para X=OR', THF o DMF, calor.

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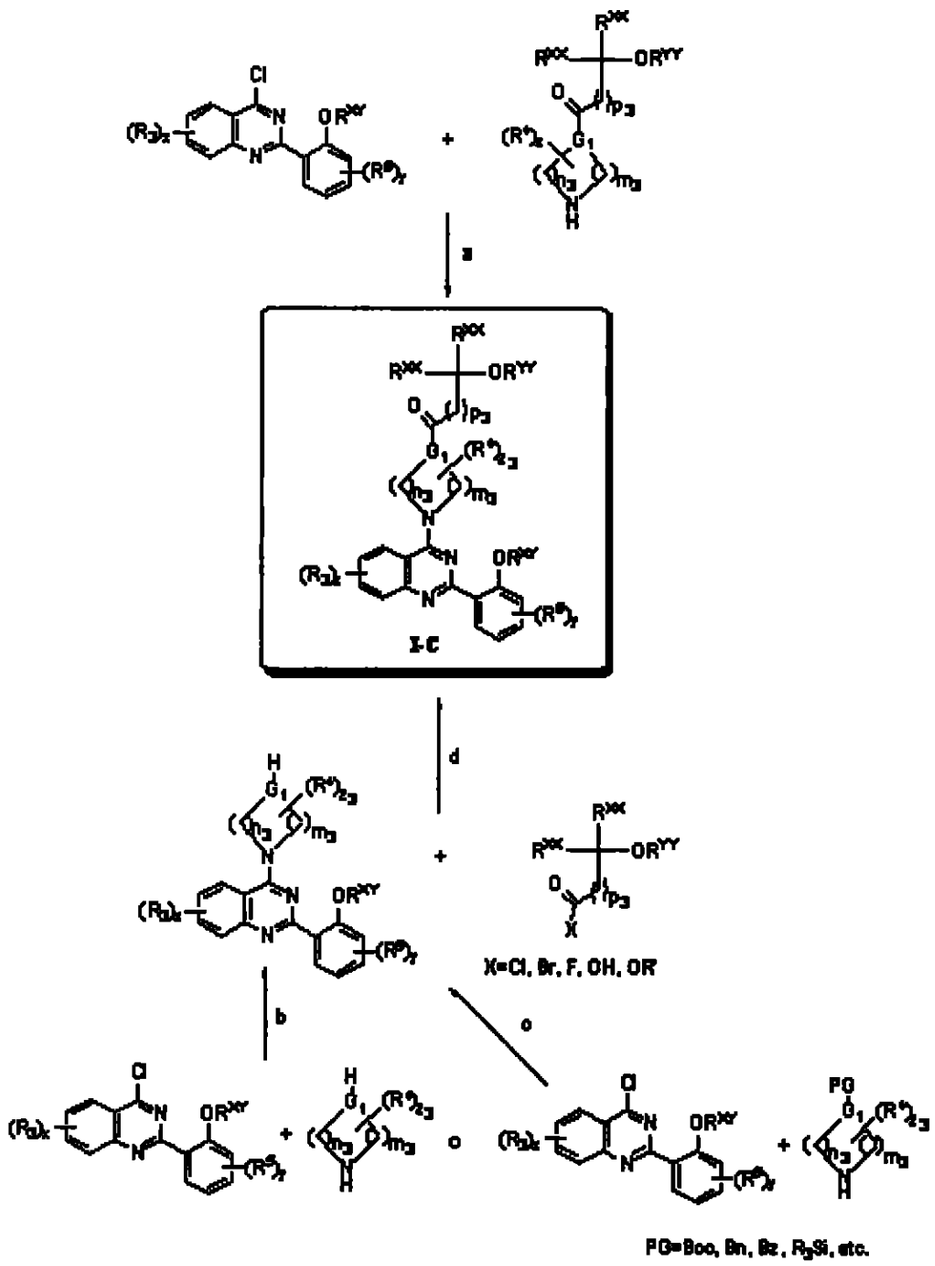
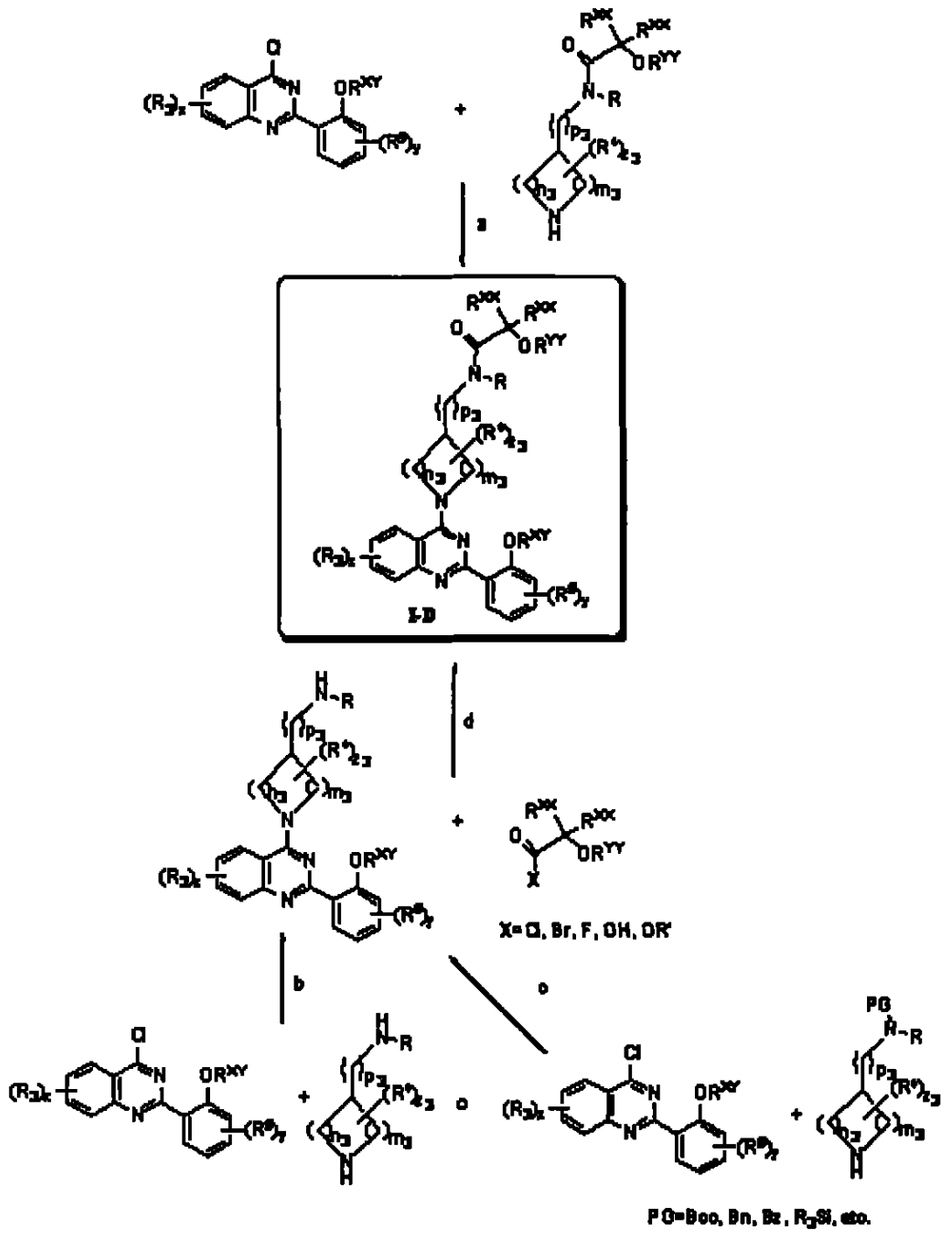
[00173] Esquema I-C para la fórmula I-C:



[00174] Condiciones: a) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; b) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; c) i. DCM o THF, trietilamina, 0 °C hasta temperatura ambiente, ii. Desproteger: 1:1 TFA / DCM, ta, para Boc; H_2, Pd / C para Bn; NaOH para Bz, TBAF para R3Si, etc.; d) Para haluros ácidos, DCM o THF, trietilamina; para ácidos carboxílicos, EDC, HOBt, trietilamina, DMF; para X=OR', THF o DMF, calor.

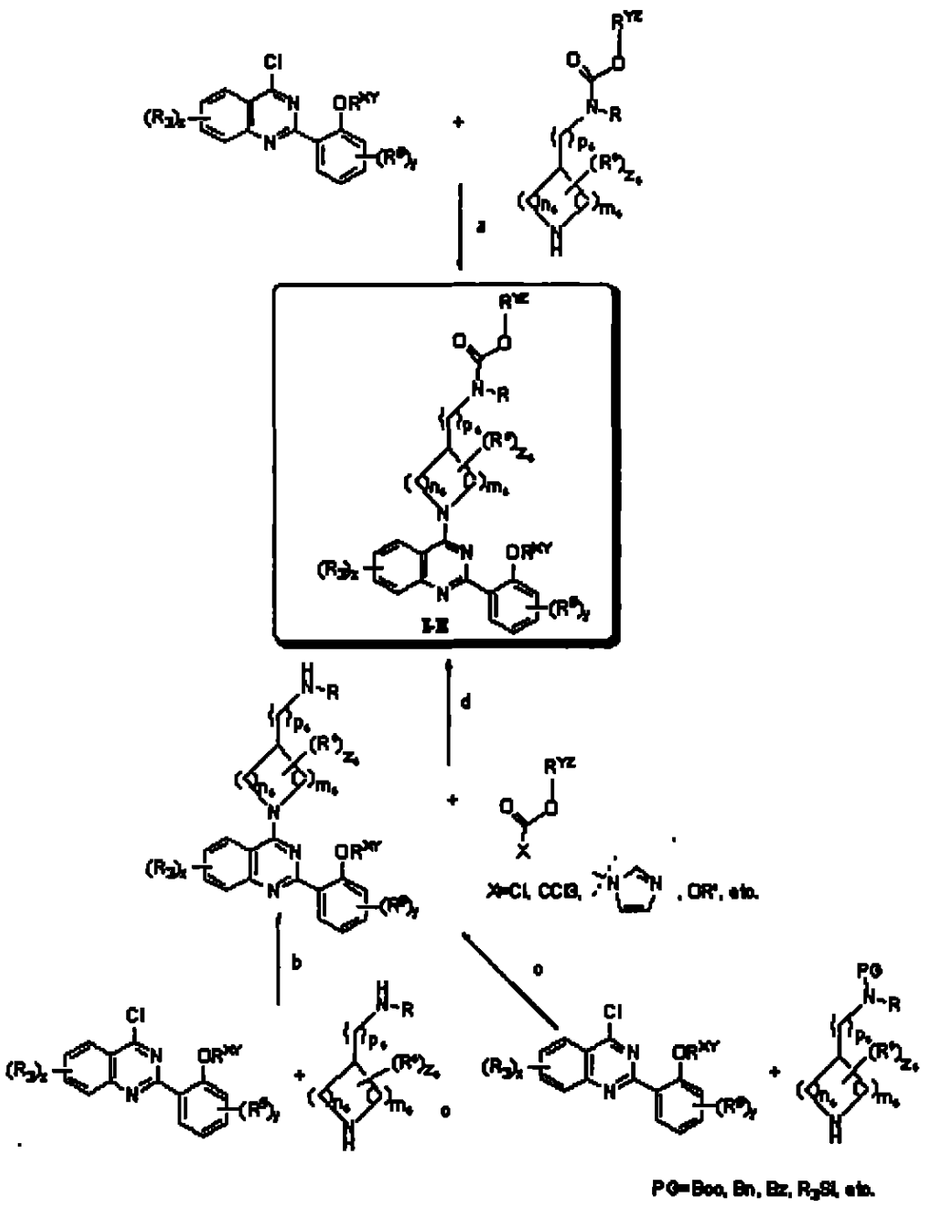
[00175] Esquema I-D para fórmula I-D:



[00176] Condiciones: a) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; b) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; c) i. DCM o THF, trietilamina, 0 °C hasta

temperatura ambiente, ii. Desprotección: 1:1 TFA / DCM, ta, para Boc; H_2, Pd / C para Bn; NaOH para Bz, TBAF para R3Si, etc.; d) Para haluros ácidos, DCM o THF, trietilamina; para ácidos carboxílicos, EDC, HOBt, trietilamina, DMF; para X=OR', THF o DMF, calor.

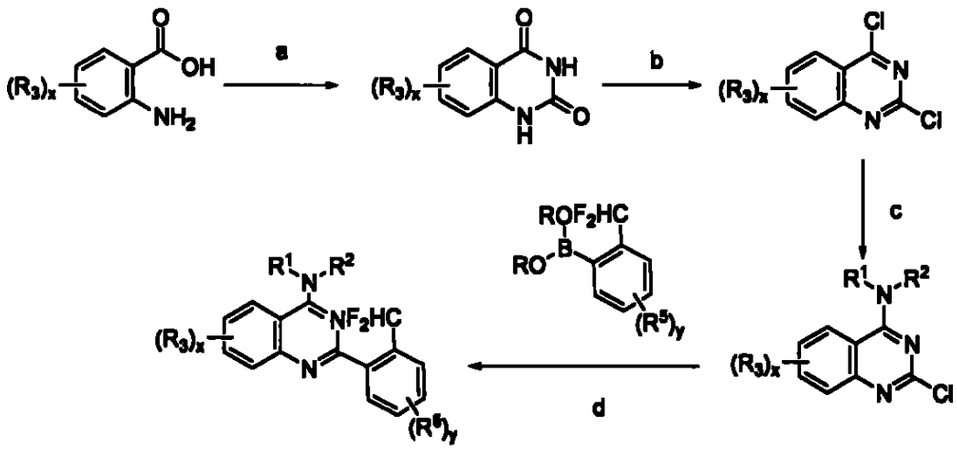
[00177] Esquema I-E para fórmula I-E:



[00178] Condiciones: a) DCM o THF, trietilamina, 0 °C hasta temperatura ambiente; b) DCM o THF, trietilamina, 0 °C hasta

temperatura ambiente; c) i. DCM o THF, trietilamina, 0 °C hasta temperatura ambiente, ii. Desprotección: 1:1 TFA / DCM, ta, para Boc; H_2, Pd / C para Bn; NaOH para Bz, TBAF para R3Si, etc.; d) Para X=Cl, CCl_3, imidazolilo, OR', etc., DCM o THF, trietilamina, ta o calor.

[00179] Esquema I-F para preparar compuestos de fórmula I-F:



[00180] Condiciones: a) AcOH, KOCN; b) $POCl_3$; c) Et_3N, DCM, R^1R^2NH; d) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, H_2O.

[00181] *5. Usos, formulación y administración*

[00182] El documento WO 2004/078733 describe un género de bloqueadores de canales de sodio que abarcan los compuestos de la presente invención. Sin embargo, los compuestos de la presente invención exhiben propiedades inesperadas

establecidas, por debajo de las cuales se consideran terapéuticamente más útil.

[00183] En una forma de realización, ciertos compuestos de la presente invención son útiles como inhibidores mejorados de canales de sodio.

[00184] En otra forma de realización, ciertos compuestos de la presente invención poseen selectividad mejorada para inhibir un canal de sodio, por ejemplo, NaV 1.8, respecto de uno o más de los demás canales de sodio. Son particularmente útiles los compuestos con actividad deseablemente baja contra NaV 1.2 o NaV 1.5.

[00185] En otra forma de realización, ciertos compuestos de la presente invención tienen inhibidores mejorados de NaV 1.8.

[00186] En otra forma de realización, ciertos compuestos de la presente invención tienen solubilidad acuosa mejorada, por ejemplo, un pH fisiológicamente relevante.

[00187] En otra forma de realización más, ciertos compuestos de la presente invención tienen propiedades farmacocinéticas y/o farmacodinámicas mejoradas y, en consecuencia, están mejor adecuadas para la administración *in-vivo* con fines terapéuticos. Dichas propiedades incluyen biodisponibilidad oral, cinética de depuración, eficacia, etc.

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[00188] En otra forma de realización, ciertos compuestos de la presente invención tienen actividad deseablemente bajas contra el canal hERG.

[00189] En otra forma de realización, ciertos compuestos de la presente invención tienen actividad deseablemente bajas contra las isoformas clave de la familia de enzima de citocromo P450, incluso isozimas CYP3A4, CYP2C9, CYP1A2, CYP2C19 o CYP2D6.

[00190] En otra forma de realización, ciertos compuestos de la presente invención tienen actividad deseablemente bajas contra el canal CaV 1.2 y/o Kv 1.5.

[00191] En consecuencia, en una forma de realización de la presente invención, los compuestos tienen una o más de las siguientes propiedades inesperadas y terapéuticamente beneficiosos: potente inhibición de canal NaV 1.8, selectividad para un canal de sodio, por ejemplo, NaV 1.8 sobre uno o más de los demás canales de sodio, solubilidad acuosa mejorada, propiedades farmacocinéticas y/o farmacodinámicas mejoradas, deseablemente baja actividad contra el canal hERG, deseablemente baja actividad contra isoformas clave de la familia de enzimas de citocromo P450 o deseablemente baja actividad CaV de tipo L 1.2 y/o Kv1.5. La presencia de dichas propiedades, individualmente o en combinación, torna a los compuestos más adecuadas para la

administración a humanos para tratar diversas enfermedades tal como se estableció más adelante.

[00192] La frase "actividad deseablemente baja" tal como se usa en la presente significa un nivel de actividad de un compuesto contra un blanco/enzima suficientemente baja para que dicha actividad se considere ventajosa (por ejemplo, mitigar un factor de riesgo), cuando se evalúa la adecuación de dicho compuesto para la administración en humanos.

[00193] Los presentes compuestos son útiles para el tratamiento de enfermedades, trastornos y condiciones que incluyen, sin limitaciones dolor agudo, crónico, neuropático o inflamatorio, artritis, migraña, cefaleas acuminadas, neuralgia de trigémino, neuralgia herpética, neuralgias generales, epilepsia o condiciones epilépticas, trastornos neurodegenerativos, trastornos psiquiátricos tales como ansiedad y depresión, miotonía, arritmia, trastornos del movimiento, trastornos neuroendocrinos, ataxia, esclerosis múltiple, síndrome de intestino irritable e incontinencia. Conforme a ello, en otro aspecto de la presente invención se proveen composiciones farmacéuticamente aceptables, en donde dichas composiciones comprende cualquiera de los compuestos tal como se describe en la presente y opcionalmente comprende un portador, coadyuvante o vehículo farmacéuticamente aceptable. En ciertas formas de realización, dichas

composiciones opcionalmente también comprende uno o más agentes terapéuticos adicionales.

[00194] De acuerdo con una forma de realización, los compuestos de la presente invención son útiles para tratar una enfermedad seleccionada de dolor por cáncer de fémur; dolor óseo crónico no maligno; artritis reumatoide; osteoartritis; estenosis espinal; dolor lumbar neuropático; dolor lumbar neuropático; síndrome de dolor miofascial; fibromialgia; dolor articular temporomandibular; dolor visceral crónico, incluso, abdominal; pancreático; dolor IBS; dolor por cefalea crónica; migraña; cefalea por tensión, incluso cefalea acuminada; dolor neuropático crónico, incluso, neuralgia posherpética; neuropatía diabética; neuropatía asociada con HIV; neuralgia de trigémino; neuropatía de Charcot-Marie Toot; neuropatías sensoriales hereditarias; lesión de nervios periféricos; neuromas dolorosos; descargas ectópicas proximal y distal; radiculopatía; dolor neuropático inducido por quimioterapia; dolor neuropático inducido por radioterapia; dolor posmastectomía; dolor central; dolor por lesión de médula espinal; dolor post-accidente cerebrovascular; dolor talámico; síndrome doloroso de complejo regional; dolor fantasma; dolor intratable; dolor agudo, dolor agudo postoperatorio; dolor musculoesquelético agudo; dolor articular; dolor lumbar mecánico; dolor de cuello; tendinitis; dolor por

lesión/ejercicio; dolor visceral agudo, incluso dolor abdominal; pielonefritis; apendicitis; colecistitis; obstrucción intestinal; hernias; etc.; dolor torácico, incluso dolor cardiaco; dolor pelviano, dolor cólico renal, dolor obstétrico agudo, incluso, dolor de parto; dolor por cesárea; dolor inflamatorio agudo, por quemadura y traumatismo; dolor intermitente agudo, incluso, endometriosis; dolor agudo por herpes zoster; anemia por célula falciforme; pancreatitis aguda; dolor sistémico; dolor orofacial, incluso dolor por sinusitis, dolor dental; dolor por esclerosis múltiple (MS); dolor en depresión; dolor por lepra; dolor por enfermedad de Behcet; adiposis dolorosa; dolor flebítico; dolor por Guillain-Barre; piernas dolorosas y dedos de los pies movibles; síndrome de Haglund; dolor por eritromelalgia; dolor por enfermedad de Fabri; enfermedad vesical y urogenital, incluso, incontinencia urinaria; vejiga hiperactiva; síndrome de vejiga dolorosa; cistitis intersticial (IC); y prostatitis.

[00195] En otra forma de realización, los compuestos de la presente invención son útiles para tratar trastornos de vías urinarias inferiores. Véase, por ejemplo, publicación de patente internacional No. WO 2004/066990, cuyo contenido se incorpora en la presente por referencia.

[00196] También se apreciará que ciertos de los compuestos de la presente invención pueden existir en forma libre para el

tratamiento, o cuando corresponde, como su derivado farmacéuticamente aceptable. De acuerdo con la presente invención, un derivado farmacéuticamente aceptable incluye, sin limitaciones, profármacos, sales, ésteres, sales de dichos ésteres farmacéuticamente aceptables, o cualquier otro aducto o derivado, las cuales tras la administración a un paciente que lo necesite es capaz de proveer, directa o indirectamente, un compuesto tal como se describe en otra parte en la presente, o como su metabolito o residuo.

[00197] Tal como se usa en la presente, el término "sal farmacéuticamente aceptable" se refiere a las sales que, dentro del alcance del sano criterio médico, son adecuadas para el uso en contacto con los tejidos de humanos y animales inferiores sin indebida toxicidad, irritación, respuesta alérgica, y similares y son comparables con una relación razonable de riesgo/beneficio. Una "sal farmacéuticamente aceptable" significa cualquier sal no tóxica o sal de un éster de un compuesto de esta invención que, después de administrarlo a un receptor, es capaz de proveer, ya sea directa o indirectamente, un compuesto de esta invención o un metabolito de acción inhibidora o uno de sus residuos. Tal como se usa en la presente, el término "metabolito de acción inhibidora o uno de sus residuos" significa que un metabolito

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o uno de sus residuos también es un inhibidor del canal blanco.

[00198] Las sales farmacéuticamente aceptables son bien conocidas en el arte. Por ejemplo, S. M. Berge *y otro*, describen sales farmacéuticamente aceptables en detalle en *J. Pharmaceutical Sciences*, **1977**, *66*, 1-19, incorporado en la presente como referencia. Las sales farmacéuticamente aceptables de los compuestos de la presente invención incluyen los derivados de adecuados ácidos y bases inorgánicos, y orgánicos. Son ejemplos de sales por adición de ácidos no tóxicos farmacéuticamente aceptables de un grupo amino formado con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido sulfúrico y ácido perclórico o con ácidos orgánicos tales como ácido acético, ácido oxálico, ácido maleico, ácido tartárico, ácido cítrico, ácido succínico o ácido malónico o al usar otros métodos empleados en el arte tales como intercambio iónico. Otras sales farmacéuticamente aceptables incluyen sales de adipato, alginato, ascorbato, aspartato, bencensulfonato, benzoato, bisulfato, borato, butirato, canforato, canforsulfonato, citrato, ciclopentanpropionato, digluconato, dodecilsulfato, etansulfonato, formiato, fumarato, glucoheptonato, glicerofosfato, gluconato, hemisulfato, heptanoato, hexanoato, yodhidrato, 2-hidroxi-etanosulfonato, lactobionato, lactato,

laurato, laurilsulfato, malato, maleato, malonato, metansulfonato, 2-naftalensulfonato, nicotinato, nitrato, oleato, oxalato, palmitato, pamoato, pectinato, persulfato, 3-fenilpropionato, fosfato, picrato, pivalato, propionato, estearato, succinato, sulfato, tartrato, tiocianato, p-toluensulfonato, undecanoato, valerato, y similares. Las sales derivadas de bases incluyen sales de metales alcalinos, metales alcalinotérreos, amonio y N^+(alquilo C_{1-4})$_4$. La presente invención también contempla la cuaternización de cualquier grupo básico que contiene nitrógeno de los compuestos descritos en la presente. Los productos hidro- o liposolubles o dispersables se pueden obtener por dicha cuaternización. Las sales representativas de metales alcalinos o alcalinotérreos incluyen las de sodio, litio, potasio, calcio, magnesio, y similares. Otras sales farmacéuticamente aceptables incluyen, cuando corresponde, cationes no tóxicos amonio, amonio cuaternario y amina formados con contraiones tales como haluro, hidróxido, carboxilato, sulfato, fosfato, nitrato, alquilo inferior sulfonato y arilsulfonato.

[00199] Tal como se describió con anterioridad, las composiciones farmacéuticamente aceptables de la presente invención también comprenden un portador, coadyuvante o vehículo farmacéuticamente aceptable que, tal como se usa en la presente, incluye cualquiera y todos los solventes,

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diluyentes, u otro vehículo líquido, auxiliar de dispersión o suspensión, agentes tensioactivos, agentes isotónicos, agentes espesantes o emulsificantes, conservadores, ligadores sólidos, lubricantes y similares, como sea adecuado para la particular forma de dosificación deseada. Remington's Pharmaceutical Sciences, 16° Edición, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) describe diversos portadores utilizados en la formulación de composiciones farmacéuticamente aceptables y las técnicas conocidas para su preparación. Excepto cuando cualquier medio portador convencional es incompatible con los compuestos de la invención, tales como al producir cualquier efecto biológico indeseable o de otro modo interactúa en forma deletérea con cualquier otro componente de la composición farmacéuticamente aceptable, su uso se contempla dentro del alcance de la presente invención. Algunos ejemplos de materiales que pueden servir como portador farmacéuticamente aceptable incluyen, sin limitaciones, intercambiadores iónicos, alúmina, estearato de aluminio, lecitina, proteínas séricas, tales como albúmina sérica humana, sustancias buffer tales como fosfatos, glicina, ácido sórbico, o sorbato de potasio, mezclas parciales de glicéridos de ácidos grasos de vegetales saturados, agua, sales o electrólitos, tales como sulfato de protamina, fosfato de hidrógeno disodio, fosfato de hidrógeno potasio, cloruro de sodio, sales de zinc, silice

coloidal, trisilicato de magnesio, polivinilpirrolidona, poliacrilatos, ceras, polímeros de bloque de polietileno-polioxipropileno, lanolina, azúcares tales como lactosa, glucosa y sacarosa; almidones tales como almidón de maíz y almidón de papa; celulosa y sus derivados tales como carboximetilcelulosa sódica, etilcelulosa y acetato de celulosa; tragacanto en polvo; malta; gelatina; talco; excipientes tales como manteca de cacao y ceras de supositorios; aceites tales como aceite de maní, aceite de algodón; aceite de sasafrás; aceite de sésamo; aceite de oliva; aceite de maíz y aceite de poroto de soja; glicoles tales como propilenglicol o polietilenglicol; ésteres tales como oleato de etilo y laureato de etilo; agar; agentes buffer tales como hidróxido de magnesio e hidróxido de aluminio; ácido algínico; agua libre de pirógenos; solución fisiológica isotónica; solución de Ringer; alcohol etílico y soluciones buffer fosfato, además de otros lubricantes compatibles no tóxicos tales como laurilsulfato de sodio y estearato de magnesio, además de agentes colorantes, agentes liberadores, agentes de recubrimiento, agentes edulcorantes, saborizantes y perfumantes, conservadores y antioxidantes también pueden estar presentes en la composición, de acuerdo con el criterio del formulador.

[00200] *Usos de los compuestos y composiciones farmacéuticamente aceptables*

[00201] En otro aspecto más, un método para tratar o reducir la gravedad de dolor agudo, crónico, neuropático o inflamatorio, artritis, migraña, cefaleas acuminadas, neuralgia de trigémino, neuralgia herpética, neuralgias generales, epilepsia o condiciones epilépticas, trastornos neurodegenerativos, trastornos psiquiátricos tales como ansiedad y depresión, miotonía, arritmia, trastornos del movimiento, trastornos neuroendocrinos, ataxia, esclerosis múltiple, síndrome de intestino irritable, incontinencia, dolor visceral, dolor de osteoartritis, neuralgia posherpética, neuropatía diabética, dolor radicular, ciático, dolor de espalda, dolor de cabeza o cuello, dolor severo o intratable, dolor nociceptivo, dolor intenso, dolor posquirúrgico o dolor por cáncer que comprende administrar una cantidad efectiva de un compuesto o una composición farmacéuticamente aceptable que comprende un compuesto a un sujeto que lo necesita. En ciertas formas de realización, un método para el tratamiento o reducción de la gravedad de dolor agudo, crónico, neuropático o inflamatorio comprende administrar una cantidad efectiva de un compuesto o una composición farmacéuticamente aceptable a un sujeto que lo necesita. En otras determinadas formas de realización, un

método para el tratamiento o reducción de la gravedad de dolor radicular, ciático, dolor de espalda, dolor de cabeza o dolor de cuello comprende administrar una cantidad efectiva de un compuesto o una composición farmacéuticamente aceptable a un sujeto que lo necesita. En otras formas más de realización, un método para el tratamiento o reducción de la gravedad de dolor severo o intratable, dolor agudo, dolor posquirúrgico, dolor de espalda o dolor por cáncer comprende administrar una cantidad efectiva de un compuesto o una composición farmacéuticamente aceptable a un sujeto que lo necesita.

|00202| En ciertas formas de realización de la presente invención, una "cantidad efectiva" del compuesto o composición farmacéuticamente aceptable es aquella cantidad efectiva para tratar o reducir la gravedad de uno o varios de dolor agudo, crónico, neuropático o inflamatorio, artritis, migraña, cefaleas acuminadas, neuralgia de trigémino, neuralgia herpética, neuralgias generales, epilepsia o condiciones epilépticas, trastornos neurodegenerativos, trastornos psiquiátricos tales como ansiedad y depresión, miotonía, arritmia, trastornos del movimiento, trastornos neuroendocrinos, ataxia, esclerosis múltiple, síndrome de intestino irritable, incontinencia, dolor visceral, dolor de osteoartritis, neuralgia posherpética, neuropatía diabética, dolor radicular, ciático, dolor de espalda, dolor de cabeza o

cuello, dolor severo o intratable, dolor nociceptivo, dolor intenso, dolor posquirúrgico o dolor por cáncer.

[00203] Los compuestos y composiciones, de acuerdo con el método de la presente invención, se pueden administrar usando cualquier cantidad y cualquier vía de administración efectiva para tratar o reducir la gravedad de uno o varios de dolor agudo, crónico, neuropático o inflamatorio, artritis, migraña, cefaleas acuminadas, neuralgia de trigémino, neuralgia herpética, neuralgias generales, epilepsia o condiciones epilépticas, trastornos neurodegenerativos, trastornos psiquiátricos tales como ansiedad y depresión, miotonía, arritmia, trastornos del movimiento, trastornos neuroendocrinos, ataxia, esclerosis múltiple, síndrome de intestino irritable, incontinencia, dolor visceral, dolor de osteoartritis, neuralgia posherpética, neuropatía diabética, dolor radicular, ciático, dolor de espalda, dolor de cabeza o cuello, dolor severo o intratable, dolor nociceptivo, dolor intenso, dolor posquirúrgico o dolor por cáncer. La cantidad exacta requerida variará entre sujetos, según la especie, la edad, y la condición general del sujeto, la severidad de la infección, el agente particular, su modo de administración, y similares. Los compuestos de la invención de preferencia se formulan en una forma de dosificación unitaria para facilitar la administración y la uniformidad de la dosificación. La

expresión "forma de dosificación unitaria" tal como se usa en la presente se refiere a una unidad físicamente discreta de agente apropiado para el paciente tratado. Sin embargo, se comprenderá que el uso total diario de los compuestos y composiciones de la presente invención será decidido por el médico a cargo dentro del alcance del sano criterio médico. El nivel de dosis efectiva específico para cada paciente u organismo particular dependerá de diversos factores que incluyen el trastorno tratado y la severidad del trastorno; la actividad del compuesto específico empleado; la composición específica empleada; la edad, el peso corporal, la salud general, el sexo y la dieta del paciente en el momento de la administración, la vía de administración, y la velocidad de excreción del compuesto específico empleado; la duración del tratamiento; los fármacos usados en combinación o junto con el compuesto específico empleado, y factores similares bien conocidos en las artes médicas. El término "paciente", tal como se usa en la presente, significa un animal, de preferencia un mamífero, y con mayor preferencia un humano.

[00204] Las composiciones farmacéuticamente aceptables de la presente invención se pueden administrar a humanos y otros animales por vía oral, parenteral, por rocío de inhalación, tópica (como por polvos, ungüentos o gotas), bucal, como un spray oral o nasal o similares, según la gravedad de la

infección en tratamiento. En ciertas formas de realización, los compuestos de la invención se pueden administrar por vía oral o parenteral en niveles de dosis de aproximadamente 0,01 mg/kg a aproximadamente 50 mg/kg y con preferencia de aproximadamente 1 mg/kg a aproximadamente 25 mg/kg, de peso corporal del individuo por día, una o varias veces diarias, para obtener el efecto terapéutico deseado.

[00205] Las formas de dosificación líquidas para la administración oral incluyen, sin limitaciones, emulsiones, microemulsiones, soluciones, suspensiones, jarabes y elixires farmacéuticamente aceptables. Además de los compuestos activos, las formas de dosificación líquidas pueden contener diluyentes inertes de uso común usados en el arte tales como, por ejemplo, agua u otros solventes, agentes solubilizantes y emulsificantes tales como alcohol etílico, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, dimetilformamida, aceites (en particular, aceites de semilla de algodón, maní, maíz, germen, oliva, ricino, y sésamo), glicerol, alcohol tetrahidrofurfurílico, polietilenglicoles y ésteres de ácidos grasos de sorbitano, y sus mezclas. Además de los diluyentes inertes, las composiciones orales también pueden incluir coadyuvantes tales

como agentes humectantes, agentes emulsificantes y de suspensión, agentes edulcorantes, saborizantes y perfumantes.

[00206] Las preparaciones inyectables, por ejemplo, las suspensiones inyectables estériles acuosas u oleaginosas se pueden formular de acuerdo con el arte conocido mediante adecuados agentes dispersantes o humectantes y agentes de suspensión. La preparación inyectable estéril también puede ser una solución, suspensión o emulsión inyectable estéril en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo, como una solución en 1,3-butanodiol. Entre los vehículos y solventes adecuados que se pueden emplear se cuentan agua, solución de Ringer, solución de cloruro de sodio U.S.P. e isotónica. Además, se emplean convencionalmente aceites fijos estériles como medio solvente o de suspensión. Con este fin, se puede emplear cualquier aceite fijo suave, incluso mono o diglicéridos sintéticos. Además, se usan ácidos grasos tales como ácido oleico en la preparación de inyectables.

[00207] Las formulaciones inyectables se pueden esterilizar, por ejemplo, por filtración a través de un filtro que retiene bacterias, o al incorporar agentes esterilizantes en la forma de composiciones sólidas estériles que se pueden disolver o dispersar en agua estéril u otro medio inyectable estéril antes del uso.

[00208] A fin de prolongar el efecto de un compuesto de la presente invención, a menudo es deseable frenar la absorción del compuesto por inyección subcutánea o intramuscular. Esto se puede lograr mediante el uso de una suspensión líquida de material cristalino o amorfo con escasa solubilidad en agua. La tasa de absorción del compuesto luego depende de su tasa de disolución que, a su vez, puede depender del tamaño del cristal y la forma cristalina. Alternativamente, la absorción retrasada de una forma de compuesto de administración parenteral se logra al disolver o suspender el compuesto en un vehículo oleoso. Las formas inyectables de depósito se preparan al formar matrices de microcápsulas del compuesto en polímeros biodegradables tales como poliláctido-poliglucólido. Según la relación entre el compuesto y el polímero y la naturaleza del polímero particular empleado, se puede controlar la tasa de liberación del compuesto. Los ejemplos de otros polímeros biodegradables incluyen poli(ortoésteres) y poli(anhídridos). Las formulaciones inyectables de depósito también se preparan al atrapar el compuesto en liposomas o microemulsiones compatibles con los tejidos corporales.

[00209] Las composiciones para administración rectal o vaginal de preferencia son supositorios que se pueden preparar al mezclar los compuestos de la presente invención con adecuados excipientes o portadores no irritantes tales como manteca de

cacao, polietilenglicol o una cera de supositorio que son sólidos a temperatura ambiente pero líquidos a temperatura corporal y en consecuencia se funden en el recto o la cavidad vaginal y liberan el compuesto activo.

[00210] Las formas de dosificación sólida para administración oral incluyen cápsulas, comprimidos, píldoras, polvos y gránulos. En dichas formas de dosificación sólida, el compuesto activo se mezcla con al menos un excipiente o portado inerte, farmacéuticamente aceptable tales como citrato de sodio o fosfato dicálcico y/o a) rellenos o extensores tales como almidones, lactosa, sacarosa, glucosa, manitol, y ácido silícico, b) ligadores tales como, por ejemplo, carboximetilcelulosa, alginatos, gelatina, polivinilpirrolidona, sacarosa y acacia, c) humectantes tales como glicerol, d) agentes desintegrantes tales como agar-agar, carbonato de calcio, almidón de papa o tapioca, ácido algínico, ciertos silicatos, y carbonato de sodio, e) agentes retrasantes de solución tales como parafina, f) aceleradores de la absorción tales como compuestos de amonio cuaternario, g) agentes humectantes tales como, por ejemplo, alcohol cetílico y monoestearato de glicerol, h) absorbentes tales como caolín y arcilla bentonita, y i) lubricantes tales como talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, laurilsulfato de sodio, y sus

mezclas. En el caso de cápsulas, comprimidos y píldoras, la forma de dosificación también puede comprender agentes buffer.

|00211| Las composiciones sólidas de un tipo similar también se pueden emplear como rellenos en cápsulas de gelatina con relleno blando o duro que usan excipientes tales como lactosa o azúcar de leche además polietilenglicoles de alto peso de natural y similares. Las formas de dosificación sólida de comprimidos, grageas, cápsulas, píldoras y gránulos se pueden preparar con cubiertas y vainas tales como cubiertas entéricas y otras cubiertas bien conocidas en el arte de la formulación farmacéutica. Opcionalmente pueden contener agentes opacificantes y también pueden ser una composición que libera solo el(os) ingrediente(s) activo, o de preferencia, en cierta parte del tracto intestinal, opcionalmente, en forma retardada. Los ejemplos de composiciones incluyentes que se pueden usar incluyen sustancias poliméricas y ceras. Las composiciones sólidas de tipo similar también se pueden usar como rellenos en cápsulas de gelatina blanda o dura rellenas mediante excipientes tales como lactosa o azúcar de leche además de polietilenglicoles de alto peso molecular, y similares.

|00212| Los compuestos activos también pueden estar en forma microencapsulada con uno o más excipientes, tal como se observó con anterioridad. Las formas de dosificación sólida de

comprimidos, grageas, cápsulas, píldoras y gránulos se pueden preparar con cubiertas y vainas tales como cubiertas entéricas, cubiertas de liberación controlada y otras cubiertas bien conocidas en el arte de la formulación farmacéutica. En dichas formas de dosificación sólida se puede mezclar el compuesto activo con al menos un diluyente inerte tal como sacarosa, lactosa o almidón. Dichas formas de dosificación también pueden comprender, como en la práctica normal, sustancias distintas de diluyentes inertes, por ejemplo, lubricantes de compresión y otros auxiliares de compresión tales como estearato de magnesio y celulosa microcristalina. En el caso de cápsulas, comprimidos y píldoras, las formas de dosificación también pueden comprender agentes buffer. Opcionalmente pueden contener agentes opacificantes y también pueden ser de una composición que solo libere el(os) ingrediente(s) activo(s), o de preferencia, en cierta parte del tracto intestinal, opcionalmente, en forma retardada. Los ejemplos de composiciones de inclusión que se pueden usar incluyen sustancias poliméricas y ceras.

[00213] Las formas de dosificación para administración tópica o transdérmica de un compuesto de la presente invención incluyen ungüentos, pastas, cremas, lociones, geles, polvos, soluciones, rocíos, inhalantes o parches. El componente activo se mezcla en condiciones estériles con un portador

farmacéuticamente aceptable y cualquier conservante o buffer según necesidad. También se contemplan dentro del alcance de la presente invención la formulación oftálmica, gotas óticas y gotas ópticas. Además, la presente invención contempla el uso de parches transdérmicos, que tienen la ventaja adicional de proveer la provisión controlada de un compuesto al cuerpo. Dichas formas de dosificación se pueden preparar al disolver o dispersar el compuesto en el medio adecuado. También se pueden usar mejoradotes de absorción para mejorar el flujo del compuesto a través de la piel. La velocidad se puede controlar ya sea al proveer una membrana de control de la velocidad o al dispersar el compuesto en una matriz de polímero o gel.

[00214] También se apreciará que los compuestos y las composiciones farmacéuticamente aceptables de la presente invención se puedan emplear en terapias combinadas, es decir, los compuestos y composiciones farmacéuticamente aceptables se pueden administrar de forma concurrente, antes o después de una o varias otras terapias o procedimientos médicos deseados. La combinación particular de terapias (terapéuticas o procedimientos) para emplear en un régimen combinado tendrá en cuenta la compatibilidad de las terapéuticas y/o procedimientos deseados y el efecto terapéutico deseado por conseguir. También se apreciará que las terapias empleadas puedan lograr el efecto deseado para el mismo trastorno (por

ejemplo, un compuesto de la invención se puede administrar concurrentemente con otro agente usado para tratar el mismo trastorno) o se pueden lograr diferentes efectos (por ejemplo, el control de cualquier efecto adverso). Tal como se usa en la presente, los agentes terapéuticos adicionales que se administran normalmente para tratar o prevenir una enfermedad o condición patológica particular se conocen como "apropiados para la enfermedad o condición patológica que está en tratamiento". Por ejemplo, los agentes terapéuticos de ejemplo adicionales incluyen, pero sin limitación: analgésicos no opioides (indoles tales como Etodolac, Indometacina, Sulindac, Tolmetina; naftilalcanones tales como Nabumetona; oxicams tal como Piroxicam; derivados de para-aminofenol, tal como Acetaminofeno; ácidos propiónicos tales como Fenoprofeno, Flurbiprofeno, Ibuprofeno, Cetoprofeno, Naproxeno, Naproxeno sódico, Oxaprozina; salicilatos tales como Aspirina, Colina trisalicilato de magnesio, Diflunisal; fenamatos tales como ácido meclofenámico, ácido mefenámico; y pirazoles tal como Fenilbutazona); o agonistas de opioides (narcóticos) (tales como Codeína, Fentanilo, Hidromorfona, Levorfanol, Meperidina, Metadona, Morfina, Oxicodona, Oximorfona, Propoxifeno, Buprenorfina, Butorfanol, Dezocina, Nalbufina y Pentazocina). Adicionalmente, se pueden utilizar enfoques analgésicos no farmacológicos junto con la administración de uno o varios

compuestos de la invención. Por ejemplo, también se pueden utilizar enfoques anestesiológicos (infusión intraespinal, bloqueo neural), neuroquirúrgicos (neurólisis de las vías del SNC), neuroestimulantes (estimulación nerviosa eléctrica transcutánea, estimulación de la columna dorsal), fisiáticos (terapia física, dispositivos ortóticos, diatermia) o psicológicos (métodos de hipnosis cognitiva, métodos de biorretroalimentación o de comportamiento). En general, se describen agentes o enfoques terapéuticos adicionales apropiados en The Merck Manual, Seventeenth Edition, Ed. Mark H. Beers y Robert Berkow, Merck Research Laboratories, 1999 y en la página web de la Food and Drug Administration, www.fda.gov, cuyos contenidos íntegros se incorporan en la presente por referencia.

[00215] La cantidad de agente terapéutico adicional presente en las composiciones de la presente invención no será mayor que la cantidad que normalmente se administraría en una composición que comprende ese agente terapéutico como único agente activo. De preferencia la cantidad de agente terapéutico adicional en las composiciones descritas en la presente variarán de aproximadamente 50% a 100% de la cantidad normalmente presente en una composición que comprende ese agente como único agente terapéuticamente activo.

|00216| Los compuestos de la presente invención o sus composiciones farmacéuticas también se pueden usar para recubrir un dispositivo médico implantable, tales como prótesis, válvulas artificiales, injertos vasculares, stents y catéteres. Conforme a ello, la presente invención, en otro aspecto, incluye una composición para cubrir un dispositivo implantable que comprende un compuesto de la presente invención tal como se describe en general con anterioridad y en clases y subclases de la presente y un portador apropiado para cubrir dicho dispositivo implantable. En otro aspecto más, la presente invención incluye un dispositivo implantable recubierto con una composición que comprende un compuesto de la presente invención tal como se describió en general con anterioridad y en clases y subclases de la presente y un portador apropiado para cubrir dicho dispositivo implantable. Las cubiertas adecuadas y la preparación general de dispositivos implantables adecuados se describen en las patentes de los Estados Unidos N.° 6.099.562; 5.886.026; y 5.304.121. Las cubiertas generalmente son materiales poliméricos biocompatibles tales como un polímero de hidrogel, polimetildisiloxano, policaprolactona, polietilenglicol, ácido poliláctico, acetato de etilenvinilo, y sus mezclas. Las cubiertas opcionalmente pueden estar recubiertas por una cubierta superior adecuada de fluorosilicona, polisacáridos,

polietilenglicol, fosfolípidos o sus combinaciones para impartir características de liberación controlada a la composición.

[00217] Otro aspecto de la invención se refiere a la inhibición de la actividad de NaV1.8 en una muestra biológica o un paciente, que comprende la administración al paciente o la puesta en contacto de dicha muestra biológica con un compuesto de la presente invención o una composición que comprenden dicho compuesto. El término "muestra biológica", tal como se usa en la presente, incluye, sin limitación, cultivos celulares o sus extractos; muestras de tejido u órgano o sus extractos; material de biopsia obtenido de un mamífero o sus extractos; y sangre, saliva, orina, heces, semen, lágrimas u otros fluidos corporales o sus extractos.

[00218] La inhibición de la actividad de NaV1.8 en una muestra biológica es de utilidad para una variedad de fines que son conocidos por el experto en el arte. Los ejemplos de tales fines incluyen, pero sin limitación, el estudio de canales iónicos de sodio en fenómenos biológicos y patológicos; y la evaluación comparativa de nuevos inhibidores de los canales iónicos de sodio.

[00219] A fin de que se pueda entender la invención descrita en la presente de forma más completa, se establecen los siguientes ejemplos. Se deberá entender que estos ejemplos

tienen sólo una finalidad ilustrativa y no se construyeron como limitativos de esta invención de manera alguna.

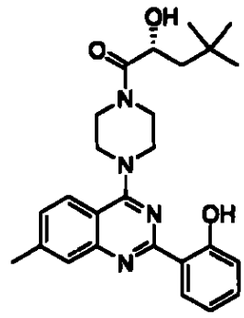
EJEMPLOS

[00220] Métodos de LC/MS generales

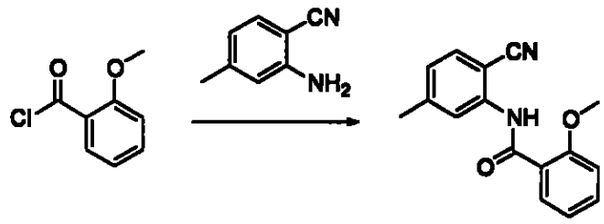
[00221] Se adquirieron datos de LC/MS con bombas PESciex API-150-EX LC/MS, Shimadzu LC-8A, automuestreador Gilson 215, módulo de inyección Gilson 819, 3,0 ml/min de velocidad de flujo, gradiente del 10-99% de CH_3CN (0,035% de TFA) / H_2O (0,05% de TFA), columna Phenomenex Luna 5u C_18 (50 x 4,60 mm), detector Shimadzu SPD-10A UV/Vis, detector Cedex 75 ELSD.

[00222] Ejemplo 101

[00223] **(R)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4,4-dimetilpentan-1-ona**



[00224] **N-(2-Ciano-5-metil-fenil)-2-metoxi-benzamida**



[00225] A una solución agitada de 4-metil-2-aminobenzonitrilo (100 g, 0,75 mol) en 800 ml de CH_2Cl_2 se añadió trietilamina (77,4 g, 0,76 mol) y dimetilaminopiridina (4,62 g, 0,037 mol). La solución se enfrió hasta 0-5 °C y se agregó cloruro de o-anisoílo (129 g, 0,75 mol) durante 1 h mientras se mantenía la temperatura de reacción a 0-5 °C. La reacción se agitó luego a 30-40 °C durante 3 h. Se agregó agua (400 ml) y la mezcla se agitó durante 15 minutos. La capa orgánica se separó y la solución acuosa se extrajo con CH_2Cl_2 (600 ml). Las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron al vacío para obtener un residuo sólido, al que se añadieron 800 ml de hexano. La suspensión se agitó y se filtró para dar *N*-(2-ciano-5-metil-fenil)-2-metoxi-benzamida en forma de un polvo amarillo (180 g, 90%). P. f. 147-149 °C. ^{1}H RMN ($CDCl_3$) δ 2,429 (s, 3H), 4,2 (s, 3H), 6,8-7,2 (m, 3H), 7,4-7,6 (m, 2H), 8,2-8,4 (d, 1H), 8,6 (s, 1H), 10,8 (bs, 1H); ^{13}C RMN ($CDCl_3$) δ 22,68, 55,7, 99, 111,27, 116,7, 120,3, 121,1, 124,15, 131,7,

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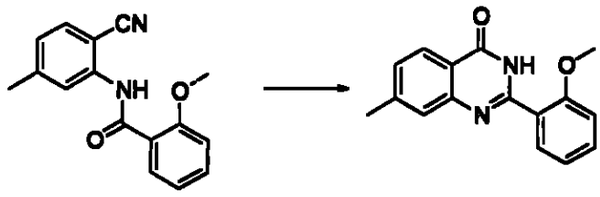
703

132,25, 133,67, 141,32, 141,1, 157,2, 163. M/z (obs., $[m+H]^+$) = 268.

[00226] **2-(2-metoxifenil)-7-metil-3*H*-quinazolin-4-ona**

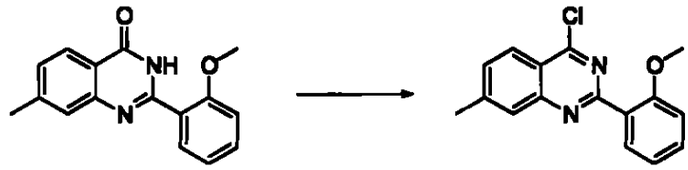
[00227]



[00228] A una suspensión agitada mecánicamente de *N*-(2-ciano-5-metilfenil)-2-metoxibenzamida (180 g, 0,67 mol) en 1,8 L de etanol bajo una atmósfera de N_2 se añadió solución de hidróxido de sodio 6 N (310 g en 1,25 L de agua). A la mezcla anterior, se añadió lentamente 30% de peróxido de hidrógeno (350 ml, 3,64 mol). La solución se calentó luego lentamente hasta 80 °C y se mantuvo a esta temperatura durante 4 h. La mezcla de reacción se concentró a presión reducida para eliminar etanol, dando una suspensión que se neutralizó con agua helada (1,8 L) y se acidificó con ácido acético hasta pH 5-6 para dar un residuo sólido. El sólido se filtró y se lavó con agua, luego se disolvió en 5,5 L de CH_2Cl_2 y se lavó con agua (2x18 L). La capa orgánica se secó sobre sulfato de sodio y el solvente se eliminó a presión reducida para dar un sólido de color amarillo claro (100 g, 54%). P.f. 165-170 °C. ^1H RMN ($CDCl_3$) δ 2,429 (s, 3H), 4,2 (s,3), 6,8-7,2 (m, 3H), 7,4-7,6

(m, 2H), 8,2-8,4 (d, 1H), 8,6 (s, 1H), 10,8 (bs, 1H); ^{13}C RMN ($CDCl_3$) [], 21,68, 55,6, 111,3, 118,2, 119,6, 121,1, 125,7, 127,14, 127,64, 130,96, 132,56, 144,9, 149,06, 150,42, 157,25, 161,52. M/z (obs., $[m+H]^+$) = 268.

[00229] **4-cloro-2-(2-metoxi-fenil)-7-metil-quinazolina**

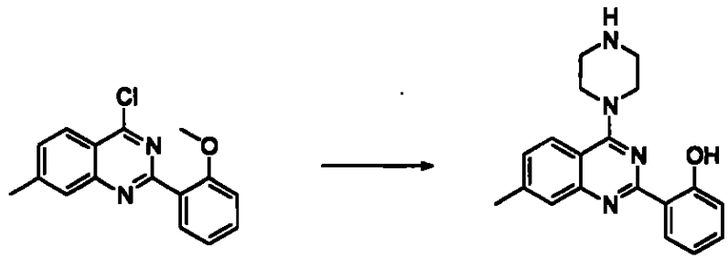


[00230]

[00231] A una suspensión agitada mecánicamente de 2-(2-metoxifenil)-7-metil-3*H*-quinazolin-4-ona (100 g, 0,37 mol) en 1 L de tolueno se añadió diisopropiletilamina (100 ml), seguido de oxicloruro de fósforo (69 g, 0,45 mol). La reacción se calentó luego hasta 80 °C durante 4 h. La mezcla de reacción se destiló a presión reducida para eliminar tolueno y el residuo resultante se disolvió en 2,2 L de CH_2Cl_2. Se añadió agua helada y el pH se ajustó a 8-9 con solución saturada acuosa de bicarbonato de sodio mientras se mantenía la temperatura a menos de 20 °C. La capa orgánica resultante se separó y la solución acuosa se extrajo con CH_2Cl_2, luego las capas orgánicas combinadas se secaron sobre sulfato de sodio y se destilaron a presión reducida. El producto crudo se disolvió 2:1 CH_2Cl_2/hexano y la solución se pasó a través de gel de sílice (2,5 kg, 60-120 de malla), seguido del lavado

del lecho de sílice con 2:1 CH_2Cl_2/hexano hasta eluir el producto. Las fracciones puras se recogieron y combinaron y el solvente se eliminó a presión reducida. Se agregó hexano (500 ml) y la mezcla se agitó y se filtró para dar 4-cloro-2-(2-metoxi-fenil)-7-metil-quinazolina as en forma de un sólido blanquecino (77 g, 72%). P. f. 161-164 °C. ^{1}H RMN ($CDCl_3$) δ 2,6 (s, 3H), 3,9 (s, 3H), 6,9-7,2 (m, 2H), 7,4-7,6 (m, 2H), 7,7-8 (d, 2H), 8,2 (d, 1H); ^{13}C RMN ($CDCl_3$) δ 22,23, 56,06, 112,2, 120,26, 120,69, 125,34, 127,94, 130,45, 131,08, 131,08. M/z (obs., $[m+H]^+$) = 285.

[00232] 2-(7-Metil-4-piperazin-1-il-quinazolin-2-il)-fenol

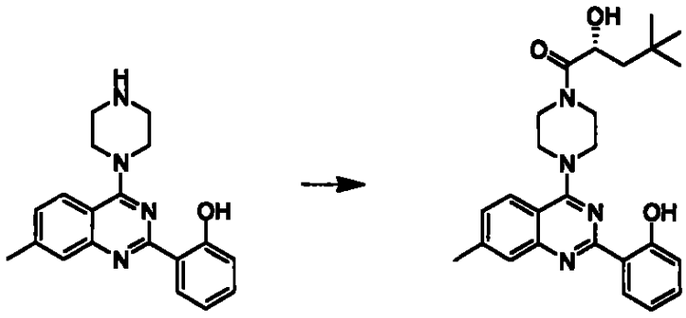


[00233]

[00234] Una solución agitada de 4-cloro-2-(2-metoxifenil)-7-metilquinazolina (91 g, 320 mmol) y CH_2Cl_2 (2,0 L) bajo una atmósfera de N_2 se enfrió hasta -30 °C. Se añadió tribromuro de boro (957 ml, 957 mmol, 1,0 M en CH_2Cl_2) gota a gota durante un período de 30 minutos a -30 / -40 °C. El baño de enfriamiento se retiró y la mezcla se dejó calentar hasta 25 °C. La mezcla se vertió cuidadosamente en una solución agitada de $NaHCO_3$

acuoso saturado (4,0 L). La porción orgánica se separó, se secó sobre $MgSO_4$ y se evaporó hasta sequedad. El sólido resultante se suspendió en CH_2Cl_2 (400 ml) bajo una atmósfera de N_2, seguido de la adición de trietilamina (64,8 g, 640 mmol). La solución se enfrió hasta -10 °C. Una solución de piperazina (55,0 g, 640 mmol) en CH_2Cl_2 (400 ml) se añadió en una única porción y la solución se agitó a temperatura ambiente durante 1 hora. La temperatura de la solución se elevó hasta 23 °C después de la adición de la piperazina. La solución se dividió en CH_2Cl_2 y H_2O. La porción orgánica se secó sobre $MgSO_4$ y se evaporó hasta sequedad. El residuo se purificó mediante cromatografía en gel de sílice usando 5% de MeOH en CH_2Cl_2 para obtener un sólido pardo. El sólido resultante se trituró con 1:1 Et_2O/hexanos para obtener un sólido amarillo que se secó al vacío para dar 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol en forma de un sólido de color amarillo claro (93,0 g, 290 mmol, 91%). LC/MS: *m/z* 321,1 $(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00235] **(*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4,4-dimetilpentan-1-ona**



[00236] Método A

[00237] Se colocó 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,16 mmol) en un tubo cargado con una barra de agitación seguido de ácido (R)-2-hidroxi-4,4-dimetilpentanoico en 1 ml de DMF y trietilamina (31,57 mg, 0,312 mmol) y la reacción se enfrió hasta 0 °C. Luego se añadió HATU (71 mg, 0,187 mmol) y la reacción se dejó bajo agitación a 0 °C durante 10 minutos y luego se dejó calentar hasta temperatura ambiente. La reacción se completó después de 40 minutos, se filtró y se purificó por HPLC en fase inversa para dar la sal de TFA de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4,4-dimetilpentan-1-ona. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,75 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00238] Método B

[00239] Se suspendió 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (250 mg, 0,74 mmol) en DMF anhidra (5 ml) y se enfrió hasta 0 °C de temperatura interna. Bajo una

atmósfera de N_2, se añadió ácido (R)-2-hidroxi-4,4-dimetilpentanoico (125,4 mg, 0,858 mmol) seguido de trietilamina (0,218 ml, 1,56 mmol). A esta solución agitada se añadió HATU (356 mg, 0,936 mmol). Después de la adición completa de HATU, la mezcla se dejó calentar hasta 10 °C. Al cabo de 45 min, la reacción se completó y se neutralizó con una porción equivalente de agua helada. Se formó un precipitado amarillo que se recogió por filtración al vacío y se disolvió en CH_2Cl_2. Esta solución se desecó con Na_2SO_4, se filtró y se concentró para dar un aceite viscoso de color amarillo-anaranjado. El material crudo se purificó mediante cromatografía en gel de sílice usando 88% de CH_2Cl_2-hexanos (1:1) y 12% de EtOAc para obtener (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4,4-dimetilpentan-1-ona en forma de una espuma de color amarillo pálido (265 mg, 76%). LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,75 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,46 (dd, *J* = 8,2, 1,8 Hz, 1H), 8,02 (d, *J* = 8,5 Hz, 1H), 7,70 (s, 1H), 7,41-7,37 (m, 2H), 6,97-6,93 (m, 2H), 4,89 (d, *J* = 7,2 Hz, 1H), 4,49-4,44 (m, 1H), 4,06-3,67 (m,8), 2,52 (s, 3H), 1,56 (dd, *J* = 14,3, 3,0 Hz, 1H), 1,42 (dd, *J* = 14,3, 8,8 Hz, 1H), 0,97 (s, 9H)

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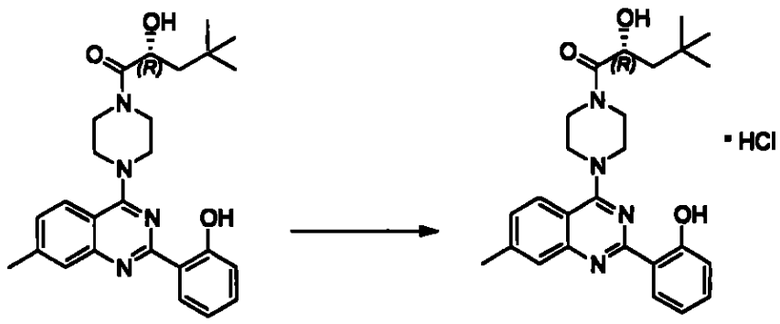
[00240] Clorhidrato de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4,4-



dimetilpentan-1-ona

[00241] Se disolvió (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4,4-dimetilpentan-1-ona (265 mg, 0,367 mmol) en CH_2Cl_2 anhidro (3 ml) seguido de la adición de Et_2O (6 ml) bajo una atmósfera de N_2. Se agregó una solución de HCl 2,0 M en Et_2O (0,296 ml, 0,591 mmol) durante un minuto. La solución de reacción cambió de una solución de color amarillo claro a una suspensión de color blanquecino cremoso. Tras la adición completa de la solución de HCl, la reacción se dejó bajo agitación durante 10 minutos adicionales. El producto se recogió por filtración al vacío, se lavó con 3 ml de Et_2O y se secó al vacío para obtener clorhidrato de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4,4-dimetilpentan-1-ona en forma de un sólido blanco (261 mg, 91%). LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,79 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,33 (d, *J* = 7,6 Hz, 1H),

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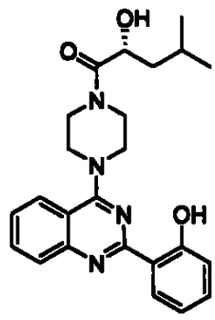
8,07 (d, J = 8,6 Hz, 1H), 7,75 (s, 1H), 7,47-7,43 (m, 2H), 7,04-6,98 (m, 2H), 4,47-4,44 (m, 1H), 4,13-4,04 (m, 4H), 3,91-3,68 (m, 4H), 2,54 (s, 3H), 1,57 (dd, J = 14,3, 3,1 Hz, 1H), 1,42 (dd, J = 14,3, 8,8 Hz, 1H), 0,97 (s, 9H).

[00242] Ejemplo 102

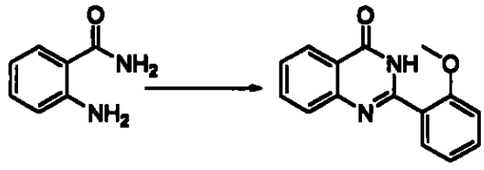
[00243] **(*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**



[00244]

[00245] **2-(2-metoxifenil)quinazolin-4(3*H*)-ona**

[00246] Método A



[00247] A una mezcla enfriada (0-5 °C) de antranilamida (350 g, 2,57 mol) y trietilamina (286 g, 2,83 mol) en THF (2,5 L) se añadió gota a gota cloruro de o-anisoílo (437 g, 2,57 mol) mientras se mantenía la temperatura entre 0-20 °C. La suspensión resultante se agitó a temperatura ambiente durante

711 706

la noche. El solvente se evaporó al vacío y el residuo se lavó varias veces con agua. El residuo húmedo se suspendió en NaOH acuoso 2 M (13 L) y la mezcla se calentó a reflujo. Al cabo de 20 minutos, se obtuvo una solución clara. Después de 1 h de reflujo, la solución límpida se enfrió en un baño de agua helada y luego se acidificó hasta pH 6 con HCl acuoso concentrado. La suspensión se filtró y el residuo se lavó minuciosamente con agua. El sólido blanco se secó por destilación azeotrópica con tolueno. Se obtuvo 2-(2-metoxifenil)quinazolin-4(3*H*)-ona (567 g) en 82%. ^{1}H-RMN (200 MHz, Me_2SO-d_6): δ 3,90 (s, 3 H), 7,20 (m, 2 H), 7,60 (t, 2 H), 7,85 (m, 3 H), 8,20 (d, 1 H), 12,20 (s, 1 H).

[00248] Método B

[00249] En un recipiente de base redonda de 2 litros y tres bocas equipado con un agitador superior y condensador de reflujo, antranilamida (20,0 g, 147 mmol) y carbonato de potasio (28,4 g, 206 mmol) se suspendieron en 1 L de éter seco y se calentó a reflujo. Se añadió cloruro de *o*-anisoílo (32,5 g, 191 mmol) lentamente a la mezcla de reflujo. Después de 3 horas a reflujo, la mezcla de reacción se dejó enfriar hasta temperatura ambiente, el éter se eliminó a presión reducida y el residuo resultante se filtró y se lavó con agua. El sólido resultante se suspendió luego en 600 ml de solución acuosa de NaOH al 5% y se hirvió durante una hora. La reacción se dejó

712 709

enfriar hasta temperatura ambiente y se neutralizó con ácido acético, tras lo cual se precipitó la 2-(2-metoxifenil)quinazolin-4(3*H*)-ona. El producto se recogió por filtración, se lavó con agua y se secó durante la noche al vacío para obtener 27 g (73%) de 2-(2-metoxifenil)quinazolin-4(3H)-ona pura. LC/MS: *m/z* 253,0 $(M+H)^+$ a 3,22 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (DMSO) δ 3,86 (s, 3H), δ 7,09 (t, 1H), δ 7,18 (d, 1H), δ 7,53 (m, 2H), δ 7,70 (m, 2H), δ 7,80 (m, 1H), δ 8,14 (d, 1H), δ 12,11 (s, 1H); ^{13}C RMN (DMSO) δ 55,75, δ 111,86, δ 120,89, δ 120,97, δ 122,74, δ 125,75, δ 126,45, δ 127,26, δ 130,41, δ 132,13, δ 134,32, δ 148,97, δ 152,48, δ 157,12, δ 161,35

[00250] 4-cloro-3,4-dihidro-2-(2-metoxifenil)quinazolina

[00251]

[00252] Una suspensión de 2-(2-metoxifenil)quinazolin-4(3*H*)-ona (567 g, 2,1 mol) en cloruro de fosforilo (2 L, 21 mol) y se llevó a reflujo una cantidad catalítica de *N,N*-dimetilanilina. La reacción se inició de inmediato con la producción de gas (HCl) tras la adición de *N,N*-dimetilanilina. Una vez terminada la producción de gas, la mezcla se enfrió

713 716

hasta temperatura ambiente. El exceso de $POCl_3$ se evaporó. La solución negra resultante se enfrió hasta temperatura ambiente y lentamente se vertió en hielo y agua, mientras se mantenía la temperatura a menos de 5 °C. La suspensión fría se extrajo con diclorometano. El extracto se secó sobre sulfato de sodio y se filtró y el solvente se eliminó al vacío. El material crudo se purificó por cromatografía en columna (gel de sílice, CH_2Cl_2). Rendimiento: 189 g (33%) de 4-cloro-3,4-dihidro-2-(2-metoxifenil)quinazolina. ^{1}H-RMN (300 MHz, Me_2SO-d_6): δ 3,85 (s, 3 H), 7,15 (t, 1 H), 7,25 (d, 1 H), 7,60 (t, 2 H), 7,70 (d, 1 H), 7,8 (d, 1 H), 7,9 (t, 1 H), 8,2 (d, 1 H).

[00253] 2-(4-cloroquinazolin-2-il)fenol

[00254]

[00255] A una solución de 4-cloro-2-(2-metoxifenil)quinazolina (1,0 g, 3,7 mmol) en 40 ml de CH_2Cl_2 a -78 °C se añadieron gota a gota 5 equivalentes de 1·M de BBr_3. Tras la adición completa, se retiró el baño de enfriamiento y la reacción se neutralizó con $NaHCO_3$ después de 90 minutos. El producto se extrajo dos veces con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de

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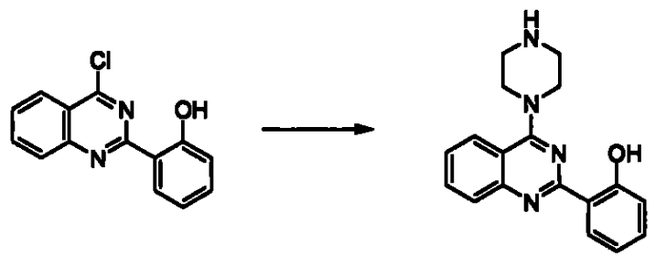
cromatografía en gel de sílice usando 60:40 CH_2Cl_2: hexanos dio 2-(4-cloroquinazolin-2-il)fenol (700 mg, 74%). LC/MS: *m/z* 257,1 $(M+H)^+$ a 3,75 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,44 (m, 1H), 8,24 (m, 3H), 7,89 (m, 1H), 7,49 (m, 1H), 7,05 (m, 2H).

[00256] **2-(4-(Piperazin-1-il)quinazolin-2-il)fenol**



[00257]

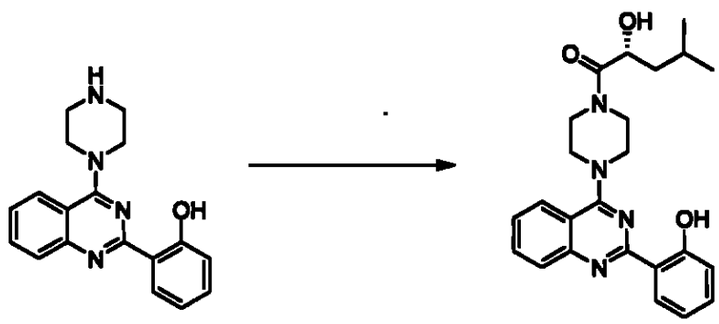
[00258] A una solución de 2-(4-cloroquinazolin-2-il)fenol (2,0 g, 7,8 mmol) en CH_2Cl_2 a 0 °C se añadió rápidamente una solución de piperazina (2,01 g, 23,4 mmol) y trietilamina (2,17 ml, 15,6 mmol) en 10 ml de CH_2Cl_2. La reacción se calentó hasta temperatura ambiente y se agitó durante 5 horas. La reacción se neutralizó con 25 ml de agua y se extrajo con (3x15) ml de CH_2Cl_2. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para obtener 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (1,98 g, 83%). LC/MS: *m/z* 307,3 $(M+H)^+$ a 1,47 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,43 (d, *J* = 10,1 Hz, 1H), 8,04 (d, *J* = 8,3 Hz, 1H), 7,85 (m, 2H), 7,53 (m, 1H), 7,38 (m,

715 716

1H), 6,95 (m, 2H), 3,85 (t, *J* = 4,8 Hz, 4H), 2,94 (t, *J* = 4,8 Hz, 4H).

[00259] (*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona

[00260]

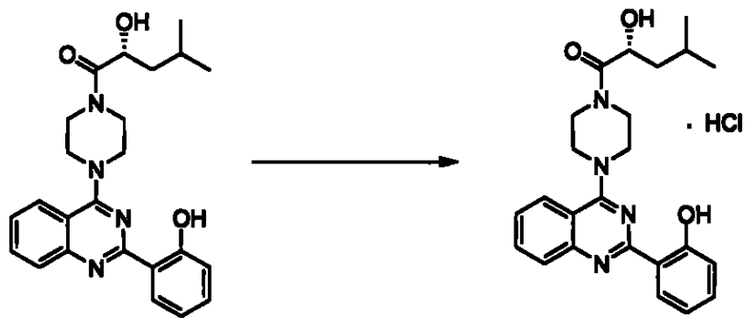


[00261] A una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (250 mg, 0,82 mmol) en CH_2Cl_2 (6 ml) se añadió trietilamina (227 µL, 1,63 mmol) seguido de la adición de ácido (R)-2-hidroxi-4-metilpentanoico (140 mg, 1,06 mmol) y HATU (403 mg, 1,06 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h y luego se neutralizó con H_2O. La capa acuosa se extrajo dos veces con CH_2Cl_2, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en 50:50 CH_2Cl_2:hexanos dio (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona (265 mg, 77%). LC/MS: *m/z* 421,30 $(M+H)^+$ a 2,57 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). H RMN (400 MHz, DMSO-d6) δ 8,47 (dd, *J* = 8,3, 1,7 Hz, 1H), 8,12 (d, *J* = 8,3 Hz, 1H) 7,88 (m, 2H), 7,57 (m, 1H), 7,40 (m, 1H), 6,96 (m,

716 779

2H), 4,92 (d, *J* = 7,2 Hz, 1H), 4,39 (m, 1H), 3,95 (m, 4H), 3,76 (m, 4H), 1,80 (m, 1H), 1,43 (m, 2H), 0,92 (q, *J* = 3,8 Hz, 6H).

[00262] Clorhidrato de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona



[00263]

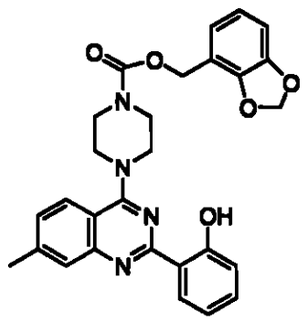
[00264] A una solución de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona (265 mg, 0,63 mmol) en CH_2Cl_2 (3 ml) bajo una atmósfera inerte se añadieron 10 ml de éter seguido de la adición gota a gota de HCl 2 M (0,315 ml, 0,63 mmol). La reacción se agitó durante 30 min antes de filtrar el precipitado formado para obtener clorhidrato de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona (261 mg, 91%). LC/MS: *m/z* 421,3 $(M+H)^+$ a 2,60 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,28 (dd, *J* = 7,9, 1,6 Hz, 1H), 8,19 (d, *J* = 8,4

717 717

Hz, 1H), 7,96 (d, *J* = 3,9 Hz, 2H), 7,65 (m, 1H), 7,48 (m, 1H), 7,04 (m, 2H), 4,37 (m, 1H), 4,10 (m, 4H), 3,80 (m, 4H), 1,77 (m, 1H), 1,41 (m, 2H), 0,91 (dd, *J* = 6,6, 3,1 Hz, 6H).

[00265] Ejemplo 103

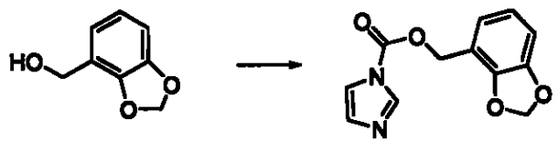
[00266] **4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo**



[00267]

[00268] **1*H*-imidazol-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo**

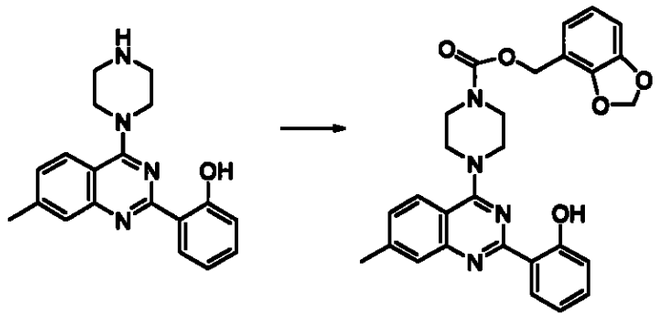
[00269]



[00270] Una solución de (benzo[d][1,3]dioxol-7-il)metanol (2 g, 13,14 mmol) y di(1*H*-imidazol-1-il)metanona (4,26 g, 26,28 mmol) en 20 ml de CH_2Cl_2 se calentó durante la noche a 50 °C. La reacción se neutralizó con agua, se extrajo con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 10-70% de EtOAc

en CH_2Cl_2 dio 1*H*-imidazol-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo (2,8 g, 86%).

[00271] 4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo

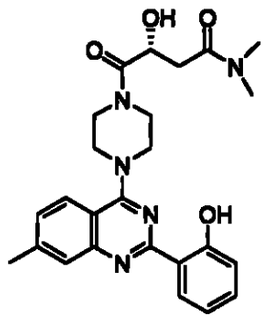


[00272]

[00273] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,16 mmol), 1H-imidazol-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo (78 mg, 0,32 mmol) y trietilamina (44,6 µL, 0,32 mmol) en DMSO (500 µL) se calentó en un sintetizador a microondas a 200 °C durante 10 minutos. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 499,3 $(M+H)^+$ a 2,97 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

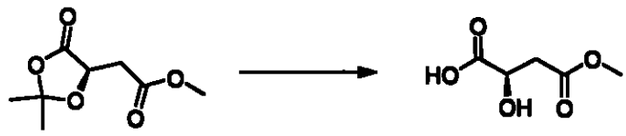
[00274] Ejemplo 104

|00275| **(*R*)-3-Hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-N,N-dimetil-4-oxobutanamida**



|00276|

|00277| **Ácido (*R*)-3-(metoxicarbonil)-2-hidroxipropanoico**



|00278|

|00279| Se agitó 2-((*R*)-2,2-dimetil-5-oxo-1,3-dioxolan-4-il)acetato de metilo (17,1 g, 90,9 mmol) en una mezcla 1:1 de THF:HCl 1 M (200 ml) durante 1 h a temperatura ambiente. Después de la adición de NaCl a la capa acuosa prácticamente saturada, la mezcla se extrajo con EtOAc y los extractos se secaron sobre Na_2SO_4 y se concentró para obtener ácido (*R*)-3-(metoxicarbonil)-2-hidroxipropanoico en forma de un aceite. ^1H RMN (400 MHz, $CDCl_3$) δ 4,58-4,55 (m, 1H), 3,75 (s, 3H), 2,98-2,84 (m, 2H).

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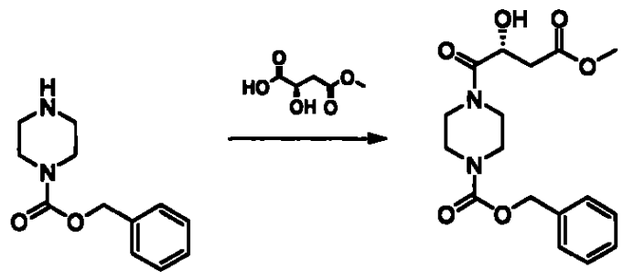
[00280] Éster bencílico del ácido 4-((*R*)-2-hidroxi-3-metoxicarbonil-propionil)-piperazin-1-carboxílico



[00281]

[00282] Se añadió EDCI (3,6 g, 19 mmol) a una solución de ácido (*R*)-3-(metoxicarbonil)-2-hidroxipropanoico (2,8 g, 19 mmol) y HOBt (2,6 g, 19 mmol) en DMF (200 ml). Tras agitar esta mezcla durante 5 min, se agregaron piperazin-1-carboxilato de bencilo (4,2 g, 3,6 ml, 19 mmol) y trietilamina (2,6 ml, 19 mmol) y se agitó durante 3 días a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con EtOAc. Después de lavar las capas orgánicas con salmuera y agua, secar sobre Na_2SO_4 y concentrar, la purificación por medio de cromatografía en gel de sílice usando 0-10% de $MeOH/CH_2Cl_2$ dio éster bencílico del ácido 4-((R)-2-hidroxi-3-metoxicarbonil-propionil)-piperazin-1-carboxílico en forma de un aceite (2,19 g, 33%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,40-7,31 (m, 5H), 5,15 (s, 2H), 4,79-4,74 (m, 1H), 3,95 (d, J = 8,0 Hz, 1H), 3,79-3,74 (m, 1H), 3,74 (s, 3H), 3,71-3,44 (m, 7H), 2,62 (d, J = 5,8 Hz, 2H).

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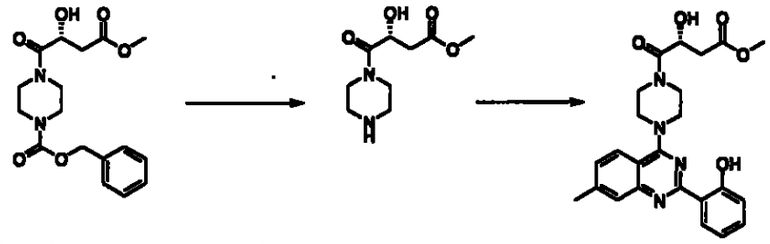
[00283] 3-hidroxi-4-(4-(2-(2-hidroxifenil)-7-

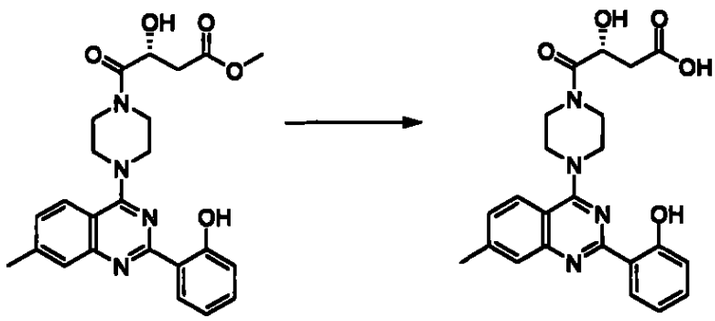


metilquinazolin-4-il)piperazin-1-il)-4-oxobutanoato de (*R*)-metilo

[00284] Se agitaron éster bencílico del ácido 4-((*R*)-2-hidroxi-3-metoxicarbonil-propionil)-piperazin-1-carboxílico (0,52 g, 1,5 mmol) y MeOH (15 ml) con Pd/C al 10% bajo una atmósfera de H_2 a presión ambiente durante la noche. Tras filtrar y evaporar el solvente, el residuo se extrajo en CH_2Cl_2 y se agregaron 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,40 g, 1,50 mmol) más trietilamina (0,41 ml, 3,00 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, se lavó con agua, se secó sobre Na_2SO_4 y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de MeOH/CH_2Cl_2 dio 3-hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-oxobutanoato de (*R*)-metilo (0,38 g, 57%). LC/MS: *m/z* 451,1 $(M+H)^+$ a 2,18 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

722 716

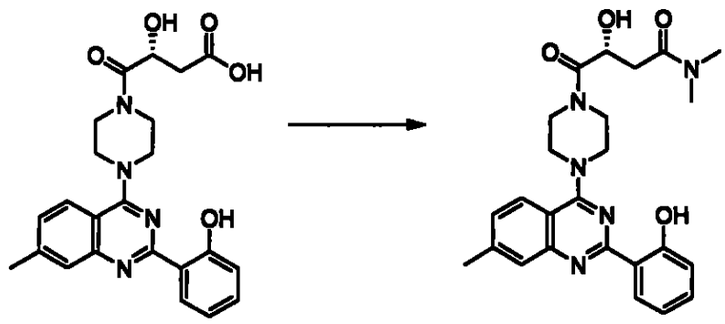
[00285] **Ácido (*R*)-3-hidroxi-4-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-oxo-butírico**



[00286]

[00287] Se añadió $LiOH \cdot H_2O$ (19,8 mg, 0,47 mmol) a una solución de éster metílico del ácido (R)-3-hidroxi-4-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-oxo-butírico (71 mg, 0,16 mmol) en 2 ml THF:H_2O (1:1) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se acidificó con HCl 1 M y luego se extrajo con EtOAc. Tras secar la capa orgánica sobre Na_2SO_4, se concentró y luego se purificó por cromatografía en gel de sílice usando 0-15% de MeOH/CH_2Cl_2 para proveer ácido (*R*)-3-hidroxi-4-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-oxo-butírico (52 mg, 75%). LC/MS: *m/z* 437,3 $(M+H)^+$ a 2,04 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00288] **(*R*)-3-Hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-*N*,*N*-dimetil-4-oxobutanamida**

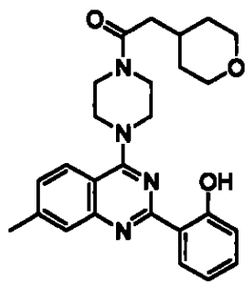


[00289]

[00290] Se agitaron ácido (*R*)-3-hidroxi-4-{4-[2-(2-hidroxifenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-oxo-butírico (17 mg, 0,039 mmol) y HATU (16 mg, 0,043 mmol) en DMF (0,5 ml). Tras añadir dimetilamina (2 M en THF, 0,10 ml, 0,19 mmol), la mezcla de reacción se agitó a temperatura ambiente durante 5 h. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-3-hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-N,N-dimetil-4-oxobutanamida en forma de la sal de TFA. LC/MS: *m/z* 436,3 $(M+H)^+$ a 1,94 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00291] Ejemplo 105

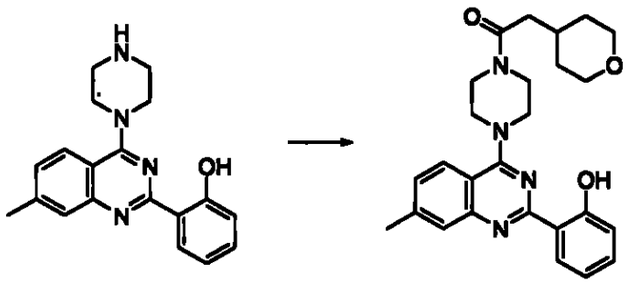
[00292] **(2-(tetrahidro-2*H*-piran-4-il)-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona**



[00293]

[00294] **(2-(tetrahidro-2*H*-piran-4-il)-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona**

[00295]



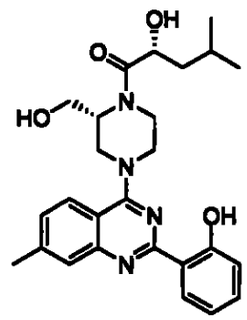
[00296] A una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (30 mg, 0,09 mmol) en DMF (1 ml) se añadió ácido 2-(tetrahidro-2*H*-piran-4-il)acético (13,5 mg, 0,09 mmol) seguido de la adición de trietilamina (25 µL), luego HATU (44 mg) a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (2-(tetrahidro-2*H*-piran-4-il)-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona en forma de la sal

de TFA. LC/MS: *m/z* 447,10 $(M+H)^+$ a 2,32 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

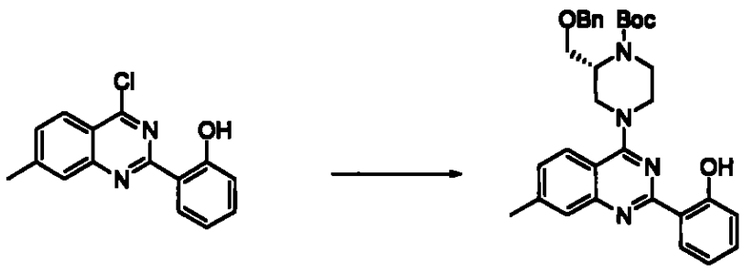
[00297] Ejemplo 106

[00298] **(R)-2-Hidroxi-1-((R)-2-(hidroximetil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**

[00299]



[00300] **2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (R)-ter-butilo**



[00301]

[00302] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)fenol (450 mg, 1,66 mmol) en 10 ml de DMF se añadió una solución de 2-((benciloxi)metil)piperazin-1-carboxilato de (*R*)-*ter*-butilo (610 mg, 1,99 mmol) en DMF y trietilamina (0,46 ml). La mezcla de reacción se calentó luego a reflujo a 85 °C

durante 30 minutos, se neutralizó con agua, se extrajo dos veces con CH_2Cl_2, se secó sobre Na_2SO_4 y se concentró para dar 2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (*R*)-ter-butilo (760 mg, 85%). Este material se usó en la siguiente etapa sin ulterior purificación. LC/MS: *m/z* 541,5 $(M+H)^+$ a 3,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00303] 2-(4-((*R*)-3-((benciloxi)metil)piperazin-1-il)-7-metilquinazolin-2-il)fenol

[00304]

[00305] A una solución de 2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (R)-ter-butilo (760 mg, 1,72 mmol) en 15 ml de CH_2Cl_2 se añadió 10 ml de TFA. La reacción se agitó durante 1 hora. TFA se eliminó al vacío y la reacción se neutralizó usando una solución 1 M de NaOH. La capa acuosa se extrajo dos veces con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró para obtener 2-(4-((*R*)-3-((benciloxi)metil)piperazin-1-il)-7-metilquinazolin-2-il)fenol (570 mg, 92%). Este material se usó

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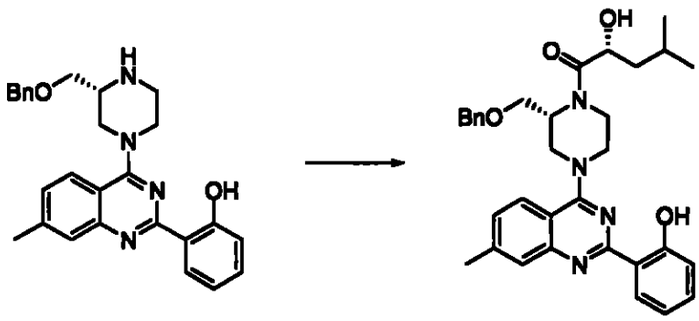
en la siguiente etapa sin ulterior purificación. LC/MS: *m/z* 441,5 $(M+H)^+$ a 2,44 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00306] (*R*)-1-((*R*)-2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona

[00307]



[00308] A una solución de 2-(4-((*R*)-3-((benciloxi)metil)piperazin-1-il)-7-metilquinazolin-2-il)fenol (100 mg, 0,22 mmol) en DMF (1 ml) se añadió ácido (R)-2-hidroxi-4-metilpentanoico (30 mg, 0,22 mmol) seguido de la adición de trietilamina (61 µL), luego HATU (109 mg) a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-1-((*R*)-2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 555,7 $(M+H)^+$ a 3,13 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

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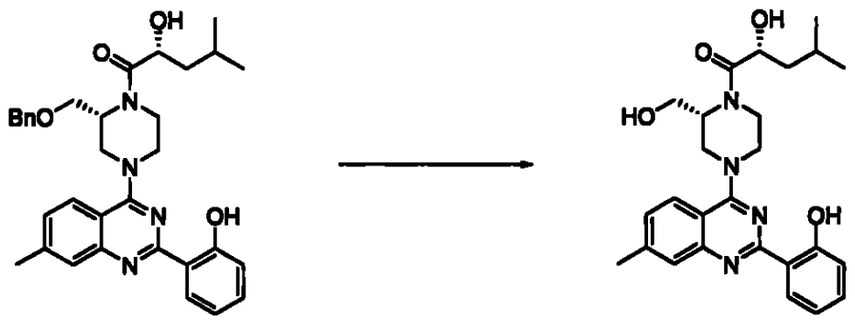
[00309] **(*R*)-2-Hidroxi-1-((*R*)-2-(hidroximetil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-**



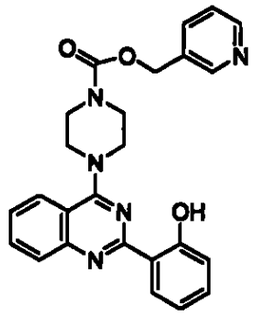
metilpentan-1-ona

[00310]

[00311] A una solución de trifluoroacetato de (*R*)-1-((*R*)-2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (29,6 mg, 0,053 mmol) en etanol se añadió $Pd(OH)_2$ (188 mg) y la reacción se calentó a 50 °C bajo una atmósfera de H_2 a presión ambiente. La reacción se filtró y la purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-2-hidroxi-1-((*R*)-2-(hidroximetil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 465,50 $(M+H)^+$ a 2,47 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00312] Ejemplo 107

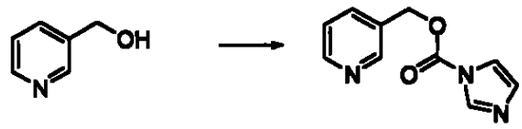
[00313] **4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (piridin-3-il)metilo**



[00314]

[00315] **1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo**

[00316]

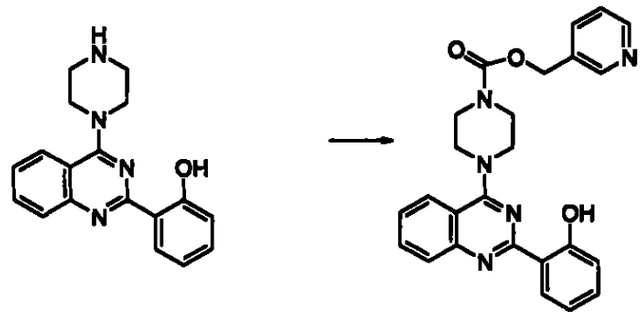


[00317] Una solución de (piridin-3-il)metanol (2 g, 18,32 mmol) y di(1*H*-imidazol-1-il)metanona (5,94 g, 36,65 mmol) en 20 ml de CH_2Cl_2 se calentó durante la noche a 50 °C. La reacción se neutralizó con agua, se extrajo dos veces con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 10-70% de EtOAc en CH_2Cl_2 dio 1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo (3,1 g, 84%). LC/MS: *m/z* 204,1 $(M+H)^+$ a 0,39 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, $CDCl_3$) δ 8,74 (d, *J* = 1,9 Hz, 1H), 8,68 (dd, *J* = 4,8,

730 727

1,4 Hz, 1H), 8,16 (s, 1H), 7,81 (m, 1H), 7,44 (s, 1H), 7,38 (m, 1H), 7,09 (s, 1H), 5,46 (s, 2H).

[00318] 4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (piridin-3-il)metilo

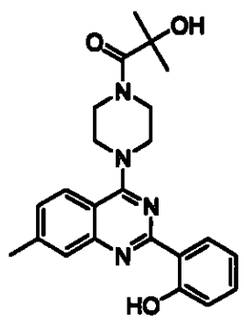


[00319]

[00320] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,16 mmol), 1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo (67 mg, 0,32 mmol) y trietilamina (44,6 µL, 0,32 mmol) en DMSO (500 µL) se calentó en un sintetizador a microondas a 200 °C durante 10 minutos. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (piridin-3-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 442,50 $(M+H)^+$ a 1,97 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00321] Ejemplo 108

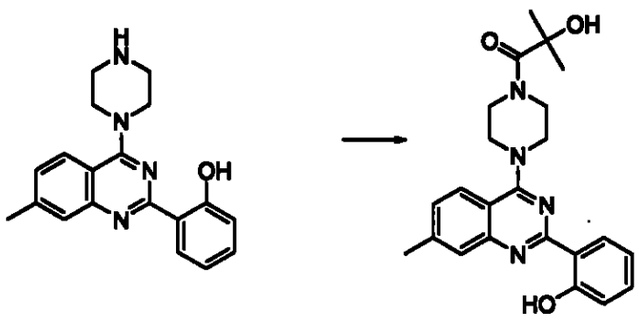
[00322] 2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-metilpropan-1-ona



[00323]

[00324] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-metilpropan-1-ona**

[00325]

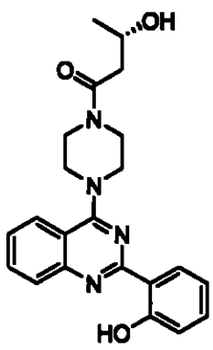


[00326] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,22 mmol) en DMF (0,5 ml) se añadió a ácido 2-hidroxi-2-metilpropanoico (29,6 mg, 0,284 mmol). Le siguió la adición de trietilamina (61 µL), luego una solución de HATU (108 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-

metilpropan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 407,50 $(M+H)^+$ a 2,21 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

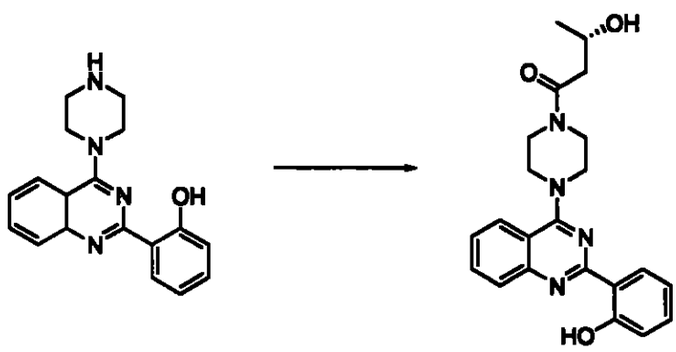
[00327] Ejemplo 109

[00328] **(*S*)-3-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona**



[00329]

[00330] **(*S*)-3-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona**



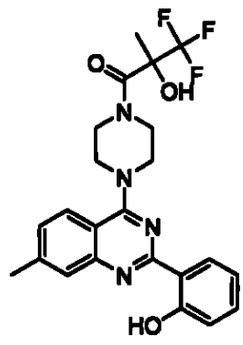
[00331]

[00332] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió a ácido (*S*)-3-hidroxibutanoico (31,0 mg, 0,297 mmol). Le siguió la adición de trietilamina (63 µL), luego una solución de HATU (113 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*S*)-3-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 393,1 $(M+H)^+$ a 2,04 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00333] Ejemplo 110

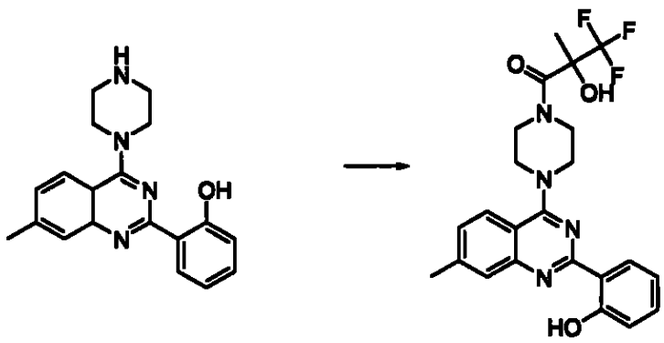
[00334] **2-(Trifluorometil)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona**

[00335]



734 731

[00336] **2-(Trifluorometil)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona**



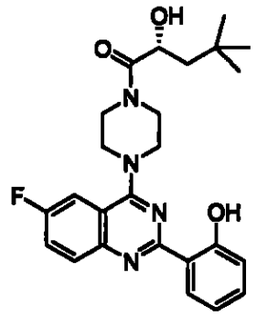
[00337]

[00338] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,22 mmol) en DMF (0,5 ml) se añadió a ácido 2-(trifluorometil)-2-hidroxipropanoico (45 mg, 0,284 mmol). Le siguió la adición de trietilamina (61 µL), luego una solución de HATU (108 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-(trifluorometil)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 461,1 $(M+H)^+$ a 2,56 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00339] Ejemplo 111

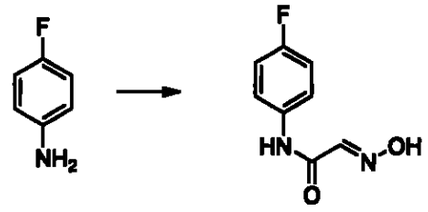
735 732

[00340] **(*R*)-1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona**



[00341]

[00342] **(*E*)-*N*-(4-Fluorofenil)-2-(hidroxiimino)acetamida**

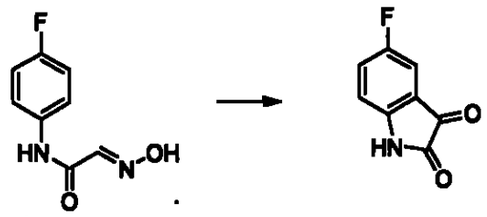


[00343]

[00344] 4-Fluoroanilina (58,2 g, 0,50 mol) se añadió lentamente a una solución acuosa al 10% de HCl. Esta suspensión se añadió a una mezcla de hidrato de cloral (95 g, 0,55 mol) y sulfato de sodio (0,5 kg) en 750 ml de agua con agitación mecánica. Se añadió clorhidrato de hidroxilamina (116 g, 1,63 mol) disuelto en agua (250 ml) y la suspensión resultante se calentó a 100 °C. Después de alcanzar esta temperatura, se retiró la manta de calentamiento de inmediato y la solución se enfrió hasta temperatura ambiente. El precipitado formado se recogió por filtración, se lavó con

agua (2x300 ml) y se secó en un horno de vacío a 60 °C. Rendimiento: 78,2 g de *N*-(4-fluorofenil)-2-hidroxiiminoacetamida en forma de un sólido blanquecino.

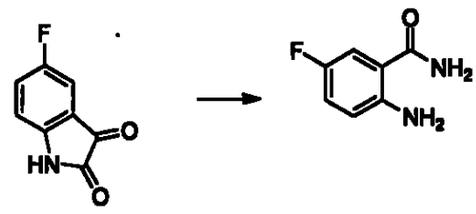
[00345] 5-Fluoroindolin-2,3-diona



[00346]

[00347] Ácido sulfúrico concentrado (200 ml) se calentó a 50 °C y *N*-(4-fluorofenil)-2-hidroxiiminoacetamida se añadió lentamente. La solución negra se calentó cuidadosamente a 90 °C. A esta temperatura, fue necesario un ligero enfriamiento para mantener la temperatura a 90 °C. Cuando no se produjo más calor, la mezcla de reacción se calentó a 90 °C durante media hora más. La solución de color rojo oscuro se enfrió hasta temperatura ambiente y se vertió en 3 L de agua helada y 1 L de acetato de etilo con agitación vigorosa. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo (1x1 L, 1x0,5 L). Los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se evaporaron hasta sequedad. Rendimiento: 35,3 g (52%) de un sólido de color rojo oscuro, 5-fluoro-1*H*-indol-2,3-diona.

[00348] 2-Amino-5-fluorobenzamida



[00349]

[00350] 5-Fluoro-1*H*-indol-2,3-diona (35,3 g, 213 mmol) se calentó en ácido acético (300 ml), 1 ml de ácido sulfúrico concentrado y 22 ml de peróxido de hidrógeno acuoso al 35% a 70 °C. La solución se mantuvo a esa temperatura una hora y media durante lo cual se formó un sólido en la mezcla de reacción. Tras enfriar hasta temperatura ambiente, este sólido se recogió por filtración y se lavó tres veces con agua. El sólido húmedo se suspendió en 150 ml de agua y se añadieron 40 ml de una solución acuosa al 25% de amoníaco. Esta mezcla se agitó a temperatura ambiente 3 días. El sólido formado se recogió por filtración y se lavó dos veces con agua. El sólido se secó por destilación azeotrópica con tolueno (3 x 100 ml) para obtener 2-amino-5-fluorobenzamida (9,5 g). Los filtrados combinados se extrajeron con acetato de etilo (2x100 ml). Los extractos combinados se secaron sobre sulfato de sodio, se filtraron y se evaporaron hasta sequedad para obtener 2-amino-5-fluorobenzamida (3,5 g) en forma de un sólido blanquecino. Ambas fracciones se combinaron para usar en la siguiente etapa de reacción.

[00351] **6-Fluoro-2-(2-metoxifenil)-3*H*-quinazolin-4-ona**

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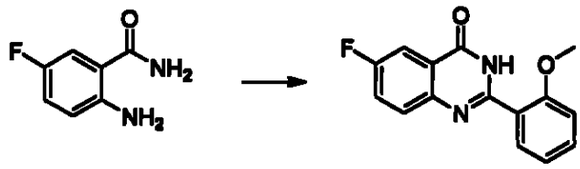

[00352]

[00353] Se añadió cloruro de *o*-anisoílo (15,7 g, 92 mmol) gota a gota a una solución de aminobenzamida 2-amino-5-fluorobenzamida (13,0 g, 84 mmol) y trietilamina (16 ml, 110 mmol) en tetrahidrofurano (100 ml) enfriada en un baño de hielo. Inmediatamente se empezó a formar un precipitado. La agitación de la solución se continuó durante 5 horas a temperatura ambiente. El precipitado formado se recogió por filtración y se lavó dos veces con éter dietílico y se secó a 50 °C al vacío. El sólido seco se suspendió en solución acuosa 2 N de hidróxido de sodio (250 ml) y se calentó a reflujo hasta obtener una solución límpida (3 horas). La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró. El filtrado se acidificó hasta pH<1 con HCl acuoso concentrado. El precipitado formado se recogió por filtración y se lavó dos veces con agua, dos veces con metanol y dos veces con éter dietílico. El sólido se secó en un horno a 45 °C para obtener 6-fluoro-2-(2-metoxifenil)-3*H*-quinazolin-4-ona (18,2 g, 80%) en forma de un sólido blanco.

[00354] **4-cloro-6-fluoro-2-(2-metoxifenil)quinazolina**

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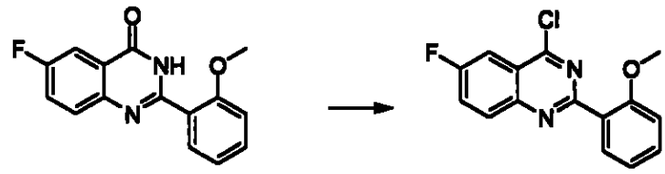


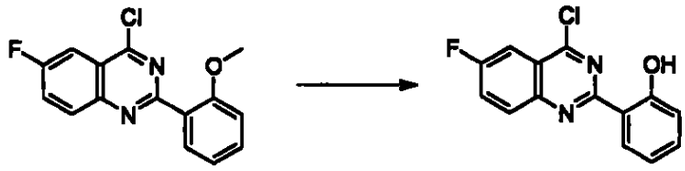
[00355] Una suspensión de 6-fluoro-2-(2-metoxifenil)-3*H*-quinazolin-4-ona (14,0 g, 52 mmol), *N*,*N*-dimetilanilina (6,6 ml, 52 mmol) y oxicloruro de fósforo (4,8 ml, 52 mmol) en benceno (100 ml) se calentó a reflujo hasta obtener una solución clara, oscura (1 hora). La mezcla de reacción se enfrió hasta temperatura ambiente y el volumen se redujo a presión reducida. El residuo oleoso negro se vertió en 300 g de hielo. Se añadió diclorometano (600 ml) con agitación vigorosa y la temperatura se mantuvo a menos de 5 °C en todos los momentos. El pH se controló y se añadió hidróxido de sodio acuoso 1 N se añadió hasta que el pH fuera de 10-11. La mezcla se agitó durante una hora a una temperatura inferior a 5 °C y el pH se mantuvo entre 10-11 por adición de hidróxido de sodio acuoso 1 N. Las capas se separaron y la capa orgánica se lavó con hidróxido de sodio acuoso 1 N helado (2x200 ml). Los heptanos (300 ml) se añadieron a la capa orgánica. Esta mezcla se filtró a través de un tapón corto de gel de sílice y se eluyó con diclorometano/heptanos (2:1). Todas las fracciones que contienen producto se combinaron y se evaporaron hasta sequedad. El residuo se trituró con heptanos para obtener 4-

740 734

cloro-6-fluoro-2-(2-metoxifenil)-quinazolina (11,5 g, 76%) en forma de un sólido blanco.

[00356] **2-(4-cloro-6-fluoroquinazolin-2-il)fenol**

[00357]



[00358] Una solución de 4-cloro-6-fluoro-2-(2-metoxifenil)quinazolina (3,0 g, 10,3 mmol) en CH_2Cl_2 (15 ml) se enfrió hasta -78 °C. Luego, se añadió BBr_3 1 M (51,95 ml, 59,95 mmol) gota a gota. La reacción se calentó hasta temperatura ambiente y se neutralizó con $NaHCO_3$ y se extrajo dos veces con CH_2Cl_2. La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 5-20% de CH_2Cl_2 en hexanos dio 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (1,61 g, 57%). LC/MS: *m/z* 275,1 $(M+H)^+$ a 3,8 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00359] **2-(6-Fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol**

[00360]

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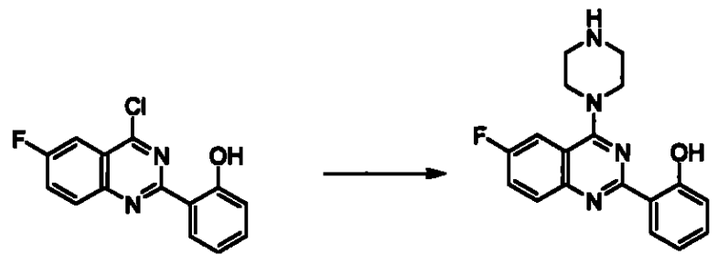

[00361] A una solución agitada de 2-(6-fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (500 mg, 1,82 mmol) en CH_2Cl_2 (20 ml) a 0 °C, bajo una atmósfera de N_2 se añadió rápidamente una solución de piperazina (0,263 g, 7,28 mmol) y trietilamina (0,35 ml, 2,55 mmol) en CH_2Cl_2. La mezcla se agitó durante 1 h y luego se neutralizó con H_2O, se extrajo dos veces con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-5% de MeOH en CH_2Cl_2 dio 2-(6-fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (400 mg, 68%). LC/MS: *m/z* 325,5 $(M+H)^+$ a 2,12 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,42 (m, 1H), 7,97 (m, 1H), 7,78 (m, 2H), 7,39 (m, 1H), 6,95 (m, 2H), 3,83 (t, *J* = 4,9 Hz, 4H), 2,92 (t, *J* = 4,9 Hz, 4H).

[00362] (R)-1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona

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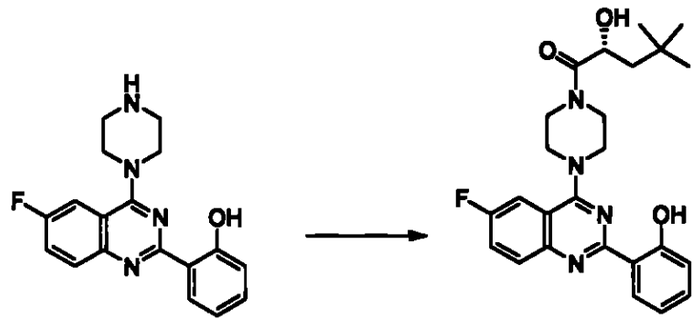


[00363]

[00364] Método A

[00365] A una solución de 2-(6-fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (25 mg, 0,08 mmol) en DMF (1 ml) se añadió ácido (R)-2-hidroxi-4,4-dimetilpentanoico (20,28 mg, 0,14 mmol) seguido de la adición de trietilamina (25 µL), luego HATU (44 mg) a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))-H_2O) dio (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 453,52 $(M+H)^+$ a 3,21 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

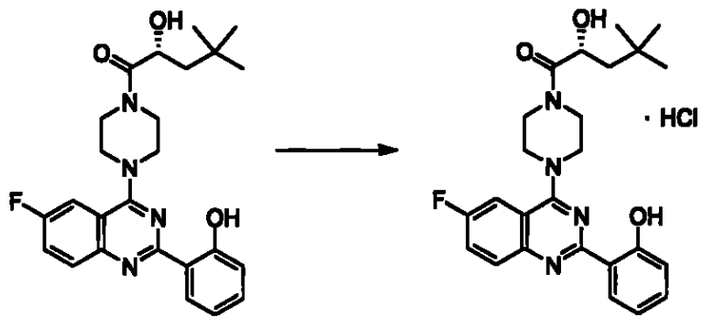
[00366] Método B

[00367] A una solución de 2-(6-fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (200 mg, 0,61 mmol) en CH_2Cl_2 (5 ml) se añadió trietilamina (170 µL, 1,22 mmol) seguido de la adición de ácido (R)-2-hidroxi-4,4-dimetilpentanoico (116 mg, 0,79 mmol), luego HATU (301 mg, 0,79 mmol). Se añadieron 3 ml

743 746

adicionales de CH_2Cl_2 y la reacción se agitó durante 3 h. Después de neutralizar con agua, la mezcla se extrajo dos veces con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en 50:50 CH_2Cl_2:hexanos dio como resultado (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona (240 mg, 86%). *m/z*: M+1 *obs* = 453,5; t_R = 3,19 minutos ^1H RMN (400 MHz, DMSO-d6) δ 8,46 (m, 1H), 8,01 (m, 1H), 7,84 (m, 2H), 7,40 (m, 1H), 6,96 (m, 2H), 4,89 (d, *J* = 7,1 Hz, 1H), 4,45 (m, 1H), 3,97 (m, 4H), 3,76 (m, 4H), 1,56 (m, 1H), 1,42 (m, 1H), 0,97 (s, 9H).

[00368] Clorhidrato de (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona



[00369]

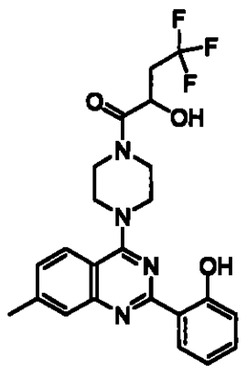
[00370] A una solución de (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona (230 mg, 0,51 mmol) en CH_2Cl_2 (3 ml) bajo una atmósfera inerte se añadió gota a gota una solución 2 M de

744 741

HCl en éter (2,55 ml, 0,51 mmol). A ello se añadió luego éter (15 ml) que resultó en la formación de un precipitado que se dejó bajo agitación durante una hora. El producto se recogió por filtración al vacío y se secó para obtener clorhidrato de (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona (230 mg, 92%). LCMS: *m/z* 453,5 $(M+H)^+$ a 3,19 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,40 (dd, *J* = 7,8, 1,4 Hz, 1H), 8,04 (m, 1H), 7,88 (m, 2H), 7,43 (m, 1H), 6,99 (m, 2H), 4,45 (dd, *J* = 8,8, 3,0 Hz, 1H), 4,02 (m, 4H), 3,79 (m, 4H), 1,56 (m, 1H), 1,42 (m, 1H), 0,97 (s, 9H).

[00371] Ejemplo 112

[00372] **4,4,4-Trifluoro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona**



[00373]

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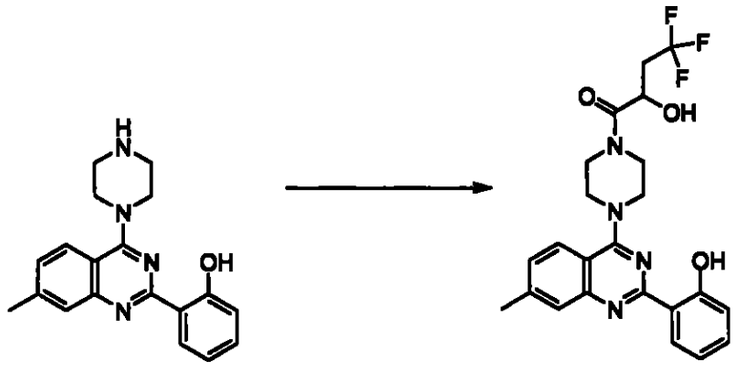
[00374] **4,4,4-Trifluoro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona**



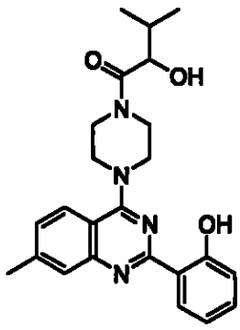
[00375]

[00376] 2-(7-Metil-4-(piperazin-1-il)quinazolin-2-il)fenol (87 mg, 0,27 mmol), ácido 4,4,4-trifluoro-2-hidroxibutanoico (43 mg, 0,27 mmol), HATU (0,12 g, 0,33 mmol) y trietilamina (45 µL, 0,33 mmol) se agitaron en DMF (3 ml) a temperatura ambiente durante la noche. La mezcla se diluyó con agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera y agua, se secó sobre Na_2SO_4 y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-20% de EtOAc en 1:1 CH_2Cl_2: hexanos dio 4,4,4-trifluoro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona as un sólido blanquecino (86 mg, 66%). ^1H RMN (400 MHz, $CDCl_3$) δ 8,46 (dd, *J* = 8,0, 1,7 Hz, 1H), 7,77 (d, *J* = 8,5 Hz, 1H), 7,70 (s, 1H), 7,41-7,37 (m, 1H), 7,31 (dd, *J* = 8,5, 1,5 Hz, 1H), 7,05-7,03

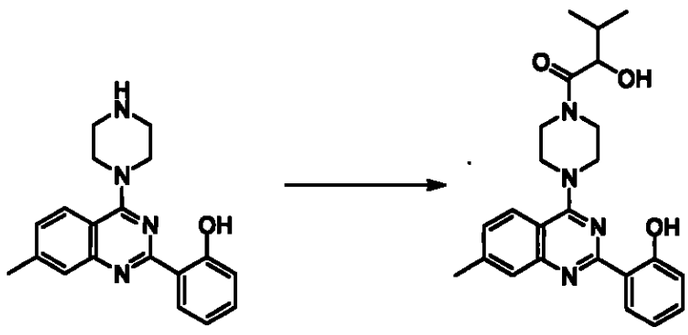
(m, 1H), 6,97-6,93 (m, 1H), 4,80-4,75 (m, 1H), 4,07-3,68 (m, 9H), 2,56 (s, 3H), 2,50-2,39 (m, 2H); LC/MS: *m/z* 461,3 $(M+H)^+$ a 2,49 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00377] Ejemplo 113

[00378] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilbutan-1-ona**

[00379] 

[00380] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilbutan-1-ona**

[00381] 

[00382] Método A

[00383] En una atmósfera de N_2, se agitó una mezcla de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (25 mg, 0,08 mmol), ácido 2-hidroxi-3-metilbutanoico (9 mg, 0,08 mmol), BOP (35 mg, 0,08 mmol), trietilamina (22 µL, 0,16 mmol) y DMF (0,2

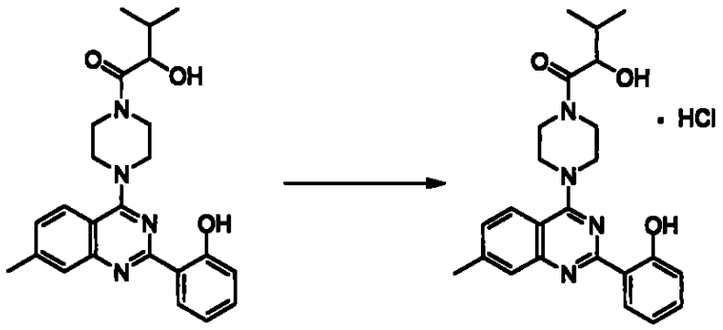
ml) a temperatura ambiente durante 1 hora. La mezcla de reacción se purificó luego por HPLC preparativa en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilbutan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 421,10 $(M+H)^+$ a 2,76 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00384] Método B

[00385] A una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (250 mg, 0,78 mmol) en CH_2Cl_2 (6 ml) se añadió trietilamina (217 µL, 1,56 mmol) seguido de la adición de ácido 2-hidroxi-3-metilbutanoico (120 mg, 1,0 mmol) y HATU (380 mg, 1,00 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h y luego se neutralizó con H_2O. La capa acuosa se extrajo con CH_2Cl_2, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en 50:50 CH_2Cl_2:hexanos dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilbutan-1-ona (230 mg, 70%). LC/MS: *m/z* 421,3 $(M+H)^+$ a 2,43 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,45 (m, 1H), 8,01 (d, *J* = 8,5 Hz, 1H), 7,70 (s, 1H), 7,39 (m, 2H), 6,95 (m, 2H), 4,79 (d, *J* = 7,2 Hz, 1H), 4,11 (dd, *J* =

7,0, 5,9 Hz, 1H), 3,87 (m, 8H), 2,52 (s, 3H), 1,91 (m, 1H), 0,88 (dd, *J* = 22,8, 6,7 Hz, 6H).

[00386] Clorhidrato de 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilbutan-1-ona



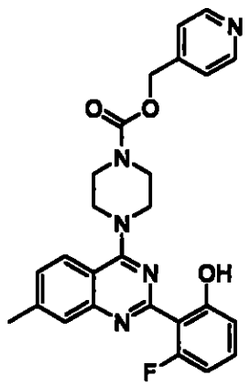
[00387]

[00388] A una solución de 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilbutan-1-ona (230 mg, 0,54 mmol) en CH_2Cl_2 (3 ml) bajo una atmósfera inerte se añadió éter (12 ml) seguido de la adición gota a gota de solución de HCl 2 M en éter (0,27 ml, 0,54 mmol) que dio como resultado la formación de un precipitado que se agitó durante una hora y luego se recogió por filtración al vacío y se secó para obtener clorhidrato de 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilbutan-1-ona (205 mg, 83%). LC/MS: *m/z* 421,3 $(M+H)^+$ a 2,48 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,25 (d, *J* = 7,9 Hz, 1H), 8,08 (d, *J* = 8,5 Hz, 1H), 7,74 (s, 1H), 7,48

(t, J = 6,6 Hz, 2H), 7,04 (m, 2H), 4,10 (m, 5H), 3,79 (m, 4H), 2,53 (s, 3H), 1,90 (m, 1H), 0,87 (dd, J = 16,3, 6,7 Hz, 6H)

[00389] Ejemplo 114

[00390] **4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo**

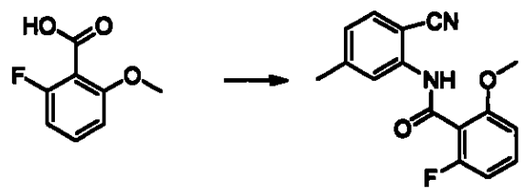


[00391]

[00392]

[00393] ***N*-(2-Ciano-5-metil-fenil)-2-fluoro-6-metoxi-benzamida**

[00394]



[00395] Se añadió ácido 6-fluoro-2-anisoico (110 g, 0,70 mol) en porciones durante 15 minutos a una mezcla de cloruro de tionilo (230 ml, 3,2 mol), tolueno (200 ml) y DMF (1 ml).

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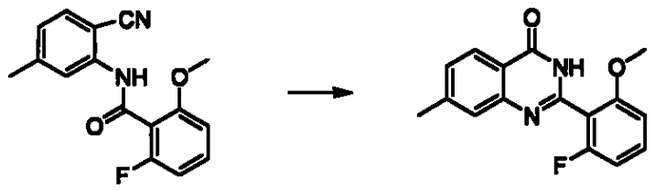
La mezcla resultante se agitó durante la noche a temperatura ambiente. La solución se evaporó hasta sequedad y se añadió gota a gota a una solución enfriada en baño de hielo de antranilonitrilo (92,5 g, 0,70 mol) en piridina (200 ml). El embudo de goteo se enjuagó con una cantidad mínima de acetonitrilo. La mezcla resultante se agitó durante la noche a temperatura ambiente bajo una atmósfera de nitrógeno y se vertió posteriormente en 2 L de agua helada. La suspensión resultante se agitó vigorosamente durante 1 hora. El sólido formado se recogió por filtración y se lavó dos veces con agua. La torta filtrante se disolvió en 2 L de diclorometano y esta solución se lavó con HCl acuoso 1 N (400 ml) y con NaCl acuoso saturado (400 ml), se secó sobre sulfato de sodio, se filtró y se evaporó hasta sequedad para dar *N*-(2-ciano-5-metilfenil)-2-fluoro-6-metoxibenzamida (186 g, 93%) en forma de un sólido amarronado. ^{1}H-RMN ($CDCl_3$, 200 MHz): δ 9,09 (s, 1H), 8,58 (s, 1H), 7,59-7,42 (m, 2H), 7,09-7,02 (m, 1H), 6,94-6,83 (m, 2H), 4,11 (s, 3H), 2,57 (s, 3H) ppm.

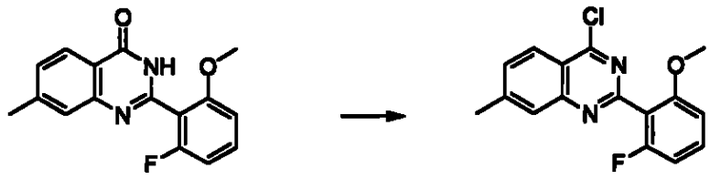
[00396] 2-(2-Fluoro-6-metoxi-fenil)-7-metil-3*H*-quinazolin-4-ona

[00397]



|00398| A una suspensión de *N*-(2-ciano-5-metilfenil)-2-fluoro-6-metoxibenzamida (31,5 g, 111 mmol) en etanol (626 ml) se añadió solución acuosa de NaOH 6 M (205 ml). Al cabo de 10 minutos, se añadió H_2O_2 acuoso al 30% (60 ml), formando una suspensión. La reacción se calentó a reflujo durante 18 h y se enfrió hasta temperatura ambiente. Se agregaron NaOH (22,2 g, 0,56 mol) y H_2O_2 acuoso 30% (26 ml) y la reacción se calentó a reflujo durante seis horas. La reacción se enfrió hasta temperatura ambiente, se añadió H_2O_2 acuoso al 30% (45 ml) y la reacción se calentó a reflujo durante 18 h. La reacción se enfrió hasta temperatura ambiente, se agregaron NaOH (10 g, 0,25 mol) y H_2O_2 acuoso al 30% (70 ml) y la reacción se calentó a reflujo durante seis horas. La reacción se enfrió hasta temperatura ambiente y se vertió sobre hielo (800 ml). El pH se ajustó a 3-4 por adición de solución concentrada de HCl y el sólido blanquecino precipitado se filtró y se lavó con agua (3 x 40 ml). El sólido se secó al vacío para proveer 2-(2-fluoro-6-metoxi-fenil)-7-metil-3*H*-quinazolin-4-ona (28 g, 89%).

|00399| **4-cloro-2-(2-fluoro-6-metoxifenil)-7-metilquinazolina**

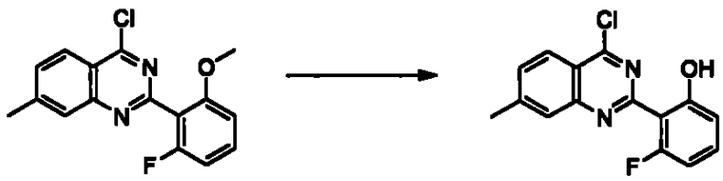


[00400]

[00401] En una atmósfera de N_2, se suspendió 2-(2-fluoro-6-metoxifenil)-7-metilquinazolin-4(3*H*)-ona (20 g, 70,35 mmol) en benceno (300 ml), seguido de la adición de *N*,*N*-dimetilanilina (26,8 ml, 211,05 mmol), luego $POCl_3$ (13,11 ml, 140,7 mmol). La reacción se calentó a reflujo y se observó la terminación de la formación del producto al cabo de 1,5 h. Tras enfriar hasta temperatura ambiente, la mezcla se vertió lentamente sobre 1 litro de hielo. La solución se diluyó luego con CH_2Cl_2 y el pH se ajustó a 7 usando una solución acuosa saturada de $NaHCO_3$. Las capas se dividieron, se separaron y se extrajeron con CH_2Cl_2. Todas las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron en un aceite oscuro. El material crudo se purificó por cromatografía en gel de sílice usando 75% de CH_2Cl_2/ 25% de hexanos para obtener 4-cloro-2-(2-fluoro-6-metoxifenil)-7-metilquinazolina en forma de un sólido amarillo (18,82 g, 88%). LC/MS: *m/z* 302,9 $(M+H)^+$ a 3,28 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, $CDCl_3$) δ 8,22 (d, *J* = 8,5 Hz, 1H), 7,95 (s,

1H), 7,60 (dd, J = 8,6, 1,5 Hz, 1H), 7,42-7,40 (m, 1H), 6,86-6,84 (m, 2H), 3,81 (s, 3H), 2,64 (s, 3H)

[00402] 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol

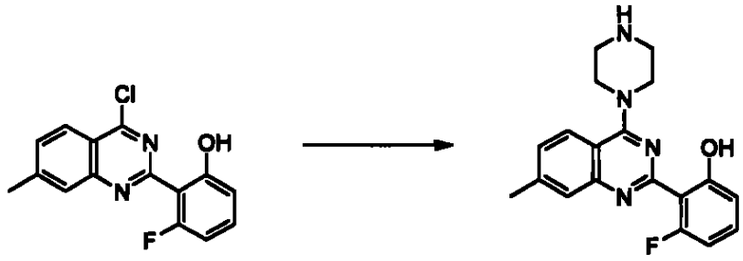


[00403]

[00404] En una atmósfera de N_2, se disolvió 4-cloro-2-(2-fluoro-6-metoxifenil)-7-metilquinazolina (7,0 g, 23,12 mmol) en CH_2Cl_2 (110 ml) y se enfrió hasta -50 °C de temperatura interna usando un baño de hielo seco/acetona. Se añadió una solución 1,0 M de BBr_3 en CH_2Cl_2 (115,6 ml, 115,6 mmol) gota a gota a través de un embudo de adición mientras se mantenía la temperatura interna a -50 °C. La mezcla de reacción se dejó calentar hasta 0 °C y la reacción se completó después de 1,5 h. Se neutralizó luego lentamente con solución acuosa saturada de $NaHCO_3$ hasta pH 7. Después de dividir en CH_2Cl_2 y H_2O, la mezcla se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron en un sólido marrón. La purificación por medio de cromatografía en gel de sílice usando 75% de CH_2Cl_2/ 25% de hexanos dio 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol en forma de un sólido

amarillo (4,37 g, 66%). LC/MS: *m/z* 289,1 $(M+H)^+$ a 3,71 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, $CDCl_3$) δ 8,22 (d, *J* = 8,5 Hz, 1H), 7,95 (s, 1H), 7,60 (dd, *J* = 8,6, 1,5 Hz, 1H), 7,42-7,36 (m, 1H), 6,86-6,82 (m, 2H), 3,81 (s, 3H), 2,64 (s, 3H)

[00405] 3-Fluoro-2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol

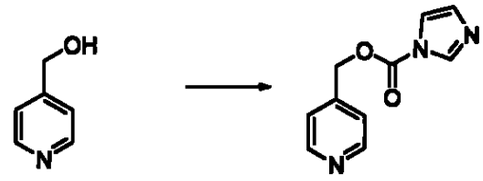


[00406]

[00407] 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (4,37 g, 15,14 mmol) se suspendió en CH_2Cl_2 (65 ml) bajo una atmósfera de N_2 y se colocó en un baño de agua helada. A esta solución se añadió una solución de piperazina (4,00 g, 45,42 mmol) y trietilamina (4,2 ml, 30,28 mmol) en CH_2Cl_2 (15 ml) en una porción. Tras agitar la reacción durante 30 minutos, se dividió en CH_2Cl_2 y H_2O y se separó y la capa acuosa se extrajo dos veces más con CH_2Cl_2. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró en un sólido de color amarillo brillante que se purificó mediante cromatografía en gel de sílice usando una mezcla 95%/5% de CH_2Cl_2/MeOH para obtener 3-

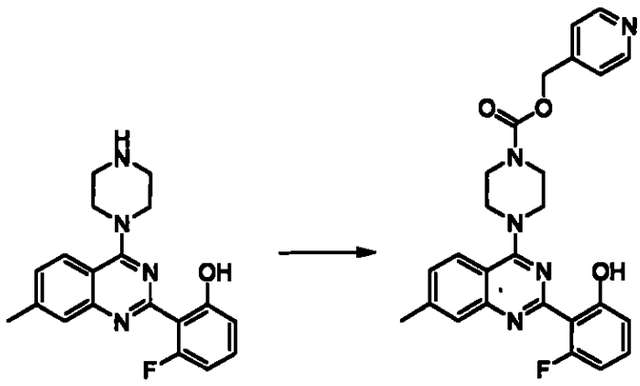
fluoro-2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (4,32 g, 85%) en forma de un sólido de color amarillo brillante. LC/MS: *m/z* 339,3 $(M+H)^+$ a 1,80 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 7,92 (d, *J* = 8,5 Hz, 1H), 7,63 (s, 1H), 7,39-7,30 (m, 2H), 6,78 (d, *J* = 8,3 Hz, 1H), 6,74-6,69 (m, 1H), 3,83 (t, *J* = 4,8 Hz, 4H), 2,88 (t, *J* = 4,9 Hz, 4H).

[00408] 1*H*-imidazol-1-carboxilato de (piridin-4-il)metilo

[00409] 

[00410] Una solución de (piridin-4-il)metanol (2,0 g, 18,3 mmol) y di(1*H*-imidazol-1-il)metanona (5,94 g, 36,6 mmol) en 20 ml de CH_2Cl_2 se calentó durante la noche a 50 °C La reacción se neutralizó con agua, se extrajo con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 10-70% de EtOAc en CH_2Cl_2 dio 1*H*-imidazol-1-carboxilato de (piridin-4-il)metilo (3 g, 81%). LC/MS: *m/z* 204,3 $(M+H)^+$ a 0,38 min (v). ^1H RMN (400 MHz, $CDCl_3$) δ 8,69 (dd, *J* = 4,4, 1,6 Hz, 2H), 8,20 (t, *J* = 0,9 Hz, 1H), 7,47 (t, *J* = 1,5 Hz, 1H), 7,34 (dd, *J* = 4,4, 1,6 Hz, 2H), 7,11 (dd, *J* = 1,6, 0,8 Hz, 1H), 5,45 (s, 2H).

[00411] 4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo

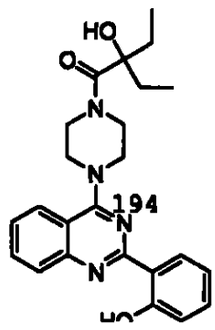


[00412]

[00413] Se agregaron 3-fluoro-2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,15 mmol), 1*H*-imidazol-1-carboxilato de (piridin-4-il)metilo (53 mg, 0,26 mmol) y trietilamina (30,4 mg, 0,3 mmol) en un tubo, seguido de la adición de DMSO (1 ml). La mezcla se agitó a temperatura ambiente durante 18 h y luego se filtró y se purificó por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) lo que dio 4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo. LC/MS: *m/z* 474,30 (M+H)+ a 1,19 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

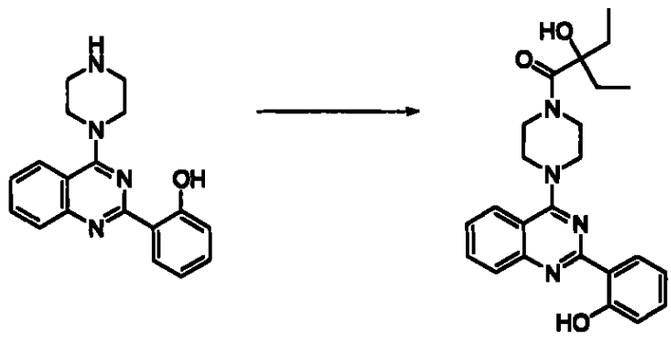
[00414] Ejemplo 115

[00415] **2-Etil-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona**



[00416]

[00417] **2-Etil-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona**



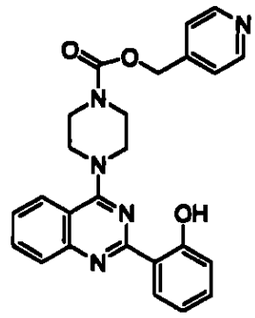
[00418]

[00419] A una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió ácido 2-etil-2-hidroxibutanoico (39,30 mg, 0,297 mmol). Le siguió la adición de trietilamina (63 µL), luego una solución de HATU (113 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-etil-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 421,3 $(M+H)^+$ a 2,51 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00420] Ejemplo 116

758 750

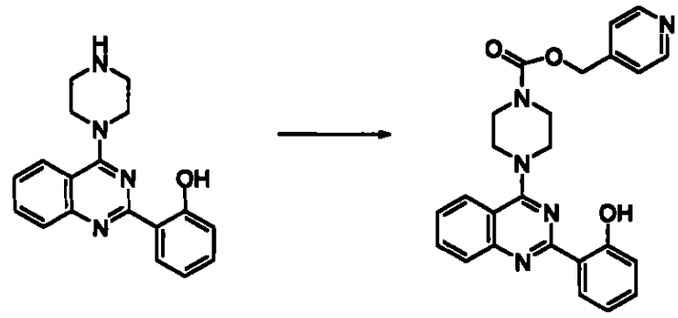
[00421] **4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo**



[00422]

[00423] **4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo**

[00424]

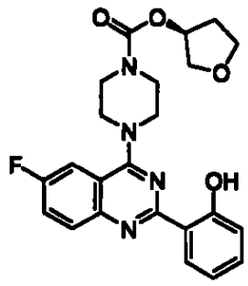


[00425] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,16 mmol), 1*H*-imidazol-1-carboxilato de (piridin-4-il)metilo (67 mg, 0,32 mmol) y trietilamina (45 µL, 0,32 mmol) en DMSO (500 µL) se calentó en un sintetizador a microondas a 200 °C durante 10 minutos. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O

(0,05% de TFA)) dio 4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 442,50 $(M+H)^+$ a 1,96 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

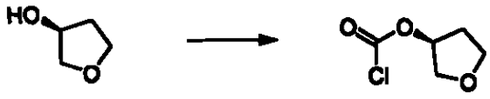
[00426] Ejemplo 117

[00427] **4-(6-fluoro-2-(2-hidroxifenil) quinazolin-4-il)piperazin-1-carboxilato de (S)-tetrahidrofuran-3-ilo**



[00428]

[00429] **Cloroformiato de (S)-tetrahidrofuran-3-ilo**



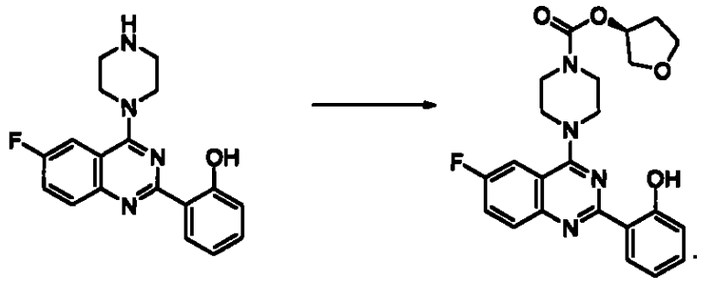
[00430]

[00431] Una solución agitada de (*S*)-tetrahidrofuran-3-ol (7,9 g, 90 mmol) en CH_2Cl_2 anhidro (50 ml) bajo una atmósfera de N_2 se enfrió en un baño de hielo y se añadió una solución al 20% de fosgeno en tolueno (134 ml, 270 mmol) lentamente. La reacción se dejó calentar hasta temperatura ambiente durante la noche y el solvente se eliminó al vacío para obtener

cloroformiato de (*S*)-tetrahidrofuran-3-ilo (12,1 g, 85%) en forma de un líquido claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 5,42-5,39 (m, 1H), 4,01-3,84 (m, 4H), 2,31-2,13 (m, 2H).

[00432] 4-(6-fluoro-2-(2-hidroxifenil) quinazolin-4-il)piperazin-1-carboxilato de (S)-tetrahidrofuran-3-ilo

[00433]

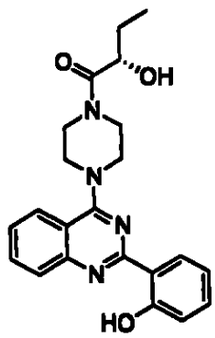


[00434] A una solución de 2-(6-fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (25 mg, 0,08 mmol) en DMF (1 ml) se añadió trietilamina (22 µL, 0,16 mmol) seguido de la adición gota a gota de cloroformiato de (S)-tetrahidrofuran-3-ilo (12 mg, 0,08 mmol) a 0 °C. La reacción se completó de inmediato después de la adición del cloroformiato. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (*S*)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,79 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00435] Ejemplo 118

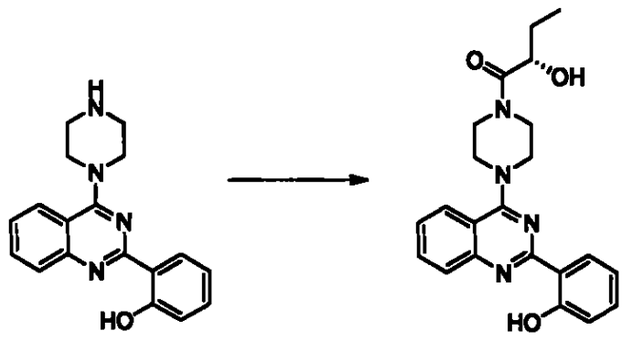
761 757

[00436] **(R)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona**



[00437]

[00438] **(R)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona**



[00439]

[00440] Método A

[00441] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió a ácido (R)-2-hidroxibutanoico (31 mg, 0,297 mmol), seguido de la adición de trietilamina (63 µL), luego una solución de HATU

762 758

(113 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 421,30 $(M+H)^+$ a 2,51 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

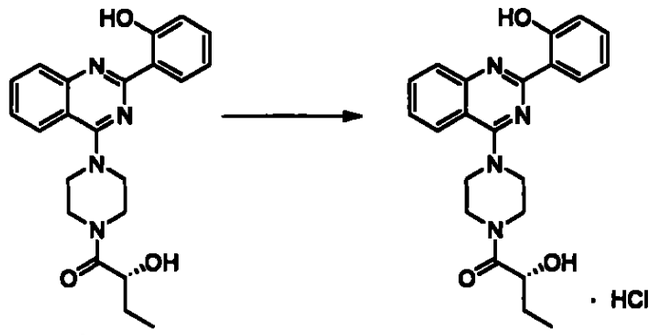
[00442] Método B

[00443] A una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (250 mg, 0,82 mmol) en CH_2Cl_2 (6 ml) se añadió trietilamina (227 µL, 1,63 mmol) seguido de la adición de ácido (R)-2-hidroxibutanoico (110 mg, 1,06 mmol) y HATU (380 mg, 1,00 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h y luego se neutralizó con H_2O. La capa acuosa se extrajo dos veces con CH_2Cl_2, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en 50:50 CH_2Cl_2:hexanos dio (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona (280 mg, 88%). LC/MS: *m/z* 393,3 $(M+H)^+$ a 2,17 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,47 (m, 1H), 8,12 (d, *J* = 8,3 Hz, 1H), 7,89 (m, 2H), 7,57 (m, 1H), 7,40 (m, 1H), 6,96 (m, 2H), 4,92 (d, *J* = 7,1 Hz, 1H),

763

3,88 (m, 8H), 1,67 (m, 1H), 1,51 (m, 1H), 0,91 (t, *J* = 7,4 Hz, 3H).

[00444] Clorhidrato de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona



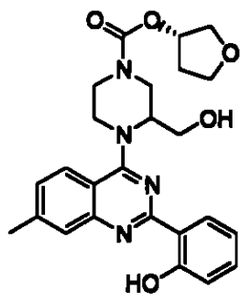
[00445]

[00446] A una solución de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona (280 mg, 0,71 mmol) en CH_2Cl_2 bajo una atmósfera de N_2 se añadió una solución 2 M de HCl en éter (0,355 ml, 0,71 mmol), seguido de la adición de éter que dio como resultado la formación de un precipitado que se agitó durante una hora y luego se filtró y se secó para obtener clorhidrato de (R)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona (272 mg, 90%). LC/MS: *m/z* 393,1 $(M+H)^+$ a 2,23 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,27 (dd, *J* = 7,9, 1,6 Hz, 1H), 8,19 (d, *J* = 8,4 Hz, 1H), 7,96 (m, 2H), 7,65 (m, 1H), 7,48 (m, 1H), 7,04 (m, 2H), 4,26

(dd, J = 7,7, 4,8 Hz, 1H), , 4,03 (m, 4H), 3,79 (m, 5H), 1,65 (m, 1H), 1,50 (m, 1H), 0,90 (t, J = 7,4 Hz, 3H).

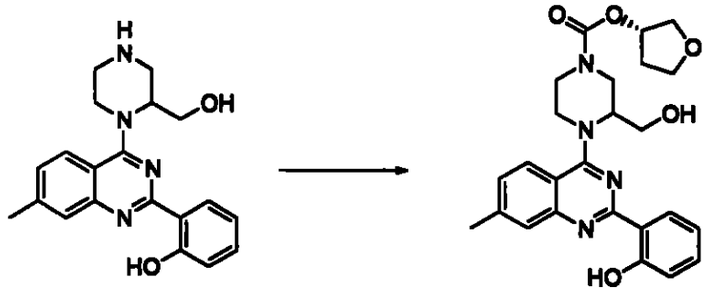
[00447] Ejemplo 119

[00448] **tetrahidro-furan-3-iléster del ácido (*S*)-3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico**



[00449]

[00450] **tetrahidro-furan-3-iléster del ácido (*S*)-3-Hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico**



[00451]

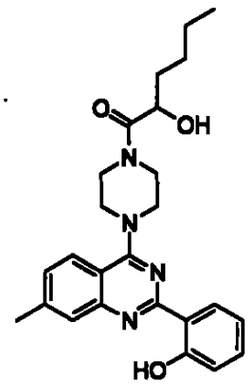
[00452] A 2-[4-(2-hidroximetil-piperazin-1-il)-7-metil-quinazolin-2-il]-fenol (69,2 mg, 0,19 mmol) en 650 µL de CH_2Cl_2

965 257

a 0 °C se añadió cloroformiato de (S)-tetrahidro-furan-3-ol (26,8 mg, 0,17 mmol), seguido de trietilamina (30 µL, 0,22 mmol). La mezcla de reacción se agitó durante una hora y luego se diluyó con 5 ml de CH_2Cl_2 y 5 ml de agua y la capa orgánica se separó y se secó sobre Na_2SO_4. El solvente se eliminó a presión reducida y el residuo se sometió a purificación usando 30-100% de EtOAc-hexanos para dar el producto deseado. LC/MS: *m/z* 465,2 $(M+H)^+$ a 2,5 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

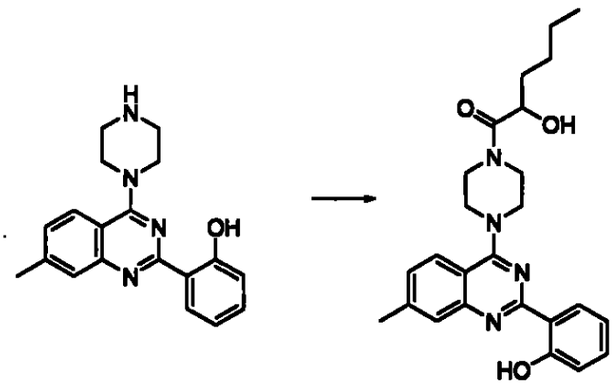
|00453| Ejemplo 120

|00454| **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)hexan-1-ona**



|00455|

|00456| **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)hexan-1-ona**

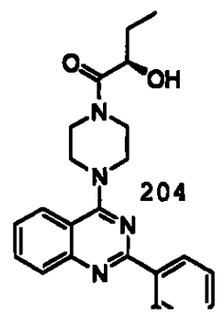


[00457]

[00458] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,22 mmol) en DMF (0,5 ml) se añadió a ácido 2-hidroxihexanoico (37,5 mg, 0,284 mmol). Le siguió la adición de trietilamina (61 µL), luego una solución de HATU (108 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)hexan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 435,3 $(M+H)^+$ a 2,65 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00459] Ejemplo 121

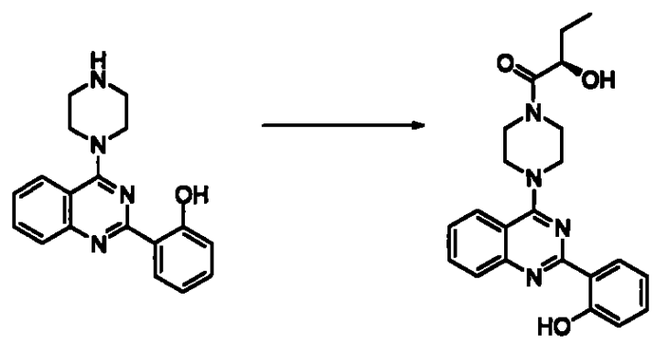
[00460] **(R)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-**



il)piperazin-1-il)butan-1-ona

[00461]

[00462] (*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona

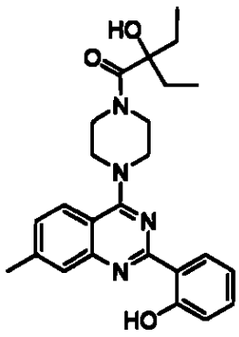


[00463]

[00464] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió a ácido (R)-2-hidroxibutanoico (31 mg, 0,297 mmol). Le siguió la adición de trietilamina (63 µL), luego una solución de HATU (113 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 393,3 $(M+H)^+$ a 2,21 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

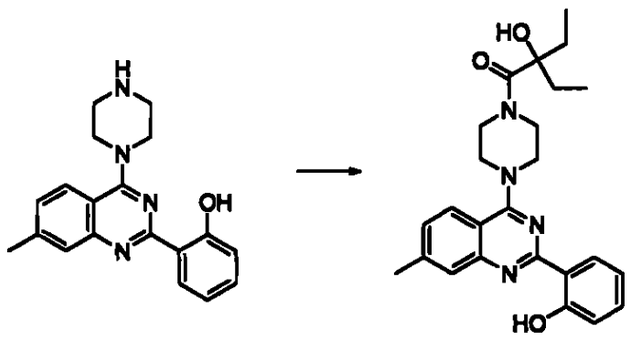
[00465] Ejemplo 122

|00466| **2-Etil-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona**



|00467|

|00468| **2-Etil-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona**



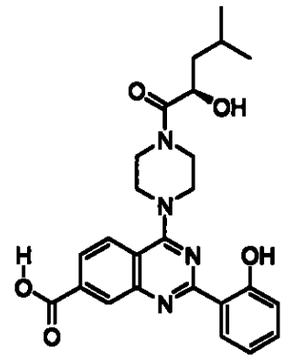
|00469|

|00470| Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,22 mmol) en DMF (0,5 ml) se añadió a ácido 2-etil-2-hidroxibutanoico (37,5 mg, 0,284 mmol). Le siguió la adición de trietilamina (61 µL), luego una solución de HATU (108 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La

purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-etil-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 435,3 $(M+H)^+$ a 2,56 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

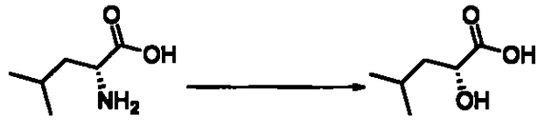
|00471| Ejemplo 123

|00472| **Ácido 4-[4-((*R*)-2-Hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-7-carboxílico**



|00473|

|00474| **Ácido (*R*)-α-hidroxiisocaproico**



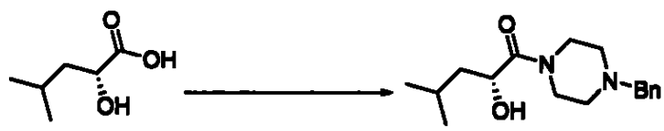
|00475|

|00476| A una solución enfriada (0-5 °C) de D-leucina (200 g, 1,5 mol) en ácido sulfúrico (3 L, 1 M) se añadió gota a

gota una solución de nitrito de sodio (240 g, 3,5 mol) en agua (1 L) mientras se mantenía la temperatura entre 0-5 °C. La mezcla de reacción se agitó a temperatura ambiente durante la noche. La solución se saturó con cloruro de sodio y se extrajo con éter ter-butilmetílico (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se filtraron y el solvente se eliminó al vacío. Se aisló ácido (*R*)-α-hidroxiisocaproico en forma de un sólido blanco con un rendimiento del 67% (132 g).

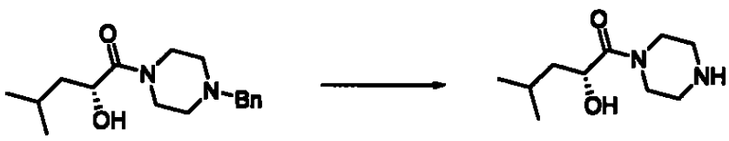
|00477| 1-(4-bencil-piperazin-1-il)-2-hidroxi-4-metil-pentan-1-ona

|00478|



|00479| A una solución enfriada (0-5 °C) de ácido (*R*)-α-hidroxiisocaproico (64,5 g, 0,5 mol), 1-bencilpiperazina (88 g, 0,5 mol) y trietilamina (71 ml, 0,5 mol) en CH_2Cl_2 (850 ml) se añadió en porciones HOBt (68 g, 0,5 mol) y EDCI·HCl (96 g, 0,5 mol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La capa orgánica se lavó con agua (3x) y una vez con salmuera, se secó sobre Na_2SO_4 y se filtró y el solvente se eliminó al vacío. Se usó 1-(4-bencil-piperazin-1-il)-2-hidroxi-4-metil-pentan-1-ona cruda (132 g, 91%) se usó en la siguiente etapa sin ulterior purificación.

[00480] 2-Hidroxi-4-metil-1-piperazin-1-il-pentan-1-ona



[00481] A una solución de 1-(4-bencil-piperazin-1-il)-2-hidroxi-4-metil-pentan-1-ona (132 g) en metanol (1 L) se añadió Pd/C (20 g, 10% en peso de Pd sobre carbón). La mezcla de reacción se agitó a temperatura ambiente durante la noche bajo una atmósfera de hidrógeno. La mezcla de reacción se filtró a través de Celite y el solvente se eliminó al vacio. 2-Hidroxi-4-metil-1-piperazin-1-il-pentan-1-ona se obtuvo en forma de un aceite (68 g, 74%).

[00482] Ácido 1,2,3,4-tetrahidro-2,4-dioxoquinazolin-7-carboxilico

[00483] A una mezcla agitada de 2-aminobencen-1,4-dioato de dimetilo (10,5 g, 50 mmol) y AcOH (3,4 ml, 60 mmol) en H_2O (200 ml) se añadió KOCN (8,1 g, 100 mmol). La mezcla de reacción se calentó a 100 °C durante 3 h. Tras enfriar en un baño de hielo, se añadió lentamente NaOH (24 g, 600 mmol) a la mezcla y se agitó durante otras 3 h a temperatura ambiente. La acidificación con HCl concentrado resultó en la formación de

772 776

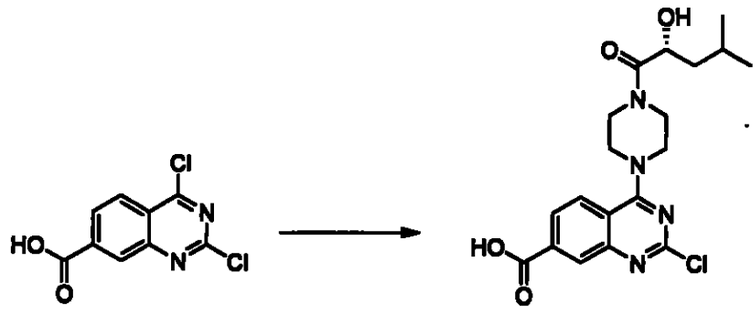
un sólido amarillo que se filtró, se lavó con agua y se secó al vacío (8,3 g). Los datos de RMN mostraron que el sólido consistía en una mezcla 3:1 del ácido 1,2,3,4-tetrahidro-2,4-dioxoquinazolin-7-carboxílico deseado y un subproducto. Esta mezcla se usó en la siguiente etapa sin ulterior purificación. ^{1}H RMN (400 MHz, DMSO-d6) δ 7,98 (d, *J* = 8,2 Hz, 1H), 7,75 (d, *J* = 1,2 Hz, 1H), 7,67 (dd, *J* = 8,2, 1,4 Hz, 1H).

[00484] Ácido 2,4-dicloroquinazolin-7-carboxílico

[00485] Una mezcla de ácido 1,2,3,4-tetrahidro-2,4-dioxoquinazolin-7-carboxílico (1,0 g, 4,9 mmol), $POCl_3$ (10 ml) y dimetilanilina (0,5 ml, 3,94 mmol) se calentó a 90 °C durante 3 h. Tras enfriar y verter la mezcla de reacción sobre hielo, se extrajo con EtOAc. Los extractos combinados se lavaron con agua, se secaron sobre Na_2SO_4 y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-10% de MeOH/CH_2Cl_2 dio ácido 2,4-dicloroquinazolin-7-carboxílico en forma de un sólido amarillo (0,45 g, 38%). ^{1}H RMN (400 MHz, DMSO-d6) δ 8,46 (d, *J* = 1,4 Hz, 1H), 8,42 (d, *J* = 8,7 Hz, 1H), 8,30 (dd, *J* = 8,6, 1,5 Hz, 1H); LC/MS: *m/z*

243,1 $(M+H)^+$ a 2,49 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00486] Ácido 2-cloro-4-[4-((R)-2-hidroxi-4-metil-pentanoil)-piperazin-1-il]-quinazolin-7-carboxílico



[00487]

[00488] A una solución de ácido 2,4-dicloroquinazolin-7-carboxílico (0,45 g, 1,9 mmol) en CH_2Cl_2 (20 ml) se añadió (*R*)-2-hidroxi-4-metil-1-piperazin-1-il-pentan-1-ona (0,37 g, 1,9 mmol) y trietilamina (0,52 ml, 3,7 mmol). La mezcla de reacción se agitó durante la noche a temperatura ambiente y luego se purificó por cromatografía en gel de sílice usando 0-10% de MeOH/CH_2Cl_2 para obtener ácido 2-cloro-4-[4-((*R*)-2-hidroxi-4-metil-pentanoil)-piperazin-1-il]-quinazolin-7-carboxílico (0,58 g, 77%). LC/MS: *m/z* 407,3 $(M+H)^+$ a 2,44 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00489] Ácido 4-[4-((R)-2-hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-7-carboxílico

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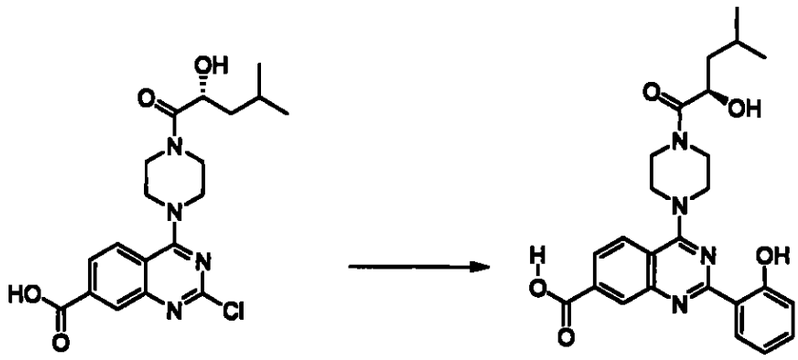
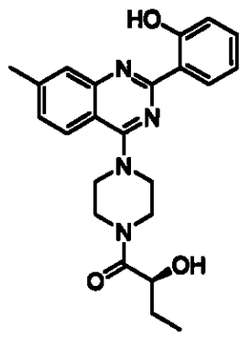
[00490]



[00491] Una mezcla de ácido 2-cloro-4-[4-((*R*)-2-hidroxi-4-metil-pentanoil)-piperazin-1-il]-quinazolin-7-carboxílico (114 mg, 0,28 mmol), 2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenol (88 µL, 0,42 mmol) $Pd(dppf)Cl_2$ (14 mg, 0,017 mmol) y K_2CO_3 (155 mg, 1,1 mmol) en DMF (4 ml) y H_2O (1 ml) se calentó en un vial sellado a microondas a 170 °C durante 6 minutos. Tras filtrar y evaporar de los solventes, la mezcla se purificó usando HPLC preparativa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar ácido 4-[4-((*R*)-2-hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-7-carboxílico en forma de la sal de TFA. LC/MS: *m/z* 465,3 $(M+H)^+$ a 2,50 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00492] Ejemplo 124

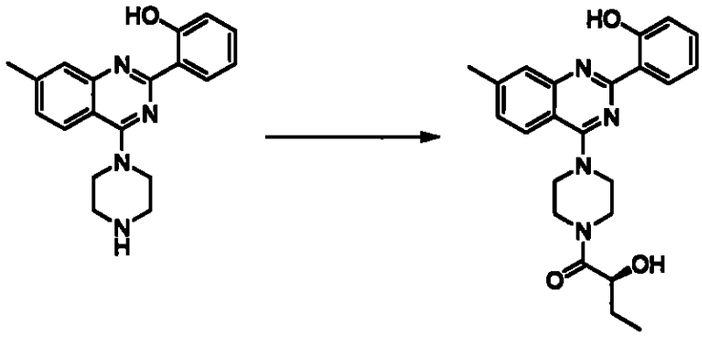
[00493] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona**



[00494]

[00495] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona**

[00496]

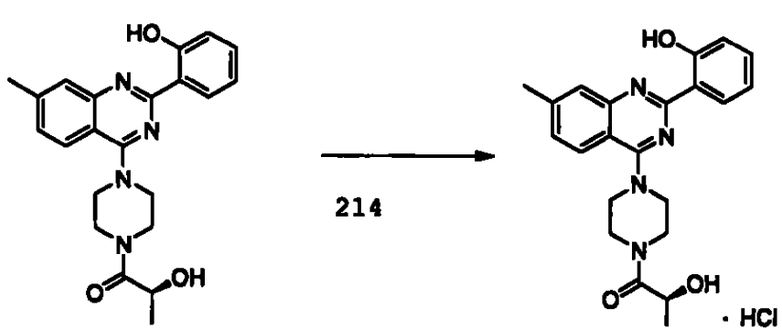


[00497] Método A: Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,22 mmol) en DMF (0,5 ml) se añadió a ácido (*S*)-2-hidroxibutanoico (31 mg, 0,297 mmol). Le siguió la adición de trietilamina (63 µL), luego una solución de HATU (113 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-

metilquinazolin-4-il)piperazin-1-il)butan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 407,5 $(M+H)^+$ a 2,31 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00498] Método B: A una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (250 mg, 0,78 mmol) en CH_2Cl_2 (6 ml) se añadió trietilamina (217 µL, 1,56 mmol) seguido de la adición de ácido (*S*)-2-hidroxibutanoico (105 mg, 1,0 mmol) y HATU (380 mg, 1,00 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h y luego se neutralizó con H_2O. La capa acuosa se extrajo dos veces con CH_2Cl_2, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en 50:50 CH_2Cl_2:hexanos dio (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona (300 mg, 95%). LC/MS: *m/z* 407,5 $(M+H)^+$ a 2,31 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,45 (m, 1H), 8,01 (d, *J* = 8,5 Hz, 1H), 7,70 (s, 1H), 7,39 (m, 2H), 6,95 (m, 2H), 4,92 (d, *J* = 7,0 Hz, 1H), 4,28 (q, *J* = 6,5 Hz, 1H), 3,89 (m, 8H), 2,52 (s, 3H), 1,67 (m, 1H), 1,51 (m, 1H), 0,91 (t, *J* = 7,4 Hz, 3H)

[00499] **Clorhidrato de (*S*)-2-Hidroxi-1-(4-(2-(2-**



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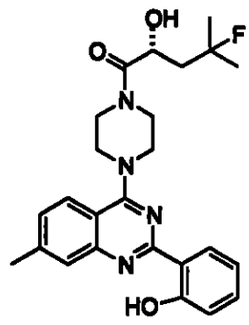
hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona

[00500]

[00501] A una solución de (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona (300 mg, 0,73 mmol) en CH_2Cl_2 se añadió una solución 2 M de HCl en éter (0,365 ml, 0,73 mmol), seguido de la adición de éter hasta que la sal se precipitara, que se agitó durante una hora, se recogió por filtración al vacío y se secó para obtener clorhidrato de (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona (270 mg, 84%). LC/MS: *m/z* 407,5 $(M+H)^+$ a 2,31 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,26 (dd, *J* = 7,9, 1,6 Hz, 1H), 8,07 (d, *J* = 8,6 Hz, 1H), 7,73 (s, 1H), 7,47 (m, 2H), 7,03 (m, 2H), 4,26 (dd, *J* = 7,7, 4,8 Hz, 1H), 4,08 (m, 4H), 3,79 (m, 4H), 2,53 (s, 3H), 1,65 (m, 1H), 1,50 (m, 1H), 0,89 (t, *J* = 7,4 Hz, 3H).

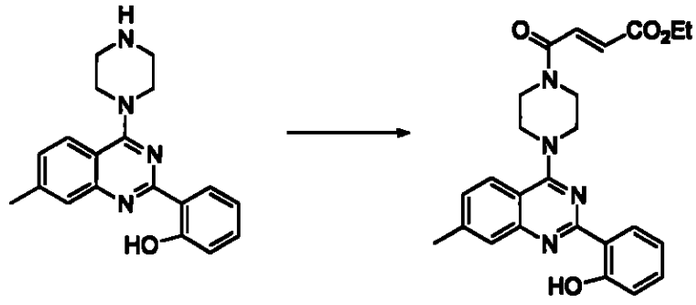
[00502] Ejemplo 125

[00503] **(*R*)-4-Fluoro-2-hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona**



[00504]

[00505] **Éster etílico del ácido 4-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-oxo-but-2-enoico**

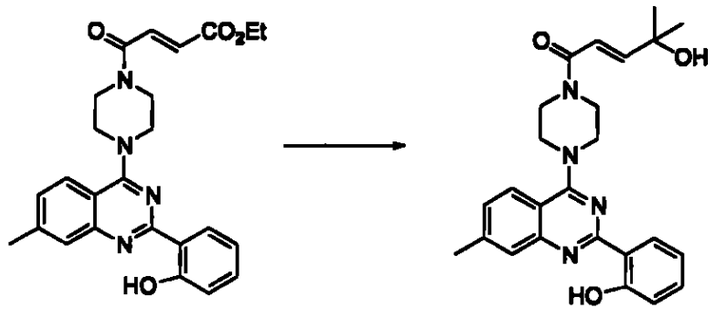


[00506]

[00507] A 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol (787 mg, 2,46 mmol) en 8 ml de CH_2Cl_2 a temperatura ambiente se añadieron secuencialmente éster monoetílico de ácido but-2-enodioico (531 mg, 3,69 mmol), trietilamina (686 µL, 4,92 mmol), BOP (1,63 g, 3,69 mmol). La mezcla de reacción se agitó durante 20 min y se diluyó con agua y CH_2Cl_2. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar un aceite. El residuo se sometió a

purificación por LC en fase normal usando 10-100% de EtOAc-hexanos para dar éster etílico del ácido 4-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-oxo-but-2-enoico (1,00 g, 91% de rendimiento). LC/MS: *m/z* 447,3 $(M+H)^+$ a 2,93 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00508] 4-Hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pent-2-en-1-ona

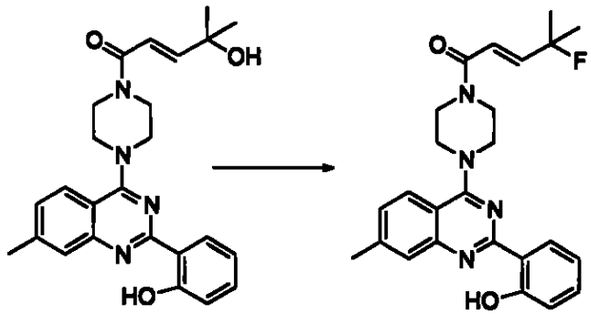


[00509]

[00510] A éster etílico del ácido 4-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-oxo-but-2-enoico (655 mg, 1,47 mmol) en 2 ml de éter dietílico a -20 °C se añadió bromuro de metilmagnesio (8,4 ml, 11,7 mmol, 1,4 M THF/tolueno) y la mezcla de reacción se dejó calentar hasta 0 °C durante 15 minutos. La mezcla se diluyó con 10 ml de agua y 15 ml de CH_2Cl_2. La emulsión resultante se filtró y la capa orgánica se separó y se secó sobre Na_2SO_4. El solvente se eliminó a presión reducida para dar el alcohol. LC/MS: *m/z*

433,5 $(M+H)^+$ a 2,56 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

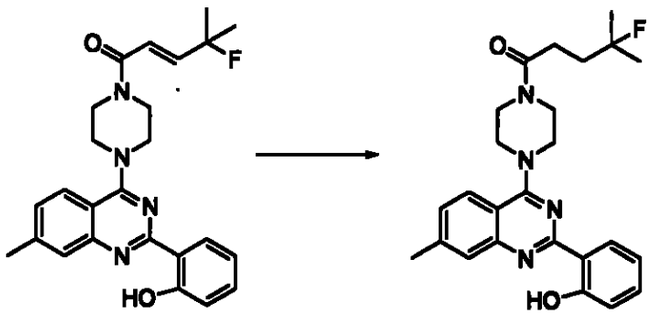
[00511] 4-Fluoro-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pent-2-en-1-ona



[00512]

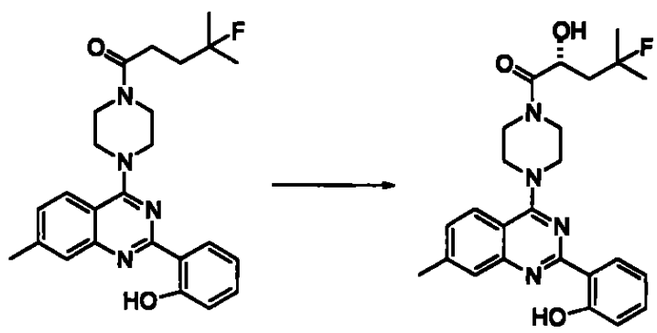
[00513] A 4-hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pent-2-en-1-ona (330 mg, 0,76 mmol) a -78 °C en 3 ml de CH_2Cl_2 se añadió trifluoruro de (dietilamino)azufre (185 mg, 1,15 mmol). La mezcla de reacción se agitó -78 °C durante 2,5 h. La mezcla de reacción se diluyó con 10 ml de agua y 10 ml de CH_2Cl_2. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar un aceite. El residuo se sometió a purificación por LC en fase normal usando 10-100% de EtOAc-hexanos para dar 4-fluoro-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pent-2-en-1-ona (133 mg, 40% de rendimiento). LC/MS: *m/z* 435,43 $(M+H)^+$ a 2,92 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00514] **4-Fluoro-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona**

[00515] 

[00516] A 4-fluoro-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pent-2-en-1-ona (228 mg) en 1,5 ml de metanol se añadió Pd/C (34 mg, 10% en peso de Pd sobre carbón) y la mezcla de reacción se hidrogenó con un balón de hidrógeno durante 1 h. La mezcla resultante se filtró a través de Celite y el solvente se eliminó para dar 4-fluoro-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona. LC/MS: *m/z* 437,4 $(M+H)^+$ a 2,86 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00517] **(*R*)-4-Fluoro-2-hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona**

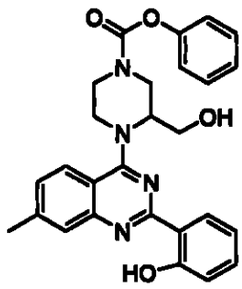


[00518]

[00519] A 4-fluoro-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona (225 mg, 0,53 mmol) en 500 µL de THF se añadió una solución 2,7 M de LDA (0,8 ml, 2,1 mmol) a -78 °C. La solución resultante se agitó a -78 °C durante 25 min y luego se añadió lentamente (1*R*)-(-)-(10-canforsulfonil)oxaziridina (361 mg, 1,6 mmol) en 1,5 ml de THF. La mezcla de reacción se dejó calentar hasta -45 °C durante 30 min y luego se diluyó con agua y CH_2Cl_2. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa en fase inversa usando 10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar (*R*)-4-fluoro-2-hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 453,4 $(M+H)^+$ a 2,79 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

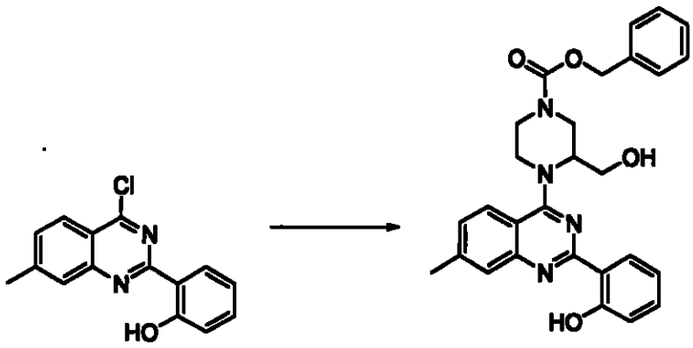
[00520] Ejemplo 126

[00521] Éster fenílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico



[00522]

[00523] Éster bencílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico

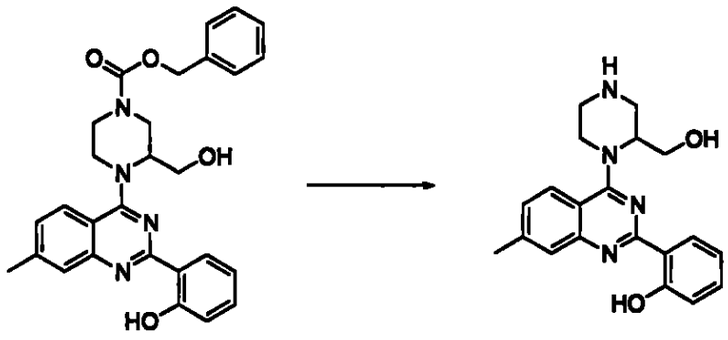


[00524]

[00525] A 2-(4-cloro-7-metil-quinazolin-2-il)-fenol (245 mg, 0,91 mmol) en 3,0 ml de CH_2Cl_2 se añadió éster bencílico del ácido 3-hidroximetil-piperazin-1-carboxílico (226 mg, 0,58 mmol) y trietilamina (190 µL, 1,37 mmol). La mezcla de

reacción se agitó durante 12 horas a temperatura ambiente y éster bencílico del ácido 3-hidroximetil-piperazin-1-carboxílico adicional (100 mg, 0,4 mmol) y trietilamina (200 µL, 1,4 mmol) y la mezcla de reacción se calentó a 40 °C durante 6 h. La mezcla de reacción se enfrió y se diluyó con 5 ml de CH_2Cl_2 y 5 ml de agua y la capa orgánica se separó y se secó sobre Na_2SO_4. El solvente se eliminó a presión reducida y el residuo se purificó por cromatografía en gel de sílice al eluir con 20-85% de EtOAc/hexanos para dar éster bencílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico (216 mg, 65 %). LCMS: *m/z* 485 $(M+H)^+$ a 3,03 min (10%-99% de CH_3CN/H_2O).

[00526] 2-[4-(2-Hidroximetil-piperazin-1-il)-7-metil-quinazolin-2-il]-fenol



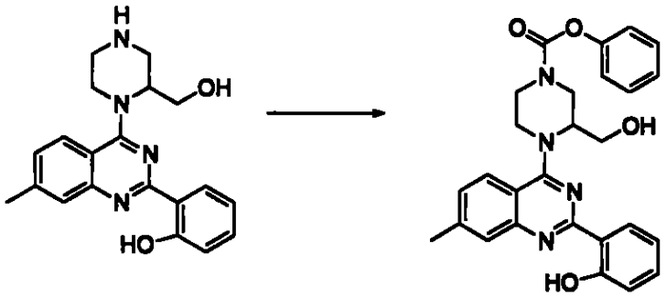
[00527]

[00528] A éster bencílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico (200 mg, 0,41 mmol) en 1,7 ml de metanol se añadió

39 mg de Pd/C (10% en peso de Pd sobre carbón). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno durante 3 h. La mezcla se filtró a través de Celite y el solvente se eliminó para dar 2-[4-(2-hidroximetil-piperazin-1-il)-7-metil-quinazolin-2-il]-fenol. LCMS: *m/z* 351,2 $(M+H)^+$ a 2,11 min (10%-99% de CH_3CN/H_2O).

[00529] Éster fenílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico

[00530]

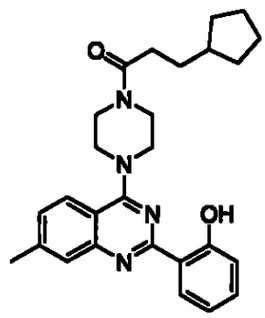


[00531] A 2-[4-(2-hidroximetil-piperazin-1-il)-7-metil-quinazolin-2-il]-fenol (31,9 mg, 0,091 mmol) en 300 µL de CH_2Cl_2 se añadió a 0 °C secuencialmente trietilamina (13,9 µL) y cloroformiato de fenilo (14,3 mg, 0,091 mmol). La mezcla de reacción se agitó durante 30 min y se calentó hasta temperatura ambiente y se agitó durante 40 minutos más. Al final de este período, el solvente se eliminó y el residuo se disolvió en DMSO y se purificó por HPLC preparativa en fase inversa usando 10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de

TFA) como eluyente para dar éster fenílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico en forma de la sal de TFA. LC/MS: *m/z* 471,2 (M+H)+ a 2,93 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

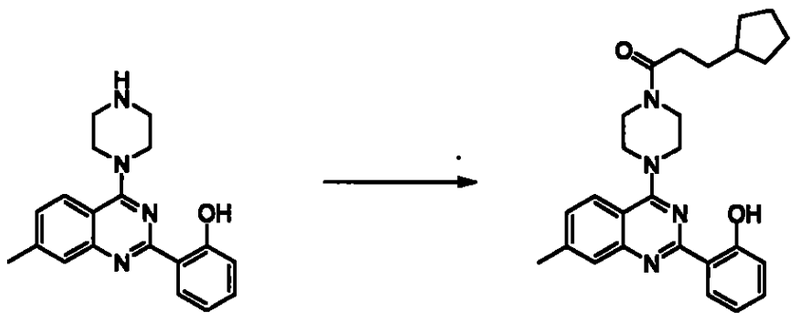
[00532] Ejemplo 127

[00533] **3-Ciclopentil-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona**



[00534]

[00535] **3-Ciclopentil-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona**



[00536]

[00537] Método A

[00538] A 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (53 mg, 0,17 mmol) se añadieron secuencialmente cloruro de 3-ciclopentilpropanoílo (29 mg, 0,19 mmol) en 550 µL de CH_2Cl_2 y trietilamina (28 µL, 0,2 mmol). La mezcla se agitó a 0 °C durante 20 minutos. Tras añadir H_2O y CH_2Cl_2, las fases se separaron y la capa orgánica se secó sobre Na_2SO_4 y se concentró al vacío. La purificación usando HPLC preparativa en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 3-ciclopentil-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 445,5 $(M+H)^+$ a 2,32 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

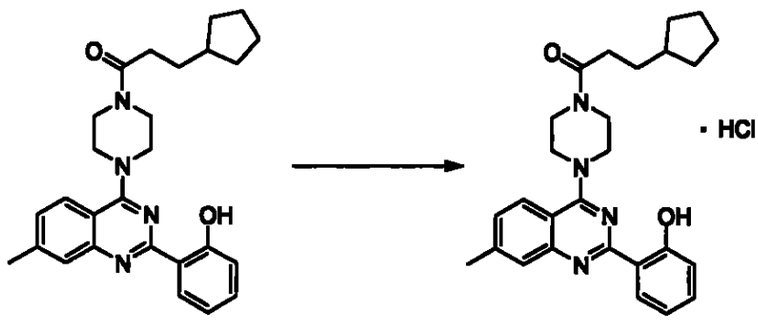
[00539] Método B

[00540] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (200 mg, 0,62 mmol) en CH_2Cl_2 (6,0 ml) se agitó bajo una atmósfera de N_2. Luego se añadió trietilamina

(170 µL, 1,24 mmol) y la reacción se enfrió hasta -10/-20 °C. Tras añadir cloruro de 3-ciclopentilpropanoílo (96 µL en 600 µL de THF, 0,62 mmol), la mezcla de reacción se agitó durante 30 minutos. Se añadió CH_2Cl_2 y la fase orgánica se lavó 2x con H_2O, se secó sobre Na_2SO_4 y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en 50:50 CH_2Cl_2: hexanos dio 3-ciclopentil-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona (240 mg, 86%). LC/MS: *m/z* 445,50 $(M+H)^+$ a 3,07 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,45 (dd, *J* = 8,2, 1,8 Hz, 1H), 8,00 (d, *J* = 8,5 Hz, 1H), 7,69 (s, 1H), 7,39 (m, 2H), 6,95 (m, 2H), 3,95 (dd, *J* = 19,9, 5,6 Hz, 4H), 3,74 (m, 4H), 2,52 (s, 3H), 2,38 (t, *J* = 7,8 Hz, 2H), 1,76 (m, 3H), 1,55 (m, 6H), 1,16 (m, 2H).

[00541] Clorhidrato de 3-ciclopentil-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona

[00542]

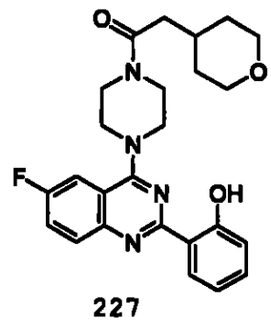


En una atmósfera de N_2, se añadió una solución de HCl 1 M en éter dietílico (0,54 ml, 0,54 mmol) gota a gota a una solución agitada de 3-ciclopentil-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona (240 mg, 0,54 mmol) en CH_2Cl_2 (20 ml). Al cabo de 10 min, se añadió éter hasta que se formó un precipitado. El sólido se recogió por filtración y se secó al vacío para dar clorhidrato de 3-ciclopentil-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona (230 mg, 88%). LC/MS: *m/z* 445,30 $(M+H)^+$ a 3,08 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,26 (d, *J* = 8,0 Hz, 1H), 8,09 (d, *J* = 8,5 Hz, 1H), 7,78 (s, 1H), 7,50-7,46 (m, 2H), 7,09 (d, *J* = 8,1 Hz, 1H), 7,04-7,00 (m, 1H), 4,15-4,11 (m, 4H), 3,79-3,74 (m, 4H), 2,54 (s, 3H), 2,37 (t, *J* = 7,7 Hz, 2H), 1,82-1,74 (m, 3H), 1,60-1,45 (m, 6H), 1,12-1,08 (m, 2H)

[00543]

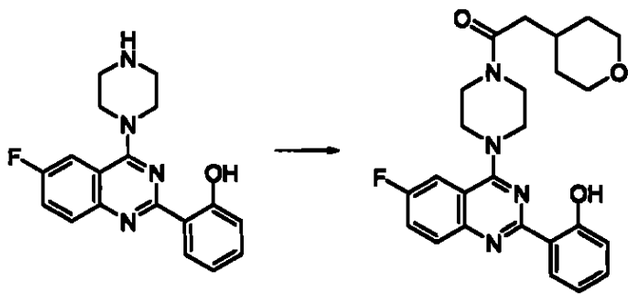
[00544] Ejemplo 128

[00545] **1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-(tetrahidro-2*H*-piran-4-il)etanona**



[00546]

[00547] **1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-(tetrahidro-2*H*-piran-4-il)etanona**

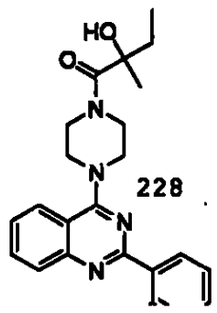


[00548]

[00549] 2-(6-Fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (25 mg, 0,077 mmol), ácido 2-(tetrahidro-2*H*-piran-4-il)acético (14,3 mg, 0,10 mmol), trietilamina (22µL, 0,154 mmol) y HATU (38 mg, 0,10 mmol) se agitaron en DMF (1 ml) durante la noche. La purificación por HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-(tetrahidro-2*H*-piran-4-il)etanona. LC/MS: *m/z* 451,5 $(M+H)^+$ a 2,60 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00550] Ejemplo 129

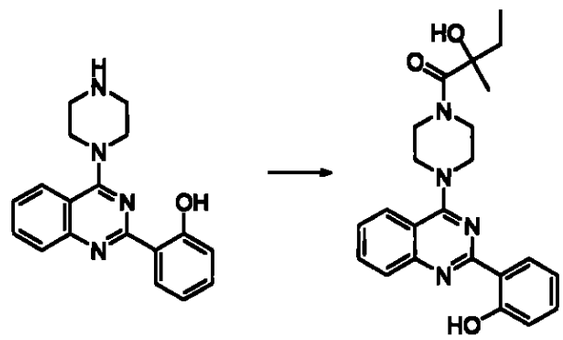
[00551] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-**



il)piperazin-1-il)-2-metilbutan-1-ona

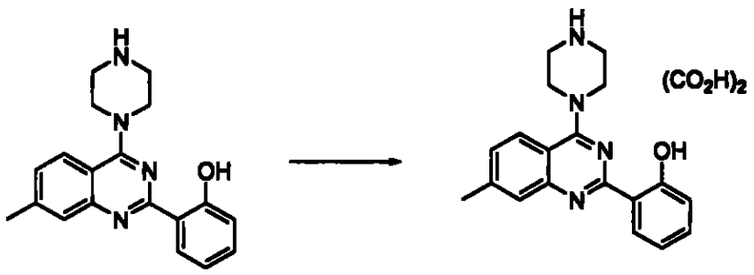
[00552]

[00553] 2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-metilbutan-1-ona



[00554]

[00555] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió al ácido 2-hidroxi-2-metilbutanoico (39,3 mg, 0,297 mmol). Le siguió la adición de trietilamina (63 µL) y una solución de HATU (113 mg) en 0,5 ml de DMF a temperatura ambiente.



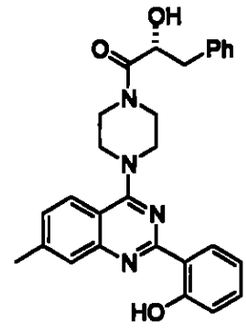
[00556]

[00557] La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN

(0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-metilbutan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 407,5 $(M+H)^+$ a 2,31 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00558] Ejemplo 130

[00559] **(R)-2-Hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-2-fenil-etanona**

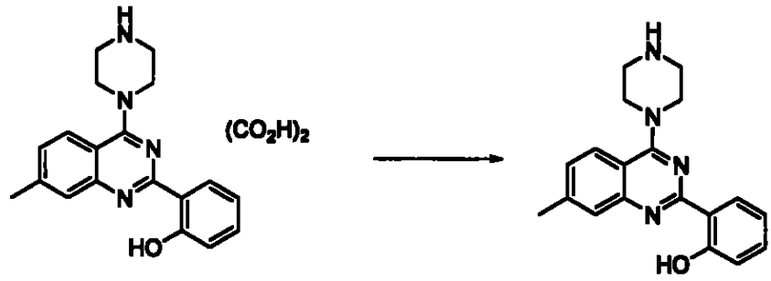


[00560] **Sal de oxalato de 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol**

[00561] A 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol (30,6 g, 95,4 mmol) en 900 ml de CH_2Cl_2 se añadió ácido oxálico (9,45 g, 105 mmol, 1,1 eq.) disuelto en 36 ml de metanol. La solución turbia resultante se agitó durante 3 h y el sólido resultante se filtró, se lavó con hexanos y se secó para dar 29,3 g (75 %) la sal de oxalato de 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol. LC/MS: *m/z* 321,2 $(M+H)^+$ a 2,36 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

~~237~~
793

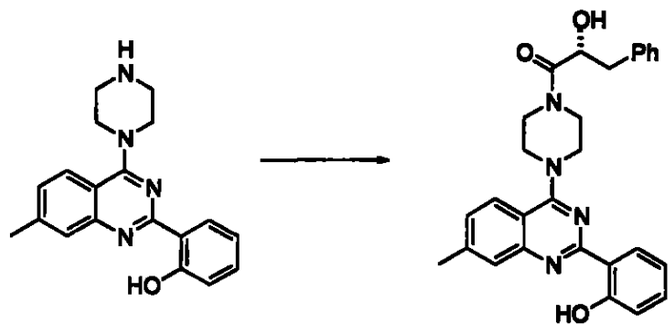
[00562] **2-(7-Metil-4-piperazin-1-il-quinazolin-2-il)-fenol**



[00563]

[00564] A la sal de oxalato de 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol (1,32 g, 3,2 mmol) en 10 ml de CH_2Cl_2 se añadió trietilamina (2,2 ml, 16,0 mmol) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se diluyó con 10 ml de agua y la capa orgánica se separó y se secó sobre Na_2SO_4. El solvente se eliminó a presión reducida para dar 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol en forma de un aceite que se usó sin ulterior purificación.

[00565] **(*R*)-2-Hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-2-fenil-etanona**

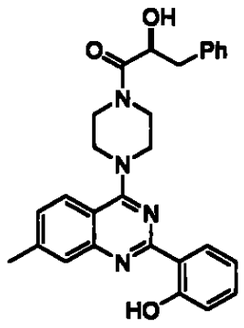


[00566]

[00567] A 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol (64 mg, 0,19 mmol) en 600 µL de CH_2Cl_2 se añadieron secuencialmente ácido 3-(*R*)-fenil-láctico (35 mg, 0,21 mmol), BOP (93 mg, 0,21 mmol) y trietilamina (27,7 µL, 0,2 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 1,5 h, se diluyó con 10 ml de cloruro de metileno y se lavó con agua (2 x 10 ml). El solvente se eliminó a presión reducida para dar un aceite que se purificó por LC en fase normal (35%-100% de EtOAc/hexanos) para dar (*R*)-2-hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-2-fenil-etanona. LC/MS: *m/z* 469,3 $(M+H)^+$ a 2,87 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

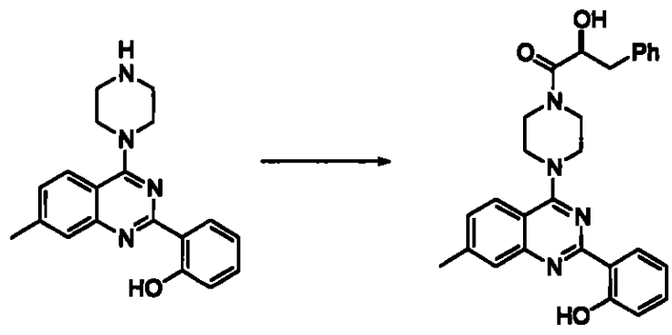
[00568] Ejemplo 131

[00569] **(*S*)-2-Hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-2-fenil-etanona**



[00570]

[00571] **(*S*)-2-Hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-2-fenil-etanona**

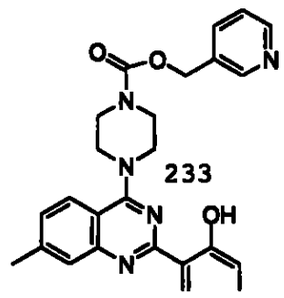


[00572]

[00573] A 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol (79,9 mg, 0,25 mmol) en 800 µL de CH_2Cl_2 se añadieron secuencialmente ácido 3-(*R*)-fenil-láctico (41,4 mg, 0,25 mmol), BOP(110 mg, 0,25 mmol), trietilamina (34,7 µL, 0,25 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 1,5 h, se diluyó con 10 ml de cloruro de metileno y se lavó con agua (2 x 10 ml). El solvente se eliminó a presión reducida para dar un aceite que se purificó por LC en fase normal (35%-100% de EtOAc/hexanos) para dar (*S*)-2-hidroxi-1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-2-fenil-etanona. LC/MS: *m/z* 469,4 $(M+H)^+$ a 2,88 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00574] Ejemplo 132

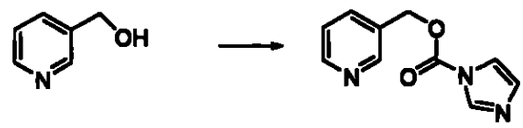
[00575] **4-(2-(2-Hidroxifenil)-7-metilquinazolin-4-**



il)piperazin-1-carboxilato de (piridin-3-il)metilo

[00576]

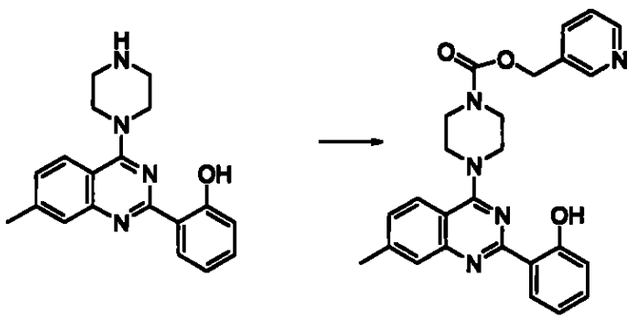
[00577] 1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo



[00578]

[00579] Una solución de (piridin-3-il)metanol (2 g, 18,32 mmol) y di(1*H*-imidazol-1-il)metanona (5,94 g, 36,65 mmol) en 20 ml de CH_2Cl_2 se calentó durante la noche a 50 °C La reacción se lavó con agua, se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por medio de cromatografía en gel de silice usando 10-70% de EtOAc en CH_2Cl_2 dio 1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo (3 g, 81%). LC/MS: *m/z* 204,1 $(M+H)^+$ a 0,39 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, $CDCl_3$) δ 8,74 (d, *J* = 1,9 Hz, 1H), 8,68 (dd, *J* = 4,8, 1,4 Hz, 1H), 8,16 (s, 1H), 7,81 (m, 1H), 7,44 (s, 1H), 7,38 (m, 1H), 7,09 (s, 1H), 5,46 (s, 2H).

[00580] 4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-3-il)metilo



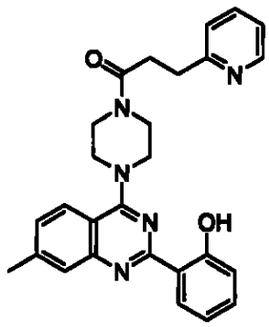
[00581]

[00582] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,16 mmol), 1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo (67 mg, 0,32 mmol) y trietilamina (44,6 µL, 0,32 mmol) en DMSO (500 µL) se calentó en un sintetizador a microondas a 200 °C durante 10 minutos. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-3-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 456,5 $(M+H)^+$ a 2,04 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00583] Ejemplo 133

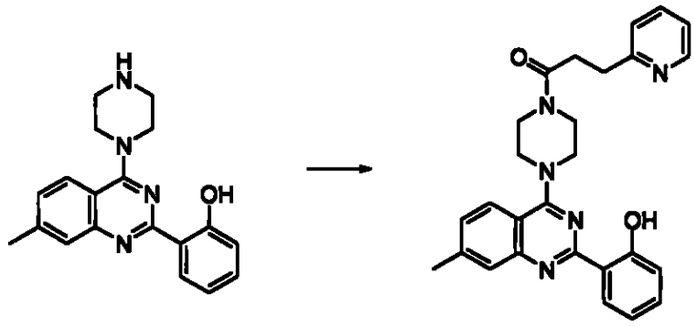
[00584] **1-(4-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-(piridin-2-il)propan-1-ona**

[00585]



[00586] 1-(4-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-(piridin-2-il)propan-1-ona

[00587]

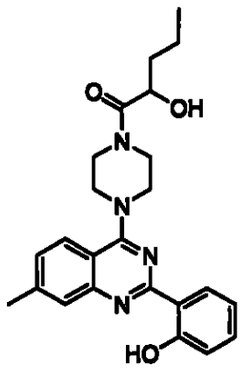


[00588] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (30 mg, 0,09 mmol) en DMF (0,5 ml) se añadió a un ácido 3-(piridin-2-il)propanoico (21,23 mg, 0,14 mmol). Se agregó trietilamina (25 µL), seguido de una solución de HATU (45 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-(piridin-2-il)propan-1-

ona en forma de la sal de TFA. LC/MS: *m/z* 454,3 $(M+H)^+$ a 1,94 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

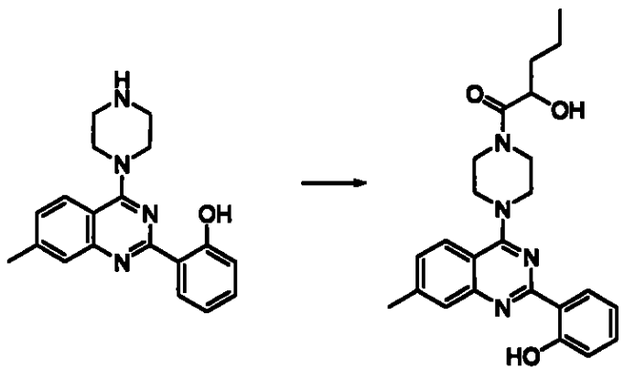
[00589] Ejemplo 134

[00590] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)pentan-1-ona**



[00591]

[00592] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)pentan-1-ona**

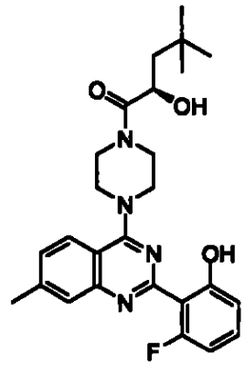


[00593]

[00594] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,22 mmol) en DMF (0,5 ml) se añadió a ácido 2-hidroxipentanoico (33,6 mg, 0,28 mmol). Le siguió la adición de trietilamina (61 µL) y una solución de HATU (108 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)pentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 421,1 $(M+H)^+$ a 2,46 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

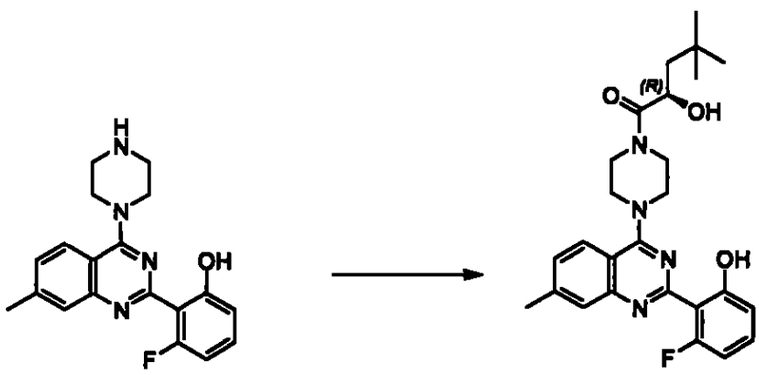
[00595] Ejemplo 135

[00596] **(*R*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona**



[00597]

[00598] **(*R*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona**



[00599]

[00600] Método A

[00601] Se colocó 3-fluoro-2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,15 mmol) en un tubo cargado con una barra de agitación, ácido (R)-2-hidroxi-4,4-dimetilpentanoico (26 mg, 0,18 mmol) en 1 ml de DMF y trietilamina (30 mg, 41 µL, 0,29 mmol) y el tubo se enfrió hasta 0 °C. Se agregó HATU (68 mg, 0,18 mmol) y la reacción se agitó a 0 °C durante 10 minutos y luego se dejó calentar hasta temperatura ambiente. Al cabo de 40 minutos, la reacción se filtró y se purificó por HPLC en fase inversa para dar la sal de TFA de (*R*)-1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-

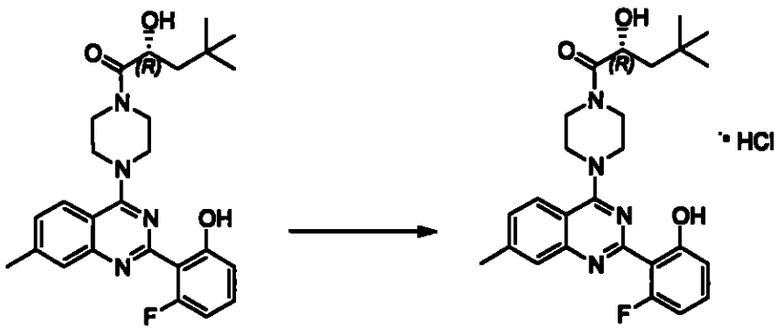
dimetilpentan-1-ona. LC/MS: *m/z* 467,1 $(M+H)^+$ a 2,59 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00602] Método B

[00603] 3-Fluoro-2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (250 mg, 0,74 mmol) se suspendió en DMF anhidra (5 ml) y se enfrió hasta 0 °C (temperatura interna). En una atmósfera de N_2, se añadió ácido (R)-2-hidroxi-4,4-dimetilpentanoico (118,4 mg, 0,81 mmol) seguido de trietilamina (0,207 ml, 1,48 mmol). A esta solución agitada se añadió HATU (337 mg, 0,888 mmol). Después de la adición completa de HATU, la mezcla se dejó calentar hasta 10 °C. Al cabo de 45 min, la reacción se completó y se neutralizó con una porción equivalente de agua helada. Se formó un precipitado amarillo que se recogió por filtración al vacío, se disolvió en CH_2Cl_2 y la solución de CH_2Cl_2 se desecó con Na_2SO_4, se filtró y se concentró en un aceite viscoso de color amarillo-anaranjado. El material crudo se purificó mediante cromatografía en gel de sílice usando 70% de CH_2Cl_2/hexanos (1:1) y 30% de EtOAc para obtener (*R*)-1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona en forma de un sólido amarillo (171 mg, 50%). LC/MS: *m/z* 467,1 $(M+H)^+$ a 2,63 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,02 (d, *J* = 8,6 Hz, 1H), 7,69 (s, 1H), 7,43 (dd, *J*

= 8,6, 1,5 Hz, 1H), 7,37-7,32 (m, 1H), 6,80 (d, *J* = 8,3 Hz, 1H), 6,76-6,71 (m, 1H), 4,87 (d, *J* = 7,2 Hz, 1H), 4,47-4,43 (m, 1H), 4,01-3,75 (m, 8H), 2,52 (s, 3H), 1,55 (dd, *J* = 14,3, 3,0 Hz, 1H), 1,40 (dd, *J* = 14,3, 8,8 Hz, 1H), 0,96 (s, 9H)

[00604] Clorhidrato de (*R*)-1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona



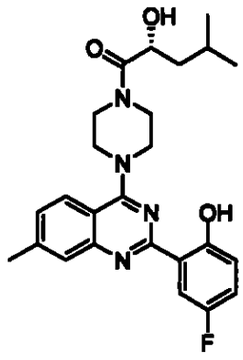
[00605]

[00606] (*R*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona (171 mg, 0,367 mmol) se disolvió en CH_2Cl_2 anhidro (2 ml) seguido de la adición de Et_2O (6 ml) bajo una atmósfera de N_2. Una solución de HCl 2,0 M en Et_2O (0,184 ml, 0,367 mmol) se añadió durante un minuto. La solución de reacción cambió de una solución de color amarillo claro a una suspensión blanca lechosa. Tras la adición completa de la solución de HCl, la reacción se dejó bajo agitación durante 10 minutos adicionales. El producto se recogió por filtración al

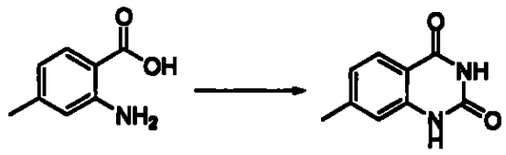
vacío y se secó al vacío para obtener clorhidrato de (*R*)-1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4,4-dimetilpentan-1-ona en forma de un sólido de color amarillo claro (170 mg, 92%). LC/MS: *m/z* 467,3 $(M+H)^+$ a 2,60 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,17 (d, *J* = 8,3 Hz, 1H), 7,66 (s, 1H), 7,56 (d, *J* = 8,1 Hz, 1H), 7,48-7,43 (m, 1H), 6,92-6,83 (m, 2H), 4,44-4,41 (m, 1H), 3,87-3,68 (m, 8H), 2,56 (s, 3H), 1,55 (dd, *J* = 14,3, 3,0 Hz, 1H), 1,41 (dd, *J* = 14,3, 8,8 Hz, 1H), 0,96 (s, 9H).

[00607] Ejemplo 136

[00608] **(*R*)-1-(4-(2-(5-Fluoro-2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**

[00609] 

[00610] **7-Metilquinazolin-2,4(1*H*,3*H*)-diona**

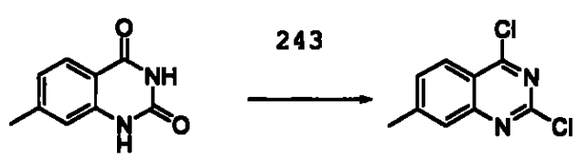


[00611]

[00612] A una suspensión de ácido 2-amino-4-metilbenzoico (58,9 g, 390 mmol) en agua (1,5 L) y ácido acético glacial (50 ml) se añadió gota a gota una solución de cianato de potasio (80,5 g, 993 mmol) en agua (300 ml). Después de terminar con la adición y agitar a temperatura ambiente durante media hora, se añadieron pellets de hidróxido de sodio (500 g) a tal velocidad que la temperatura se mantuvo a menos de 50 °C (con enfriamiento con hielo). Durante la adición, la mezcla se volvió una solución límpida durante un breve período y tras continuar con la adición de hidróxido de sodio, se comenzó a formar un precipitado de color crema. La suspensión se enfrió hasta 0-5 °C y el precipitado se recogió por filtración y se lavó dos veces con agua (150 ml). El sólido se vertió en agua (1 L) y se acidificó con HCl acuoso concentrado (30%, 150 ml). El sólido se recogió por filtración y se lavó con agua (150 ml) para obtener 7-metilquinazolin-2,4(1*H*,3*H*)-diona (57,0 g, 83%) tras secar a 45 °C al vacío.

[00613] **2,4-Dicloro-7-metil-quinazolina**

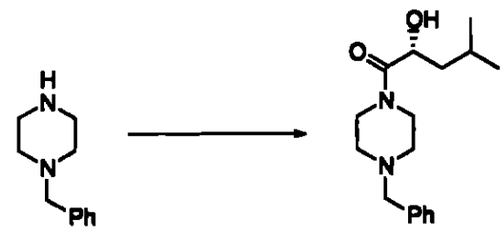
[00614]



866

|00615| 7-Metilquinazolin-2,4(1*H*,3*H*)-diona (57,0 g, 324 mmol) se calentó a reflujo durante la noche en oxicloruro de fósforo (250 ml) en un recipiente equipado con un tubo de control de cloruro de calcio. La solución oscura límpida se enfrió en un baño de hielo y se vertió lentamente en 2 L de agua helada. El sólido de color marrón chocolate se recogió por filtración y se lavó con agua helada (150 ml). El sólido se disolvió en diclorometano (500 ml) y se filtró. El filtrado se lavó con una solución saturada de NaCl, se secó sobre Na_2SO_4, se filtró y se evaporó hasta sequedad para dar 43,0 g de 2,4-dicloro-7-metil-quinazolina cruda. Este material se disolvió en heptanos calientes (0,5 L) y se filtró mientras estaba caliente y después de enfriar hasta temperatura ambiente, el sólido precipitado se recogió por filtración y se lavó con pentano (100 ml). El sólido se purificó por cromatografía en gel de sílice con diclorometano como eluyente para obtener 2,4-dicloro-7-metil-quinazolina (28,5 g, 41%) en forma de un sólido blanquecino.

|00616| **1-(4-bencil-piperazin-1-il)-2-(*R*)-hidroxi-4-metil-**

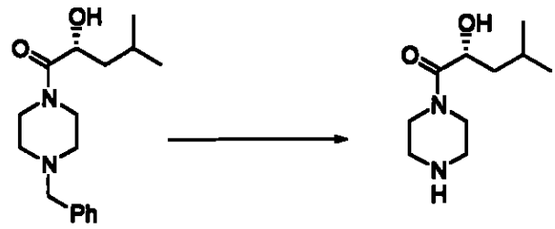


pentan-1-ona

[00617]

[00618] Se añadió ácido (R)-α-hidroxiisocaproico (52,1 g, 0,394 mol) se añadió a una solución de 1-bencilpiperazina (69,46 g, 0,394 mol) en CH_2Cl_2 (500 ml). La mezcla se enfrió en hielo y se añadió Et_3N (57 ml, 0,5 mol), seguido de HOBt (53,25 g, 0,394 mol) y EDCI·HCl (76,0 g, 0,396 mol). La mezcla de reacción se dejó calentar hasta temperatura ambiente durante la noche. La capa orgánica se lavó con agua (3x200 ml). Las capas acuosas combinadas se re-extrajeron con CH_2Cl_2 (3x25 ml). Las capas orgánicas combinadas se lavaron con agua (3x20 ml), se secaron sobre Na_2SO_4 y se concentraron para dar 1-(4-bencil-piperazin-1-il)-2-(*R*)-hidroxi-4-metil-pentan-1-ona en forma de un aceite marrón (109 g, 0,375 mol, 95%). ^1H RMN (300 MHz, $CDCl_3$): δ 7,35-7,24 (m, 5H); 4,35 (dd, *J*= 10 Hz, 2 Hz, 1H); 3,77-3,55 (m, 4H); 3,52 (s, 2H); 3,36 (m, 2H); 4,45 (m, 4H); 1,97 (m, 1H); 1,47-1,38 (m, 1H); 1,29-1,21 (m, 1H); 0,96 (d, *J*= 6 Hz, 3H); 0,94 (d, *J*= 6 Hz, 3H).

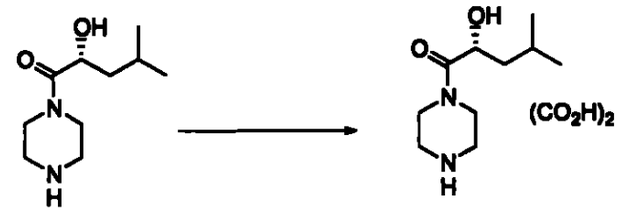
[00619] **2-(R)-hidroxi-4-metil-1-piperazin-1-il-pentan-1-ona**



[00620]

[00621] 1-(4-bencil-piperazin-1-il)-2-(*R*)-hidroxi-4-metil-pentan-1-ona (109 g, 0,375 mol) se disolvió en MeOH (0,5 L). Los cristales se formaron después de la adición de Pd/C al 10% (16 gramos). La mezcla se hidrogenó bajo 1-4 bar de presión de hidrógeno durante dos días. El catalizador se filtró, el filtrado se concentró para dar 2-(R)-hidroxi-4-metil-1-piperazin-1-il-pentan-1-ona en forma de un aceite amarronado (72,7 g, 0,363 mol, 97%). ^{1}H RMN (300 MHz, $CDCl_3$): δ 4,36 (dd, *J*= 10 Hz, 2 Hz, 1H); 3,76-3,66 (m, 1H); 3,62-3,52 (m, 1H); 3,37 (m, 2H); 2,99 (br. s, 2H); 2,89 (br. m, 4H); 1,96 (m, 1H); 1,48-1,38 (m, 1H); 1,29-1,21 (m, 1H); 0,96 (d, *J*= 9 Hz, 3H); 0,94 (d, *J*= 9 Hz, 3H).

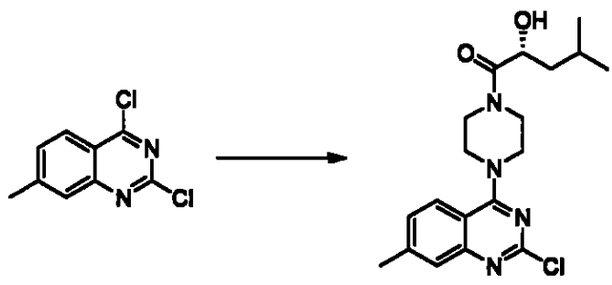
[00622] **Oxalato de 2-(R)-hidroxi-4-metil-1-piperazin-1-il-pentan-1-ona**



[00623]

[00624] El producto anterior se disolvió en etanol (250 ml). Se añadió ácido oxálico dihidratado (45,76 g, 0,363 mol). La suspensión espesa se diluyó con etanol (250 ml) y se agitó a temperatura ambiente durante 3 horas. La sal se filtró, se lavó con etanol (2x100 ml) y se secó al vacío sobre perlas de secado. Rendimiento: 89,0 gramos (0,307 mol, 84%) de oxalato de 2-(R)-hidroxi-4-metil-1-piperazin-1-il-pentan-1-ona en forma de un sólido blanco. ^{1}H RMN (300 MHz, D_2O): δ 4,68 (dd, *J*=3,3, 9,9 Hz, 1H); 3,95 (m, 4H); 3,35 (m, 4H); 1,80 (m, 1H); 1,59 (m, 1H); 1,41 (m, 1H); 0,96 (d, *J*= 6,5 Hz, 3H); 0,95 (d, *J*= 6,5 Hz, 3H).

[00625] **(*R*)-1-(4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**

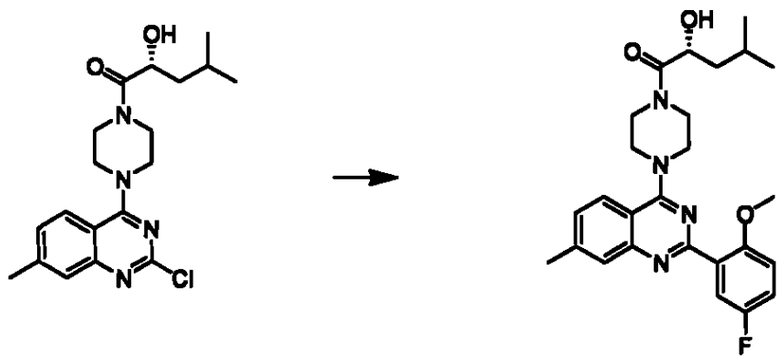


[00626]

[00627] A una solución de 2,4-dicloro-7-metilquinazolina (2,09 g, 9,83 mmol) en CH_2Cl_2 (10 ml) a 0 °C se añadió trietilamina (2,74 ml, 19,66 mmol), seguido de la adición de (*R*)-2-hidroxi-4-metil-1-(piperazin-1-il)pentan-1-ona (1,97 g,

9,83 mmol). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante la noche. La mezcla se neutralizó luego con agua y se extrajo dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener (*R*)-1-(4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (6,78 g, 95%). LC/MS: *m/z* 377,5 $(M+H)^+$ a 2,61 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00628] (*R*)-1-(4-(2-(5-Fluoro-2-metoxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona



[00629]

[00630] (*R*)-1-(4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (50 mg, 0,13 mmol), ácido 5-fluoro-2-metoxifenilborónico (27 mg, 0,16 mmol), $Pd(Ph_3P)_4$ (9,2 mg, 0,008 mmol) y K_2CO_3 (37 mg, 0,27 mmol) se colocaron en un tubo de microondas cargado con una barra de agitación. Se

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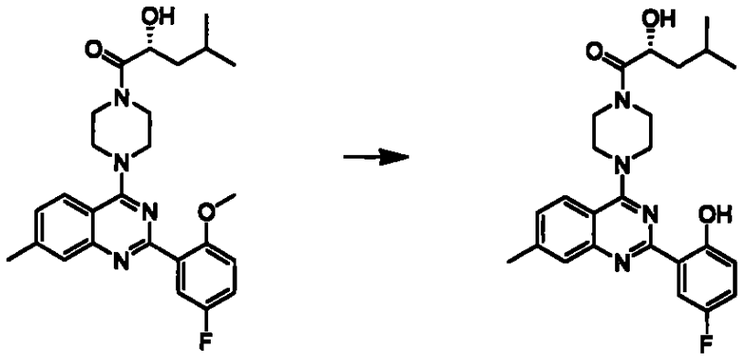
añadieron acetonitrilo (2 ml) y H_2O (400 µL) y el recipiente se tapón y se calentó a 160 °C durante 12 minutos en el reactor a microondas. La reacción se dividió en EtOAc y H_2O, las capas se separaron y la capa acuosa se extrajo una vez más con EtOAc. Los extractos orgánicos se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron en un gel anaranjado. La reacción se purificó por cromatografía en gel de sílice usando 10%-30% de EtOAc en CH_2Cl_2/hexanos (2:1) para obtener (*R*)-1-(4-(2-(5-fluoro-2-metoxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de una espuma blanca (70%). LC/MS: *m/z* 467,30 $(M+H)^+$ a 2,38 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00631] (R)-1-(4-(2-(5-Fluoro-2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona

[00632]

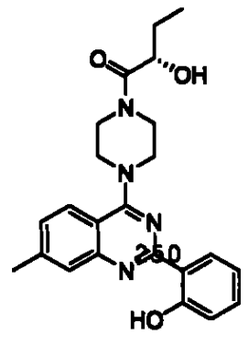


[00633] (*R*)-1-(4-(2-(5-Fluoro-2-metoxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (30 mg, 0,064 mmol) se disolvió en 1,5 ml de CH_2Cl_2 anhidro. El recipiente se selló con un septo, se colocó bajo una atmósfera de N_2 y se enfrió hasta -78 °C y se añadieron 0,32 ml de una solución 1 M de BBr_3 en CH_2Cl_2 durante 2 minutos. La reacción se dejó calentar hasta temperatura ambiente. Al cabo de 5 horas, la reacción se neutralizó con solución acuosa saturada de $NaHCO_3$ y se dividió en CH_2Cl_2 y agua y las capas se separaron. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró en un aceite rojo. La reacción se purificó por HPLC en fase inversa para dar (*R*)-1-(4-(2-(5-fluoro-2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 453,30 $(M+H)^+$ a 3,02 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00634] Ejemplo 137

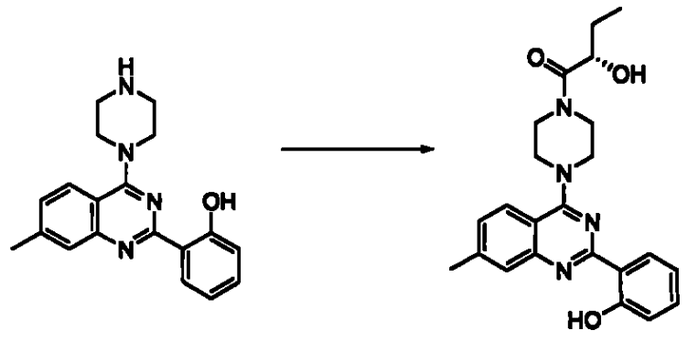
[00635] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona**

[00636]



[00637] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona**

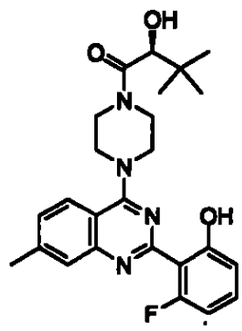
[00638]



[00639] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,22 mmol) en DMF (0,5 ml) se añadió a ácido (*S*)-2-hidroxibutanoico (29,6 mg, 0,284 mmol). Le siguió la adición de trietilamina (61 µL) y una solución de HATU (108 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)H_2O (0,05% de TFA)) dio (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)butan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 407,3 $(M+H)^+$ a 2,28 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00640] Ejemplo 138

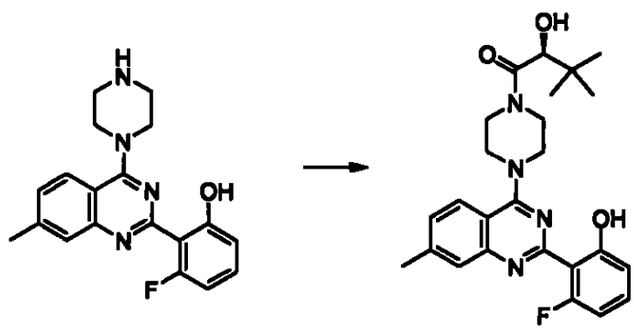
[00641] (*S*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-3,3-



dimetilbutan-1-ona

[00642]

[00643] (*S*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-3,3-dimetilbutan-1-ona



[00644]

[00645] 3-Fluoro-2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (30 mg, 0,09 mmol), ácido (*S*)-2-hidroxi-3,3-dimetilbutanoico (15,24 mg, 0,12 mmol), trietilamina (25 µL, 0,18 mmol) y HATU (45,6 mg, 0,12 mmol) se agitaron en DMF (1

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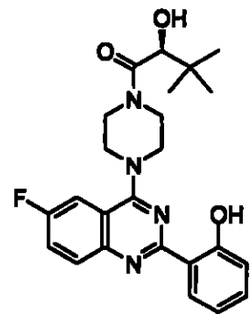
ml) durante la noche. La purificación mediante HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*S*)-1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-3,3-dimetilbutan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 453,3 $(M+H)^+$ a 2,43 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

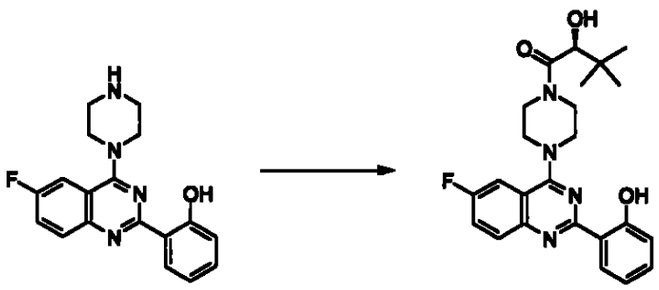
[00646] Ejemplo 139

[00647] **(*S*)-1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-3,3-dimetilbutan-1-ona**



[00648]

[00649] **(*S*)-1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-3,3-dimetilbutan-1-ona**

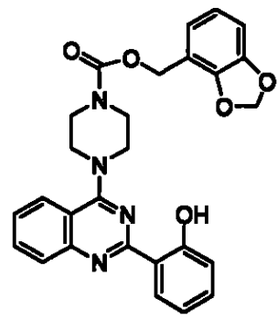


[00650]

[00651] 2-(6-Fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (30 mg, 0,09 mmol), ácido (*S*)-2-hidroxi-3,3-dimetilbutanoico (16 mg, 0,12 mmol), trietilamina (25 ml, 0,18 mmol) y HATU (45,6 mg, 0,12 mmol) se agitaron en DMF (1 ml) durante la noche. La purificación mediante HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*S*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-3,3-dimetilbutan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,95 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

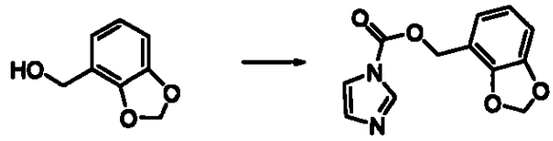
[00652] Ejemplo 140

4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo



|00653|

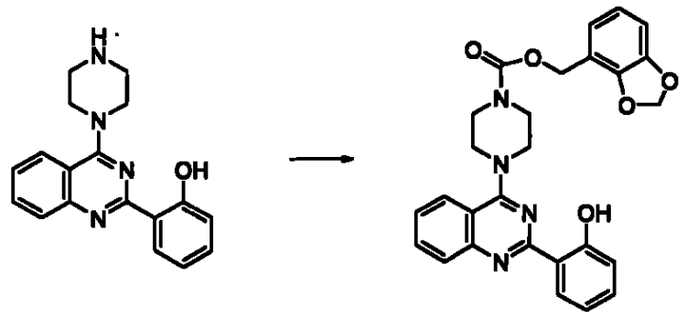
|00654| **1*H*-imidazol-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo**



|00655|

|00656| Una solución de (benzo[d][1,3]dioxol-7-il)metanol (2,0 g, 13,1 mmol) y di(1*H*-imidazol-1-il)metanona (4,26 g, 26,2 mmol) en 20 ml de CH_2Cl_2 se calentó durante la noche a 50 °C La reacción se neutralizó con agua y se extrajo con CH_2Cl_2 y las capas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 10-70% de EtOAc en CH_2Cl_2 dio 1H-imidazol-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo (2,8 g, 86%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,15 (t, *J* = 0,9 Hz, 1H), 7,44 (t, *J* = 1,4 Hz, 1H), 7,07 (dd, *J* = 1,6, 0,8 Hz, 1H), 6,95 (m, 2H), 6,84 (m, 1H), 6,01 (s, 2H), 5,33 (s, 2H).

[00657] **4-(4a,8a-dihidro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo**

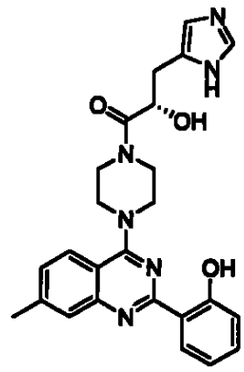


[00658]

[00659] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,16 mmol), 1H-imidazol-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo (78 mg, 0,32 mmol) y trietilamina (44,6 µL, 0,32 mmol) en DMSO (500 µL) se calentó en un sintetizador a microondas a 200 °C durante 10 minutos. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (benzo[d][1,3]dioxol-7-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 485,5 $(M+H)^+$ a 2,94 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

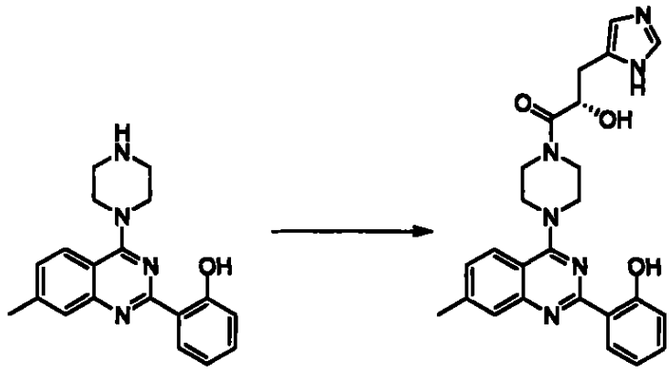
[00660] Ejemplo 141

[00661] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-(1*H*-imidazol-5-il)propan-1-ona**



[00662]

[00663] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-(1*H*-imidazol-5-il)propan-1-ona**



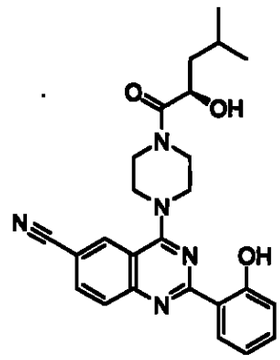
[00664]

[00665] 2-(7-Metil-4-(piperazin-1-il)quinazolin-2-il)fenol (87 mg, 0,27 mmol), ácido (*S*)-2-hidroxi-3-(1*H*-imidazol-5-il)propanoico (64 mg, 0,41 mmol), trietilamina (76 µL, 0,54 mmol) y BOP (180 mg, 0,41 mmol) en 1 ml de CH_2Cl_2 se agitaron a temperatura ambiente durante 1,5 h. La mezcla de reacción se

diluyó con H_2O y CH_2Cl_2. La capa orgánica se secó sobre Na_2SO_4 y se concentró. La purificación usando 1-15% de MeOH en CH_2Cl_2 dio (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-(1*H*-imidazol-5-il)propan-1-ona. LC/MS: *m/z* 459,3 $(M+H)^+$ a 2,13 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00666] Ejemplo 142

[00667] **4-[4-((*R*)-2-Hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-6-carbonitril**



[00668]

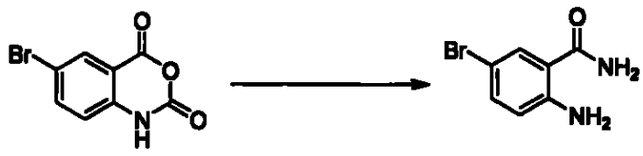
[00669] **6-Bromo-1*H*-benzo[d][1,3]oxazin-2,4-diona**

[00670]

[00671] Se añadió bromo (35 ml, 660 mmol) gota a gota a una suspensión de anhidrido isatoico (100 g, 610 mmol) en 1,6 L de

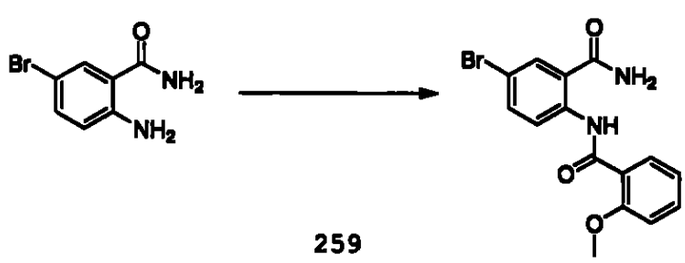
agua a 50 °C. Esta temperatura se mantuvo durante 2 horas más. Tras enfriar la solución hasta temperatura ambiente, el sólido se filtró y se lavó dos veces con agua y dos veces con acetona, dando como resultado 125,6 g (85%) de 6-bromo-1*H*-benzo[d][1,3]oxazin-2,4-diona en forma de un sólido rosado.

[00672] **2-Amino-5-bromo-benzamida**

[00673] 

[00674] 6-Bromo-1*H*-benzo[d][1,3]oxazin-2,4-diona (56,0 g, 230 mmol) se suspendió en NH_4OH acuoso 1 N (600 ml, 2,6 equivalentes) y la suspensión se agitó durante 3 d a temperatura ambiente. Tras filtrar, el sólido recogido se lavó con agua y posteriormente se disolvió en tetrahidrofurano. Esta solución se filtró, se evaporó hasta sequedad y se secó por destilación azeotrópica repetida con tolueno. El sólido se suspendió en CH_2Cl_2, se filtró y se lavó una vez CH_2Cl_2 con dando como resultado 35,4 g (71,2%) de 2-amino-5-bromo-benzamida.

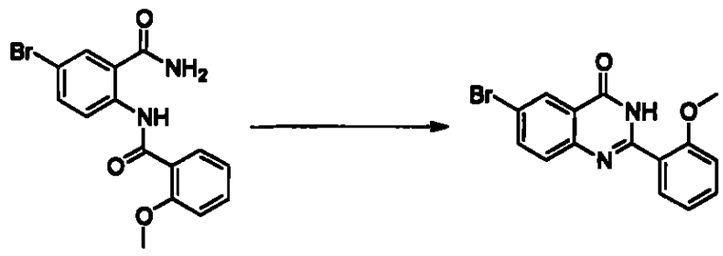
[00675] **2-(*o*-Anisoil)-amino-5-bromo-benzamida**



[00676]

[00677] A una solución de 2-amino-5-bromo-benzamida (29,2 g, 136 mmol) y trietilamina (25,0 ml, 173 mmol) en THF (500 ml) se añadió gota a gota cloruro de o-anisoílo (24,0 g, 140 mmol). La agitación a temperatura ambiente se continuó durante 3 h, tras lo cual el precipitado formado se filtró y se lavó una vez con THF y dos veces con diclorometano dando como resultado 2-(*o*-anisoil)-amino-5-bromo-benzamida (51,4 g, 84%) con 1 equivalente de clorhidrato de trietilamina.

[00678] **6-Bromo-2-(2-metoxi-fenil)-3*H*-quinazolin-4-ona**



[00679]

[00680] 2-(*o*-Anisoil)-amino-5-bromo-benzamida (50,8 g, 105 mmol) se suspendió en NaOH acuoso 2 N (500 ml) y se calentó a reflujo hasta obtener una solución límpida (1,5 h). La solución se enfrió hasta temperatura ambiente y se filtró. El filtrado se acidificó con HCl acuoso concentrado y el precipitado formado se filtró y se lavó dos veces con HCl acuoso 1 N y dos veces con agua. El sólido se secó por destilación azeotrópica repetida con tolueno dando como

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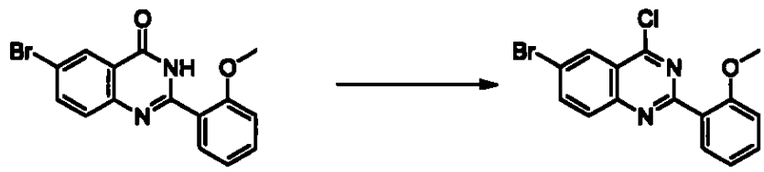
resultado 6-bromo-2-(2-metoxi-fenil)-3*H*-quinazolin-4-ona (31,3 g, 91%).

[00681] 6-Bromo-4-cloro-2-(2-metoxifenil)quinazolina

[00682]



[00683] Método A

[00684] 6-Bromo-2-(2-metoxifenil)quinazolin-4(3*H*)-ona (674 mg, 2,0 mmol), $POCl_3$ (624 mg, 4 mmol) y *N*, *N*-dimetilanilina (740 mg, 6,1 mmol) se disolvieron en benceno (12 ml) y se calentaron a reflujo durante 3 h. La mezcla de reacción se diluyó con EtOAc y la fase orgánica se lavó con $NaHCO_3$ saturado acuoso (1x) y H_2O (2x), se secó sobre Na_2SO_4 y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-5% de EtOAc en CH_2Cl_2/hexanos (1:1) dio 6-bromo-4-cloro-2-(2-metoxifenil)quinazolina. LC/MS: *m/z* 348,9 $(M+H)^+$ a 3,66 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00685] Método B

[00686] 6-Bromo-2-(2-metoxifenil)quinazolin-4(3*H*)-ona (0,31 g, 0,94 mmol), $POCl_3$ (86 µL, 0,94 mmol) y *N*,*N*-dimetilanilina (180 µL, 1,4 mmol) se calentaron a reflujo en tolueno seco durante 3 h. Se agregó $POCl_3$ adicional (0,94 mmol) y la reacción se calentó a reflujo durante una hora adicional. La

mezcla de reacción se diluyó con EtOAc y agua. La capa acuosa se alcalinizó con $NaHCO_3$ y las capas se separaron. Después de lavar la fase orgánica con agua, se secó sobre Na_2SO_4 y se concentró, la purificación por medio de cromatografía en gel de sílice usando 0-50% de EtOAc en 1:1 hexanos:CH_2Cl_2 dio 6-bromo-4-cloro-2-(2-metoxifenil)quinazolina en forma de un sólido amarillo (144 mg, 44%). ^1H RMN (400 MHz, $CDCl_3$) δ 8,45-8,45 (m, 1H), 8,04-7,99 (m, 2H), 7,82 (dd, *J* = 7,6, 1,7 Hz, 1H), 7,49-7,45 (m, 1H), 7,12-7,08 (m, 1H), 7,06 (d, *J* = 8,4 Hz, 1H), 3,90 (s, 3H); LC/MS: *m/z* 350,9 $(M+H)^+$ a 3,56 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00687] **2-(6-Bromo-4-cloroquinazolin-2-il)fenol**

[00688]

[00689] Método A

[00690] 6-Bromo-4-cloro-2-(2-metoxifenil)quinazolina (393 mg, 1,12 mmol) se disolvió en CH_2Cl_2 (3 ml) y el recipiente se inundó con N_2. Tras enfriar la mezcla de reacción hasta -78 °C, se añadió BBr_3 1 M en CH_2Cl_2 (3,37 ml, 3,37 mmol) gota a gota, luego la reacción se calentó lentamente hasta temperatura ambiente y se agitó durante 2 h. Después de neutralizar la mezcla con solución acuosa saturada de $NaHCO_3$ (1x), se transfirió en un embudo de separación con CH_2Cl_2. La capa

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orgánica se lavó con H_2O (2x), se secó sobre Na_2SO_4 y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-5% de EtOAc y CH_2Cl_2:hexanos (1:1) dio 2-(6-bromo-4-cloroquinazolin-2-il)fenol (229 mg, 61%). LC/MS: *m/z* 335,30 $(M+H)^+$ a 4,18 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00691] Método B

[00692] Una solución de 6-bromo-4-cloro-2-(2-metoxifenil)quinazolina (0,14 g, 0,4 mmol) en CH_2Cl_2 (ml) se enfrió en un baño de hielo seco/acetona. Una solución de BBr_3 1,0 M en CH_2Cl_2 (1,2 ml, 1,2 mmol) se añadió lentamente. El baño de enfriamiento se eliminó y la reacción se agitó a temperatura ambiente durante 2 h. La reacción se diluyó con CH_2Cl_2 y se alcalinizó con una solución saturada de $NaHCO_3$. La capa orgánica se separó, se lavó con agua, se secó sobre Na_2SO_4 y se evaporó para dar 6-bromo-4-cloro-2-(2-hidroxifenil)quinazolina (0,15 g).

[00693] **(*R*)-1-(4-(6-Bromo-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**

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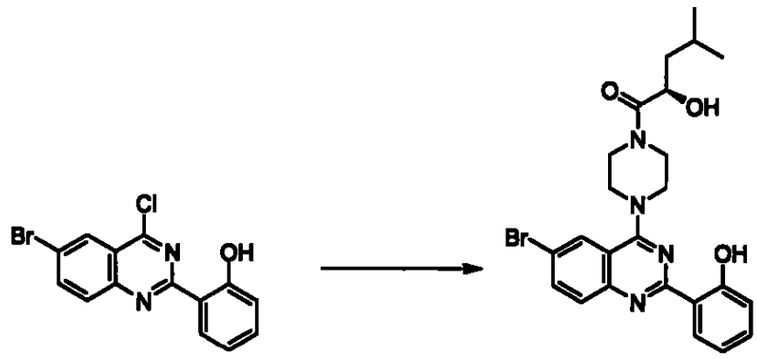


[00694]

[00695] Método A

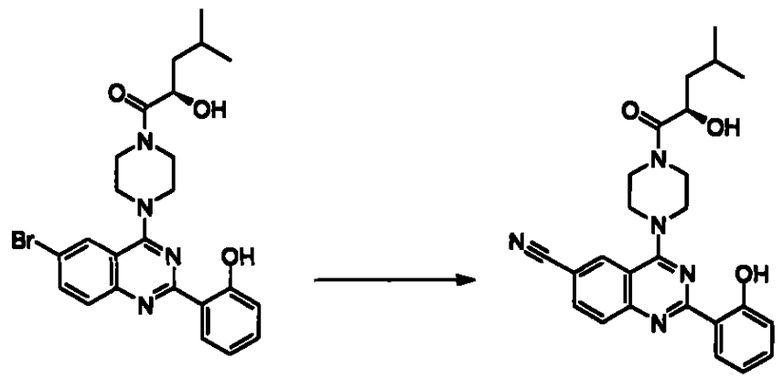
[00696] A una solución de 2-(6-bromo-4-cloroquinazolin-2-il)fenol (228 mg, 0,68 mmol), trietilamina (129 µL, 0,92 mmol) y CH_2Cl_2 (6 ml) se añadió (*R*)-2-hidroxi-4-metil-1-(piperazin-1-il)pentan-1-ona (185 mg, 0,92 mmol) disuelta en CH_2Cl_2 (3 ml). El recipiente se inundó con N_2 y se agitó durante 3 horas. La mezcla de reacción se transfirió luego a un embudo de separación con CH_2Cl_2 y la fase orgánica se lavó con H_2O (2x), se secó sobre Na_2SO_4 y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0 al 20% de EtOAc y CH_2Cl_2:hexanos (1:1) dio (*R*)-1-(4-(6-bromo-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (285 mg, 84%). LC/MS: *m/z* 500,30 $(M+H)^+$ a 3,29 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00697] Método B

[00698] Una solución de 6-bromo-4-cloro-2-(2-hidroxifenil)quinazolina (75 mg, 0,22 mmol), (*R*)-2-hidroxi-4-metil-1-piperazin-1-il-pentan-1-ona (60 mg, 0,3 mmol),

trietilamina (42 µL, 0,3 mmol) y CH_2Cl_2 (2 ml) se agitó a temperatura ambiente durante la noche. Tras diluir con CH_2Cl_2, la mezcla de reacción se lavó con H_2O, se secó sobre Na_2SO_4 y se concentró. El material crudo se purificó por cromatografía en gel de sílice usando 0-10% de MeOH/CH_2Cl_2 para dar (*R*)-1-{4-[6-bromo-2-(2-metoxi-fenil)-quinazolin-4-il]-piperazin-1-il}-2-hidroxi-4-metil-pentan-1-ona (40 mg, 36%). LC/MS: *m/z* 449,3 $(M+H)^+$ a 3,26 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00699] 4-[4-((*R*)-2-Hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-6-carbonitrilo



[00700]

[00701] Método A

[00702] Una mezcla de (*R*)-1-{4-[6-bromo-2-(2-metoxi-fenil)-quinazolin-4-il]-piperazin-1-il}-2-hidroxi-4-metil-pentan-1-ona (20 mg, 0,04 mmol), $Zn(CN)_2$ (4,7 mg, 0,04 mmol) y $Pd(PPh_3)_4$ (1,4 mg, 1,4 µmol) en DMF (0,5 ml) se calentó en un

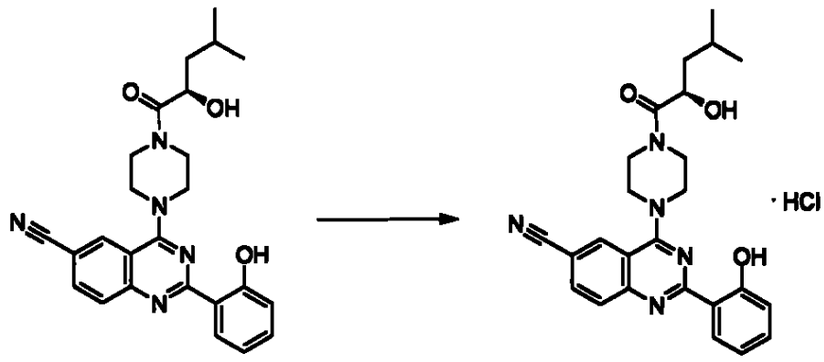
sintetizador a microondas a 200 °C durante 15 minutos. La purificación por HPLC preparativa dio 4-[4-((*R*)-2-hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-6-carbonitrilo en forma de la sal de TFA. LC/MS: *m/z* 446,3 $(M+H)^+$ a 3,17 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00703] Método B

[00704] (*R*)-1-(4-(6-Bromo-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (188 mg, 0,38 mmol), $Zn(CN)_2$ (44 mg, 0,38 mmol) y $Pd(Ph_3)_4$ (6,5 mg, 0,0112 mmol) se disolvieron en DMF (4 ml) y la mezcla de reacción se calentó en un sintetizador a microondas a 200 °C durante 15 minutos. Se añadió EtOAc (50 ml) y la mezcla se lavó dos veces con H_2O. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-40% de EtOAc en CH_2Cl_2:hexanos (1:1) dio 4-[4-((*R*)-2-hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-6-carbonitrilo (127 mg, 75%). LC/MS: *m/z* 446 $(M+H)^+$ a 3,24 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,60 (d, *J* = 1,5 Hz, 1H), 8,46 (dd, *J* = 8,4, 1,8 Hz, 1H), 8,15 (dd, *J* = 8,7, 1,7 Hz, 1H), 8,00 (d, *J* = 8,7 Hz, 1H), 7,45-7,41 (m, 1H), 6,99-6,95 (m, 2H), 4,94 (d, *J* = 7,0 Hz, 1H), 4,39-4,36 (m,

1H), 4,14-4,04 (m, 4H), 3,89-3,67 (m, 4H), 1,82-1,76 (m, 1H), 1,47-1,37 (m, 2H), 0,93-0,91 (m, 6H).

|00705| Clorhidrato de 4-[4-((*R*)-2-Hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-6-carbonitrilo



|00706|

|00707| 4-[4-((*R*)-2-Hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-6-carbonitrilo (137 mg, 0,31 mmol) se disolvió en la cantidad mínima de CH_2Cl_2. Tras agitar la solución bajo una atmósfera de N_2 durante 30 minutos, se añadió HCl 1 M en éter (0,31 ml, 0,31 mmol) gota a gota a la solución y se agitó durante 10 minutos. Se añadió un precipitado de éter a la sal de clorhidrato de 4-[4-((*R*)-2-hidroxi-4-metil-pentanoil)-piperazin-1-il]-2-(2-hidroxi-fenil)-quinazolin-6-carbonitrilo, que se filtró y se secó para obtener 136 mg de sólido (91%). LC/MS: *m/z* 446 $(M+H)^+$ a 3,21 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H

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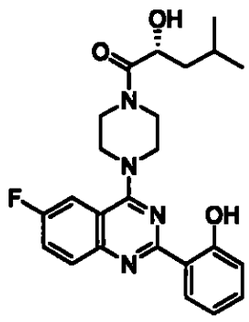
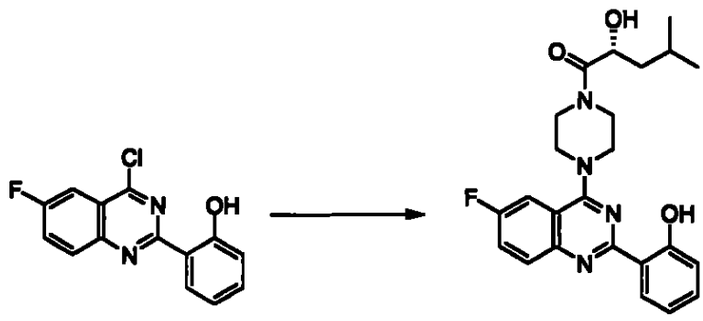
RMN (400 MHz, DMSO-d6) δ 8,62 (s, 1H), 8,43-8,41 (m, 1H), 8,17 (dd, *J* = 8,7, 1,5 Hz, 1H), 8,02 (d, *J* = 8,7 Hz, 1H), 7,47-7,43 (m, 1H), 7,00-6,96 (m, 2H), 4,39-4,36 (m, 1H), 4,18-4,00 (m, 4H), 3,91-3,68 (m, 4H), 1,85-1,75 (m, 1H), 1,51-1,35 (m, 2H), 0,94-0,91 (m, 6H); ^{13}C RMN (100 MHz, DMSO-d6) δ 172,5, 161,7, 160,6, 135,1, 133,6, 132,4, 129,7, 126,9, 118,8, 118,4, 118,2, 117,4, 113,3, 107,3, 66,9, 48,7, 48,1, 43,5, 42,8, 41,1, 24,0, 23,4, 21,6.

[00708] Ejemplo 143

[00709] **(*R*)-1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**

[00710] 

[00711] **(*R*)-1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**



[00712]

[00713] Método A

[00714] A una solución de 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (25 mg, 0,09 mmol) en DMF (1 ml) se añadió trietilamina (25 µL, 0,18 mmol) seguido de la adición de oxalato de (R)-2-hidroxi-4-metil-1-(piperazin-1-il)pentan-1-ona (52 mg, 0,18 mmol) a 0 °C. La reacción se agitó durante 2 horas y la purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,99 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00715] Método B

[00716] A una mezcla de 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (200 mg, 0,72 mmol) y CH_2Cl_2 (7 ml) se añadió oxalato de (R)-2-hidroxi-4-metil-1-(piperazin-1-il)pentan-1-ona (275 mg, 0,95 mmol). La reacción se completó después de dos horas.

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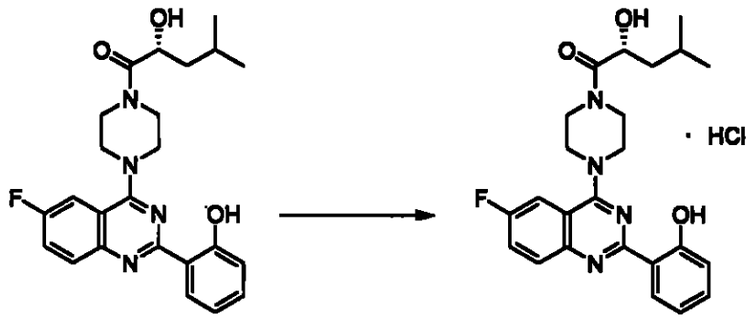
La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en una mezcla 50:50 de CH_2Cl_2:hexanos dio (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (289 mg, 91%). LC/MS: *m/z* 439,30 $(M+H)^+$ a 3,00 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,46 (m, 1H), 8,02 (m, 1H), 7,84 (m, 2H), 7,40 (m, 1H), 6,97 (m, 2H), 4,92 (d, *J* = 7,2 Hz, 1H), 4,38 (m, 1H), 3,98 (m, 4H), 3,76 (m, 4H), 1,80 (m, 1H), 1,42 (m, 2H), 0,92 (q, *J* = 3,8 Hz, 6H).

[00717] Clorhidrato de (*R*)-1-(4-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona

[00718]



[00719] A una solución de (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (285 mg, 0,65 mmol) en CH_2Cl_2 (2 ml) bajo una atmósfera de N_2 se añadió éter (10 ml), seguido de la adición gota a gota de una solución 2 M de HCl en éter (0,325 ml, 0,65

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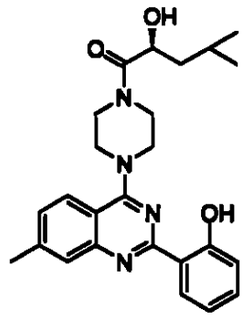
mmol). Se formó un precipitado que se agitó durante 30 min, se recogió por filtración al vacío y se secó para obtener clorhidrato de (*R*)-1-(4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (284 mg, 92%). LC/MS: *m/z* 439,30 $(M+H)^+$ a 3,00 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)): ^1H RMN (400 MHz, DMSO-d6) δ 8,32 (dd, *J* = 8,1, 1,5 Hz, 1H), 8,02 (m, 1H), 7,92 (dd, *J* = 9,7, 2,7 Hz, 1H), 7,85 (m, 1H), 7,45 (m, 1H), 7,01 (m, 2H), 4,37 (dd, *J* = 9,2, 4,1 Hz, 1H), 4,04 (m, 4H), 3,83 (m, 4H), 1,76 (m, 1H), 1,41 (m, 2H), 0,90 (dd, *J* = 6,6, 3,7 Hz, 6H).

[00720] Ejemplo 144

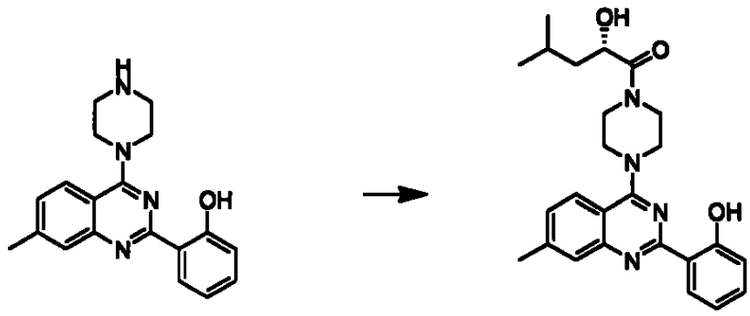
[00721] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**



[00722]

[00723] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**

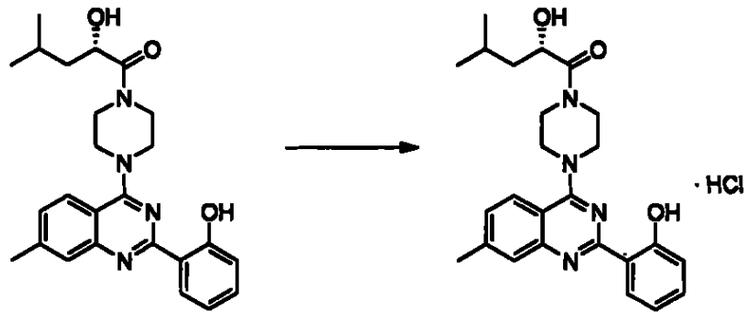
[00724]



[00725] En una atmósfera de N_2, se añadió BOP (137 mg, 0,31 mmol) en una única porción a una solución agitada de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (100 mg, 0,31 mmol), ácido (*S*)-2-hidroxi-4-metilpentanoico (41 mg, 0,31 mmol) y trietilamina (43 µL, 0,31 mmol) en DMF (0,5 ml). Tras agitar la mezcla durante 1 h a temperatura ambiente, se dividió en H_2O y éter. La fase orgánica se lavó con H_2O (3x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 1:1 acetato de etilo / hexano dio (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona en forma de un sólido blanco. LC/MS: *m/z* 435,3 $(M+H)^+$ a 2,62 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,44 (dd, *J* = 8,2, 1,7 Hz, 1H), 7,99 (d, *J* = 8,5 Hz, 1H), 7,67 (s, 1H), 7,40-7,36 (m, 2H), 6,96-6,93 (m, 2H), 4,92 (d, *J* = 7,2 Hz, 1H) 4,41-4,36 (m, 1H), 4,06-3,67 (m, 8H), 2,51 (s, 3H), 1,85-1,73 (m, 1H), 1,49-1,35 (m, 2H), 0,93-0,91 (m, 6H).

[00726] Clorhidrato de (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona

[00727]

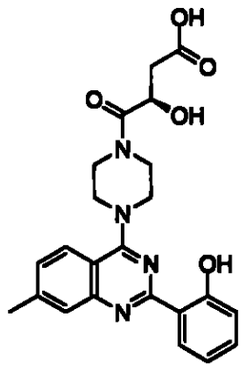


[00728] (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona (90 mg, 0,20 mmol) se disolvió en 1 ml de CH_2Cl_2 y se trató con 1 equivalente de HCl 2,0 M en éter (100 µL, 0,20 mmol). El precipitado formado se filtró y se secó al vacío para obtener clorhidrato de (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona.

LC/MS: *m/z* 435,5 $(M+H)^+$ a 2,62 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,27 (d, *J* = 6,8 Hz, 1H), 8,09 (d, *J* = 8,6 Hz, 1H), 7,78 (s, 1H), 7,50-7,45 (m, 2H), 7,09 (d, *J* = 8,2 Hz, 1H), 7,03-6,99 (m, 1H), 4,39-4,35 (m, 1H), 4,16-3,68 (m, 8H), 2,54 (s, 3H), 1,84-1,72 (m, 1H), 1,49-1,35 (m, 2H), 0,93 (d, *J* = 2,8 Hz, 6H).

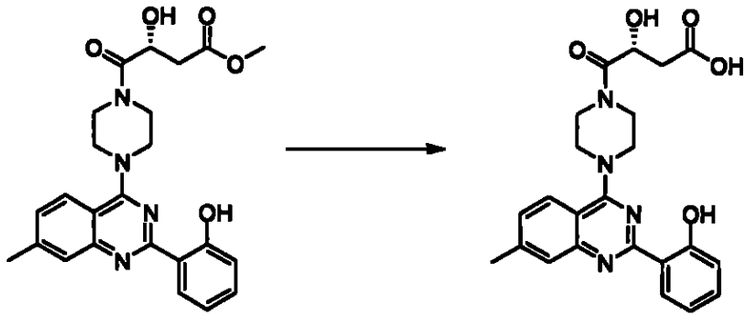
[00729] Ejemplo 145

[00730] **Ácido (*R*)-3-hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-oxobutanoico**



[00731]

[00732] **Ácido (*R*)-3-hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-oxobutanoico**



[00733]

[00734] 3-hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-oxobutanoato de (*R*)-metilo (88 mg, 0,20 mmol) y $LiOH \cdot H_2O$ (33 mg, 0,78 mmol) se agitaron en THF:H_2O 1:1 a temperatura ambiente durante 3 h.

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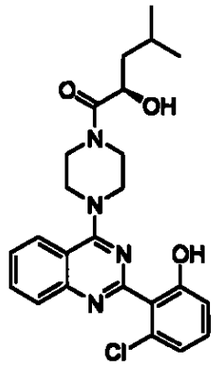
Después de acidificar con HCl 1 M y extraer con EtOAc, los extractos orgánicos se lavaron con agua, se secaron sobre Na_2SO_4 y se concentraron. El material crudo se purificó luego por cromatografía en gel de sílice usando 0-10% de MeOH/CH_2Cl_2 para obtener ácido (*R*)-3-hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-oxobutanoico (75 mg, 88%). LC/MS: *m/z* 437,3 $(M+H)^+$ a 2,04 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00735] Ejemplo 146

[00736] **(*R*)-1-(4-(2-(2-cloro-6-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**



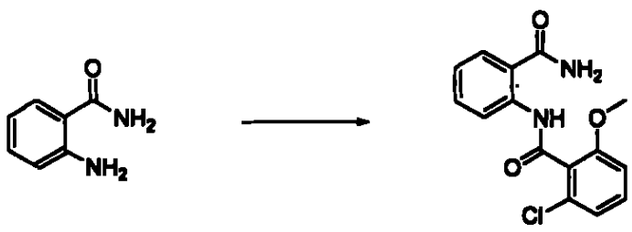
[00737]

[00738] **2-Amino-benzamida**

[00739]

[00740] Se suspendió anhidrido isatoico (40 g, 245 mmol) en 650 ml NH_4OH 1 N (2,5 equiv) y se agitó a temperatura ambiente durante 3 días. El precipitado se filtró y se lavó con agua. El producto luego se disolvió en THF, se filtró y se concentró hasta sequedad. El producto se secó por destilación azeotrópica con tolueno y se lavó con CH_2Cl_2 para obtener 10,9 g (32,7%) de 2-amino-benzamida.

[00741] **2-cloro-*N*-2-metoxi-benzamida de la fenilamida del ácido 2-carboxílico**

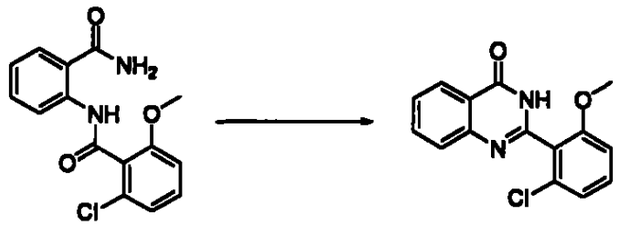


[00742]

[00743] 2-Amino-benzamida (6,9 g, 50,8 mmol) se disolvió en 50 ml de piridina y se enfrió hasta 0 °C. Se añadió cloruro de 2-cloro-6-metoxi-benzoílo gota a gota a la solución. Después de completar la adición, la reacción se dejó agitar a temperatura ambiente durante tres días, que resultó en la

formación de una solución marrón turbia. La mezcla de reacción se vertió luego en 150 ml de agua helada. El precipitado se filtró y se lavó dos veces con agua, dos veces con THF y finalmente dos veces con CH_2Cl_2 para obtener 2-cloro-*N*-2-metoxi-benzamida de fenilamida del ácido 2-carboxílico (13,3 g, 43,7 mmol, 86%).

[00744] **2-(2-cloro-6-metoxi-fenil)-3*H*-quinazolin-4-ona**



[00745]

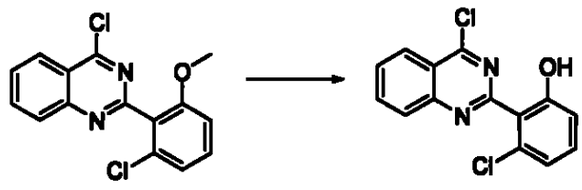
[00746] Se suspendió 2-cloro-*N*-2-metoxi-benzamida de fenilamida del ácido 2-carboxílico (13 g, 42,7 mmol) en 100 ml de una solución de NaOH 2 N y se calentó a reflujo. Después de calentar a reflujo durante 3 horas, se añadieron otros 25 ml de una solución de NaOH 2 N y la reacción se calentó a reflujo durante otra hora. La mezcla se enfrió hasta temperatura ambiente y se acidificó con ácido acético hasta pH 5. El precipitado formado se recogió por filtración. El producto se purificó sobre alúmina usando EtOAc como un eluyente para dar 1,7 g (5,9 mmol, 14%) de 2-(2-cloro-6-metoxi-fenil)-3*H*-quinazolin-4-ona.

[00747] **4-cloro-2-(2-cloro-6-metoxi-fenil)-quinazolina**

[00748]

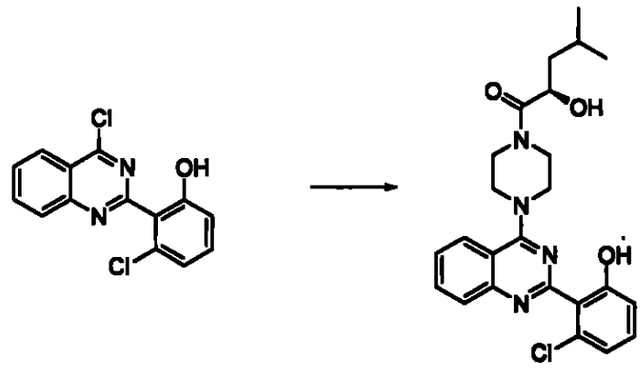
[00749] Se disolvió 2-(2-cloro-6-metoxi-fenil)-3*H*-quinazolin-4-ona (1,7 g, 5,9 mmol) en 25 ml de benceno. Luego, se agregaron *N*,*N*-dimetilanilina (1,15 ml, 9 mmol) y $POCl_3$ (1,65 ml, 17,7 mmol). La mezcla de reacción se calentó a reflujo durante 3 horas mientras la suspensión amarilla cambiaba a un color rojo oscuro. La mezcla se enfrió y se diluyó con 50 ml de tolueno. La solución se vertió en hielo. Se añadió $NaHCO_3$ acuoso saturado mientras se agitaba y enfriaba la mezcla, hasta que el pH quedó constante en 7. Las capas se separaron y la capa acuosa se extrajo con 100 ml de tolueno. Las capas de tolueno se combinaron y se lavaron con 100 ml de solución acuosa saturada de NaCl, 150 ml de HCl 0,5 N, 150 ml de $NaHCO_3$ acuoso al 5% y solución acuosa saturada de NaCl. La capa de tolueno se secó sobre Na_2SO_4, se filtró y se concentró hasta sequedad para obtener 1,87 g de producto impuro. El producto se purificó sobre gel de sílice con heptano/CH_2Cl_2 (2:1) como un eluyente para obtener 4-cloro-2-(2-cloro-6-metoxi-fenil)-quinazolina (1,22 g, 64%).

[00750] **3-cloro-2-(4-cloroquinazolin-2-il)fenol**

[00751] 

[00752] A una solución de 4-cloro-2-(2-cloro-6-metoxifenil)quinazolina (300 mg, 0,98 mmol) en 10 ml de CH_2Cl_2 se añadieron gota a gota 5 equivalentes de una solución 1 M de BBr_3 en CH_2Cl_2 a -78 °C. La reacción se calentó hasta temperatura ambiente y se completó en 30 minutos. La reacción se neutralizó con una solución acuosa saturada de $NaHCO_3$ solución hasta pH 7. La capa acuosa se extrajo con CH_2Cl_2, y los extractos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron para obtener 3-cloro-2-(4-cloroquinazolin-2-il)fenol. LC/MS: *m/z* 291,3 $(M+H)^+$ a 3,16 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00753] **(*R*)-1-(4-(2-(2-cloro-6-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**

[00754] 

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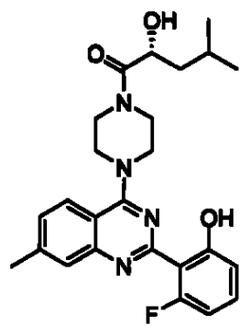
[00755] A una solución de 3-cloro-2-(4-cloroquinazolin-2-il)fenol (42 mg, 0,14 mmol) en 2 ml de CH_2Cl_2 se añadió trietilamina (40 µL) seguido de la adición de (*R*)-2-hidroxi-4-metil-1-(piperazin-1-il)pentan-1-ona (37,5 mg, 0,187 mmol). La reacción se completó después de 1 hora. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-1-(4-(2-(2-cloro-6-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 455,5 $(M+H)^+$ a 2,45 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

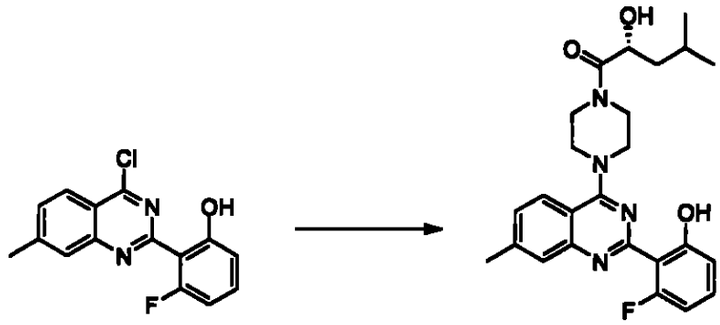
[00756] Ejemplo 147

[00757] **(*R*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**

[00758]



[00759] **(*R*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**



[00760]

[00761] Método A

[00762] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (50 mg, 0,174 mmol) en 1 ml de DMF se añadió trietilamina (35,2 mg, 0,348 mmol), seguido de la adición de (*R*)-2-hidroxi-4-metil-1-(piperazin-1-il)pentan-1-ona (42,1 mg, 0,21 mmol). Tras agitar la reacción durante 1 hora, se filtró y se purificó por HPLC preparativa en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*R*)-1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 453,3 (M+H)+ a 2,40 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00763] Método B

|00764| 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (300 mg, 1,04 mmol) en CH_2Cl_2 (5 ml) se enfrió usando un lote de agua helada. A esta solución agitada se añadió (*R*)-2-hidroxi-4-metil-1-(piperazin-1-il)pentan-1-ona (312 mg, 1,56 mmol), seguido de trietilamina (210 mg, 291 µL, 2,08 mmol). Al cabo de dejar calentar la reacción hasta temperatura ambiente, se agitó durante la noche. La mezcla se dividió en agua y CH_2Cl_2 y se separó y la capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron en un aceite amarillo viscoso. La purificación por medio de cromatografía en gel de sílice usando 0-30% de EtOAc en CH_2Cl_2/hexanos (2:1) dio (*R*)-1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de una espuma/sólido de color amarillo brillante (413 mg, 88%). LC/MS: *m/z* 453,1 $(M+H)^+$ a 2,44 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,01 (d, *J* = 8,5 Hz, 1H), 7,68 (s, 1H), 7,42 (d, *J* = 8,5 Hz, 1H), 7,37-7,32 (m, 1H), 6,80 (d, *J* = 8,3 Hz, 1H), 6,76-6,71 (m, 1H), 4,91 (d, *J* = 7,2 Hz, 1H), 4,40-4,35 (m, 1H), 4,02-3,65 (m, 8H), 2,52 (s, 3H), 1,82-1,73 (m, 1H), 1,47-1,34 (m, 2H), 0,91 (dd, *J* = 6,5, 4,1 Hz, 6H).

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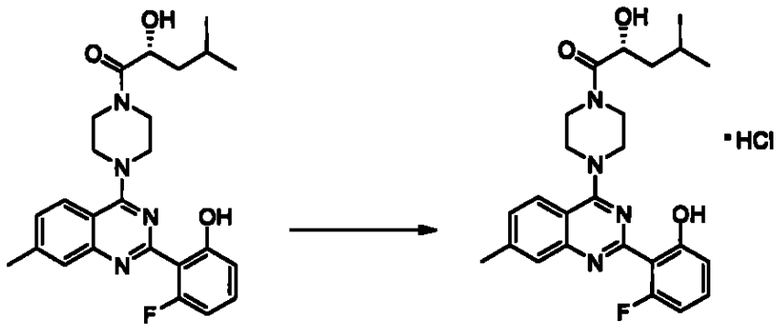
845

[00765] Clorhidrato de (*R*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona



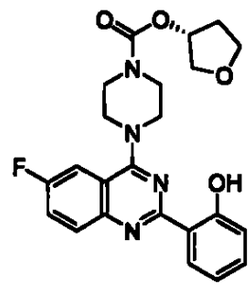
[00766]

[00767] (*R*)-1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (406 mg, 0,898 mmol) se disolvió en CH_2Cl_2 anhidro (3 ml) seguido de la adición de Et_2O (6 ml) bajo una atmósfera de N_2. Una solución de HCl 2,0 M en Et_2O (0,449 ml, 0,898 mmol) se añadió durante 2 minutos. La solución de reacción cambió de una solución de color amarillo claro a una suspensión blanca turbia. Tras la adición completa de la solución de HCl, la reacción se dejó bajo agitación durante 15 minutos adicionales. El producto se recogió por filtración al vacío y se secó al vacío para obtener clorhidrato de (*R*)-1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de un sólido blanco (403 mg, 92%). LC/MS: *m/z* 453,5 $(M+H)^+$ a 2,44 min (10%-99% de

CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,20 (d, *J* = 8,7 Hz, 1H), 7,71 (s, 1H), 7,60-7,60 (m, 1H), 7,50-7,44 (m, 1H), 6,99 (d, *J* = 8,4 Hz, 1H), 6,87 (t, *J* = 9,1 Hz, 1H), 4,36-4,33 (m, 1H), 4,25-3,67 (m, 8H), 2,57 (s, 3H), 1,83-1,71 (m, 1H), 1,49-1,35 (m, 2H), 0,91 (d, *J* = 6,7 Hz, 6H).

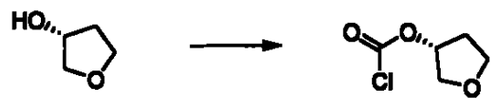
[00768] Ejemplo 148

[00769] **4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (R)-tetrahidrofuran-3-ilo**



[00770]

[00771] **cloroformiato de (R)-tetrahidrofuran-3-ilo**



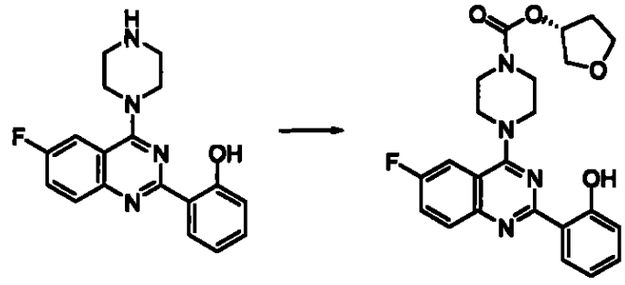
[00772]

[00773] Una solución agitada de (*R*)-tetrahidrofuran-3-ol (7,9 g, 90 mmol) en CH_2Cl_2 anhidro (50 ml) bajo una atmósfera de N_2 se enfrió en un baño de hielo y se añadió una solución al 20% de fosgeno en tolueno (134 ml, 270 mmol) lentamente. La

reacción se dejó calentar hasta temperatura ambiente durante la noche y el solvente se eliminó al vacío para obtener cloroformiato de (R)-tetrahidrofuran-3-ilo (12,1 g, 85%) en forma de un líquido claro.

|00774|

|00775| **4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (R)-tetrahidrofuran-3-ilo**



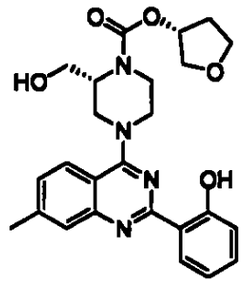
|00776|

|00777| 2-(6-Fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (25 mg, 0,08 mmol), cloroformiato de (R)-tetrahidrofuran-3-ilo (12 mg, 0,08 mmol), trietilamina (22 µL, 0,154 mmol) y HATU (38 mg, 0,10 mmol) se agitaron en DMF (1 ml) durante la noche. La purificación mediante HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (R)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,80 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

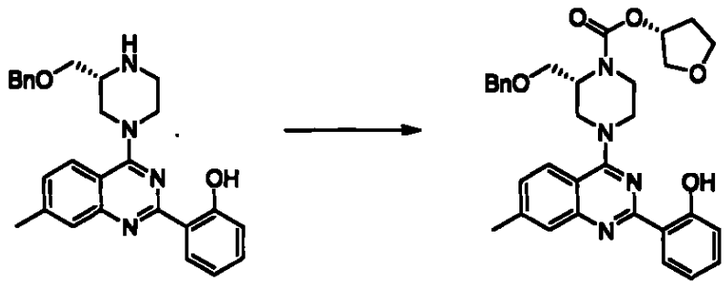
|00778| Ejemplo 149

[00779] **2-(hidroximetil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (2*R*)-(R)-tetrahidrofuran-3-ilo**

[00780]



[00781] **2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (2*R*)-(*R*)-tetrahidrofuran-3-ilo**

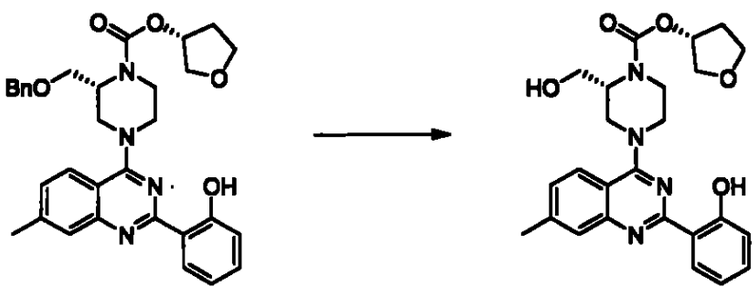


[00782]

[00783] A una solución de 2-(4-((*R*)-3-((benciloxi)metil)piperazin-1-il)-7-metilquinazolin-2-il)fenol (75 mg, 0,17 mmol) en DMF (1 ml) se añadió trietilamina (47 µL) seguido de la adición gota a gota de cloroformiato de (R)-tetrahidrofuran-3-ilo (25 mg, 0,17 mmol) a 0 °C. La reacción se calentó hasta temperatura ambiente y se agitó durante 10

minutos. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (2*R*)-(R)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 455,3 $(M+H)^+$ a 2,95 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00784] 2-(hidroximetil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (2*R*)-(*R*)-tetrahidrofuran-3-ilo



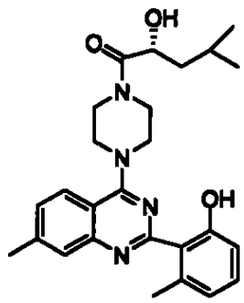
[00785]

[00786] A una solución de sal de TFA de 2-((benciloxi)metil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (2*R*)-(R)-tetrahidrofuran-3-ilo (94 mg, 0,17 mmol) en etanol se añadió $Pd(OH)_2$ (78 mg) y la reacción se calentó a 50 °C bajo una atmósfera de H_2 a presión ambiente. La reacción se filtró y la purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio trifluoroacetato de 2-(hidroximetil)-4-(2-(2-

hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (2*R*)-(R)-tetrahidrofuran-3-ilo. LC/MS: *m/z* 465,5 $(M+H)^+$ a 2,23 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00787] Ejemplo 150

[00788] **(*R*)-2-Hidroxi-1-(4-(2-(2-hidroxi-6-metilfenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**



[00789]

[00790] **Ácido 2-metoxi-6-metil-benzoico**

[00791]

[00792] Se añadió 2-metoxi-6-metilbenzoato de etilo (30,4 g, 0,157 mol) a 100 ml de NaOH 3,2 M (2 equiv) y 150 ml de EtOH caliente. La mezcla se calentó a reflujo durante la noche después de eliminar el EtOH al vacío. La mezcla acuosa se acidificó con HCl 5 M hasta pH 3. Se agregó CH_2Cl_2 (200 ml) y las capas se separaron. La capa acuosa se extrajo dos veces

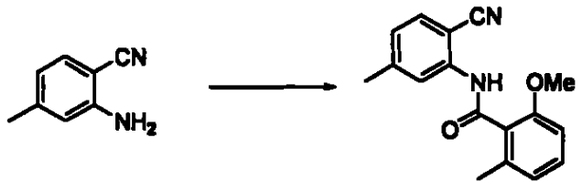
con 200 ml de CH_2Cl_2 y las capas orgánicas se combinaron y se secaron sobre Na_2SO_4. La filtración de Na_2SO_4 y la concentración de CH_2Cl_2 hasta sequedad dieron como resultado 21,4 g (0,129 mol, 82,3%) de ácido 2-metoxi-6-metil-benzoico.

[00793] **Cloruro de 2-metoxi-6-metil-benzoílo**

[00794]

[00795] Se calentó ácido 2-metoxi-6-metil-benzoico (21,4 g, 0,129 mol) a reflujo durante 3 horas en 230 ml de cloruro de tionilo. El exceso de cloruro de tionilo se eliminó a presión reducida. La co-evaporación del residuo con tolueno dio 23,8 g de cloruro de 2-metoxi-6-metil-benzoílo.

[00796] **N-(2-Ciano-5-metil-fenil)-2-metoxi-6-metil-benzamida**

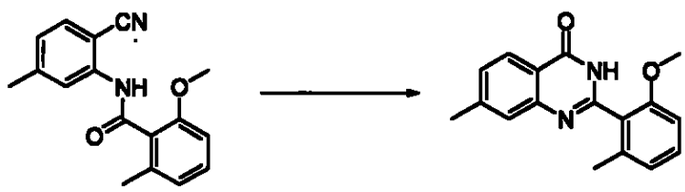


[00797]

[00798] 2-Amino-4-metil-benzonitrilo (15,4 g, 0,117 mol) se disolvió en 100 ml de piridina y se enfrió hasta 0 °C. A esta mezcla se añadió gota a gota cloruro de 2-metoxi-6-metilbenzoílo (24 g, 0,13 mol, 1,1 equiv). Durante la adición, la temperatura no excedió los 2 °C. La reacción se agitó a

temperatura ambiente durante 48 horas. La mezcla se vertió en 400 ml de agua helada y el precipitado se recogió por filtración y se lavó con agua. El producto crudo se disolvió en 600 ml de CH_2Cl_2 y la solución se lavó dos veces con 500 ml de una solución de HCl 1 N y una vez con 400 ml de una solución acuosa saturada de NaCl. La capa de CH_2Cl_2 se secó sobre Na_2SO_4, se filtró y se concentró hasta sequedad para obtener 25,44 g (0,09 mol, 77,6%) de *N*-(2-ciano-5-metil-fenil)-2-metoxi-6-metil-benzamida.

[00799] **2-(2-metoxi-6-metil-fenil)-7-metil-3*H*-quinazolin-4-ona**



[00800]

[00801] *N*-(2-Ciano-5-metil-fenil)-2-metoxi-6-metil-benzamida (25 g, 0,09 mol) se suspendió en 500 ml de EtOH y se añadieron 121,3 g de NaOH acuoso al 33% (1 mol, 11 equiv). A esto se añadió una solución al 35% de H_2O_2 (50 ml, 0,58 mol) y la reacción se calentó a reflujo. Se añadió más H_2O_2 gota a gota hasta que se aclaró la mezcla de reacción. El EtOH se eliminó a presión reducida y el precipitado formado se eliminó por filtración. La solución se acidificó con ácido acético hasta

pH 5 y el precipitado formado se recogió por filtración. El precipitado se lavó dos veces con agua y una vez con éter dietílico. El producto se purificó sobre alúmina usando EtOAc/heptano (1:1) en forma de eluyente. Se llevó a cabo otra purificación sobre gel de sílice con el mismo eluyente para obtener 2-(2-metoxi-6-metil-fenil)-7-metil-3*H*-quinazolin-4-ona (1,61 g).

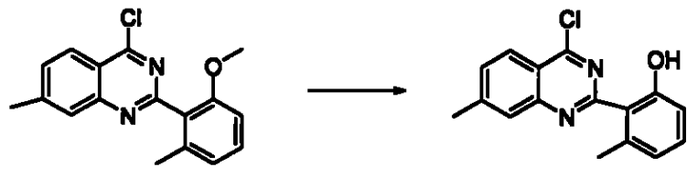
|00802| **4-cloro-2-(2-metoxi-6-metil-fenil)-7-metil-quinazolina**

|00803|

|00804| 2-(2-metoxi-6-metil-fenil)-7-metil-3*H*-quinazolin-4-ona (1,61 g, 5,74 mmol) se suspendió en benceno después de añadir *N,N*-dimetilanilina (1,1 ml, 8,62 mmol) y $POCl_3$ (1,61 ml, 17,27 mmol). La mezcla de reacción se calentó a reflujo durante 3 horas hasta que el color cambió de amarillo a rojo oscuro. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con 40 ml de tolueno y se vertió en hielo. Se añadió $NaHCO_3$ saturado acuoso cuidadosamente hasta que el pH quedó constante a 7 y no se formó más gas. Las capas se separaron y la capa acuosa se extrajo con tolueno. Las capas

orgánicas se combinaron y se lavaron con respectivamente 50 ml de NaCl acuoso saturado, 60 ml de HCl 0,5 N, 40 ml de $NaHCO_3$ al 5% y 50 ml de NaCl saturado acuoso. La solución se secó sobre Na_2SO_4 y se evaporó hasta sequedad para obtener 1,7 g de producto impuro. El producto se filtró a través de gel de sílice y se lavó con CH_2Cl_2:heptano (2:1) para obtener de 4-cloro-2-(2-metoxi-6-metil-fenil)-7-metil-quinazolina (1,22 g, 71%).

[00805] **2-(4-cloro-7-metilquinazolin-2-il)-3-metilfenol**



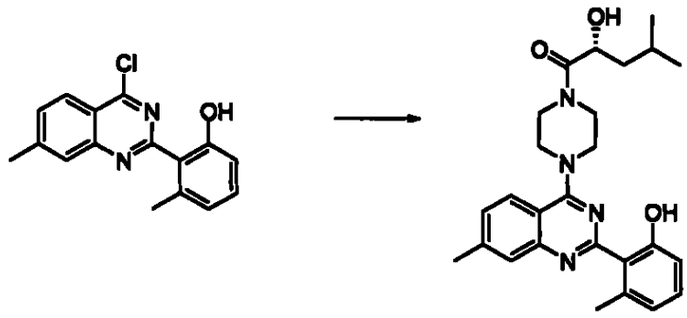
[00806]

[00807] A una solución de 4-cloro-2-(2-metoxi-6-metilfenil)-7-metilquinazolina (669 mg, 2,24 mmol) en 7 ml de CH_2Cl_2 se añadieron gota a gota 5 equivalentes de una solución 1 M de BBr_3 en CH_2Cl_2 a -78 °C. La reacción se calentó hasta temperatura ambiente y se completó en 30 minutos. La reacción se neutralizó con una solución acuosa saturada de $NaHCO_3$ hasta que el pH fuera neutro. La capa acuosa se extrajo con CH_2Cl_2, se secó sobre $MgSO_4$, se filtró y se concentró para obtener 2-(4-cloro-7-metilquinazolin-2-il)-3-metilfenol. LC/MS: *m/z*

848
855

285,1 $(M+H)^+$ a 3,94 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00808] **(*R*)-2-Hidroxi-1-(4-(2-(2-hidroxi-6-metilfenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**

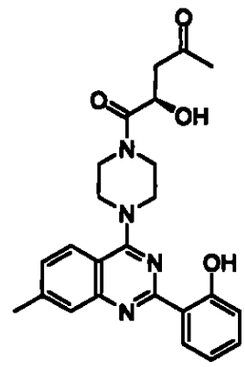


[00809]

[00810] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)-3-metilfenol (60 mg, 2,1 mmol) en 2 ml de CH_2Cl_2 se añadió trietilamina seguido de la adición de (*R*)-2-hidroxi-4-metil-1-(piperazin-1-il)pentan-1-ona (54,8 mg, 2,73 mmol). La reacción se completó después de 1 hora. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-2-hidroxi-1-(4-(2-(2-hidroxi-6-metilfenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,22 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

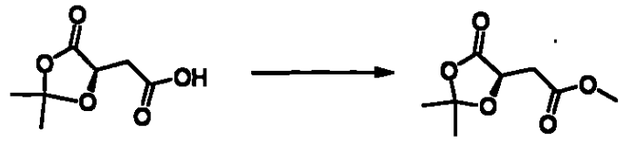
[00811] Ejemplo 151

[00812] **(*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)pentano-1,4-diona**



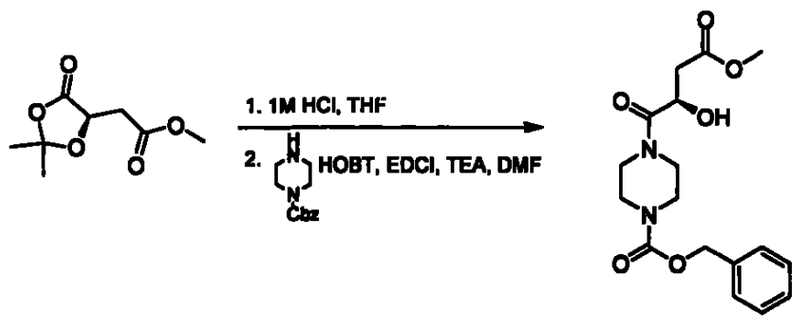
[00813]

[00814] **2-((*R*)-2,2-dimetil-5-oxo-1,3-dioxolan-4-il)acetato de metilo**

[00815] 

[00816] Ácido 2-((*R*)-2,2-dimetil-5-oxo-1,3-dioxolan-4-il)acético (15,8 g, 90,9 mmol) en una mezcla 3:1 de THF:MeOH (100 ml) se enfrió en un baño de hielo. Tras añadir $TMSCHN_2$ 2,0 M (50 ml, 100 mmol), se retiró el baño y la mezcla se agitó a temperatura ambiente durante 3 h. El solvente se evaporó y el material crudo se purificó mediante cromatografía en gel de sílice usando 0-50% de EtOAc/hexanos para dar 2-((*R*)-2,2-dimetil-5-oxo-1,3-dioxolan-4-il)acetato de metilo. ^1H RMN (400 MHz, $CDCl_3$) δ 4,73 (dd, *J* = 6,6, 3,8 Hz, 1H), 3,74 (s, 3H), 2,95 (dd, *J* = 17,0, 3,9 Hz, 1H), 2,81 (dd, *J* = 17,0, 6,6 Hz, 1H), 1,63 (s, 3H), 1,57 (s, 3H).

[00817] **Éster bencílico del ácido 4-((*R*)-2-Hidroxi-3-**



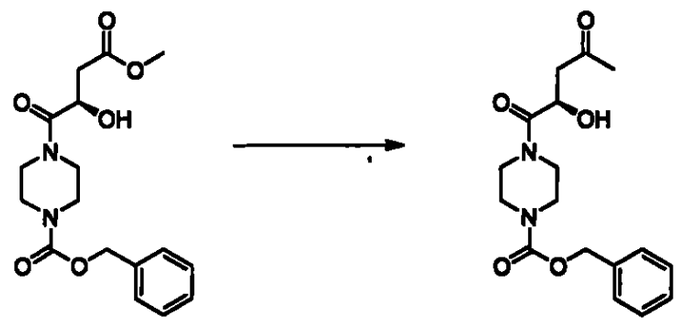
metoxicarbonil-propionil)-piperazin-1-carboxílico

[00818]

[00819] Se agitó 2-((*R*)-2,2-dimetil-5-oxo-1,3-dioxolan-4-il)acetato de metilo (17,1 g, 90,9 mmol) en una mezcla 1:1 de THF: HCl 1 M (200 ml) durante 1 h a temperatura ambiente. Después de la adición de NaCl a la capa acuosa prácticamente saturada, la mezcla se extrajo con EtOAc y los extractos se secaron sobre Na_2SO_4 y se concentraron. Al aceite resultante disuelto en DMF seca (500 ml) se añadió HOBt (13,5 g, 100 mmol) y EDCI (19,2 g, 100 mmol). Tras agitar durante 5 min, se agregaron piperazin-1-carboxilato de bencilo (19,3 ml, 100 mmol) y trietilamina (13,9 ml, 100 mmol) a la mezcla de reacción, que se dejó bajo agitación a temperatura ambiente durante la noche. La purificación por medio de cromatografía en gel de sílice usando 0-10% de MeOH/CH_2Cl_2 dio un aceite incoloro de éster bencílico del ácido 4-((R)-2-hidroxi-3-metoxicarbonil-propionil)-piperazin-1-carboxílico (6,71 g,

21%). LC/MS: *m/z* 351,5 $(M+H)^+$ a 2,67 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00820] Éster bencílico del ácido 4-((R)-2-Hidroxi-4-oxo-pentanoil)-piperazin-1-carboxílico



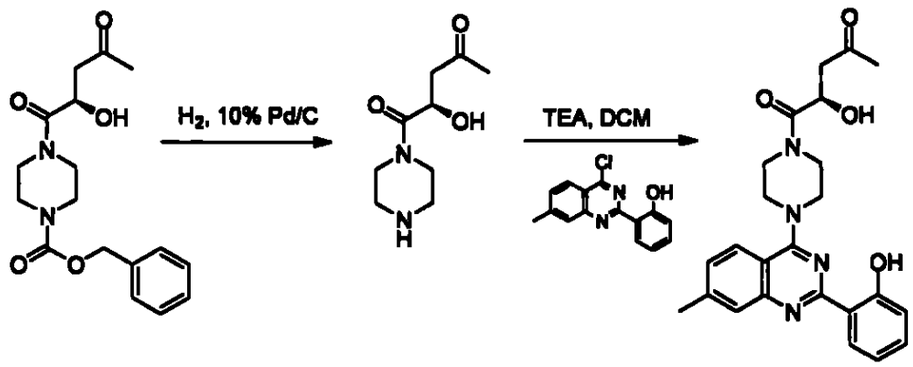
[00821] A una solución de éster bencílico del ácido 4-((R)-2-hidroxi-3-metoxicarbonil-propionil)-piperazin-1-carboxílico (8,5 g, 24,0 mmol) en THF (240 ml) enfriada en un baño de hielo seco y acetona, se añadió MeMgBr 1,4 M (61 ml, 85 mmol). La reacción se dejó calentar lentamente hasta temperatura ambiente durante la noche. Después de neutralizar la mezcla con NH_4Cl saturado y extraer con EtOAc, los extractos orgánicos combinados se lavaron con agua, se secaron sobre Na_2SO_4 y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-10% de $MeOH/CH_2Cl_2$ dio éster bencílico del ácido 4-((*R*)-2-hidroxi-4-oxo-pentanoil)-piperazin-1-carboxílico en forma de un aceite incoloro (0,9 g, 11%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,39-7,31 (m, 5H), 5,15 (s, 2H), 4,79-4,74 (m, 1H), 4,00 (d, *J* = 7,8 Hz, 1H), 3,75-3,45 (m, 8H), 2,85 (dd, *J* = 16,6, 7,3 Hz, 1H), 2,63 (dd, *J* = 16,6, 3,4 Hz, 1H),

859

2,26 (s, 3H); LC/MS: *m/z* 335,1 $(M+H)^+$ a 2,17 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00822] (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)pentano-1,4-diona

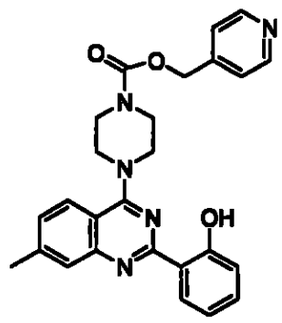
[00823]



[00824] Una mezcla de éster bencílico del ácido 4-((*R*)-2-hidroxi-4-oxo-pentanoil)-piperazin-1-carboxílico (0,13 g, 0,39 mmol) y MeOH (4 ml) se agitó con 10 mg de Pd/C (10% en peso de Pd sobre carbón) bajo una atmósfera de H_2 a presión ambiente durante la noche. Tras filtrar y evaporar el solvente, el residuo se extrajo en CH_2Cl_2 y se añadieron 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,11 g, 0,39 mmol) y trietilamina (0,11 ml, 0,78 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, se lavó con agua, se secó sobre Na_2SO_4 y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de MeOH/CH_2Cl_2 dio (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)pentano-1,4-diona en forma de un sólido

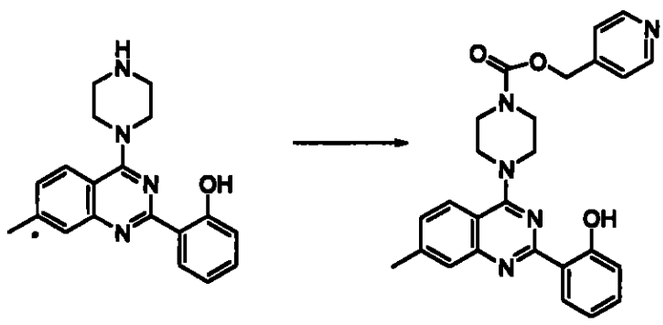
amarillo (91 mg, 54%). LC/MS: *m/z* 435,5 $(M+H)^+$ a 2,13 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00825] **4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo**



[00826]

[00827] **4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo**



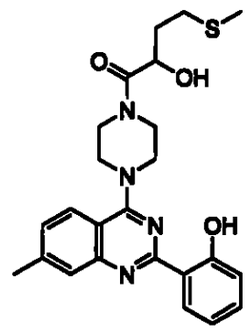
[00828]

[00829] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,16 mmol), 1*H*-imidazol-1-carboxilato de (piridin-4-il)metilo (67 mg, 0,32 mmol) y trietilamina (44,6 µL, 0,32 mmol) en DMSO (500 µL) se calentó

en un sintetizador a microondas a 200 °C durante 10 minutos. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-4-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 456,5 $(M+H)^+$ a 2,02 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

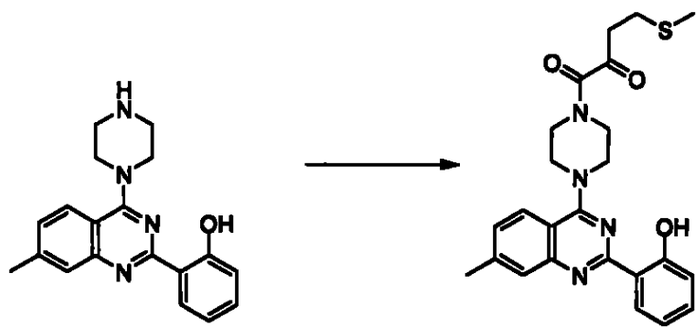
[00830] Ejemplo 153

[00831] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-(metiltio)butan-1-ona**



[00832]

[00833] **1-(4-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-(metiltio)butano-1,2-diona**

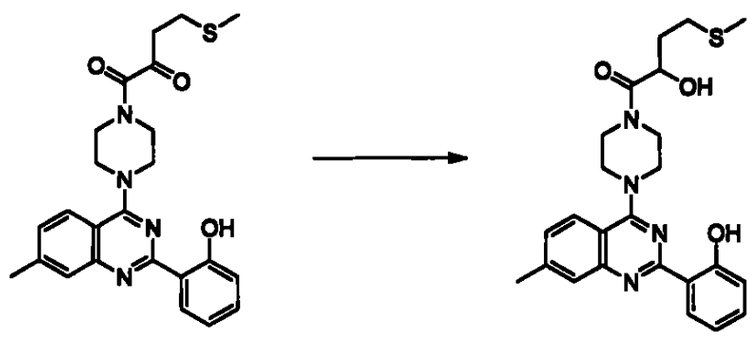


[00834]

[00835] Una mezcla de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (200 mg, 0,63 mmol), 4-metilsulfanil-2-oxo-butirato de sodio (160 mg, 0,94 mmol), BOP (414 mg, 0,94 mmol) y trietilamina (348 µL, 2,5 mmol) en 2,1 ml de CH_2Cl_2 se agitó a temperatura ambiente durante 1 h. Tras añadir solución saturada de $NaHCO_3$, la mezcla se extrajo con CH_2Cl_2. Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron para dar 1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-(metiltio)butano-1,2-diona. LC/MS: *m/z* 451,2 $(M+H)^+$ a 3,10 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00836] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-(metiltio)butan-1-ona**

863

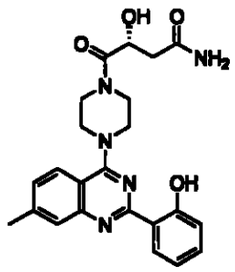


[00837]

[00838] $NaBH_4$ (34 mg, 0,88 mmol) se añadió a 1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-(metiltio)butano-1,2-diona (200 mg, 0,44 mmol) en 1,5 ml de MeOH y la mezcla de reacción se agitó a 0 °C durante 20 minutos La mezcla de reacción se dejó calentar hasta temperatura ambiente, se añadió $NaHCO_3$ saturado y la capa acuosa se extrajo con CH_2Cl_2. La capa orgánica se secó sobre Na_2SO_4 y se concentró. La purificación usando HPLC preparativa en fase inversa con 10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-(metiltio)butan-1-ona en forma de la sal de TFA. (LC/MS: *m/z* 453,4 $(M+H)^+$ a 2,73 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

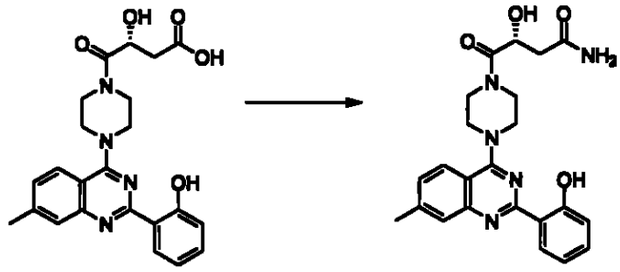
[00839] Ejemplo 154

[00840] **(R)-3-Hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-oxobutanamida**



[00841]

[00842] **(*R*)-3-Hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-oxobutanamida**



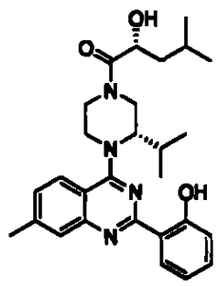
[00843]

[00844] Se agitaron ácido (*R*)-3-hidroxi-4-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il)-4-oxo-butírico (17 mg, 0,039 mmol) y HATU (16 mg, 0,043 mmol) en DMF (0,5 ml). Tras añadir NH_3 0,5 M en dioxano (0,38 ml, 0,19 mmol), la mezcla de reacción se agitó a temperatura ambiente durante 5 h. La purificación por HPLC preparativa en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-3-hidroxi-4-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-oxobutanamida en forma de la sal de TFA. LC/MS: *m/z* 436,3 $(M+H)^+$ a 1,94 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00845] Ejemplo 155

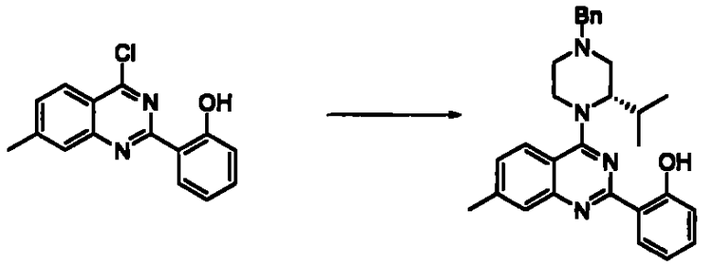
[00846] (R)-2-Hidroxi-1-((S)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)-3-isopropilpiperazin-1-il)-4-metilpentan-1-ona

[00847] 2-(4-((S)-4-bencil-2-isopropilpiperazin-1-il)-7-



metilquinazolin-2-il)fenol

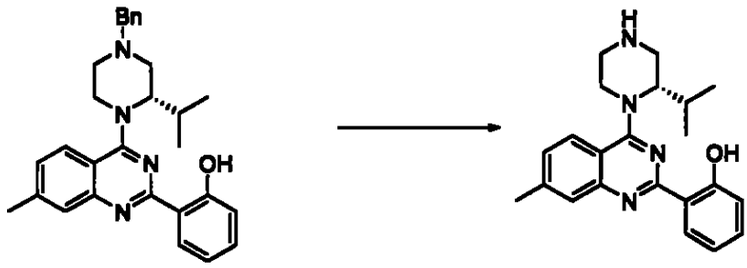
[00848]



[00849] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)fenol (200 mg, 0,74 mmol) en 10 ml de DMF se añadió (S)-1-bencil-3-isopropilpiperazina seguido de la adición de trietilamina (206 µL). La reacción se calentó a 85 °C durante dos horas. La reacción se neutralizó con agua tras enfriarla hasta temperatura ambiente. La capa acuosa se extrajo dos veces con CH_2Cl_2 y los extractos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. La reacción se purificó mediante cromatografía en gel de sílice usando un sistema de

solventes 1:1 de hexanos:CH_2Cl_2 para obtener 2-(4-((*S*)-4-bencil-2-isopropilpiperazin-1-il)-7-metilquinazolin-2-il)fenol (230 mg, 64%). LC/MS: *m/z* 453,5 $(M+H)^+$ a 2,61 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

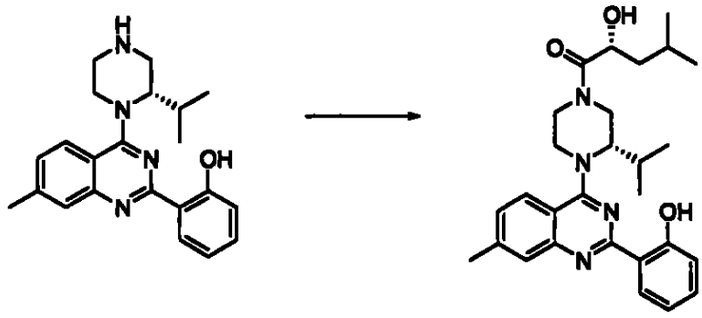
[00850] 2-(4-((*S*)-2-Isopropilpiperazin-1-il)-7-metilquinazolin-2-il)fenol



[00851]

[00852] Se añadieron 20 mg de Pd/C a un recipiente de base redonda y el recipiente se inundó con nitrógeno seguido de evacuación de la atmósfera al vacío. Al recipiente se añadió luego una solución de 2-(4-((*S*)-4-bencil-2-isopropilpiperazin-1-il)-7-metilquinazolin-2-il)fenol (200 mg, 0,44 mmol) en metanol, seguido de la adición de formiato de amonio (32 mg, 0,88 mmol). La reacción se calentó a reflujo durante la noche. La reacción se filtró a través de un lecho de Celite para eliminar el catalizador. El solvente se evaporó para obtener 2-(4-((*S*)-2-isopropilpiperazin-1-il)-7-metilquinazolin-2-il)fenol (126 mg). LC/MS: *m/z* 363,5 $(M+H)^+$ a 2,13 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00853] **(*R*)-2-Hidroxi-1-((*S*)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)-3-isopropilpiperazin-1-il)-4-metilpentan-1-ona**

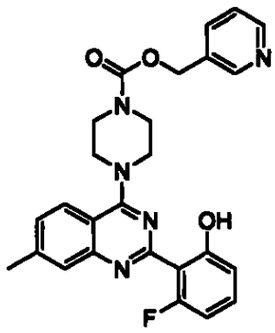


[00854]

[00855] A una solución de 2-(4-((*S*)-2-isopropilpiperazin-1-il)-7-metilquinazolin-2-il)fenol (70 mg, 0,19 mmol) en DMF (0,5 ml) se añadió ácido (R)-2-hidroxi-4-metilpentanoico (32,6 mg, 0,247 mmol). Le siguió la adición de trietilamina (52 µL) y una solución de HATU (94 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se completó en una hora. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-2-hidroxi-1-((*S*)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)-3-isopropilpiperazin-1-il)-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 477,5 $(M+H)^+$ a 2,96 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

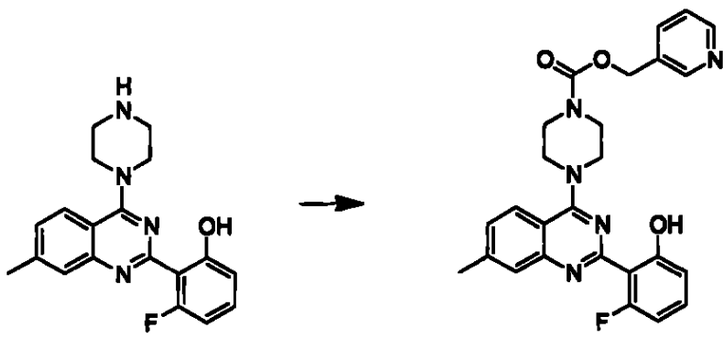
[00856] Ejemplo 156

[00857] 4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-3-il)metilo



[00858]

[00859] 4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (piridin-3-il)metilo



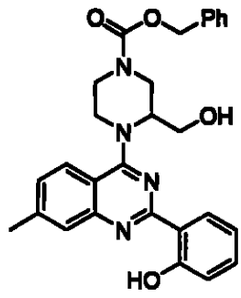
[00860]

[00861] 3-Fluoro-2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (50 mg, 0,15 mmol), 1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo (53 mg, 0,26 mmol), trietilamina (30,4 mg, 0,3 mmol) y DMSO (1 ml) se agitaron durante 18 horas a temperatura ambiente. La reacción se purificó por HPLC preparativa en fase inversa para dar 4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato

de (piridin-3-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 474,30 $(M+H)^+$ a 1,19 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

|00862| Ejemplo 157

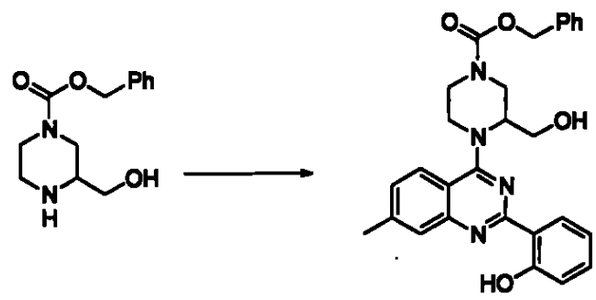
|00863| **Éster bencílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico**



|00864|

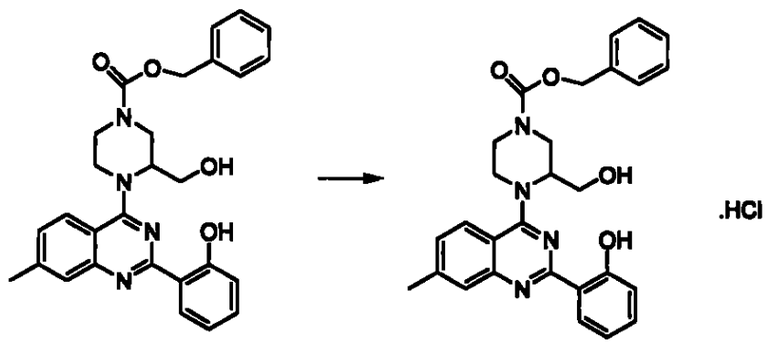
|00865| **Éster bencílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico**

|00866|



[00867] A 2-(4-cloro-7-metil-quinazolin-2-il)-fenol (245 mg, 0,91 mmol) en 3,0 ml de CH_2Cl_2 se añadieron secuencialmente éster bencílico del ácido 3-hidroximetil-piperazin-1-carboxílico (336,3 mg, 1,34 mmol) y trietilamina (190 ml, 1,37 mmol) y la mezcla de reacción se calentó a 40 °C durante 6 h. La mezcla de reacción se enfrió y se extrajo con agua (2 x 10 ml) y la capa orgánica se separó y se secó sobre Na_2SO_4. El solvente se eliminó a presión reducida para dar un aceite. El residuo se purificó por LC en fase normal (20-85% de EtOAc-hexanos) para dar éster bencílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico (216 mg, 64% de rendimiento). LC/MS: *m/z* 485,4 (M+H)+ a 3,02 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00868] Clorhidrato de 3-(hidroximetil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de bencilo

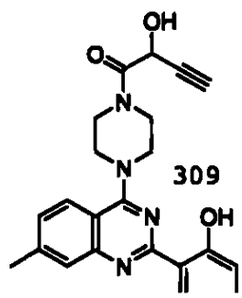


[00869]

[00870] Una solución de HCl 2,0 M en Et_2O (212 µL, 0,42 mmol) se añadió lentamente a temperatura ambiente a una solución agitada de éster bencílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico (206 mg, 0,42 mmol) en 500 µL de CH_2Cl_2. La reacción se agitó durante 1 hora. Los solventes se eliminaron a presión reducida y el residuo se trituró con Et_2O y se filtró para dar clorhidrato de 3-(hidroximetil)-4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de bencilo. LC/MS: *m/z* 485,5 (M+H)+ a 3,07 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

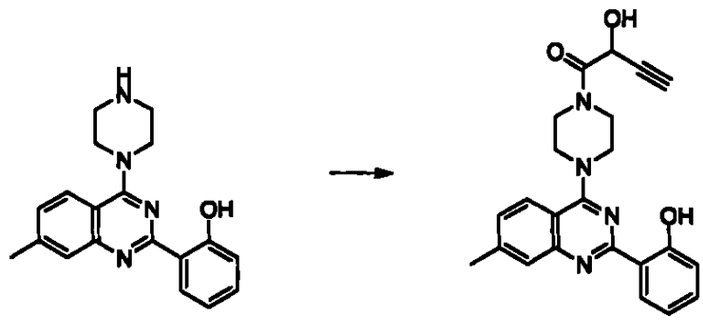
[00871] Ejemplo 158

[00872] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)but-3-in-1-ona**



[00873]

[00874] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)but-3-in-1-ona**



[00875]

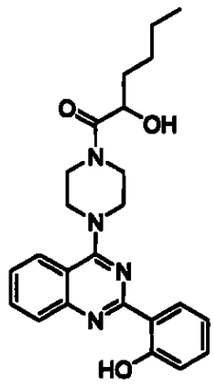
[00876] A una mezcla de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (75 mg, 0,23 mmol) en 0,78 ml de CH_2Cl_2 se añadieron sucesivamente ácido 2-hidroxibut-3-inoico (30 mg, 0,30 mmol), BOP (134 mg, 0,30 mmol) y trietilamina (36 mg, 49 µL, 0,35 mmol). La mezcla se agitó a 0 °C durante 30 minutos. La purificación por medio de cromatografía en gel de sílice usando 0-100% de acetato de etilo/hexanos dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)but-3-in-1-ona. (LC/MS: *m/z* 403,5 $(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00877] Ejemplo 159

[00878] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)hexan-1-ona**

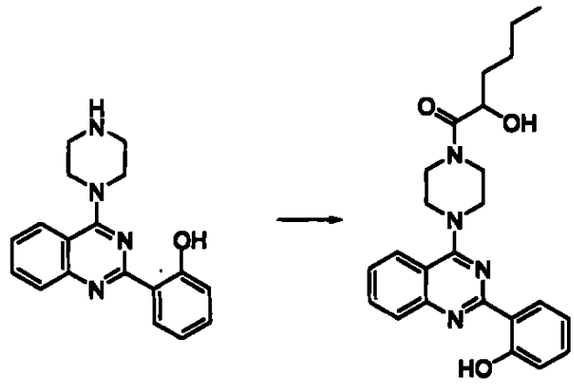
866

873



[00879]

[00880] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)hexan-1-ona**



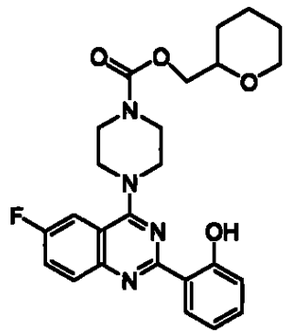
[00881]

[00882] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió a ácido 2-hidroxihexanoico (39,3 mg, 0,297 mmol). Se agregó trietilamina (63 µL) a temperatura ambiente, luego una solución de HATU (113 mg) en 0,5 ml de DMF. La reacción se agitó durante la noche. La purificación usando HPLC en fase

inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-metilbutan-1-ona. LC/MS: *m/z* 421,3 $(M+H)^+$ a 2,60 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00883] Ejemplo 160

[00884] **4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (tetrahidro-2*H*-piran-2-il)metilo**



[00885]

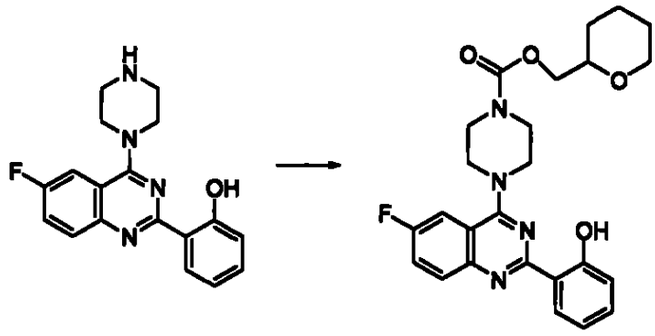
[00886] **1*H*-imidazol-1-carboxilato de (tetrahidro-2*H*-piran-2-il)metilo**

[00887]

[00888] Una solución de (tetrahidro-2*H*-piran-2-il)metanol (1 g, 8,60 mmol) y di(1*H*-imidazol-1-il)metanona (2,8 g, 17,2

mmol) en 17 ml de CH_2Cl_2 se calentó durante la noche a 50 °C La reacción se neutralizó con agua, se extrajo con CH_2Cl_2, se secó sobre $MgSO_4$, se filtró y se concentró. ^1H RMN (400 MHz, $CDCl_3$) δ 8,15 (t, *J* = 0,9 Hz, 1H), 7,44 (t, *J* = 1,4 Hz, 1H), 7,07 (dd, *J* = 1,6, 0,8 Hz, 1H), 6,95 (m, 2H), 6,84 (m, 1H), 6,01 (s, 2H), 5,33 (s, 2H)

[00889] 4-(6-fluoro-2-(2-hidroxifenil) quinazolin-4-il)piperazin-1-carboxilato de (tetrahidro-2*H*-piran-2-il)metilo



[00890]

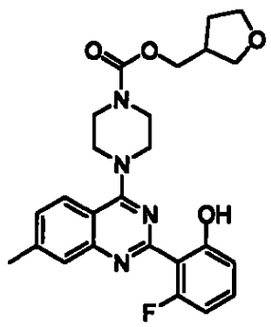
[00891] 2-(6-Fluoro-4-(piperazin-1-il)quinazolin-2-il)fenol (25 mg, 0,077 mmol), 1*H*-imidazol-1-carboxilato de (tetrahidro-2*H*-piran-2-il)metilo (48,5 mg, 0,23 mmol), trietilamina (22µL, 0,154 mmol) y HATU (38 mg, 0,10 mmol) se agitaron en DMF (1 ml) durante la noche. La purificación mediante HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 4-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-carboxilato de (tetrahidro-2*H*-piran-2-il)metilo en forma de la

sal de TFA. LC/MS: *m/z* 467,3 $(M+H)^+$ a 3,13 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

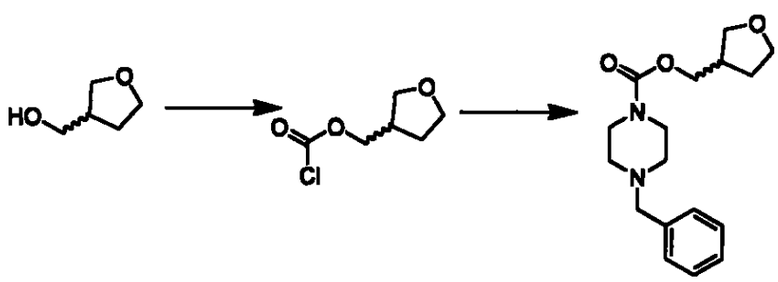
[00892] Ejemplo 162

[00893] **4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (tetrahidrofuran-3-il)metilo**

[00894]



[00895] **Tetrahidro-furan-3-ilmetiléster del ácido 4-bencil-piperazin-1-carboxílico**



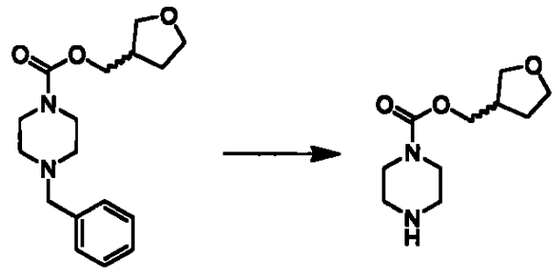
[00896]

[00897] A una solución enfriada (0 °C) de trifosgeno (5,0 g, 17 mmol) en 50 ml de diclorometano bajo una atmósfera de nitrógeno se añadió gota a gota una solución de tetrahidro-3-furanmetanol (5,4 g, 53 mmol) en 10 ml de diclorometano. Se

añadió piridina (4,3 ml, 53 mmol) gota a gota y la solución se calentó hasta temperatura ambiente. Al cabo de 2 horas a temperatura ambiente, una mezcla de trietilamina (7,5 ml, 52 mmol) y se agregó *N*-bencilpiperazina (9,5 ml, 54 mmol) gota a gota con enfriamiento. La mezcla resultante se calentó a reflujo durante 1 hora. La solución se agitó a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno. La mezcla se lavó con solución acuosa de bicarbonato de sodio (5%, 2 x 50 ml) y con una solución de NaCl acuoso saturado (50 ml). La capa orgánica se secó sobre sulfato de sodio, se filtró y se evaporó hasta sequedad. El residuo se co-evaporó tres veces con tolueno (50 ml) para obtener tetrahidro-furan-3-ilmetiléster del ácido 4-bencil-piperazin-1-carboxílico (13,0 g, 81%) en forma de un aceite amarronado.

[00898] Tetrahidro-furan-3-ilmetiléster del ácido piperazin-1-carboxílico.

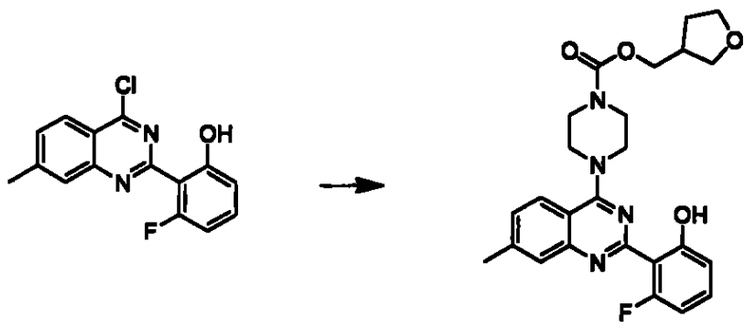
[00899]



[00900] Se añadió tetrahidro-furan-3-ilmetiléster del ácido 4-bencil-piperazin-1-carboxílico (11,0 g) en 100 ml de etanol. Se agregó paladio en carbono (10% Pd/C, 0,5 g) y se aplicó una

atmósfera de hidrógeno durante la noche a temperatura ambiente. La solución se filtró a través de Celite para eliminar el catalizador y la torta de Celite se enjuagó con 50 ml de etanol. Los filtrados combinados se evaporaron hasta sequedad para obtener tetrahidro-furan-3-ilmetiléster del ácido piperazin-1-carboxílico (8,0 g) en forma de un aceite incoloro.

[00901] **4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (tetrahidrofuran-3-il)metilo**



[00902]

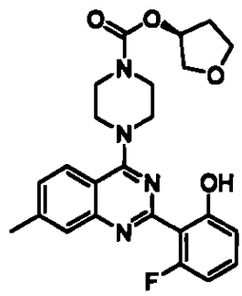
[00903] Se disolvió 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (50 mg, 0,174 mmol) en 1 ml de DMF, seguido de la adición de trietilamina (35,2 mg, 0,348 mmol). Luego se agregó piperazin-1-carboxilato de (tetrahidrofuran-3-il)metilo (45 mg, 0,21 mmol). Al cabo de 1 hora a temperatura ambiente, la reacción se completó. Se filtró y se purificó por HPLC preparativa en fase inversa para dar 4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato

de (tetrahidrofuran-3-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 467,3 $(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

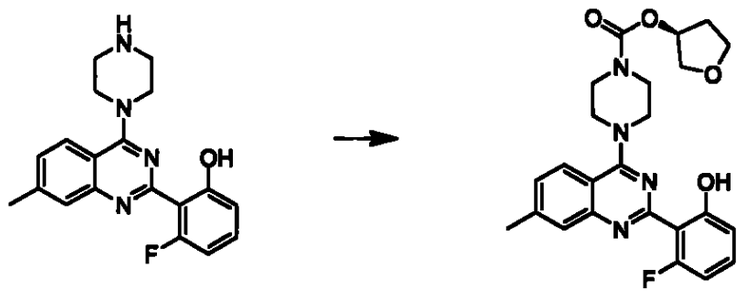
[00904] Ejemplo 163

[00905] **4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (S)-tetrahidrofuran-3-ilo**

[00906]



[00907] **4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (S)-tetrahidrofuran-3-ilo**

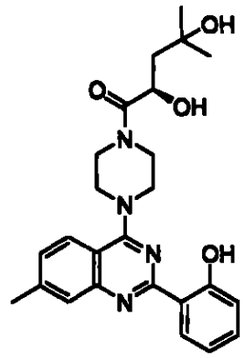


[00908]

[00909] 2-(7-Metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,21 mmol) se disolvió en 1 ml de DMF anhidra bajo una atmósfera de N_2 y se enfrió hasta 0 °C. Se disolvió cloroformiato de (S)-tetrahidrofuran-3-ilo (34,3 mg, 0,228 mmol) en 150 µL de DMF anhidra y se añadió gota a gota a la reacción, seguido de trietilamina (42 mg, 0,41 mmol). Al cabo de 1 hora, la reacción se completó y se filtró y se purificó por HPLC en fase inversa para dar 4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-carboxilato de (*S*)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 453,3 $(M+H)^+$ a 2,25 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

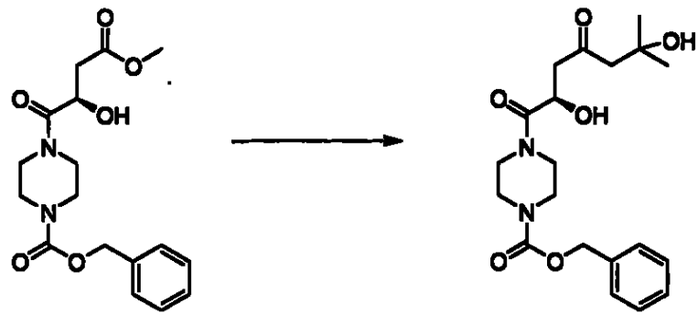
[00910] Ejemplo 164

[00911] **(*R*)-2,6-Dihidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-6-metilheptano-1,4-diona**



[00912]

[00913] **Éster bencílico del ácido 4-((*R*)-2,6-dihidroxi-6-metil-4-oxo-heptanoil)-piperazin-1-carboxílico**



[00914]

[00915] A una solución de éster bencílico del ácido 4-((R)-2-hidroxi-3-metoxicarbonil-propionil)-piperazin-1-carboxílico (5,26 g, 15,0 mmol) en THF (150 ml) enfriada en un baño de hielo seco y acetona se añadió MeMgBr 1,4 M (32 ml, 45 mmol). La reacción se dejó calentar lentamente hasta temperatura ambiente durante la noche. Después de neutralizar la mezcla con NH_4Cl saturado y extraer con EtOAc, los extractos orgánicos combinados se lavaron con agua, se secaron sobre Na_2SO_4 y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-10% de $MeOH/CH_2Cl_2$ dio éster bencílico del ácido 4-((*R*)-2-hidroxi-4-oxo-pentanoil)-piperazin-1-carboxílico en un aceite incoloro (0,79 g, 15%). ^1H RMN (400 MHz, $CDCl_3$) δ 7,40-7,31 (m, 5H), 5,15 (s, 2H), 4,71-4,68 (m, 1H), 4,05 (d, *J* = 6,8 Hz, 1H), 3,80-3,73 (m, 1H), 3,62-3,42 (m, 6H), 3,31-3,23 (m, 1H), 1,72-1,61 (m, 2H), 1,35 (s, 3H), 1,30 (s, 3H); LC/MS: *m/z* 351,3 $(M+H)^+$ a 2,22 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

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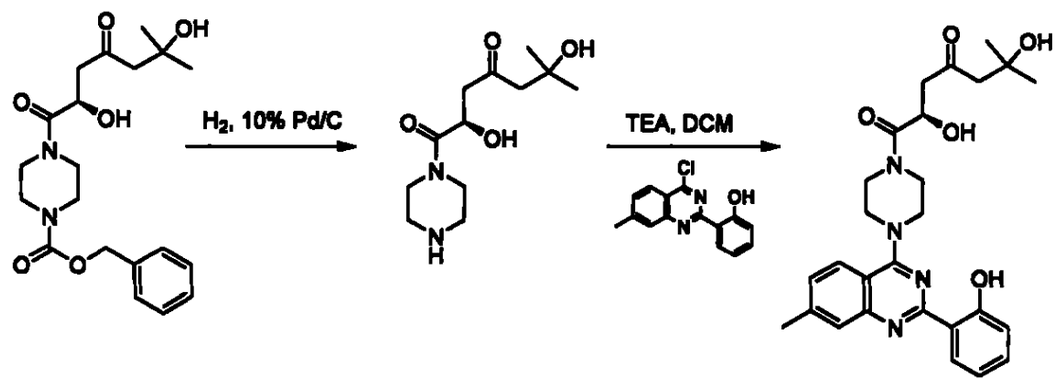
[00916] **(*R*)-2,4-Dihidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**

[00917]



[00918] Una mezcla de éster bencílico del ácido 4-((*R*)-2,6-dihidroxi-6-metil-4-oxo-heptanoil)-piperazin-1-carboxilico (0,79 g, 2,20 mmol) y MeOH (25 ml) se agitó con 40 mg de Pd/C (10% en peso de Pd sobre carbón) bajo una atmósfera de H_2 a presión ambiente durante la noche. Tras filtrar y evaporar el solvente, el residuo se extrajo en CH_2Cl_2 y se añadieron 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,61 g, 2,20 mmol) y trietilamina (0,63 ml, 4,50 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche y luego se diluyó con CH_2Cl_2, se lavó con agua, se secó sobre Na_2SO_4 y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-10% de MeOH/CH_2Cl_2 dio (*R*)-2,6-dihidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-6-metilheptano-1,4-diona en forma de un sólido amarillo (372 mg, 37%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,45 (dd, *J* = 7,9, 1,6 Hz,

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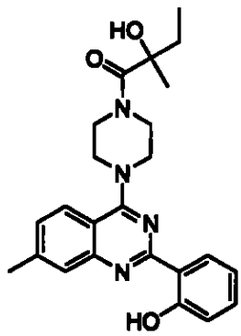
1H), 7,75 (d, J = 8,5 Hz, 1H), 7,67 (s, 1H), 7,40-7,36 (m, 1H), 7,29 (dd, J = 8,5, 1,4 Hz, 1H), 7,03 (d, J = 8,2 Hz, 1H), 6,96-6,92 (m, 1H), 4,81-4,76 (m, 1H), 4,09 (d, J = 6,8 Hz, 1H), 4,03-3,77 (m, 6H), 3,75-3,67 (m, 2H), 3,28 (s, 1H), 2,55 (s, 3H), 1,78-1,69 (m, 2H), 1,40 (s, 3H), 1,33 (s, 3H); ^{13}C RMN (100 MHz, $CDCl_3$) δ 173,1, 164,0, 161,3, 160,5, 150,1, 144,5, 132,7, 129,2, 127,7, 126,8, 124,4, 119,3, 118,5, 117,7, 112,7, 70,6, 66,4, 49,9, 49,0, 46,1, 44,5, 42,4, 30,6, 29,2, 21,9; LC/MS: m/z 451,1 $(M+H)^+$ a 2,12 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00919] Ejemplo 165

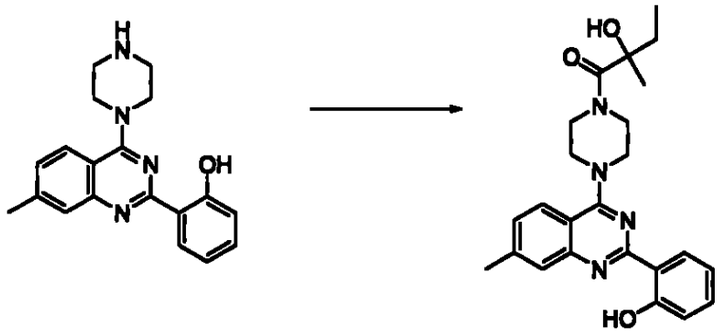
[00920] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-metilbutan-1-ona**



[00921]

[00922] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-metilbutan-1-ona**

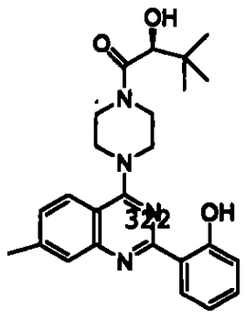
[00923]



[00924] Una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,22 mmol) en DMF (0,5 ml) se añadió a ácido 2-hidroxi-2-metilbutanoico (33,6 mg, 0,284 mmol). Se añadió trietilamina (61 µL), seguido de una solución de HATU (108 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-metilbutan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 421,3 $(M+H)^+$ a 2,40 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00925] Ejemplo 166

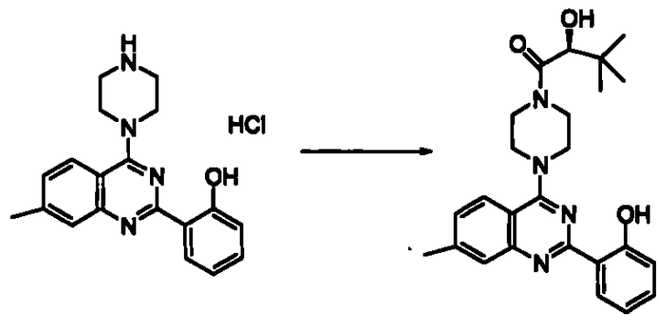
(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3,3-dimetilbutan-1-ona



885

[00926]

[00927] **(*S*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3,3-dimetilbutan-1-ona**

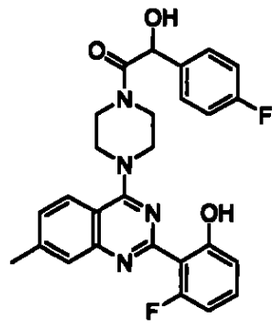


[00928]

[00929] Clorhidrato de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (30 mg, 0,09 mmol), ácido (*S*)-2-hidroxi-3,3-dimetilbutanoico (16 mg, 0,12 mmol), trietilamina (37,5 µL, 0,27 mmol) y HATU (45,6 mg, 0,12 mmol) se agitaron en DMF (1 ml) durante la noche. La purificación mediante HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*S*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3,3-dimetilbutan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 434,53 $(M+H)^+$ a 2,61 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

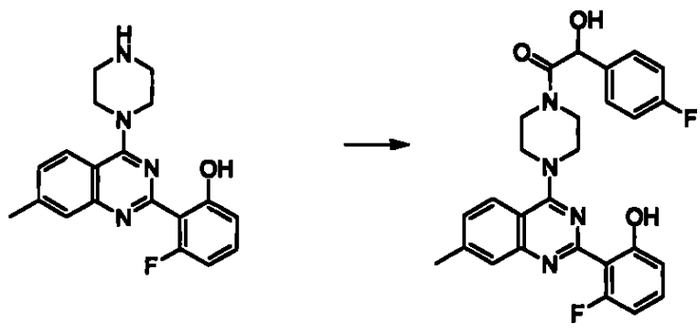
[00930] Ejemplo 167

[00931] **1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-(4-fluorofenil)-2-hidroxietanona**



[00932]

[00933] **1-(4-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-(4-fluorofenil)-2-hidroxietanona**



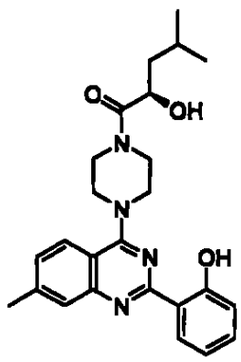
[00934]

[00935] 3-Fluoro-2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (30 mg, 0,09 mmol), ácido 2-(4-fluorofenil)-2-hidroxiacético (19,62 mg, 0,12 mmol), trietilamina (25 µL, 0,18 mmol) y HATU (45,6 mg, 0,12 mmol) se agitaron en DMF (1 ml) durante la noche. La purificación mediante HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 1-(4-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-(4-fluorofenil)-2-hidroxietanona en forma

de la sal de TFA. LC/MS: *m/z* 491,3 $(M+H)^+$ a 2,46 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

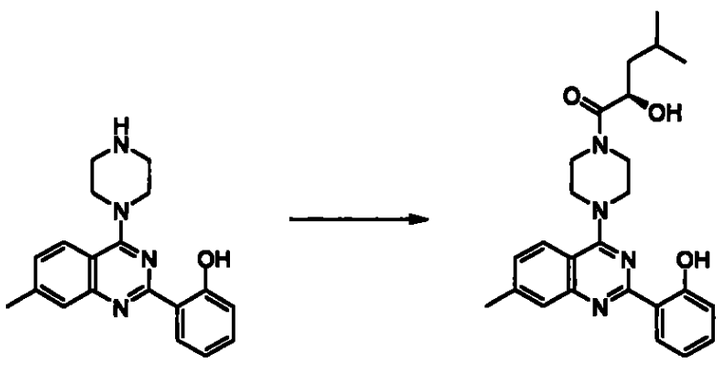
[00936] Ejemplo 168

[00937] **(*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**



[00938]

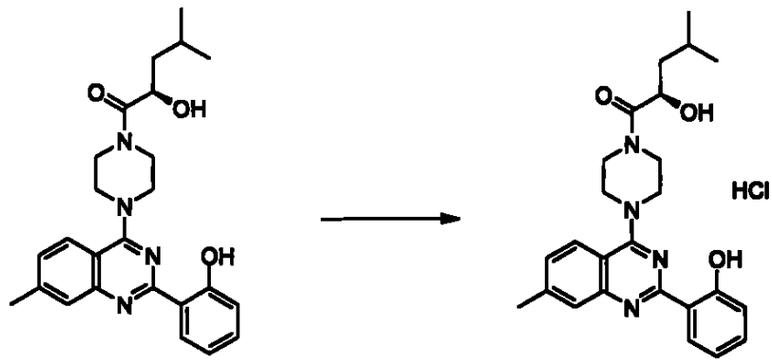
[00939] **(*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona**



[00940]

[00941] En una atmósfera de N_2, se añadió BOP (138 mg, 0,31 mmol) en una única porción a una solución agitada de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (100 mg, 0,31 mmol), ácido (R)-2-hidroxi-4-metilpentanoico (41 mg, 0,31 mmol) y trietilamina (43 µL, 0,31 mmol) en DMF (0,5 ml). Tras agitar la mezcla durante 1 h a temperatura ambiente, se dividió en H_2O y éter. La fase orgánica se lavó con H_2O (3x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 20% de EtOAc y 80% de CH_2Cl_2 dio (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona en forma de un sólido de color amarillo claro (89 mg, 60%). LC/MS: *m/z* 435,1 (M+H)+ a 2,93 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, $CDCl_3$) δ 8,46 (dd, *J* = 7,9, 1,7 Hz, 1H), 7,76 (d, *J* = 8,5 Hz, 1H), 7,66 (s, 1H), 7,41-7,37 (m, 1H), 7,30 (dd, *J* = 8,5, 1,5 Hz, 1H), 7,06-7,04 (m, 1H), 6,98-6,94 (m, 1H), 4,51-4,45 (m, 1H), 4,04-3,80 (m, 6H), 3,72-3,62 (m, 3H), 2,56 (s, 3H), 2,12-1,99 (m, 1H), 1,57-1,49 (m, 1H), 1,38-1,32 (m, 1H), 1,05 (d, *J* = 6,6 Hz, 3H), 1,00 (d, *J* = 6,7 Hz, 3H).

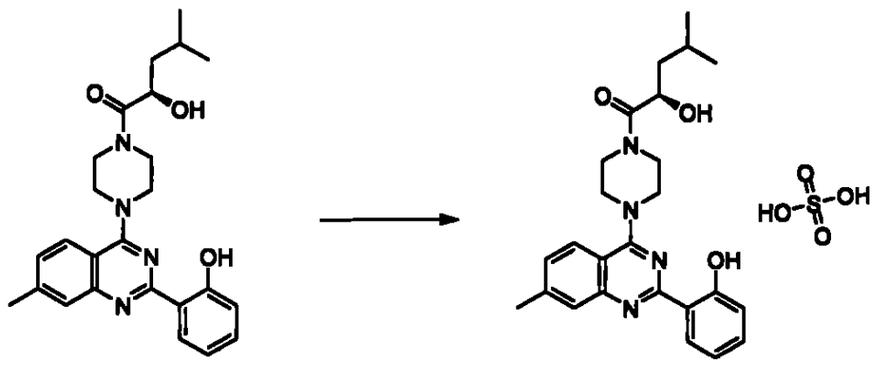
[00942] Clorhidrato de (*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona



[00943]

[00944] (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona (90 mg, 0,20 mmol) se disolvió en 1 ml de CH_2Cl_2 y se trató con 1 equivalente de HCl 2,0 M en éter (100 µL, 0,20 mmol). El precipitado formado se filtró y se secó al vacío para obtener clorhidrato de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona. LC/MS: *m/z* 435,1 (M+H)+ a 2,84 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, CD_3OD) δ 8,39-8,37 (m, 1H), 8,18 (d, *J* = 8,6 Hz, 1H), 7,78 (s, 1H), 7,61-7,55 (m, 2H), 7,15-7,11 (m, 2H), 4,57 (dd, *J* = 9,5, 3,5 Hz, 1H), 4,49-4,32 (m, 4H), 4,07-3,79 (m, 4H), 2,62 (s, 3H), 1,97-1,87 (m, 1H), 1,65-1,58 (m, 1H), 1,53-1,47 (m, 1H), 1,03-1,00 (m, 6H).

[00945] Sulfato de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona

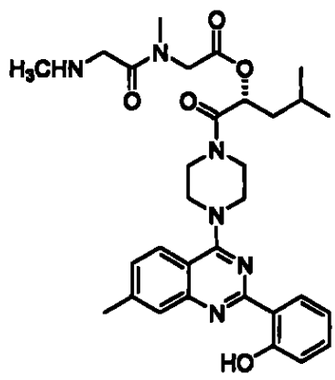


[00946]

[00947] A una solución amarilla agitada de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona (200 mg, 0,46 mmol) y THF (0,9 ml) bajo una atmósfera de N_2 se añadió una solución de H_2SO_4 concentrada (95,9%) (26 µL, 0,46 mmol) y CH_3CN (0,75 ml) en una única porción. Un precipitado blanco se formó lentamente durante un período de 1 h. El sólido se filtró y se secó al vacío para obtener sulfato de (*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-4-metilpentan-1-ona en forma de un sólido blanco (229 mg, 94%). LC/MS: *m/z* 435,3 (M+H)+ a 2,81 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,20 (dd, *J* = 7,9, 1,5 Hz, 1H), 8,12 (d, *J* = 8,6 Hz, 1H), 7,77 (s, 1H), 7,53-7,49 (m, 2H), 7,10-7,03 (m, 2H), 4,39-4,35 (m, 1H), 4,30-4,04 (m, 4H), 3,93-3,69 (m, 4H), 2,55 (s, 3H), 1,86-1,73 (m, 1H), 1,52-1,33 (m, 2H), 0,93-0,91 (m, 6H).

[00948] Ejemplo 169

[00949] **1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carbonil)-3-metil-butiléster del ácido (R)-[Metil-(2-metilamino-acetil)-amino]-acético**

[00950] 

[00951] **Ácido {[2-(*ter*-Butoxicarbonil-metil-amino)-acetil]-metil-amino}-acético**

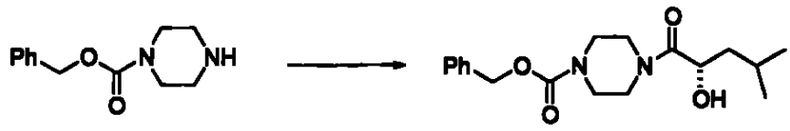
[00952]

[00953] A ácido (*ter*-butoxicarbonil-metil-amino)-acético (2,73 g, 14,4 mmol) en 70 ml de THF se añadieron secuencialmente diisopropiletilamina (7,5 ml, 14,4 mmol) y HBTU (5,47 g, 14,4 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante una hora. A esta mezcla de reacción se añadió éster etílico de ácido metilamino-acético (2,22 g, 14,4 mmol) en una porción y la mezcla de reacción se calentó a 65 °C durante 12 h. La mezcla de reacción se enfrió,

se diluyó con una solución de $NaHCO_3$ saturado y se extrajo con EtOAc. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar éster etílico del ácido {[2-(*ter*-butoxicarbonil-metil-amino)-acetil]-metil-amino}-acético.

El éster se extrajo en 49 ml de metanol y se añadió una solución 1 M de NaOH (25,1 ml, 25 mmol). La mezcla de reacción se calentó a 65 °C durante 3 h. La mezcla de reacción se enfrió y metanol se eliminó a presión reducida. El residuo se diluyó con 50 ml de agua y se acidificó con ácido acético glacial hasta que el pH fuera de 5. Esta solución se extrajo con EtOAc (50 ml) y la capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar ácido {[2-(*ter*-Butoxicarbonil-metil-amino)-acetil]-metil-amino}-acético en forma de un aceite.

[00954] Éster bencílico del ácido 4-(2(*R*)-hidroxi-4-metil-pentanoil)-piperazin-1-carboxílico

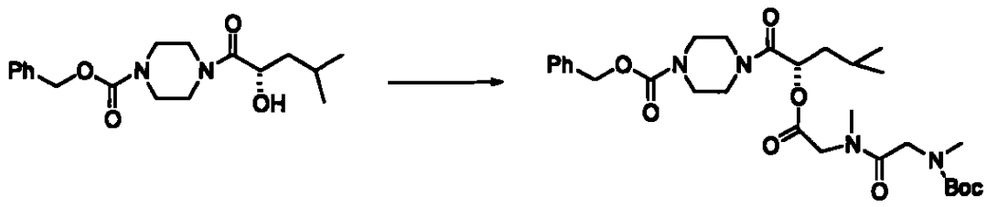


[00955]

[00956] A un ácido (*R*)-2-hidroxi-4-metil-pentanoico (1,71 g, 12,9 mmol) en 48 ml de DMF se añadieron secuencialmente trietilamina (4,9 ml, 35. mmol), HOBt (1,75 g, 12,9 mmol),

EDCI·HCl (2,48 g, 12,9 mmol) y éster bencílico del ácido piperazin-1-carboxílico (2,59 g, 11,8 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 4 h y luego se diluyó con EtOAc (50 ml) y se extrajo con 50 ml de agua. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar un aceite. El residuo se sometió a purificación por LC en fase normal usando 40-85% de EtOAc-hexanos para dar (1,92 g, 49% de rendimiento) de éster bencílico del ácido 4-(2(*R*)-hidroxi-4-metil-pentanoil)-piperazin-1-carboxílico como el producto deseado. LC/MS: *m/z* 335,4 $(M+H)^+$ a 2,96 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00957] Éster bencílico del ácido 4-[2-(2-{[2-(ter-Butoxicarbonil-metil-amino)-acetil]-metil-amino}-acetoxi)-4-metil-pentanoil]-piperazin-1-carboxílico

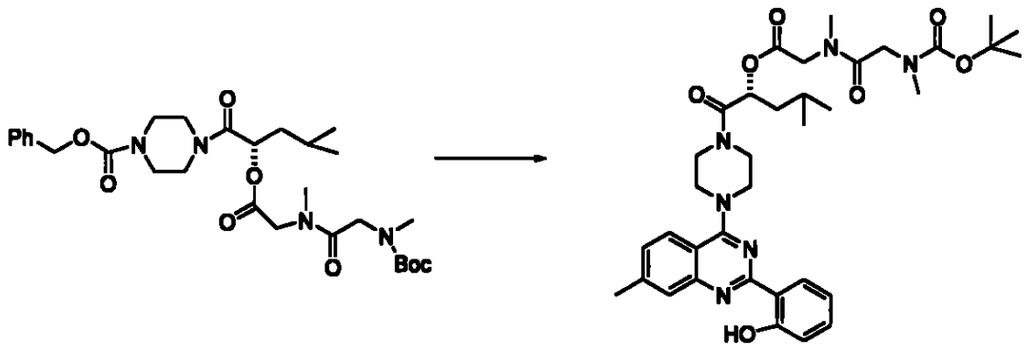


[00958]

[00959] Al ácido {[2-(*ter*-butoxicarbonil-metil-amino)-acetil]-metil-amino}-acético (427 mg, 1,57 mmol) en 2 ml de THF se añadieron secuencialmente HBTU (624 mg, 1,2 mmol), diisopropiletilamina (860 µL, 4,71 mmol) a temperatura

ambiente. Al cabo de 5 min, se agregó éster bencílico del ácido 4-(2-hidroxi-4-metil-pentanoil)-piperazin-1-carboxílico (403 mg 1,2 mmol) en 2 ml de THF a la mezcla de reacción y la solución se calentó a 65 °C durante 12 h. La mezcla de reacción se enfrió y se diluyó con 20 ml de CH_2Cl_2 y 10 ml de agua. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar un aceite. El residuo se sometió a purificación por LC en fase normal usando 30-100% de EtOAc-hexanos para dar éster bencílico del ácido 4-[2-(2-{[2-(*ter*-butoxicarbonil-metil-amino)-acetil]-metil-amino}-acetoxi)-4-metil-pentanoil]-piperazin-1-carboxílico (283 mg, 41% de rendimiento). LC/MS: *m/z* 577 $(M+H)^+$ a 3,43 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00960] Éster 1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carbonil}-3-metil-butílico del ácido {[2-(*ter*-Butoxicarbonil-metil-amino)-acetil]-metil-amino}-acético

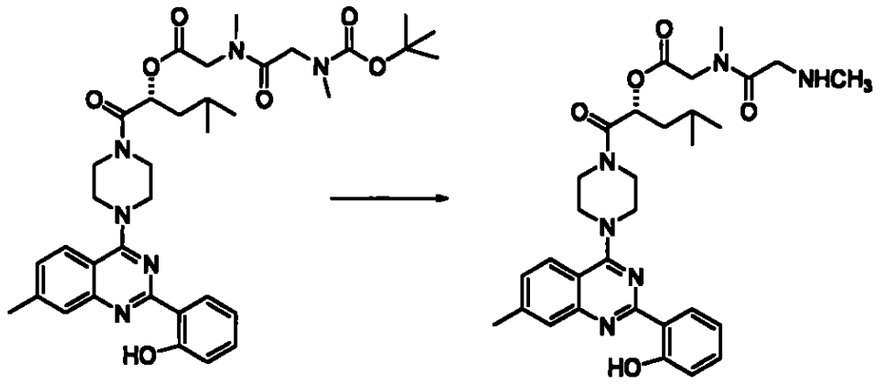


[00961] Al éster bencílico del ácido 4-[2-(2-{[2-(*ter*-butoxicarbonil-metil-amino)-acetil]-metil-amino}-acetoxi)-4-

metil-pentanoil]-piperazin-1-carboxílico (208 mg, 0,49 mmol) en 1,6 ml de metanol se añadieron 70 mg de Pd/C (10% en peso de Pd sobre carbón). La mezcla de reacción se hidrogenó usando un balón de H_2 durante 4 h a temperatura ambiente. La mezcla luego se filtró a través de Celite y el solvente se eliminó para dar éster 3-metil-1-(piperazin-1-carbonil)-butílico del ácido {[2-(*ter*-butoxicarbonil-metil-amino)-acetil]-metil-amino}-acético.

La amina se extrajo en 1 ml de CH_2Cl_2 y se trató con 2-(4-cloro-7-metil-quinazolin-2-il)-fenol (53 mg, 0,19 mmol) y 49 µL de trietilamina y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con 10 ml de CH_2Cl_2 y 10 ml de agua. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar éster 1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carbonil}-3-metil-butílico del ácido {[2-(*ter*-butoxicarbonil-metil-amino)-acetil]-metil-amino}-acético. LC/MS: *m/z* 677,4 $(M+H)^+$ a 3,25 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

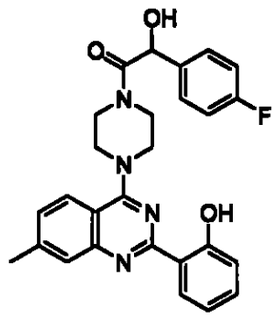
[00962] Éster 1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carbonil}-3-metil-butílico del ácido [metil-(2-metilamino-acetil)-amino]-acético

[00963] 

[00964] Al éster 1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carbonil}-3-metil-butílico del ácido {[2-(*ter*-butoxicarbonil-metil-amino)-acetil]-metil-amino}-acético (42 mg, 0,062 mmol) se añadieron 300 µL de HCl 1,25 M en metanol a temperatura ambiente y la mezcla de reacción se agitó durante 12 h. El solvente se eliminó y el residuo se purificó con LC en fase inversa usando 10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) como eluyente para dar éster 1-{4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carbonil}-3-metil-butílico del ácido [metil-(2-metilamino-acetil)-amino]-acético en forma de la sal de TFA. LC/MS: *m/z* 577,4 (M+H)+ a 2,50 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00965] Ejemplo 170

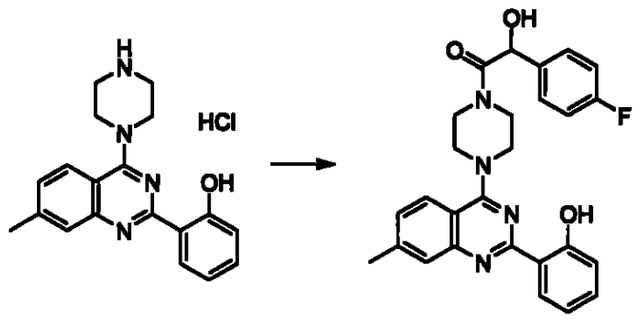
[00966] **2-(4-Fluorofenil)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona**



[00967]

[00968] **2-(4-Fluorofenil)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona**

[00969]

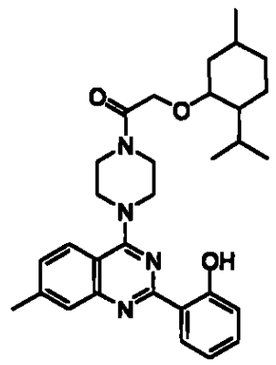


[00970] Clorhidrato de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (preparado análogamente a la sal de oxalato de 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol, ver Ejemplo 130; 30 mg, 0,09 mmol), ácido 2-(4-fluorofenil)-2-hidroxiacético (20 mg, 0,12 mmol), trietilamina (37,5 µL, 0,27 mmol) y HATU (45 mg, 0,12 mmol) se agitaron en DMF (1 ml) durante la noche. La purificación por HPLC preparativa en fase

inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-(4-fluorofenil)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona en forma de la sal de TFA. LC/MS: *m/z* 473,1 $(M+H)^+$ a 2,63 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00971] Ejemplo 171

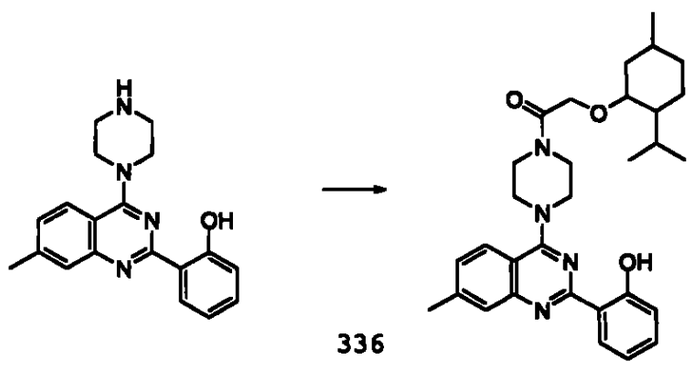
[00972] **2-(2-Isopropil-5-metilciclohexiloxi)-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona**



[00973]

[00974] **2-(2-Isopropil-5-metilciclohexiloxi)-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona**

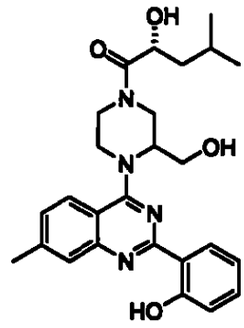
[00975]



[00976] A una solución de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (30 mg, 0,09 mmol) en DMF (1 ml) se añadió de trietilamina (25 µL) seguido de la adición gota a gota de cloruro de 2-(2-isopropil-5-metilciclohexiloxi)acetilo (21 µL, 0,09 mmol) a 0 °C. La reacción se calentó hasta temperatura ambiente y la purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-(2-isopropil-5-metilciclohexiloxi)-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)etanona en forma de la sal de TFA. LC/MS: *m/z* 517,5 $(M+H)^+$ a 3,49 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

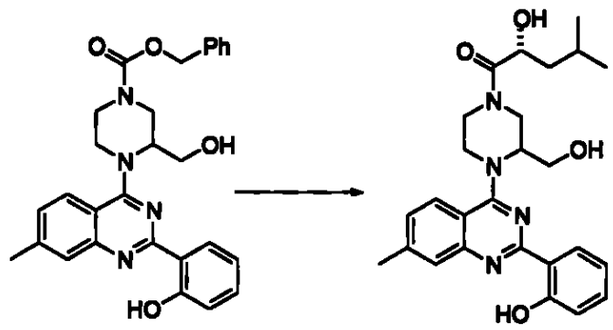
[00977] Ejemplo 172

[00978] **(R)-2-Hidroxi-1-{3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona**



[00979]

[00980] **(*R*)-2-Hidroxi-1-{3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona**



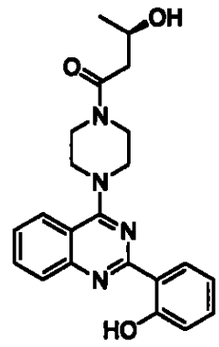
[00981]

[00982] Al éster bencílico del ácido 3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-carboxílico (200 mg, 0,41 mmol) en 1,7 ml de metanol se añadió 39 mg de Pd /C (10% en peso de Pd sobre carbón). La mezcla de reacción se sometió a hidrogenación usando un balón de H_2 durante 3 h. La mezcla de reacción se filtró a través de Celite y el solvente se eliminó para dar 2-[4-(2-hidroximetil-piperazin-1-il)-7-metil-quinazolin-2-il]-fenol. Esta amina se trató con ácido (*R*)-2-hidroxi-4-metil-pentanoico (60 mg, 0,45 mmol), BOP (200 mg, 0,45 mmol) y 115 µL de trietilamina en 1,6 ml de DMF a temperatura ambiente durante 12 h. La mezcla de reacción se diluyó con 20 ml de CH_2Cl_2 y 20 ml de agua y la capa orgánica se separó y se secó sobre Na_2SO_4. El solvente se

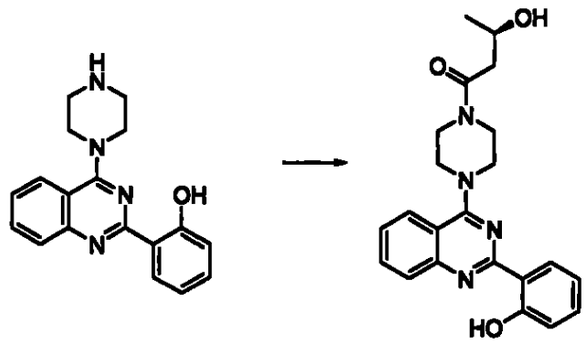
eliminó a presión reducida y el residuo se sometió a purificación usando 60-100% de EtOAc-hexanos para dar (*R*)-2-hidroxi-1-{3-hidroximetil-4-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperazin-1-il}-4-metil-pentan-1-ona. LC/MS: *m/z* 465 (M+H)+ a 2,77 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00983] Ejemplo 173

[00984] **(R)-3-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona**

[00985] 

[00986] **(R)-3-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona**

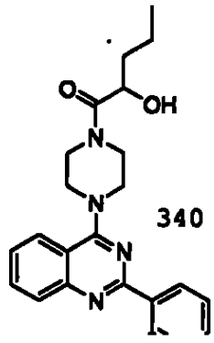


[00987]

[00988] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió a ácido (*R*)-3-hidroxibutanoico (31 mg, 0,30 mmol). Luego, se agregó trietilamina (63 µL), seguido de una solución de HATU (113 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*R*)-3-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)butan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 393,1 $(M+H)^+$ a 2,03 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[00989] Ejemplo 174

[00990] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-**



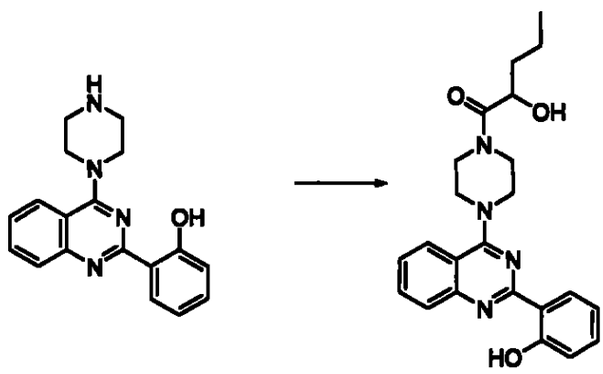
340

903

il)piperazin-1-il)pentan-1-ona

[00991]

[00992] **2-Hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)pentan-1-ona**

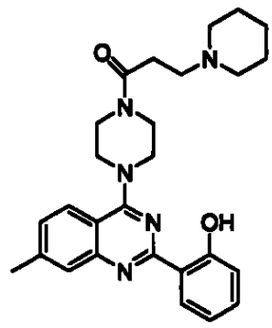


[00993]

[00994] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió a ácido 2-hidroxipentanoico (35 mg, 0,30 mmol). A esto le siguió la adición de trietilamina (63 µL) y una solución de HATU (113 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)-2-metilbutan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 407,5 $(M+H)^+$ a 2,41 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

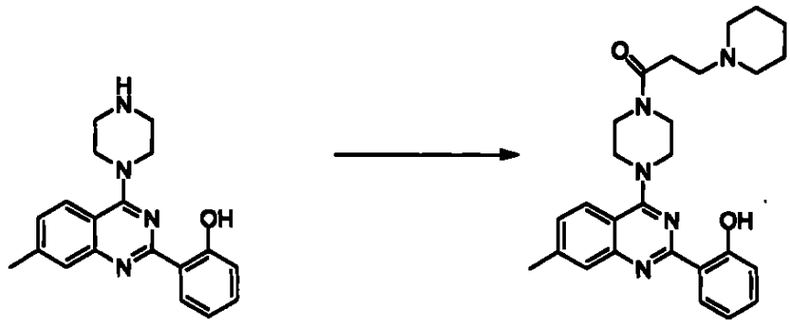
[00995] Ejemplo 175

[00996] 1-(4-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-(piperidin-1-il)propan-1-ona



[00997]

[00998] 1-(4-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-(piperidin-1-il)propan-1-ona



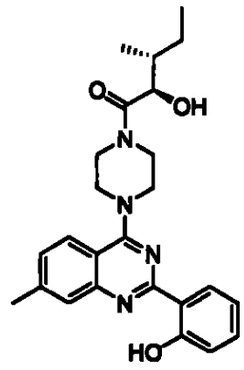
[00999]

[001000] A1 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (53 mg, 0,17 mmol) se añadieron secuencialmente cloruro de 3-(piperidin-1-il)propanoílo (33 mg, 0,19 mmol) en 28 µL de CH_2Cl_2 y trietilamina (28 µL, 0,2 mmol). La mezcla se agitó a 0 °C durante 20 minutos. Tras añadir H_2O y CH_2Cl_2, las fases se separaron y la capa orgánica se secó sobre Na_2SO_4 y se

concentró al vacío. La purificación usando HPLC preparativa en fase inversa con 10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) dio 3-ciclopentil-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 460,5 $(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

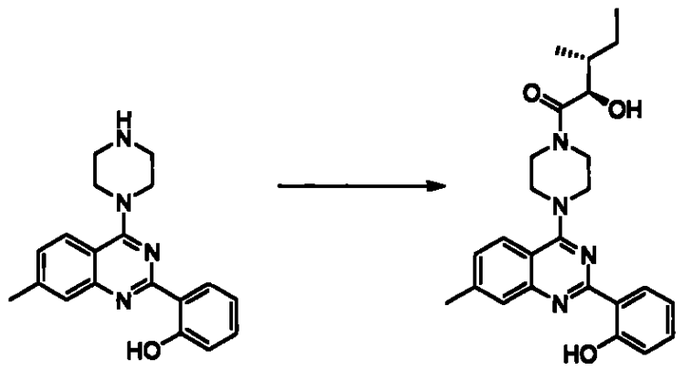
[001001] Ejemplo 176

[001002] **(2*R*,3*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilpentan-1-ona**



[001003]

[001004] **(2*R*,3*R*)-2-Hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilpentan-1-ona**

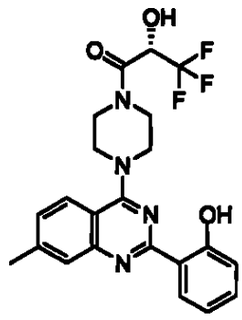


[001005]

[001006] A 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (80 mg, 0,25 mmol) en 800 µL de CH_2Cl_2 se añadió (2*R*,3*R*)-2-hidroxi-3-metil-pentanoato de sodio (50 mg, 0,33 mmol), BOP (144 mg, 0,33 mmol) y trietilamina (52 µL, 0,38 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Tras añadir H_2O y CH_2Cl_2, las capas se separaron y la capa orgánica se secó sobre Na_2SO_4 y se concentró. La purificación por HPLC preparativa en fase inversa usando 10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) dio (2*R*,3*R*)-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)-3-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 435,5 $(M+H)^+$ a 2,62 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

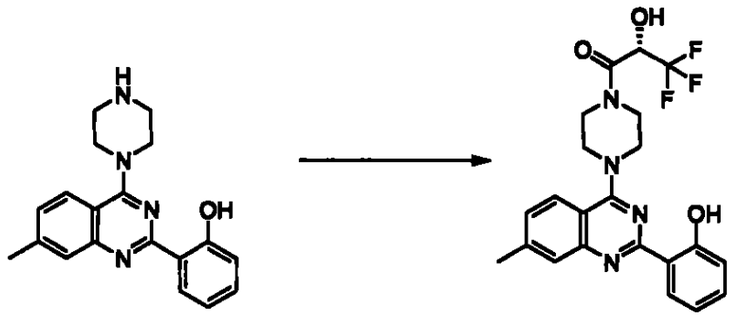
[001007] Ejemplo 177

[001008] **(*S*)-3,3,3-Trifluoro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona**



[001009]

[001010] **(*S*)-3,3,3-Trifluoro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona**



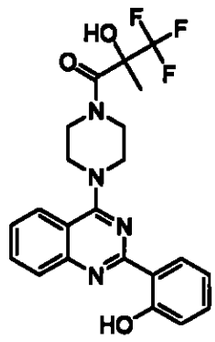
[001011]

[001012] Una mezcla de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (64 mg, 0,2 mmol), ácido (*S*)-3,3,3-trifluoro-2-hidroxipropanoico (29 mg, 0,2 mmol), HATU (76 mg, 0,2 mmol) y trietilamina (28 µL, 0,2 mmol) en DMF (1 ml) se

agitó a temperatura ambiente durante la noche. La purificación por HPLC preparativa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (*S*)-3,3,3-trifluoro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 447,1 $(M+H)^+$ a 2,53 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

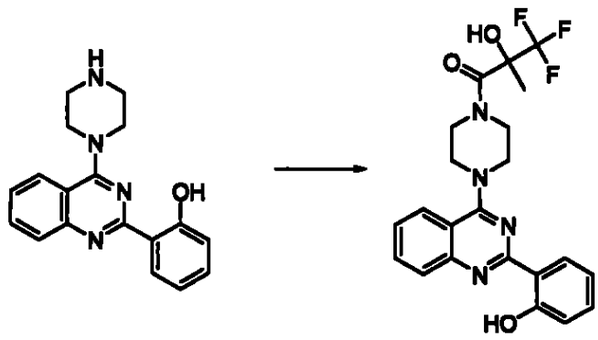
[001013] Ejemplo 178

[001014] **2-(Trifluorometil)-2-hidroxi-1-(4-(2-(2-hidroxifenil) quinazolin-4-il)piperazin-1-il)propan-1-ona**



[001015]

[001016] **2-(Trifluorometil)-2-hidroxi-1-(4-(2-(2-hidroxifenil) quinazolin-4-il)piperazin-1-il)propan-1-ona**

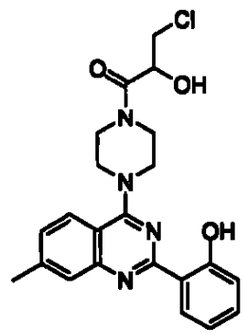


[001017]

[001018] Una solución de 2-(4-(piperazin-1-il)quinazolin-2-il)fenol (70 mg, 0,23 mmol) en DMF (0,5 ml) se añadió un ácido 2-(trifluorometil)-2-hidroxipropanoico (47,0 mg, 0,297 mmol). Luego, se agregó trietilamina (63 µL), seguido de una solución de HATU (113 mg) en 0,5 ml de DMF a temperatura ambiente. La reacción se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 2-(trifluorometil)-2-hidroxi-1-(4-(2-(2-hidroxifenil)quinazolin-4-il)piperazin-1-il)propan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 447,3 $(M+H)^+$ a 2,50 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

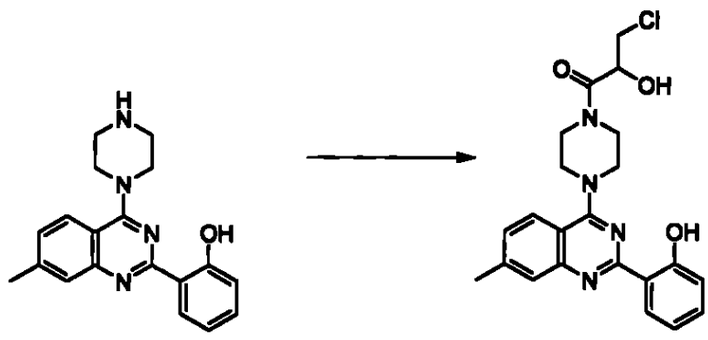
[001019] Ejemplo 179

[001020] **3-cloro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona**



[001021]

[001022] **3-cloro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona**



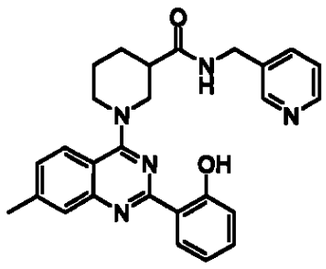
[001023]

[001024] Una mezcla de 2-(7-metil-4-(piperazin-1-il)quinazolin-2-il)fenol (121 mg, 0,38 mmol), ácido 3-cloro-2-hidroxipropanoico (61 mg, 0,49 mmol), BOP (217 mg, 0,49 mmol) y trietilamina (79 µL, 0,56 mmol) en 1,2 ml de CH_2Cl_2 se agitó a temperatura ambiente durante 1 h. La reacción se lavó con agua y la capa orgánica se secó sobre Na_2SO_4 y se concentró. La purificación por HPLC preparativa en fase inversa usando 10-

99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) dio 3-cloro-2-hidroxi-1-(4-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperazin-1-il)propan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 427,2 $(M+H)^+$ a 2,59 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001025] Ejemplo 201

[001026] **1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)-*N*-((piridin-3-il)metil)piperidin-3-carboxamida**

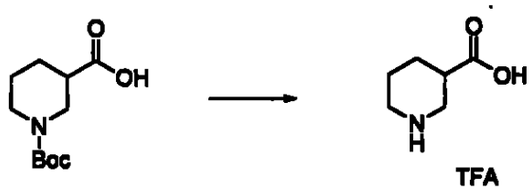


[001027]

[001028] **Ácido piperidin-3-carboxílico**

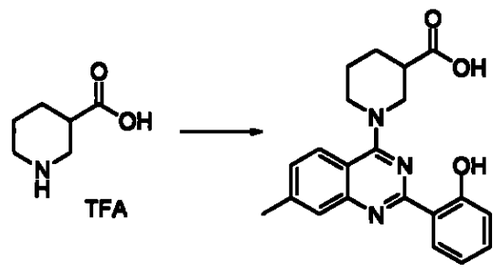
[001029]

[001030] A una solución de 1-(*ter*-butoxicarbonil)piperidin-3-carboxílico (500 mg, 2,18 mmol) en CH_2Cl_2 (10 ml) se añadió TFA (5 ml). La mezcla de reacción se agitó durante una hora. Se



eliminó el exceso de TFA a presión reducida y el ácido piperidin-3-carboxílico se usó sin neutralización para la siguiente etapa. LC/MS: *m/z* 1303 $(M+H)^+$ a 0,35 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

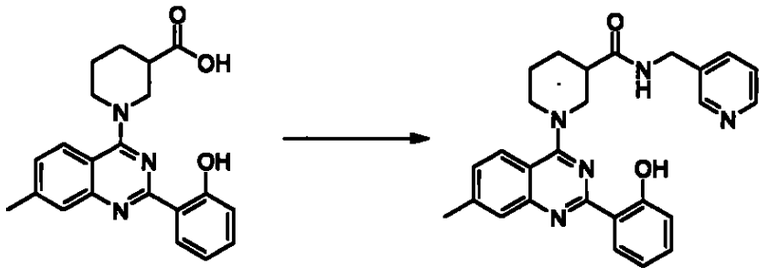
[001031] Ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-carboxílico



[001032]

[001033] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,449 mg, 1,66 mmol) en CH_2Cl_2 se añadió 5 equivalentes de trietilamina seguido de la adición de ácido piperidin-3-carboxílico en forma de una sal de TFA. La reacción se agitó durante 2 horas y se neutralizó con agua. Las capas se separaron y los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron para dar ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-carboxílico que se usó sin ulterior purificación. LC/MS: *m/z* 364,3 $(M+H)^+$ a 2,22 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001034] **1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)-*N*-((piridin-3-il)metil)piperidin-3-carboxamida**

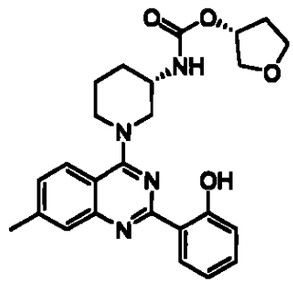


[001035]

[001036] Una solución de ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-carboxílico (45 mg, 0,12 mmol), (piridin-3-il)metanamina (14 µL, 0,136 mmol) y trietilamina (25 mg, 35 µL, 0,25 mmol) en 500 µL de DMF se enfrió hasta 0 °C y se añadió HATU (57 mg, 0,15 mmol). La reacción se calentó hasta temperatura ambiente, se agitó durante la noche y se purificó por HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)-*N*-((piridin-3-il)metil)piperidin-3-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 454,5 $(M+H)^+$ a 1,87 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

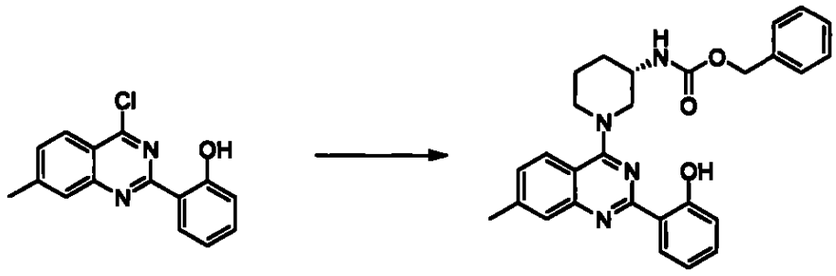
[001037] Ejemplo 203

[001038] **(*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo**



[001039]

[001040] **(*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de bencilo**



[001041]

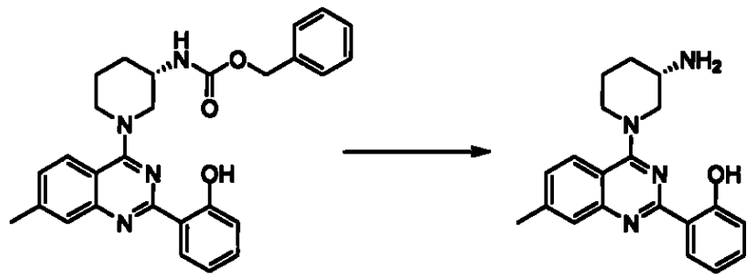
[001042] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)fenol (1,15 g, 4,26 mmol) en CH_2Cl_2 (25 ml) a 0 °C bajo una atmósfera inerte se añadió lentamente una solución de (*S*)-piperidin-3-ilcarbamato de bencilo (1,0 g, 4,26 mmol) y trietilamina (1,18 ml, 8,52 mmol) en CH_2Cl_2 (10 ml). La reacción se dejó calentar hasta temperatura ambiente y luego se neutralizó con agua. La mezcla se extrajo con CH_2Cl_2 y las capas orgánicas se combinaron, se secaron sobre $MgSO_4$ y se concentró para obtener (*S*)-1-(2-(2-hidroxifenil)-7-

915

metilquinazolin-4-il)piperidin-3-ilcarbamato de bencilo (2,03 g). Este material se usó sin ulterior purificación. LC/MS: *m/z* 469,1 $(M+H)^+$ a 2,86 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001043] 2-(4-((*S*)-3-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol

[001044]

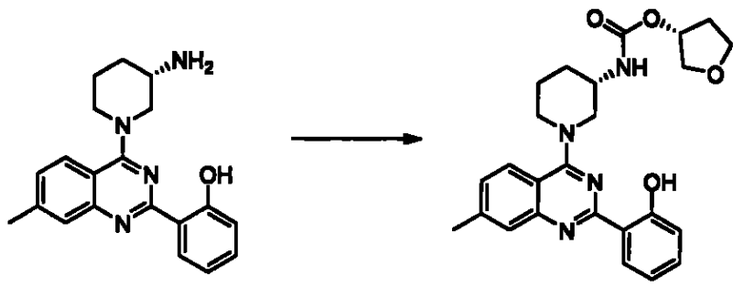


[001045] Se añadió Pd/C (175 mg, 10% en peso de Pd sobre carbón) a un recipiente de base redonda y el recipiente se inundó con N_2. A este recipiente se añadió luego MeOH (10 ml). Después de purgar nuevamente el recipiente con N_2, se añadió (*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato (1,75 g, 3,74 mmol) disuelto en EtOAc (60 ml) y MeOH (50 ml). Después de inundar el recipiente 3 veces con N_2 y evacuarlo al vacío, se pasó H_2 a través de la mezcla vigorosamente agitada durante 4 h hasta completar la hidrogenación. La mezcla se filtró a través de un taco de Celite. El filtrado se concentró para obtener 2-(4-((*S*)-3-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,62 g,

50%). LC/MS: *m/z* 335,5$(M+H)^+$ a 1,50 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001046] (*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo

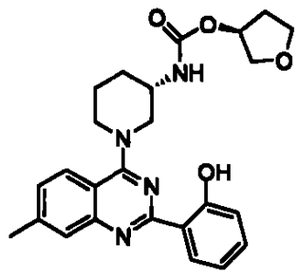
[001047]



[001048] 2-(4-((*S*)-3-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol), cloroformiato de (R)-tetrahidrofuran-3-ilo (22,6 mg, 0,15 mmol) y trietilamina (30 mg, 0,3 mmol) se agitaron en DMF (1 ml) a 0 °C. Después de dejar calentar la reacción hasta temperatura ambiente, se purificó por medio de HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar (*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 449,35 $(M+H)^+$ a 1,52 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

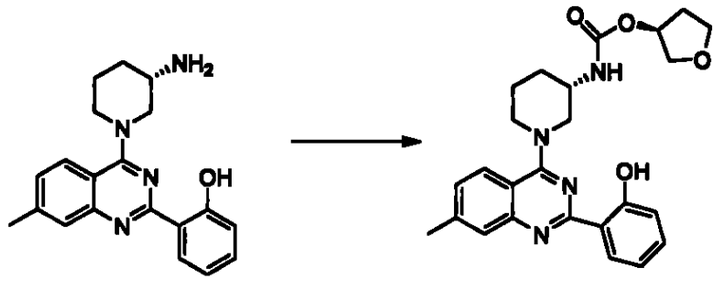
[001049] Ejemplo 204

[001050] (*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo



[001051]

[001052] **(*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo**



[001053]

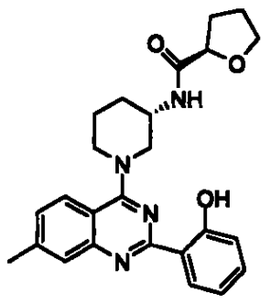
[001054] 2-(4-((*S*)-3-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol), cloroformiato de (S)-tetrahidrofuran-3-ilo (22,6 mg, 0,15 mmol) y trietilamina (30 mg, 0,3 mmol) se agitaron en DMF (1 ml) a 0 °C. Después de dejar calentar la reacción hasta temperatura ambiente, se purificó por medio de HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS:

m/z 449,3 $(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

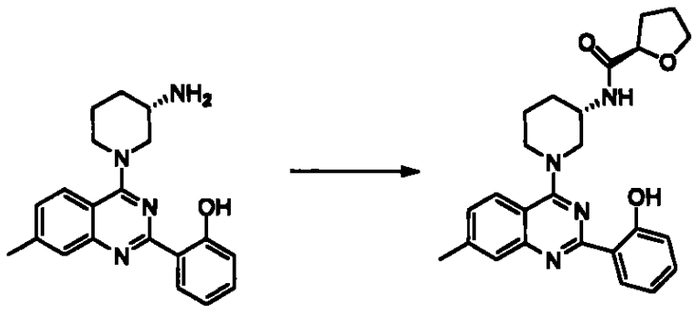
[001055] Ejemplo 205

[001056] **(2*R*)-tetrahidro-*N*-((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)furan-2-carboxamida**

[001057]



[001058] **(2*R*)-tetrahidro-*N*-((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)furan-2-carboxamida**



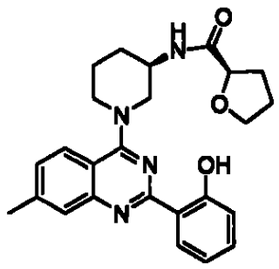
[001059]

[001060] 2-(4-((*S*)-3-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol), ácido (*R*)-tetrahidrofuran-2-carboxílico (22,6 mg, 0,195 mmol), trietilamina (30 mg, 0,3 mmol) y HATU (74,14 mg, 0,195 mmol) se agitaron a temperatura

ambiente en DMF durante 1 h. La purificación mediante HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (2*R*)-tetrahidro-*N*-((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)furan-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 433,3$(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

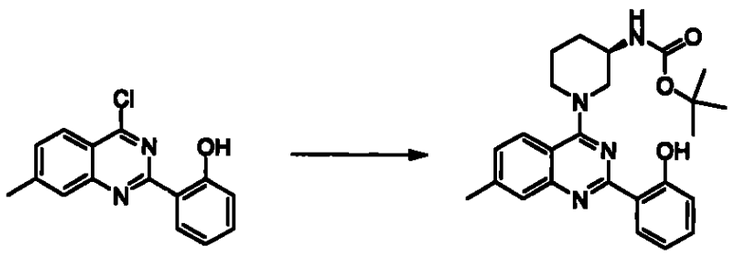
[001061] Ejemplo 206

[001062] **(2*R*)-tetrahidro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)furan-2-carboxamida**



[001063]

[001064] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de ter-butilo**



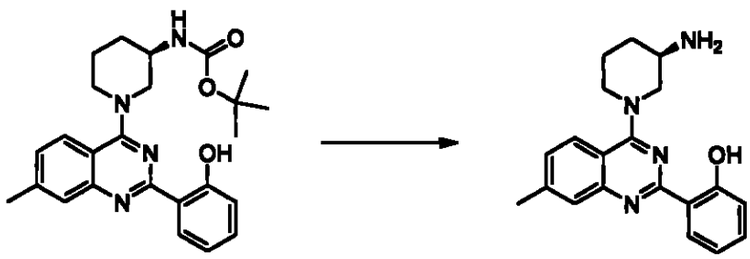
[001065]

[001066] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,5 g, 1,84 mmol) en CH_2Cl_2 (10 ml) a 0 °C se añadió

gota a gota una solución de (*R*)-piperidin-3-ilcarbamato de *ter*-butilo (0,37 g, 1,84 mmol) en CH_2Cl_2 (5 ml), luego trietilamina (0,51 ml, 3,68 mmol). La mezcla se dejó calentar hasta temperatura ambiente y se agitó durante 3 h. Después de neutralizar con agua, se extrajo con CH_2Cl_2. Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$ y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 5:1 CH_2Cl_2: hexanos dio (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de *ter*-butilo (0,54 g, 68%). LC/MS: *m/z* 435,5$(M+H)^+$ a 2,80 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001067] 2-(4-((*R*)-3-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol.

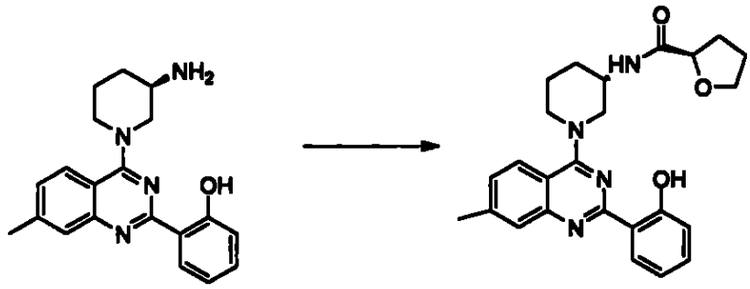
[001068]



[001069] (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de *ter*-butilo (0,54 g, 1,24 mmol) se disolvió en CH_2Cl_2 (15 ml) seguido de la adición de TFA (8 ml). La reacción se agitó durante 1,5 h y los solventes se evaporaron hasta un líquido oleoso que se diluyó con CH_2Cl_2 y se neutralizó con una solución acuosa 1 M de NaOH. La capa

orgánica se separó y la capa acuosa se lavó dos veces con CH_2Cl_2. Tras secar las fases orgánicas combinadas sobre $MgSO_4$, se filtraron y se concentraron para obtener 2-(4-((*R*)-3-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol como un sólido (0,354 g, 85%). LC/MS: *m/z* 335,7$(M+H)^+$ a 1,42 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001070] (2*R*)-tetrahidro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)furan-2-carboxamida



[001071]

[001072] 2-(4-((*R*)-3-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol), (*R*)-tetrahidrofuran-2-carboxílico (22,6 mg, 0,15 mmol), trietilamina (30 mg, 0,3 mmol) y HATU (74,14 mg, 0,195 mmol) se agitaron a temperatura ambiente en DMF durante 1 h. La purificación mediante HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (2*R*)-tetrahidro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)furan-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 433,3$(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

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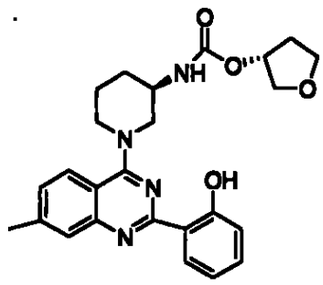
[001073] Ejemplo 207

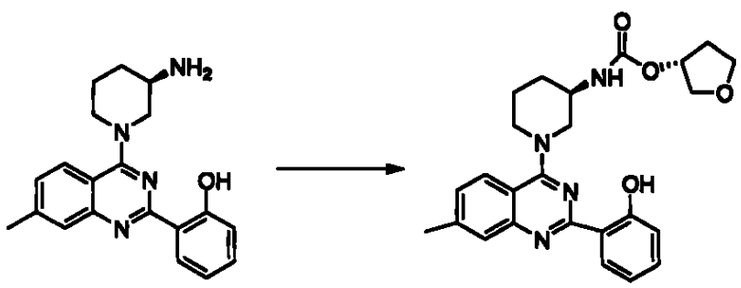
[001074] **(R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo**

[001075]



[001076] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo**

[001077]



[001078] Una solución de 2-(4-((*R*)-3-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol) en DMF (0,5 ml) se enfrió hasta 0 °C. Luego, una solución de trietilamina (30 mg, 0,3 mmol) y cloroformiato de (R)-tetrahidrofuran-3-ilo (22,6 mg, 0,15 mmol) en DMF (0,5 ml) se añadió gota a gota. La mezcla se dejó calentar hasta temperatura ambiente durante un período de 30 min antes de purificarla usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

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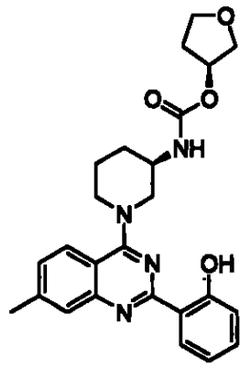
para obtener (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 449,5$(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

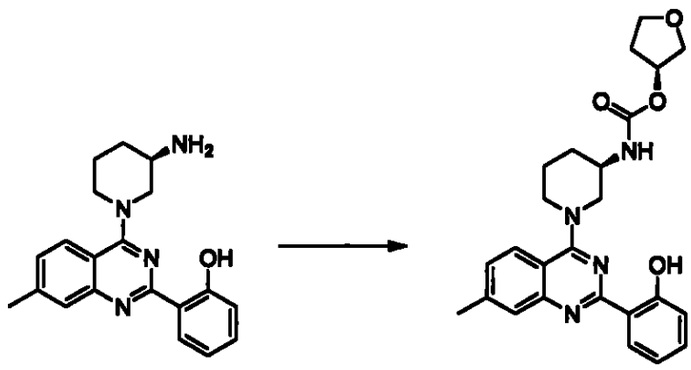
[001079] Ejemplo 208

[001080] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo**



[001081]

[001082] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo**

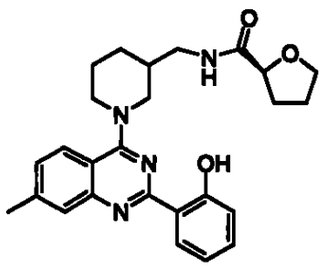


[001083]

[001084] A una solución de 2-(4-((*R*)-3-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol) en DMF (0,5 ml) se enfrió hasta 0 °C. Luego se añadió una solución de cloroformiato de (S)-tetrahidrofuran-3-ilo (22,6 mg, 0,15 mmol) en DMF (0,5 ml), seguido de trietilamina (30 mg, 0,3 mmol). La mezcla se dejó calentar hasta temperatura ambiente durante un periodo de 30 min antes de purificarla usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 449,5$(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

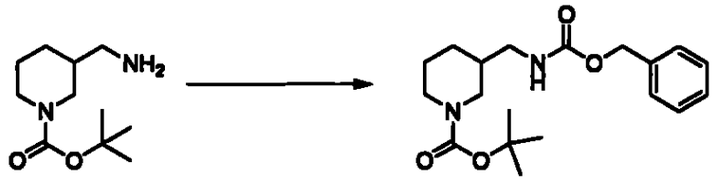
[001085] Ejemplo 209

[001086] **(2*S*)-tetrahidro-*N*-((1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metil)furan-2-carboxamida**



[001087]

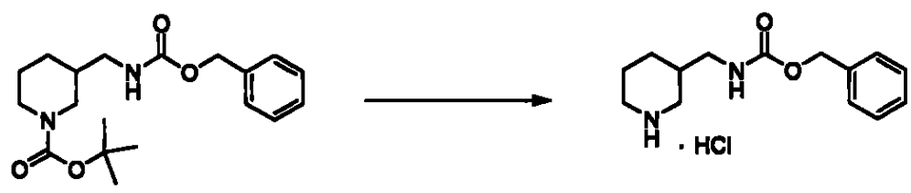
[001088] **Éster ter-butílico del ácido 3-(benciloxicarbonilamino-metil)-piperidin-1-carboxílico**

[001089] 

[001090] Se disolvió éster ter-butílico del ácido 3-aminometil-piperidin-1-carboxílico (3,6 g, 16,8 mmol) en 42 ml de CH_2Cl_2 anhidro bajo una atmósfera de N_2 y se enfrió en un baño de agua helada. Se agregó trietilamina (4,7 ml, 33,6 mmol) seguido de la adición gota a gota de cloroformiato de bencilo (3,55 ml, 25,2 mmol). Al cabo de 16 horas, la mezcla de reacción se dividió en CH_2Cl_2/H_2O y se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Todos los extractos orgánicos se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron para dar un aceite amarillo claro. La purificación por cromatografía en gel de sílice usando 97% de CH_2Cl_2/3% de MeOH dio el producto en forma de un aceite

incoloro claro (55%). LC/MS: *m/z* 349,3 $(M+H)^+$ a 3,22 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

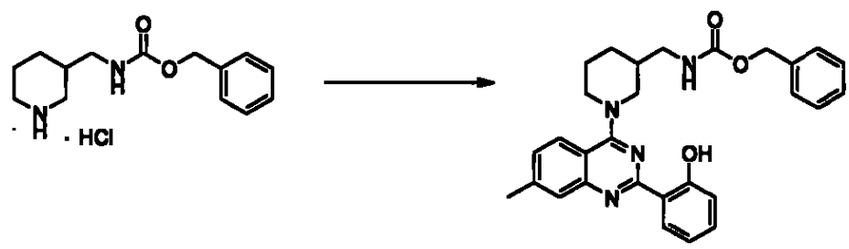
[001091] Clorhidrato de (piperidin-3-il)metilcarbamato de bencilo



[001092]

[001093] Se trató (1-(*ter*-butoxicarbonil)piperidin-3-il)metilcarbamato de bencilo (3,22 g, 9,25 mmol) con una solución de HCl 4,0 M en dioxano (11,3 ml, 46,25 mmol). Se observó la formación de un precipitado blanco. Al cabo de 3 h, la reacción se completó. El solvente y el exceso de HCl se eliminaron a presión reducida para obtener clorhidrato de (piperidin-3-il)metilcarbamato de bencilo en forma de un sólido blanco. LC/MS: *m/z* 249,3 $(M+H)^+$ a 1,28 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001094] (1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo



[001095]

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[001096] 2-(4-cloro-7-metilquinazolin-2-il)fenol (1,5 g, 5,54 mmol) se suspendió en CH_2Cl_2 anhidro (15 ml) y se enfrió hasta 0 °C bajo una atmósfera de N_2. Una mezcla de clorhidrato de (piperidin-3-il)metilcarbamato de bencilo (1,73 g, 6,09 mmol) en CH_2Cl_2 (20 ml) y trietilamina (23 ml, 16,67 mmol) se añadió gota a gota. La mezcla de reacción se dejó calentar hasta temperatura ambiente y la reacción se completó después de una hora. Luego se dividió en CH_2Cl_2/H_2O y se separó y la fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró en un sólido anaranjado. La purificación por cromatografía en gel de sílice usando 98% de CH_2Cl_2/2% de EtOAc dio (1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo en forma de sólido amarillo brillante (1,75 g, 66%). LC/MS: *m/z* 483,5 $(M+H)^+$ a 2,81 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001097] **2-(4-(3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol**

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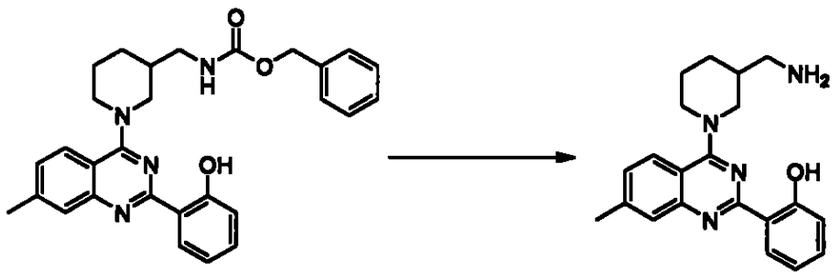

[001098]

[001099] Una mezcla de (1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo (1,75 g, 3,63 mmol) y EtOH/EtOAc (50 ml/20 ml) se calentó hasta obtener una solución homogénea. Tras enfriar hasta temperatura ambiente, se añadió Pd/C (175 mg, 10% en peso de Pd sobre carbón) y el recipiente se selló con un septo. El mismo recipiente se cargó tres veces con N_2 y se evacuó al vacío. La mezcla se agitó luego bajo una atmósfera de H_2 a presión ambiente durante 1 h. El producto se recogió por filtración a través de un tapón de Celite, al eluir con MeOH. El filtrado se concentró en un sólido amarillo (1,26 g) para dar 2-(4-(3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol. LC/MS: *m/z* 349,3 $(M+H)^+$ a 1,80 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001100] **(2*S*)-tetrahidro-*N*-((1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metil)furan-2-carboxamida**

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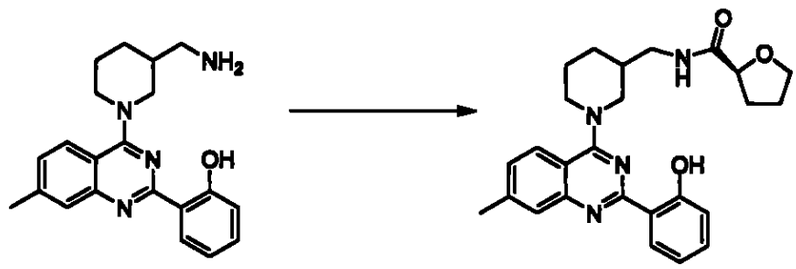
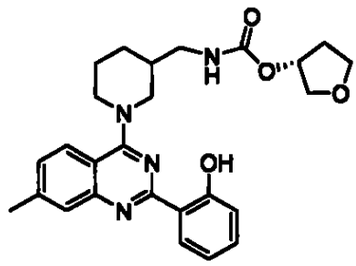


[001101]

[001102] 2-(4-(3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió en un baño de agua helada. A esto se añadió ácido (*S*)-tetrahidrofuran-2-carboxílico (24,0 mg, 19,8 µL, 0,2 mmol) y trietilamina (50 µL, 0,34 mmol). Al cabo de 5 minutos, se agregó HATU (78,3 mg, 0,2 mmol) en una porción y la reacción se dejó calentar hasta temperatura ambiente durante la noche. La purificación por HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (2*S*)-tetrahidro-N-((1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metil)furan-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 447,5 $(M+H)^+$ a 2,27 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

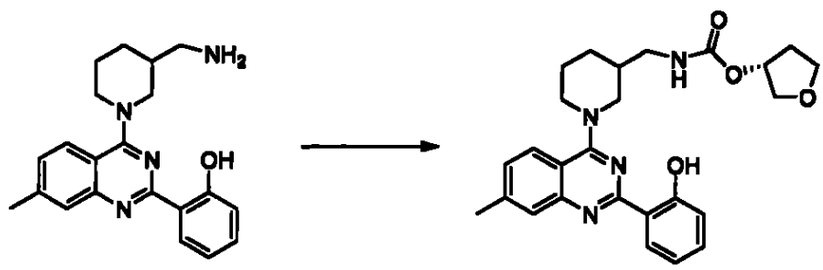
[001103] Ejemplo 210

[001104] **(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo**



[001105]

[001106] (1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo



[001107]

[001108] 2-(4-(3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF (0,5 ml) y se colocó en un baño de agua helada. Se disolvió cloroformiato de (R)-tetrahidrofuran-3-ilo (31 mg, 0,2 mmol) en DMF (0,1 ml) y se añadió gota a gota, seguido de la adición de trietilamina (50 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de la

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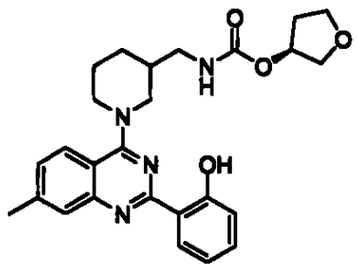
sal de TFA. LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001109] Ejemplo 211

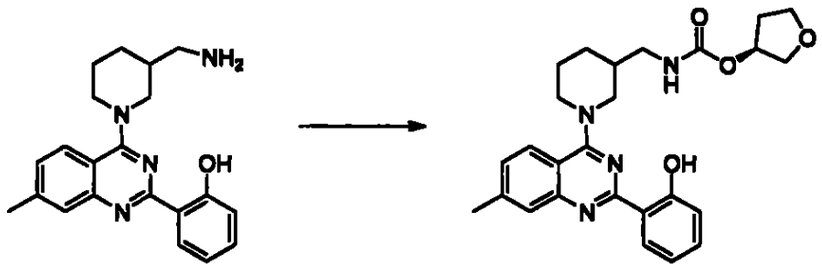
[001110] **(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo**

[001111]



[001112] **(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo**

[001113]

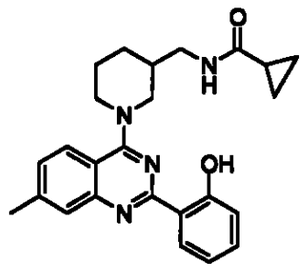


[001114] 2-(4-(3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) disuelto en DMF (0,5 ml) se enfrió hasta 0 °C. Se disolvió cloroformiato de (S)-tetrahidrofuran-3-ilo (31 mg, 0,2 mmol) en DMF (0,1 ml) y se añadió gota a gota a la mezcla de reacción, seguido de la adición de trietilamina (50 µL, 0,34 mmol). La reacción se

dejó calentar hasta temperatura ambiente y se agitó durante la noche. La reacción se purificó por HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001115] Ejemplo 212

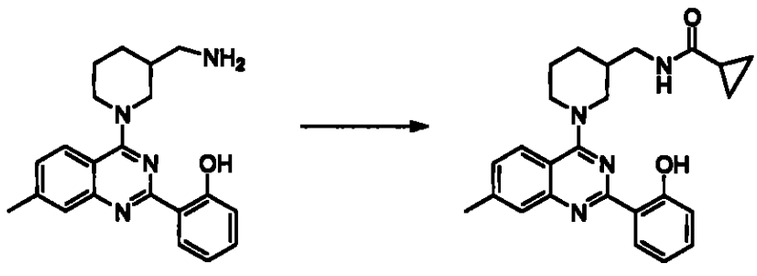
[001116] **N-((1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metil)ciclopropancarboxamida**



[001117]

[001118] **N-((1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metil)ciclopropancarboxamida**

[001119]



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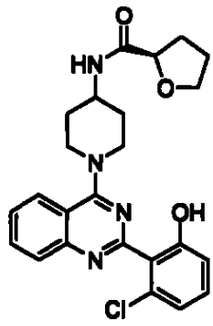
[001120] 2-(4-(3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF (0,5 ml) y se enfrió hasta 0 °C. Se disolvió cloruro de ciclopropancarbonilo (15,7 mg, 0,2 mmol) en DMF (0,1 ml) y se añadió gota a gota, seguido de la adición de trietilamina (50 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante la noche. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio *N*-((1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metil)ciclopropancarboxamida en forma de la sal de TFA. LC/MS: *m/z* 417,0 $(M+H)^+$ a 2,30 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

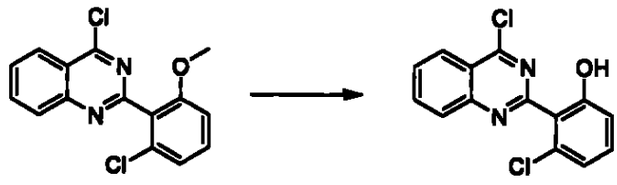
[001121] Ejemplo 213

[001122] **(2*R*)-*N*-(1-(2-(2-cloro-6-hidroxifenil)quinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida**



[001123]

[001124] **3-cloro-2-(4-cloroquinazolin-2-il)fenol**



[001125]

[001126] A una solución de 4-cloro-2-(2-cloro-6-metoxifenil)quinazolina (0,3 g, 0,98 mmol) en CH_2Cl_2 a -78 °C se añadió 5 equivalentes de solución 1 M de BBr_3 (4,9 ml, 4,9 mmol) en CH_2Cl_2. La reacción se completó después de 30 minutos Después de dejarla calentar hasta temperatura ambiente, la mezcla de reacción se neutralizó con $NaHCO_3$ acuosa a pH 7, las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2. Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtró y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 2:1 CH_2Cl_2:hexanos dio como resultado 3-cloro-2-(4-cloroquinazolin-2-il)fenol (0,17 g, 60%). LC/MS: *m/z* 291,1$(M+H)^+$ a 3,16 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001127] **(2R)-*N*-(1-(2-(2-cloro-6-hidroxifenil)quinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida**

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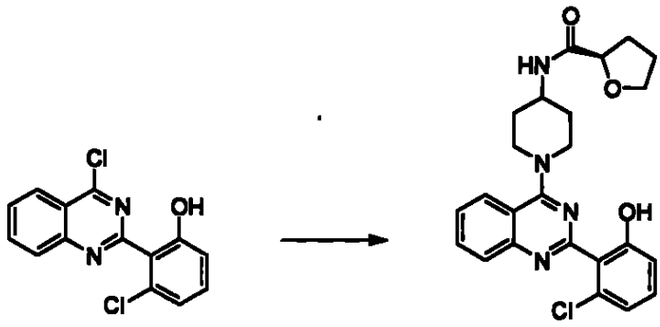
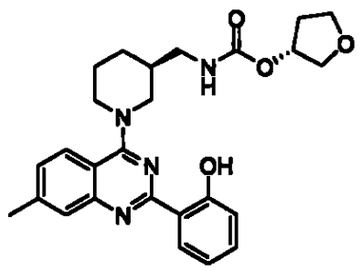


[001128]

[001129] A 0 °C, a una solución de 3-cloro-2-(4-cloroquinazolin-2-il)fenol (42 mg, 0,144 mmol) en CH_2Cl_2 se añadió trietilamina (80 µL, 0,58 mmol) seguido de la adición de (*R*)-tetrahidro-*N*-(piperidin-4-il)furan-2-carboxamida a oxalato. Después de dejar calentar la reacción hasta temperatura ambiente, se purificó por medio de HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (2*R*)-*N*-(1-(2-(2-cloro-6-hidroxifenil)quinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 453,5(M+H)$^+$ a 1,98 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001130] Ejemplo 214

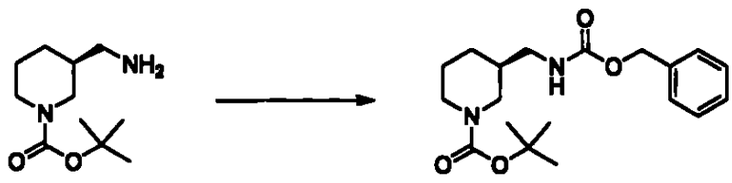
[001131] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo**



[001132]

[001133] **Método 1**

[001134] **((*S*)-1-(ter-butoxicarbonil)piperidin-3-il)metilcarbamato de bencilo**



[001135]

[001136] 3-(aminometil)piperidin-1-carboxilato de (*S*)-*ter*-butilo (1,00 g, 4,67 mmol) se disolvió en 14 ml de CH_2Cl_2 anhidro bajo una atmósfera de N_2 y se enfrió hasta 0 °C. Se añadió trietilamina (1,30 ml, 945 mg, 9,34 mmol) seguido de la adición gota a gota de cloroformiato de bencilo (0,99 ml, 1,20 g, 7,00 mmol). Al cabo de 16 h, la mezcla de reacción se dividió en H_2O y CH_2Cl_2 y se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron en un aceite de color amarillo claro. La purificación por medio de

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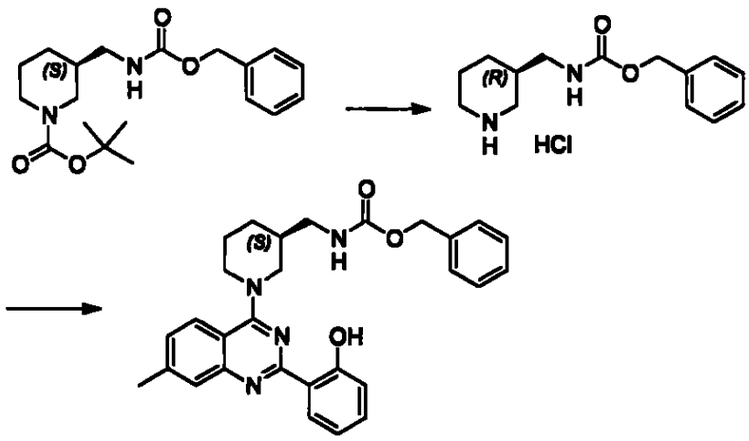
cromatografía en gel de sílice usando 97% de CH_2Cl_2/3% de MeOH dio ((*S*)-1-(*ter*-butoxicarbonil)piperidin-3-il)metilcarbamato de bencilo en forma de un aceite incoloro claro (895 mg, 55%). LC/MS: *m/z* 349,5 $(M+H)^+$ a 3,21 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001137] ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo



[001138]

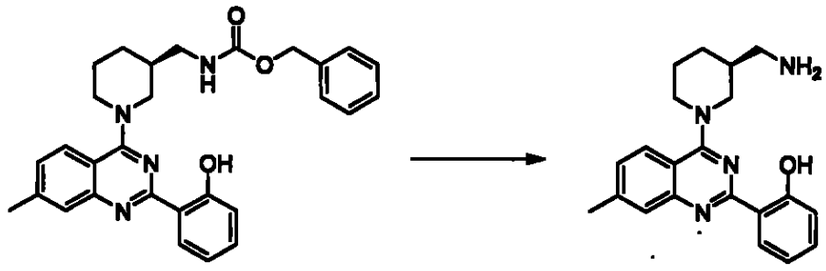
[001139] ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo (895 mg, 2,57 mmol) se trató con una solución de HCl 4,0 M en dioxano (3,2 ml, 12,85 mmol). Se observó la formación de un precipitado blanco. Al cabo de 3 h, se vio por TLC la conversión completa del material de partida. El solvente y el exceso de HCl se eliminaron a presión reducida para obtener clorhidrato de

((*R*)-piperidin-3-il)metilcarbamato de bencilo en forma de un sólido blanco.

Este sólido se suspendió en DMF/CH_2Cl_2 (3 ml/3 ml), seguido de la adición de 2-(4-cloro-7-metilquinazolin-2-il)fenol (696 mg, 2,57 mmol) y trietilamina (1,8 ml, 1,3 g, 12,85 mmol). La mezcla se agitó a temperatura ambiente bajo una atmósfera de N_2 durante 16 h. La reacción se dividió en H_2O/CH_2Cl_2 y se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron a presión reducida. La purificación por medio de cromatografía en gel de sílice usando 0-5% de MeOH en CH_2Cl_2 dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo en forma de un aceite amarillo espeso (610 mg, 49%). LC/MS: *m/z* 483,3 $(M+H)^+$ a 2,83 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001140] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol

[001141]



[001142] A una mezcla de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo

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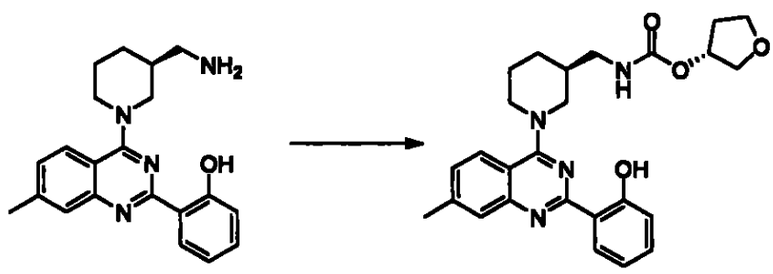
(610 mg, 1,26 mmol) y EtOH (15 ml) en un recipiente de base redonda se añadió Pd/C (61 mg, 10% en peso de Pd sobre carbón) y el recipiente se selló con un septo. La atmósfera en el recipiente se evacuó, se purgó con N_2 y se equipó con un balón cargado con H_2. La mezcla se agitó luego bajo una atmósfera de H_2 a presión ambiente durante 3 h. Tras filtrar a través de un tapón de Celite, usando MeOH como el solvente de elución, la mezcla de reacción se concentró en un sólido amarillo 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (441 mg). LC/MS: *m/z* 349,3 $(M+H)^+$ a 1,52 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,43-8,45 (m, 1H), 7,95 (d, *J* = 8,5 Hz, 1H), 7,64 (s, 1H), 7,35-7,39 (m, 2H), 6,92-6,96 (m, 2H), 4,52 (d, *J* = 12,5 Hz, 1H), 4,41 (d, *J* = 13,2 Hz, 1H), 3,26-3,29 (m, 2H), 3,02-3,08 (m, 1H), 2,55-2,61 (m, 1H), 2,45-2,48 (m, 1H), 1,84-1,91 (m, 2H), 1,65-1,77 (m, 3H), 1,24-1,36 (m, 1H).

[001143] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo**



[001144]

[001145] Método A

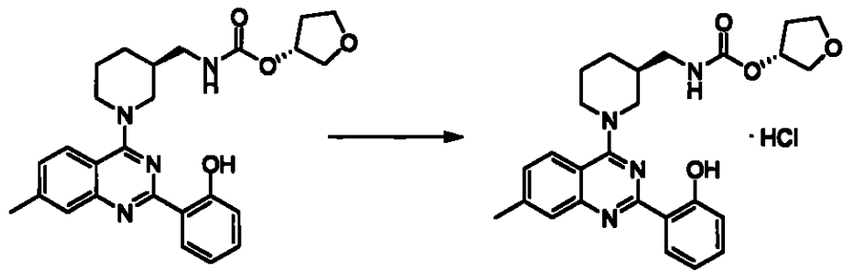
[001146] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C y cloroformiato de (R)-tetrahidrofuran-3-ilo (31 mg, 0,2 mmol) disuelto en DMF (100 µL) se añadió gota a gota seguido de trietilamina (35 mg, 48 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente. La reacción se completó después de dos horas. La purificación usando HPLC en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,32 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001147] Método B

[001148] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (127 mg, 0,364 mmol) se disolvió en 5 ml de DMF anhidra y se enfrió hasta 0 °C y se añadió una

solución de cloroformiato de (R)-tetrahidrofuran-3-ilo (65,4 mg, 0,436 mmol) en 200 µL de DMF gota a gota seguido de la adición de trietilamina (74 mg, 0,10 ml, 0,73 mmol). La reacción se dejó calentar hasta temperatura ambiente. La reacción se completó después de dos horas. La mezcla se dividió en H_2O y CH_2Cl_2 y se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron en un sólido amarillo. La purificación por medio de cromatografía en gel de sílice usando 98% de CH_2Cl_2/2% de MeOH dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de un sólido blanquecino (116 mg, 69%). LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,41-8,43 (m, 1H), 7,86 (d, *J* = 8,5 Hz, 1H), 7,65 (s, 1H), 7,33-7,44 (m, 3H), 6,90-6,95 (m, 2H), 5,11 (dd, *J* = 6,2, 4,6 Hz, 1H), 4,38 (t, *J* = 14,5 Hz, 2H), 3,68-3,79 (m, 3H), 3,60-3,63 (m, 1H), 3,28-3,31 (m, 1H), 2,98-3,07 (m, 3H), 2,50 (s, 3H), 2,06-2,15 (m, 1H), 1,85-1,91 (m, 4H), 1,70 (d, *J* = 12,9 Hz, 1H), 1,24-1,37 (m, 1H).

[001149] Clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo



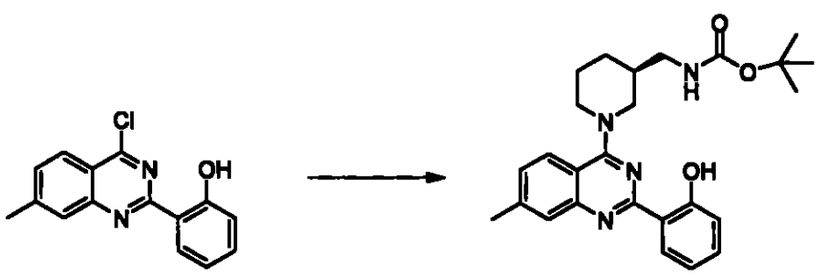
[001150]

[001151] ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo (116 mg, 0,251 mmol) se suspendió en 8 ml de CH_2Cl_2 anhidro y se calentó bien hasta formar una solución homogénea. Después de enfriar la reacción hasta temperatura ambiente, se añadió una solución 2,0 M de HCl en Et_2O (0,126 ml, 0,251 mmol) en una porción. La mezcla de reacción se diluyó con 25 ml de Et_2O y el producto precipitó de la solución. La reacción se agitó durante 30 minutos adicionales antes de filtrar el sólido y se secó para obtener clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de un sólido de color amarillo claro (99 mg, 70%). LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,22 (d, *J* = 7,7 Hz, 1H), 7,95 (d, *J* = 8,5 Hz, 1H), 7,75 (s, 1H), 7,42-7,49 (m, 3H), 6,97-7,08 (m, 2H), 5,08 (dd, *J* = 6,1, 4,6 Hz, 1H), 4,52-4,54 (m, 2H), 3,66-3,78 (m, 3H), 3,58-3,60 (m, 1H), 3,48 (t, *J* = 10,7 Hz, 1H), 3,23 (t, *J* =

11,5 Hz, 1H), 3,00 (t, *J* = 6,3 Hz, 2H), 2,53 (s, 3H), 2,05-2,14 (m, 1H), 1,80-1,91 (m, 4H), 1,72 (d, *J* = 9,0 Hz, 1H), 1,34-1,43 (m, 1H).

[001152] **Método 2**

[001153] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de ter-butilo**



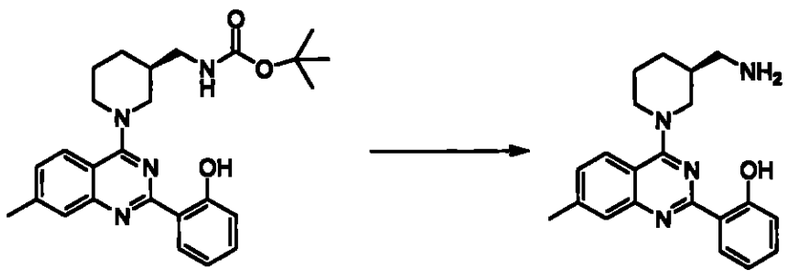
[001154]

[001155] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,478 g, 1,76 mmol) en CH_2Cl_2 se añadió trietilamina (0,98 ml, 0,712 g, 7,04 mmol) y la mezcla se enfrió hasta 0 °C. A la mezcla de reacción se añadió oxalato de ((*R*)-piperidin-3-il)metilcarbamato de *ter*-butilo (preparado análogamente a la sal de oxalato de 2-(7-metil-4-piperazin-1-il-quinazolin-2-il)-fenol, ver Ejemplo 130; 700 mg, 2,3 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante la noche. La reacción se neutralizó con agua y la capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-2% de

EtOAc en CH_2Cl_2 dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de *ter*-butilo (700 mg, 88%). LC/MS: *m/z* 449,5 $(M+H)^+$ a 2,77 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001156] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol

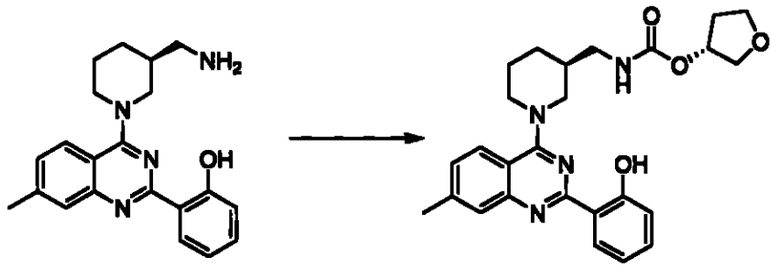
[001157]



[001158] A ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato (700 mg, 1,56 mmol) se añadieron 20 ml de CH_2Cl_2 seguido de adición de 7 ml de TFA. Al cabo de la reacción se agitó durante 1 hora se neutralizó con una solución acuosa 1,0 M de NaOH. La mezcla se dividió en H_2O y CH_2Cl_2 y se separó y la capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (400 mg, 74%). LC/MS: *m/z* 349,3 $(M+H)^+$ a 1,52 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,43-8,45 (m, 1H), 7,95 (d, *J* = 8,5 Hz, 1H), 7,64 (s, 1H),

7,35-7,39 (m, 2H), 6,92-6,96 (m, 2H), 4,52 (d, *J* = 12,5 Hz, 1H), 4,41 (d, *J* = 13,2 Hz, 1H), 3,26-3,29 (m, 2H), 3,02-3,08 (m, 1H), 2,55-2,61 (m, 1H), 2,45-2,48 (m, 1H), 1,84-1,91 (m, 2H), 1,65-1,77 (m, 3H), 1,24-1,36 (m, 1H).

[001159] ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo



[001160]

[001161] A una solución de 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (210 mg, 0,6 mmol) en DMF a 0 °C se añadieron cloroformiato de (R)-tetrahidrofuran-3-ilo (0,09 g, 0,6 mmol) y trietilamina (167 µL, 1,2 mmol) de forma simultánea. Luego, a los 15 minutos de la adición, la reacción se completó y se neutralizó con agua, se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para dar ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo (150 mg, 54%). LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,41-8,43 (m, 1H), 7,86 (d, *J* = 8,5 Hz, 1H), 7,65 (s, 1H), 7,33-7,44 (m,

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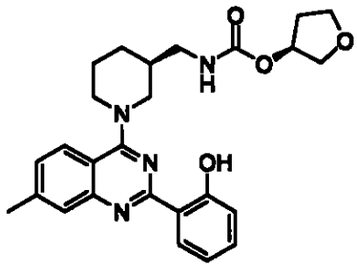
3H), 6,90-6,95 (m, 2H), 5,11 (dd, *J* = 6,2, 4,6 Hz, 1H), 4,38 (t, *J* = 14,5 Hz, 2H), 3,68-3,79 (m, 3H), 3,60-3,63 (m, 1H), 3,28-3,31 (m, 1H), 2,98-3,07 (m, 3H), 2,50 (s, 3H), 2,06-2,15 (m, 1H), 1,85-1,91 (m, 4H), 1,70 (d, *J* = 12,9 Hz, 1H), 1,24-1,37 (m, 1H).

[001162] Ejemplo 215

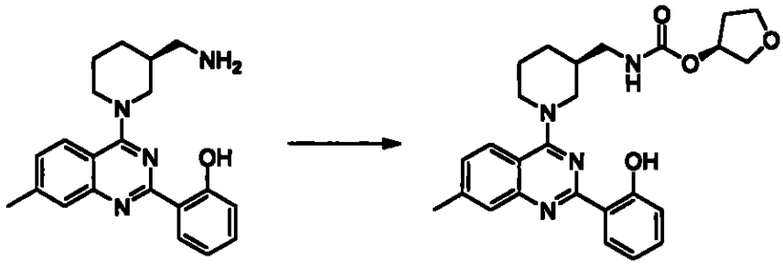
[001163] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (*S*)-tetrahidrofuran-3-ilo**



[001164]

[001165] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (*S*)-tetrahidrofuran-3-ilo**

[001166]



[001167] Método A

[001168] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C y cloroformiato de (S)-tetrahidrofuran-3-ilo (31 mg, 0,2 mmol) en DMF (100 µL) se añadió gota a gota seguido de trietilamina (35 mg, 48 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente. La reacción se completó después de dos horas. La purificación usando HPLC preparativa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((S)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001169] Método B

[001170] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (126,8 mg, 0,364 mmol) se disolvió en 5 ml de DMF anhidra y se enfrió hasta 0 °C y una solución de cloroformiato de (S)-tetrahidrofuran-3-ilo (65,4 mg, 0,436 mmol) en 200 µl de DMF se añadió gota a gota seguido de la adición de trietilamina (74 mg, 0,102 ml, 0,728 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de dos horas. La mezcla se dividió en H_2O y CH_2Cl_2, se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las fases orgánicas combinadas se secaron sobre Na_2SO_4,

se filtraron y se concentraron en un sólido amarillo. La purificación por medio de cromatografía en gel de sílice usando 98% de CH_2Cl_2/2% de MeOH dio ((S)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de un sólido blanquecino (116 mg, 69%). LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)),1H RMN (400 MHz, DMSO-d6) δ 8,42 (dd, *J* = 8,1, 1,7 Hz, 1H), 7,86 (d, *J* = 8,6 Hz, 1H), 7,66 (s, 1H), 7,34-7,43 (m, 3H), 6,91-6,95 (m, 2H), 5,10-5,11 (m, 1H), 4,38 (t, *J* = 12,4 Hz, 2H), 3,65-3,77 (m, 4H), 2,98-3,08 (m, 3H), 2,04-2,13 (m, 1H), 1,80-1,87 (m, 4H), 1,68-1,74 (m, 1H), 1,30-1,38 (m, 1H).

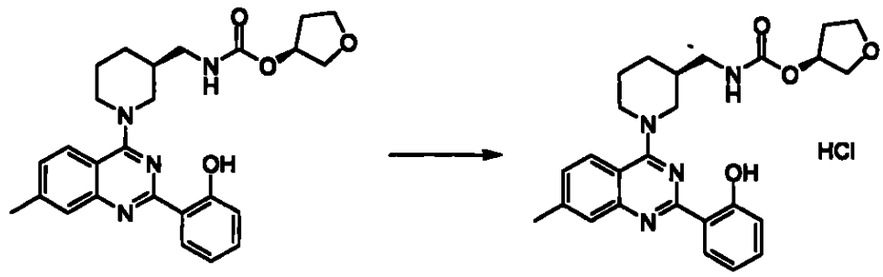
[001171] Método C

[001172] A una solución de 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (175 mg, 0,5 mmol) en DMF a 0 °C se añadieron cloroformiato de (S)-tetrahidrofuran-3-ilo (75 mg, 0,5 mmol) y trietilamina (137 µL, 1,0 mmol) de forma simultánea. Diez a quince minutos después de la adición, la reacción se completó y se neutralizó con agua y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 98% de CH_2Cl_2/2% de MeOH dio ((S)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo

(150 mg, 54%). LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,42 (dd, *J* = 8,1, 1,7 Hz, 1H), 7,86 (d, *J* = 8,6 Hz, 1H), 7,66 (s, 1H), 7,34-7,43 (m, 3H), 6,91-6,95 (m, 2H), 5,10-5,11 (m, 1H), 4,38 (t, *J* = 12,4 Hz, 2H), 3,65-3,77 (m, 4H), 2,98-3,08 (m, 3H), 2,04-2,13 (m, 1H), 1,80-1,87 (m, 4H); 1,68-1,74 (m, 1H), 1,30-1,38 (m, 1H).

[001173] Clorhidrato de ((S)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo

[001174]

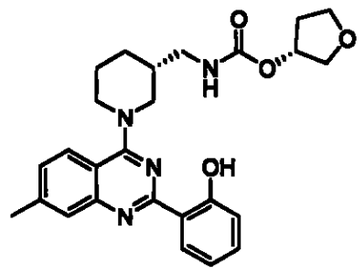


[001175] ((S)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo (115 mg, 0,251 mmol) se suspendió en 8 ml de CH_2Cl_2 anhidro y calentó bien hasta formarse una solución homogénea. Tras enfriar hasta temperatura ambiente, se añadió una solución 2,0 M de HCl en Et_2O (0,126 ml, 0,251 mmol) en una porción. La mezcla de reacción se diluyó con 25 ml de Et_2O y el producto se precipitó de la solución. La reacción se agitó durante 30

minutos adicionales antes de filtrar el sólido y se secó para obtener clorhidrato de ((S)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo (108 mg, 86%) en forma de un sólido de color amarillo claro. LC/MS: *m/z* 463,5$(M+H)^+$ a 2,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)),1H RMN (400 MHz, DMSO-d6) δ 8,18 (d, *J* = 6,6 Hz, 1H), 7,94 (d, *J* = 8,6 Hz, 1H), 7,73 (s, 1H), 7,44-7,51 (m, 2H), 7,00-7,07 (m, 2H), 5,06-5,09 (m, 1H), 4,52-4,62 (m, 2H), 3,62-3,74 (m, 4H), 3,23-3,29 (m, 1H), 3,00 (d, *J* = 6,8 Hz, 2H), 2,52 (s, 3H), 2,02-2,11 (m, 1H), 1,61-2,01 (m, 4H), 1,24-1,43 (m, 2H), 0,84-0,89 (m, 1H).

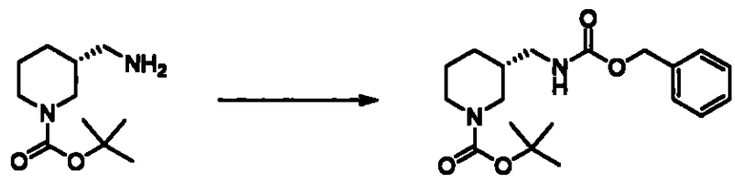
[001176] Ejemplo 216

[001177] **((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo**



[001178]

[001179] **((R)-1-(ter-butoxicarbonil)piperidin-3-il)metilcarbamato de bencilo**



[001180]

[001181] Se disolvió 3-(aminometil)piperidin-1-carboxilato de (R)-ter-butilo (1,00 g, 4,67 mmol) en 14 ml de CH_2Cl_2 anhidro bajo una atmósfera de N_2 y se enfrió hasta 0 °C. Se agregó trietilamina (1,30 ml, 945 mg, 9,34 mmol) seguido de la adición gota a gota de cloroformiato de bencilo (0,99 ml, 1,20 g, 7,00 mmol). Al cabo de 16 h, la reacción se completó. La mezcla se dividió en H_2O y CH_2Cl_2 y se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron en un aceite de color amarillo claro. La purificación por medio de cromatografía en gel de sílice usando 97% de CH_2Cl_2/3% de MeOH dio ((R)-1-(ter-butoxicarbonil)piperidin-3-il)metilcarbamato de bencilo en forma de un aceite incoloro claro(1,2 g, 74%). LC/MS: *m/z* 349,5 $(M+H)^+$ a 3,21 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001182] **((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo**

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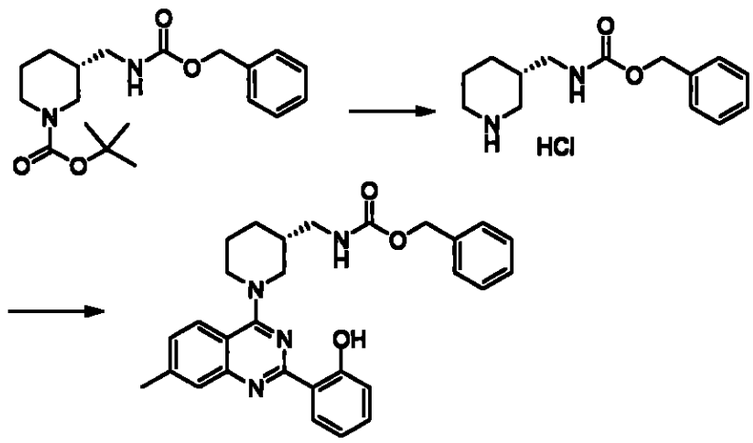
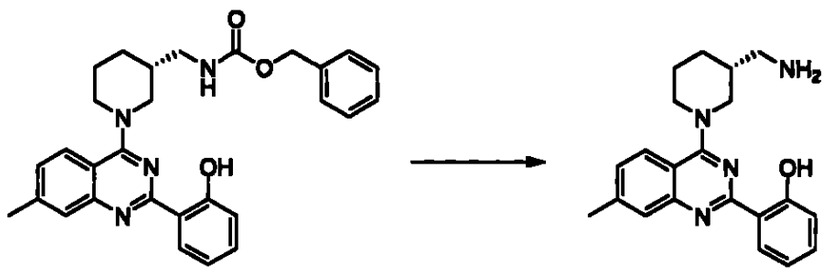


[001183]

[001184] ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo (1,2 g, 3,54 mmol) se trató con solución de HCl 4,0 M en dioxano (4,3 ml, 17,2 mmol). Se observó la formación de un precipitado blanco. La reacción se completó después de tres horas. El solvente y el exceso de HCl se eliminaron a presión reducida para obtener clorhidrato de ((S)-piperidin-3-il)metilcarbamato de bencilo en forma de un sólido blanco. Este sólido se suspendió en DMF/CH_2Cl_2 (3 ml/3 ml), seguido de la adición de 2-(4-cloro-7-metilquinazolin-2-il)fenol (958 mg, 3,54 mmol) y luego trietilamina (1,8 ml, 1,3 g, 12,85 mmol). La mezcla se agitó a temperatura ambiente bajo una atmósfera de N_2 durante 16 h. La reacción se dividió luego en H_2O y CH_2Cl_2, se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se

concentraron a presión reducida. La purificación por medio de cromatografía en gel de sílice usando 0-5% de MeOH en CH_2Cl_2 dio ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo en forma de un aceite amarillo espeso (855 mg, 51%). LC/MS: *m/z* 483,5 $(M+H)^+$ a 2,81 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001185] 2-(4-((*R*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol

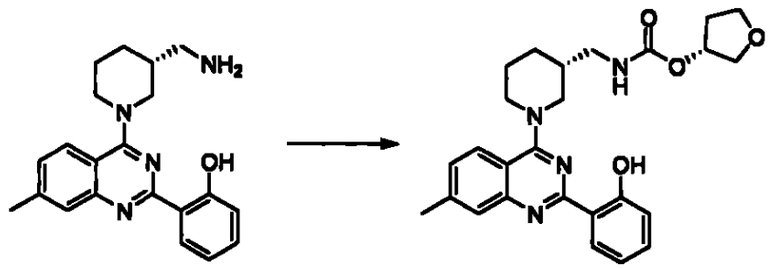


[001186]

[001187] A una mezcla de ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de bencilo (855 mg, 1,77 mmol) y EtOH (15 ml) en un recipiente de base redonda se añadió Pd/C (86 mg, 10% en peso de Pd sobre carbón) y el recipiente se selló con un septo. La atmósfera en el recipiente se evacuó, se purgó con N_2 y equipado con un balón cargado con H_2. La mezcla se agitó bajo una atmósfera de H_2 a presión ambiente durante 3 h. Tras filtrar a través de un tapón de Celite usando MeOH como el solvente de elución, la mezcla de reacción se concentró en 2-(4-((*R*)-3-

(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (625 mg) en forma de un sólido amarillo. LC/MS: *m/z* 349,3 $(M+H)^+$ a 1,82 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001188] ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo



[001189]

[001190] Método A

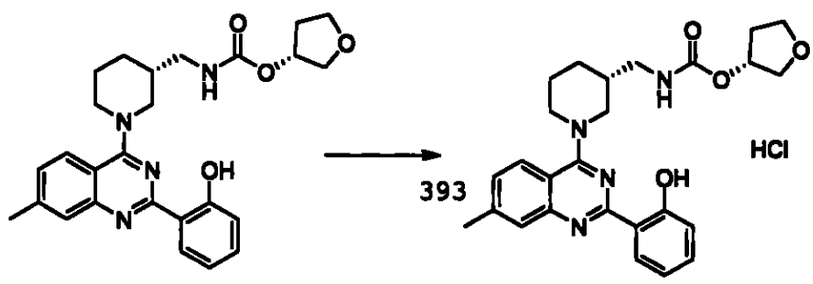
[001191] 2-(4-((*R*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C, después de añadir el cloroformiato de (R)-tetrahidrofuran-3-ilo (31 mg, 0,2 mmol) disuelto en DMF (100 µL) gota a gota seguido de la adición de trietilamina (35 mg, 48 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de dos horas. La purificación usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de la

sal de TFA. LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,35 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001192] Método B

[001193] A una solución agitada de 2-(4-((*R*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (150 mg, 0,43 mmol) bajo una atmósfera de N_2 a 0 °C se añadió trietilamina (87 mg, 0,86 mmol) seguido de la adición gota a gota de cloroformiato de (R)-tetrahidrofuran-3-ilo (65 mg, 0,43 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante 2 h. La mezcla se dividió en H_2O y CH_2Cl_2 y se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 4:1 CH_2Cl_2:EtOAc dio ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo. LC/MS: *m/z* 463,5$(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001194] Clorhidrato de ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo



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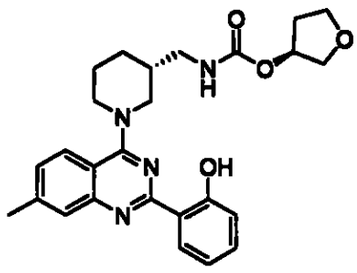
[001195]

[001196] A una solución de ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo (0,085 g, 0,18 mmol) en 9 ml de CH_2Cl_2 se añadió gota a gota una solución de HCl 2,0 M en éter (0,09 ml, 0,18 mmol). Luego se añadió éter (20 ml), lo que llevó a la precipitación del clorhidrato de de ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo que se filtró y se secó (85 mg, 95%). LC/MS: *m/z* 463,5$(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001197] Ejemplo 217

[001198] **((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo**

[001199] 

[001200] **((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo**

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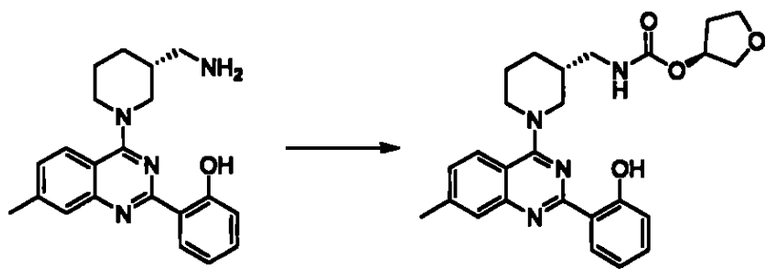


[001201]

[001202] Método A

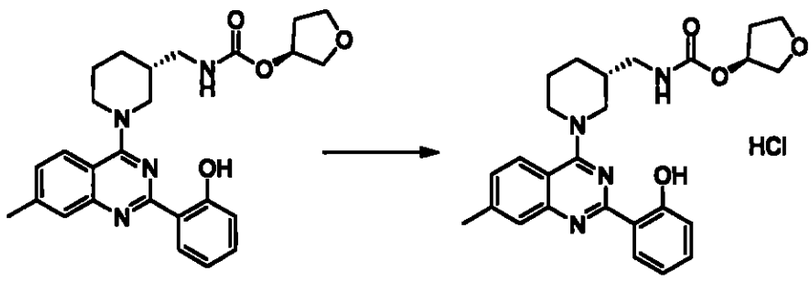
[001203] 2-(4-((*R*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C, después de añadir cloroformiato de (S)-tetrahidrofuran-3-ilo (31 mg, 0,2 mmol) disuelto en DMF (100 µL) gota a gota seguido de trietilamina (35 mg, 48 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 463,5 $(M+H)^+$ a 2,35 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001204] Método B

[001205] A una solución agitada de 2-(4-((*R*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (200 mg, 0,57 mmol) en DMF bajo una atmósfera de N_2 a 0 °C se añadió

trietilamina (115 mg, 1,14 mmol) seguido de la adición gota a gota de cloroformiato de (S)-tetrahidrofuran-3-ilo (86 mg, 0,57 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante 2 h. La mezcla se dividió en H_2O y CH_2Cl_2 y se separó y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 4:1 CH_2Cl_2:EtOAc dio ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo. LC/MS: *m/z* 463,5$(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001206] Clorhidrato de (((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo



[001207]

[001208] A una solución de ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en 12 ml de CH_2Cl_2 se añadió gota a gota

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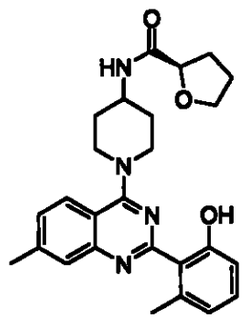
una solución de HCl 2,0 M en éter (0,13 ml, 0,25 mmol). A la solución se añadieron luego 20 ml de éter lo que condujo a la precipitación de clorhidrato de (((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo que se filtró y se secó (116 mg, 92%). LC/MS: *m/z* 463,5$(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

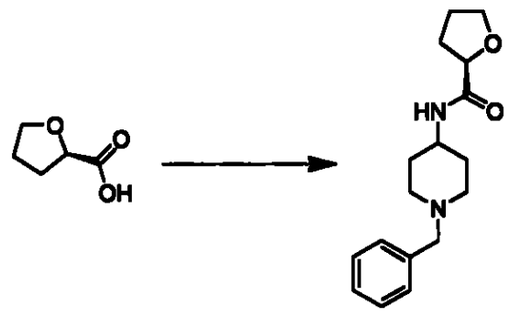
[001209] Ejemplo 218

[001210] **(2*R*)-tetrahidro-*N*-(1-(2-(2-hidroxi-6-metilfenil)-7-metilquinazolin-4-il)piperidin-4-il)furan-2-carboxamida**



[001211]

[001212] **(1-bencil-piperidin-4-il)-amida del ácido (*R*)-tetrahidrofuran-2-carboxílico**

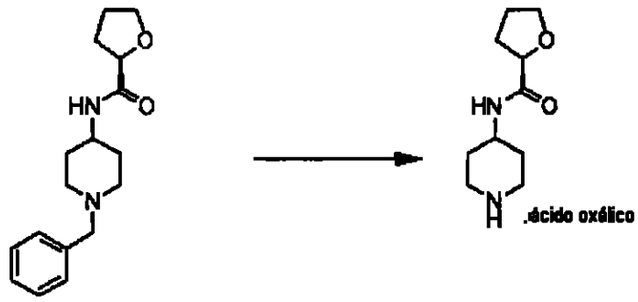


[001213]

[001214] Una solución de ácido (*R*)-tetrahidro-2-furoico (58,5 g, 504 mmol) y cloruro de oxalilo (86 ml, 1,0 mol) en 100 ml de CH_2Cl_2 se calentaron a reflujo durante 2 horas en un recipiente equipado con un tubo de control de $CaCl_2$. Tras enfriar la solución hasta temperatura ambiente, los solventes y el exceso de cloruro de oxalilo se eliminaron por evaporación a presión reducida. El cloruro de ácido resultante se disolvió en 200 ml de CH_2Cl_2 y se añadió gota a gota a una solución de diclorhidrato de 1-bencil-4-aminopiperidina (142 g, 539 mmol) y trietilamina (240 ml, 1,7 mol) en 300 ml de CH_2Cl_2 enfriado en un baño de hielo. La mezcla resultante se agitó durante 2 horas a temperatura ambiente y posteriormente se lavó dos veces con 300 ml porciones de $NaHCO_3$ acuoso al 5% y 300 ml de solución acuosa saturada de NaCl, se secó sobre Na_2SO_4, se filtró y se evaporó hasta sequedad a presión reducida. El residuo sólido se trituró con 500 ml de heptanos, se recogió por filtración y se lavó dos veces con porciones de

200 ml de heptanos. El sólido se secó al aire a 45 °C para obtener (1-bencil-piperidin-4-il)-amida del ácido (*R*)-tetrahidrofuran-2-carboxílico (128 g, 88%) en forma de un sólido blanquecino. ^{1}H-RMN (300 MHz, $CDCl_3$): δ 7,35-7,20 (m, 5H), 6,58 (bs, 1H), 4,29 (dd, *J*= 5,9, 8,4 Hz, 1H), 3,92-3,77 (m, 2H), 3,48 (s, 2H), 2,82-2,74 (m, 2H), 2,32-2,21 (m, 1H), 2,19-1,95 (m, 3H), 1,94-1,78 (m, 4H), 1,58-1,40 (m, 2H) ppm.

[001215] Piperidin-4-ilamida del ácido (*R*)-tetrahidro-furan-2-carboxílico en forma de una sal de oxalato

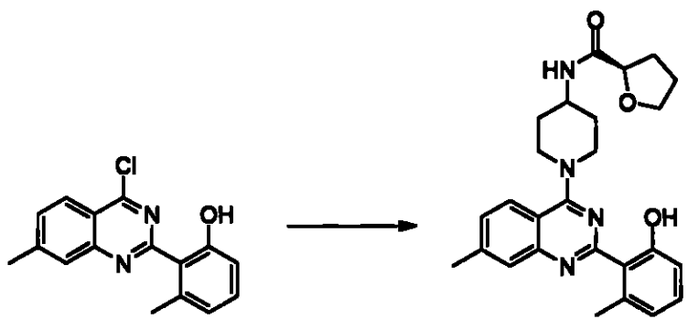


[001216]

[001217] (1-bencil-piperidin-4-il)-amida del ácido (R)-tetrahidro-furan-2-carboxílico (128 g, 444 mmol) se disolvió en 300 ml de etanol y 50 ml de ácido acético. Se agregó paladio sobre carbón activado (5 g). Se aplicó una presión de hidrógeno de 5 bares y se continuó la hidrogenación hasta que no se consumiera más hidrógeno (aproximadamente 5 días). La suspensión se filtró a través de Celite y el filtrado se evaporó hasta sequedad a presión reducida. El residuo y ácido oxálico (50 g, 555 mmol) se suspendieron en 500 ml de 2-propanol y se calentó hasta disolver los sólidos. Después de

enfriar, la sal de oxalato de piperidin-4-ilamida del ácido *R*-tetrahidro-furan-2-carboxílico cristalizó y se recogió por filtración para obtener piperidin-4-ilamida del ácido (R)-tetrahidro-furan-2-carboxílico en forma de una sal de oxalato (99,0 g, 77%) en forma de un sólido blanquecino. ^{1}H-RMN (300 MHz, DMSO-d_6): δ 7,84 (d, *J* =7,8 Hz, 1H), 5,90 (bs, 2H), 4,18-4,14 (m, 1H), 3,89-3,67 (m, 3H), 3,25-3,20 (m, 2H), 2,94-2,71 (m, 2H), 2,13-2,00 (m, 1H), 1,56-1,58 (m, 6H) ppm.

[001218] (2R)-tetrahidro-*N*-(1-(2-(2-hidroxi-6-metilfenil)-7-metilquinazolin-4-il)piperidin-4-il)furan-2-carboxamida



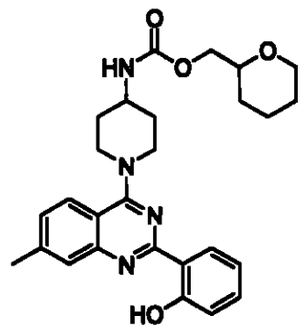
[001219]

[001220] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)-3-metilfenol (60 mg, 2,1 mmol) en DMF (1 ml) se añadió trietilamina (1,17 ml, 8,4 mmol) y (*R*)-tetrahidro-*N*-(piperidin-4-il)furan-2-carboxamida en forma de una sal de oxalato (80 mg, 2,73 mmol). Esta mezcla se agitó durante 2 h a temperatura ambiente antes de purificar por medio de HPLC en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05%

de TFA) para obtener (2*R*)-tetrahidro-*N*-(1-(2-(2-hidroxi-6-metilfenil)-7-metilquinazolin-4-il)piperidin-4-il)furan-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 447,5(M+H)$^+$ a 2,19 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

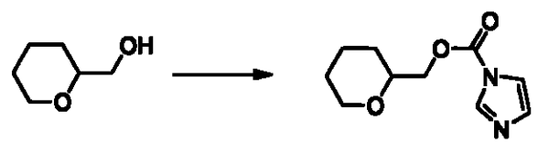
[001221] Ejemplo 219

[001222] **Éster tetrahidro-piran-2-ilmetílico del ácido**



[001223] **Ácido {1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-carbámico**

[001224] **1*H*-imidazol-1-carboxilato de (tetrahidro-2*H*-piran-2-il)metilo**



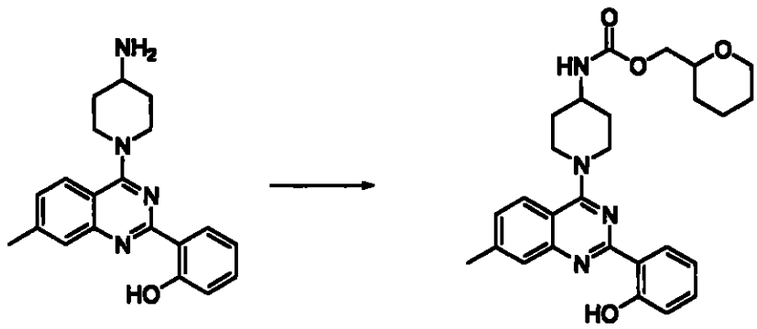
[001225]

[001226] Una mezcla de (tetrahidro-2*H*-piran-2-il)metanol (369 mg, 3,18 mmol) y di(1*H*-imidazol-1-il)metanona (1,0 g, 6,36 mmol) en CH_3Cl 0,3 M (10 ml) se agitó a 50 °C durante 3 h. Después de dejar enfriar la reacción hasta temperatura

ambiente, el solvente se evaporó a presión reducida para dar 1*H*-imidazol-1-carboxilato de (tetrahidro-2H-piran-2-il)metilo (412 mg) que se usó sin ulterior purificación. LC/MS: *m/z* 211,1(M+H)$^+$ a 0,94 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

|001227| Éster tetrahidro-piran-2-ilmetílico del ácido {1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-carbámico.

|001228|

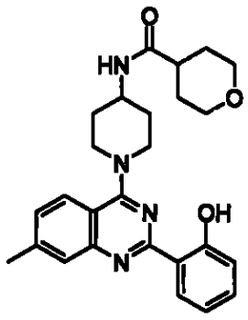


|001229| A 2-[4-(4-amino-piperidin-1-il)-7-metil-quinazolin-2-il]-fenol (100 mg, 0,3 mmol) en 1 ml de CH_2Cl_2 se añadieron secuencialmente trietilamina (62,5 µL, 0,45 mmol) y éster tetrahidro-piran-2-ilmetílico del ácido imidazol-1-carboxílico (94 mg, 0,45 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 12 h y a 45 °C durante 3 h. La mezcla de reacción se enfrió y se diluyó con agua y CH_2Cl_2. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar un aceite. El residuo se purificó por HPLC en fase inversa usando 10%-99% de CH_3CN

(0,035% de TFA)/H_2O (0,05% de TFA) como eluyente para dar el producto deseado éster tetrahidro-piran-2-ilmetílico del ácido {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-carbámico en forma de la sal de TFA. LC/MS: *m/z* 477,4 (M+H)+ a 2,84 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

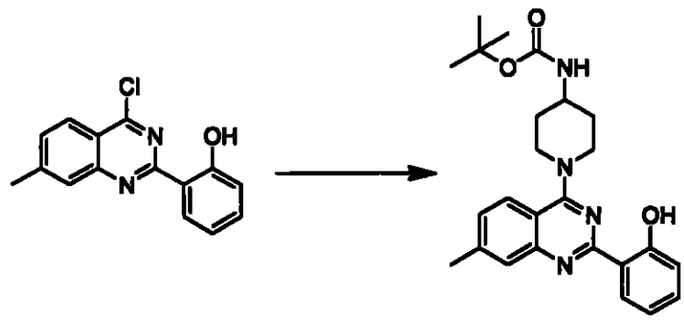
|001230| Ejemplo 220

|001231| **tetrahidro-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2*H*-piran-4-carboxamida**



|001232|

|001233| **1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo**

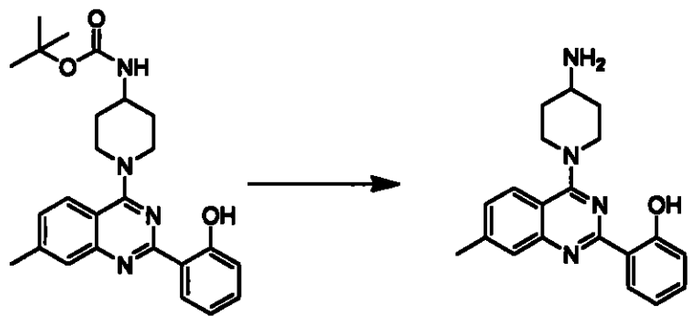


[001234]

[001235] A una suspensión enfriada (0-5 °C) de 2-(4-cloro-7-metilquinazolin-2-il)fenol (50,2 g, 186 mmol) en diclorometano (200 ml) se añadió lentamente una solución de piperidin-4-ilcarbamato de *ter*-butilo (39,0 g, 195 mmol) y trietilamina (56 ml, 390 mmol) en diclorometano (200 ml). La mezcla resultante se agitó durante la noche a temperatura ambiente. Se agregó agua (400 ml) y las capas se separaron. La capa acuosa se extrajo con diclorometano (2 x 200 ml) y las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se evaporaron hasta sequedad a presión reducida. El residuo se purificó por cromatografía en columna (SiO_2, elueyente: diclorometano/heptanos 4:6-1:0). Se obtuvieron dos fracciones: 38,7 g de 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo en forma de un sólido amarillo y una fracción menos pura (26,1 g) que se purificó por recristalización en metanol para obtener 1-(2-(2-

hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo. Ambas fracciones se combinaron (17,0 g, 69%).

[001236] 2-(4-(4-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol

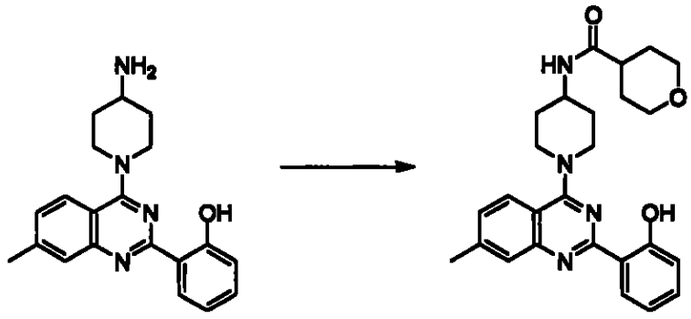


[001237]

[001238] 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo (55,7 g, 128 mmol) se disolvió en diclorometano (200 ml) y se añadió ácido trifluoroacético (215 ml) lentamente (atención: producción de gas inmediata). La solución resultante se agitó durante la noche a temperatura ambiente bajo una atmósfera de nitrógeno y se evaporó hasta sequedad. Al residuo se añadieron cantidades iguales de agua y diclorometano (300 ml). La emulsión obtenida se alcalinizó hasta pH 9 con NaOH acuoso al 33%. La emulsión se clarificó con la adición de metanol y las capas se separaron. La capa acuosa se extrajo con diclorometano (200 ml) y los extractos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se evaporaron hasta sequedad

para obtener 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol crudo. El material crudo se purificó por cromatografía en columna (SiO_2, 2% metanol en diclorometano) para obtener 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (44 g, 97%) en forma de un sólido amarillo. ^{1}H-RMN (300 MHz, $CDCl_3$): δ 8,52 (dd, *J*=2,1, 8,1 Hz, 1H), 7,77 (d, *J*=8,4 Hz, 1H), 7,62 (s, 1H), 7,37 (dt, *J*=1,5, 7,2 Hz, 1H), 7,22 (dd, *J*=1,5, 9,0 Hz, 1H), 7,04 (dd, *J*=1,2, 6,9 Hz, 1H), 6,92 (dt, *J*=1,2, 7,2 Hz, 1H), 4,49-4,39 (m, 2H), 3,34 (dt, *J*=2,4, 12,2 Hz, 2H), 3,12-3,02 (m, 1H), 2,54 (s, 3H), 2,09-2,00 (m, 2H), 1,68-1,55 (m, 2H), 1,40-1,25 (m, 2H) ppm.

[001239] tetrahidro-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2*H*-piran-4-carboxamida



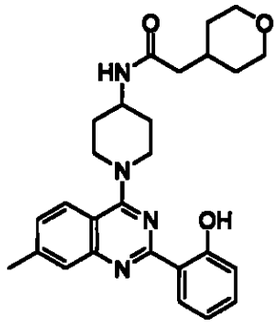
[001240]

[001241] A una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (30 mg, 0,09 mmol) en DMF (1 ml) se añadió ácido tetrahidro-2*H*-piran-4-carboxílico (17,5 mg, 0,13 mmol) seguido de la adición de trietilamina (25 µL, 0,18 mmol)

y HATU (44 mg, 0,117 mmol). La reacción se agitó durante 16 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener tetrahidro-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2*H*-piran-4-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 447,5$(M+H)^+$ a 2,19 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

|001242| Ejemplo 221

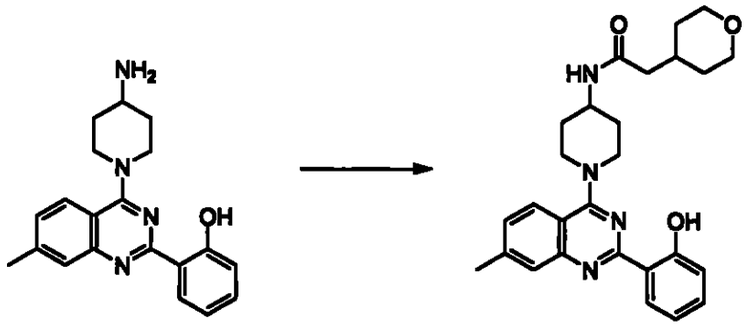
|001243| **2-(tetrahidro-2*H*-piran-4-il)-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)acetamida**



|001244|

|001245| **2-(tetrahidro-2*H*-piran-4-il)-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)acetamida**

463
970



[001246]

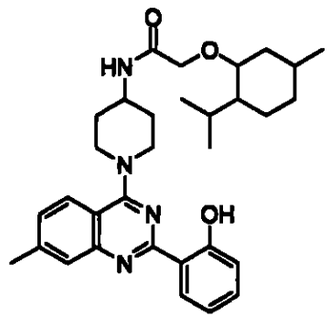
[001247] A una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (30 mg, 0,09 mmol) en DMF (1 ml) se añadió ácido 2-(tetrahidro-2*H*-piran-4-il)acético (13 mg, 0,09 mmol) seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (44 mg, 0,117 mmol). La reacción se agitó durante 16 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-(tetrahidro-2*H*-piran-4-il)-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)acetamida en forma de la sal de TFA. LC/MS: *m/z* 461,5$(M+H)^+$ a 2,22 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001248] Ejemplo 222

964

971

[001249] **2-(2-Isopropil-5-metilciclohexiloxi)-*N*-(1-(2-(2-**



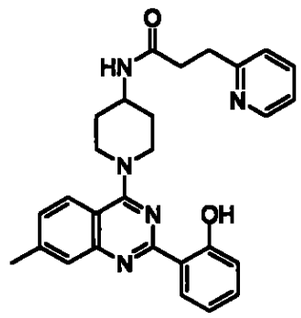
hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)acetamida

[001250] **2-(2-Isopropil-5-metilciclohexiloxi)-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)acetamida**

[001251] A una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (30 mg, 0,09 mmol) en DMF (1 ml) a 0 °C se añadió trietilamina (25 µL, 0,18 mmol) seguido de la adición de cloruro de 2-(2-isopropil-5-metilciclohexiloxi)acetilo (21 mg, 0,09 mmol). La reacción se agitó durante 16 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-(2-isopropil-5-metilciclohexiloxi)-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)acetamida en forma de la sal de TFA. LC/MS: *m/z* 531,3$(M+H)^+$ a 3,08 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

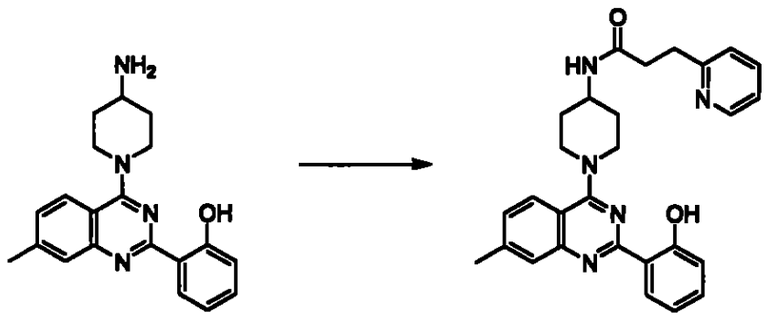
[001252] Ejemplo 223

[001253] ***N*-(1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-3-(piridin-2-il)propanamida**



[001254]

[001255] ***N*-(1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-3-(piridin-2-il)propanamida**



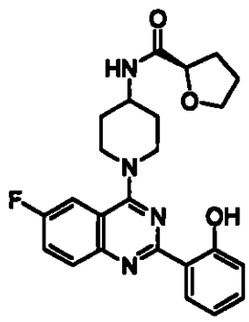
[001256]

[001257] A una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (30 mg, 0,09 mmol) en DMF (1 ml) se añadió ácido 3-(piridin-2-il)propanoico (20 mg, 0,13 mmol) seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (44 mg, 0,117 mmol). La reacción se agitó durante 16 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-3-

(piridin-2-il)propanamida en forma de la sal de TFA. LC/MS: *m/z* 468,3 $(M+H)^+$ a 1,86 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

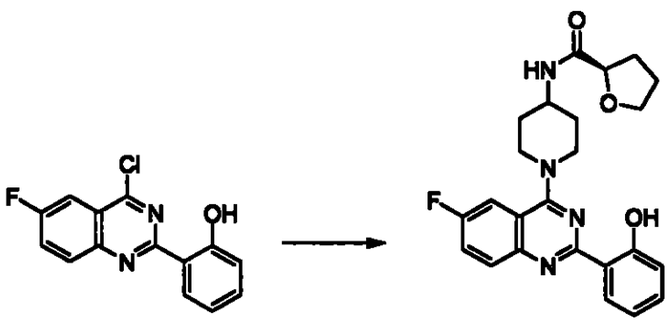
[001258] Ejemplo 224

[001259] **(2*R*)-*N*-(1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida**



[001260]

[001261] **(2*R*)-*N*-(1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida**



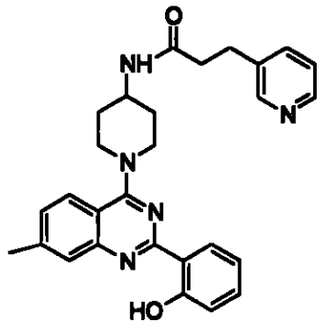
[001262]

[001263] A una solución de 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (25 mg, 0,09 mmol) en CH_2Cl_2 (1 ml) se añadió oxalato

de (*R*)-tetrahidro-*N*-(piperidin-4-il)furan-2-carboxamida (33 mg, 0,117 mmol), seguido de la adición de trietilamina (50 µL, 0,36 mmol). La reacción se agitó durante 2 h antes de filtrar y purificar por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (2*R*)-*N*-(1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 437,1$(M+H)^+$ a 2,54 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

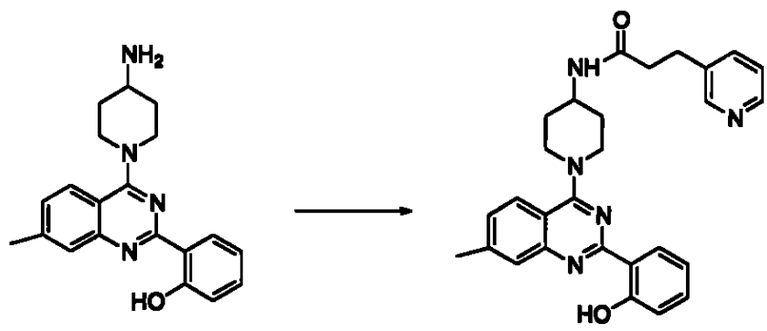
[001264] Ejemplo 225

[001265] **N-{1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-3-piridin-3-il-propionamida**



[001266]

[001267] **N-{1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-3-piridin-3-il-propionamida**

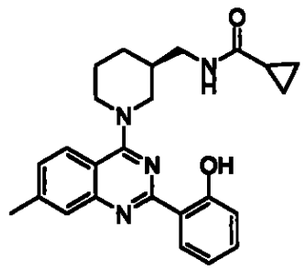


[001268]

[001269] A 2-[4-(4-amino-piperidin-1-il)-7-metil-quinazolin-2-il]-fenol (238 mg, 0,71 mmol) en 2,4 ml de CH_2Cl_2 se añadieron secuencialmente ácido 3-piridin-3-il-propiónico (118,3 mg, 0,78 mmol), trietilamina (129 µL, 0,92 mmol) y BOP (346 mg, 0,78 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 40 min y se diluyeron con agua y CH_2Cl_2. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar un aceite. El residuo se purificó por LC en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) como eluyente para dar el producto deseado en forma de la sal de TFA. LC/MS: *m/z* 468,6 (M+H)+ a 2,19 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

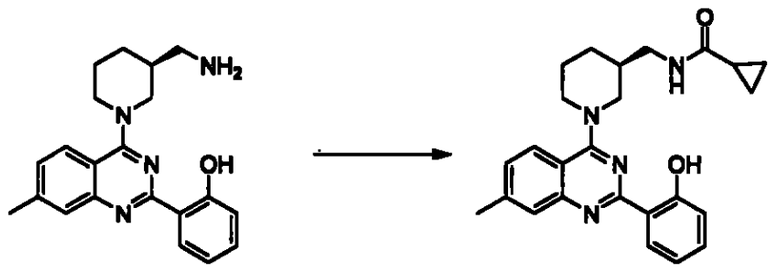
[001270] Ejemplo 226

[001271] ***N*-(((*S*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metil)ciclopropancarboxamida**



[001272]

[001273] ***N*-(((*S*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metil)ciclopropancarboxamida**



[001274]

[001275] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (35 mg, 0,10 mmol) se disolvió en DMF (1 ml). Se añadió ácido ciclopropancarboxílico (9,7 mg, 0,11 mmol), seguido de la adición de trietilamina (28 µL, 0,2 mmol) y la mezcla se enfrió en un baño de agua helada. Se agregó HATU (42 mg, 0,11 mmol) en una porción y la reacción se dejó calentar hasta temperatura ambiente mientras se agitaba durante 16 h. La mezcla de reacción se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar N-(((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-

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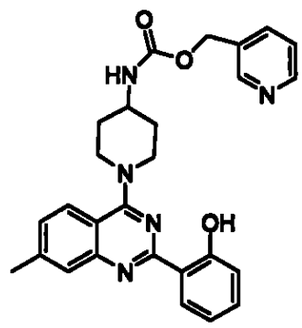
il)metil)ciclopropancarboxamida en forma de la sal de TFA. LC/MS: *m/z* 417,5 $(M+H)^+$ a 2,30 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

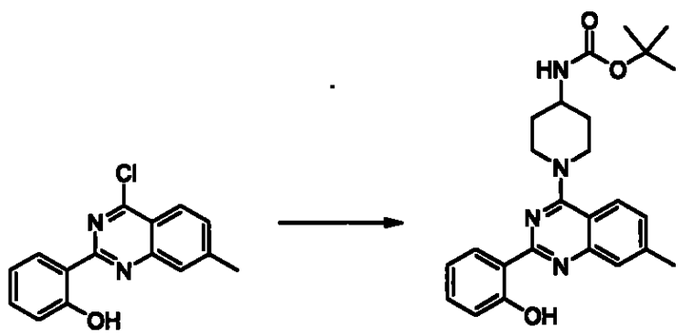
[001276] Ejemplo 227

1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de (piridin-3-il)metilo

[001277]



[001278] **1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo**

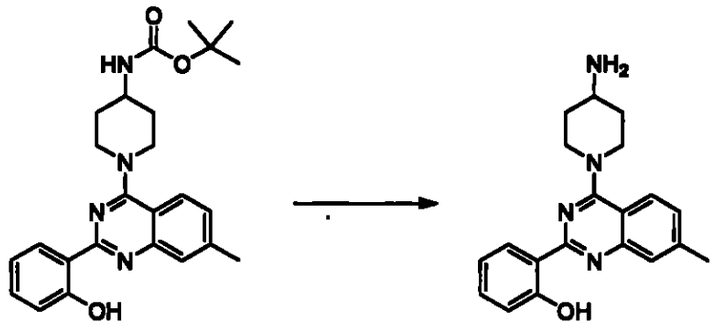


[001279]

[001280] A una suspensión de 2-(4-cloro-7-metilquinazolin-2-il)fenol (2,0 g, 7,38 mmol) en CH_2Cl_2 (25 ml) a 0 °C bajo una

atmósfera de N_2 se añadió gota a gota una solución de *ter*-butilo piperidin-4-ilcarbamato de (1,92 g, 9,6 mmol) en CH_2Cl_2 (10 ml) y trietilamina (2,0 ml, 14,76 mmol). La reacción se agitó durante 6 horas, luego se neutralizó con agua (25 ml) y las capas se separaron. La fase acuosa se extrajo dos veces con CH_2Cl_2 (10 ml) y las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para dar 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo en forma de un sólido amarillo (3,24 g, 100%). LC/MS: *m/z* 435,3 $(M+H)^+$ a 2,79 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001281] **2-(4-(4-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol**

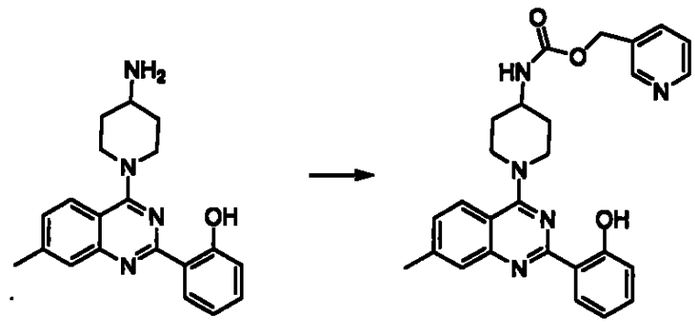


[001282]

[001283] Se disolvió 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo (3,21 g, 7,39 mmol) en CH_2Cl_2 (55 ml). Se añadió TFA (50 ml) y la reacción se agitó durante 1 hora. Después de evaporar los solventes al vacío, el

material crudo se diluyó con CH_2Cl_2 y se neutralizó con una solución de NaOH 1 N. Las capas se separaron y la capa acuosa se extrajo tres veces con CH_2Cl_2 (30 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para dar 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol en forma de un sólido amarillo (2,06 g, 83%). LC/MS: *m/z* 335,3 $(M+H)^+$ a 1,42 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001284] 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de (piridin-3-il)metilo



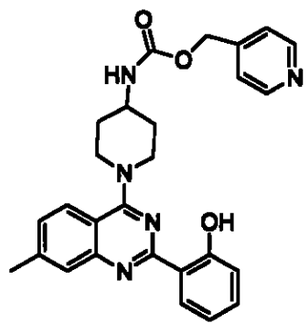
[001285]

[001286] A una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol) en DMSO (1 ml) se añadió 1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo (53 mg, 0,263 mmol) y trietilamina (30,4 mg, 42 µL, 0,3 mmol). La reacción se agitó durante la noche a temperatura ambiente y luego se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato

de (piridin-3-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 470,5 $(M+H)^+$ a 1,98 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001287] Ejemplo 228

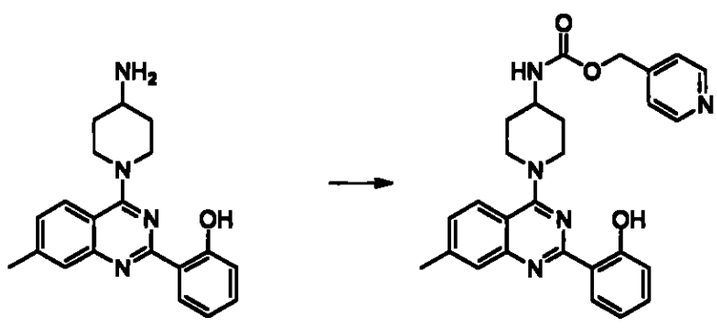
[001288] **1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de (piridin-4-il)metilo**



[001289]

[001290] **1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de (piridin-4-il)metilo**

[001291]



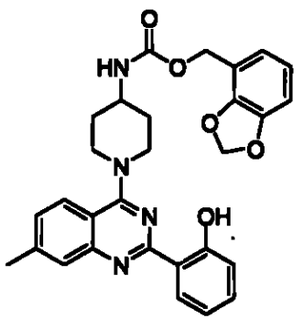
[001292] A una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol) en DMSO (1 ml)

se añadió 1*H*-imidazol-1-carboxilato de (piridin-4-il)metilo (53 mg, 0,263 mmol) y trietilamina (30,4 mg, 42 µL, 0,3 mmol). La reacción se agitó durante la noche a temperatura ambiente y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar (piridin-4-il)metilo 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de en forma de la sal de TFA. LC/MS: *m/z* 470,5 $(M+H)^+$ a 1,98 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

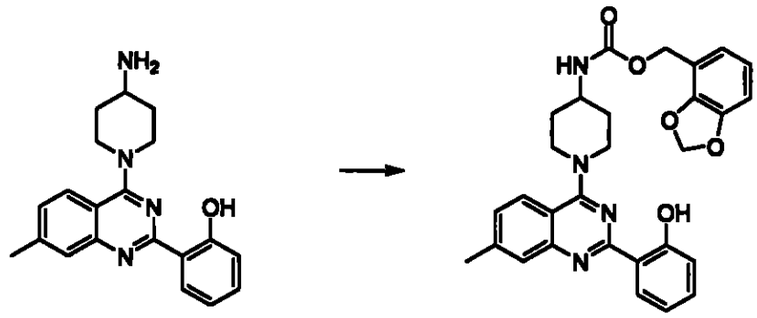
[001293] Ejemplo 229

[001294] **1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de (benzo[d][1,3]dioxol-7-il)metilo**

[001295]



[001296] **1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de (benzo[d][1,3]dioxol-7-il)metilo**

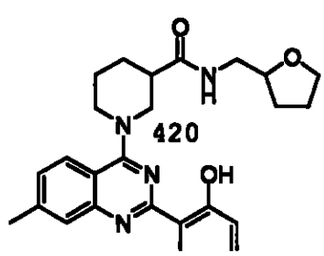


[001297]

[001298] A una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol) en DMSO (1 ml), se añadió 1H-imidazol-1-carboxilato de (benzo[d][1,3]dioxol-4-il)metilo (65 mg, 0,263 mmol), seguido de la adición de trietilamina (30,4 mg, 42 µL, 0,3 mmol). La reacción se agitó durante la noche a temperatura ambiente y luego se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de (benzo[d][1,3]dioxol-7-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 513,3 $(M+H)^+$ a 2,82 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

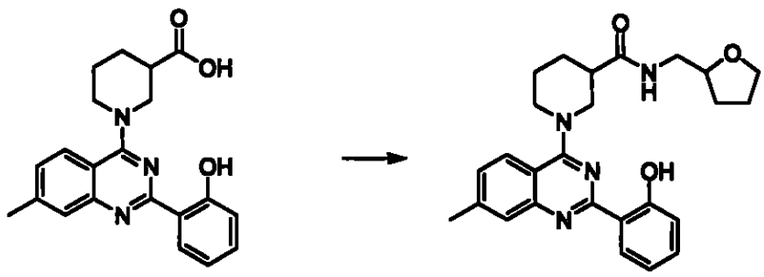
[001299] Ejemplo 230

[001300] **N-((tetrahidrofuran-2-il)metil)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-carboxamida**



[001301]

[001302] ***N*-((tetrahidrofuran-2-il)metil)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-carboxamida**



[001303]

[001304] Una solución de ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-carboxílico (45 mg, 0,12 mmol) en 500 µL de DMF se enfrió hasta 0 °C y se añadieron (tetrahidrofuran-2-il)metanamina (13,2 mg, 0,13 mmol) y trietilamina (25 mg, 35 µL, 0,25 mmol). Al cabo de diez minutos, se añadió HATU (57 mg, 0,15 mmol) a la mezcla de reacción en una porción. La reacción se dejó calentar hasta temperatura ambiente, se agitó durante la noche y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dando como resultado *N*-((tetrahidrofuran-2-il)metil)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 447,3 $(M+H)^+$ a 2,21 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001305] Ejemplo 231

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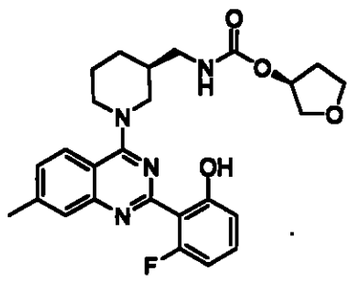
[001306] ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (*S*)-



tetrahidrofuran-3-ilo

[001307]

[001308] Piperidin-3-ilmetilcarbamato de *ter*-butilo

[001309]

[001310] Una solución fría de HCl en MeOH (preparada por adición de cloruro de acetilo (13,5 ml, 14,9 g, 0,19 mol) a 1 L de MeOH) se añadió a una solución fría de piridin-3-ilmetilcarbamato de *ter*-butilo (41,0 gramos, 0,20 mol) en MeOH (100 ml). La solución se transfirió a un aparato de hidrogenación Parr a 12 °C. Se añadió PtO_2 (3 g) y se aplicaron 12 bar de presión de H_2. Al cabo de 16 horas, ^1H RMN de una muestra concentrada indicó que la reacción estaba completa. El catalizador se filtró y se añadió NaOH concentrado acuoso (20 ml) para neutralizar el HCl. La solución se concentró para eliminar la masa de MeOH y se extrajo con éter ter-

butilmetílico (4x200 ml). Las capas orgánicas combinadas se lavaron con solución acuosa saturada de NaCl, se secaron sobre Na_2SO_4 y se concentraron para dar el producto (40,16 g, 0,187 mol, 95%) en forma de un aceite amarillo que se cristalizó al reposar. ^1H RMN (300 MHz, $CDCl_3$): δ 4,62 (bs. s, 1H), 3,06-2,94 (m, 4H), 2,52 (dt, J= 12 Hz, 3Hz, 1H), 2,28 (dd, J= 12 Hz, 10Hz, 1H), 1,82-1,72 (m, 1H), 1,70-1,51 (m, 3H), 1,49-1,34 (m, 1H), 1,42 (s, 9H), 1,06 (dq, J= 12 Hz, 4Hz, 1H).

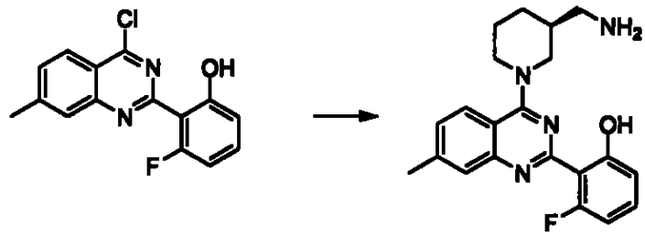
[001311] Piperidin-3-ilmetilcarbamato de (*R*)-ter-butilo

[001312]

[001313] A una solución de *piperidin-3-ilmetilcarbamato de ter-butilo* (162 g, 0,758 mol) en EtOH se añadió ácido (+)-dianisoiltartárico (316 g, 0,756 mol). La suspensión se calentó hasta volverse clara y se dejó enfriar hasta temperatura ambiente durante la noche. La sal precipitada se recristalizó tres veces en EtOH. La sal se lavó con EtOH (2x200 ml) y se secó al aire. Se eliminó el solvente residual al vacío. La sal se extrajo en éter ter-butilmetílico y NaOH acuoso al 10%. La capa orgánica se separó y la capa acuosa se extrajo con éter ter-butilmetílico (3x200 ml). Más producto se extrajo después de la adición de NaOH acuoso al 30% a la capa

acuosa. Las capas orgánicas combinadas se lavaron con agua y solución acuosa saturada de NaCl, se secaron sobre Na_2SO_4 y se concentró para dar (R)-piperidin-3-ilmetilcarbamato de ter-butilo en forma de un sólido cristalino blanco (41,3 g, 0,192 mol, 25%). Para las determinaciones ee, se extrajeron muestras de la sal en CH_2Cl_2 y NaOH acuoso 1 N. La capa orgánica se lavó con agua, se secó sobre Na_2SO_4 y se filtró. Se agregó una gota de isocianato de 1-naftilo y al cabo de 15 minutos, se añadió una gota de morfolina para neutralizar el exceso de isocianato. Las sustancias volátiles se evaporaron al cabo de otros 15 minutos. La muestra se disolvió en EtOH para HPLC quiral (Chiralcel OD-H; heptano/EtOH/Et_2NH 90/10/0,2; 0,5 ml/min; Rt (*R*): 46 min, Rt (*S*): 57 min, Rt (*N*-(naftalen-1-il)morfolin-4-carboxamida): 64 min.

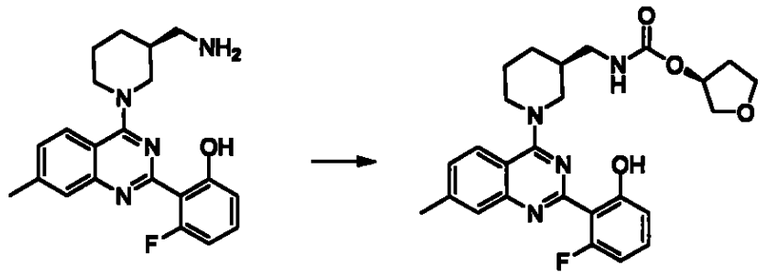
[001314] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol



[001315] 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (1,0 g, 3,46 mmol) se disolvió en 15 ml de CH_2Cl_2 anhidro bajo una atmósfera de N_2 y se enfrió usando un baño de hielo y se añadió éster ter-butílico del ácido piperidin-3-ilmetil-

carbámico/ácido oxálico (1,16 g, 3,81 mmol) en porciones, seguido de trietilamina (1,05 g, 1,45 ml, 10,4 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 1,5 horas. La mezcla se dividió en CH_2Cl_2 y H_2O y se separó y la capa acuosa se extrajo una vez más con CH_2Cl_2. Los extractos orgánicos se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron en un sólido amarillo. Este sólido se suspendió en 40 ml de CH_2Cl_2 y se añadieron 20 ml de TFA. La reacción se completó después de 1 hora. El solvente y el exceso de TFA se eliminaron al vacío, el residuo se redisolvió en CH_2Cl_2 y el pH se ajustó a 7 usando una solución acuosa 1 M de NaOH. La reacción se dividió en CH_2Cl_2 y H_2O y se separó y la capa acuosa se extrajo una vez más con CH_2Cl_2. Los extractos orgánicos se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron para obtener de 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (900 mg, 71% de rendimiento general) en forma de un sólido amarillo. LC/MS: *m/z* 367,3 $(M+H)^+$ a 1,35 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001316] ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (*S*)-tetrahidrofuran-3-ilo



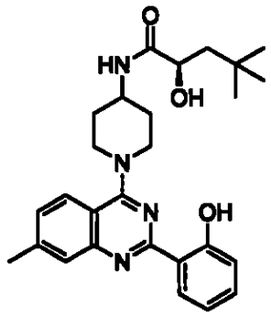
[001317]

[001318] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (40 mg, 0,11 mmol) se disolvió en DMF anhidra (800 µL) y se enfrió hasta 0 °C, después de lo cual se añadió cloroformiato de (S)-tetrahidrofuran-3-ilo (16,3 mg, 0,12 mmol) disuelto en DMF (100 µL) gota a gota seguido de trietilamina (22 mg, 30,3 µL, 0,218 mmol). La reacción se dejó calentar hasta temperatura ambiente y después de 2 h, la reacción se completó. La mezcla se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 481,1 $(M+H)^+$ a 2,17 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

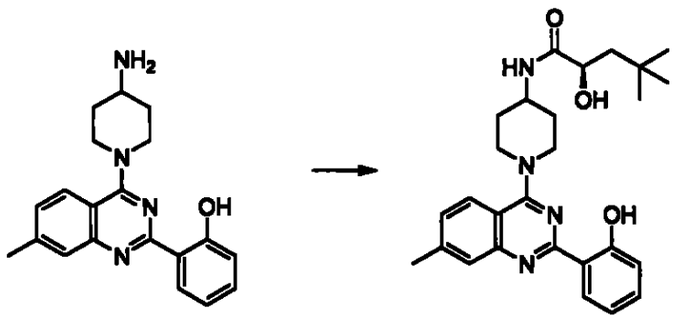
[001319] Ejemplo 232

[001320] **(2*R*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-4,4-dimetilpentanamida**

[001321]



[001322] **(2*R*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-4,4-dimetilpentanamida**



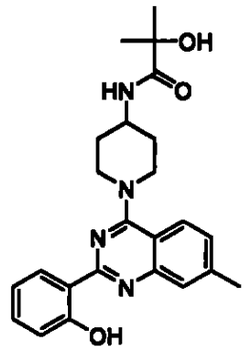
[001323]

[001324] 2-(4-(4-Aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol) se disolvió en DMF (1 ml) y se enfrió hasta 0 °C. Se añadió ácido (2*R*)-hidroxi-4,4-dimetil-pentanoico (26,3 mg, 0,18 mmol) seguido de la adición de trietilamina (42 µL, 0,3 mmol). Al cabo de diez minutos, se añadió HATU (68 mg, 0,18 mmol) en una porción. La reacción se agitó a 0 °C durante 10 minutos y luego se dejó calentar hasta temperatura ambiente. La reacción se completó después de 40

minutos, luego se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar (2*R*)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-4,4-dimetilpentanamida en forma de la sal de TFA. LC/MS: *m/z* 463,3 $(M+H)^+$ a 2,58 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001325] Ejemplo 233

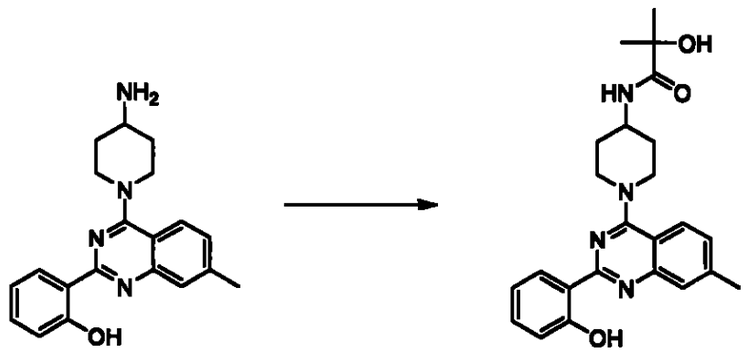
[001326] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-metilpropanamida**



[001327]

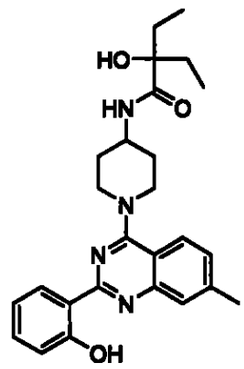
[001328] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-metilpropanamida**

[001329]



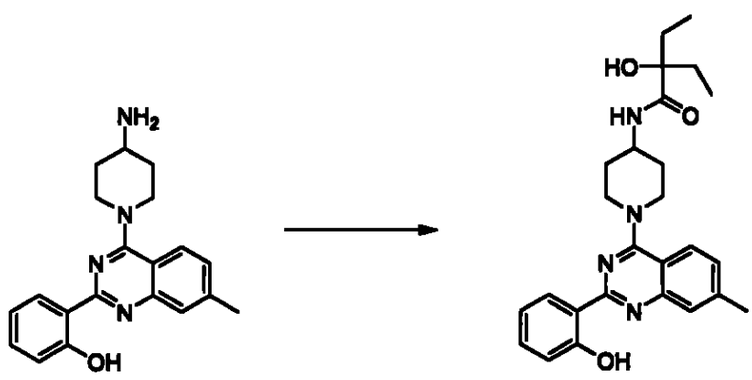
[001330] A ácido 2-hidroxi-2-metilpropanoico (28 mg, 0,27 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,07 g, 0,21 mmol) en DMF (0,5 ml), seguido de la adición de trietilamina (0,058 ml, 0,42 mmol) y una solución de HATU (0,103 g, 0,273 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-metilpropanamida en forma de la sal de TFA. LC/MS: *m/z* 421,2$(M+H)^+$ a 2,17 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001331] **2-Etil-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida**



[001332]

[001333] **2-Etil-2-hidroxi-N-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida**



[001334]

[001335] A ácido 2-etil-2-hidroxibutanoico (36 mg, 0,27 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,07 g, 0,21 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,058 ml, 0,42 mmol) y una solución HATU (0,103 g, 0,273 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó

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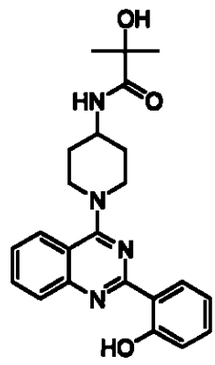
usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-etil-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida en forma de la sal de TFA. LC/MS: *m/z* 449,2$(M+H)^+$ a 2,42 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

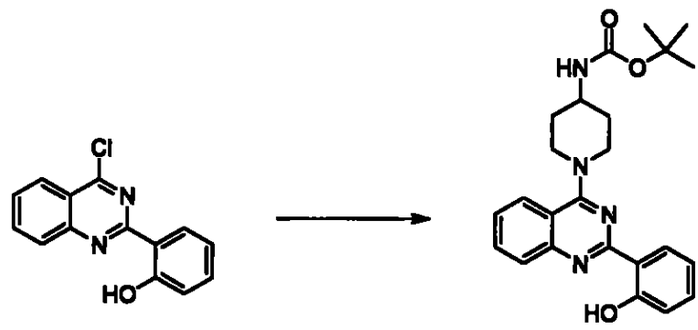
[001336] Ejemplo 235

[001337] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-2-metilpropanamida**



[001338]

[001339] **1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo**

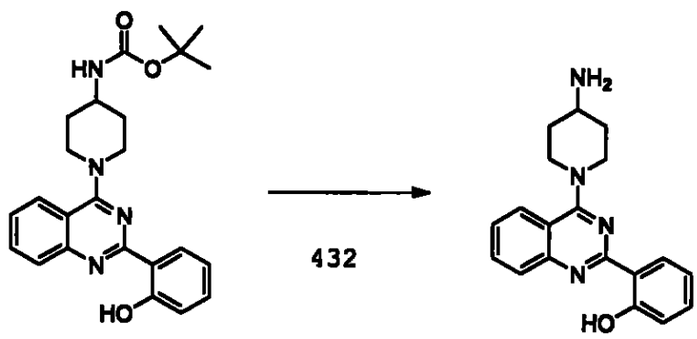


[001340]

[001341] A una suspensión de 2-(4-cloroquinazolin-2-il)fenol (2,0 g, 7,79 mmol) en CH_2Cl_2 (25 ml) a 0 °C bajo una atmósfera de N_2, se añadió gota a gota piperidin-4-ilcarbamato de *ter*-butilo (2,08 g, 10,13 mmol) y trietilamina (2,20 ml, 15,8 mmol) en CH_2Cl_2 (10 ml). La reacción se agitó durante la noche, se neutralizó con agua y se extrajo con CH_2Cl_2 y las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener 1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo (3,27 g, 100% - residuo de solvente). LC/MS: *m/z* 421,3$(M+H)^+$ a 2,70 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001342] **2-(4-(4-Aminopiperidin-1-il)quinazolin-2-il)fenol**

[001343]



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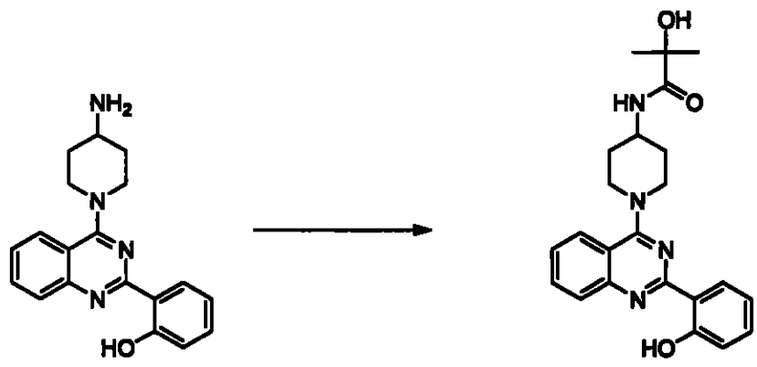
[001344] A una solución de 1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo (3,27 g, 8,09 mmol) en CH_2Cl_2 (75 ml) se añadió TFA (50 ml). La reacción se completó después de 45 minutos. Después de evaporar los solventes al vacío, el material crudo se diluyó con CH_2Cl_2 y se neutralizó por adición de una solución acuosa de NaOH 1 N. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2×15 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener 2-(4-(4-aminopiperidin-1-il)quinazolin-2-il)fenol como un sólido (2,09 g, 84%). LC/MS: *m/z* 321,3$(M+H)^+$ a 1,28 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001345] **2-Hidroxi-N-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-2-metilpropanamida**



[001346]

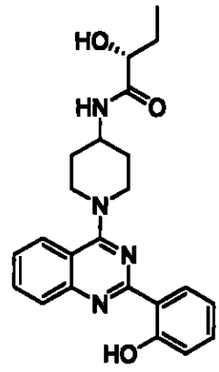
[001347] A ácido 2-hidroxi-2-metilpropanoico (27 mg, 0,28 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-

il)quinazolin-2-il)fenol (0,07 g, 0,22 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,061 ml, 0,44 mmol) y una solución de HATU (0,107 g, 0,284 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-2-metilpropanamida en forma de la sal de TFA. LC/MS: *m/z* 407,5$(M+H)^+$ a 2,04 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001348] Ejemplo 236

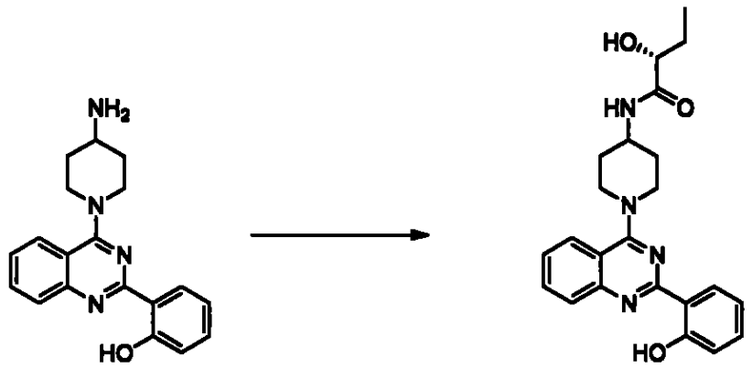
[001349] **(2R)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida**

[001350]



[001351] **(2*R*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida**

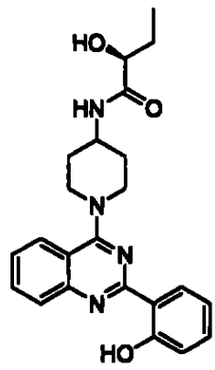
[001352]



[001353] A ácido (R)-2-hidroxibutanoico (30 mg, 0,28 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)quinazolin-2-il)fenol (0,07 g, 0,22 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,061 ml, 0,44 mmol) y una solución de HATU (0,107 g, 0,284 mmol) disuelto en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (2*R*)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida en forma de la sal de TFA. LC/MS: *m/z* 407,3$(M+H)^+$ a 2,08 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001354] Ejemplo 237

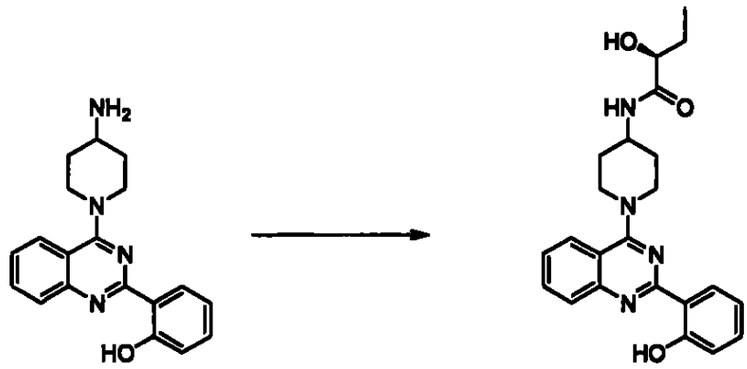
[001355] **(2*S*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida**



[001356]

[001357] **(2*S*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida**

[001358]

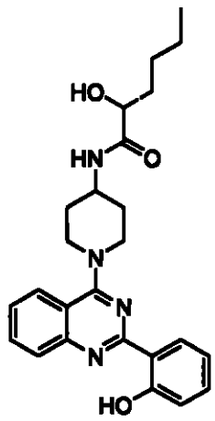


[001359] A ácido (*S*)-2-hidroxibutanoico (30 mg, 0,28 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)quinazolin-2-il)fenol (0,07 g, 0,22 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,061 ml, 0,44 mmol) y una solución de HATU (0,107 g, 0,284 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de

TFA)) para obtener (2*S*)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida en forma de la sal de TFA. LC/MS: *m/z* 407,3(M+H)$^+$ a 2,09 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

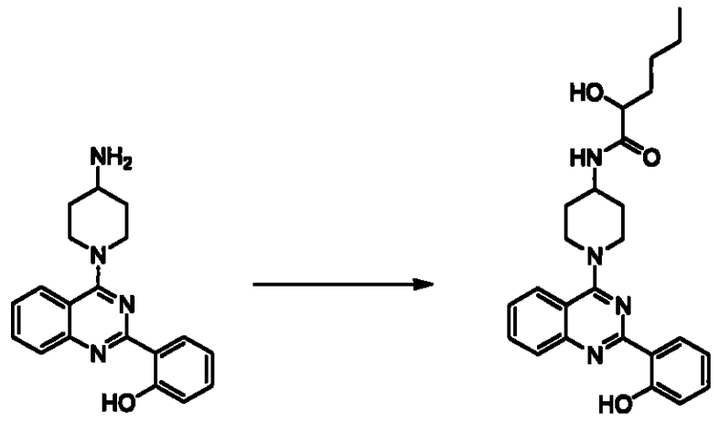
[001360] Ejemplo 238

[001361] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)hexanamida**



[001362]

[001363] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)hexanamida**



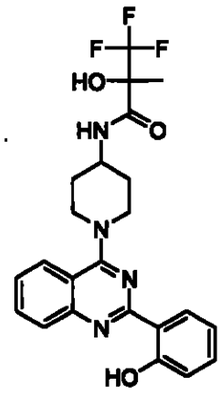
[001364]

[001365] A ácido 2-hidroxihexanoico (38 mg, 0,28 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)quinazolin-2-il)fenol (0,07 g, 0,22 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,061 ml, 0,44 mmol) y una solución de HATU (0,107 g, 0,284 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)hexanamida en forma de la sal de TFA. LC/MS: *m/z* 435,3$(M+H)^+$ a 2,4 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001366] Ejemplo 239

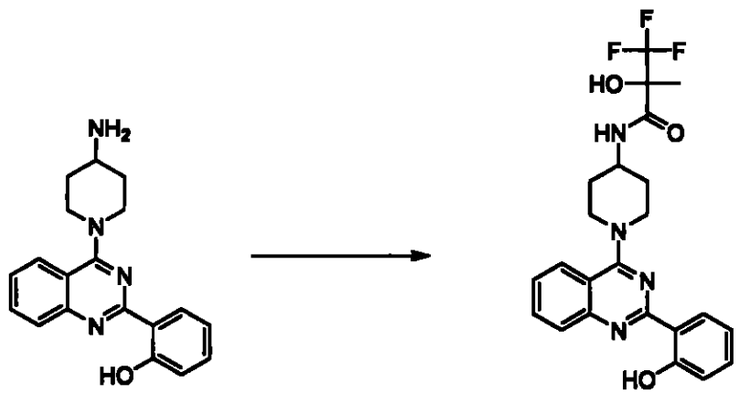
1001

[001367] **2-(Trifluorometil)-2-hidroxi-*N*-(1-(2-(2-**



hidroxifenil)quinazolin-4-il)piperidin-4-il)propanamida

[001368] **2-(Trifluorometil)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)propanamida**



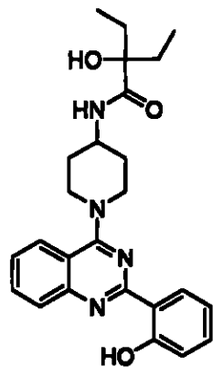
[001369]

[001370] A ácido 2-(trifluorometil)-2-hidroxipropanoico (45 mg, 0,28 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)quinazolin-2-il)fenol (0,07 g, 0,22 mmol) disuelto en DMF (0,5 ml) seguido de la adición de trietilamina (0,061 ml, 0,44 mmol) y una solución de HATU (0,107 g, 0,284

mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-(trifluorometil)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)propanamida en forma de la sal de TFA. LC/MS: *m/z* 461,1$(M+H)^+$ a 2,4 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001371] Ejemplo 240

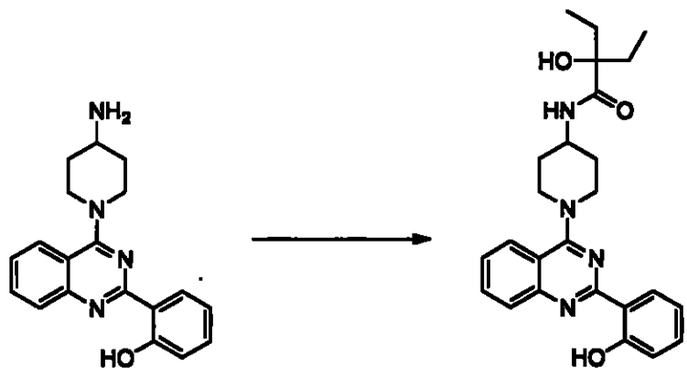
[001372] **2-Etil-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida**



[001373]

[001374] **2-Etil-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida**

1003

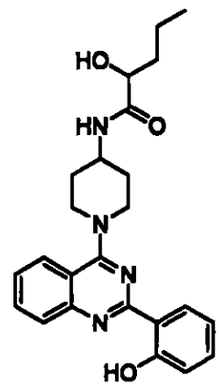


[001375]

[001376] A ácido 2-etil-2-hidroxibutanoico (38 mg, 0,28 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)quinazolin-2-il)fenol (0,07 g, 0,22 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,061 ml, 0,44 mmol) y una solución de HATU (0,107 g, 0,284 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-etil-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)butanamida en forma de la sal de TFA. LC/MS: *m/z* 435,5$(M+H)^+$ a 2,29 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001377] Ejemplo 241

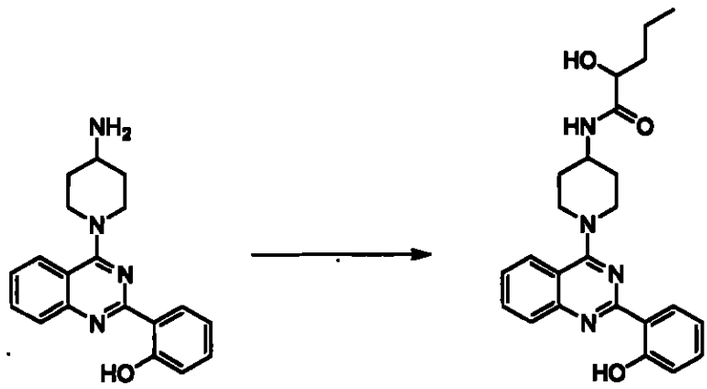
[001378] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)pentanamida**



[001379]

[001380] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)pentanamida**

[001381]

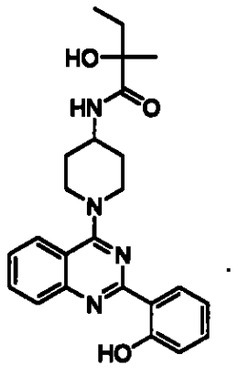


[001382] A ácido 2-hidroxipentanoico (34 mg, 0,28 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)quinazolin-2-il)fenol (0,07 g, 0,22 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,061 ml, 0,44 mmol) y una solución de HATU (0,107 g, 0,284 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de

TFA)) para obtener 2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)pentanamida en forma de la sal de TFA. LC/MS: *m/z* 421,1 $(M+H)^+$ a 2,24 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

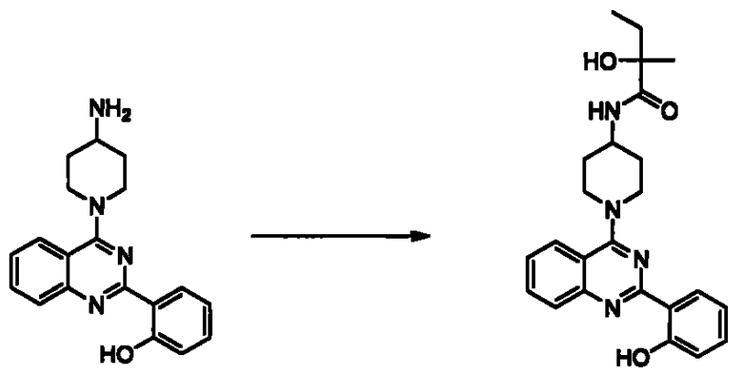
[001383] Ejemplo 242

[001384] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-2-metilbutanamida**



[001385]

[001386] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-2-metilbutanamida**



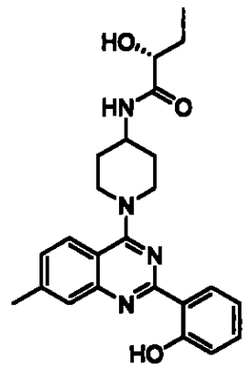
[001387]

[001388] A ácido 2-hidroxi-2-metilbutanoico (34 mg, 0,28 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)quinazolin-2-il)fenol (0,07 g, 0,22 mmol) en DMF (0,5 ml), seguido de la adición de trietilamina (0,061 ml, 0,44 mmol) y una solución de HATU (0,107 g, 0,284 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-hidroxi-*N*-(1-(2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-il)-2-metilbutanamida en forma de la sal de TFA. LC/MS: *m/z* 421,3$(M+H)^+$ a 2,18 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001389] Ejemplo 243

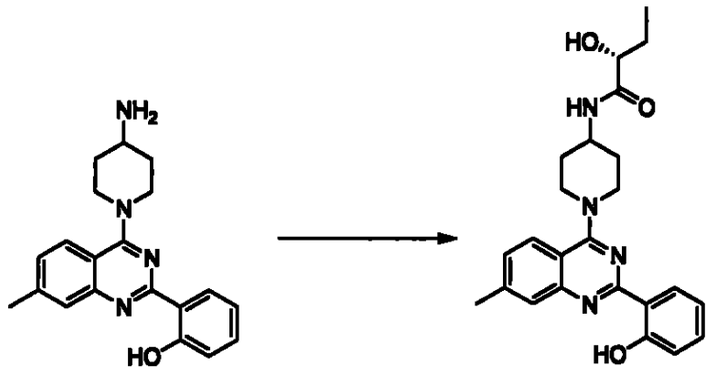
[001390] **(2*R*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida**

1007 1996



[001391]

[001392] **(2*R*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida**



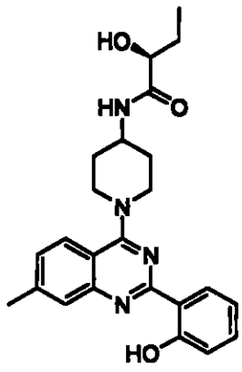
[001393]

[001394] A ácido (R)-2-hidroxibutanoico (28 mg, 0,27 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,07 g, 0,21 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,058 ml, 0,42 mmol) y una solución de HATU (0,103 g, 0,273 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó

usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA).) para obtener (2*R*)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida en forma de la sal de TFA. LC/MS: *m/z* 421,3$(M+H)^+$ a 2,18 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

[001395] Ejemplo 244

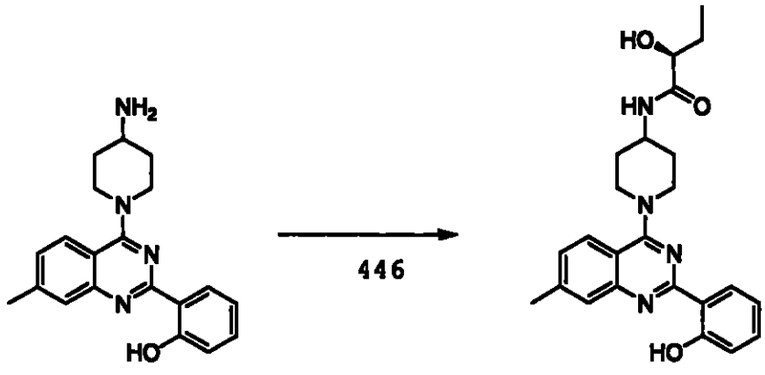
[001396] **(2*S*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida**



[001397]

[001398] **(2*S*)-2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida**

[001399]



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[001400] A ácido (*S*)-2-hidroxibutanoico (28 mg, 0,27 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,07 g, 0,21 mmol) en DMF (0,5 ml), seguido de la adición de trietilamina (0,058 ml, 0,42 mmol) y una solución de HATU (0,103 g, 0,273 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, luego se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (2*S*)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)butanamida en forma de la sal de TFA. LC/MS: *m/z* 421,3$(M+H)^+$ a 2,18 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

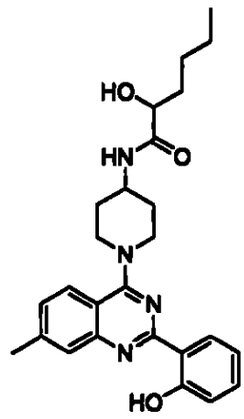
[001401] Ejemplo 245

[001402] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)hexanamida**

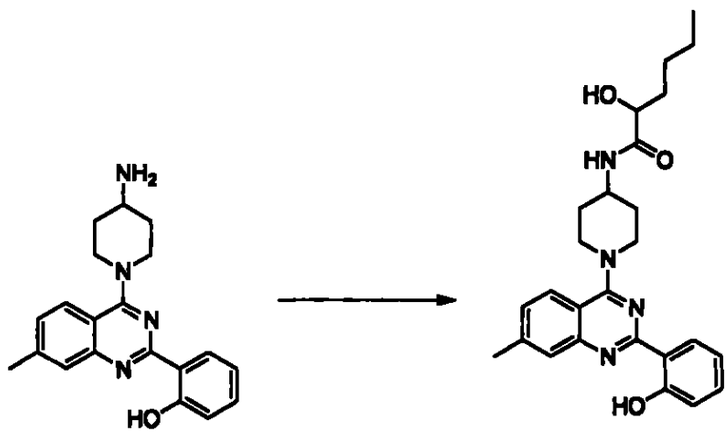
[001403]

1009

1010



[001404] **2-Hidroxi-N-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)hexanamida**



[001405]

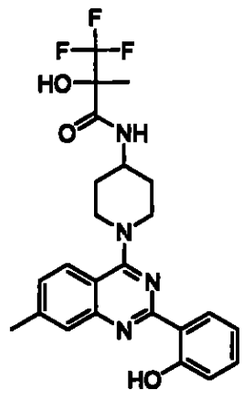
[001406] A ácido 2-hidroxihexanoico (36 mg, 0,27 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,07 g, 0,21 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,058 ml, 0,42 mmol) y una solución de HATU (0,103 g, 0,273 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó

usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)hexanamida en forma de la sal de TFA. LC/MS: *m/z* 449,3$(M+H)^+$ a 2,45 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

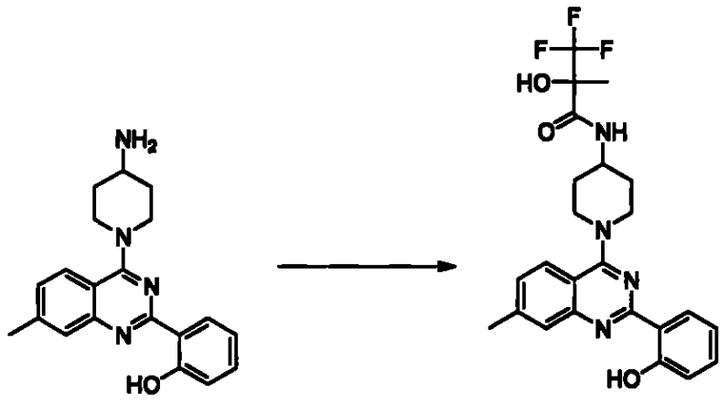
[001407] Ejemplo 246

[001408] **2-(Trifluorometil)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)propanamida**

[001409]



[001410] **2-(Trifluorometil)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)propanamida**

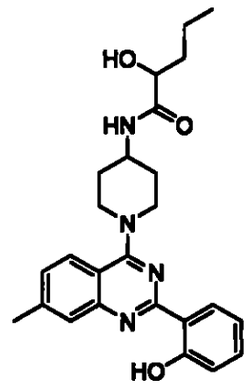


[001411]

[001412] A ácido 2-(trifluorometil)-2-hidroxipropanoico (43 mg, 0,27 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,07 g, 0,21 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,058 ml, 0,42 mmol) y una solución de HATU (0,103 g, 0,273 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-(trifluorometil)-2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)propanamida en forma de la sal de TFA. LC/MS: *m/z* 475,1$(M+H)^+$ a 2,46 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

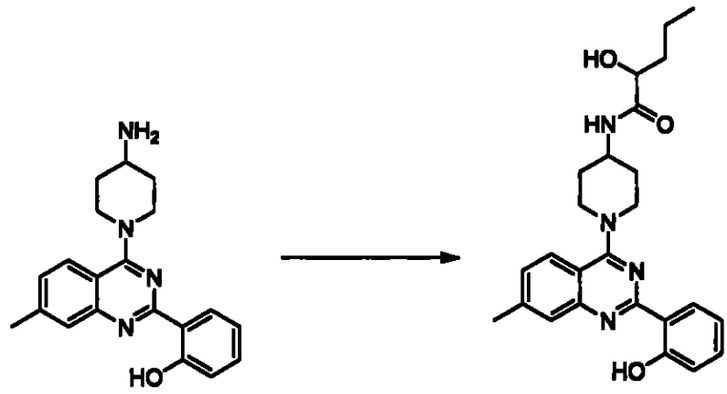
[001413] Ejemplo 247

[001414] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)pentanamida**



[001415]

[001416] **2-Hidroxi-N-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)pentanamida**



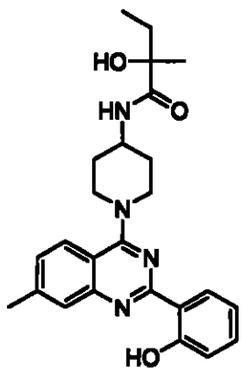
[001417]

[001418] A ácido 2-hidroxipentanoico (32 mg, 0,27 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,07 g, 0,21 mmol) en DMF (0,5 ml), seguido de la adición de trietilamina (0,058 ml, 0,42 mmol) y una solución de HATU (0,103 g, 0,273 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se

purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)pentanamida en forma de la sal de TFA. LC/MS: *m/z* 435,3$(M+H)^+$ a 2,31 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

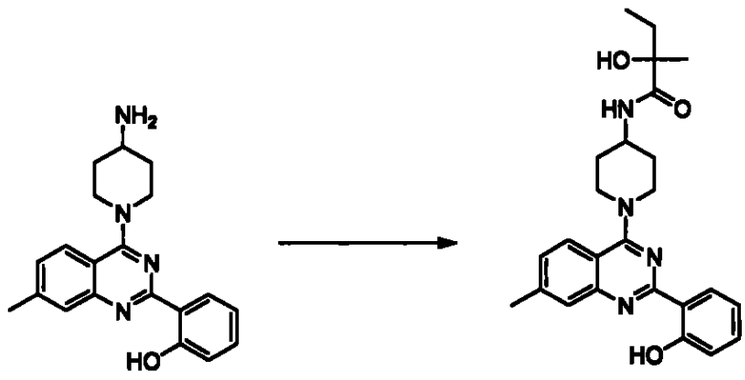
[001419] Ejemplo 248

[001420] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-metilbutanamida**



[001421]

[001422] **2-Hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-metilbutanamida**

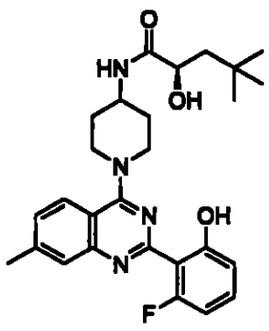


[001423]

[001424] A ácido 2-hidroxi-2-metilbutanoico (32 mg, 0,27 mmol) se añadió una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)fenol (0,07 g, 0,21 mmol) en DMF (0,5 ml) seguido de la adición de trietilamina (0,058 ml, 0,42 mmol) y una solución de HATU (0,103 g, 0,273 mmol) en DMF (0,5 ml). La reacción se agitó durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-hidroxi-*N*-(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-metilbutanamida en forma de la sal de TFA. LC/MS: *m/z* 435,3$(M+H)^+$ a 2,24 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001425] Ejemplo 249

[001426] **(2R)-*N*-(1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-hidroxi-4,4-**

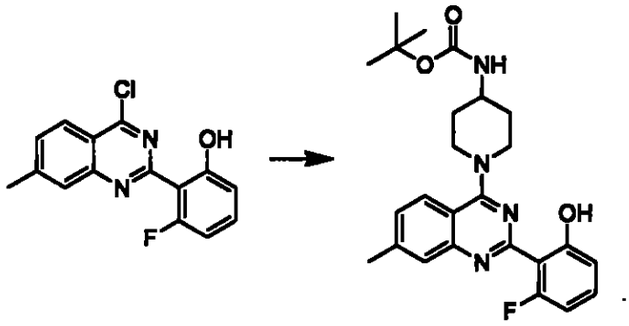


dimetilpentanamida

[001427]

[001428] **1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo**

[001429]



[001430] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (700 mg, 2,42 mmol) en 10 ml de CH_2Cl_2 a 0 °C se añadió trietilamina (0,67 ml, 4,8 mmol) seguido de la adición de piperidin-4-ilcarbamato de *ter*-butilo (630 mg, 3,14 mmol) bajo una atmósfera de N_2. La reacción se calentó

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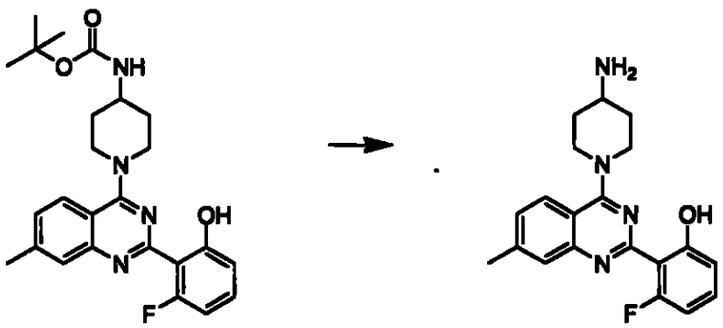
gradualmente hasta temperatura ambiente y se agitó durante la noche. La mezcla de reacción luego se neutralizó con agua y las capas se separaron. La capa acuosa se extrajo dos veces con CH_2Cl_2 y las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener 1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo (1,05 g, 96%) LC/MS: *m/z* 453,3$(M+H)^+$ a 2,60 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

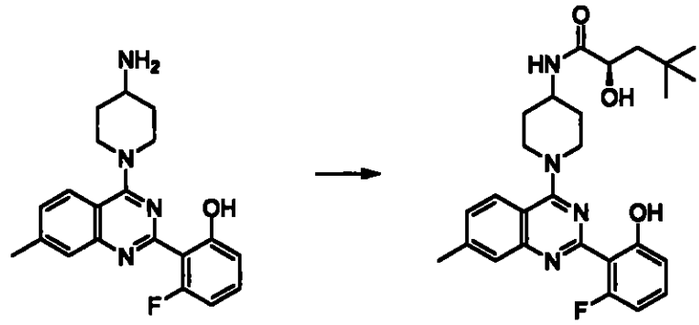
[001431] 2-(4-(4-Aminopiperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol



[001432] A una solución de 1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo (1,05 g, 2,3 mmol) en 20 ml de CH_2Cl_2 se añadió lentamente TFA (5 ml). La reacción se agitó durante una hora antes de evaporarla hasta sequedad. Al residuo se añadió CH_2Cl_2 y la reacción se neutralizó usando una solución acuosa de NaOH 1 M. La capa acuosa se extrajo dos veces con CH_2Cl_2 y las capas

orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (0,75 g, 92%). LC/MS: *m/z* 353,3$(M+H)^+$ a 1,35 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001433] (2*R*)-*N*-(1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-hidroxi-4,4-



dimetilpentanamida

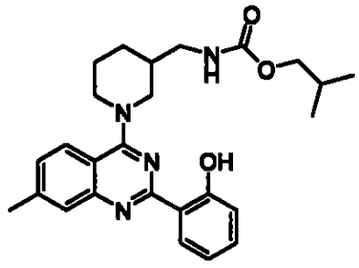
[001434]

[001435] A una solución de 2-(4-(4-aminopiperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (50 mg, 0,14 mmol) en 1 ml de DMF a 0 °C se añadió ácido (R)-2-hidroxi-4,4-dimetilpentanoico (25 mg, 0,17 mmol), seguido de la adición de trietilamina (29 mg, 0,28 mmol). Se agregó HATU (65 mg, 0,17 mmol) y la reacción se agitó a 0 °C durante 10 minutos más y luego se calentó hasta temperatura ambiente. La reacción se completó después de 40 minutos, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O

(0,05% de TFA)) para dar (2*R*)-*N*-(1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-4-il)-2-hidroxi-4,4-dimetilpentanamida en forma de la sal de TFA. LC/MS: *m/z* 481,3 $(M+H)^+$ a 2,42 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

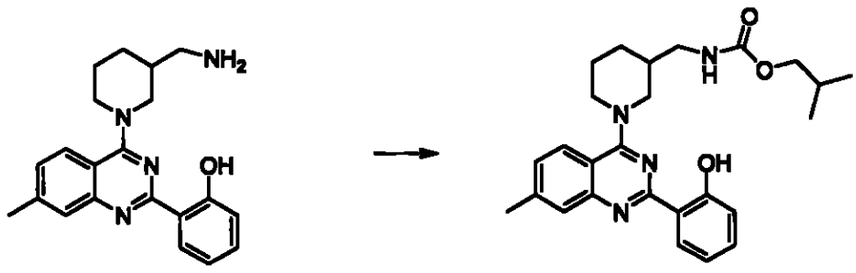
[001436] Ejemplo 250

[001437] **(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo**



[001438]

[001439] **(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo**



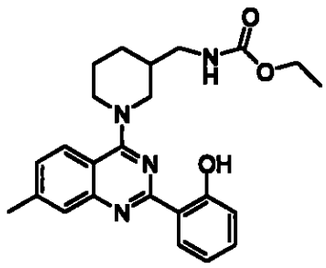
[001440]

[001441] 2-(4-(3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en

DMF anhidra (1 ml) y se enfrió hasta 0 °C, tras lo cual se añadió cloroformiato de isobutilo (27 µL, 0,2 mmol) disuelto en DMF (100 µL) gota a gota seguido de trietilamina (35 mg, 48 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo en forma de la sal de TFA. LC/MS: *m/z* 449,5 $(M+H)^+$ a 2,77 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

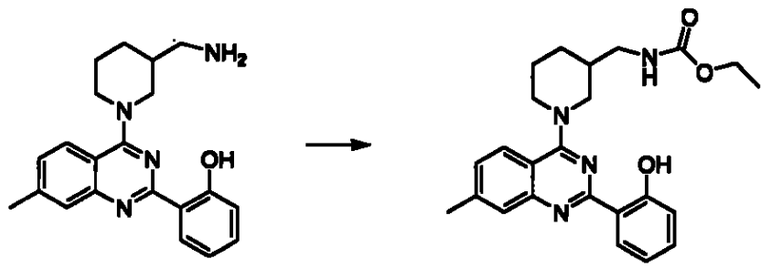
[001442] Ejemplo 251

[001443] **(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo**



[001444]

[001445] **(1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo**



[001446]

[001447] 2-(4-(3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C, después de lo cual se añadió cloroformiato de etilo (20 µL, 0,2 mmol) disuelto en DMF (100 µL) gota a gota seguido de la adición de trietilamina (35 mg, 48 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo en forma de la sal de TFA. LC/MS: *m/z* 421,0 $(M+H)^+$ a 2,48 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001448] Ejemplo 252

[001449] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo**

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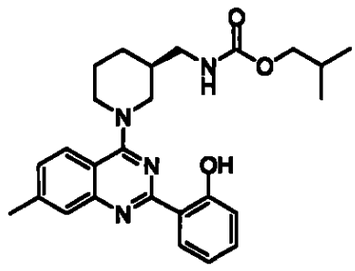
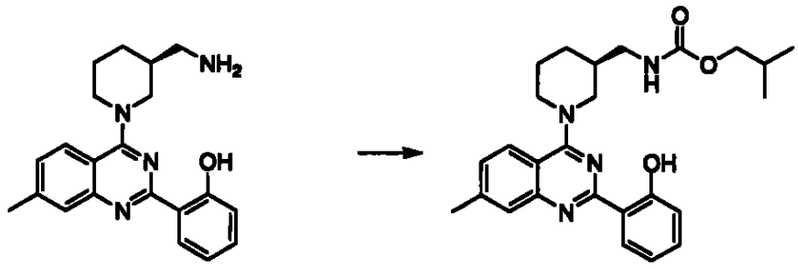


[001450]

[001451] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo**



[001452]

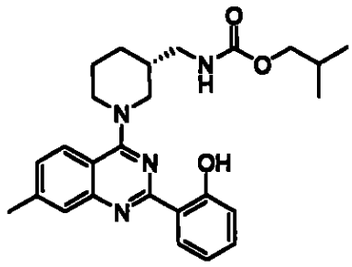
[001453] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,17 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C, tras lo cual se añadió cloroformiato de isobutilo (27 µL, 0,2 mmol) disuelto en DMF (100 µL) gota a gota seguido de la adición de trietilamina (35 mg, 48 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((S)-1-(2-(2-

hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo en forma de la sal de TFA. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,80 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001454] Ejemplo 253

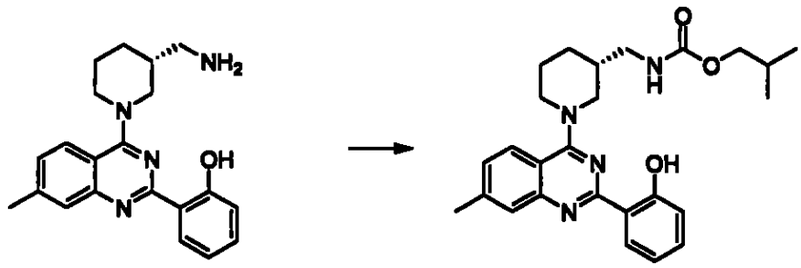
[001455] **((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo**

[001456]



[001457] **((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo**

[001458]



[001459] 2-(4-((*R*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (60 mg, 0,172 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C, tras lo cual se añadió cloroformiato de isobutilo (27 µL, 0,21 mmol) disuelto

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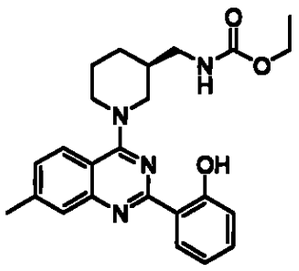
en DMF (100 µL) gota a gota seguido de la adición de trietilamina (35 mg, 48 µL, 0,34 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo en forma de la sal de TFA. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,78 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001460] Ejemplo 254

[001461] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo**



[001462]

[001463] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo**

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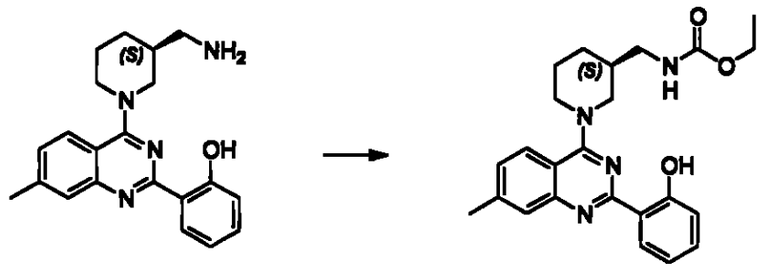


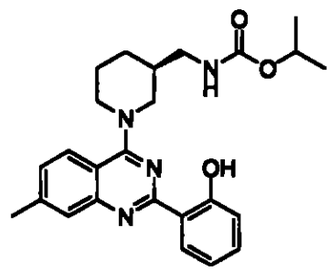
[001464]

[001465] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (35 mg, 0,10 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C, tras lo cual se añadió cloroformiato de etilo (10,5 µL, 0,11 mmol) disuelto en DMF (100 µL) gota a gota seguido de trietilamina (20,2 mg, 27,8 µL, 0,2 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo en forma de la sal de TFA. LC/MS: *m/z* 421,1 $(M+H)^+$ a 2,50 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001466] Ejemplo 255

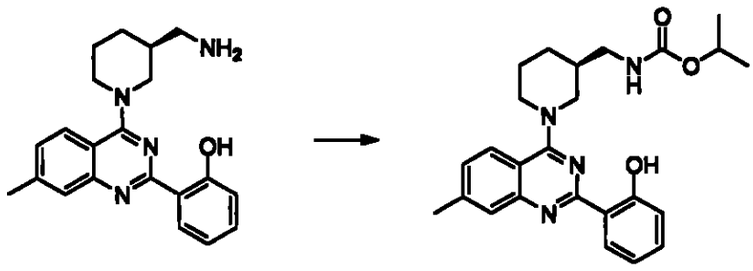
[001467] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isopropilo**

[001468]



[001469] ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isopropilo

[001470]



[001471] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (35 mg, 0,10 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C, tras lo cual se añadió cloroformiato de isopropilo (1 M solución en tolueno, 98,1 mg, 110 µL, 0,11 mmol) disuelto en DMF (100 µL) gota a gota, seguido de trietilamina (20,2 mg, 27,8 µL, 0,2 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isopropilo en forma de la

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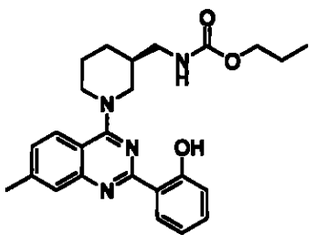
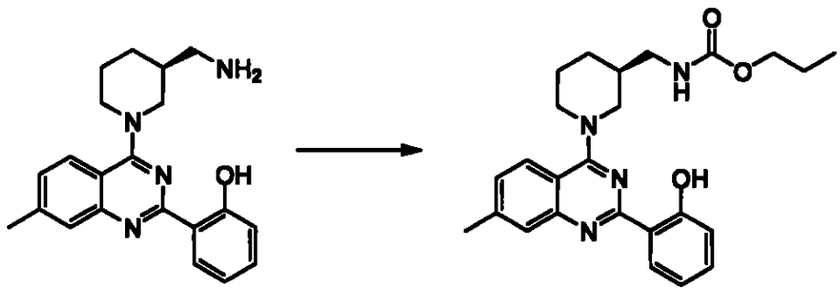
sal de TFA. LC/MS: *m/z* 435,5 $(M+H)^+$ a 2,61 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001472] Ejemplo 256

[001473] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de propilo**



[001474] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de propilo**

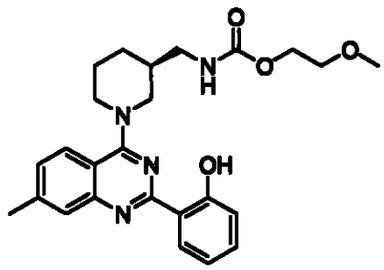


[001475] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (35 mg, 0,10 mmol) se disolvió en DMF anhidra (1 ml) y se enfrió hasta 0 °C, tras lo cual se añadió cloroformiato de propilo (12,4 µL, 0,11 mmol) disuelto en DMF (100 µL) gota a gota seguido de trietilamina (20,2 mg, 27,8 µL, 0,2 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La

purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de propilo en forma de la sal de TFA. LC/MS: *m/z* 435,5 $(M+H)^+$ a 2,61 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

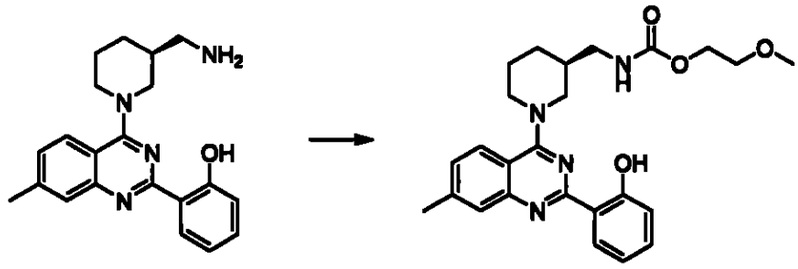
[001476] Ejemplo 257

[001477] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-**



il)piperidin-3-il)metilcarbamato de 2-metoxietilo

[001478] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo**



[001479]

[001480] 2-(4-((*S*)-3-(Aminometil)piperidin-1-il)-7-metilquinazolin-2-il)fenol (35 mg, 0,1 mmol) se disolvió en

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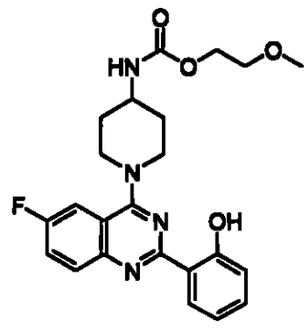
DMF anhidra (1 ml) y se enfrió hasta 0 °C, tras lo cual se añadió cloroformiato de 2-metoxietilo (11,6 µL, 0,1 mmol) disuelto en DMF (100 µL) gota a gota seguido de trietilamina (20,2 mg, 27,8 µL, 0,2 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo en forma de la sal de TFA. LC/MS: *m/z* 451,1 $(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001481] Ejemplo 258

[001482] **1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-ilcarbamato de 2-metoxietilo**



[001483]

[001484] **2-(4-(4-Aminopiperidin-1-il)-6-fluoroquinazolin-2-il)fenol**

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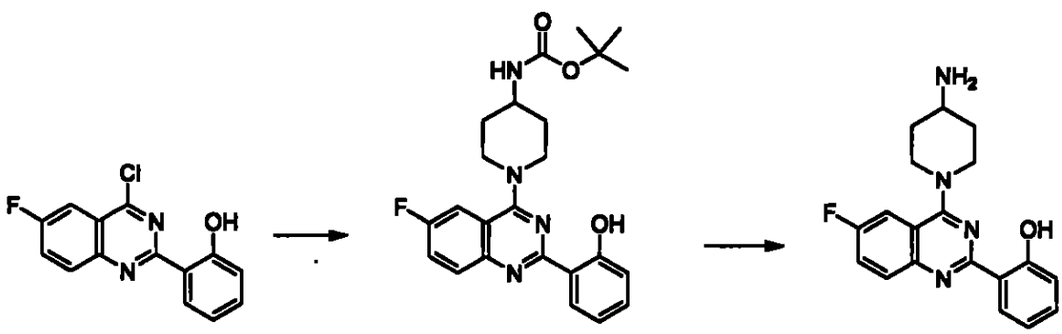
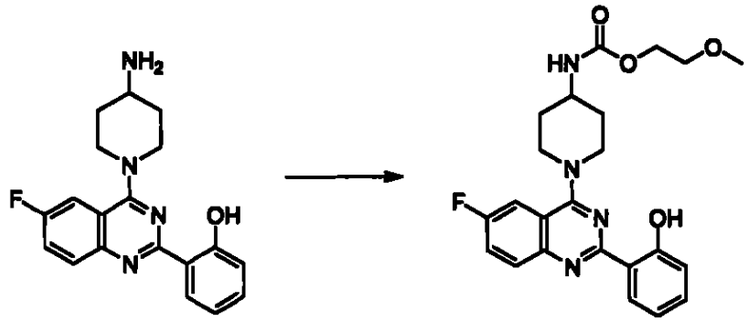


[001485]

[001486] A una solución agitada de 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (0,20 g, 0,73 mmol) en CH_2Cl_2 (5ml) se añadió gota a gota una solución de piperidin-4-ilcarbamato de *ter*-butilo (0,19 g, 0,95 mmol) y trietilamina (203 µL, 147 mg, 1,46 mmol) en CH_2Cl_2. La reacción se agitó durante 3 h y luego se neutralizó con agua. La capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener 1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo. El residuo se disolvió en 10 ml de CH_2Cl_2 y 3 ml TFA. La reacción se agitó durante 2 horas y se neutralizó con una solución acuosa 1,0 M de NaOH. La mezcla se dividió en H_2O/CH_2Cl_2 y se separó y la capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener 2-(4-(4-aminopiperidin-1-il)-6-fluoroquinazolin-2-il)fenol. LC/MS: *m/z*

339,3$(M+H)^+$ a 1,87 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001487] 1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-ilcarbamato de 2-metoxietilo

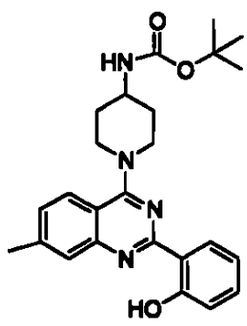


[001488]

[001489] Una solución de 2-(4-(4-aminopiperidin-1-il)-6-fluoroquinazolin-2-il)fenol (50 mg, 0,15 mmol) en DMF (1 ml) se enfrió hasta -40 °C (temperatura externa). A ello se añadió trietilamina (41 µL, 30 mg, 0,29 mmol) y una solución de cloroformiato de 2-metoxietilo (17 µL, 20 mg, 0,15 mmol) en 100 µL de DMF gota a gota. La reacción se dejó calentar hasta temperatura ambiente y se agitó durante 2 h. La purificación mediante HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio 1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)piperidin-4-ilcarbamato de 2-metoxietilo en forma de la sal de TFA. LC/MS: *m/z* 441,5$(M+H)^+$ a 2,6 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001490] Ejemplo 259

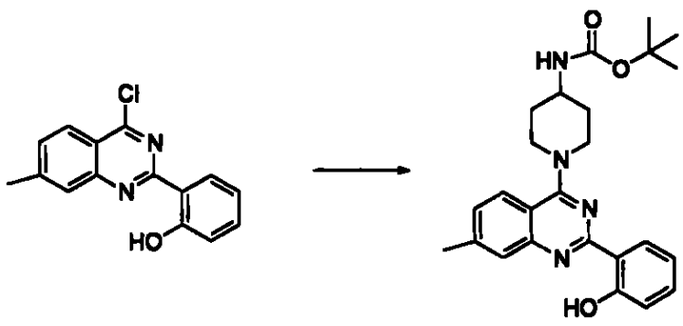
[001491] Éster ter-butílico del ácido {1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-carbámico



[001492]

[001493] Éster ter-butílico del ácido {1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-carbámico

[001494]

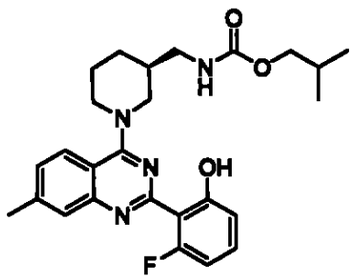


[001495] A éster ter-butílico del ácido piperidin-4-il-carbámico (887 mg, 4,4 mmol) en 10 ml de CH_2Cl_2 se añadieron secuencialmente trietilamina (720 µL, 5,2 mmol) y 2-(4-cloro-7-metil-quinazolin-2-il)-fenol (1,0 g, 3,7 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y luego se diluyó con agua y CH_2Cl_2. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida.

El residuo se sometió a purificación por medio de HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar éster ter-butílico del ácido {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-carbámico en forma de la sal de TFA. LC/MS: *m/z* 435,2 (M+H)+ a 3,03 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

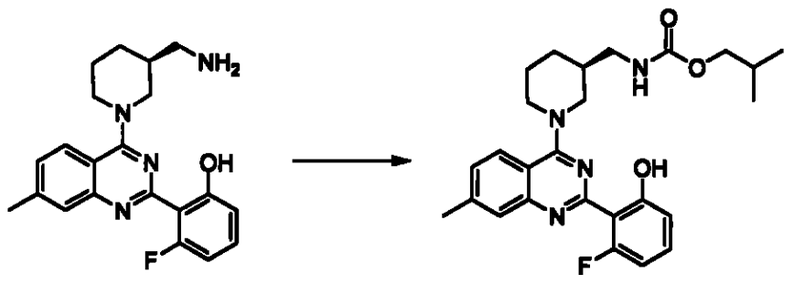
[001496] Ejemplo 260

[001497] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo**



[001498]

[001499] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo**

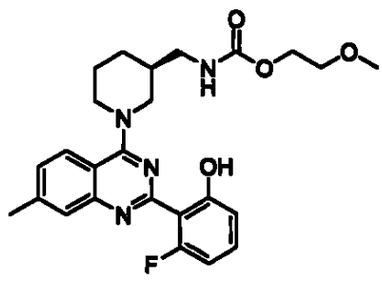


[001500]

[001501] A una solución de 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (40 mg, 0,11 mmol) en DMF (400 µL) a 0 °C se añadió gota a gota cloroformiato de isobutilo (15,7 µL, 0,12 mmol) en DMF (400 µL), seguido de la adición de trietilamina (30 µL, 0,22 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de isobutilo en forma de la sal de TFA. LC/MS: *m/z* 467,1 $(M+H)^+$ a 2,56 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001502] Ejemplo 261

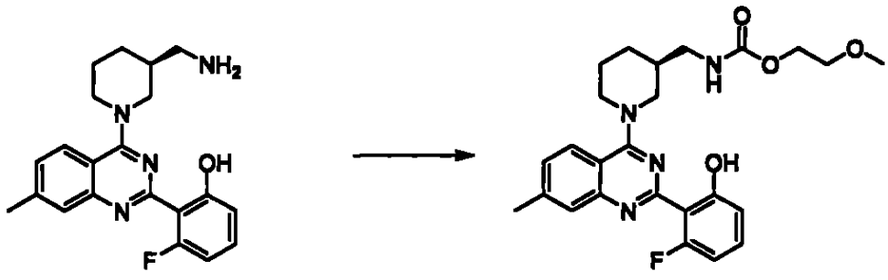
[001503] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo**



[001504]

[001505] Método A

[001506] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo**



[001507]

[001508] A una solución de 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (40 mg, 0,11 mmol) en DMF (400 µL) a 0 °C se añadió gota a gota cloroformiato de 2-metoxietilo (12,6 µL, 0,11 mmol) en DMF (400 µL), seguido de la adición de trietilamina (30 µL, 0,22 mmol). La reacción se dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de

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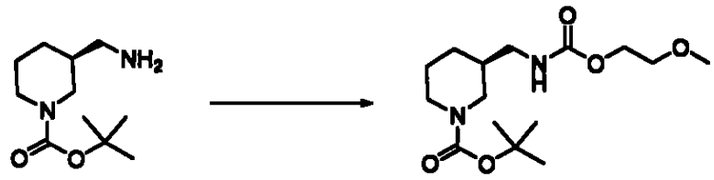
CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo en forma de la sal de TFA. LC/MS: *m/z* 469,1 $(M+H)^+$ a 2,20 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001509] Método B

[001510] **((*S*)-1-(*ter*-butoxicarbonil)piperidin-3-il)metilcarbamato de 2-metoxietilo**

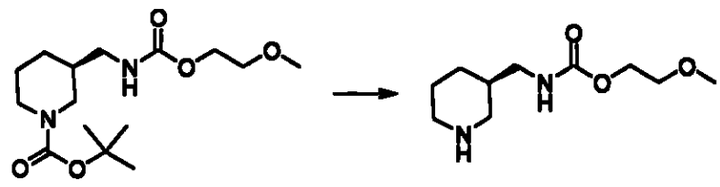


[001511]

[001512] A una solución de 3-(aminometil)piperidin-1-carboxilato de (*S*)-*ter*-butilo (500 mg, 2,33 mmol) en CH_2Cl_2 a -10 °C se añadió trietilamina (650 µL, 4,66 mmol) seguido de la adición gota a gota de cloroformiato de 2-metoxietilo (325 µL, 2,79 mmol). La reacción se calentó hasta temperatura ambiente y se neutralizó con agua. La capa acuosa se extrajo con CH_2Cl_2 y los extractos combinados se secaron sobre $MgSO_4$, se filtró y se evaporó. La purificación por medio de cromatografía en gel de sílice usando 0 al 10% de EtOAc en CH_2Cl_2 dio como resultado ((*S*)-1-(*ter*-butoxicarbonil)piperidin-3-il)metilcarbamato de 2-

metoxietilo (496 mg, 67%). LC/MS: *m/z* 317,3 $(M+H)^+$ a 2,56 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001513] **((*R*)-piperidin-3-il)metilcarbamato de 2-metoxietilo**



[001514]

[001515] A ((*S*)-1-(*ter*-butoxicarbonil)piperidin-3-il)metilcarbamato de 2-metoxietilo (496 mg, 1,6 mmol) disuelto en 10 ml de CH_2Cl_2 se añadieron 5 ml de TFA y la reacción se agitó durante 1 hora. Después de neutralizar la mezcla con una solución de NaOH 1 N se extrajo con CH_2Cl_2 y las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para dar ((*R*)-piperidin-3-il)metilcarbamato de 2-metoxietilo (300 mg, 87%) que se usó sin ulterior purificación. LC/MS: *m/z* 217,5 $(M+H)^+$ a 0,49 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001516] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo**

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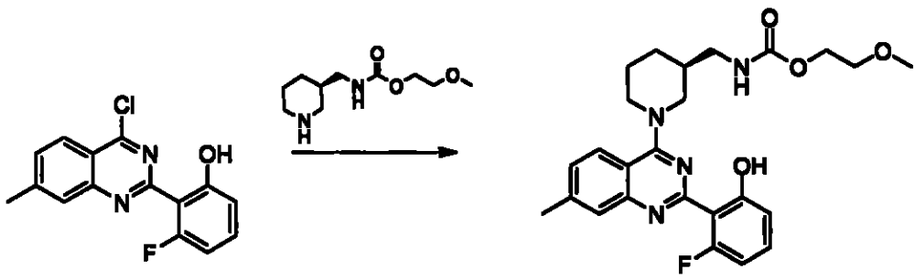
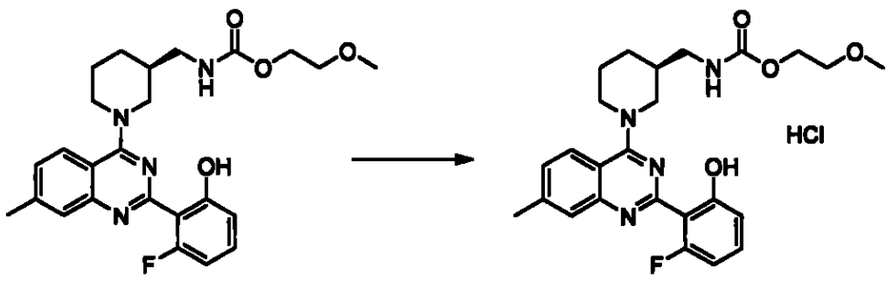


[001517]

[001518] A una solución de ((*R*)-piperidin-3-il)metilcarbamato de 2-metoxietilo (0,24 g, 1,1 mmol) y 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (250 mg, 0,865 mmol) en CH_2Cl_2 se añadió trietilamina (2,41 ml, 1,73 mmol). Tras agitar la reacción a temperatura ambiente durante 2 h, se neutralizó con agua y luego se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0%-10% de EtOAc en CH_2Cl_2 dio como resultado ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo (357 mg, 88%). LC/MS: *m/z* 469,5 $(M+H)^+$ a 2,30 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 7,86 (d, *J* = 8,5 Hz, 1H), 7,64 (s, 1H), 7,35 (m, 3H), 6,78 (d, *J* = 8,1 Hz, 1H), 6,71 (m, 2H), 4,40 (d, *J* = 12,7 Hz, 2H), 4,05 (m, 2H), 3,48 (m, 2H), 3,30 (m, 1H), 3,25 (s, 3H), 3,05 (m, 3H), 1,82 (m, 3H), 1,63 (m, 1H), 1,32 (m, 1H).

[001519] **Clorhidrato de ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo**



[001520]

[001521] A una solución de ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato (352 mg, 0,75 mmol) en CH_2Cl_2 (3 ml) se añadió gota a gota una solución de HCl 2,0 M en éter (0,375 ml, 0,75 mmol) bajo una atmósfera de N_2. Le siguió la adición de 20 ml éter que llevó a la precipitación de clorhidrato de ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietilo (350 mg, 92%) que luego se filtró y se secó. LC/MS: *m/z* 469,5 $(M+H)^+$ a 2,29 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 7,97 (d, *J* = 7,9 Hz, 1H), 7,63 (s, 1H), 7,45 (m, 3H), 6,89 (d, *J* = 8,3 Hz, 1H), 6,82 (t, *J* = 9,5 Hz, 1H), 4,54 (s, 1H), 4,03 (d, *J* = 2,7 Hz, 2H), 3,47 (t, *J* = 4,6 Hz, 4H), 3,24 (s, 3H), 2,99 (m, 2H), 2,54 (s, 3H), 1,89 (m, 3H), 1,70 (m, 1H), 1,38 (m, 1H)

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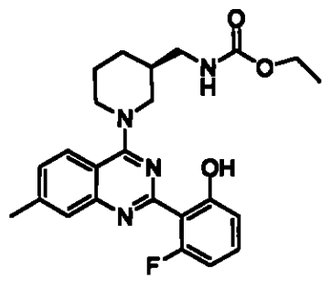
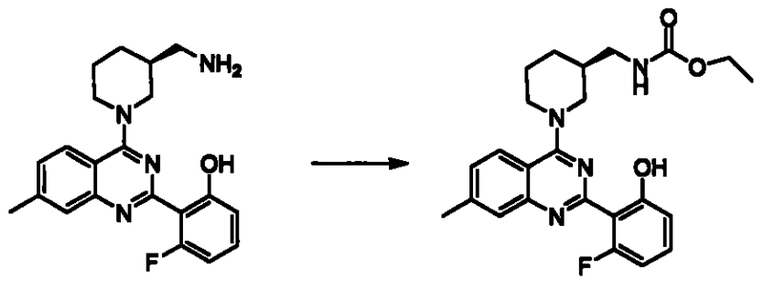
[001522] Ejemplo 262

[001523] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo**



[001524]

[001525] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo**



[001526]

[001527] Método A

[001528] A una solución de 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (40 mg, 0,11 mmol) en DMF (400 µL) a 0 °C se añadió gota a gota cloroformiato de etilo (10,4 µl, 0,10 mmol) en DMF (400 µL), seguido de la adición de trietilamina (30 µL, 0,22 mmol). La reacción se

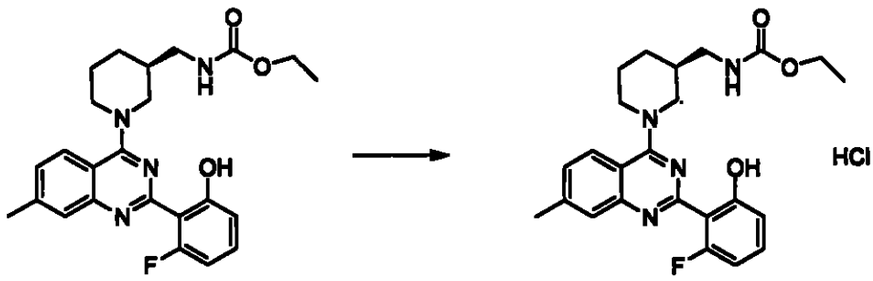
dejó calentar hasta temperatura ambiente y se completó después de 2 h. La purificación por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de 2-metoxietiletilo en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,31 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

|001529| Método B

|001530| A una solución agitada de 2-(4-((*S*)-3-(aminometil)piperidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (200 mg, 0,54 mmol) en 12 ml de THF se añadió diisopropiletilamina (188 µL, 1,08 mmol) a temperatura ambiente. La mezcla se enfrió hasta -60 °C y una solución de cloroformiato de etilo (52 µL, 0,54 mmol) en 0,6 ml de THF se añadió gota a gota. Después de dejar calentar la reacción hasta temperatura ambiente, la mezcla se dividió en H_2O y CH_2Cl_2. Las capas se separaron y la capa acuosa se extrajo dos veces more con CH_2Cl_2. Las capas orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en 50:50 hexanos:CH_2Cl_2 dio ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo (92 mg, 38%). LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,40 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05%

de TFA)). ^{1}H RMN (400 MHz, DMSO-d6) δ 7,87 (d, *J* = 8,5 Hz, 1H), 7,64 (s, 1H), 7,34 (m, 2H), 7,21 (m, 1H), 6,78 (d, *J* = 8,3 Hz, 1H), 6,70 (m, 1H), 4,40 (m, 2H), 3,98 (m, 2H), 3,27 (m, 1H), 3,05 (m, 1H), 2,97 (m, 2H), 1,84 (d, *J* = 11,0 Hz, 3H), 1,67 (d, *J* = 9,4 Hz, 1H), 1,32 (dd, *J* = 20,8, 11,3 Hz, 1H), 1,15 (t, *J* = 7,1 Hz, 3H)

[001531] Clorhidrato de ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo



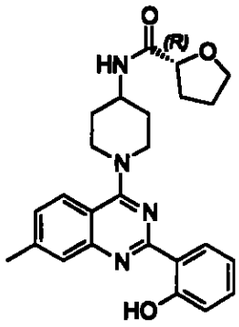
[001532]

[001533] A una solución de ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo (89 mg, 0,2 mmol) en 2 ml de CH_2Cl_2 bajo una atmósfera de N_2 se añadió éter (10 ml) seguido de la adición gota a gota de una solución 2,0 M de HCl en éter (0,1 ml, 0,2 mmol) que dio como resultado ala precipitación de clorhidrato de ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)piperidin-3-il)metilcarbamato de etilo que luego se filtró y se secó (85 mg, 90%). LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,37 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05%

de TFA)). ^{1}H RMN (400 MHz, DMSO-d6) δ 8,26 (d, *J* = 8,5 Hz, 1H), 7,57 (s, 1H), 7,45 (m, 2H), 6,81 (m, 2H), 4,57 (m, 2H), 3,89 (m, 2H), 3,52 (m, 1H), 3,36 (m, 1H), 2,95 (s, 2H), 2,52 (s, 3H), 1,86 (m, 3H), 1,66 (m, 1H), 1,39 (m, 1H), 1,07 (t, *J* = 6,6 Hz, 3H).

[001534] Ejemplo 276

[001535] {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-amida del ácido (*R*)-tetrahidro-furan-2-

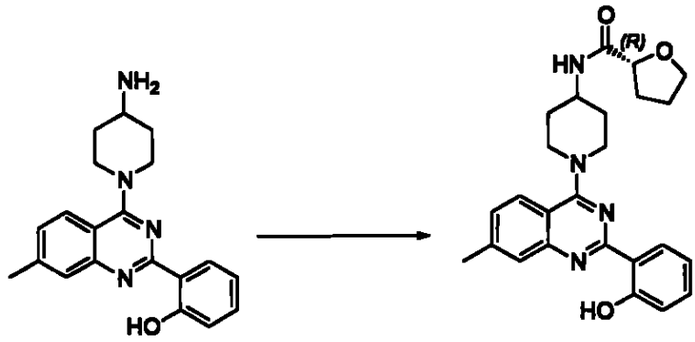


carboxílico

[001536]

[001537] {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-amida del ácido (*R*)-tetrahidro-furan-2-carboxílico

[001538]

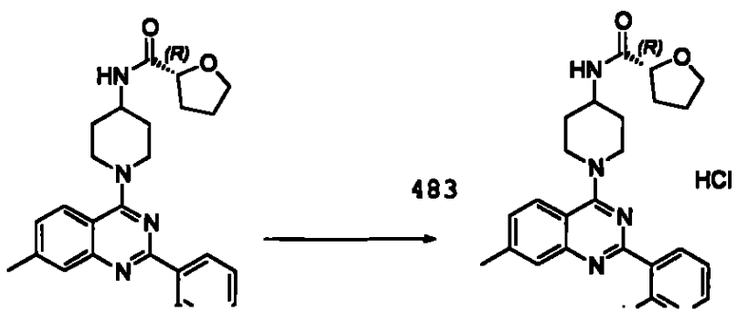


[001539] Método A: Ácido (*R*)-tetrahidrofuran-2-carboxílico (23 mg, 0,20 mmol) y HATU (84 mg, 0,22 mmol) se disolvieron en 0,75 ml de DMF, luego se añadió trietilamina (40 mg, 55 µL, 0,40 mmol), seguido de inmediato por 2-[4-(4-amino-piperidin-1-il)-7-metil-quinazolin-2-il]-fenol (67 mg, 0,20 mmol). La reacción se agitó luego durante 30 min a temperatura ambiente, se diluyó con 0,75 ml 1:1 metanol / DMSO, se filtró y se purificó por HPLC en fase inversa (2-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar (*R*)-tetrahidro-furan-2-carboxílico {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-amida en forma de la sal de TFA. LC/MS: *m/z* 433,2 $(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001540] Método B: Ácido (*R*)-tetrahidrofuran-2-carboxílico (193 mg, 1,66 mmol) se disolvió en DMF (6 ml), seguido de la adición de HATU (696 mg, 1,83 mmol). La mezcla se agitó luego durante 15 min a temperatura ambiente bajo una atmósfera de N_2. El 2-[4-(4-amino-piperidin-1-il)-7-metil-quinazolin-2-il]-

fenol (556 mg, 1,66 mmol) se disolvió en DMF (8 ml) y se añadió a la mezcla, seguido de trietilamina (336 mg, 0,463 ml, 3,32 mmol). Al cabo de 30 min, la DMF se eliminó al vacío y el producto crudo se dividió en agua y acetato de etilo. La capa acuosa se separó, se lavó con acetato de etilo y las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para dar producto crudo en forma de un aceite anaranjado. La purificación por medio de cromatografía en gel de sílice (20% de acetato de etilo / 80% 1:1 CH_2Cl_2:hexano) dio (*R*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il)-amida pura (303 mg, 42%). ^1H RMN (400 MHz, DMSO-d6) δ 8,44 (dd, *J* = 8,2, 1,5 Hz, 1H), 7,90 (d, *J* = 8,5 Hz, 1H), 7,75 (d, *J* = 8,3 Hz, 1H), 7,67 (s, 1H), 7,40-7,36 (m, 2H), 6,97-6,93 (m, 2H), 4,48-4,45 (m, 2H), 4,20 (dd, *J* = 8,2, 5,3 Hz, 1H), 4,06-3,96 (m, 1H), 3,88 (dd, *J* = 14,3, 6,6 Hz, 1H), 3,74 (dd, *J* = 14,5, 6,7 Hz, 1H), 3,43-3,32 (m, 2H), 2,51 (s, 3H), 2,16-2,07 (m, 1H), 1,89-1,69 (m, 7H). ^{13}C RMN (100 MHz, DMSO-d6) δ 171,7, 162,8, 160,7, 159,5, 149,3, 144,1, 132,5, 129,0, 127,3, 125,7, 125,4, 118,9, 118,4, 117,2, 111,9, 77,6, 68,5, 48,3, 45,5, 31,3, 31,2, 30,0, 24,9, 21,2.

[001541] **Clorhidrato de {1-[2-(2-hidroxi-fenil)-7-metil-**



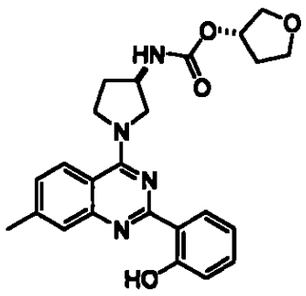
1096

quinazolin-4-il]-piperidin-4-il}-amida de ácido (*R*)-tetrahidro-furan-2-carboxílico

[001542] (*R*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-amida (303 mg, 0,701 mmol) se disolvió en 9 ml 2:1 éter seco / CH_2Cl_2 seco y se añadió HCl 2,0 M en éter gota a gota (0,35 ml, 0,70 mmol), lo que produjo un precipitado blanco que se recogió por filtración para dar clorhidrato de {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-piperidin-4-il}-amida del ácido (*R*)-tetrahidro-furan-2-carboxílico (268 mg, 82%). LC/MS: *m/z* 433,5 $(M+H)^+$ a 2,26 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,20 (dd, *J* = 7,8, 1,2 Hz, 1H), 8,00 (d, *J* = 8,6 Hz, 1H), 7,80-7,79 (m, 2H), 7,51-7,47 (m, 2H), 7,15 (d, *J* = 8,2 Hz, 1H), 7,05-7,01 (m, 1H), 4,66-4,63 (m, 2H), 4,21 (dd, *J* = 8,2, 5,2 Hz, 1H), 4,12-4,03 (m, 1H), 3,91-3,84 (m, 1H), 3,78-3,70 (m, 1H), 3,59 (t, *J* = 12,3 Hz, 2H), 2,54 (s, 3H), 2,16-2,05 (m, 1H), 1,97-1,94 (m, 2H), 1,89-1,72 (m, 5H).

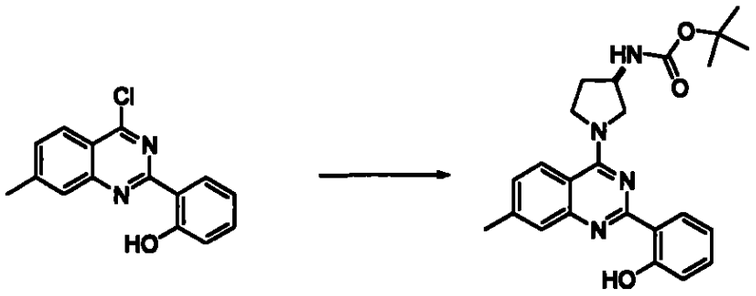
[001543] Ejemplo 301

[001544] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo**



[001545]

[001546] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de ter-butilo**

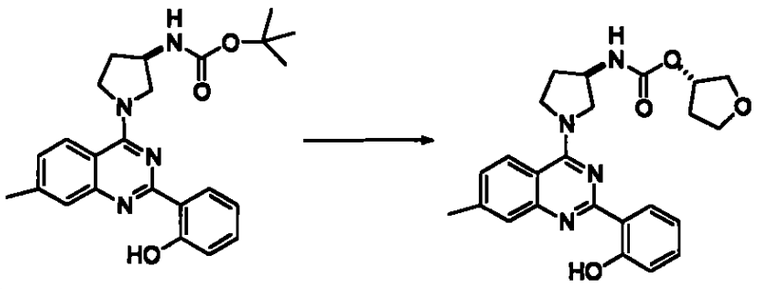


[001547]

[001548] A 2-(4-cloro-7-metil-quinazolin-2-il)-fenol (644 mg, 2,4 mmol) en 2,9 ml de DMF a temperatura ambiente se añadieron secuencialmente éster ter-butílico del ácido (*R*)-pirrolidin-3-il-carbámico (857 mg, 4,6 mmol) y trietilamina (662 µL, 4,8 mmol) y la mezcla de reacción se agitó durante 12 h. La mezcla de reacción se diluyó con agua (10 ml) y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó (Na_2SO_4) y el residuo se purificó por cromatografía en gel de sílice con 25-85% *de acetato* de etilo/hexanos para dar (*R*)-1-(2-(2-hidroxifenil)-7-

metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo (856 mg, 86%). LC/MS: *m/z* 421 $(M+H)^+$ a 2,82 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001549] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo**



[001550]

[001551] Método A

[001552] A (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo (850 mg, 2,02 mmol) se añadió a temperatura ambiente 4 ml de 1:1 TFA:CH_2Cl_2. La mezcla de reacción se agitó durante 50 min, se diluyó con 20 ml de CH_2Cl_2 y se lavó con 15 ml de solución saturada de $NaHCO_3$. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar (*R*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol en forma de un aceite que se usó sin ulterior purificación.

A 45,9 mg (0,14 mmol) de la amina del procedimiento anterior se añadieron 570 µL de CH_2Cl_2 y la solución se enfrió hasta 0 °C. A esta solución se añadieron secuencialmente 24 µL (0,17

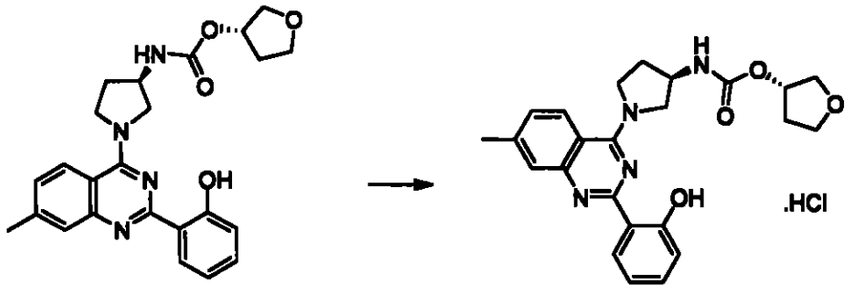
mmol) de trietilamina y 19,4 mg (0,13 mmol) de (*S*)-tetrahidro-furan-3-ol cloroformiato. La mezcla de reacción se agitó a 0 °C durante 45 min, se diluyó con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 435 $(M+H)^+$ a 2,41 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001553] Método B

[001554] A (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo (907,2 mg, 2,16 mmol) se añadió 4 ml de 1:1 TFA:CH_2Cl_2. La mezcla se agitó a temperatura ambiente durante 5 horas. La reacción se diluyó con una solución de solución acuosa saturada de $NaHCO_3$ y CH_2Cl_2. La capa orgánica se separó, se secó sobre Na_2SO_4 y se concentró a presión reducida para dar 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol. A esto free amina (640 mg, 2 mmol) se añadieron 8 ml de CH_2Cl_2 y trietilamina (335 µL, 2,4 mmol). Tras enfriar la mezcla hasta 0 °C, se añadió cloroformiato de (S)-tetrahidrofuran-3-ilo (271 mg, 1,8 mmol) y la reacción se dejó bajo agitación durante 30

minutos. La purificación en gel de sílice usando 30-100% de acetato de etilo/hexanos dio (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 14,8 (bs, 1H), 8,34 (d, *J* = 6,4 Hz, 1H), 7,83 (d, *J* = 4,0 Hz, 1H), 7,48 (bs, 1H), 7,27 (m, 1H), 7,08 (d, *J* = 8,1 Hz, 1H), 6,93 (d, *J* = 8,1 Hz, 1H), 6,82 (t, *J* = 7,5 Hz, 1H), 5,21 (s, 1H), 5,06 (s, 1H), 4,37 (s, 1H), 4,15 (m, 1H), 4,02 (s, 1H), 3,97 (d, *J* = 5,6 Hz, 1H), 3,87-3,77 (m, 5H), 2,42 (s, 3H), 2,24 (t, *J* = 6,0 Hz, 1H), 2,15-2,06 (m, 1H), 1,98 (q, *J* = 9,3 Hz, 2H).

[001555] Clorhidrato de (R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo

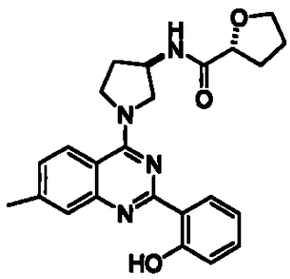


[001556] A HCl 2,0 M solución en Et_2O (192 µL, 0,38 mmol) se añadió lentamente a -20 °C a una solución agitada de (R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (167 mg, 0,38 mmol) en 700 µL de CH_2Cl_2. La reacción se dejó calentar hasta temperatura ambiente y se agitó durante 25 minutos. Los

solventes se eliminaron a presión reducida y el residuo se trituró con Et_2O y se filtró para dar clorhidrato de (R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo. LC/MS: *m/z* 435,2 $(M+H)^+$ a 2,41 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

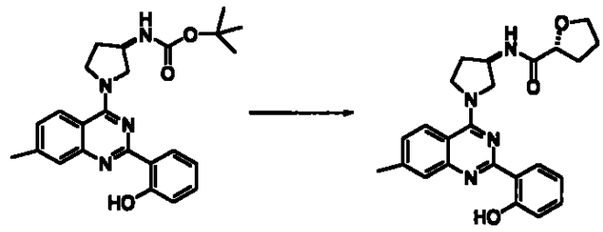
[001557] Ejemplo 302

[001558] **{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R*,*R*)-tetrahidro-furan-2-carboxílico**



[001559] **{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R*,*R*)-tetrahidro-furan-2-carboxílico**

[001560]



[001561] A 850 mg (2,02 mmol) de éster ter-butílico del ácido (*R*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-

pirrolidin-3-il)-carbámico se añadieron a temperatura ambiente 4 ml de 1:1 TFA: CH_2Cl_2. La mezcla de reacción se agitó durante 50 min y se diluyeron con 20 ml de CH_2Cl_2 y se extrajo con 15 ml de solución saturada de $NaHCO_3$. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar (*R*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol en forma de un aceite que se usó sin ulterior purificación.

A 52,6 mg (0,16 mmol) de la amina del procedimiento anterior se añadieron 600 µL de CH_2Cl_2. A esta solución se añadieron secuencialmente 27,4 µL (0,19 mmol) de trietilamina y 20,9 mg (0,18 mmol) de ácido (*R*)-tetrahidro-furan-2-carboxílico, 24,2 mg (0,18 mmol) de HOBt, 34,6 mg (0,18 mmol) de EDCI a temperatura ambiente. La mezcla de reacción se agitó durante 12 h, luego se diluyó con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R,R*)-tetrahidro-furan-2-carboxílico en forma de la sal de TFA. LC/MS: *m/z* 419 $(M+H)^+$ a 2,35 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001562] Ejemplo 303

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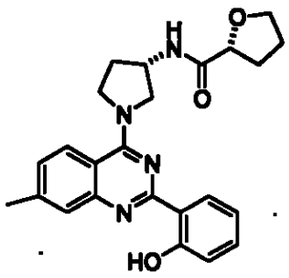
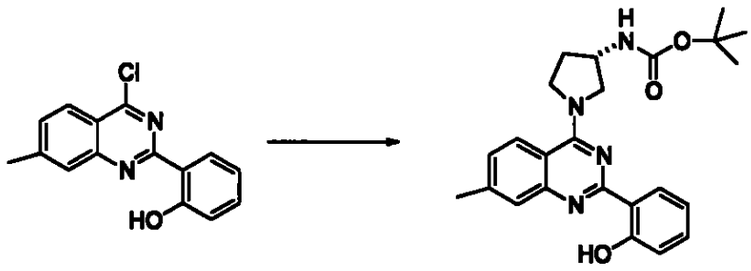
[001563] **(2*R*)-tetrahidro-*N*-((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)furan-2-carboxamida**



[001564]

[001565] **Éster ter-butílico del ácido (*S*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico**



[001566]

[001567] A 2-(4-cloro-7-metil-quinazolin-2-il)-fenol (551 mg, 2,03 mmol) en 2,5 ml de DMF a temperatura ambiente se añadieron secuencialmente éster ter-butílico del ácido (*S*)-pirrolidin-3-il-carbámico (740 mg, 3,9 mmol) y trietilamina (567 µL, 4,0 mmol) y la mezcla de reacción se agitó durante 12 h. La mezcla de reacción se diluyó con agua (10 ml) y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó (Na_2SO_4) y el

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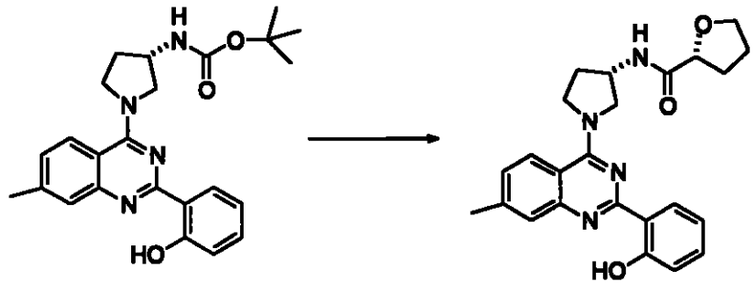
residuo se purificó mediante cromatografía en gel de sílice con 25-85% *de* acetato de etilo/hexanos para dar éster ter-butílico del ácido (*S*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico (694 mg, 81%). LC/MS: *m/z* 421 $(M+H)^+$ a 2,79 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001568] (2*R*)-tetrahidro-*N*-((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)furan-2-carboxamida



[001569]

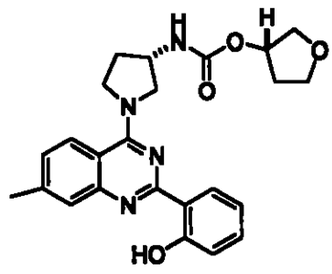
[001570] A éster ter-butílico del ácido (*S*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico (690 mg, 1,64 mmol) se añadieron a temperatura ambiente 3 ml de 1:1 TFA:CH_2Cl_2. La mezcla de reacción se agitó durante 55 min, se diluyó con 20 ml de CH_2Cl_2 y se lavó con 15 ml de solución saturada de $NaHCO_3$. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar (*S*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol en forma de un aceite que se usó sin ulterior purificación.

A la amina del procedimiento anterior (133,3 mg, 0,42 mmol) se añadieron 1,6 ml de CH_2Cl_2. A esta solución se añadieron secuencialmente trietilamina (174 µL, 1,25 mmol) y ácido (*R*)-tetrahidro-furan-2-carboxílico (57,9 mg, 0,5 mmol), HOBt (67,5 mg 0,5 mmol), EDCI (95,8 mg 0,5 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 12 h y se diluyeron con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar (2*R*)-tetrahidro-*N*-((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)furan-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 419 $(M+H)^+$ a 2,34 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001571] Ejemplo 304

[001572] **Éster tetrahidro-furan-3-ílico del ácido (*S*,*S*)-{1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico**

[001573]



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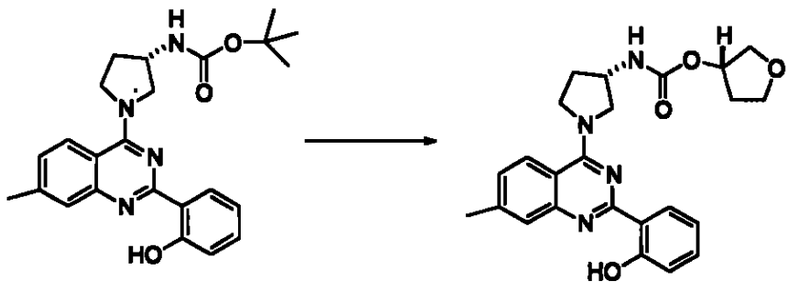
[001574] Éster tetrahidro-furan-3-ílico del ácido (*S,S*)-{1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico



[001575]

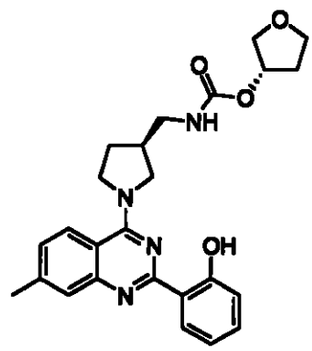
[001576] A éster ter-butílico del ácido (S)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il)-carbámico (690 mg, 1,64 mmol) se añadieron a temperatura ambiente 3 ml de 1:1 TFA:CH_2Cl_2. La mezcla de reacción se agitó durante 55 min, se diluyó con 20 ml de CH_2Cl_2 y se lavó con 15 ml de solución saturada de $NaHCO_3$. La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar (*S*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol en forma de un aceite que se usó sin ulterior purificación.

A la amina del procedimiento anterior (134,7 mg, 0,42 mmol) se añadió 1,6 ml de CH_2Cl_2 y la solución se enfrió hasta 0 °C. A esta solución se añadieron secuencialmente trietilamina (88 µL, 0,63 mmol) y cloroformiato de (*S*)-tetrahidro-furan-3-ol (82,3 mg, 0,55 mmol). La mezcla de reacción se agitó y se dejó

calentar de 0 °C hasta temperatura ambiente durante 12 h y se diluyó con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar éster tetrahidro-furan-3-ilico del ácido (*S,S*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico en forma de la sal de TFA. LC/MS: *m/z* 435 $(M+H)^+$ a 2,39 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

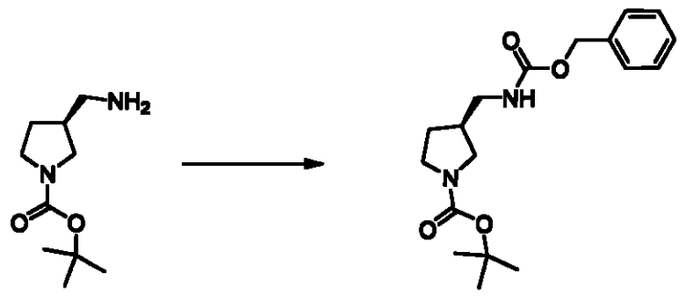
[001577] Ejemplo 305

[001578] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (*S*)-tetrahidrofuran-3-ilo**



[001579]

[001580] **((*S*)-1-(ter-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo**



[001581]

[001582] Una mezcla de 3-(aminometil)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (1,0 g, 5,0 mmol) y 50 ml de THF se enfrió en un baño de hielo. A esto se añadió cloroformiato de bencilo (0,77 ml, 5,5 mmol), seguido de trietilamina (1,39 ml, 10 mmol). Después de retirar el baño de hielo, la reacción se agitó durante 4 h. La mezcla se vertió en agua helada y se extrajo con EtOAc. Los extractos orgánicos se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando EtOAc en hexanos (0-40%) dio ((*S*)-1-(*ter*-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo (1,29 g, 77%) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,39-7,28 (m, 5H), 5,10 (s, 2H), 4,87 (s, 1H), 3,52-2,95 (m, 6H), 2,41-2,35 (m, 1H), 2,10-1,79 (m, 2H), 1,45 (s, 9H).

[001583] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo**

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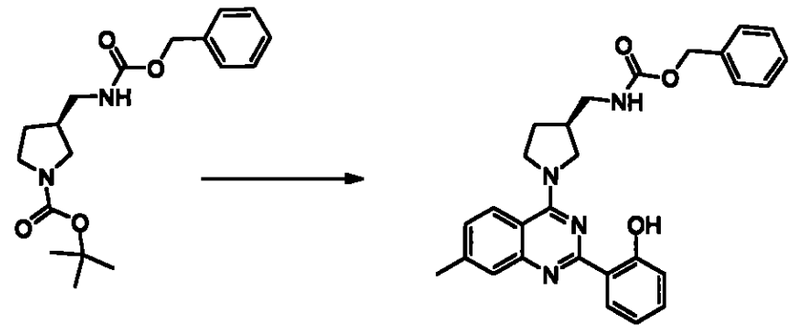
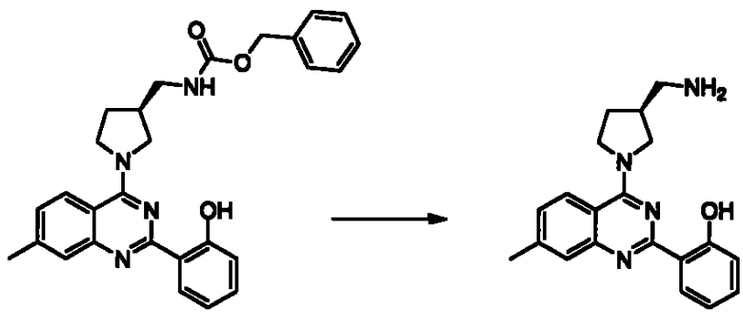
[001584]



[001585] Una solución de ((*S*)-1-(*ter*-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo (0,20 g, 0,60 mmol) y HCl 4 M en dioxano (10 ml) se agitó durante 3 h a temperatura ambiente. Después de evaporar el solvente a presión reducida, el sólido se trituró con Et_2O y se secó al vacío, luego se extrajo en CH_2Cl_2 (10 ml). A esta solución se añadió 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,16 g, 0,60 mmol) y trietilamina (0,25 ml, 1,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con CH_2Cl_2 y se lavó con agua. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-40% de EtOAc en hexanos dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo en un aceite incoloro (0,19·g, 68%). LC/MS: *m/z* 469,1 $(M+H)^+$ a 2,58 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

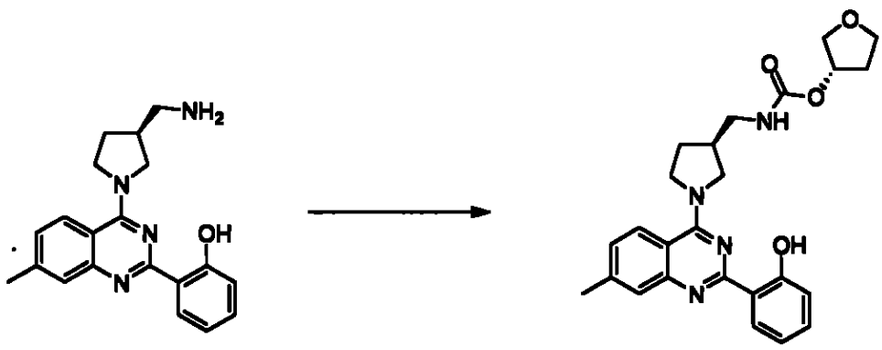
[001586] **2-(4-((*S*)-3-(Aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol**



[001587]

[001588] Una solución de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo (0,19 g, 0,41 mmol) y MeOH (5 ml) se agitó con Pd/C (20 mg, 10% en peso de Pd sobre carbón) bajo una atmósfera de H_2 a presión ambiente a presión ambiente durante la noche. La purificación por medio de cromatografía en gel de sílice usando MeOH en CH_2Cl_2 (0-10%) dio 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (27 mg, 19%). LC/MS: *m/z* 335,5 $(M+H)^+$ a 1,28 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001589] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (*S*)-tetrahidrofuran-3-ilo**

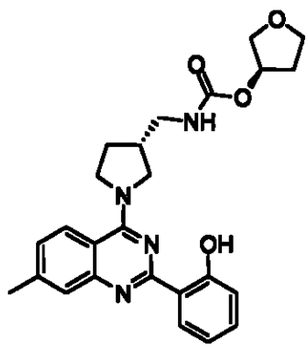


[001590]

[001591] Una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (13 mg, 0,04 mmol) y CH_2Cl_2 (0,5 ml) se enfrió en un baño de hielo. A esta mezcla se añadió cloroformiato de (S)-tetrahidrofuran-3-ilo (6 µL, 0,04 mmol), seguido de trietilamina (11 µL, 0,08 mmol). Después de retirar el baño de hielo, la reacción se agitó durante 3 h a temperatura ambiente. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,18 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

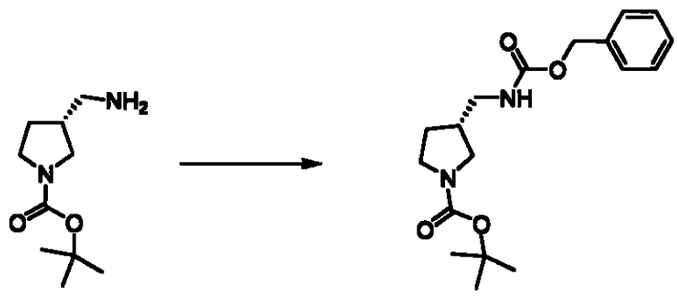
[001592] Ejemplo 306

[001593] **((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo**



[001594]

[001595] **((*R*)-1-(*ter*-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo**

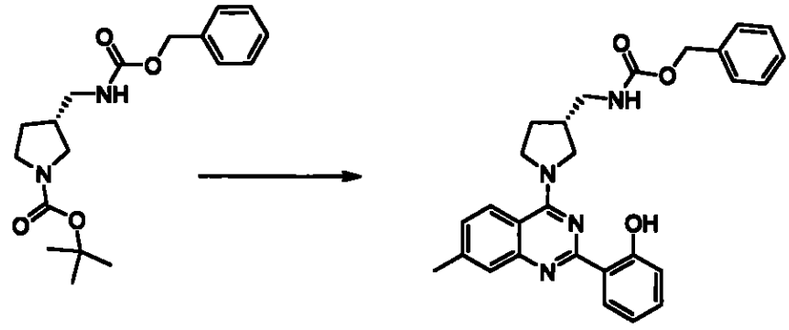


[001596]

[001597] Una solución de 3-(aminometil)pirrolidin-1-carboxilato de (*R*)-*ter*-butilo (1,0 g, 5,0 mmol) y 50 ml de THF se enfrió en un baño de hielo. A esta mezcla se añadió cloroformiato de bencilo (0,77 ml, 5,5 mmol), seguido de trietilamina (1,39 ml, 10 mmol). Después de retirar el baño de hielo, la reacción se agitó durante 4 h. La mezcla se vertió en agua helada y se extrajo con EtOAc. Los extractos orgánicos se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se

concentraron. La purificación por medio de cromatografía en gel de sílice usando EtOAc en hexanos (0-40%) dio ((*R*)-1-(*ter*-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo (1,29 g, 77%) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,39-7,28 (m, 5H), 5,10 (s, 2H), 4,87 (s, 1H), 3,52-2,95 (m, 6H), 2,41-2,35 (m, 1H), 2,10--1,79 (m, 2H), 1,45 (s, 9H).

[001598] ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo

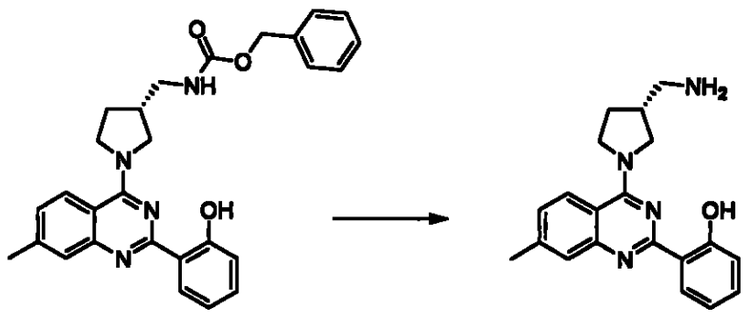


[001599]

[001600] Una solución de ((R)-1-(ter-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo (0,20 g, 0,60 mmol) y HCl 4 M en dioxano (10 ml) se agitó durante 3 h a temperatura ambiente. Después de evaporar el solvente a presión reducida, el sólido resultante se trituró con Et_2O y se secó al vacío, luego se extrajo en CH_2Cl_2 (10 ml). A esta solución se añadió 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,16 g, 0,60 mmol) y trietilamina (0,25 ml, 1,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la

noche, luego se diluyó con CH_2Cl_2 y se lavó con agua. La solución de CH_2Cl_2 se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-40% de EtOAc en hexanos dio ((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo en un aceite incoloro (0,19 g, 68%). LC/MS: *m/z* 469,1 $(M+H)^+$ a 2,58 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001601] 2-(4-((*R*)-3-(Aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol

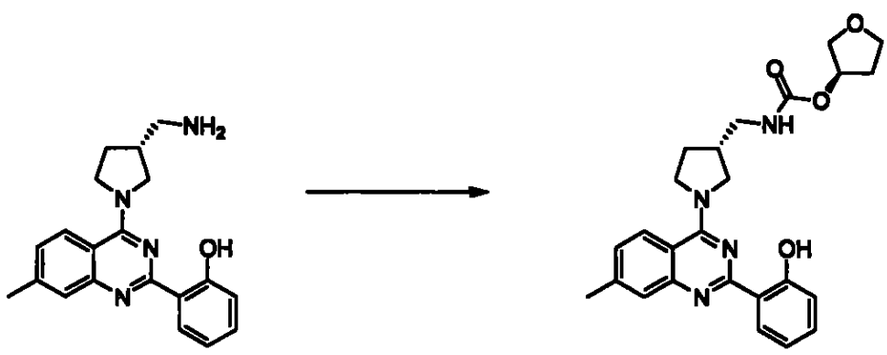


[001602]

[001603] Una solución de ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo (0,19 g, 0,41 mmol) y MeOH (5 ml) se agitó con Pd/C (20 mg, 10% en peso de Pd sobre carbón) bajo una atmósfera de H_2 a presión ambiente durante la noche. La purificación por medio de cromatografía en gel de sílice usando MeOH en CH_2Cl_2 (0-10%) dio 2-(4-((*R*)-3-(aminometil)pirrolidin-1-il)-7-

metilquinazolin-2-il)fenol (63 mg, 45%). LC/MS: *m/z* 335,7 $(M+H)^+$ a 1,23 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001604] ((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo

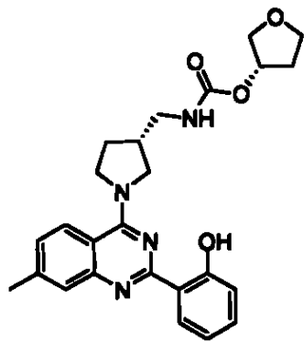


[001605]

[001606] Una solución de 2-(4-((*R*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (15 mg, 0,045 mmol) y CH_2Cl_2 (0,5 ml) se enfrió en un baño de hielo. A esta mezcla se añadió cloroformiato de (R)-tetrahidrofuran-3-ilo (7 µL, 0,045 mmol), seguido de trietilamina (13 µL, 0,090 mmol). Después de retirar el baño de hielo, la reacción se agitó a temperatura ambiente durante 3 h. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,17 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001607] Ejemplo 307

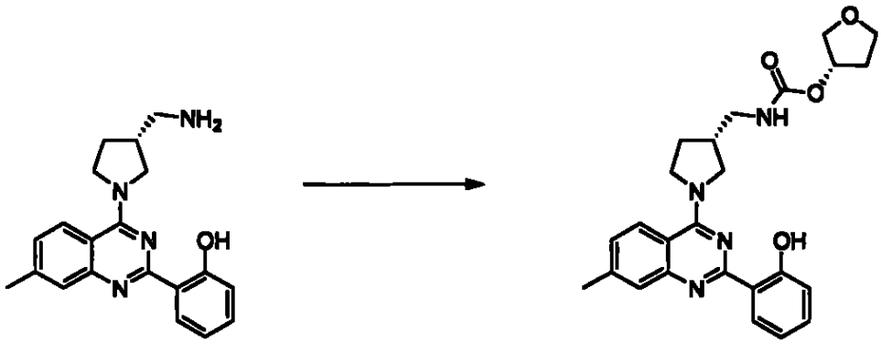
[001608] **((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (*S*)-tetrahidrofuran-3-ilo**



[001609]

[001610] **((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (*S*)-tetrahidrofuran-3-ilo**

[001611]



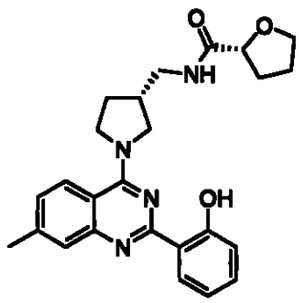
[001612] Una mezcla de 2-(4-((*R*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (15 mg, 0,045 mmol) y CH_2Cl_2 (0,5 ml) se enfrió en un baño de hielo. A esto se añadió cloroformiato de (S)-tetrahidrofuran-3-ilo (7 µL, 0,045 mmol), seguido de trietilamina (13 µL, 0,090 mmol). Después de

retirar el baño de hielo, la reacción se agitó a temperatura ambiente durante 3 h. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,18 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

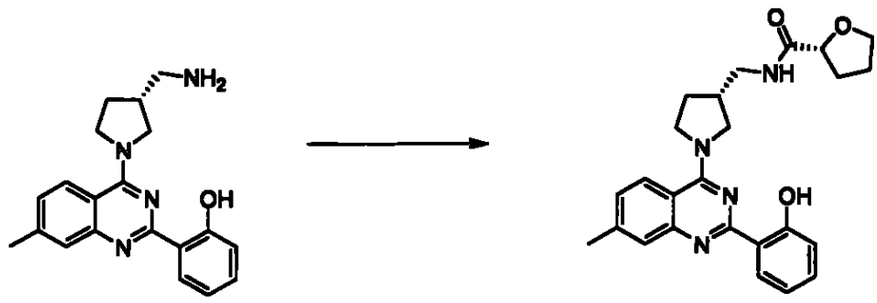
[001613] Ejemplo 308

[001614] **(2*R*)-tetrahidro-*N*-(((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metil)furan-2-carboxamida**

[001615]



[001616] **(2*R*)-tetrahidro-*N*-(((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metil)furan-2-carboxamida**



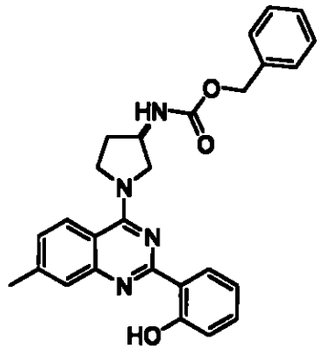
[001617]

[001618] A una solución de 2-(4-((*R*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (15 mg, 0,045 mmol) y DMF (0,5 ml) se añadió ácido (*R*)-tetrahidrofuran-2-carboxílico (6 µL, 0,062 mmol), seguido de la adición de HATU (26 mg, 67 mmol) y trietilamina (13 µL, 0,090 mmol). La reacción se agitó a temperatura ambiente durante 3 h. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio (2*R*)-tetrahidro-*N*-(((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metil)furan-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 433,5 $(M+H)^+$ a 2,11 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001619] Ejemplo 309

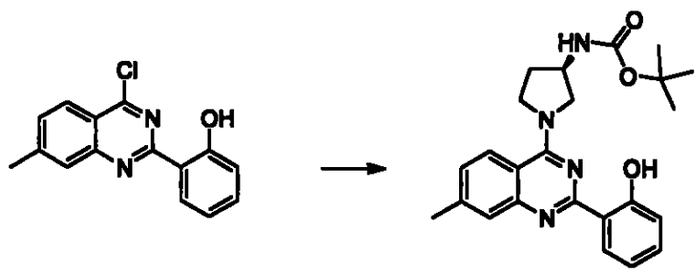
[001620] **Éster bencílico del ácido (*R*)-{1-[2-(2-Hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico**

[001621]



[001622] **Éster ter-butílico del ácido {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3R-il}-carbámico**

[001623]

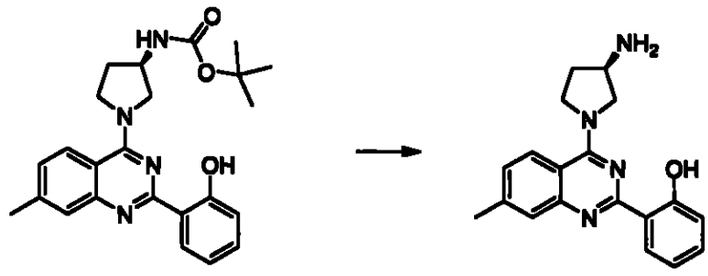


[001624] A una solución enfriada (-15 °C) de 2-(4-cloro-7-metilquinazolin-2-il)fenol (43,8 g, 0,15 mol) en CH_2Cl_2 (125 ml) se añadió gota a gota una solución de (3R)-(+)-3-(ter-butoxicarbonilamino)pirrolidina (30 g, 0,16 mol) y trietilamina (38 ml, 0,27 mol) en CH_2Cl_2 (170 ml). La adición, durante la cual la temperatura permaneció a menos de 30 °C, se completó en 20 minutos. Se retiró el enfriamiento externo y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Se agregaron agua (1 L) y CH_2Cl_2 (1 L). El precipitado

resultante se recogió por filtración, se lavó con agua y CH_2Cl_2 y se secó al aire para obtener 33 g de éster ter-butílico del ácido {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3*R*-il}-carbámico puro. Los filtrados se evaporaron para dar otro lote de éster ter-butílico del ácido {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3*R*-il}-carbámico crudo que se purificó por trituración con CH_2Cl_2. Rendimiento total: 43,5 g (70%). ^{1}H-RMN (300 MHz, $CDCl_3$): δ 8,45 (dd, *J* = 8 Hz, 1,7 Hz, 1H), 7,95 (d, *J* = 8,8 Hz, 1H), 7,57 (s, 1H), 7,37-7,31 (m, 1H), 7,18 (dd, *J* = 8,5 Hz, 1,7, 1H), 7,0 (dd, *J* = 8,3 Hz, 1,1 Hz, 1H), 6,9 (dt, *J* = 8,9 Hz, 1,4 Hz, 1H), 4,77 (bs, 1H), 4,40 (bs, 1H), 4,27-4,21 (m, 1H), 4,14-4,03 (m, 2H), 3,86 (dd, *J* = 11,8 Hz, 4,4 Hz, 1H), 2,50 (s, 3H), 2,34-2,28 (m, 1H), 2,08-2,02 (m, 1H), 1,46 (s, 9H) ppm.

[001625] 2-(4-(3R-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol

[001626]



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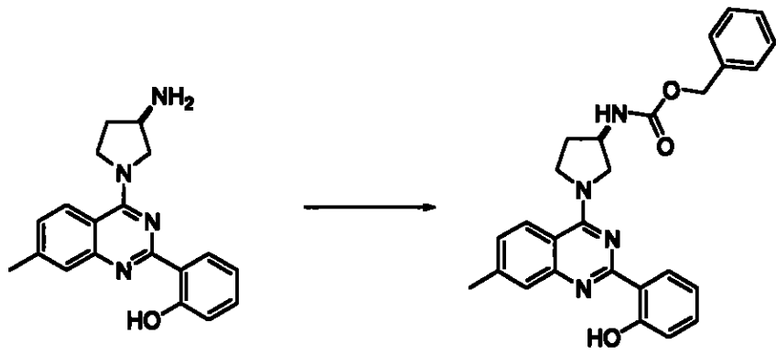
[001627] Éster ter-butílico del ácido (1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3*R*-il)-carbámico (43,5 g, 100 mmol) se agitó con CF_3CO_2H (142 ml) en CH_2Cl_2 (300 ml) a temperatura ambiente durante la noche. La solución se concentró hasta sequedad y el residuo se suspendió en Na_2CO_3 acuoso al 10% (900 ml) y se agitó durante 2 horas. La suspensión se filtró y el sólido amarillo se lavó con agua varias veces. El producto se secó al aire a 45 °C para obtener 2-(4-(3*R*-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (34,2 g) en forma de un sólido de color amarillo claro. ^{1}H-RMN (300 MHz, CD_3OD): δ 8,41 (dd, *J* = 7,4 Hz, 1,4 Hz, 1H), 8,09 (d, *J* = 8,5 Hz, 1H), 7,46 (s, 1H), 7,34-7,28 (m, 1H), 7,23 (dd, *J* = 8,8 Hz, 1,9 Hz, 1H), 6,91-6,85 (m, 2H), 4,16-4,09 (m, 2H), 4,00-3,94 (m, 1H), 3,73-3,64 (m, 2H), 2,48 (s, 3H), 2,26-2,20 (m, 1H), 1,92-1,86 (m, 1H) ppm.

[001628] Éster bencílico del ácido (*R*)-(1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il)-carbámico

[001629] Método A



[001630]

[001631] A (*R*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol (50,8 mg, 0,16 mmol) se añadieron 500 µL de CH_2Cl_2 y la solución se enfrió hasta 0 °C. A esta solución se añadieron secuencialmente trietilamina (33,2 µL, 0,24 mmol) y cloroformiato de bencilo (29,2 mg, 0,17 mmol). La mezcla de reacción se agitó de 0 °C a 5 °C durante 45 min, luego se diluyó con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar éster bencílico del ácido (*R*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico. LC/MS: *m/z* 455,2 $(M+H)^+$ a 2,81 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001632] Método B

[001633] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de bencílico**

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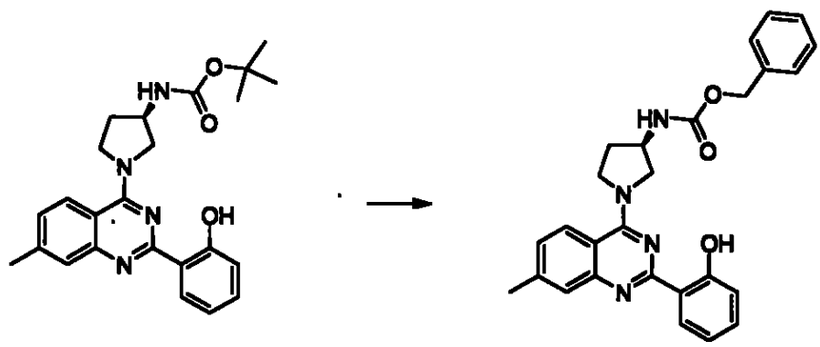

[001634]

[001635] A (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo (398 mg, 0,94 mmol) se añadieron 3 ml de 1:1 TFA: CH_2Cl_2. La mezcla se agitó luego a temperatura ambiente durante 30 minutos. La mezcla de reacción se diluyó con una solución saturada de $NaHCO_3$ y CH_2Cl_2. La capa orgánica se separó, se lavó con una solución de NaOH 1 N, se secó sobre Na_2SO_4 y se evaporó a presión reducida para dar la amina intermediaria. A esta amina (300 mg, 0,94 mmol) se añadieron 3 ml de CH_2Cl_2 y trietilamina (145 µL, 1,04 mmol). Tras enfriar la mezcla hasta 0 °C, se añadió cloroformiato de bencilo (161,6 mg, 0,94 mmol) y la reacción se agitó durante 30 minutos. La purificación por medio de cromatografía en gel de sílice usando 20-100% de acetato de etilo/hexanos dio (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de bencilo. LC/MS: *m/z* 455,2

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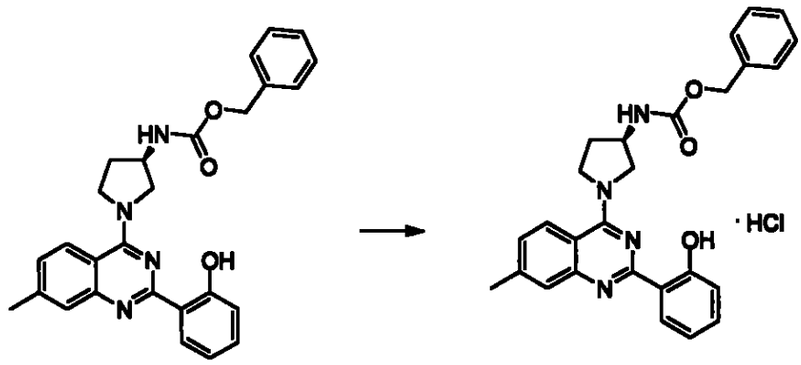
$(M+H)^+$ a 2,81 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001636] Clorhidrato de (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de bencilo

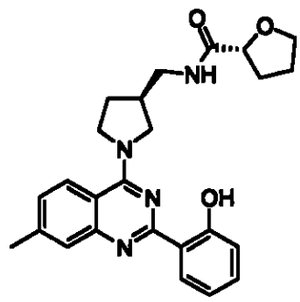


[001637]

[001638] A solución de HCl 2,0 M en Et_2O (318 µL, 0,636 mmol) se añadió lentamente a una solución agitada de (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de bencilo (289 mg, 0,636 mmol) en 2,1 ml de CH_2Cl_2. Los solventes se eliminaron a presión reducida y el residuo se trituró con Et_2O y se filtró para dar clorhidrato de (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de bencilo. LC/MS: *m/z* 455,2 $(M+H)^+$ a 2,80 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

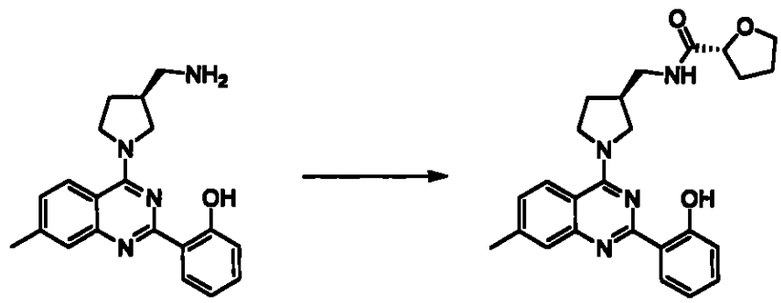
[001639] Ejemplo 310

[001640] **(2*R*)-tetrahidro-*N*-(((*S*)-1-(2-(2-hidroxifenil)-7-**



metilquinazolin-4-il)pirrolidin-3-il)metil)furan-2-carboxamida

[001641] **(2*R*)-tetrahidro-*N*-(((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metil)furan-2-carboxamida**



[001642]

[001643] A una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (25 mg, 0,075 mmol) y DMF (0,5 ml) se añadió ácido (*R*)-tetrahidrofuran-2-carboxílico (8,6 µL, 0,09 mmol), seguido de la adición de HATU (34 mg, 0,09 mmol) y trietilamina (21 µL, 0,15 mmol). La reacción se agitó a temperatura ambiente durante 3 h. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA))

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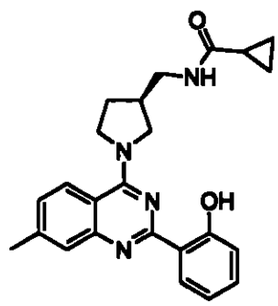
dio (2*R*)-tetrahidro-*N*-(((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metil)furan-2-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 433,5 $(M+H)^+$ a 2,13 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

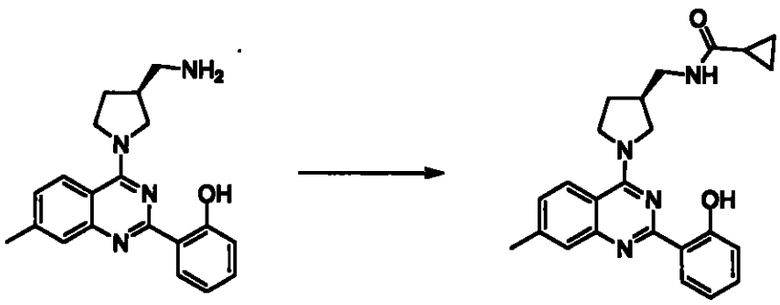
[001644] Ejemplo 311

[001645] **N-(((*S*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metil)ciclopropancarboxamida**



[001646]

[001647] **N-(((*S*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metil)ciclopropancarboxamida**

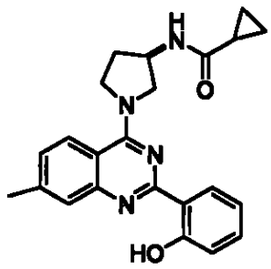


[001648] Una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (25 mg, 0,075 mmol) y CH_2Cl_2 (0,5 ml) se enfrió en un baño de hielo. A esta mezcla se

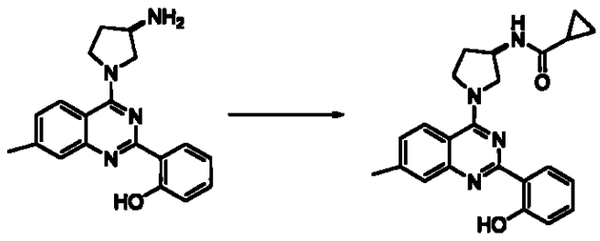
añadió cloruro de ciclopropancarbonilo (7,5 µL, 82 mmol), seguido de trietilamina (21 µL, 0,15 mmol). Después de retirar el baño de hielo, la reacción se agitó a temperatura ambiente durante 3 h. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio *N*-(((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metil)ciclopropancarboxamida en forma de la sal de TFA. LC/MS: *m/z* 403,7 $(M+H)^+$ a 2,17 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001649] Ejemplo 312

[001650] **{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R*)-ciclopropancarboxílico**



[001651] **{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R*)-ciclopropancarboxílico.**



[001652] A (*R*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol (49,3 mg, 0,15 mmol) se añadieron 500 µL de CH_2Cl_2 y la solución se enfrió hasta 0 °C. A esta solución se añadieron secuencialmente trietilamina (21,5 µL, 0,15 mmol) y cloruro de ciclopropancarbonilo (16,1 mg, 0,15 mmol). La mezcla de reacción se agitó de 0 °C a 5 °C durante 40 min y se diluyeron con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R*)-ciclopropancarboxílico en forma de la sal de TFA. LC/MS: *m/z* 389 $(M+H)^+$ a 2,38 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001653] Ejemplo 313

[001654] **Éster fenílico del ácido (*R*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico**

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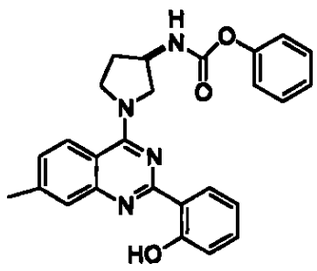
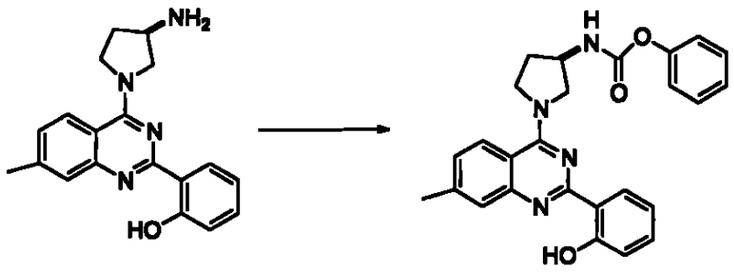
1079



[001655]

[001656] Éster fenílico del ácido (*R*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico



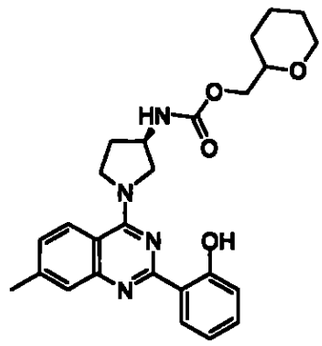
[001657]

[001658] A (*R*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol (48 mg, 0,15 mmol) se añadieron 500 µL de CH_2Cl_2 y la solución se enfrió hasta 0 °C. A esta solución se añadieron secuencialmente trietilamina (21 µL, 0,15 mmol) y cloroformiato de fenilo (22,8 mg, 0,15 mmol). La mezcla de reacción se agitó de 0 °C a 5 °C durante 40 min, se diluyó con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para

dar éster fenílico del ácido (*R*)-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-carbámico en forma de la sal de TFA. LC/MS: *m/z* 441 $(M+H)^+$ a 2,78 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001659] Ejemplo 314

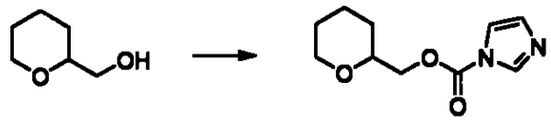
[001660] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (tetrahidro-2*H*-piran-2-il)metilo**



[001661]

[001662] **1*H*-imidazol-1-carboxilato de (tetrahidro-2*H*-piran-2-il)metilo**

[001663]



[001664] A una mezcla de (tetrahidro-2*H*-piran-2-il)metanol (369 mg, 3,17 mmol) y di(1*H*-imidazol-1-il)metanona (1,03 g, 6,35 mmol) se añadieron 10,5 ml de CH_2Cl_2. La reacción se agitó

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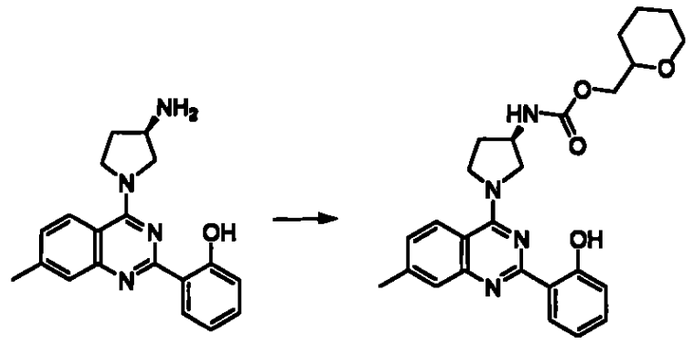
a 50 °C durante 3 horas. La mezcla de reacción se usó sin ulterior purificación. LC/MS: *m/z* 211,1 $(M+H)^+$ a 0,94 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

|001665| **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (tetrahidro-2H-piran-2-il)metilo**



|001666|

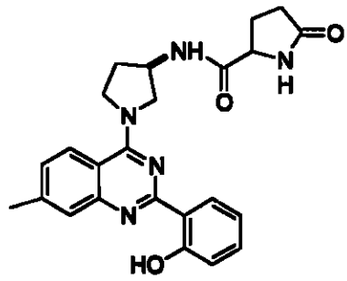
|001667| A una mezcla de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (100 mg, 0,31 mmol) y 1*H*-imidazol-1-carboxilato de (tetrahidro-2H-piran-2-il)metilo (98 mg, 0,47 mmol) se añadieron 1,04 ml de CH_2Cl_2 y trietilamina (65 µL, 47 mg, 0,46 mmol). La mezcla se agitó a temperatura ambiente durante la noche. Se añadió un equivalente adicional de 1*H*-imidazol-1-carboxilato de (tetrahidro-2H-piran-2-il)metilo (100 mg, 0,47 mmol) a la mezcla y la reacción se calentó a 45 °C durante 4 horas. La purificación por medio de cromatografía en gel de sílice usando 10%-100% de acetato de etilo/hexanos dio (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-

il)pirrolidin-3-ilcarbamato de (tetrahidro-2H-piran-2-il)metilo. LC/MS: *m/z* 463,4 $(M+H)^+$ a 2,66 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

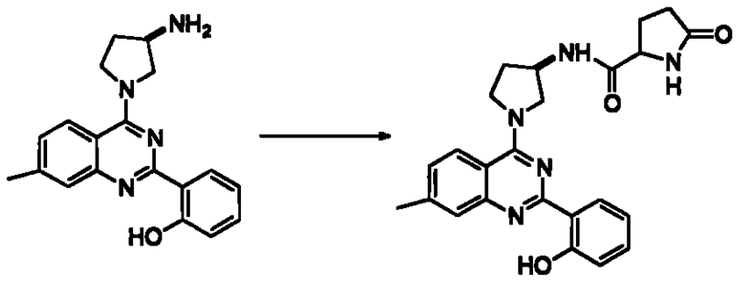
[001668] Ejemplo 315

[001669] **{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R*)-5-oxo-pirrolidin-2-carboxílico**

[001670]



[001671] **{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R*)-5-oxo-pirrolidin-2-carboxílico**



[001672]

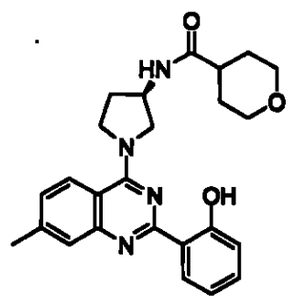
[001673] A (*R*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol (71 mg, 0,22 mmol) se añadieron 890 µL

de CH_2Cl_2. A esta solución se añadieron secuencialmente trietilamina (47 µL, 0,34 mmol) y ácido 5-oxo-pirrolidin-2-carboxílico (34,8 mg, 0,27 mmol) y BOP (119 mg, 0,27 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se diluyó con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida para dar {1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-amida del ácido (*R*)-5-oxo-pirrolidin-2-carboxílico. LC/MS: *m/z* 432,5 $(M+H)^+$ a 2,24 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

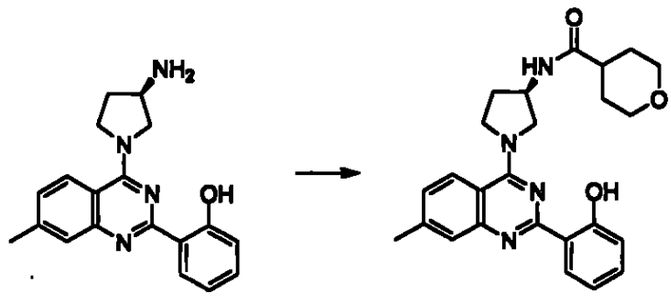
[001674] Ejemplo 316

[001675] **Tetrahidro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2*H*-piran-4-carboxamida**

[001676]



[001677] **Tetrahidro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2*H*-piran-4-carboxamida**

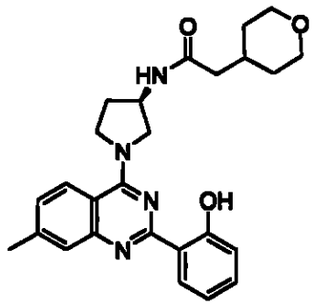


[001678]

[001679] A una solución agitada de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) en 1 ml de DMF se enfrió hasta 0 °C y se añadió ácido tetrahidro-2*H*-piran-4-carboxílico (24 mg, 0,19 mmol), seguido de la adición de trietilamina (32 mg, 44 µL, 0,31 mmol) y HATU (71,1 mg, 0,187 mmol). La reacción se agitó a 0 °C durante 10 minutos, luego se calentó gradualmente hasta temperatura ambiente, luego se filtró. La purificación mediante HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio tetrahidro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2*H*-piran-4-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 433,5 $(M+H)^+$ a 2,05 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

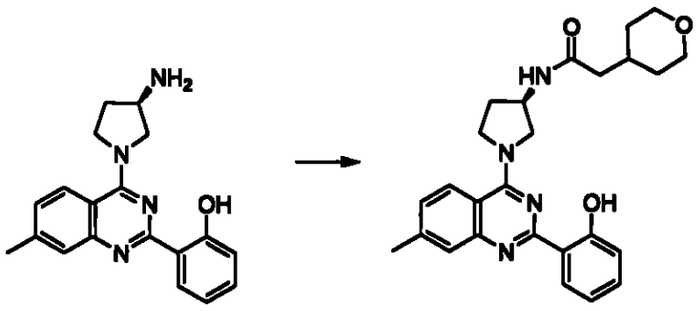
[001680] Ejemplo 317

[001681] **2-(tetrahidro-2*H*-piran-4-il)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)acetamida**



[001682]

[001683] **2-(tetrahidro-2*H*-piran-4-il)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)acetamida**



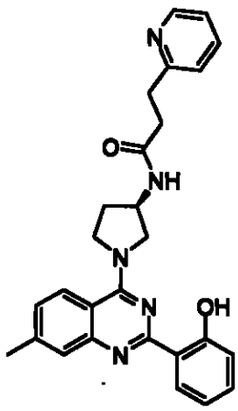
[001684]

[001685] A una solución agitada de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) en 1 ml de DMF enfriada hasta 0 °C se añadió ácido 2-(tetrahidro-2*H*-piran-4-il)acético (27 mg, 0,19 mmol), seguido de la adición de trietilamina (32 mg, 44 µL, 0,31 mmol) y HATU (71,1 mg, 0,187 mmol). La reacción se agitó a 0 °C durante 10 minutos, luego se calentó gradualmente hasta temperatura ambiente. Se filtró y se purificó por HPLC en fase

inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 2-(tetrahidro-2*H*-piran-4-il)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)acetamida en forma de la sal de TFA. LC/MS: *m/z* 477,3 $(M+H)^+$ a 2,07 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

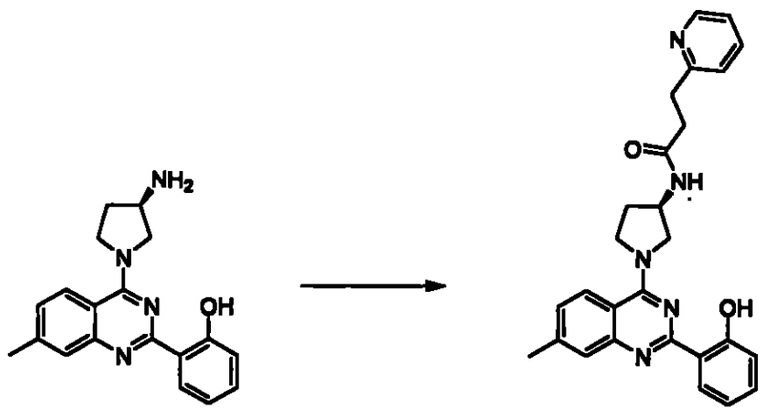
[001686] Ejemplo 318

[001687] ***N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(piridin-2-il)propanamida**



[001688]

[001689] ***N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(piridin-2-il)propanamida**

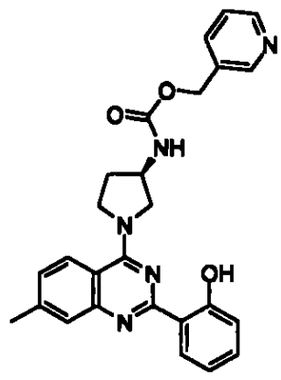


[001690]

[001691] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (0,05 g, 0,15 mmol) en DMF (1 ml) se añadió ácido 3-(piridin-2-il)propanoico (30 mg, 0,195 mmol), seguido de la adición de trietilamina (42 µL, 0,30 mmol) y HATU (74 mg, 0,195 mmol). La reacción se agitó a temperatura ambiente durante 2 h y luego se purificó mediante HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(piridin-2-il)propanamida en forma de la sal de TFA. LC/MS: *m/z* 454,3 $(M+H)^+$ a 1,79 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

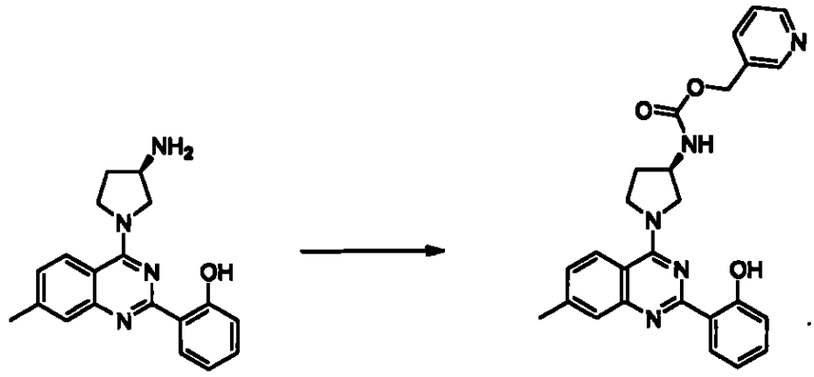
[001692] Ejemplo 319

[001693] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (piridin-3-il)metilo**



[001694]

[001695] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (piridin-3-il)metilo**



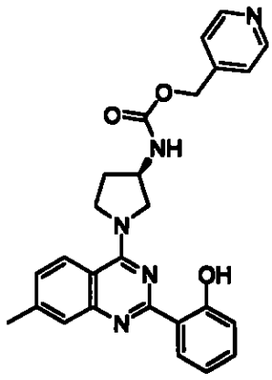
[001696]

[001697] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) en DMSO (0,5 ml) a temperatura ambiente se añadió trietilamina (43 µL, 0,31 mmol), seguido de la adición de 1*H*-imidazol-1-carboxilato de (piridin-3-il)metilo (63 mg, 0,31 mmol). La reacción se agitó a temperatura ambiente durante la noche, se filtró y se

purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (piridin-3-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 456,5 $(M+H)^+$ a 1,85 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

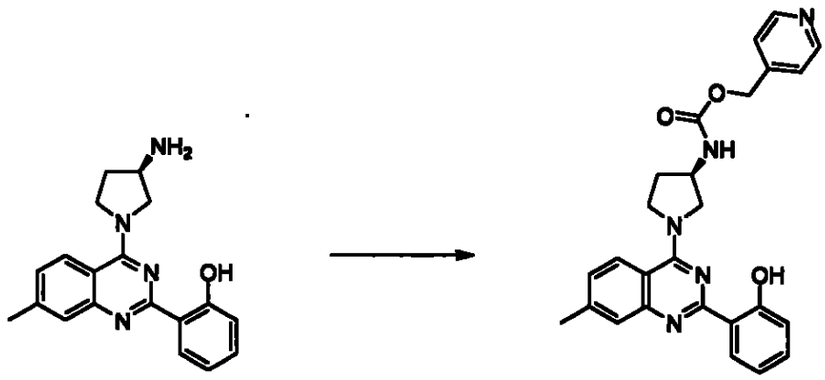
[001698] Ejemplo 320

[001699] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (piridin-4-il)metilo**



[001700]

[001701] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (piridin-4-il)metilo**

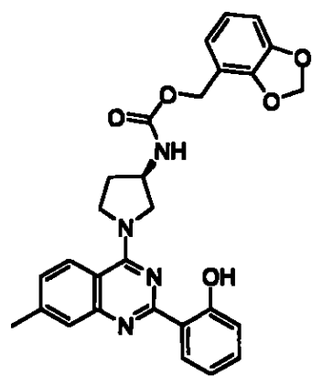


[001702]

[001703] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) en DMSO (0,5 ml) a temperatura ambiente se añadió trietilamina (43 µL, 0,31 mmol), seguido de la adición de 1*H*-imidazol-1-carboxilato de (piridin-4-il)metilo (63 mg, 0,31 mmol). La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (piridin-4-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 456,5 $(M+H)^+$ a 1,84 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

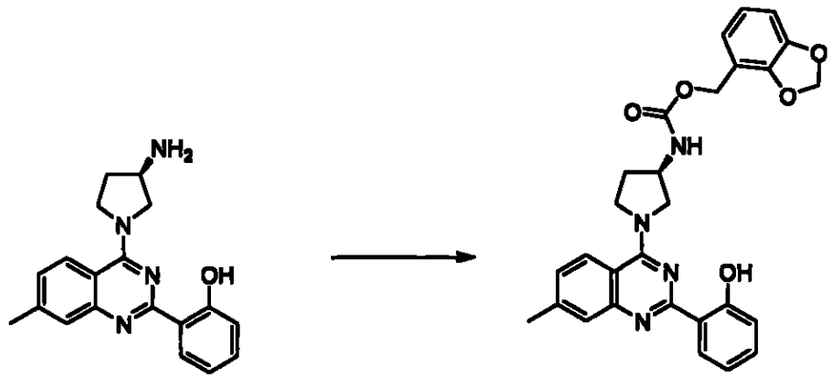
[001704] Ejemplo 321

[001705] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (benzo[d][1,3]dioxol-7-il)metilo**



[001706]

[001707] **(*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (benzo[d][1,3]dioxol-7-il)metilo**



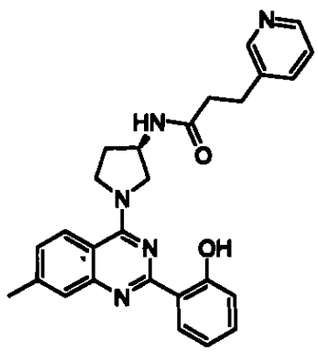
[001708]

[001709] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) en DMSO (0,5 ml) se añadió trietilamina (43 µl, 0,31 mmol), seguido de la adición de 1H-imidazol-1-carboxilato de (benzo[d][1,3]dioxol-4-il)metilo (77 mg, 0,31 mmol). La reacción se agitó a

temperatura ambiente durante la noche, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (benzo[d][1,3]dioxol-7-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 499,3 $(M+H)^+$ a 2,57 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

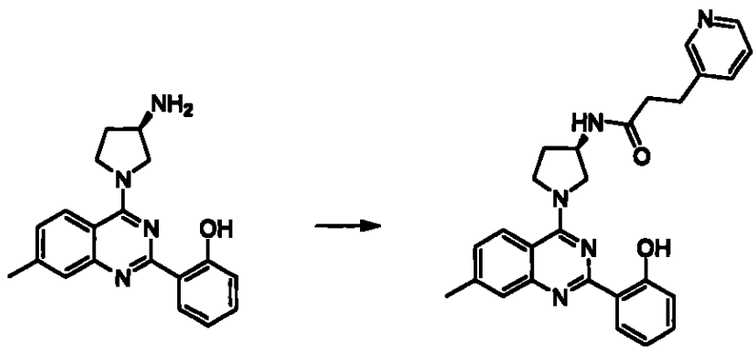
[001710] Ejemplo 322

[001711] **N-((R)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(piridin-3-il)propanamida**



[001712]

[001713] **N-((R)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(piridin-3-il)propanamida**



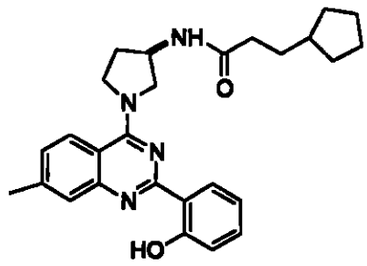
[001714]

[001715] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (249 mg, 0,778 mmol) se disolvió en 2,6 ml de CH_2Cl_2. Se añadió ácido 3-(piridin-3-il)propanoico (129 mg, 0,85 mmol) seguido de trietilamina (102 mg, 141 µL, 1,01 mmol) y BOP (378 mg, 0,85 mmol). Tras agitar la reacción durante 35 minutos a temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar *N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(piridin-3-il)propanamida en forma de la sal de TFA. LC/MS: *m/z* 454,4 $(M+H)^+$ a 2,08 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

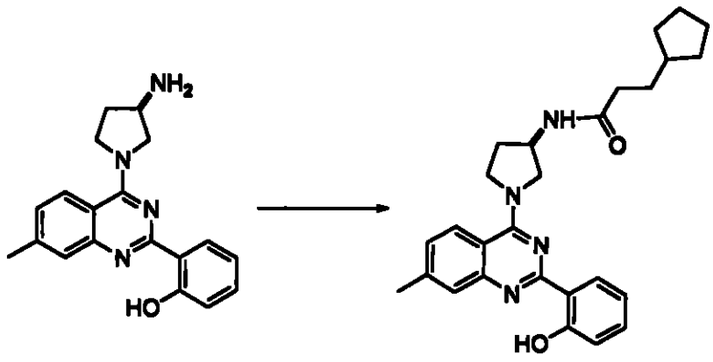
[001716] Ejemplo 323

[001717] **(*R*)-3-Ciclopentil-N-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-propionamida**

[001718]



[001719] **(*R*)-3-Ciclopentil-N-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-propionamida**



[001720]

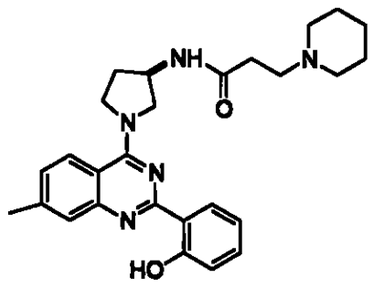
[001721] A (*R*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol (100 mg, 0,31 mmol) se añadió 1 ml de CH_2Cl_2 y la solución se enfrió hasta 0 °C. A esta solución se añadieron secuencialmente trietilamina (56,6 µL, 0,41 mmol) y cloruro de 3-ciclopentil-propionilo (57 mg, 0,35 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, luego se diluyó con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa

en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar ((*R*)-3-ciclopentil-*N*-{1-[2-(2-hidroxi-fenil)-7-metil-quinazolin-4-il]-pirrolidin-3-il}-propionamida en forma de la sal de TFA. LC/MS: *m/z* 445,4 $(M+H)^+$ a 2,85 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

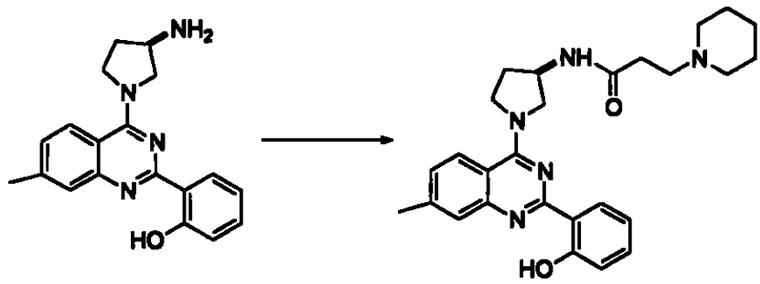
[001722] Ejemplo 324

[001723] **(*R*)-N-{1-[2-(2-Hidroxi-fenil)-quinazolin-4-il]-pirrolidin-3-il}-3-piperidin-1-il-propionamida**

[001724]



[001725] **(*R*)-N-{1-[2-(2-Hidroxi-fenil)-quinazolin-4-il]-pirrolidin-3-il}-3-piperidin-1-il-propionamida**



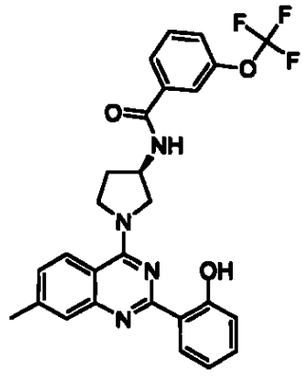
[001726]

[001727] A (*R*)-2-[4-(3-amino-pirrolidin-1-il)-7-metil-quinazolin-2-il]-fenol (58,6 mg, 0,18 mmol) se añadieron 700

µL de CH_2Cl_2. A esta solución se añadieron secuencialmente trietilamina (38,3 µL, 0,27 mmol), ácido 3-piperidin-1-il-propiónico (37,4 mg, 0,24 mmol) y BOP (119 mg, 0,27 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se diluyó con agua y CH_2Cl_2 (10 ml). La capa orgánica se separó y se secó sobre Na_2SO_4 y el solvente se eliminó a presión reducida. El residuo se purificó por HPLC preparativa en fase inversa usando 10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA) para dar (*R*)-*N*-{1-[2-(2-hidroxi-fenil)-quinazolin-4-il]-pirrolidin-3-il}-3-piperidin-1-il-propionamida en forma de la sal de TFA. LC/MS: *m/z* 460,4 $(M+H)^+$ a 2,1 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001728] Ejemplo 325

[001729] ***N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(trifluorometoxi)benzamida**



[001730]

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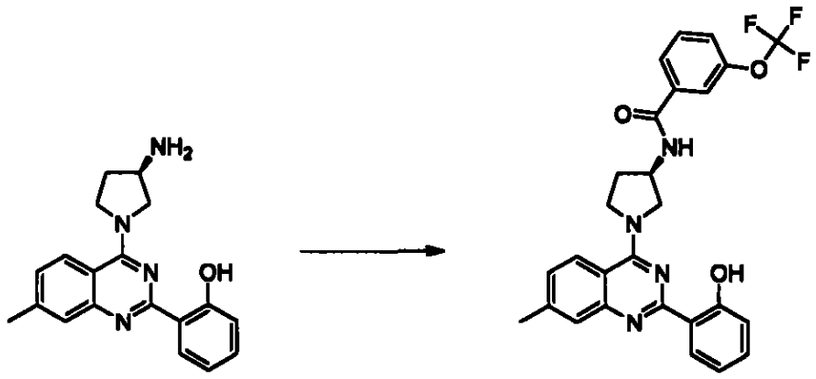
[001731] **N-((R)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(trifluorometoxi)benzamida**



[001732]

[001733] A una solución agitada de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (32 mg, 0,10 mmol) y DMF (1,0 ml) se añadió cloruro de 3-(trifluorometoxi)benzoílo (19 µL, 0,10 mmol), seguido de la adición de trietilamina (28 µL, 0,2 mmol). La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar *N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-(trifluorometoxi)benzamida en forma de la sal de TFA. LC/MS: *m/z* 509,5 $(M+H)^+$ a 2,71 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001734] Ejemplo 326

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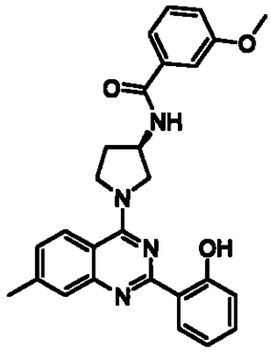
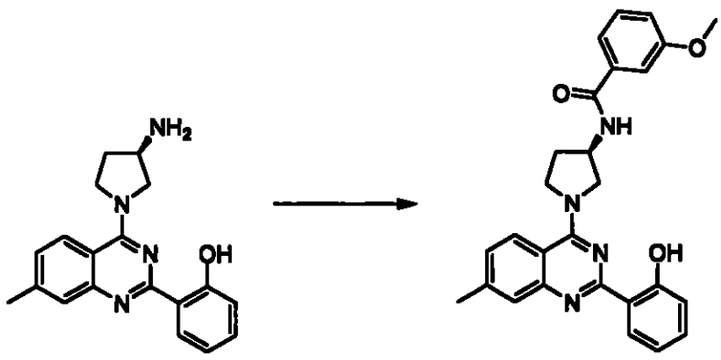
[001735] **N-((R)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-metoxibenzamida**



[001736]

[001737] **N-((R)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-metoxibenzamida**



[001738]

[001739] A una solución agitada de 2-(4-((R)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (32 mg, 0,10 mmol) y DMF (1,0 ml) se añadió cloruro de 3-metoxibenzoílo (14 µL, 0,1 mmol), seguido de la adición de trietilamina (28 µL, 0,2 mmol). La reacción se agitó a

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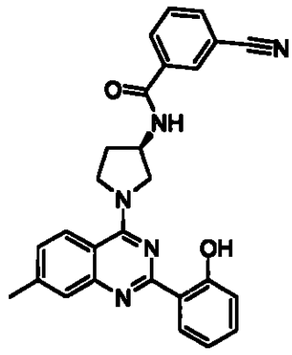
temperatura ambiente durante la noche, luego se filtró y se purificó por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar *N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-3-metoxibenzamida en forma de la sal de TFA. LC/MS: *m/z* 455,3 $(M+H)^+$ a 2,43 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

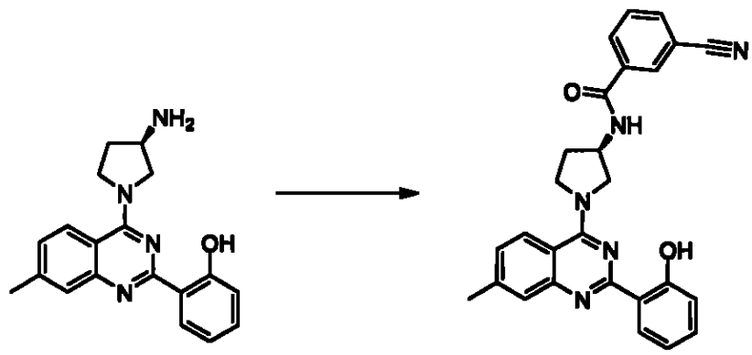
[001740] Ejemplo 327

[001741] **3-Ciano-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



[001742]

[001743] **3-Ciano-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



[001744]

[001745] A una solución agitada de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (32 mg, 0,10 mmol) y DMF (1,0 ml) se añadió cloruro de 3-cianobenzoílo (17 mg, 0,10 mmol), seguido de la adición de trietilamina (28 µL, 0,20 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se filtró y se purificó por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 3-ciano-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 450,3 $(M+H)^+$ a 2,39 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001746] Ejemplo 328

[001747] ***N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)nicotinamida**

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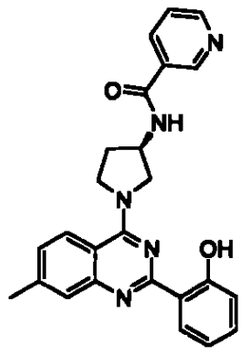
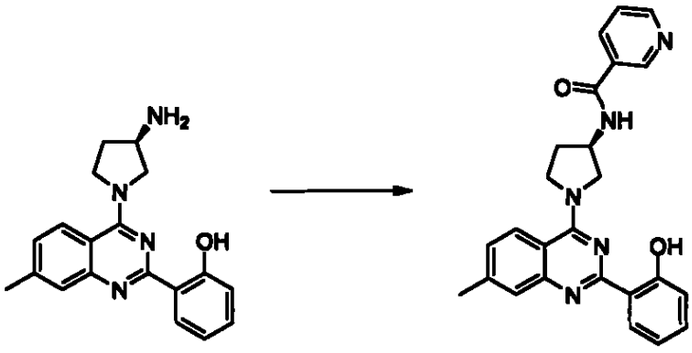


[001748]

[001749] ***N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)nicotinamida**



[001750]

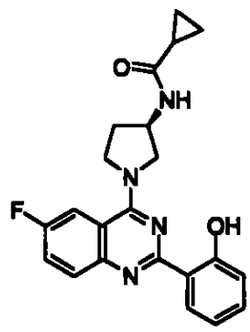
[001751] A una solución agitada de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (32 mg, 0,1 mmol) y DMF (1,0 ml) se añadió cloruro de nicotinoílo (18 mg, 0,1 mmol), seguido de la adición de trietilamina (28 µL, 0,2 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se filtró y se purificó por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de

TFA)) para dar *N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)nicotinamida en forma de la sal de TFA. LC/MS: *m/z* 426,3 $(M+H)^+$ a 1,91 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001752] Ejemplo 329

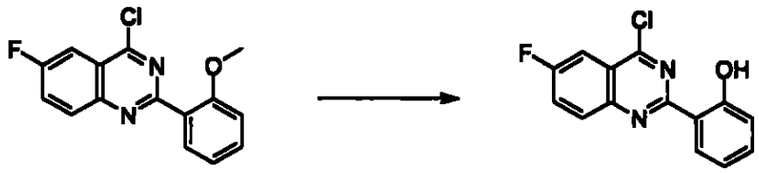
[001753] **N-((R)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida**

[001754]



[001755] Método A

[001756] **2-(4-cloro-6-fluoroquinazolin-2-il)fenol**



[001757]

[001758] Una solución de 4-cloro-6-fluoro-2-(2-metoxifenil)quinazolina (3,0 g, 10,39 mmol) en CH_2Cl_2 (15 ml) se enfrió hasta -78 °C. Se añadió una solución 1,0 M de BBr_3 en CH_2Cl_2 (52 ml, 52 mmol) gota a gota. La reacción se dejó

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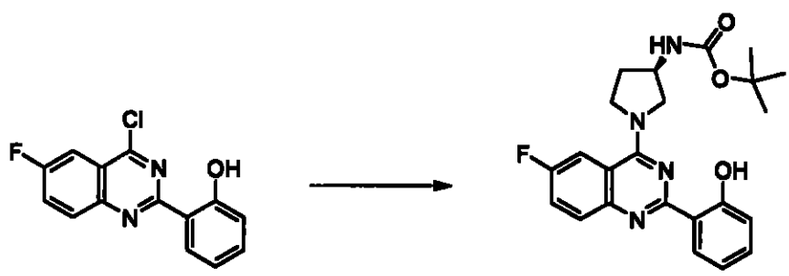
calentar hasta temperatura ambiente. Se neutralizó con una solución acuosa saturada de $NaHCO_3$ y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 5-20% de CH_2Cl_2/hexanos dio 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (1,68 g, 60%). LC/MS: *m/z* 275,3 $(M+H)^+$ a 3,39 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001759] (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo

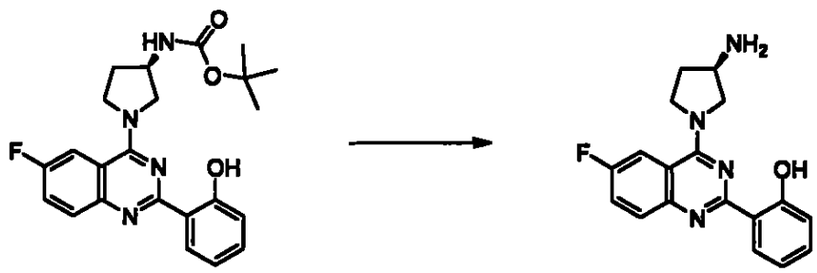
[001760]



[001761] A 0 °C bajo una atmósfera de N_2, una solución de (*R*)-pirrolidin-3-ilcarbamato de *ter*-butilo (264 mg, 1,42 mmol) y trietilamina (0,33 ml, 2,36 mmol) en CH_2Cl_2 se añadió rápidamente a una solución agitada de 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (325 mg, 1,18 mmol) en 15 ml de CH_2Cl_2. La mezcla de reacción se agitó durante 1 h antes de neutralizar con agua y la capa acuosa se extrajo dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por

medio de cromatografía en gel de sílice usando 0-10% de EtOAc/CH_2Cl_2 dio como resultado (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo. LC/MS: *m/z* 425,5 $(M+H)^+$ a 2,74 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001762] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol

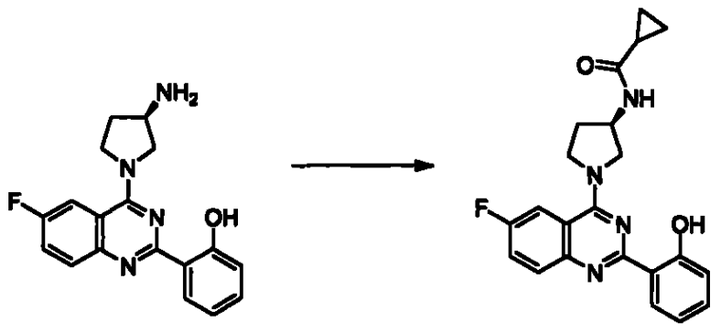


[001763]

[001764] A una solución de *ter*-butilo (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo (480 mg, 1,11 mmol) en CH_2Cl_2 (10 ml) se añadió TFA (4 ml). La reacción se agitó durante una hora, se diluyó con 10 ml de CH_2Cl_2 y se neutralizó con una solución acuosa saturada de $NaHCO_3$. La capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 3-20% de EtOAc/CH_2Cl_2 dio 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol. LC/MS:

m/z 325,5 $(M+H)^+$ a 1,26 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001765] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida**



[001766]

[001767] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,025 g, 0,08 mmol) en DMF (1,0 ml) se añadió ciclopropancarboxílico (10 mg, 0,12 mmol), seguido de la adición de trietilamina (22 µL, 0,16 mmol) y HATU (40 mg, 0,1 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida en forma de la sal de TFA. LC/MS: *m/z* 393,3 $(M+H)^+$ a 2,23 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001768] Método B

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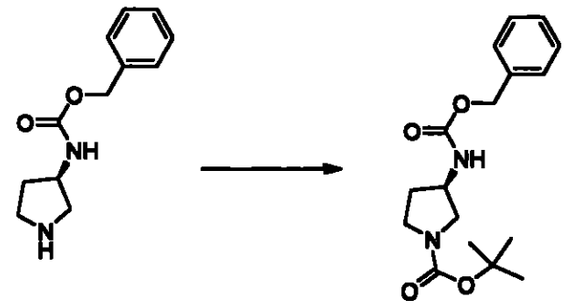
[001769] **(*R*)-1-(ter-butoxicarbonil)pirrolidin-3-ilcarbamato**

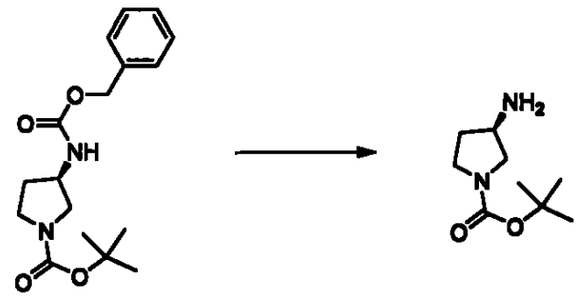


de bencilo

[001770]

[001771] A -10 °C, trietilamina (2,3 ml, 16,6 mmol) se añadió a una solución de bencil (*R*)-pirrolidin-3-ilcarbamato de oxalato (2,0 g, 6,4 mmol) en MeOH, seguido de la adición lenta de Boc_2O (1,92 ml, 8,3 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante la noche. La mezcla se neutralizó con agua y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc en CH_2Cl_2 dio (*R*)-1-(ter-butoxicarbonil)pirrolidin-3-ilcarbamato de bencilo (1,85 g, 90%). LC/MS: *m/z* 321,3 $(M+H)^+$ a 3,01 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

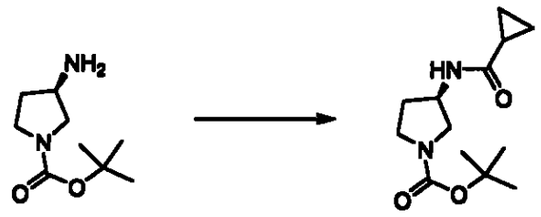
[001772] **3-aminopirrolidin-1-carboxilato de (*R*)-ter-butilo**



[001773]

[001774] En una atmósfera de N_2, una solución de (*R*)-1-(*ter*-butoxicarbonil)pirrolidin-3-ilcarbamato de bencilo (1,85 g, 5,75 mmol) en 10 ml de MeOH se añadió a un recipiente que contiene Pd/C (185 mg, 10% en peso de Pd sobre carbón). Después de evacuar el recipiente al vacío y purgarlo dos veces con N_2, la reacción se agitó durante 3 h bajo una atmósfera de H_2 a presión ambiente. La reacción se filtró a través de un lecho de Celite y el solvente se evaporó a presión reducida para obtener 3-aminopirrolidin-1-carboxilato de (*R*)-*ter*-butilo que se usó sin ulterior purificación. LC/MS: m/z 187,3 $(M+H)^+$ a 1,07 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

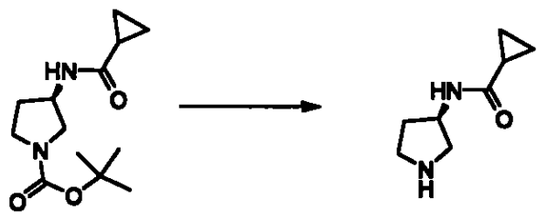
[001775] **3-(ciclopropanocarboxamido)pirrolidin-1-carboxilato de (*R*)-*ter*-butilo**



[001776]

[001777] A una mezcla de 3-aminopirrolidin-1-carboxilato de (*R*)-*ter*-butilo (500 mg, 2,68 mmol) en CH_2Cl_2 (10 ml) se añadió ciclopropancarboxílico (276 µL, 3,48 mmol), seguido de la adición de HATU (1,3 g, 3,48 mmol) y trietilamina (725 µL, 5,2 mmol). La reacción se completó después de agitar durante 1 h. Después de neutralizar con agua, la capa acuosa se extrajo dos veces con CH_2Cl_2 y los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en gel de sílice 0-20% de EtOAc/CH_2Cl_2 para obtener 3-(ciclopropanecarboxamido)pirrolidin-1-carboxilato de (*R*)-*ter*-butilo (500 mg, 73%). LC/MS: *m/z* 255,3 $(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001778] ***N*-((*R*)-Pirrolidin-3-il)ciclopropancarboxamida**



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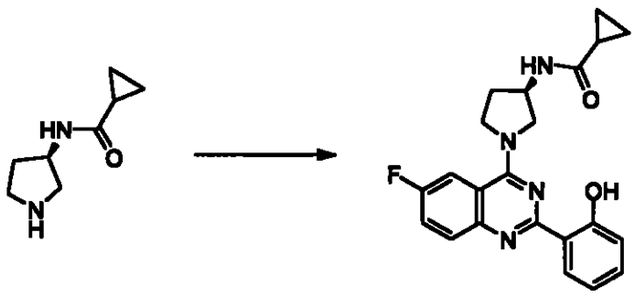
[001779]

[001780] Se añadió TFA (1 ml) a una solución de 3-(ciclopropanecarboxamido)pirrolidin-1-carboxilato de (*R*)-*ter*-butilo (500 mg, 1,96 mmol) en 5 ml de CH_2Cl_2. Tras agitar durante 30 min, la reacción se neutralizó con una solución 1 M de NaOH hasta neutralidad y se extrajo dos veces con EtOAc. Los extractos orgánicos se combinaron, se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener *N*-((*R*)-pirrolidin-3-il)ciclopropancarboxamida (250 mg) que se usó sin ulterior purificación. LC/MS: *m/z* 155,3 $(M+H)^+$ a 0,6 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001781] **N-((R)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida**



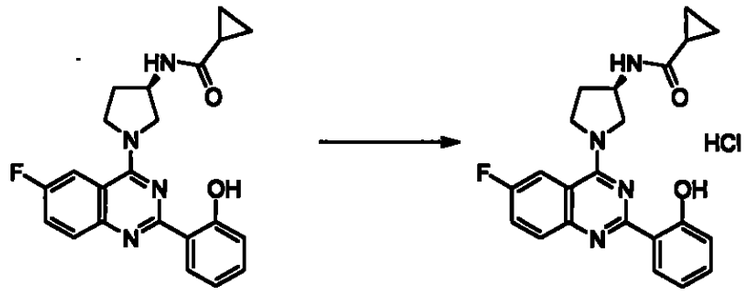
[001782]

[001783] Una mezcla de *N*-((*R*)-pirrolidin-3-il)ciclopropancarboxamida (250 mg, 0,86 mmol), 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (250 mg, 0,86 mmol) y trietilamina (0,240 ml, 1,72 mmol) en CH_2Cl_2 (10 ml) se agitó a temperatura

ambiente. La reacción se completó después de una hora. La reacción se neutralizó con agua, la capa acuosa se extrajo dos veces con CH_2Cl_2 y los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc/CH_2Cl_2 dio *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida (230 mg, 68%). LC/MS: *m/z* 393,3 $(M+H)^+$ a 2,35 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,42-8,46 (m, 2H), 8,03 (dd, *J* = 10,5, 2,6 Hz, 1H), 7,88-7,92 (m, 1H), 7,74-7,79 (m, 1H), 7,35-7,39 (m, 1H), 6,92-6,96 (m, 2H), 4,44-4,47 (m, 1H), 4,01-4,28 (m, 3H), 3,83-3,87 (m, 1H), 2,20-2,28 (m, 1H), 1,99-2,06 (m, 1H), 1,51-1,57 (m, 1H), 0,63-0,73 (m, 4H).

[001784] Clorhidrato de *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida

[001785]

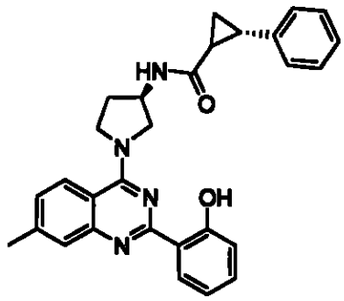


[001786] A una solución de *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-

il)ciclopropancarboxamida (225 mg, 0,57 mmol) en 5 ml de CH_2Cl_2 se añadió una solución 2 M de HCl en éter (0,28 ml, 0,57 mmol), que dio como resultado la precipitación de un sólido. Después de la adición de 20 ml de éter, la mezcla de reacción se agitó durante 1 h. Los solventes se evaporaron a presión reducida para obtener clorhidrato de *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida (225 mg, 91%). LC/MS: *m/z* 393,3 $(M+H)^+$ a 2,43 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,23 (d, *J* = 8,3 Hz, 1H), 8,04 (d, *J* = 10,6 Hz, 1H), 7,91-7,94 (m, 1H), 7,79-7,83 (m, 1H), 7,44-7,48 (m, 1H), 7,00-7,03 (m, 2H), 4,44 (t, *J* = 4,9 Hz, 1H), 4,09-4,23 (m, 3H), 3,87-3,90 (m, 1H), 2,25-2,34 (m, 1H), 2,02-2,09 (m, 1H), 1,49-1,55 (m, 1H), 0,68-0,71 (m, 4H).

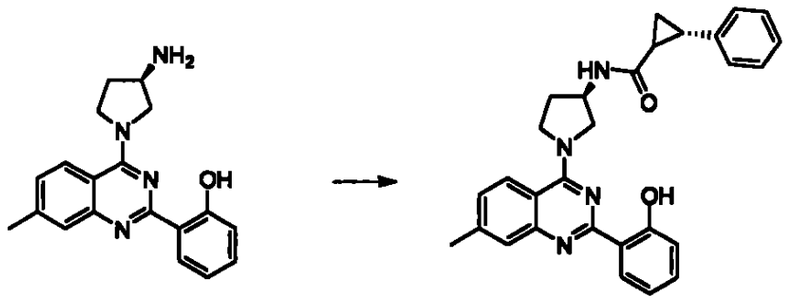
[001787] Ejemplo 330

[001788] **(2*S*)-*N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2-fenilciclopropancarboxamida**



[001789]

[001790] **(2*S*)-*N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2-fenilciclopropancarboxamida**



[001791]

[001792] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,15 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió cloruro de (2*R*)-2-fenilciclopropancarbonilo (31 mg, 0,17 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro se añadió gota a gota a la mezcla seguido de trietilamina (21 mg, 28 µL, 0,20 mmol). La reacción se agitó durante 20 minutos a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar (2*S*)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2-fenilciclopropancarboxamida en forma de la sal de TFA. LC/MS (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)), LC/MS: *m/z* 465,4 $(M+H)^+$ a 2,88 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001793] Ejemplo 331

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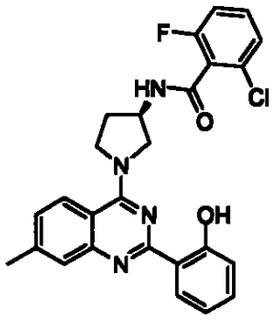
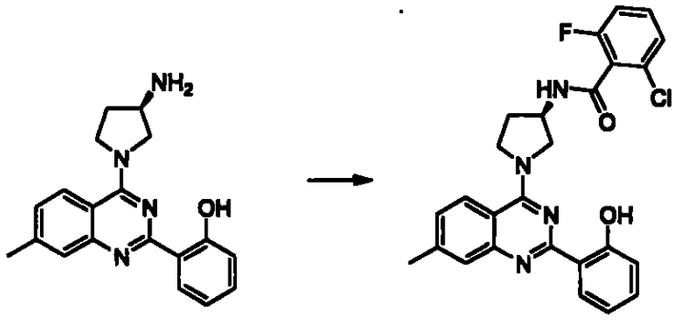
[001794] **2-cloro-6-fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



[001795]

[001796] **2-cloro-6-fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



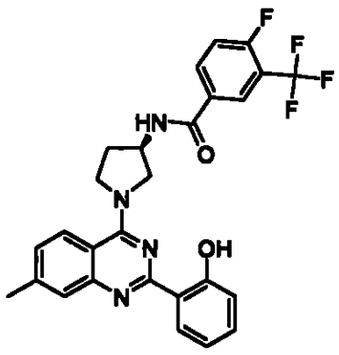
[001797]

[001798] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió cloruro de 2-cloro-6-fluorobenzoílo (36 mg, 0,18 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro se añadió gota a gota a la mezcla seguido de trietilamina (21 mg, 28 µL, 0,20 mmol). La reacción se agitó

durante 20 minutos a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 2-cloro-6-fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 477,3 $(M+H)^+$ a 2,81 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001799] Ejemplo 332

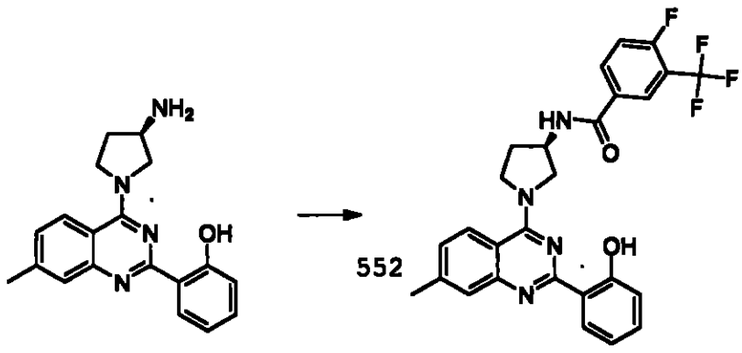
[001800] **4-Fluoro-3-(trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



[001801]

[001802] **4-Fluoro-3-(trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

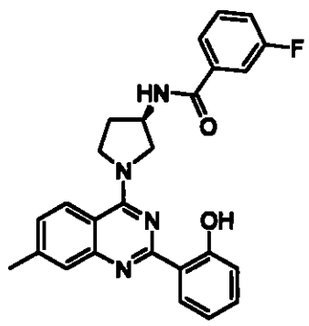
[001803]



[001804] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió cloruro de 4-fluoro-3-(trifluorometil)benzoílo (42 mg, 0,18 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro se añadió gota a gota a la mezcla seguido de trietilamina (21 mg, 28 µL, 0,20 mmol). La reacción se agitó durante 20 minutos a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 4-fluoro-3-(trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 511,5 $(M+H)^+$ a 3,07 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

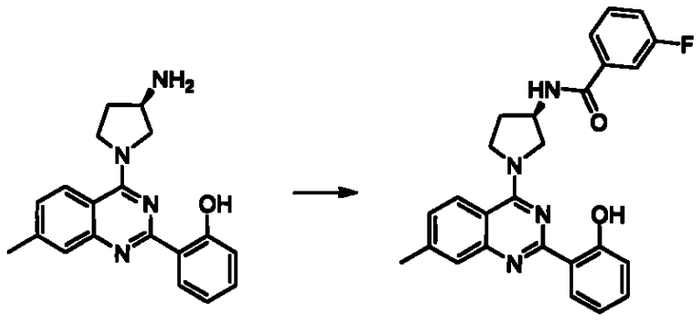
[001805] Ejemplo 333

[001806] **3-Fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



[001807]

[001808] **3-Fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



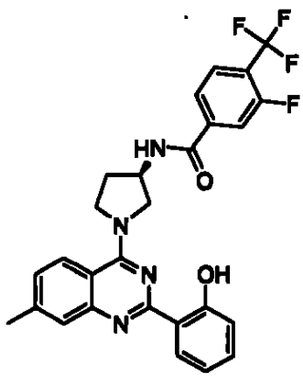
[001809]

[001810] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió cloruro de 3-fluorobenzoílo (30 mg, 0,18 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro gota a gota a la mezcla seguido de trietilamina (21 mg, 28 µL, 0,20 mmol). La reacción se agitó durante 20 minutos a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 3-fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 443,5 $(M+H)^+$ a 2,83 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001811] Ejemplo 334

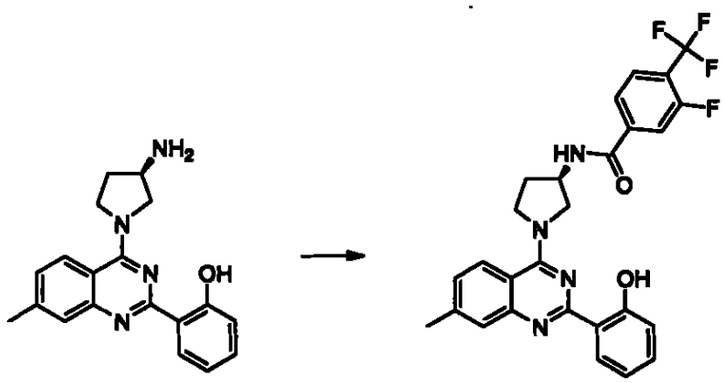
[001812] **3-Fluoro-4-(trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

[001813]



[001814] **3-Fluoro-4-(trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

[001815]

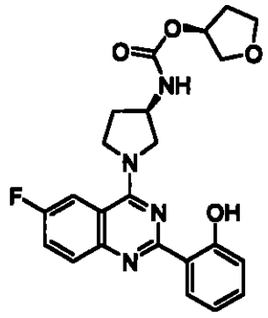


[001816] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió cloruro de 3-fluoro-4-(trifluorometil)benzoilo (42 mg, 0,18 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro gota a gota a la mezcla seguido de trietilamina (21 mg, 28 µL, 0,20 mmol). La reacción se agitó durante 20 minutos a 0 °C y se purificó por HPLC en fase

inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 3-fluoro-4-(trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 511,5 $(M+H)^+$ a 3,1 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

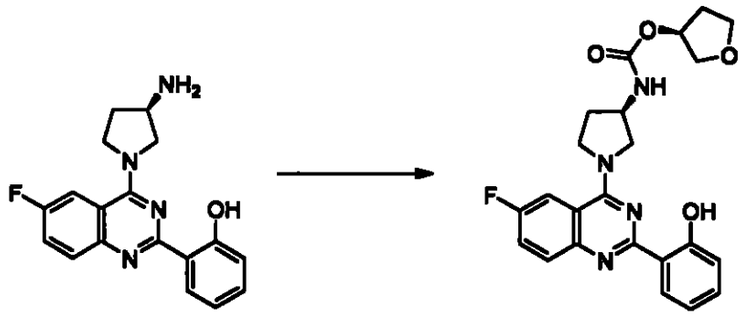
[001817] Ejemplo 335

[001818] **(*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo**



[001819]

[001820] **(*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo**

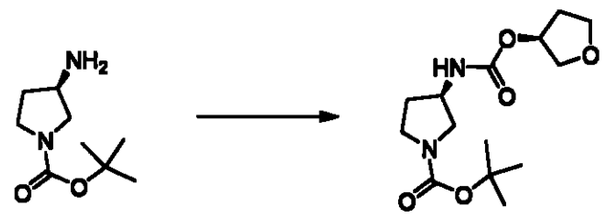


[001821]

[001822] Una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,092 mmol) en DMF (1,0 ml) se enfrió hasta -40 °C. A esta mezcla se añadió trietilamina (26 µL, 0,184 mmol), seguido de la adición de cloroformiato de (S)-tetrahidrofuran-3-ilo (0,014 g, 0,092 mmol). Después de dejar calentar la reacción hasta temperatura ambiente la mezcla se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,25 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001823] Método B

[001824] **(*R*)-1-(ter-butoxicarbonil)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo**



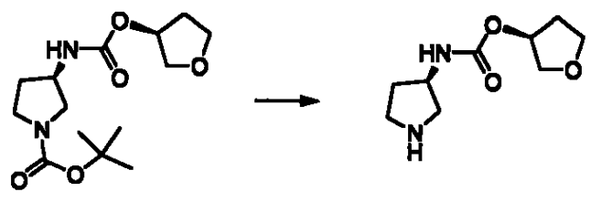
[001825]

[001826] A una solución de 3-aminopirrolidin-1-carboxilato de (*R*)-ter-butilo (500 mg, 2,6 mmol) en 5 ml de CH_2Cl_2 se añadió trietilamina (0,73 ml, 5,2 mmol) y la reacción se enfrió hasta

1120

-20 °C. Se añadió cloroformiato de (S)-tetrahidrofuran-3-ilo (525 mg, 3,48 mmol) en porciones durante un período de 10 minutos a la mezcla de reacción anterior. Después de dejar calentar la reacción hasta temperatura ambiente, se neutralizó con agua y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener (*R*)-1-(*ter*-butoxicarbonil)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo. La purificación por medio de cromatografía en gel de sílice usando 0-20% de EtOAc en CH_2Cl_2 dio (*R*)-1-(*ter*-butoxicarbonil)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (490 mg, 63%). LC/MS: *m/z* 301,3 $(M+H)^+$ a 2,35 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001827] (R)-pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo

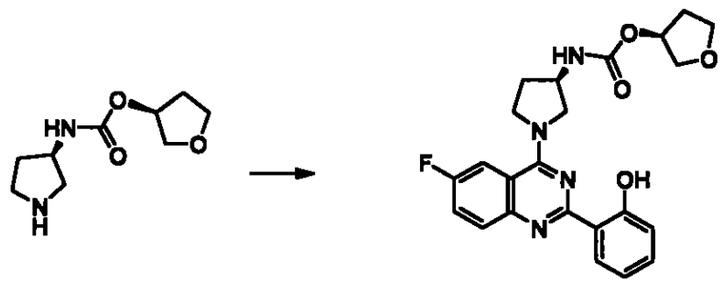


[001828]

[001829] Se añadió TFA (1 ml) a una solución de (*R*)-1-(*ter*-butoxicarbonil)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (490 mg, 1,63 mmol) en 5 ml de CH_2Cl_2. Tras agitar durante 30 min, la reacción se neutralizó con NaOH

y se extrajo dos veces con EtOAc. Los extractos orgánicos se combinaron, se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener (*R*)-pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (230 mg) que se usó sin ulterior purificación. LC/MS: *m/z* 201,3 $(M+H)^+$ a 0,59 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001830] (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo

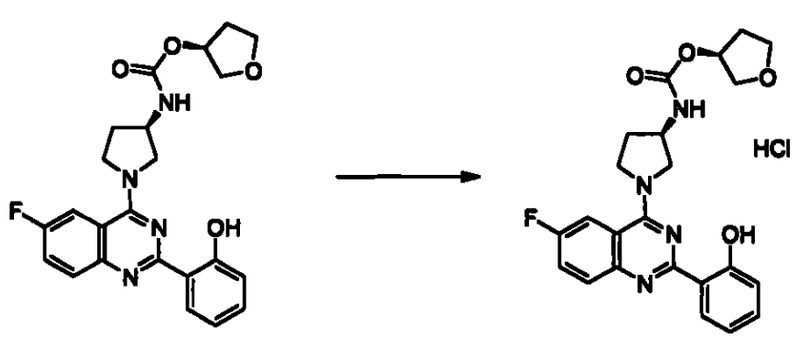


[001831]

[001832] Una mezcla de (*R*)-pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (225 mg, 1,12 mmol), 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (250 mg, 0,86 mmol) y trietilamina (0,240 ml, 1,72 mmol) en CH_2Cl_2 (10 ml) se agitó a temperatura ambiente. La reacción se completó en una hora. La reacción se neutralizó con agua, la capa acuosa se extrajo dos veces con CH_2Cl_2 y los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc/CH_2Cl_2 dio (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-

4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (250 mg, 66%). LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,40 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,43 (dd, *J* = 7,8, 1,5 Hz, 1H), 7,99 (d, *J* = 2,6 Hz, 1H), 7,87-7,91 (m, 1H), 7,74-7,79 (m, 1H), 7,70 (d, *J* = 6,2 Hz, 1H), 7,35-7,39 (m, 1H), 6,91-6,96 (m, 2H), 5,15 (s, 1H), 4,21-4,25 (m, 2H), 4,12-4,14 (m, 1H), 4,01-4,06 (m, 1H), 3,87-3,89 (m, 1H), 3,65-3,78 (m, 4H), 2,02-2,26 (m, 3H), 1,82-1,89 (m, 1H).

[001833] Clorhidrato de (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo



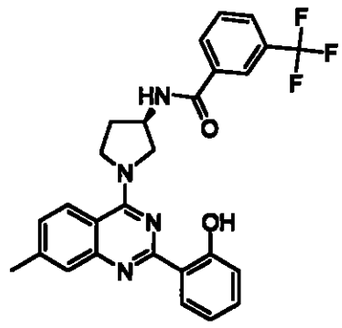
[001834]

[001835] A una mezcla de (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (250 mg, 0,57 mmol) y CH_2Cl_2 (25 ml) se añadió una solución de HCl 2,0 M en éter (0,285 ml, 0,57 mmol). Después de la adición de éter (40 ml), la reacción se

agitó durante 1 h. El sólido resultante se filtró y se secó para obtener clorhidrato de (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,25 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,18 (dd, *J* = 8,1, 1,4 Hz, 1H), 8,00 (d, *J* = 9,6 Hz, 1H), 7,90-7,94 (m, 1H), 7,78-7,83 (m, 1H), 7,45-7,49 (m, 1H), 7,00-7,03 (m, 2H), 5,10 (s, 1H), 4,09-4,25 (m, 4H), 3,90-3,92 (m, 1H), 3,62-3,75 (m, 4H), 2,22-2,27 (m, 1H), 2,03-2,14 (m, 2H), 1,83-1,91 (m, 1H).

[001836] Ejemplo 336

[001837] **3-(Trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



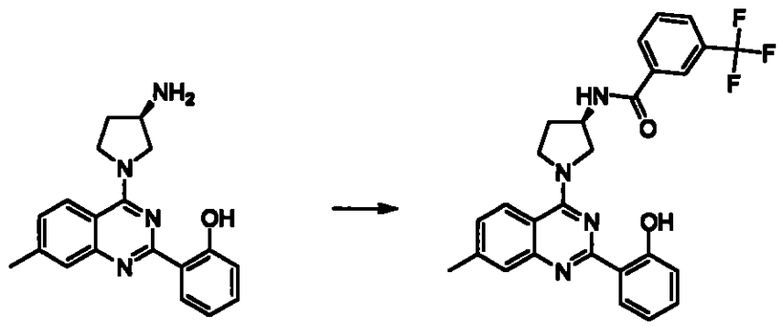
[001838]

[001839] **3-(Trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

1119

1124

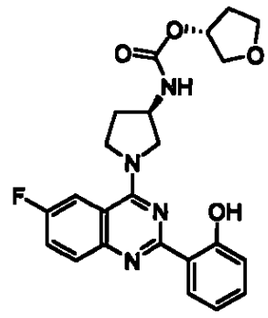
[001840]



[001841] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (130 mg, 0,406 mmol) se disolvió en 0,7 ml de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió cloruro de 3-(trifluorometil)benzoílo (42 mg, 0,18 mmol) disuelto en 0,7 ml de CH_2Cl_2 anhidro gota a gota a la mezcla seguido de trietilamina (53 mg, 74 µL, 0,52 mmol). La reacción se agitó durante 20 minutos a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 3-(trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 493,5 $(M+H)^+$ a 3,03 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

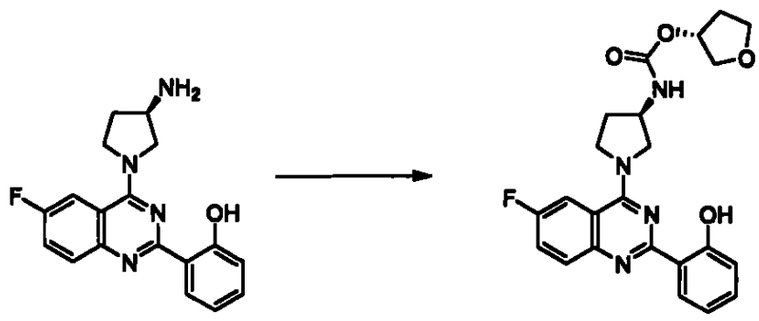
[001842] Ejemplo 337

[001843] **(*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo**



[001844]

[001845] **(*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo**



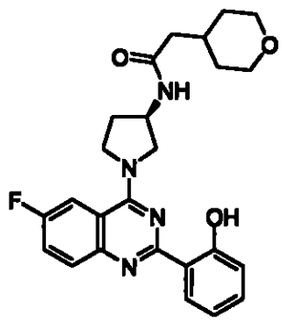
[001846]

A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,092 mmol) en DMF (1,0 ml) se enfrió hasta -40 °C, se añadió trietilamina (26 µL, 0,184 mmol), seguido de la adición de cloroformiato de (R)-tetrahidrofuran-3-ilo (0,014 g, 0,092 mmol). Después de calentar hasta temperatura ambiente, la mezcla se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*R*)-1-(6-fluoro-2-(2-

hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,25 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001847] Ejemplo 338

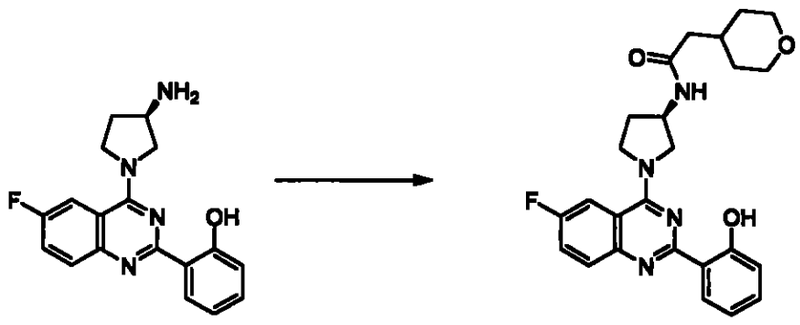
[001848] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)-2-(tetrahidro-2*H*-piran-4-il)acetamida**



[001849]

[001850] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)-2-(tetrahidro-2*H*-piran-4-il)acetamida**

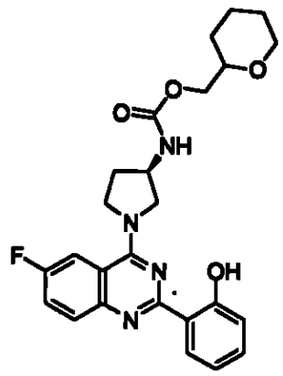
[001851]



A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,092 mmol) en DMF (1,0 ml) se añadió ácido 2-(tetrahidro-2*H*-piran-4-il)acético (0,017 g, 0,12 mmol), seguido de la adición de trietilamina (25,6 µL, 0,184 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)-2-(tetrahidro-2*H*-piran-4-il)acetamida en forma de la sal de TFA. LC/MS: *m/z* 451,5 $(M+H)^+$ a 2,15 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001852] Ejemplo 339

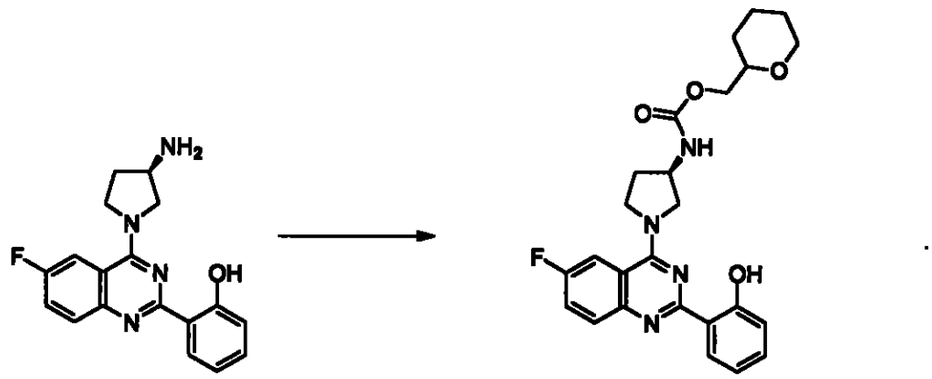
[001853] **(*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (tetrahidro-2*H*-piran-2-il)metilo**



[001854]

[001855] **(*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (tetrahidro-2H-piran-2-il)metilo**

[001856]

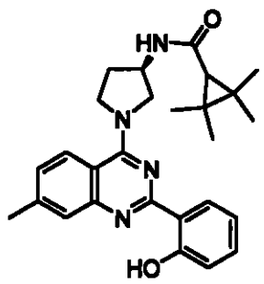


[001857] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) en DMSO (0,5 ml) a temperatura ambiente se añadió trietilamina (43 µL, 0,31 mmol), seguido de la adición de 1*H*-imidazol-1-carboxilato de (tetrahidro-2H-piran-2-il)metilo (39 mg, 0,13 mmol). La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-ilcarbamato de (tetrahidro-2H-piran-2-il)metilo en forma de la sal de TFA. LC/MS: *m/z* 467,3 $(M+H)^+$ a 3,13 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

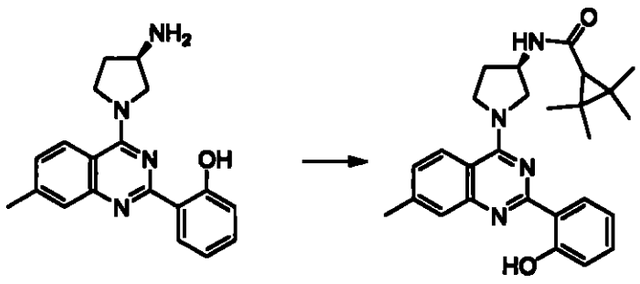
[001858] Ejemplo 340

[001859] **N-((R)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2,2,3,3-tetrametilciclopropancarboxamida**

[001860]



[001861] **N-((R)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2,2,3,3-tetrametilciclopropancarboxamida**



[001862]

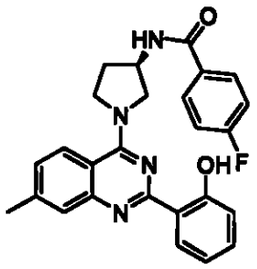
[001863] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,156 mmol) se disolvió en 0,52 ml de CH_2Cl_2 anhidro. Se añadió ácido 2,2,3,3-tetrametilciclopropancarboxílico (26,63 mg, 0,18 mmol), seguido de trietilamina (22,14 mg, 30,49 µL, 0,22 mmol) y BOP (82,93 mg, 0,18 mmol). Tras agitar la mezcla durante 30 minutos a temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O

(0,05% de TFA)) para dar *N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2,2,3,3-tetrametilciclopropancarboxamida en forma de la sal de TFA. LC/MS: *m/z* 445,4 $(M+H)^+$ a 2,95 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001864] Ejemplo 341

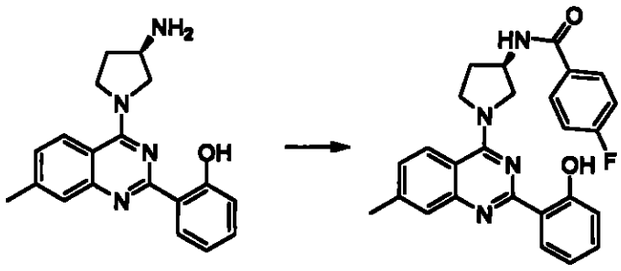
[001865] **4-Fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

[001866]



[001867] **4-Fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

[001868]

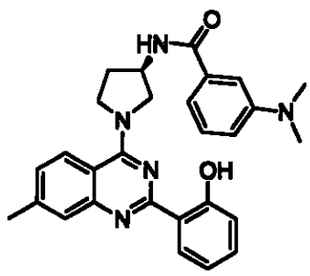


[001869] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se agregó cloruro de 4-

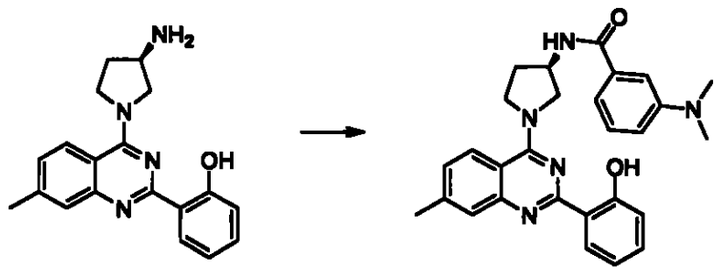
fluorobenzoilo (25 mg, 0,15 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro gota a gota a la mezcla seguido de trietilamina (19 mg, 26 µL, 0,18 mmol). La reacción se agitó durante 15 minutos a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 4-fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 443,4 $(M+H)^+$ a 2,73 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001870] Ejemplo 342

[001871] **3-(Dimetilamino)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

[001872] 

[001873] **3-(Dimetilamino)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

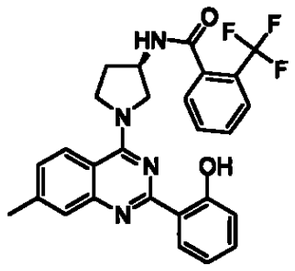


[001874]

[001875] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió clorhidrato de cloruro de 3-(dimetilamino)benzoílo (34 mg, 0,15 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro gota a gota a la mezcla seguido de trietilamina (32 mg, 44 µL, 0,31 mmol). La reacción se agitó durante 1,5 hora a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 3-(dimetilamino)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 468,4 $(M+H)^+$ a 2,39 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001876] Ejemplo 343

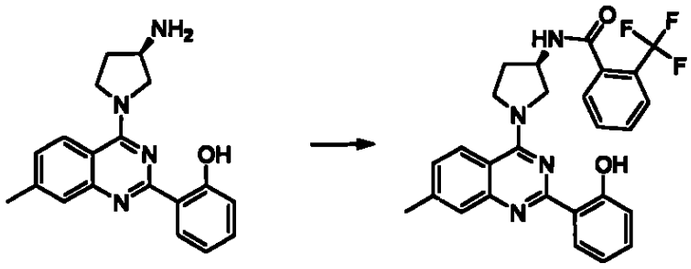
[001877] **2-(Trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**



[001878]

[001879] **2-(Trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

[001880]

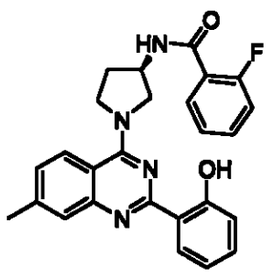


[001881] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió cloruro de 2-(trifluorometil)benzoílo (39 mg, 0,18 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro gota a gota a la mezcla seguido de trietilamina (21 mg, 28 µL, 0,20 mmol). La reacción se agitó durante 20 minutos a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 2-(trifluorometil)-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la

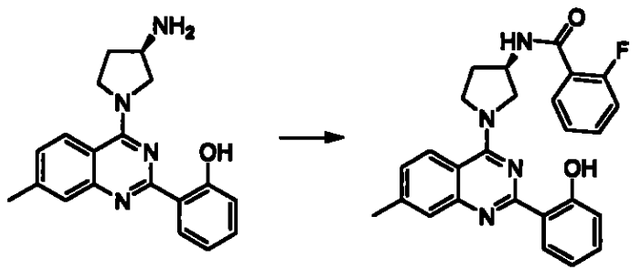
sal de TFA. LC/MS: *m/z* 493,4 $(M+H)^+$ a 2,76 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001882] Ejemplo 344

[001883] **2-Fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

[001884] 

[001885] **2-Fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida**

[001886] 

[001887] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50,6 mg, 0,158 mmol) se disolvió en 260 µL de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. Se añadió cloruro de 2-fluorobenzoílo (27 mg, 0,17 mmol) disuelto en 260 µL de CH_2Cl_2 anhidro gota a gota a la mezcla seguido de trietilamina (21 mg, 28 µL, 0,20 mmol). La reacción se agitó durante 15 minutos

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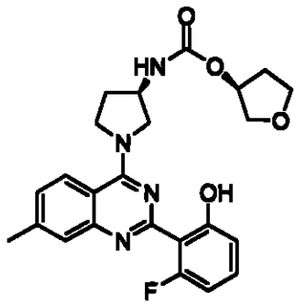
a 0 °C y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 2-fluoro-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)benzamida en forma de la sal de TFA. LC/MS: *m/z* 443,4 $(M+H)^+$ a 2,69 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001888] Ejemplo 345

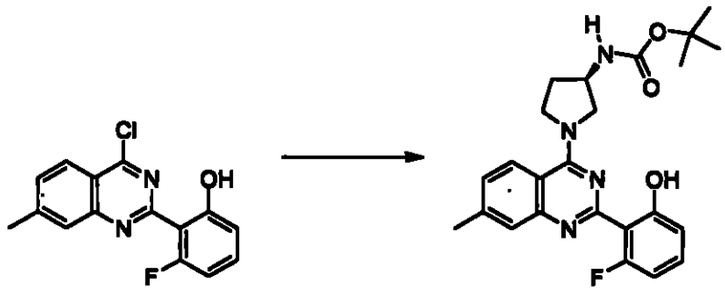


[001889] **(*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo**

[001890]

[001891] **(*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo**

[001892]



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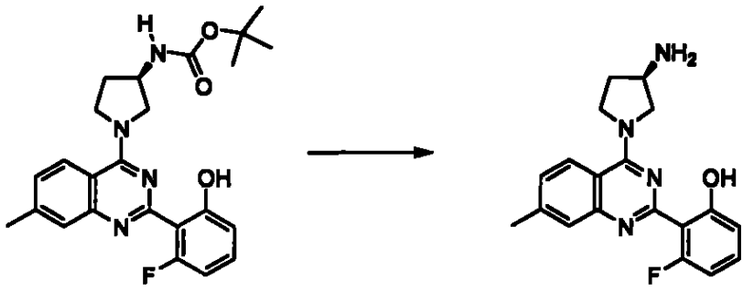
[001893] Una solución de (*R*)-pirrolidin-3-ilcarbamato de *ter*-butilo (368 mg, 1,97 mmol) y trietilamina (0,46 ml, 3,28 mmol) en CH_2Cl_2 se añadió rápidamente a una solución agitada de 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (475 mg, 1,65 mmol) en 15 ml de CH_2Cl_2 a 0 °C bajo una atmósfera de N_2. La reacción se agitó durante 1 h antes de neutralizar con agua y la capa acuosa se extrajo dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-10% de EtOAc/CH_2Cl_2 dio como resultado (*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,42 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001894] 2-(4-((*R*)-3-Aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol



[001895]

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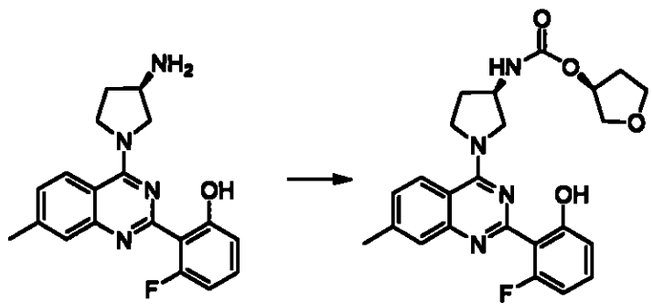
[001896] A una solución de (*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo (500 mg, 1,14 mmol) en CH_2Cl_2 (15 ml) se añadió TFA (5 ml). La mezcla se agitó durante 1 h y luego se neutralizó con una solución 1 M de NaOH y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 3-20% de EtOAc/CH_2Cl_2 dio 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol. LC/MS: *m/z* 339,5 $(M+H)^+$ a 0,56 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001897] (*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (*S*)-tetrahidrofuran-3-ilo



[001898]

[001899] Método A

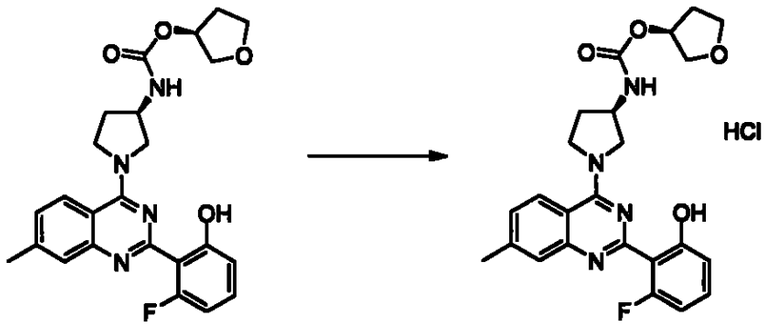
[001900] A una solución agitada de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (40 mg, 0,12 mmol) en 800 µL de DMF anhidra enfriada hasta 0 °C se añadió cloroformiato de (S)-tetrahidrofuran-3-ilo (20 mg, 19 µL, 0,13 mmol) gota a gota, seguido de la adición de trietilamina (24 mg, 33 µL, 0,23 mmol). La reacción se calentó hasta temperatura ambiente y se agitó durante la noche y el producto se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar (*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 453,3 $(M+H)^+$ a 2,05 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001901] Método B

[001902] A temperatura ambiente, se añadió *N*-etil-*N*-isopropilpropan-2-amina (155 ml, 0,88 mmol) a una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (150 mg, 0,40 mmol) en THF. La mezcla se enfrió en un baño de hielo y se agregó lentamente cloroformiato de (S)-tetrahidrofuran-3-ilo (63 mg, 0,42 mmol) durante un período de 10 minutos. Después de calentar hasta temperatura ambiente, la reacción se neutralizó con agua y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de

cromatografía en gel de sílice usando 0-10% de EtOAc en CH_2Cl_2/hexanos (1:1) dio (*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (160 mg, 84%). LC/MS: *m/z* 453,3 $(M+H)^+$ a 2,12 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,18 (d, *J* = 8,6 Hz, 1H), 7,70 (d, *J* = 6,3 Hz, 1H), 7,58 (s, 1H), 7,29-7,38 (m, 2H), 6,76 (d, *J* = 8,3 Hz, 1H), 6,67-6,72 (m, 1H), 5,14 (s, 1H), 4,23-4,24 (m, 1H), 3,99-4,13 (m, 3H), 3,64-3,85 (m, 5H), 2,50 (s, 3H), 2,07-2,22 (m, 2H), 2,00-2,03 (m, 1H), 1,85-1,90 (m, 1H).

[001903] Clorhidrato de (*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo



[001904]

[001905] A una solución de (*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (160 mg, 0,35 mmol) en 2 ml de CH_2Cl_2 se añadió solución 2 M de HCl en éter (0,176 ml, 0,35

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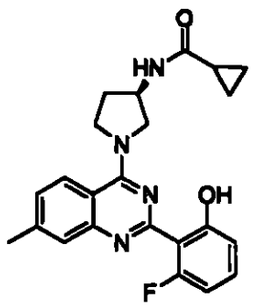
mmol) dando como resultado la precipitación de un sólido. Después de la adición de 10 ml de éter, la reacción se agitó durante 30 minutos, se filtró y el sólido resultante se secó para obtener clorhidrato de (*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de (S)-tetrahidrofuran-3-ilo (130 mg, 76%). LC/MS: *m/z* 453,3 $(M+H)^+$ a 2,13 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,29 (s, 1H), 7,57 (s, 2H), 7,43-7,49 (m, 1H), 6,83-6,89 (m, 2H), 5,08 (s, 1H), 4,23-4,42 (m, 4H), 3,62-3,73 (m, 5H), 2,24-2,34 (m, 1H), 2,04-2,11 (m, 2H), 1,86-1,92 (m, 1H).

[001906] Ejemplo 346

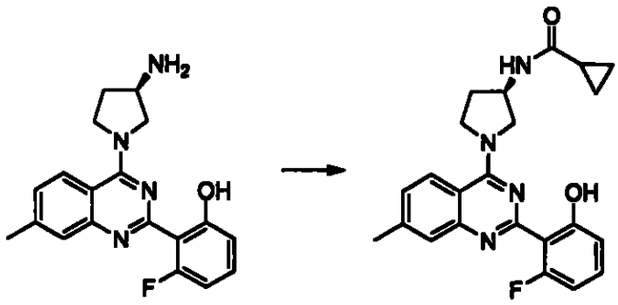
[001907] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida**

[001908]



[001909] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida**

[001910]



[001911] Método A

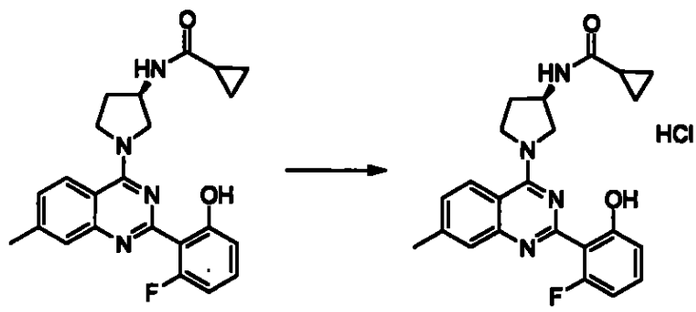
[001912] A una solución agitada de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (40 mg, 0,12 mmol) en 800 µL de DMF anhidra a 0 °C se añadió ácido ciclopropancarboxílico (11 mg, 0,13 mmol), seguido de la adición de trietilamina (24 mg, 33 µL, 0,24 mmol) y HATU (60 mg, 0,16 mmol). La mezcla se dejó calentar hasta temperatura ambiente y se agitó durante la noche. La filtración y la purificación por medio de HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio *N*-((*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida en forma de la sal de TFA. LC/MS: *m/z* 407,5 $(M+H)^+$ a 2,2 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001913] Método B

A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (100 mg, 0,295 mmol) en 10 ml de DMF, a -20 °C, se añadió ciclopropancarboxílico (23 µL,

0,30 mmol), seguido de la adición de trietilamina (82 µL, 0,59 mmol) y una solución de HATU (124 mg, 0,32 mmol) en 4 ml de DMF. La mezcla se calentó hasta temperatura ambiente y se agitó durante 1 h. Se añadió agua fría a la mezcla de reacción que dio como resultado la formación de un precipitado que se recogió por filtración y se disolvió en CH_2Cl_2. La solución se secó luego sobre $MgSO_4$, se filtró y se concentró para obtener *N*-((*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida (80 mg, 66%) LC/MS: *m/z* 407,5 $(M+H)^+$ a 2,08 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001914] Clorhidrato de N-((R)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida



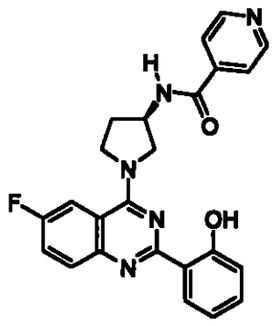
[001915]

[001916] A solución de HCl 2 M en éter (0,16 ml, 0,32 mmol) se añadió a una solución de *N*-((*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-

il)ciclopropancarboxamida (133 mg, 0,32 mmol) en CH_2Cl_2 (4 ml) bajo una atmósfera de N_2. Se añadió luego éter (15 ml) y la mezcla de reacción se agitó durante una hora. El precipitado formado luego se filtró y se secó para obtener clorhidrato de *N*-((*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)ciclopropancarboxamida (135 mg, 95%). LC/MS: *m/z* 407,5 $(M+H)^+$ a 2,07 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,32 (d, *J* = 7,6 Hz, 1H), 7,56-7,58 (m, 2H), 7,43-7,49 (m, 1H), 6,83-6,88 (m, 2H), 3,94-4,41 (m, 5H), 2,52 (s, 3H), 2,25-2,36 (m, 1H), 1,91-2,13 (m, 1H), 1,47-1,54 (m, 1H), 0,63-0,69 (m, 4H)

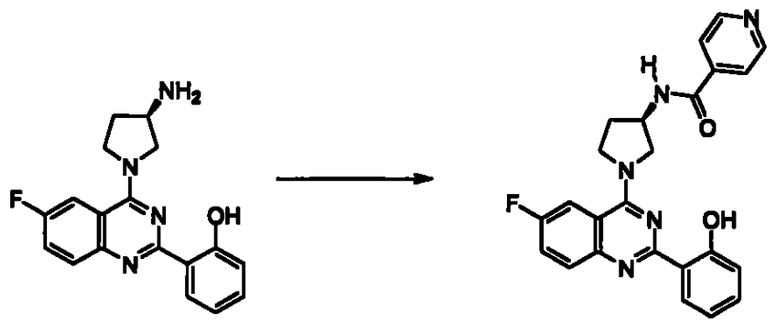
[001917] Ejemplo 347

[001918] **N-((R)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)isonicotinamida**



[001919]

[001920] **N-((R)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)isonicotinamida**



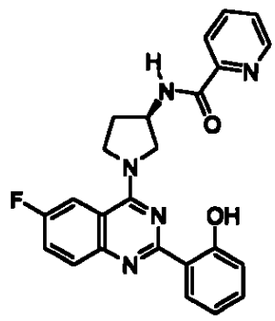
[001921]

[001922] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido isonicotínico (0,015 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)isonicotinamida en forma de la sal de TFA. LC/MS: *m/z* 430,5 $(M+H)^+$ a 1,95 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

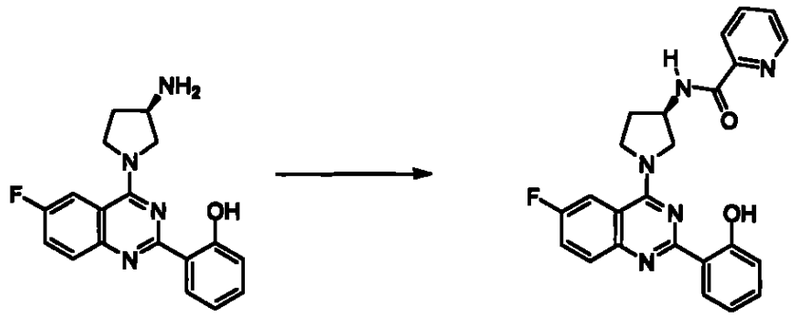
[001923] Ejemplo 348

[001924] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)picolinamida**

[001925]



[001926] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)picolinamida**



[001927]

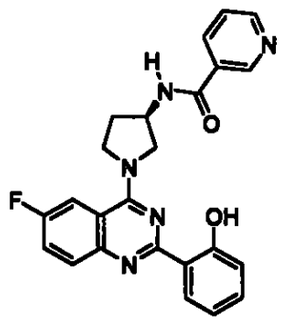
[001928] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido picolínico (0,015 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)picolinamida en forma de la sal de TFA.

LC/MS: *m/z* 430,5 $(M+H)^+$ a 2,43 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

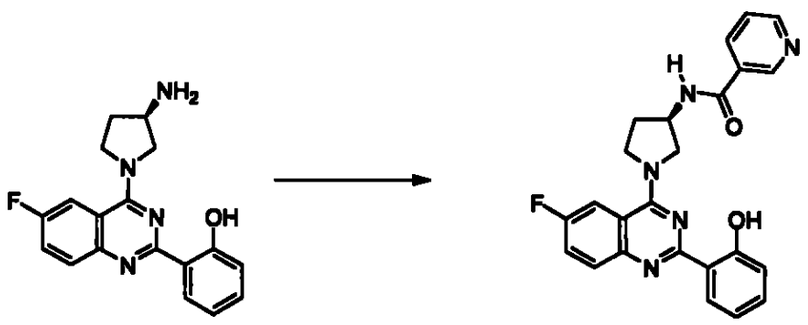
[001929] Ejemplo 349

[001930] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)nicotinamida**

[001931]



[001932] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)nicotinamida**



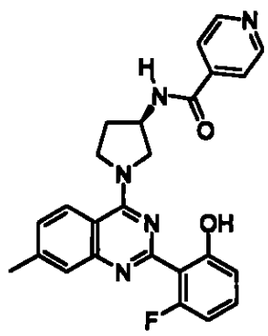
[001933]

[001934] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido nicotínico (0,015 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045

g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)nicotinamida en forma de la sal de TFA. LC/MS: *m/z* 430,5 $(M+H)^+$ a 1,98 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

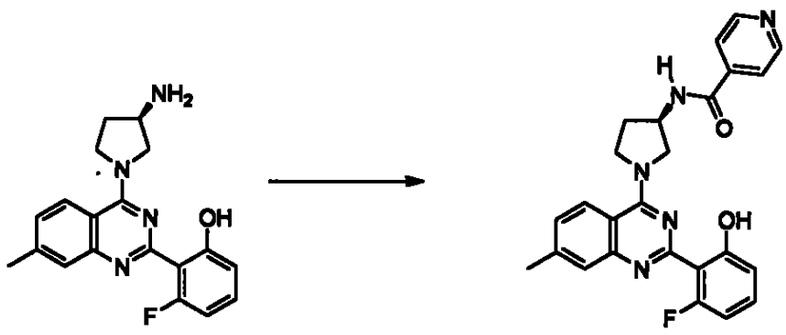
[001935] Ejemplo 350

[001936] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)isonicotinamida**



[001937]

[001938] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)isonicotinamida**



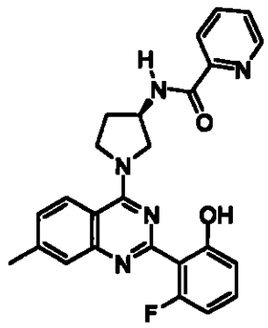
[001939]

[001940] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (0,03 g, 0,09 mmol) en DMF (0,5 ml) se añadió ácido isonicotínico (0,014 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)isonicotinamida en forma de la sal de TFA. LC/MS: *m/z* 444,5 $(M+H)^+$ a 1,85 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

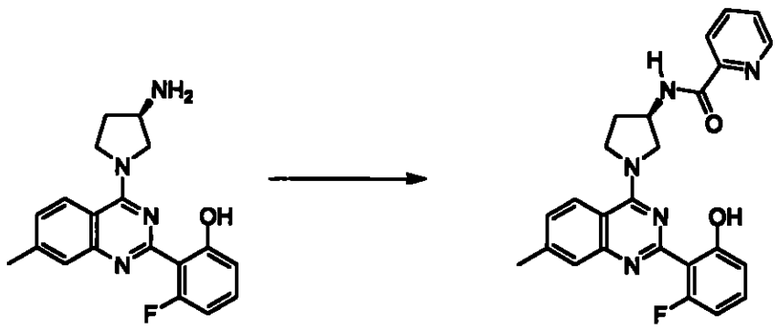
[001941] Ejemplo 351

[001942] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)picolinamida**

[001943]



[001944] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)picolinamida**



[001945]

[001946] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido picolínico (0,014 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)picolinamida en forma de

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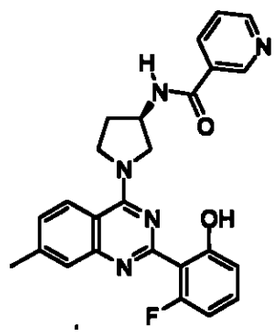
la sal de TFA. LC/MS: *m/z* 444,5 $(M+H)^+$ a 2,24 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

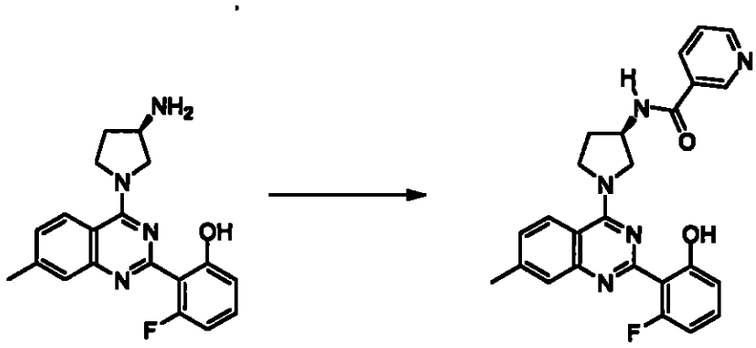
[001947] Ejemplo 352

[001948] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)nicotinamida**



[001949]

[001950] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)nicotinamida**



[001951]

[001952] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (0,03 g, 0,09 mmol) en

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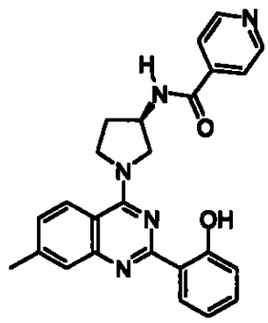
DMF (1,0 ml) se añadió ácido nicotínico (0,014 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)nicotinamida en forma de la sal de TFA. LC/MS: *m/z* 444,5 $(M+H)^+$ a 1,89 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

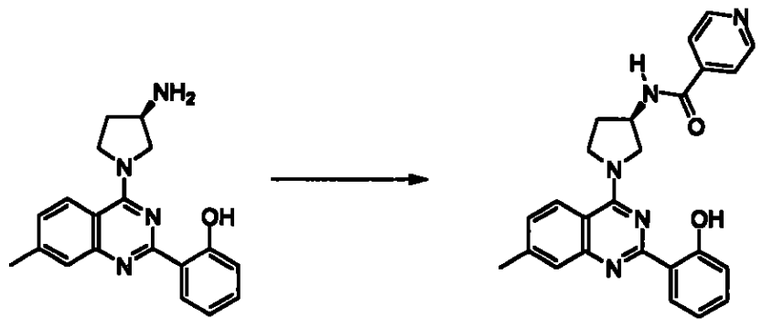
[001953] Ejemplo 353

[001954] ***N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)isonicotinamida**



[001955]

[001956] ***N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)isonicotinamida**

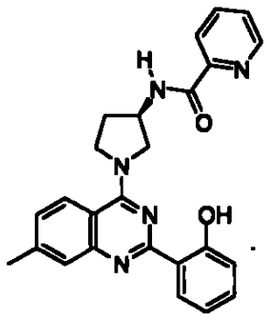


[001957]

[001958] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido isonicotínico (0,015 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)isonicotinamida en forma de la sal de TFA. LC/MS: *m/z* 426,1 $(M+H)^+$ a 1,93 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

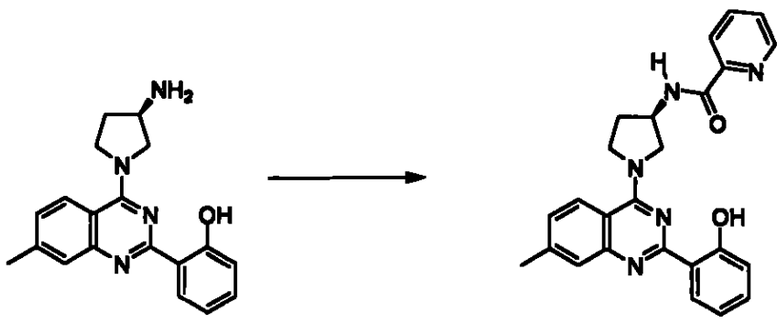
[001959] Ejemplo 354

[001960] **N-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)picolinamida**



[001961]

[001962] ***N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)picolinamida**



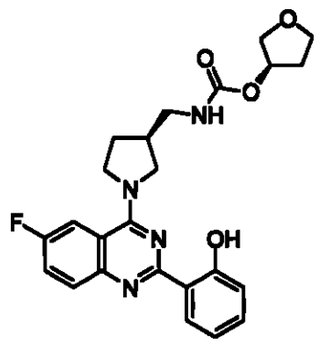
[001963]

[001964] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido picolínico (0,015 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-

il)pirrolidin-3-il)picolinamida en forma de la sal de TFA. LC/MS: *m/z* 426,1 $(M+H)^+$ a 2,33 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001965] Ejemplo 355

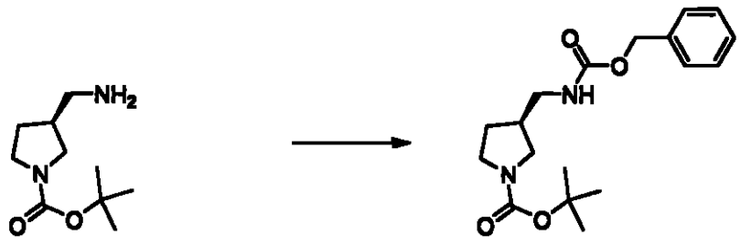
[001966] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo**



[001967]

[001968] **((*S*)-1-(ter-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo**

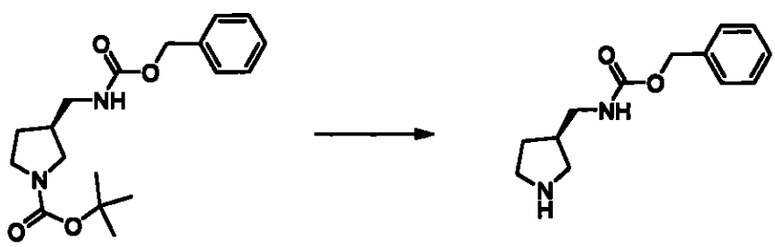
[001969]



[001970] A una solución agitada de 3-(aminometil)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (1,5 g, 7,5 mmol) en 25 ml de CH_2Cl_2 se añadió trietilamina (2,1 ml, 15 mmol) a 0 °C, seguido

de la adición gota a gota de cloroformiato de bencilo (1,58 ml, 11,2 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante la noche. La mezcla se neutralizó con agua y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 3% de MeOH en CH_2Cl_2 dio ((*S*)-1-(*ter*-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo (1,5 g, 60%). LC/MS: *m/z*: 335,5 $(M+H)^+$ a 3,01 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001971] **((*R*)-pirrolidin-3-il)metilcarbamato de bencilo**

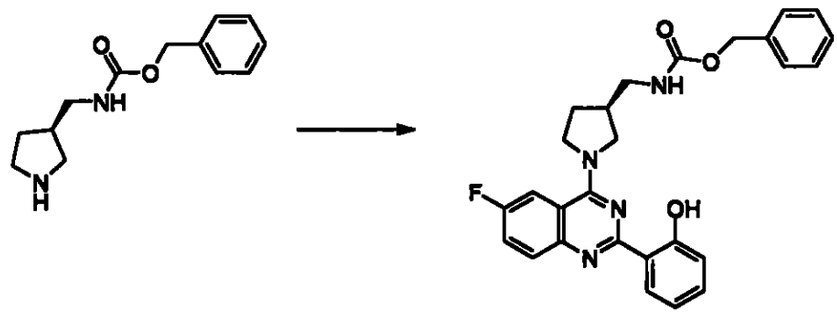


[001972]

[001973] A una solución agitada de ((*S*)-1-(*ter*-butoxicarbonil)pirrolidin-3-il)metilcarbamato (1,5 g, 4,48 mmol) en CH_2Cl_2 (20 ml) se añadió lentamente TFA (5 ml). La reacción se agitó durante 2 h. Después de retirar los solventes a presión reducida, la mezcla se neutralizó con una solución 1 M de NaOH y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron

y se concentraron para obtener ((*R*)-pirrolidin-3-il)metilcarbamato de bencilo (800 mg, 76%). LC/MS: *m/z* 335,3 $(M+H)^+$ a 1,22 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001974] ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo



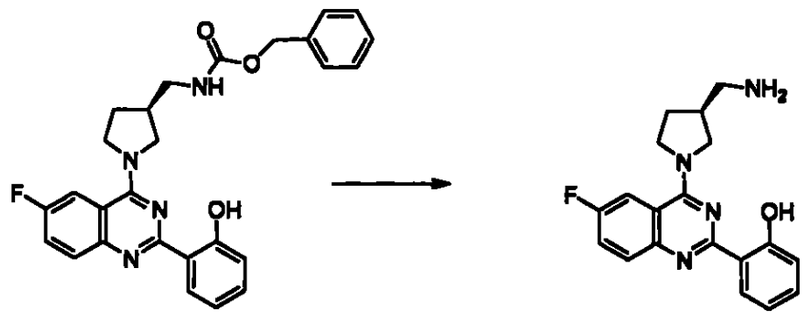
[001975]

[001976] Una solución de trietilamina (507 µL, 3,64 mmol) y ((*R*)-pirrolidin-3-il)metilcarbamato de bencilo (0,47 g, 2 mmol) en CH_2Cl_2 se añadió gota a gota a una solución de 2-(4-cloro-6-fluoroquinazolin-2-il)fenol (0,5 g, 1,82 mmol) en CH_2Cl_2 (20 ml). La reacción se agitó a temperatura ambiente durante 3 h. Después de neutralizar la reacción con agua, la fase acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 5-10% de EtOAc en CH_2Cl_2 dio como resultado ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-

il)pirrolidin-3-il)metilcarbamato de bencilo. LC/MS: *m/z* 473,1 $(M+H)^+$ a 2,91 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

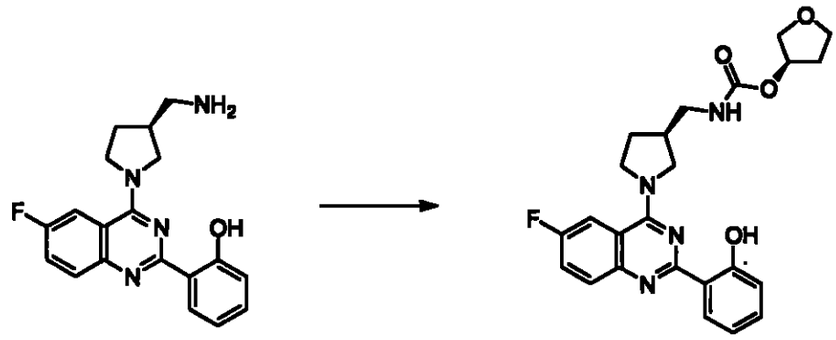
[001977] 2-(4-((*S*)-3-(Aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol

[001978]



[001979] En una atmósfera de N_2, una mezcla de ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo (0,770 g, 1,6 mmol) y MeOH (5 ml) se añadió a Pd/C (77 mg, 10% en peso de Pd sobre carbón) pesado en un recipiente de 100 ml. Después de evacuar la atmósfera en el recipiente y purgarlo con N_2 tres veces, la mezcla de reacción se agitó vigorosamente bajo una atmósfera de H_2 a presión ambiente durante la noche y luego se filtró a través de un taco de Celite, se concentró y se secó para obtener 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,45 g, 81%). LC/MS: *m/z* 459,5 $(M+H)^+$ a 2,81 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[001980] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo**

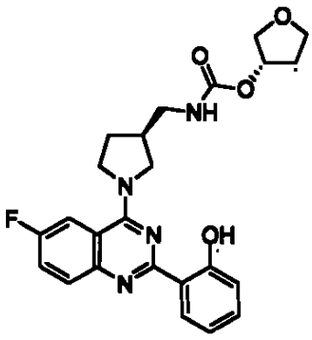


[001981]

[001982] A una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) a -60 °C (temperatura externa) se añadió trietilamina (25 ml, 0,18 mmol) y cloroformiato de (R)-tetrahidrofuran-3-ilo (13 mg, 0,09 mmol). La reacción se calentó hasta temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de (R)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 453,3 $(M+H)^+$ a 2,29 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

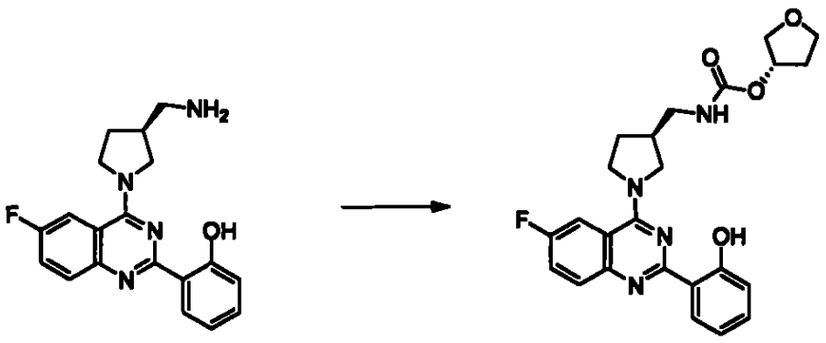
[001983] Ejemplo 356

[001984] ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo



[001985]

[001986] ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo



[001987]

[001988] A una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) a -60 °C (temperatura externa) se añadió trietilamina (25 ml, 0,18 mmol) y cloroformiato de (S)-tetrahidrofuran-3-ilo (13 mg, 0,09 mmol).

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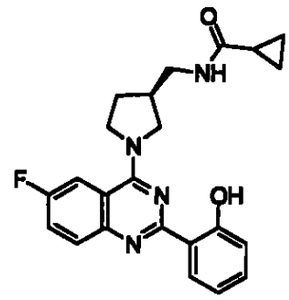
La reacción se calentó hasta temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de (S)-tetrahidrofuran-3-ilo en forma de la sal de TFA. LC/MS: *m/z* 453,3 $(M+H)^+$ a 2,29 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

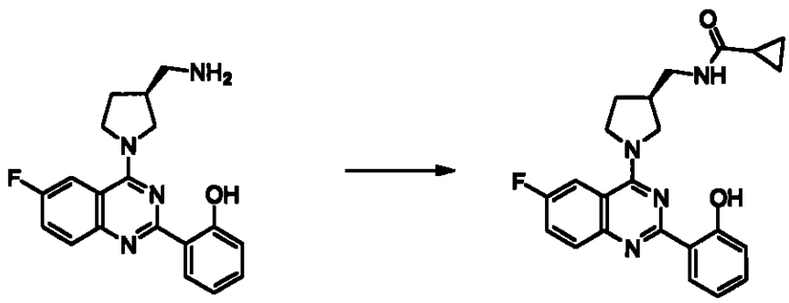
[001989] Ejemplo 357

[001990] ***N*-(((*S*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metil)ciclopropancarboxamida**



[001991]

[001992] ***N*-(((*S*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metil)ciclopropancarboxamida**

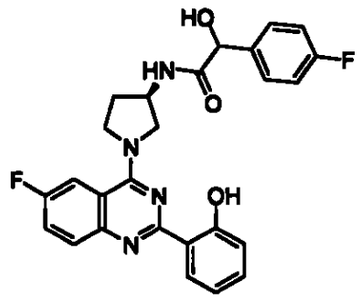


[001993]

[001994] A una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) y ácido ciclopropancarboxílico (10 mg, 0,12 mmol) en DMF (1,0 ml) se añadió trietilamina (25 µL, 0,18 mmol) seguido de la adición de HATU (45 mg, 0,117 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-(((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metil)ciclopropancarboxamida en forma de la sal de TFA. LC/MS: *m/z* 407,3 $(M+H)^+$ a 2,26 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

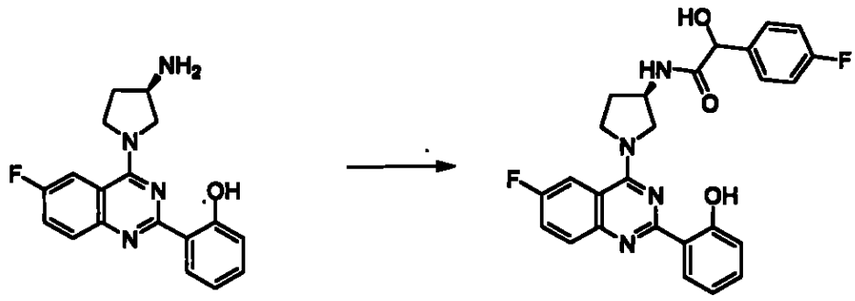
[001995] Ejemplo 358

[001996] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)-2-(4-fluorofenil)-2-hidroxiacetamida**



[001997]

[001998] ***N*-((*R*)-1-(6-Fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)-2-(4-fluorofenil)-2-hidroxiacetamida**



[001999]

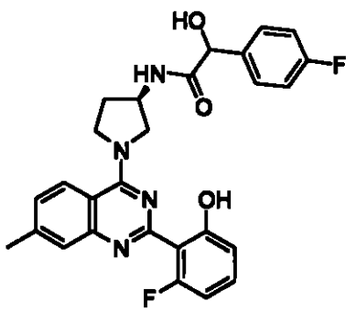
[002000] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido 2-(4-fluorofenil)-2-hidroxiacético (20 mg, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)-2-(4-

fluorofenil)-2-hidroxiacetamida en forma de la sal de TFA. LC/MS: *m/z* 477,3 $(M+H)^+$ a 2,80 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

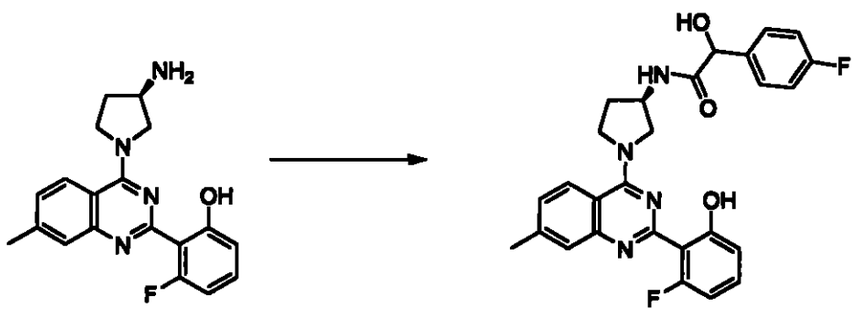
[002001] Ejemplo 359

[002002] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2-(4-fluorofenil)-2-hidroxiacetamida**

[002003]



[002004] ***N*-((*R*)-1-(2-(2-Fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2-(4-fluorofenil)-2-hidroxiacetamida**



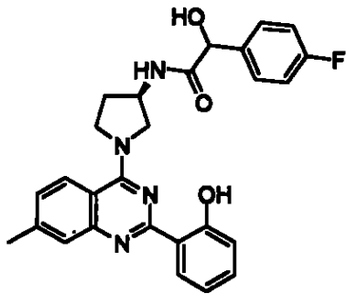
[002005]

[002006] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido 2-(4-fluorofenil)-2-hidroxiacético (0,020 g, 0,12 mmol), seguido de la adición de trietilamina (25,6 µL, 0,184 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener *N*-((*R*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-2-(4-fluorofenil)-2-hidroxiacetamida en forma de la sal de TFA. LC/MS: *m/z* 4491,3 $(M+H)^+$ a 2,46 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

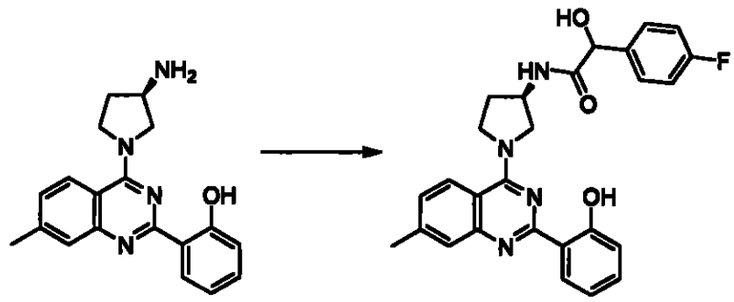
[002007] Ejemplo 360

[002008] **2-(4-Fluorofenil)-2-hidroxi-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)acetamida**

[002009]



[002010] **2-(4-Fluorofenil)-2-hidroxi-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)acetamida**



[002011]

[002012] A una solución de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) se añadió ácido 2-(4-fluorofenil)-2-hidroxiacético (0,02 g, 0,12 mmol), seguido de la adición de trietilamina (25 µL, 0,18 mmol) y HATU (0,045 g, 0,12 mmol). La reacción se agitó a temperatura ambiente durante 2 h, se filtró y se purificó usando HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-(4-fluorofenil)-2-hidroxi-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)acetamida en forma de la sal de TFA. LC/MS: *m/z* 473,1 $(M+H)^+$ a 2,32 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002013] Ejemplo 361

[002014] **(2*R*)-2-Hidroxi-*N*-((*R*)-1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-4,4-dimetilpentanamida**

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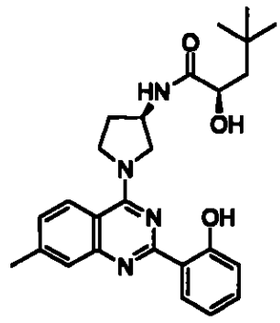
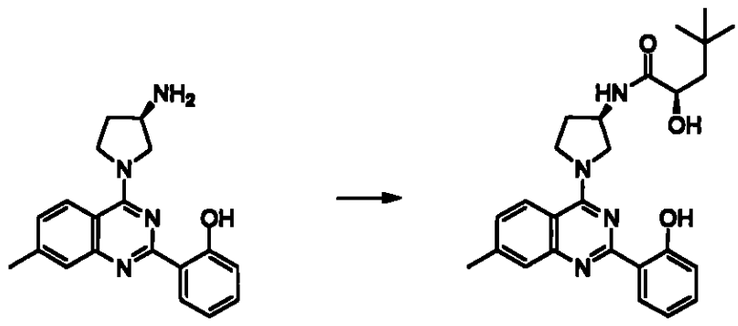


[002015]

[002016] **(2*R*)-2-Hidroxi-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-4,4-dimetilpentanamida**



[002017]

[002018] A una solución agitada de 2-(4-((*R*)-3-aminopirrolidin-1-il)-7-metilquinazolin-2-il)fenol (50 mg, 0,16 mmol) en 1 ml de DMF enfriada a 0 °C se añadió ácido (R)-2-hidroxi-4,4-dimetilpentanoico (27,3 mg, 0,187 mmol), seguido de la adición de trietilamina (32 mg, 44 µL, 0,31 mmol), luego HATU (71,1 mg, 0,187 mmol). La reacción se agitó a 0 °C durante 10 minutos, se calentó hasta temperatura ambiente, se filtró y

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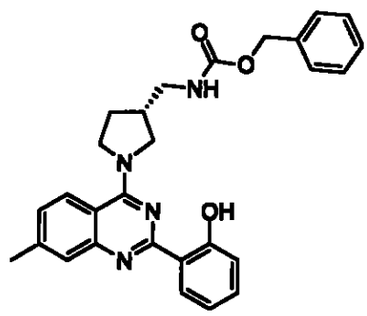
se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener (2*R*)-2-hidroxi-*N*-((*R*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)-4,4-dimetilpentanamida en forma de la sal de TFA. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,4 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

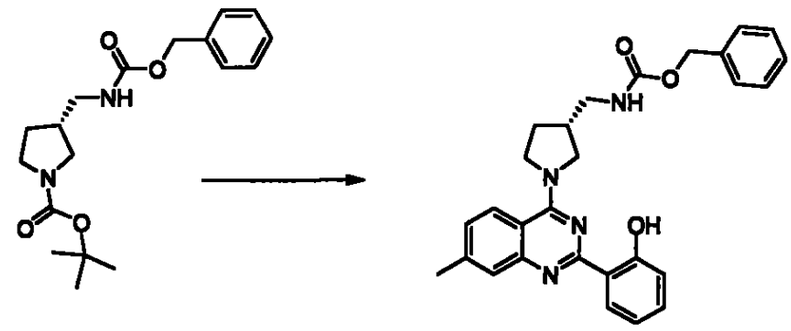
[002019] Ejemplo 362

[002020] **((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo**



[002021]

[002022] **((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo**



[002023]

[002024] Una mezcla de ((R)-1-(ter-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo (0,20 g, 0,60 mmol) y HCl 4 M (10 ml) en dioxano se agitó a temperatura ambiente durante 3 h. Después de evaporar el solvente a presión reducida, el sólido se trituró con Et_2O, se secó al vacío y se extrajo en CH_2Cl_2 (10 ml). 2-(4-cloro-7-metilquinazolin-2-il)fenol (0,16 g, 0,60 mmol) se añadió a esta solución, seguido de la adición de trietilamina (0,25 ml, 1,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con CH_2Cl_2 y se lavó con agua. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-40% de EtOAc en hexanos dio ((R)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo en un aceite incoloro (0,19 g, 68% de rendimiento). LC/MS: *m/z* 469,1 $(M+H)^+$ a 2,58 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

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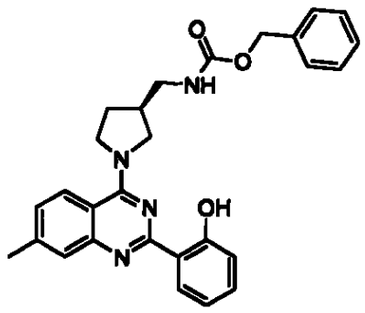
[002025] Ejemplo 363

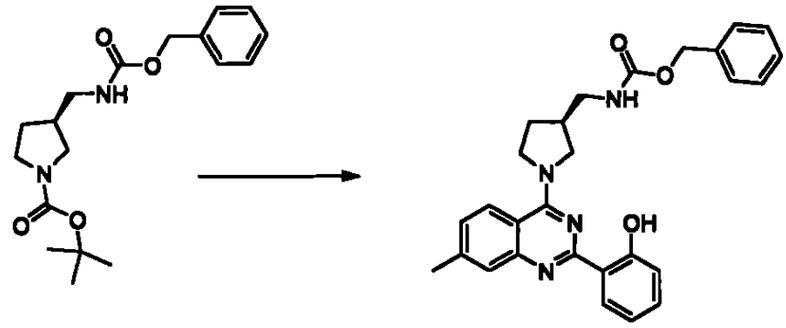
[002026] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo**



[002027]

[002028] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo**

[002029]



[002030] Una mezcla de ((*S*)-1-(*ter*-butoxicarbonil)pirrolidin-3-il)metilcarbamato de bencilo (0,20 g, 0,60 mmol) y HCl 4 M en dioxano (10 ml) se agitó durante 3 h a temperatura ambiente. Después de evaporar el solvente a presión reducida, el sólido se trituró con Et_2O, se secó al vacío y se extrajo en CH_2Cl_2 (10 ml). A esta solución se añadió 2-(4-cloro-7-

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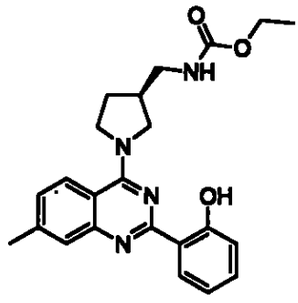
metilquinazolin-2-il)fenol (0,16 g, 0,60 mmol), seguido de la adición de trietilamina (0,25 ml, 1,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con CH_2Cl_2 y se lavó con agua. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-40% de EtOAc en hexanos dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de bencilo en un aceite incoloro (0,19 g, 68% de rendimiento). LC/MS: *m/z* 469,1 $(M+H)^+$ a 2,58 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002031] Ejemplo 364

[002032] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de etilo**



[002033]

[002034] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de etilo**

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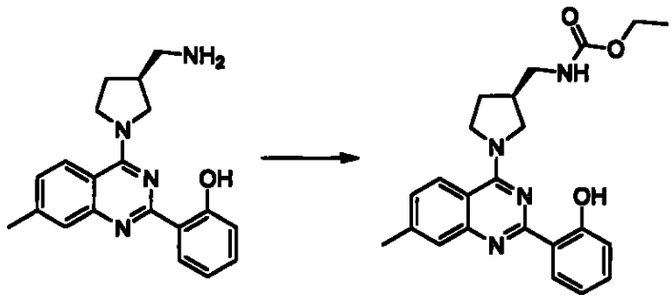
1191

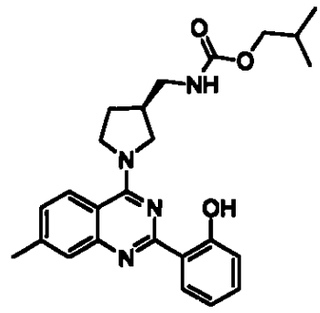
[002035]



[002036] Una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (25 mg, 0,075 mmol) en CH_2Cl_2 (1,0 ml) se enfrió en un baño de hielo. A esta mezcla se añadió cloroformiato de etilo (7,8 µL, 0,082 mmol), seguido de trietilamina (21 µL, 0,15 mmol). Después de retirar el baño de hielo, la reacción se agitó durante 3 h a temperatura ambiente. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de etilo en forma de la sal de TFA. LC/MS: *m/z* 407,1 $(M+H)^+$ a 2,29 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002037] Ejemplo 365

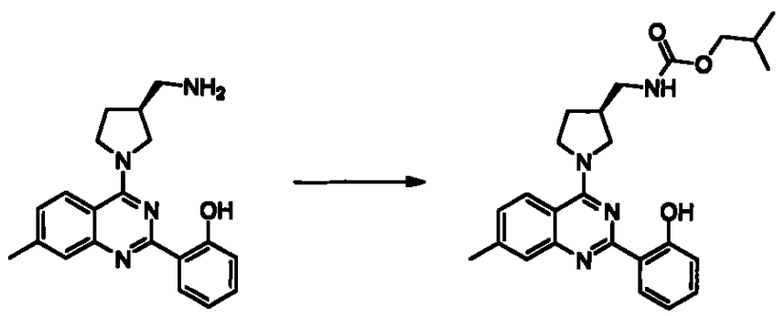
[002038] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo**



[002039]

[002040] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo**

[002041]



[002042] Método A

[002043] Una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (25 mg, 0,075 mmol) en CH_2Cl_2 (1,0 ml) se enfrió en un baño de hielo. A esta mezcla se añadió cloroformiato de isobutilo (11 µL, 0,082 mmol), seguido de la adición de trietilamina (21 µL, 0,15 mmol). Después de retirar el baño de hielo, la reacción se agitó durante 3 h a temperatura ambiente. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de

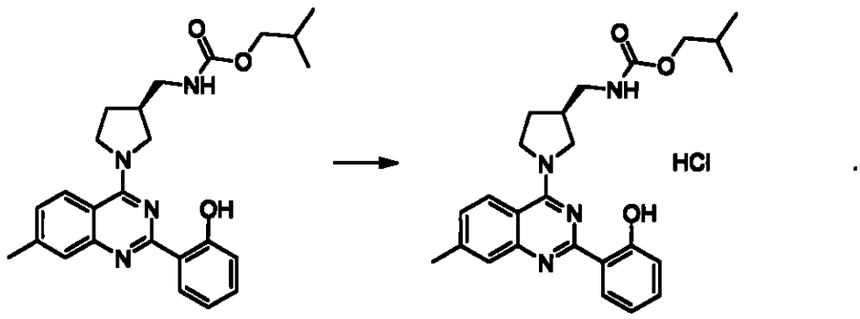
TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo en forma de la sal de TFA. LC/MS: *m/z* 435,3 $(M+H)^+$ a 2,55 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

|002044| Método B

|002045| Una mezcla de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (200 mg, 0,6 mmol), THF (6,0 ml) y CH_2Cl_2 se agitó bajo una atmósfera de N_2. Se agregó trietilamina (0,166 ml, 1,2 mmol) y la reacción se enfrió en un baño de hielo. A esto se añadió solución 1 M de cloroformiato de isobutilo (78 µL en 600 µL de THF, 0,6 mmol). Tras dejar calentar la mezcla de reacción hasta temperatura ambiente, se añadió CH_2Cl_2 y la solución orgánica se lavó dos veces con agua, luego se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-20% de EtOAc en CH_2Cl_2/hexanos (1:1) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo (183 mg, 70%). LC/MS: *m/z* 435,5 $(M+H)^+$ a 2,63 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). LC/MS: *m/z* 435 $(M+H)^+$ a 2,63 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,43 (dd, *J* = 8,2, 1,8 Hz, 1H), 8,22 (d, *J* = 8,7 Hz, 1H), 7,58 (s, 1H), 7,42-7,31 (m, 3H), 6,93-6,89 (m, 2H), 4,17-3,91 (m, 3H), 3,80-3,69 (m, 3H), 3,34-3,30 (m, 1H), 3,21-

3,07 (m, 2H), 2,49 (s, 3H), 2,16-2,08 (m, 1H), 1,88-1,74 (m, 2H), 0,88 (d, *J* = 6,7 Hz, 6H).

[002046] Clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo



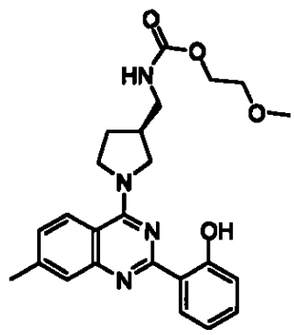
[002047]

[002048] Una solución de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo (183 mg, 0,42 mmol) en CH_2Cl_2 (1,5 ml) se agitó bajo una atmósfera de N_2. Se añadió una solución 1,0 M de HCl en éter (0,42 ml, 0,42 mmol) gota a gota a esta solución. Al cabo de 10 minutos, se añadieron 5 ml de éter y un precipitado formado que se filtró y se secó para obtener clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo (169 mg, 85%). LC/MS: *m/z* 435,5 $(M+H)^+$ a 2,64 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,31 (d, *J* = 8,7 Hz, 1H), 8,24 (d, *J* = 6,8 Hz, 1H), 7,80 (s, 1H), 7,53-7,45 (m,

2H), 7,41-7,38 (m, 1H), 7,12 (d, *J* = 8,2 Hz, 1H), 7,05-7,02 (m, 1H), 4,36-3,85 (m, 5H), 3,77-3,70 (m, 2H), 3,22-3,06 (m, 2H), 2,54 (s, 3H), 2,18-2,13 (m, 1H), 1,87-1,77 (m, 2H), 0,87 (d, *J* = 6,7 Hz, 6H).

[002049] Ejemplo 366

[002050] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo**



[002051]

[002052] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo**

[002053] Método A

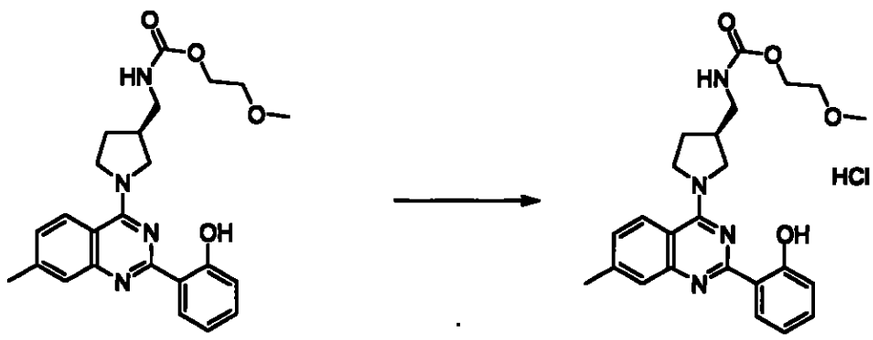
[002054] Una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (25 mg, 0,075 mmol) en CH_2Cl_2 anhidro se enfrió en un baño de hielo. Luego se añadió cloroformiato de 2-metoxietilo (8,6 µL, 0,075 mmol), seguido de la adición de trietilamina (16 µL, 0,11 mmol). Después de retirar el baño de hielo, la reacción se agitó a temperatura ambiente durante 4 h. Se agregaron agua y solución acuosa

saturada de $NaHCO_3$ y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de separar las capas acuosa y orgánica, la fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por HPLC preparativa en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo en forma de la sal de TFA. LC/MS (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)), *m/z*: M+1 *obs* = 437,3; t_R = 2,18 minutos.

|002055| Método B

|002056| Una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (0,12 g, 0,35 mmol) y trietilamina (98 µL, 0,7 mmol) en DMF anhidra (4,0 ml) se enfrió en un baño de hielo. Se añadió cloroformiato de 2-metoxietilo (40 ml, 0,35 mmol) y se retiró el baño de hielo. La solución se agitó a temperatura ambiente durante la noche. La purificación por medio de cromatografía en gel de sílice usando 0-10% de MeOH en CH_2Cl_2 dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo (0,12 g, 80%). LC/MS: *m/z* 437,5 $(M+H)^+$ a 2,20 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

|002057| Clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo

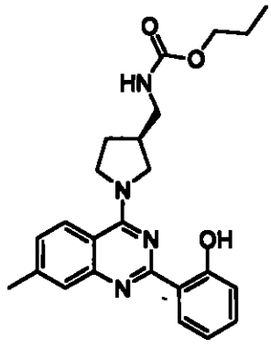


[002058]

[002059] A una solución 1,0 M de HCl en Et_2O (0,27 ml, 0,27 mmol) se añadió lentamente a una solución agitada de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo (0,12 g, 0,27 mmol) en CH_2Cl_2 (5 ml). La reacción se agitó durante 30 minutos a temperatura ambiente, luego Et_2O se añadió lentamente a la solución hasta formar un precipitado. Tras agitar durante 1 h, el sólido se filtró y se lavó con Et_2O para obtener clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo (0,10 g, 77%). LC/MS: *m/z* 437,1 $(M+H)^+$ a 2,19 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,31 (d, *J* = 8,7 Hz, 1H), 8,24 (d, *J* = 7,3 Hz, 1H), 7,77 (s, 1H), 7,52-7,48 (m, 3H), 7,10 (d, *J* = 8,1 Hz, 1H), 7,05-7,02 (m, 1H), 4,22-4,12 (m, 2H), 4,08-4,05 (m, 3H), 3,87-3,83 (m, 1H), 2H), 3,24 (s, 3H), 3,23-3,12 (m, 2H), 2,54 (s, 3H), 2,55-2,52 (m, 1H), 2,17-2,13 (m, 1H), 1,84-1,77 (m, 1H).

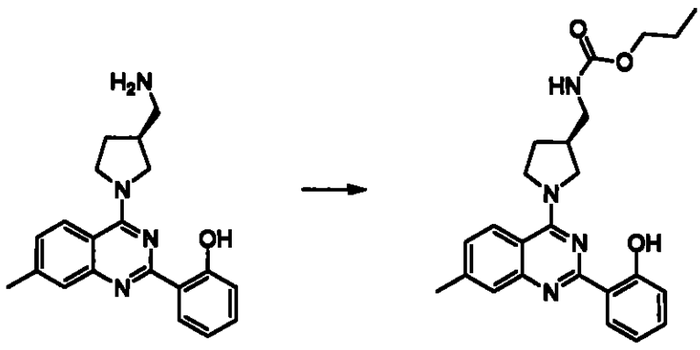
[002060] Ejemplo 367

[002061] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo**



[002062]

[002063] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo**



[002064]

[002065] Método A

[002066] Se añadieron cloroformiato de propilo (12 mg, 0,10 mmol) y trietilamina (30 mg, 42 µL, 0,30 mmol) a 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (33

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mg, 0,10 mmol) en 1 ml de DMF anhidra. La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo en forma de la sal de TFA. LC/MS: *m/z* 421,1 $(M+H)^+$ a 2,43 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002067] Método B

[002068] Una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (301 mg, 0,9 mmol) en CH_2Cl_2 (10 ml) se agitó bajo una atmósfera de N_2. Se agregó trietilamina (0,25 ml, 1,8 mmol) y la solución se enfrió hasta -30 °C. Se añadió una solución 1 M de cloroformiato de propilo (0,1 ml en 0,9 ml de CH_2Cl_2, 0,9 mmol) y la mezcla de reacción se dejó calentar hasta temperatura ambiente durante un período de 30 minutos. Tras añadir CH_2Cl_2 a la mezcla de reacción, se lavó 2 veces con agua, antes de secarla sobre Na_2SO_4, se filtrarla y se concentrarla. La purificación por medio de cromatografía en gel de sílice usando 0-20% de EtOAc en CH_2Cl_2 dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo (236 mg, 62%). LC/MS: *m/z* 421 $(M+H)^+$ a 2,54 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,43 (dd, *J* = 8,2, 1,8 Hz, 1H), 8,21 (d, *J* = 8,7 Hz, 1H), 7,58 (s, 1H),

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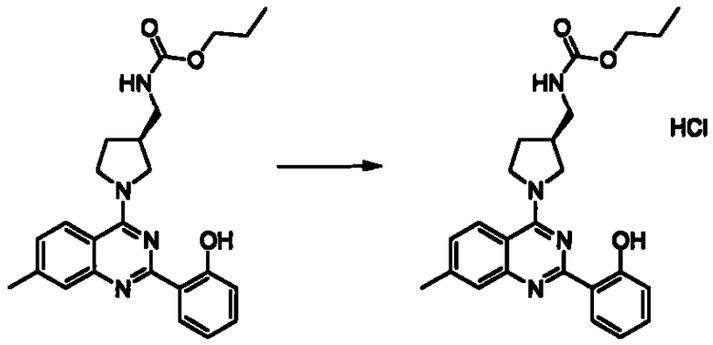
7,39-7,31 (m, 3H), 6,93-6,89 (m, 2H), 4,09-3,86 (m, 6H), 3,78-3,73 (m, 1H), 3,21-3,09 (m, 2H), 2,49 (s, 3H), 2,15-2,09 (m, 1H), 1,83-1,74 (m, 1H), 1,62-1,48 (m, 2H), 0,89-0,86 (m, 3H).

[002069] Clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo

[002070]

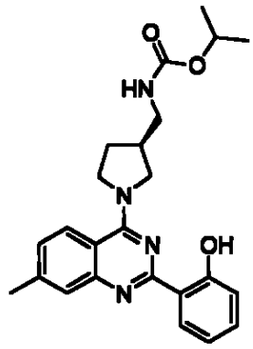


[002071] Una solución de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo (232 mg, 0,552 mmol) en CH_2Cl_2 (2 ml) se agitó bajo una atmósfera de N_2. Una solución de HCl 2,0 M en éter (0,276 ml, 0,552 mmol) gota a gota a esta solución. Al cabo de 10 minutos, se añadió éter (8 ml) hasta formarse un precipitado que se filtró y se secó para obtener clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo (223 mg, 88%). LC/MS: *m/z* 421 $(M+H)^+$ a 2,54 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,31 (d, *J* = 8,7 Hz, 1H), 8,24 (dd, *J* = 7,9, 1,4 Hz, 1H), 7,82 (s, 1H), 7,54-7,49 (m,

2H), 7,41-7,37 (m, 1H), 7,14 (d, *J* = 8,1 Hz, 1H), 7,06-7,02 (m, 1H), 4,29-3,78 (m, 7H), 3,24-3,08 (m, 2H), 2,54 (s, 3H), 2,18-2,12 (m, 1H), 1,84-1,79 (m, 1H), 1,59-1,50 (m, 2H), 0,87 (t, *J* = 7,4 Hz, 3H).

[002072] Ejemplo 368

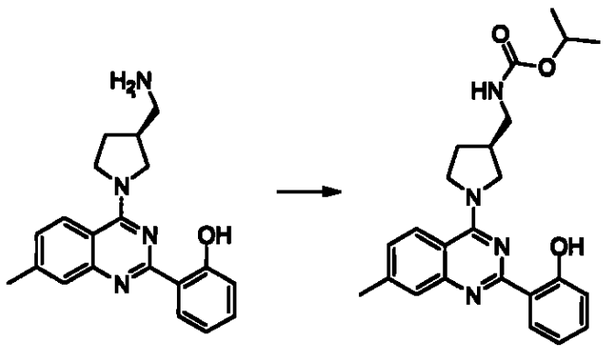
[002073] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isopropilo**



[002074]

[002075] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isopropilo**

[002076]



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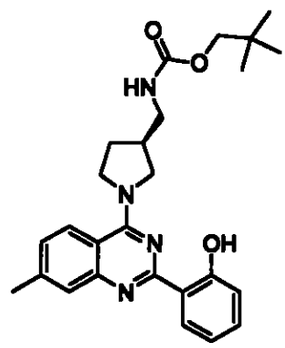
[002077] Se añadieron cloroformiato de isopropilo (12 mg, 0,10 mmol) y trietilamina (30 mg, 42 µL, 0,30 mmol) a una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (33 mg, 0,10 mmol) en 1 ml de DMF anhidra. La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isopropilo en forma de la sal de TFA. LC/MS: *m/z* 421,1 $(M+H)^+$ a 2,42 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

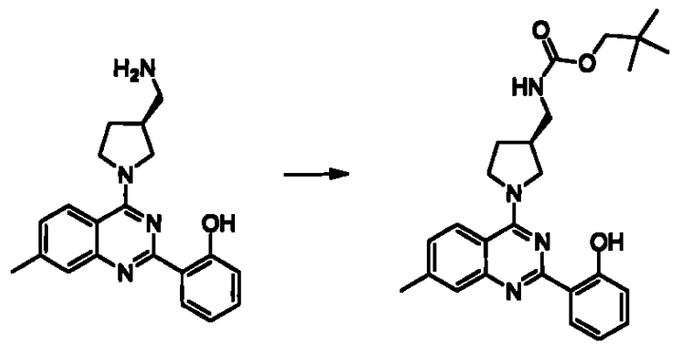
[002078] Ejemplo 369

[002079] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo**



[002080]

[002081] **((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo**



[002082]

[002083] Método A

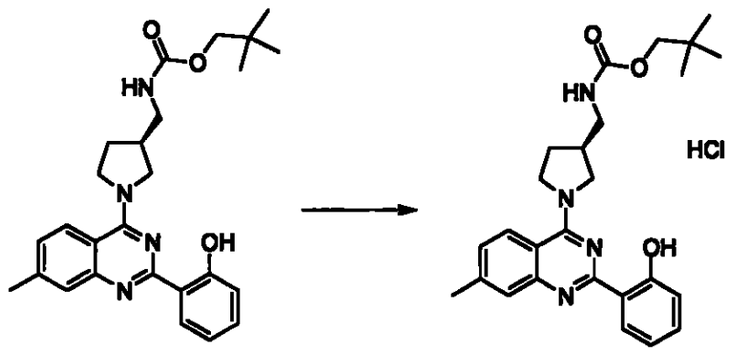
[002084] Cloroformiato de neopentilo (15 mg, 0,10 mmol) y trietilamina (30 mg, 42 µL, 0,30 mmol) se añadieron a una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (33 mg, 0,10 mmol) en 1 ml de DMF anhidra. La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo en forma de la sal de TFA. LC/MS: *m/z* 449,3 $(M+H)^+$ a 2,67 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002085] Método B

[002086] Una mezcla de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)fenol (200 mg, 0,6 mmol), THF (6,0 ml) y DMF (1 ml) se agitó bajo una atmósfera de N_2. Se agregó

trietilamina (0,166 ml, 1,2 mmol) y la reacción se enfrió en un baño de hielo. A esto se añadió solución 1 M de cloroformiato de neopentilo (89 µL en 600 µL de THF, 0,6 mmol). Tras dejar calentar la mezcla de reacción hasta temperatura ambiente durante un período de 30 minutos, se añadió CH_2Cl_2 a la mezcla de reacción y se lavó una vez con agua antes de secarla sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 0-20% de EtOAc en CH_2Cl_2/hexanos (1:1) dio ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo (222 mg, 94%). LC/MS: *m/z* 449 $(M+H)^+$ a 2,73 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, ácido acético-d4) δ 8,42 (dd, *J* = 8,1, 1,8 Hz, 1H), 8,20 (d, *J* = 8,7 Hz, 1H), 7,57 (s, 1H), 7,40-7,29 (m, 3H), 6,92-6,89 (m, 2H), 4,11-3,92 (m, 3H), 3,78-3,61 (m, 3H), 3,33-3,28 (m, 1H), 3,23-3,10 (m, 2H), 2,49 (s, 3H), 2,16-2,08 (m, 1H), 1,83-1,75 (m, 1H), 0,89 (s, 9H).

[002087] Clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo



[002088]

[002089] Una solución de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo (215 mg, 0,48 mmol) en CH_2Cl_2 (2 ml) se agitó bajo una atmósfera de N_2. Una solución 1,0 M de HCl en éter (0,48 ml, 0,48 mmol) se añadió gota a gota a esta solución. Al cabo de 10 minutos, se agregó éter (8 ml) hasta formar un precipitado, que se filtró y se secó para obtener clorhidrato de ((*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo (214 mg, 92%). LC/MS: *m/z* 449 $(M+H)^+$ a 2,75 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)). ^1H RMN (400 MHz, DMSO-d6) δ 8,31 (d, *J* = 8,7 Hz, 1H)1H), 7,85 (s, 1H), 7,54-7,49 (m, 2H), 7,47-7,45 (m, 1H), 7,16 (d, *J* = 8,2 Hz, 1H), 7,05-7,02 (m, 1H), 4,33-3,74 (m, 5H), 3,70-3,64 (m, 2H), 3,19-3,16 (m, 2H), 2,53 (s, 3H), 2,18-2,13 (m, 1H), 1,87-1,81 (m, 1H), 0,88 (s, 9H).

[002090] Ejemplo 370

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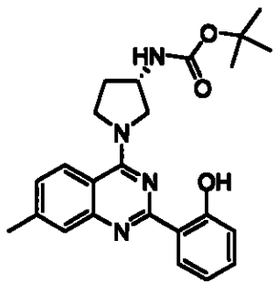
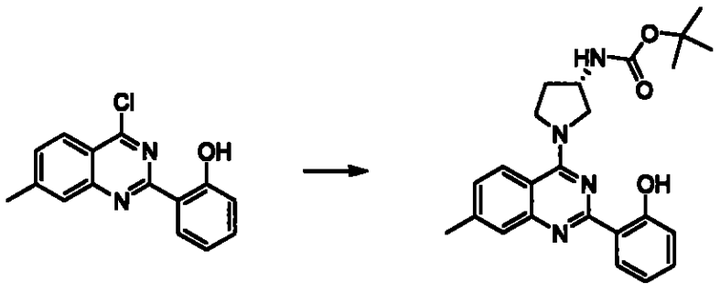
[002091] **(*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo**



[002092]

[002093] **(*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo**



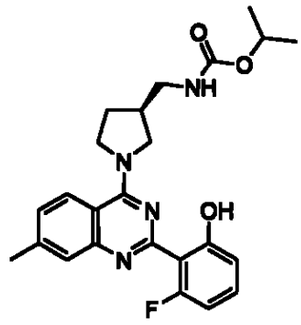
[002094]

[002095] (*S*)-pirrolidin-3-ilcarbamato de *ter*-butilo (245 mg, 1,31 mmol) se disolvió en 1,8 ml de CH_2Cl_2 anhidro y se enfrió hasta 0 °C. 2-(4-cloro-7-metilquinazolin-2-il)fenol (300 mg, 1,1 mmol) disuelto en 1,8 ml de CH_2Cl_2 anhidro se añadió gota a gota a la mezcla seguido de trietilamina (134 mg, 184 µL, 1,32 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante la noche. La purificación por medio de

cromatografía en gel de sílice usando 10-100% de acetato de etilo/hexanos dio (*S*)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-ilcarbamato de *ter*-butilo. LC/MS: *m/z* 421,0 $(M+H)^+$ a 2,84 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002096] Ejemplo 371

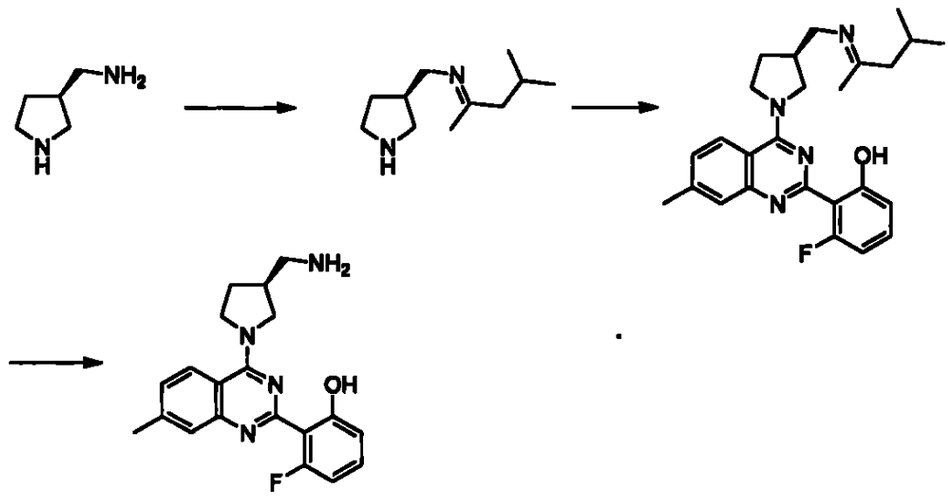
[002097] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isopropilo**



[002098]

[002099] **2-(4-((*S*)-3-(Aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol**

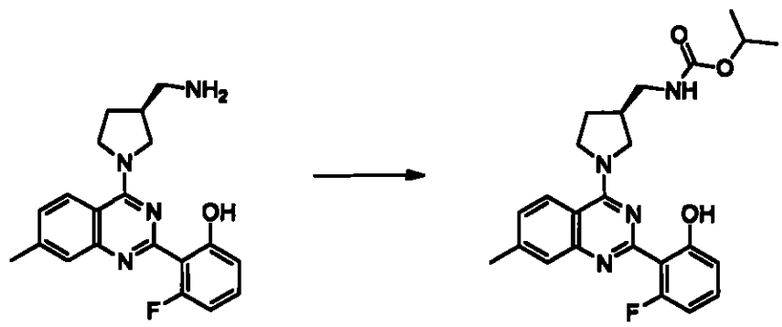
[002100]



[002101] Una mezcla de ((*S*)-pirrolidin-3-il)metanamina (0,6 g, 6,0 mmol), Na_2CO_3 (2,2 g, 21 mmol) y metilisobutilcetona (12 ml, 6,0 mmol) bajo una atmósfera de N_2 se calentó a reflujo durante la noche usando un aparato de Dean Stark. Después de dejar enfriar la reacción hasta temperatura ambiente, se añadió 2-(4-cloro-7-metilquinazolin-2-il)-3-fluorofenol (1,73 g, 5,99 mmol) y la mezcla se agitó durante la noche a temperatura ambiente bajo una atmósfera de N_2. La reacción luego se neutralizó con agua. La capa acuosa se extrajo dos veces con CH_2Cl_2. Los extractos orgánicos se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron para obtener un material crudo que contiene 2-(4-((*S*)-3-((*E*)-(4-metilpentan-2-ilidenamino)metil)pirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol que luego se hidrolizó por calentamiento a 50 °C en 80 ml de una mezcla de

agua/isopropanol (1:1) durante 6 horas. La reacción se enfrió hasta temperatura ambiente y la capa acuosa se extrajo dos veces con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. La purificación por medio de cromatografía en gel de sílice usando 5-20% de MeOH y CH_2Cl_2 dio como resultado 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (400 mg, 19% después de 3 etapas). LC/MS: *m/z* 353,1 $(M+H)^+$ a 1,22 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002102] ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isopropilo



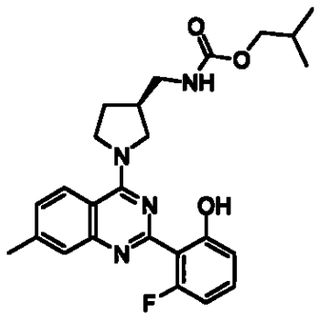
[002103]

[002104] Cloroformiato de isopropilo (10 mg, 0,09 mmol) se añadió a una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (0,03 g, 0,09 mmol) y trietilamina (25 ml, 0,18 mmol) en DMF (0,6 ml) a -78 °C (temperatura externa). La mezcla de reacción se calentó hasta

temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isopropilo en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,31 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002105] Ejemplo 372

[002106] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo**



[002107]

[002108] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo**

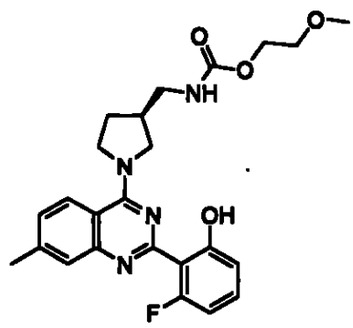
[002109] Cloroformiato de isobutilo (12 mg, 0,09 mmol) se añadió a una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (0,03 g, 0,09 mmol) y trietilamina (25 ml, 0,18 mmol) en DMF (0,6 ml) a -70 °C

(temperatura externa). La mezcla de reacción se calentó hasta temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo en forma de la sal de TFA. LC/MS: *m/z* 453,5 $(M+H)^+$ a 2,46 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

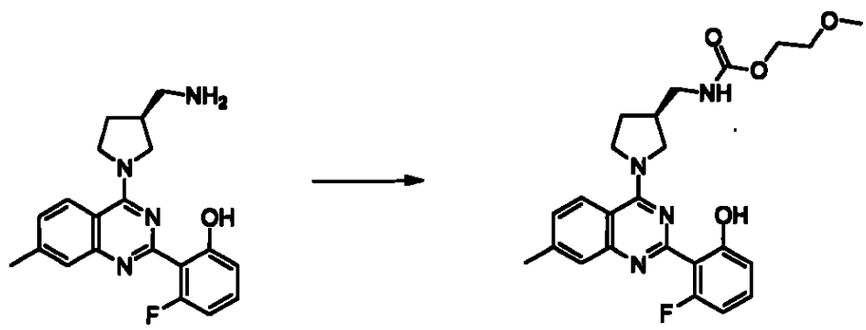
[002110] Ejemplo 373

[002111] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo**

[002112]



[002113] **((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo**

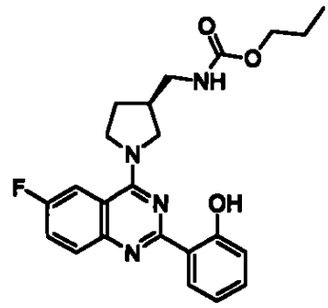


[002114]

[002115] Cloroformiato de 2-metoxietilo (12 mg, 0,09 mmol) se añadió a una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-7-metilquinazolin-2-il)-3-fluorofenol (0,03 g, 0,09 mmol) y trietilamina (25 ml, 0,18 mmol) en DMF (0,6 ml) a -78 °C. La mezcla de reacción se calentó hasta temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener 2-metoxietilo ((*S*)-1-(2-(2-fluoro-6-hidroxifenil)-7-metilquinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo en forma de la sal de TFA. LC/MS: *m/z* 455,5 $(M+H)^+$ a 2,11 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002116] Ejemplo 374

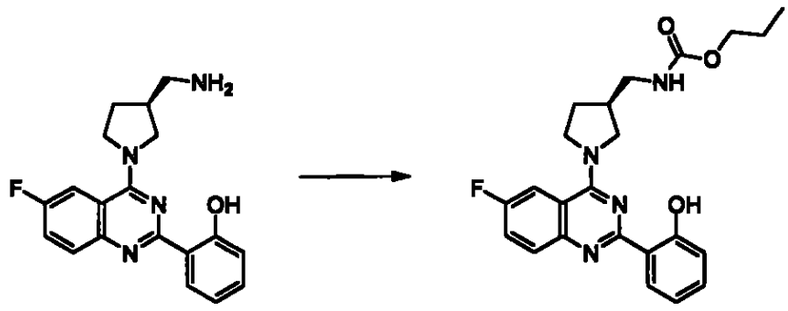
[002117] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo**



[002118]

[002119] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de propilo**

[002120]

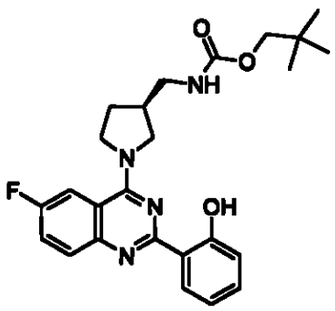


[002121] A una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) a -60 °C (temperatura externa) se añadió trietilamina (25 ml, 0,18 mmol), seguido de la adición de cloroformiato de propilo (11 mg, 0,09 mmol). La reacción se calentó hasta temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de

propilo en forma de la sal de TFA. LC/MS: *m/z* 425,3 $(M+H)^+$ a 2,31 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002122] Ejemplo 375

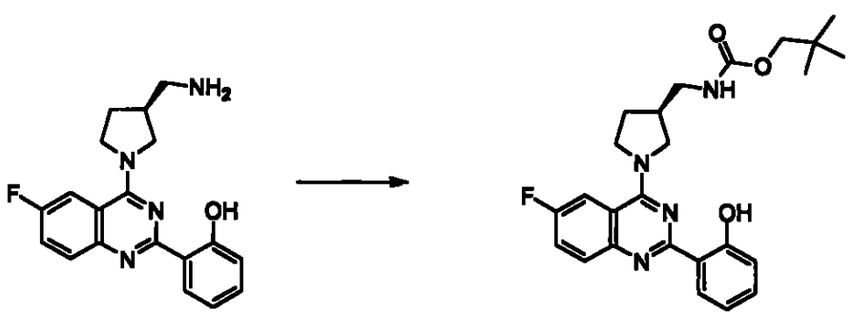
[002123] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo**



[002124]

[002125] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo**

[002126]

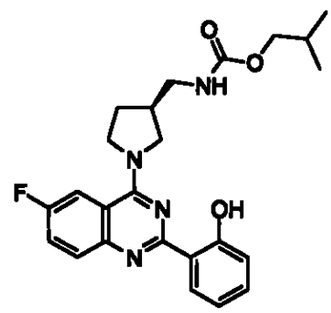


[002127] A una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) a -60 °C (temperatura externa) se añadió trietilamina (25 ml, 0,18 mmol), seguido de

la adición de cloroformiato de neopentilo (13 mg, 0,09 mmol). La reacción se calentó hasta temperatura ambiente, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para obtener ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de neopentilo en forma de la sal de TFA. LC/MS: *m/z* 453,5 $(M+H)^+$ a 2,88 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

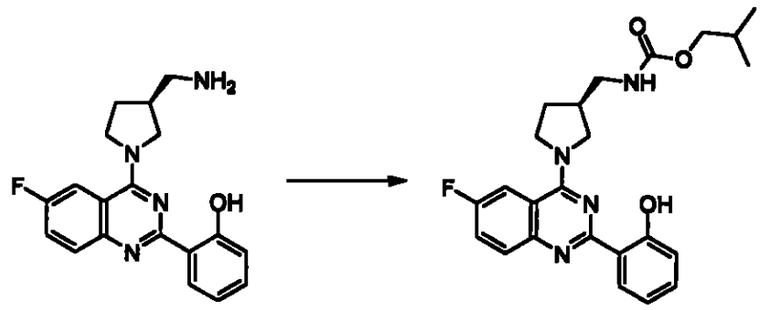
[002128] Ejemplo 376

[002129] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo**



[002130]

[002131] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo**

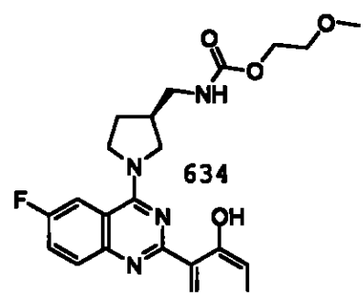


[002132]

[002133] A una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) a -60 °C (temperatura externa) se añadió trietilamina (25 ml, 0,18 mmol), seguido de la adición de cloroformiato de isobutilo (12 mg, 0,09 mmol). La reacción se calentó hasta temperatura ambiente y se filtró y la purificación por medio de HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de isobutilo en forma de la sal de TFA. LC/MS: *m/z* 439,5 $(M+H)^+$ a 2,76 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002134] Ejemplo 377

[002135] **((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-**

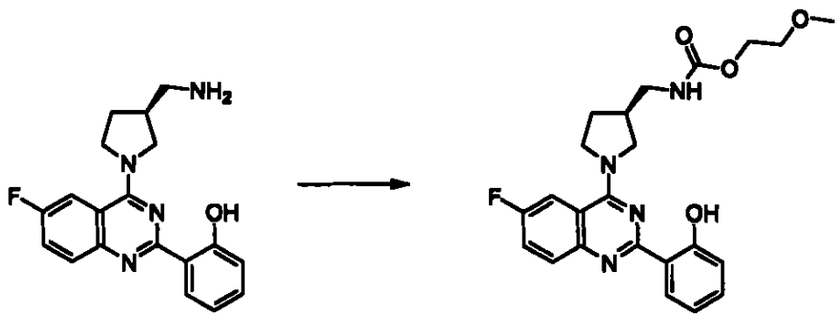


1195
1197

il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo

[002136]

[002137] ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo



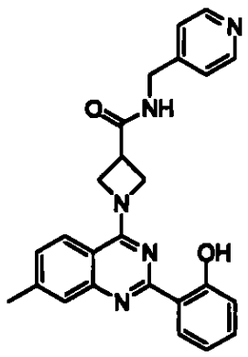
[002138]

[002139] A una solución de 2-(4-((*S*)-3-(aminometil)pirrolidin-1-il)-6-fluoroquinazolin-2-il)fenol (0,03 g, 0,09 mmol) en DMF (1,0 ml) a -60 °C (temperatura externa) se añadió trietilamina (25 ml, 0,18 mmol), seguido de la adición de cloroformiato de 2-metoxietilo (12 mg, 0,09 mmol). La reacción se calentó hasta temperatura ambiente y se filtró y la purificación por medio de HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) dio ((*S*)-1-(6-fluoro-2-(2-hidroxifenil)quinazolin-4-il)pirrolidin-3-il)metilcarbamato de 2-metoxietilo en forma de la sal de TFA. LC/MS: *m/z* 441,5 $(M+H)^+$ a 2,30 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

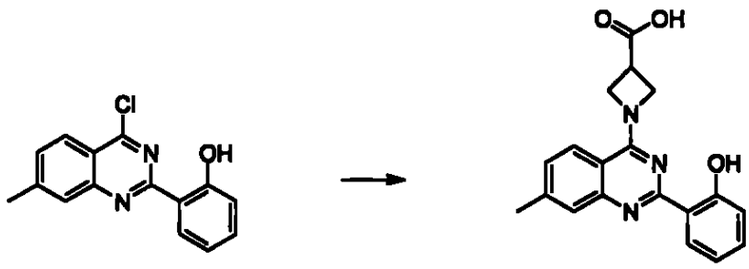
[002140] Ejemplo 401

[002141] **1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)-N-((piridin-4-il)metil)azetidin-3-carboxamida**

[002142]



[002143] **Ácido 1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxílico**

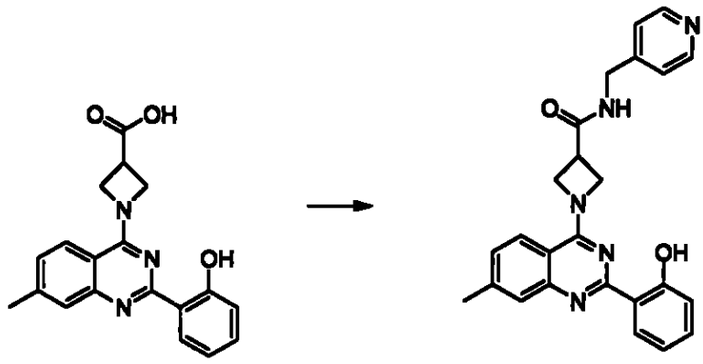


[002144]

[002145] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)fenol (2,84 g, 10,5 mmol) y ácido azetidin-3-carboxílico (1,06 g, 10,5 mmol) en DMF (100 ml) se añadió trietilamina (3,18 g, 4,39 ml, 31,5 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con H_2O (400 ml). El pH de la solución se ajustó a 3-4 por adición de una solución acuosa 1 M de HCl. El precipitado blanco se

obtenido luego se filtró, se lavó con H_2O y se purificó por cromatografía en gel de sílice usando 0-15% de MeOH-CH_2Cl_2 para dar ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxílico. LC/MS: *m/z* 336,3 $(M+H)^+$ a 1,97 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002146] 1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)-*N*-((piridin-4-il)metil)azetidin-3-carboxamida



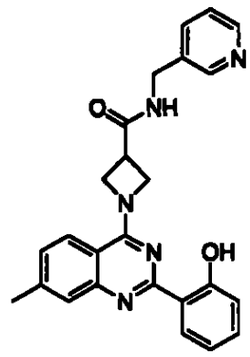
[002147]

[002148] A una solución de ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxílico (34 mg, 0,1 mmol) y HATU (57 mg, 0,15 mmol) en DMF (1 ml) se añadió (piridin-4-il)metanamina (32 mg, 30µL, 0,30 mmol). La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)-*N*-((piridin-4-il)metil)azetidin-3-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 426,3 $(M+H)^+$

a 1,72 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

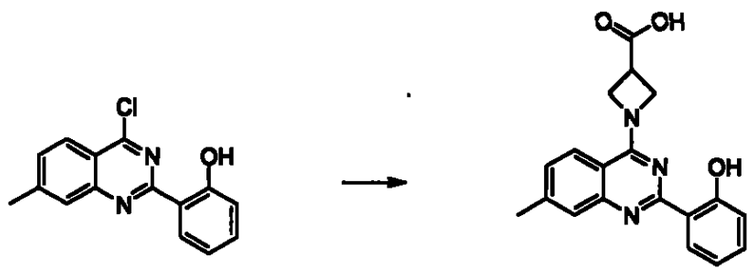
[002149] Ejemplo 402

[002150] **1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)-*N*-((piridin-3-il)metil)azetidin-3-carboxamida**



[002151]

[002152] **Ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxílico**

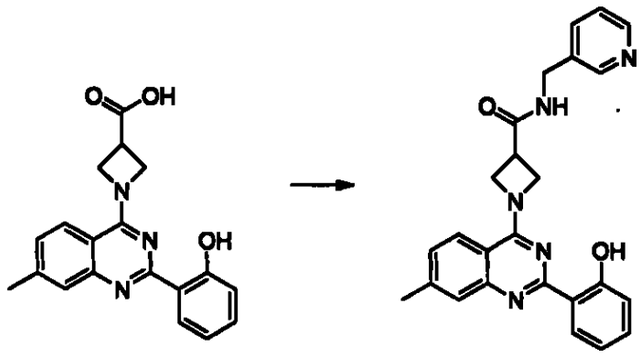


[002153]

[002154] A una solución de 2-(4-cloro-7-metilquinazolin-2-il)fenol (2,84 g, 10,5 mmol) y ácido azetidin-3-carboxílico (1,06 g, 10,5 mmol) en DMF (100 ml) se añadió trietilamina

(3,18 g, 4,39 ml, 31,5 mmol). La reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con H_2O (400 ml). El pH de la solución se ajustó a 3-4 por adición de una solución acuosa 1 M de HCl. El precipitado blanco obtenido luego se filtró, se lavó con H_2O y se purificó por cromatografía en gel de sílice usando 0-15% de MeOH-CH_2Cl_2 para dar ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxílico. LC/MS: *m/z* 336,3 $(M+H)^+$ a 1,97 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002155] 1-(2-(2-Hidroxifenil)-7-metilquinazolin-4-il)-*N*-((piridin-3-il)metil)azetidin-3-carboxamida



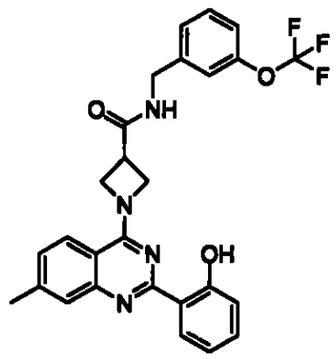
[002156]

[002157] A una solución de ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxílico (34 mg, 0,1 mmol) y HATU (57 mg, 0,15 mmol) en DMF (1 ml) se añadió (piridin-3-il)metanamina (32 mg, 30µL, 0,30 mmol). La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O

(0,05% de TFA)) para dar 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)-*N*-((piridin-3-il)metil)azetidin-3-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 426,3 $(M+H)^+$ a 1,72 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

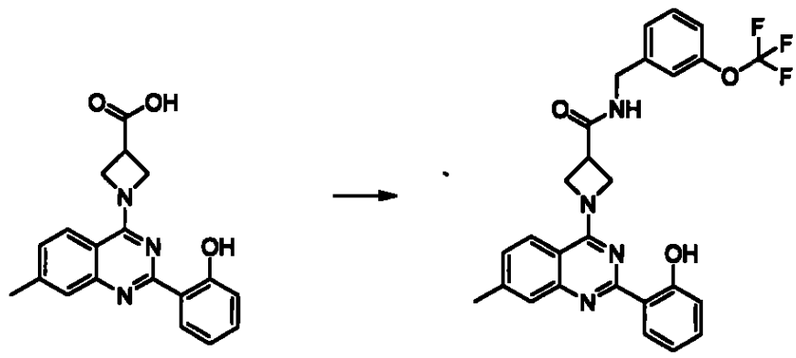
[002158] Ejemplo 403

[002159] ***N*-(3-(Trifluorometoxi)bencil)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxamida**



[002160]

[002161] ***N*-(3-(Trifluorometoxi)bencil)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxamida**



[002162]

[002163] A una solución de ácido 1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxílico (34 mg, 0,10 mmol) y HATU (57 mg, 0,15 mmol) en DMF (1 ml) se añadió (3-(trifluorometoxi)fenil)metanamina (57 µL, 0,30 mmol). La reacción se agitó a temperatura ambiente durante la noche, se filtró y se purificó por HPLC en fase inversa (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar *N*-(3-(trifluorometoxi)bencil)-1-(2-(2-hidroxifenil)-7-metilquinazolin-4-il)azetidin-3-carboxamida en forma de la sal de TFA. LC/MS: *m/z* 509,3 $(M+H)^+$ a 2,73 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

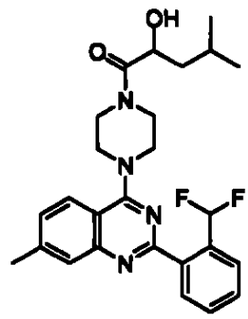
[002164] Ejemplo 501

[002165] **1-(4-(2-(2-(Difluorometil)fenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**

1197

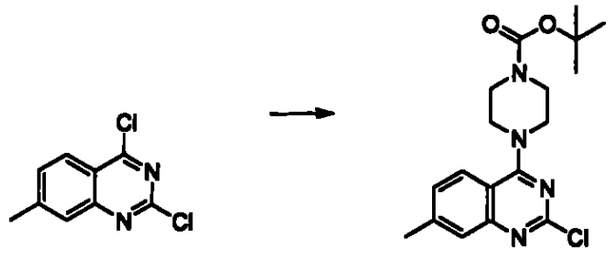
1204

[002166]



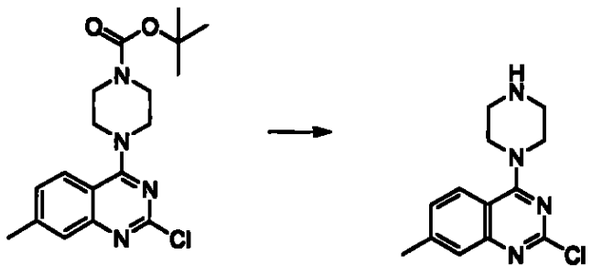
[002167] **ter-butilo 4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-carboxilato de ter-butilo**

[002168]



[002169] Una solución de 2,4-dicloro-7-metilquinazolina (0,43 g, 2,0 mmol), piperazin-1-carboxilato de *ter*-butilo (0,37 g, 2,0 mmol) y trietilamina (0,56 ml, 4,0 mmol) en CH_2Cl_2 (20 ml) se agitó a temperatura ambiente durante la noche. La solución se lavó con agua, se secó sobre Na_2SO_4 y se evaporó para dar 4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-carboxilato de *ter*-butilo (0,72 g, 99%). LC/MS: *m/z* 363,1 $(M+H)^+$ a 3,21 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

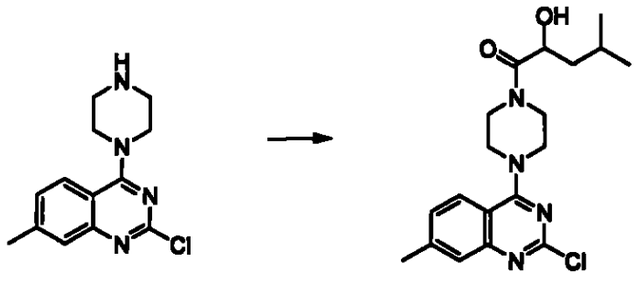
[002170] **Diclorhidrato de 2-cloro-7-metil-4-(piperazin-1-il)quinazolina**



[002171]

[002172] 4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-carboxilato de *ter*-butilo (0,72 g, 2,0 mmol) en HCl 4 M en dioxano (10 ml) se agitó a temperatura ambiente durante 5 horas. El solvente se evaporó para dar diclorhidrato de 2-cloro-7-metil-4-(piperazin-1-il)quinazolina (0,67 g, 100%). LC/MS: *m/z* 263,3 $(M+H)^+$ a 1,75 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002173] **1-(4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona**

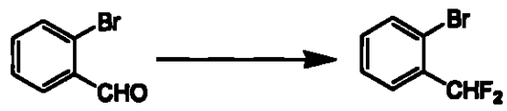


[002174]

[002175] Una solución de diclorhidrato de 2-cloro-7-metil-4-(piperazin-1-il)quinazolina (127 mg, 0,38 mmol), ácido 2-hidroxi-4-metilpentanoico (55 mg, 0,42 mmol), HATU (158 mg, 0,42 mmol) y trietilamina (163 µL, 1,2 mmol) en DMF (4 ml) se

agitó a temperatura ambiente durante 4 horas. La reacción se diluyó con agua y se extrajo con EtOAc. Los extractos combinados se lavaron con NaCl acuoso saturado y agua, se secaron sobre Na_2SO_4 y se evaporaron. La purificación por medio de cromatografía en gel de sílice usando 0-50% de EtOAc en hexanos dio 1-(4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (23 mg, 16%). LC/MS: *m/z* 377,3 $(M+H)^+$ a 2,71 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002176] 1-Bromo-2-(difluorometil)benceno



[002177]

[002178] Una mezcla de 2-bromobenzaldehído (27,1 g, 0,15 mol) y trifluoruro de (dietilamino)azufre (52 g, 0,32 mol) en benceno anhidro (250 ml) se calentó a reflujo durante la noche bajo una atmósfera de N_2. La mezcla se trató con $NaHCO_3$ (saturado acuoso) y CH_2Cl_2 y la fase orgánica se separó. La fase acuosa se extrajo con CH_2Cl_2 y las capas orgánicas combinadas se lavaron con agua y NaCl saturado acuoso. La eliminación del solvente dio 1-bromo-2-difluorometilbenceno (16 g, 52%). ^1H RMN ($CDCl_3$): δ 7,68 (d, 1H, J = 7,6), 7,62 (d,

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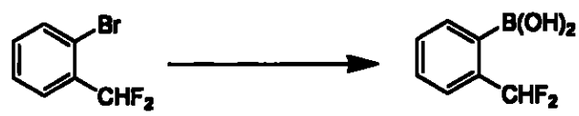
1 H, J = 7,6), 7,43 (t, 1 H, J = 7,6), 7,34 (t, 1 H, J = 7,6), 7,06-6,79 (t, 1 H, J = 55,2).

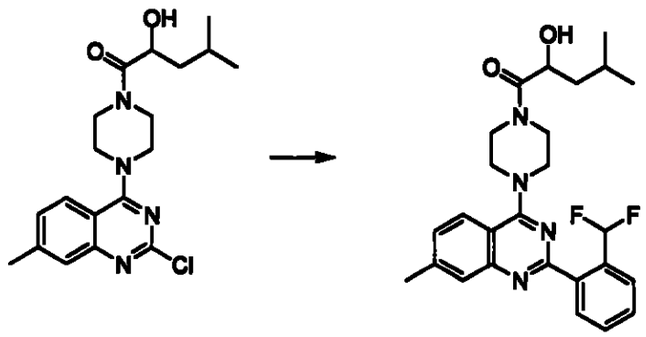
[002179] Ácido 2-(difluorometil)fenilborónico



[002180]

[002181] A una solución de 1-bromo-2-difluorometilbenceno (16 g, 0,077 mol) en THF (300 ml) se añadió *n*-BuLi (2,5 M, 46 ml, 0,12 mol) gota a gota a -78 °C. Al cabo de una hora, se agregó borato de trimetilo (16 g, 0,15 mol) gota a gota. La mezcla se calentó hasta temperatura ambiente lentamente durante la noche y luego la mezcla se trató con agua y acetato de etilo. La capa orgánica se extrajo con una solución acuosa al 10% de NaOH. La solución acuosa se acidificó con HCl acuoso diluido y se extrajo con acetato de etilo. La eliminación del solvente dio ácido 2-(difluorometil)fenilborónico (0,7 g, 5,3%). ^{1}H RMN($CDCl_3$): δ 8,28 (d, 1 H, J = 7,2), 7,86 (d, 1H, J = 7,2), 7,58-7,79 (m, 1 H), 7,73 (t, 1 H, J = 7,2), 7,65 (t, 1 H).

[002182] 1-(4-(2-(2-(Difluorometil)fenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona



[002183]

[002184] Una mezcla de 1-(4-(2-cloro-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona (23 mg, 61 µmol), ácido 2-(difluorometil)fenilborónico (13 mg, 73 µmol), $Pd(dppf)Cl_2$ (3 mg, 3,7 µmol) y K_2CO_3 (17 mg, 122 µmol) en DMF (1 ml) y H_2O (0,5 ml) se calentó en un vial sellado a microondas a 170 °C durante 6 minutos. Tras filtrar y evaporar de los solventes, la mezcla se purificó usando HPLC preparativa en fase inversa (10-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)) para dar 1-(4-(2-(2-(difluorometil)fenil)-7-metilquinazolin-4-il)piperazin-1-il)-2-hidroxi-4-metilpentan-1-ona en forma de la sal de TFA. LC/MS: *m/z* 469,3 $(M+H)^+$ a 2,44 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002185] Ejemplo 502

[002186] **(2R)-*N*-(1-(2-(2-(Difluorometil)fenil)-7-metilquinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida**

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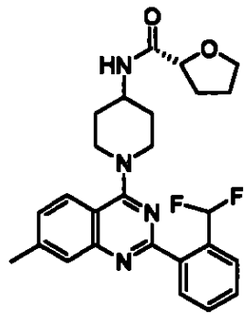
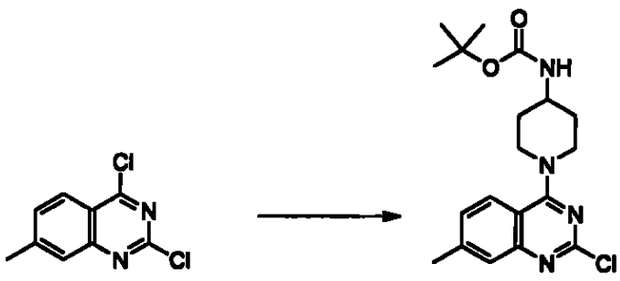


[002187]

[002188] **1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo**

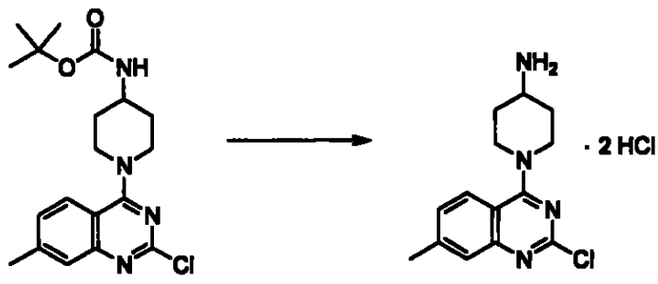


[002189]

[002190] A una solución de 2,4-dicloro-7-metilquinazolina (1,06 g, 5,0 mmol) en CH_2Cl_2 (20 ml) enfriada en un baño de hielo bajo una atmósfera de N_2 se añadió piperidin-4-ilcarbamato de *ter*-butilo (1,0 g, 5,0 mmol) disuelto en CH_2Cl_2 (30 ml). A esto se añadió trietilamina (1,4 ml, 10,0 mmol) y la reacción se dejó calentar hasta temperatura ambiente. Tras agitar durante 1 h, la solución se lavó con agua y se secó sobre Na_2SO_4. Los solventes se evaporaron para obtener 1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-

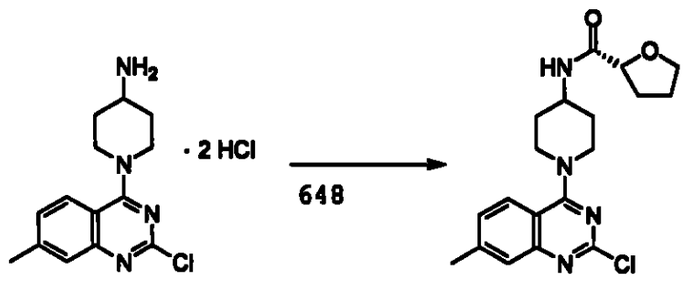
butilo en forma de un sólido amarillo (1,6 g, 85%). LC/MS: *m/z* 377,5 $(M+H)^+$ a 2,96 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002191] Diclorhidrato de 1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-amina

[002192] 

[002193] En una atmósfera de N_2, se añadió una solución de HCl 4 M en dioxano (50 ml) a 1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-ilcarbamato de *ter*-butilo (1,06 g, 2,82 mmol) y la mezcla se agitó durante 3 h. Después de evaporar los solventes, el sólido resultante se extrajo en CH_2Cl_2 y EtOAc y se concentró para obtener diclorhidrato de 1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-amina en forma de un polvo rosado claro (985 mg, 100%). LC/MS: *m/z* 277,3 $(M+H)^+$ a 1,57 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002194] (*R*)-*N*-(1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida



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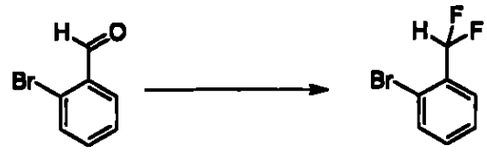
[002195]

[002196] A una mezcla de ácido (*R*)-tetrahidrofuran-2-carboxílico (0,13 ml, 1,58 mmol) en CH_2Cl_2 (2 ml) se añadió HATU (0,5 g, 1,58 mmol). Tras añadir trietilamina (0,74 ml, 5,28 mmol), la solución se agitó durante 30 min. Se añadió diclorhidrato de 1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-amina (460 mg, 1,32 mmol) y la reacción se agitó durante la noche. La solución amarilla, turbia se lavó 4 veces con H_2O y la capa acuosa se re-extrajo con CH_2Cl_2. Después de concentrar las fases orgánicas combinadas, la purificación por medio de cromatografía en gel de sílice usando 0-100% de EtOAc en hexanos dio (*R*)-*N*-(1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida (0,17 g, 33%). LC/MS: *m/z* 475,3 $(M+H)^+$ a 2,20 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002197] **1-Bromo-2-difluorometil-benceno**

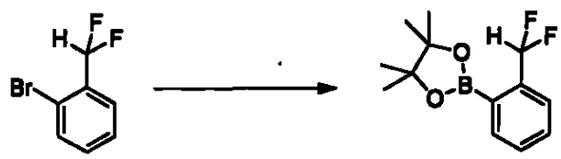


[002198]

[002199] Una solución de 2-bromobenzaldehído (55,5 g, 300 mmol) y trifluoruro de (dietilamino)azufre (75,0 g, 467 mmol) en 250 ml de diclorometano se calentó a reflujo bajo una atmósfera de nitrógeno durante la noche. La solución enfriada

se vertió en 0,5 L de $NaHCO_3$ acuoso al 15% y se agitó hasta que no se produjera más CO_2. Las capas se separaron y la capa acuosa se extrajo con 250 ml de diclorometano. Las capas orgánicas combinadas se lavaron con 250 ml de $NaHCO_3$ acuoso al 5% y NaCl saturado acuoso, se secó sobre Na_2SO_4, se filtró y se evaporó hasta sequedad a presión reducida. El material crudo se purificó por destilación al vacío y se recogió la fracción en ebullición a 62-63 °C a 12 mbar, dando como resultado 1-bromo-2-difluorometil-benceno (42,6 g, 69%) en forma de un aceite de color amarillo claro.

[002200] 2-(2-Difluorometil-fenil)-4,4,5,5-tetrametil-[1,3,2]dioxaborolano

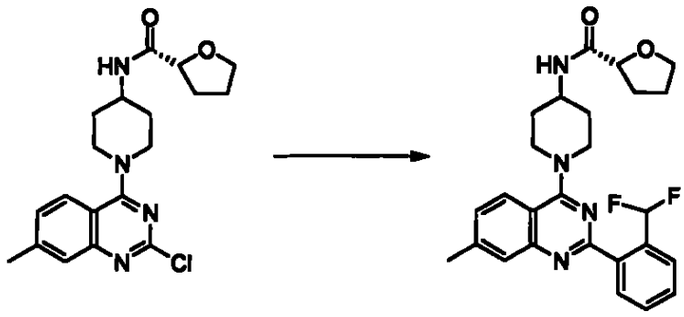


[002201]

[002202] A una solución de 1-bromo-2-difluorometil-benceno (19,8 g, 95,7 mmol) en THF seco (200 ml) a -78 °C bajo una atmósfera de nitrógeno se añadió lentamente *n*-BuLi 2,5 M en hexanos (42 ml, 105 mmol). Una vez completada la adición, se agitó la solución oscura resultante durante una hora adicional a -78 °C. Posteriormente, se añadió 2-isopropoxi-4,4,5,5-tetrametil-1,3,2-dioxaborolano (25 ml, 123 mmol) y la solución se calentó lentamente hasta temperatura ambiente. Tras agitar

durante la noche a temperatura ambiente bajo una atmósfera de nitrógeno, la solución se vertió en 400 ml agua. Se añadió acetato de etilo (300 ml) y las capas se separaron. La capa acuosa se extrajo dos veces con acetato de etilo (150 ml y 50 ml, respectivamente) y las capas orgánicas combinadas se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se evaporaron hasta sequedad a presión reducida. El aceite marrón resultante (21 g) se purificó por destilación bulbo a bulbo a $3x10^{-3}$ mbar a 90-95 °C para obtener 2-(2-difluorometil-fenil)-4,4,5,5-tetrametil-[1,3,2]dioxaborolano (14,4 g, 59%) en forma de un aceite ligeramente amarillo.

[002203] (2*R*)-*N*-(1-(2-(2-(Difluorometil)fenil)-7-metilquinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida



[002204]

[002205] A una mezcla de (*R*)-*N*-(1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida (65,2 mg, 0,17 mmol), 2-(2-(difluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (0,09 ml, 0,35 mmol), $Pd(dppf)Cl_2$ (17,1 mg, 0,02 mmol) y K_2CO_3 (48,1 mg, 0,35 mmol) se añadió DMF (3,3 ml)

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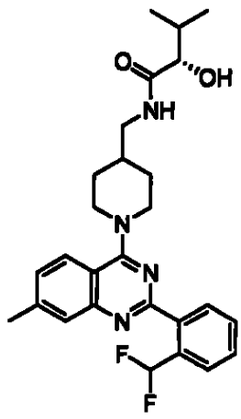
y la reacción se calentó en un sintetizador a microondas a 170 °C durante 6 min. Como la LC/MS mostró que la reacción no estaba completa, se añadieron otros 2 equivalentes de 2-(2-(difluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (0,09 ml, 0,38 mmol) y la reacción se calentó hasta 170 °C en un sintetizador a microondas durante 6 minutos. La solución se diluyó con EtOAc y se lavó con H_2O. La fracción acuosa se re-extrajo con EtOAc y las capas orgánicas se combinaron, se secaron sobre Na_2SO_4 y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-40% de EtOAc en CH_2Cl_2/hexanos (1:1) dio (2*R*)-*N*-(1-(2-(2-(difluorometil)fenil)-7-metilquinazolin-4-il)piperidin-4-il)-tetrahidrofuran-2-carboxamida (38 mg, 47%). LC/MS: *m/z* 467,3 $(M+H)^+$ a 2,20 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

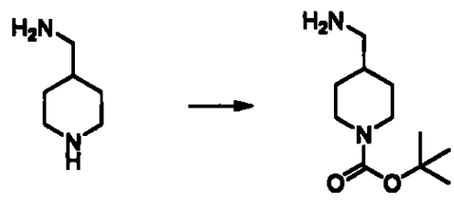
[002206] Ejemplo 503

[002207] **(2*S*)-*N*-((1-(2-(2-(Difluorometil)fenil)-7-metilquinazolin-4-il)piperidin-4-il)metil)-2-hidroxi-3-metilbutanamida**



[002208]

[002209] **4-(aminometil)piperidin-1-carboxilato de ter-butilo**



[002210]

[002211] Una solución de 4-(aminometil)-piperidina (25,3 g, 222 mmol) y benzaldehído (23,5 g, 222 mmol) en 250 ml de tolueno se calentó a reflujo durante la noche bajo una atmósfera de nitrógeno en un recipiente equipado con una trampa de Dean-Stark. La solución se enfrió hasta 0-5 °C en un baño de hielo y se añadió Boc_2O (53,2 g, 244 mmol) en una porción. El baño de hielo se retiró y se continuó agitando a temperatura ambiente durante 6 horas. La mezcla se evaporó hasta sequedad a presión reducida y el residuo se agitó durante la noche con bisulfato de potasio en agua (33,2 g $KHSO_4$ en 244 ml agua). La solución se extrajo dos veces con 200 ml

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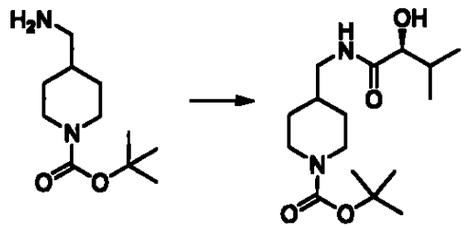
porciones de éter dietílico y se alcalinizó con 50 ml de solución acuosa al 30% de hidróxido de sodio. Después de saturar la solución con cloruro de sodio, se extrajo con diclorometano (1x 150 ml, 2 x 50 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se evaporaron hasta sequedad, dando como resultado 4-(aminometil)piperidin-1-carboxilato de *ter*-butilo (41,8 g, 88%) en forma de un aceite anaranjado.

[002212] Éster ter-butílico del ácido 4-[((*S*)-2-Hidroxi-3-metil-butirilamino)-metil]-piperidin-1-carboxílico



[002213]

[002214] HOBt (23,5 g, 174 mmol) y EDCI·HCl (33,5 g, 174 mmol) se añadieron a una mezcla de 4-(aminometil)piperidin-1-carboxilato de *ter*-butilo (37,3 g, 174 mmol), ácido (*S*)-(+)-2-hidroxi-3-metil-butanoico (20,6 g, 174 mmol) y trietilamina (50 ml, 349 mmol) en una mezcla de diclorometano (500 ml) y DMF (250 ml) enfriada en un baño de hielo. La reacción se agitó durante la noche a temperatura ambiente. Se añadió una porción adicional de EDCI·HCl (5 g) y trietilamina (4 ml) y se continuó agitando durante otras 4 horas. La mezcla se diluyó a 1 L con la adición de diclorometano y se lavó con porciones de

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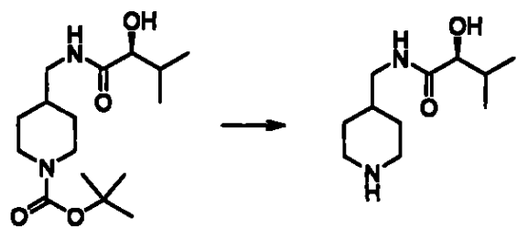
500 ml de agua, solución 1 N de HCl, solución acuosa al 5% de $NaHCO_3$, agua y solución acuosa saturada de NaCl. La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó hasta sequedad a presión reducida dando como resultado 52 g de producto crudo. Este material crudo se agitó con 200 ml de éter diisopropílico y el sólido se recogió por filtración y se lavó dos veces con porciones de 100 ml de éter diisopropílico para obtener 33 g (64%) de éster ter-butílico del ácido 4-[((*S*)-2-hidroxi-3-metil-butirilamino)-metil]-piperidin-1-carboxílico.

[002215] (*S*)-2-Hidroxi-3-metil-*N*-piperidin-4-ilmetil-butiramida

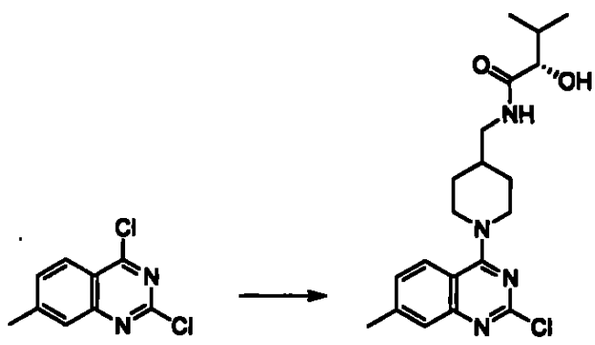


[002216]

[002217] Cloruro de acetilo (30 ml) se añadió gota a gota a 500 ml de metanol enfriado en un baño de hielo y después de completar la adición, la solución se agitó a temperatura ambiente durante 30 minutos. Se agregó éster ter-butílico del ácido 4-[((*S*)-2-hidroxi-3-metil-butirilamino)-metil]-piperidin-1-carboxílico (33 g) en 150 ml de metanol y se continuó agitando durante 2 horas a temperatura ambiente. La

solución se evaporó hasta sequedad para obtener 26,6 g de clorhidrato de (*S*)-2-hidroxi-3-metil-*N*-piperidin-4-ilmetil-butiramida en forma de un sólido blanco.

[002218] **(*S*)-*N*-((1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-il)metil)-2-hidroxi-3-metilbutanamida**

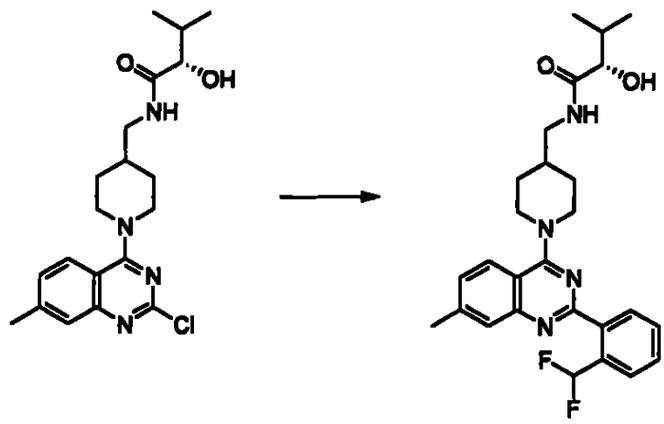


[002219]

[002220] Una solución de 2,4-dicloro-7-metilquinazolina (1,07 g, 5,0 mmol) en CH_2Cl_2 (20 ml) se enfrió en un baño de hielo. Se añadió clorhidrato de (*S*)-2-hidroxi-3-metil-N-((piperidin-4-il)metil)butanamida (1,25 g, 5,0 mmol) suspendido en 30 ml de CH_2Cl_2 se añadió en porciones, seguido de la adición de trietilamina (2,79 ml, 20,0 mmol). La reacción se dejó calentar hasta temperatura ambiente y se agitó durante 1,5 h. Después de lavar la mezcla 4 veces con H_2O, la porción acuosa se reextrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron, se concentraron y se secaron al vacío para obtener (*S*)-*N*-((1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-il)metil)-2-hidroxi-3-

metilbutanamida en forma de un sólido amarillo (1,83 g, 94%). LC/MS: *m/z* 391,3 $(M+H)^+$ a 2,32 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002221] **(2*S*)-*N*-((1-(2-(2-(Difluorometil)fenil)-7-metilquinazolin-4-il)piperidin-4-il)metil)-2-hidroxi-3-metilbutanamida**



[002222]

[002223] A una solución de (*S*)-*N*-((1-(2-cloro-7-metilquinazolin-4-il)piperidin-4-il)metil)-2-hidroxi-3-metilbutanamida (200 mg, 0,51 mmol), 2-(2-(difluorometil)fenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano (195 µL, 0,77 mmol) y K_2CO_3 (142 mg, 1,02 mmol) en una mezcla de DMF:H_2O (4:1) se añadió $Pd(dppf)Cl_2$ (25,3 mg, 0,03 mmol). La mezcla de reacción se calentó en un sintetizador a microondas a 170 °C durante 6 minutos La reacción se diluyó con EtOAc y se lavó con 30 ml solución acuosa saturada de NaCl. La porción

orgánica se lavó 3 veces con H_2O y las capas acuosas combinadas se re-extrajeron 3 veces con EtOAc. Todas las porciones orgánicas combinadas se secaron luego sobre Na_2SO_4, se filtraron y se concentraron. La purificación por medio de cromatografía en gel de sílice usando 0-70% de EtOAc en CH_2Cl_2:hexanos (1:1) dio como resultado 177 mg (71%) de (2*S*)-*N*-((1-(2-(2-(difluorometil)fenil)-7-metilquinazolin-4-il)piperidin-4-il)metil)-2-hidroxi-3-metilbutanamida que cristalizó en forma de un sólido blanco tras congelar durante 1 h. LC/MS: *m/z* 483,3 $(M+H)^+$ a 2,24 min (10%-99% de CH_3CN (0,035% de TFA)/H_2O (0,05% de TFA)).

[002224] La **Tabla 3** que figura a continuación menciona datos analíticos de compuestos de ejemplo de la presente invención.

Tabla 3

RT4
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Comp. N.°	LC-MS M+1	LC-RT min
101	449,3	2,79
102	421	2,48
103	499,3	2,97
104	464,5	2,03
105	447,1	2,32
106	465,5	2,47
107	442,5	1,97
108	407,5	2,21
109	393,1	2,04
110	461,1	2,56
111	453,5	3,21
112	461,3	2,49
113	421,1	2,76
114	474,3	1,19
115	421,3	2,51
116	442,5	1,96
117	439,5	2,79
118	393,3	2,22
119	465,2	2,5

Comp. N.°	LC-MS M+1	LC-RT min
120	435,3	2,65
121	393,3	2,21
122	435,3	2,56
123	465,3	2,5
124	407,5	2,29
125	453,4	2,79
126	471,2	2,93
127	445,5	3,32
128	451,5	2,62
129	407,5	2,31
130	469,3	2,87
131	469,4	2,88
132	456,5	2,04
133	454,3	1,94
134	421,1	2,46
135	467,1	2,59
136	453,3	3,02
137	407,3	2,28
138	453,3	2,43
139	439,5	2,95

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Comp. N.°	LC-MS M+1	LC-RT min
140	485,5	2,94
141	459,3	2,13
142	446,3	3,17
143	439,5	2,99
144	435,3	2,9
145	437,3	2,04
146	455,5	2,45
147	453,3	2,4
148	439,5	2,8
149	465,5	2,23
150	449,3	2,22
151	435,5	2,13
152	456,5	2,02
153	453,4	2,73
154	436,3	1,94
155	477,5	2,96
156	474,3	1,19
157	485,4	3,02
158	403,5	2,34
159	421,3	2,6

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Comp. N.°	LC-MS M+1	LC-RT min
160	467,3	3,13
162	467,3	2,33
163	453,3	2,25
164	451,3	2,18
165	421,3	2,4
166	434,53	2,61
167	491,3	2,46
168	435,3	2,91
169	577,4	2,5
170	473,1	2,63
171	517,5	3,49
172	465	2,77
173	393,1	2,03
174	407,5	2,41
175	460,5	2,33
176	435,5	2,62
177	447,1	2,53
178	447,3	2,5
179	427,2	2,59
180	435,2	2,88

Comp. N.°	LC-MS M+1	LC-RT min
181	435,3	2,69
182	435,3	2,5
183	435,3	2,5
184	449,3	2,5
185	449,3	2,56
201	454,5	1,87
203	449,3	2,34
204	449,3	2,33
205	433,3	2,33
206	433,5	2,34
207	449,5	2,34
208	449,5	2,33
209	447,5	2,27
210	463,5	2,34
211	463,5	2,34
212	417	2,3
213	453,5	1,98
214	463,5	2,32
215	463,5	2,36
216	463,5	2,35

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Comp. N.°	LC-MS M+1	LC-RT min
217	463,5	2,35
218	447,5	2,02
219	477,4	2,84
220	447,5	2,19
221	461,5	2,22
222	531,3	3,08
223	468,3	1,86
224	437,1	2,54
225	468,6	2,19
226	417,5	2,3
227	470,5	1,98
228	470,5	1,98
229	513,3	2,82
230	447,3	2,21
231	481,1	2,17
232	463,3	2,58
233	421,2	2,17
234	449,2	2,42
235	407,5	2,04
236	407,3	2,08

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Comp. N.°	LC-MS M+1	LC-RT min
237	407,5	2,09
238	435,3	2,4
239	461,1	2,4
240	435,5	2,29
241	421,1	2,24
242	421,3	2,18
243	421,3	2,18
244	421,3	2,18
245	449,3	2,45
246	475,1	2,46
247	435,3	2,31
248	435,3	2,24
249	481,3	2,42
250	449,5	2,77
251	421	2,48
252	449,3	2,8
253	449,5	2,78
254	421,1	2,5
255	435,5	2,61
256	435,5	2,61

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Comp. N.°	LC-MS M+1	LC-RT min
257	451,1	2,34
258	441,5	2,6
259	435,2	3,03
260	467,1	2,56
261	469,1	2,2
262	439,3	2,31
264	435,1	2,6
265	449,3	2,72
266	449,2	2,55
267	449,3	2,58
268	449,1	2,54
269	449,5	2,57
270	435,2	2,88
271	447,2	2,46
272	449,2	2,57
273	449,2	2,57
274	463,4	2,42
275	463,4	2,43
276	433,2	2,33
277	433,2	2,32

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Comp. N.°	LC-MS M+1	LC-RT min
278	449,2	2,85
279	435,4	2,61
301	435	2,41
302	419	2,35
303	419	2,34
304	435	2,39
305	449,3	2,18
306	449,3	2,16
307	449,3	2,18
308	433,5	2,11
309	455,2	2,81
310	433,5	2,13
311	403,7	2,17
312	389,2	2,38
313	441	2,78
314	463,4	2,66
315	432,5	2,24
316	433,5	2,05
317	447,3	2,07
318	454,3	1,79

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Comp. N.°	LC-MS M+1	LC-RT min
319	456,5	1,85
320	456,5	1,84
321	499,3	2,57
322	454,4	2,08
323	445,4	2,85
324	460,4	2,1
325	509,5	2,71
326	455,3	2,43
327	450,3	2,39
328	426,3	1,91
329	393,3	2,23
330	465,4	2,88
331	477,3	2,81
332	511,5	3,07
333	443,5	2,83
334	511,5	3,1
335	439,5	2,25
336	493,5	3,03
337	439,5	2,25
338	451,5	2,15

Comp. N.°	LC-MS M+1	LC-RT min
339	467,3	2,5
340	445,4	2,95
341	443,4	2,73
342	468,4	2,39
343	493,4	2,76
344	443,3	2,69
345	453,3	2,05
346	407,5	2,2
347	430,5	1,95
348	430,5	2,43
349	430,5	1,98
350	444,5	1,85
351	444,5	2,24
352	444,5	1,89
353	426,1	1,93
354	426,1	2,33
355	453,3	2,29
356	453,3	2,29
357	407,3	2,26
358	477,3	2,8

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Comp. N.°	LC-MS M+1	LC-RT min
359	491,3	2,24
360	473,1	2,32
361	449,3	2,4
362	469,1	2,58
363	469,1	2,58
364	407,7	2,3
365	435,3	2,57
366	437,3	2,18
367	421,1	2,44
368	421,1	2,43
369	449,3	2,67
370	421	2,84
371	439,5	2,31
372	453,5	2,46
373	455,5	2,11
374	425,3	2,31
375	453,5	2,88
376	439,5	2,76
377	441,5	2,3
401	426,3	1,72

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Comp. N.°	LC-MS M+1	LC-RT min
402	426,3	1,72
403	509,3	2,73
404	393,2	1,95
405	421,2	2,29
406	421,2	2,2
407	435,4	2,23
408	435,4	2,16
409	421,2	2,15
410	421,1	2,4
411	435,2	2,24
412	405,2	2,09
413	435,4	2,16
414	435,2	2,17
415	449,2	2,25
416	435,3	2,25
417	419,4	2,06
418	421,2	2,57
419	423,2	2,15
420	407,2	2,42
501	467,3	2,14

Comp. N.°	LC-MS M+1	LC-RT min
502	469,3	2,44
503	483,3	2,24
504	455,4	2,91
505	367,9	2,79
506	339,9	2,38
507	469,3	2,97
508	441,3	2,54
509	455,5	2,13
510	469,5	2,37
511	471,3	2,28
512	467,3	2,14
513	483,3	2,25
514	483,3	2,24

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[002225] Métodos:

[002226] (A)Micromass MUX LCT 4 canales LC/MS, bomba Waters 60F, aparato de automuestreo de sonda Gilson 215 4, módulo de inyección Gilson 849, velocidad de flujo 1,5 ml/min/columna, 10-99% de gradiente de CH_3CN (0,035 % de TFA) / H_2O (0,05 % de TFA), columnas Phenomenex Luna 5u C18 (50 x 4,60 mm), detector de UV Waters MUX UV-2488, detectores Cedex 75 ELSD.

[002227] (B)PESciex API-150-EX LC/MS, bombas Shimadzu LC-8A, aparato de automuestreo Gilson 215, módulo de inyección Gilson 819, velocidad de flujo 3,0 ml/min, 10-99% de gradiente de CH_3CN (0,035 % de TFA) / H_2O (0,05 % de TFA), columna Phenomenex Luna 5u C18 (50 x 4,60 mm), detector Shimadzu SPD-10A UV/Vis, detector Cedex 75 ELSD.

[002228] (C)PESciex API-150-EX LC/MS, bombas Shimadzu LC-8A, aparato de automuestreo Gilson 215, módulo de inyección Gilson 819, velocidad de flujo 3,0 ml/min, 40-99% de gradiente de CH_3CN (0,035 % de TFA) / H_2O (0,05 % de TFA), columna Phenomenex Luna 5u C18 (50 x 4,60 mm), detector Shimadzu SPD-10A UV/Vis, Cedex 75 ELSD.

[002229] **ENSAYOS PARA DETECTAR Y MEDIR LAS PROPIEDADES INHIBIDORAS DE NaV DE LOS COMPUESTOS**

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[002230] A) Métodos ópticos para ensayar las propiedades de inhibición de NaV de los compuestos:

[002231] Los compuestos de la invención son útiles como antagonistas de canales iónicos de sodio regulados por voltaje. Las propiedades antagonistas de los compuestos de prueba se evaluaron como sigue. Se colocaron células que expresan el NaV de interés en placas de microtitulación. Al cabo de un periodo de un periodo de incubación, las células se tiñeron con colorantes fluorescentes sensibles al potencial transmembrana. Los compuestos de prueba se añadieron a la placa de microtitulación. Las células se estimularon con un medio químico o eléctrico para evocar un cambio de potencial de membrana dependiente de NaV a partir de los canales desbloqueados, que se detectó y midió con colorantes sensibles a potenciales de transmembrana. Los antagonistas se detectaron como respuesta disminuida de potencial de membrana al estímulo. El ensayo óptico de potencial de membrana utilizó sensores FRET sensibles a voltaje descritos por González y Tsien (Véase, González, J. E. y R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J **69**(4): 1272-80 y González, J. E. y R. Y. Tsien (1997) "Improved indicators of cell membrane potential that use fluorescence resonance energy transfer" Chem Biol **4**(4): 269-77) en combinación con instrumentación para medir

cambios de fluorescencia tales como el lector de sonda iónica/voltaje (VIPR®) (Véase González, J. E., K. Oades, y otro (1999) "Cell-based assays e instrumentation for screening ion-channel targets" Drug Discov Today 4(9): 431-439).

[002232] B) Método VIPR® de ensayo óptico de potencial de membrana con estimulación química

[002233] Manipulación celular y carga de colorante

[002234] 24 horas antes del ensayo en VIPR, se siembran células CHO con expresión endógena de NaV regulado por voltaje de tipo NaV1,2 en placas de 96 cavidades recubiertas por polilisina con 60.000 células por cavidad. Otros subtipos se realizaron en modo análogo en una línea celular que expresa el NaV de interés.

1) El día del ensayo se aspiró el medio y las células se lavaron dos veces con 225 µL de Solución Bat #2 (BS#2).
2) Se preparó una solución 15 uM de CC2-DMPE al mezclar solución madre de 5 mM de cumarina con 10% de Pluronic 127 1:1 y luego se disolvió la mezcla en el volumen adecuado de BS#2.
3) Luego de eliminar Bat de las placas de 96 cavidades, las células se cargaron con 80 µL de solución CC2-DMPE. Las placas se incubaron en oscuridad durante 30 minutos a temperatura ambiente.

4) Mientras se tiñeron las células con cumarina se preparó una solución 15 µL de oxonol en BS#2. Además de $DiSBAC_2(3)$, esta solución debería contener 0,75 mM de ABSC1 y 30 µL de veratridina (preparada de 10 mM EtOH de solución madre, Sigma #V-5754).

5) Al cabo de 30 minutos, se eliminó CC2-DMPE y las células se lavaron dos veces con 225 µL de BS#2. Como antes, el volumen residual debería ser 40 µL.

6) Tras extraer bat, las células se cargaron con 80 µL de la solución $DiSBAC_2(3)$, después de añadir el compuesto de prueba, disuelto en DMSO, para obtener la concentración de prueba deseada a cada cavidad desde la placa de adición del fármaco y se mezcló exhaustivamente. El volumen en cada cavidad debería ser de alrededor de 121 µL. Las células luego se incubaron durante 20-30 minutos.

7) Una vez completada la incubación, las células están listas para ser ensayadas en VIPR® con un protocolo de adición de sodio. 120 µL de solución Bat #1 se añade para estimular la despolarización dependiente de NaV. Se usaron 200 µL de tetracaína como control positivo de antagonista para bloquear el canal NaV.

[002235] Análisis de datos de VIPR®:

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[002236] Los datos se analizaron y se informaron como relaciones normalizadas de intensidad de emisión con sustracción de fondo medidas en canales de 460 nm y 580 nm. Las intensidades de fondo luego se restan de cada canal de ensayo. Las intensidades de fondo se obtienen al medir las intensidades de emisión durante los mismos periodos a partir de cavidades de ensayo tratadas en forma idéntica en donde no hay células. La respuesta en función del tiempo luego se informa como las relaciones obtenidas usando la siguiente fórmula:

$$R(t) = \frac{(\text{intensidad}_{460\ nm} - \text{fondo}_{460\ nm})}{(\text{intensidad}_{580\ nm} - \text{fondo}_{580\ nm})}$$

[002237] Los datos también se reducen al calcular las relaciones inicial (R_i) y final (R_f). Hay valores de relación promedio durante parte o todo el periodo de pre-estimulación y durante los puntos de muestra durante el periodo de estimulación. Luego se calcula la respuesta al estímulo $R_. = R_f/R_i$. Para el análisis de la ventana del agregado de Na^+, la línea de base es de 2-7 s y la respuesta final se toma en muestra a los 15-24 s.

[002238] Las respuestas control se obtienen al realizar ensayos en presencia de un compuesto con las propiedades deseadas (control positivo), tales como tetracaína y en ausencia de agentes farmacológicas (control negativo). Las respuestas a los controles negativos (*N*) y positivos (*P*) se calculan como antes. La actividad antagonista del compuesto *A* se define como:

$A = \frac{R-P}{N-P} * 100$ .donde R es la relación de respuesta al compuesto de prueba

Soluciones [mM]

Solución Bat #1:NaCl 160, KCl 4,5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7,4 con NaOH

Solución Bat #2 TMA-Cl 160, $CaCl_2$ 0,1, $MgCl_2$ 1, HEPES 10, pH 7,4 con KOH (concentración final K ~ 5 mM)

CC2-DMPE:preparado como solución madre de 5 mM en DMSO y almacenado a -20°C

$DiSBAC_2(3)$:preparado como solución madre 12 mM en DMSO y almacenado a -20°C

ABSC1:preparado como solución madre 200 mM en H_2O destilada y almacenado a temperatura ambiente

[002239] Cultivo celular

[002240] Las células CHO se cultivan en DMEM (Medio Eagle modificado de Dulbecco; GibcoBRL #10569-010) suplementado con 10% FBS (suero bovino fetal, calificado; GibcoBRL #16140-071) y 1% Pen-Strep (penicilina-estreptomicina; GibcoBRL #15140-122). Las células se cultivaron en frascos con tapa ventilada, en 90% de humedad y 10% CO_2, has 100% de confluencia. Generalmente se dividen por tripsinización 1:10 o 1:20, según las necesidades programadas y se cultivó durante 2-3 días antes de la siguiente división.

[002241] C) Método VIPR® de ensayo óptico de potencial de membrana con estimulación eléctrica

[002242] El siguiente es un ejemplo de cómo se mide la actividad de inhibición de NaV1,3 usando el método de potenciales ópticos de membrana #2. Se realizan otros subtipos en un modo análogo en una línea celular que expresa el NaV de interés.

[002243] Células HEK293 que expresan en forma estable NaV1.3 se plaquearon en placas de microtitulación de 96 cavidades. Al cabo de un periodo de incubación adecuado, las células se

tiñeron con colorantes sensibles a voltaje CC2-DMPE/DiSBAC2(3) como sigue.

[002244] ***Reactivos:***

100 mg/ml Pluronic F-127 (Sigma #P2443), en DMSO seco

10 mM $DiSBAC_2(3)$ (Aurora #00-100-010) en DMSO seco

10 mM CC2-DMPE (Aurora #00-100-008) en DMSO seco

200 mM ABSC1 en H_20

Solución salina balanceada de Hank (Hyclone #SH30268,02) suplementado con 10 mM HEPES (Gibco #15630-080)

[002245] ***Protocolo de carga:***

[002246] **2X CC2-DMPE = 20 µM CC2-DMPE:** 10 mM CC2-DMPE se agitaron con fuerza con un volumen equivalente de 10% de pluronic, seguido de agitación intensa en la cantidad requerida de HBSS que contiene 10 mM HEPES. Cada placa celular requiere 5 ml de 2X CC2-DMPE. Se agregaron 50 µL de 2X CC2-DMPE en las cavidades que contienen células lavadas, que resultaron en una concentración final de 10 µM. Las células se tiñeron durante 30 minutos en oscuridad a temperatura ambiente.

[002247] **2X $DISBAC_2(3)$ con ABSC1 = 6 µM $DISBAC_2(3)$ y 1 mM ABSC1:** La cantidad requerida de 10 mM $DISBAC_2(3)$ se añadió a un tubo cónico de 50 ml y se mezcló con 1 µL 10% de pluronic

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por cada ml de solución a preparar y se agitaron juntos. Luego se añadió HBSS/HEPES para prepara una solución 2X. Finalmente se añadió ABSC1.

[002248] La solución 2X DiSBAC$_2$(3) se puede usar para solvatar las placas de compuesto. Nótese que las placas de compuesto se preparan en una concentración de fármaco 2X. Se volvió a lavar la placa teñida hasta un volumen residual de 50 µL. Se añadió 50 uL/cavidad de 2X DiSBAC$_2$(3) c/ ABSC1. Se tiñó durante 30 minutos en oscuridad a temperatura ambiente.

[002249] El instrumento de estimulación eléctrica y los métodos de uso se describen en los métodos de ensayo de canales iónicos PCT/US01/21652, incorporados en la presente por referencia. El instrumento comprende un manipulador de placa de microtitulación, un sistema óptico para excitar el colorante de cumarina mientas se registraron de forma simultánea las emisiones de cumarina y oxonol, un generador formador de ondas, un amplificador regulado por corriente o voltaje y un dispositivo para insertar también electrodos. Bajo el control integrado por computadora, este instrumento pasa los protocolos de estímulo eléctrico programado por el usuario a las células centro de las cavidades de la placa de microtitulación.

[002250] Reactivos

[002251] Buffer de ensayo #1

140 mM NaCl, 4,5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 10 mM glucosa, pH 7,40, 330 mOsm

Solución madre de Pluronic (1000X): 100 mg/ml pluronic 127 en DMSO seco

Solución madre de Oxonol sumergido (3333X): 10 mM $DiSBAC_2(3)$ en DMSO seco

Solución madre de Cumarina (1000X): 10 mM CC2-DMPE en DMSO seco

Solución madre de ABSC1 (400X): 200 mM ABSC1 en agua

[002252] Protocolo de ensayo

1. Insertar o usar los electrodos en cada cavidad a ensayar.
2. Usar el amplificador controlado por corriente para proveer pulsos de onda de estimulación para 3 s. Se realizaron dos segundos de registro de preestímulo para obtener las intensidades no estimuladas. Se realizaron cinco segundos de registro de post-estimulación para examinar la relajación al estado de reposo.

[002253] Análisis de datos

[002254] Los datos se analizaron e informaron como relaciones normalizadas de intensidades de emisión con sustracción del fondo medidas en los canales de 460 nm y 580 nm. Las

intensidades de fondo luego se restan de cada canal de ensayo. Las intensidades de fondo se obtienen al medir las intensidades de emisión durante los mismos periodos a partir de cavidades de ensayo tratadas en forma idéntica en donde no hay células. La respuesta en función del tiempo luego se informa como las relaciones obtenidas usando la siguiente fórmula:

$$R(t) = \frac{(\text{intensidad}_{460\ nm} - \text{fondo}_{460\ nm})}{(\text{intensidad}_{580\ nm} - \text{fondo}_{580\ nm})}$$

[002255] Los datos también se reducen al calcular las relaciones inicial (R_i) y final (R_f). Hay valores de relación promedio durante parte o todo el periodo de pre-estimulación y durante los puntos de muestra durante el periodo de estimulación. Luego se calcula la respuesta al estímulo $R_. = R_f/R_i$.

[002256] Las respuestas control se obtienen al realizar ensayos en presencia de un compuesto con las propiedades deseadas (control positivo), tales como tetracaína y en ausencia de agentes farmacológicas (control negativo). Las respuestas a los controles negativos (*N*) y positivos (*P*) se calculan como

antes. La actividad antagonista del compuesto *A* se define como:

$A = \frac{R-P}{N-P} * 100$ .donde R es la relación de respuesta al compuesto de prueba.

[002257] ENSAYOS ELECTROFISIOLÓGICAS PARA LA ACTIVIDAD DE NaV Y LA INHIBICIÓN DE COMPUESTOS DE PRUEBA

[002258] Se usó electrofisiología para evaluar la eficacia y la selectividad de bloqueadores de canales de sodio en las neuronas del ganglio de la raíz dorsal. Se aislaron neuronas de rata de los ganglios de la raíz dorsal y se mantuvieron en cultivo durante 2 a 10 días en presencia de NGF (50 ng/ml) (medio de cultivo que consistió en NeurobasalA suplementado con B27, glutamina y antibióticos). Se identificaron neuronas de pequeño diámetro (nociceptores, 8-12 µm de diámetro) visualmente y se sondaron con electrodos de vidrio de punta fina conectados con un amplificador (Axon Instruments). El modo de "placa de voltaje" se usó para evaluar el IC50 del compuesto con las células a - 60 mV. Además, el modo "de placa de corriente" se empleó para probar la eficacia de los compuestos en el bloqueo de la generación del potencial de acción en respuesta a las inyecciones de corriente. Los

resultados de estos experimentos contribuyeron a la definición del perfil de eficacia de los compuestos.

[002259] ENSAYO DE PLACA DE VOLTAJE EN NEURONAS DRG

[002260] Se registraron corrientes resistentes a TTX de somas DRG usando la variación de célula entera de la técnica de placa de parche. Los registros se realizaron a temperatura ambiente (~22° C) con electrodos de vidrio de borosilicato de paredes gruesas (WPI; resistencia 3-4 MΩ usando un amplificador Axopatch 200B (Axon Instruments). Luego de establecer la configuración de célula entera, se dejaron aproximadamente 15 minutos APRA equilibrar la solución pipeteada dentro de la célula, antes de comenzar el registro. Las corrientes se filtraron por debajo de 2-5 kHz y se tomaron muestras digitales a 10 kHz. Se compensó la resistencia de la serie 60-70% y se controló continuamente durante el experimento. El potencial de unión líquida (-7 mV) entre la solución pipeteada intracelular y la solución de registro externa no se justificó en el análisis de datos. Las soluciones de prueba se aplicaron a las células con un sistema de perfusión rápida impulsado por gravedad (SF-77; Warner Instruments).

[002261] Se determinaron las relaciones dosis-respuesta en modo de placa de voltaje al despolarizar repetidamente la célula respecto del potencial de mantenimiento específico del

experimento con un potencial de prueba de +10mV una vez cada 60 segundos. Se permitieron efectos bloqueadores en meseta antes de proceder a la siguiente concentración de prueba.

[002262] Soluciones

[002263] Solución intracelular (en mM): Cs-F (130), NaCl (10), $MgCl_2$ (1), EGTA (1,5), $CaCl_2$ (0,1), HEPES (10), glucosa (2), pH = 7,42, 290 mOsm.

[002264] Solución extracelular (en mM): NaCl (138), $CaCl_2$ (1,26), KCl (5,33), KH_2PO_4 (0,44), $MgCl_2$ (0,5), $MgSO_4$ (0,41), $NaHCO_3$ (4), Na_2HPO_4 (0,3), glucosa (5,6), HEPES (10), CdCl2 (0,4), NiCl2 (0,1), TTX ($0,25 \times 10^{-3}$).

[002265] ENSAYO DE PLACA DE CORRIENTE PARA INHIBICIÓN DE LA ACTIVIDAD DE CANAL NaV DE LOS COMPUESTOS

[002266] Se clampearon con corriente en configuración de célula entera con un amplificador Multiplamp 700A (Axon Inst). Se llenaron pipetas de borosilicato (4-5 MOhm) con (en mM):150 gluconato de K, 10 NaCl, 0,1 EGTA, 10 Hepes, 2 $MgCl_2$, (con buffer a pH 7,34 con KOH). Las células se bañaron en (en mM): 140 NaCl, 3 KCl, 1 MgCl, 1 CaCl y 10 Hepes). Se llevó a cero el potencial de pipeta antes de la formación del sello; los potenciales de unión líquida no se corrigieron durante la

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adquisición. Los registros se realizaron a temperatura ambiente.

[002267] Según estos procedimientos, se halló que los compuestos representativos de la presente invención poseen la actividad y la selectividad deseada de canal de sodio regulado por voltaje.

[002268] ENSAYOS PARA DETECTAR Y MEDIR PROPIEDADES DE INHIBICIÓN DE CaV 1,2 L-TipO DE LOS COMPUESTOS

[002269] A) métodos ópticos para analizar propiedades de inhibición de CaV de los compuestos:

[002270] Los compuestos de la invención son útiles como antagonistas de canales iónicos de calcio regulados por voltaje. Las propiedades antagonistas de los compuestos de prueba se evaluaron como sigue. Se colocaron células que expresan el CaV de interés en placas de microtitulación. Al cabo de un periodo de un periodo de incubación, las células se tiñeron con colorantes fluorescentes sensibles al potencial transmembrana. Los compuestos de prueba se añadieron a la placa de microtitulación. Las células se estimularon con un medio eléctrico para evocar un cambio de potencial de membrana dependiente de CaV a partir de los canales desbloqueados, que se detectó y midió con colorantes sensibles a potenciales de

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transmembrana. Los antagonistas se detectaron como respuesta disminuida de potencial de membrana al estímulo. El ensayo óptico de potencial de membrana utilizó sensores FRET sensibles a voltaje descritos por (Véase González, J. E. y R. Y. Tsien (1995) "Voltage sensing by fluorescence resonance energy transfer in single cells" Biophys J **69**(4): 1272-80 y González, J. E. y R. Y. Tsien (1997) "Improved indicators of cell membrana potential that use fluorescence resonance energy transfer" Chem Biol **4**(4): 269-77) en combinación con instrumentación para medir cambios de fluorescencia tales como el lector de sonda iónica/voltaje (VIPR®) (Véase Gonzalez, J. E., K. Oades, y otro (1999) "Cell-based assais and instrumentation for screening ion-channel targets" Drug Discov Today **4**(9): 431-439).

[002271] Método VIPR® de ensayo óptico de potencial de membrana con estimulación eléctrica

Control positivo (100% de bloqueo)

El control positivo para este ensayo era 125 uM de mibefradilo, obtenido por agregado de 25 uL de solución 250 uM a las placas de ensayo que contiene 25 uL de buffer de ensayo. Cada placa de ensayo incluye cavidades control positivas.

Control negativo (sin bloqueo)

El control negativo (línea de base) para este ensayo es

DMSO. Esto se logró por agregado de 25 uL de 1% DMSO (un buffer de ensayo) a las placas de ensayo que contienen 25 uL de buffer de ensayo. Cada placa de ensayo incluyó cavidades control negativas.

Sustracción del fondo

El fondo de fluorescencia de plástico en placas de ensayo (o del buffer de ensayo) se evaluó al correr una placa son células a través de EVIPR con la misma configuración óptica. Los valores promedio de fondo para cada hilera y cada longitud de onda se restaron en MOD3 antes del cálculo de cambio de relación y de actividad.

Reactivos

Buffer de ensayo:

Bat Y (Preparado por Vertex Lab Support)

140mM TMA-Cl

4,5mM KCl

1mM $MgCl_2$

10mM HEPES, pH7,4

10mM glucosa

Osmolaridad = 295mOsm (280-310 rango aceptable)

500mM $BaCl_2$ (Sigma #B0750), en H_2O

100 mg/ml Pluronic F-127 (Sigma #P2443), en DMSO seco

10mM $DiSBAC_2(3)$ (Aurora #00-100-010) en DMSO seco

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10mM CC2-DMPE (Aurora #00-100-008) en DMSO seco

200mM Ácido amarillo 17 (Aurora #VABSC) en H_2O

Volumen de ensayo

50uL

DMSO Conc de ensayo

0,5% (1uL de 75% DMSO/25% agua, factor de dilución de 160)

Tiempo de incubación de compuestos

20-25 minutos

Instrumentación

Esta pantalla se condujo en el sistema Allegro™. El sistema se diagrama a continuación:

El Allegro™ es equipado con una unidad de placa de almacenamiento de compuesto (apilador). El apilador mantiene un grupo de bandejas (cada bandeja sostiene 12 placas de compuesto). Las bibliotecas fueron recibidos del manejo de compuestos, como manchas previas (1uL/cavidad de compuesto y controles) en placas intermedias en formato de 384 cavidades, además de una solución madre 1,6mM en 75% DMSO/25% de H_2O desionizada. Las placas se diluyeron en 80uL de solución de colorante oxonol para crear una solución madre 2X. SE integraron tres lectores EVIPR al sistema Allegro mediante un brazo robótica Mitsubishi. Solo se usó un EVIPR por corrida.

Condición de instrumentación

óptica:

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Frecuencia de lectura: 10Hz

Longitud de onda de excitación: 400nm

Longitudes de onda de emisión: 460nm y 560nm

Estimulación eléctrica:

Ancho de pulso: 11,1 ms

Corriente de estimulación: 0,8 amps

Frecuencia de estimulación: 90Hz

Tiempo de pre-estimulación: 2 s

Tiempo de estimulación: 3 s

Tiempo de post-estimulación: 1 s

Forma de onda: onda cuadrada bifásica

Condiciones de lavado de placa:

Las condiciones para lavado de ELx405 dejan un volumen residual de 25uL.

Tipo de placa: 384

de ciclos: 3

Remojar/agitar: No

Dispensa:volumen dispensado100

Velocidad de flujo dispensado1

Altura de dispensado80

Dispensado horizontal pos-20

Horiz en disp pos-5

Aspirado:altura de aspirado48

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horizontal aspir pos-18

horiz asp pos-5

tasa de aspiración 0

retraso de aspiración 0

retraso final de asp 500

Procedimiento de ensayo

Procedimiento corrido en HTS Allegro™:

1. **Carrusel:** Placas de ensayo (placas de células) cargadas en un carrusel de módulo #1 (CO_2 = 5%, temperatura ambiente y Rh)

2. **Barrera:** placas de ensayo recuperadas del carrusel y se pasaron a través de la barrera ambiental (los pasos restantes se condujeron a temperatura ambiente y CO_2 ambiente)

3. **Lavado:** placas de ensayo lavado con Bat Y en Biotek ELx405.

4. **Dispensador de reactivos múltiples (MRD):** 25uL de CC2-DMPE (y volumen igual de Pluronic) en Bat Y se agregó a cada cavidad para obtener 10uM.

5. **Barrera:** placas de ensayo pasadas por la barrera.

6. **Carrusel:** 30-minutos de incubación a temperatura ambiente.

7. **Barrera:** placas de ensayo pasadas a través de la barrera.

8. **Lavado**: placas de ensayo lavadas con Bat Y en Biotek ELx405

9. **Estación de transferencia de alta densidad:**

a. 80uL de solución de carga de colorante oxonol (4uM DiSBAC2(3), 1mM VABSC y 30mM $BaCl_2$ en BatY) se agregaron a las placas de compuesto (premanchadas con 1uL de compuesto) usando un MultiDrop (fuera de la línea)

b. Placas mezcladas (3 veces con 20uL) en CiBiWell (fuera de la línea). Las placas se cargaron en la bandeja del compuesto.

c. La bandeja de compuesto se recuperó del apilador de bandejas de compuesto y se leyeron los códigos de barra de la placa de compuesto.

d. Se leyó el código de barras de la placa de ensayo y se llevó a la cubierta SciClone

e. 25uL de compuesto más oxonol aspirado de placa de compuesto en cubierta de SciClone y se transfirió a la placa de ensayo.

i. Volumen final de ensayo = 50uL

ii. concentración final del compuesto = 10uM

f. Puntas de SciClone lavadas en DMSO y 5% de etanol en agua para eliminar transporte externo.

10. **Carrusel**: se incubaron las placas de ensayo durante 20 minutos a temperatura ambiente

11. **Barrera**: placas de ensayo pasadas a través de la barrera

12. **Brazo robótico Mitsubishi**: recupera la placa de ensayo de la salida de la barrera, entrega las placas de células a EVIPR 384-1 y envía comandos para iniciar la corrida de EVIPR.

Ventana de ensayo

Criterios de ventana de ensayo:

Placas de pasaje ≤ 0,5, placas rechazadas > 0,5

$$\textit{Ventana de ensayo} = \frac{3(SD_{FullBlock} + SD_{Baseline})}{(AVE_{Baseline} - AVE_{FullBlock})} = 1 - Z'$$

Reducción de datos

Los archivos EVIPR se redujeron para disminuir la cantidad de datos bombeados a la base de datos. Se filtraron dos "ventanas" de interés de cada archivo EVIPR. Cada ventana es una sección de la respuesta medida en cada cavidad. La primera ventana se midió antes de la estimulación. Las muestras de la segunda ventana dieron picos de respuesta. La relación de las dos se usó para determinar le tamaño de respuesta.

Análisis de datos

Una vez recogidos los datos en VIPR, se archivaron y cargaron, en forma reducida, a Mod3. Una vez en Mod3, cada placa

individual de ensayo se sometió a QC (en búsqueda de ventana aceptable y rango dinámico).

[002272] Ensayo HERG

[002273] La inhibición de hERG se analizó en una línea celular de pulmón de hámster chino (CHL) transducida en forma estable con el gen estructural de hERG. Las células que expresan gran cantidad de canales hERG dieron por resultado 500pA a 1,5nA de hERG hacia fuera de corrientes de K^+. El método usó un instrumento de placa plana (IonWorks HT, Molecular Devices) que permitió mediciones electrofisiológicas globales medias en formato de 384 cavidades. La potencia de inhibición de hERG se midió a 1,1µM, 3,3µM, 10µM y 30µM del compuesto estudiado. El compuesto se añadió de un buffer de adición acuoso 3x.

[002274] Los compuestos de la presente invención exhiben una actividad deseablemente baja contra hERG.

[002275] Ensayo de isozima CYP-450

[002276] Preparación de compuesto:

1. El compuesto deseado se plaqueó (2mM en 75% DMSO/25% H_2O) con un robot de distribución de muestra Pieso (PSDR™) con 8nL por cavidad.
2. El compuesto se centrifugó brevemente a aproximadamente 1000 rpm para cambiar la caída del compuesto hasta el fondo de la cavidad.

3. PVP 10K (excipiente, 0,2% en 75% DMSO/25% H_2O) se plaqueó con a PSDR™ a 100nL por cavidad.

4. El compuesto y PVP 10K se centrifugaron brevemente a aproximadamente 1000 rpm para asegurar una adecuada mezcla de compuesto y excipiente.

5. El secado de las placas se inició usando vació de hogar durante al menos 3 horas.

6. Las placas se transfirieron a aparato de alto vacío (50 militros) el proceso de secado se continuó durante al menos 15 horas.

[002277] Se empleó el siguiente protocolo de ensayo para una isozima CYP-450 deseada (CYP3A4, CYP2C9, CYP1A2, CYP2C19 o CYP2D6).

[002278] Protocolo de ensayo

Todos los reactivos siguientes se añadieron usando un dispensador de reactivo volador (FRD™).

1. 800 nL de dH_2O se añadió al control de actividad en cavidades al 100%, compuesto y control de fondo.

2. 800 nL del fármaco control adecuado (3A4:clotrimazol, 2C9:miconazol, 1A2:ticlopidina, 2C19:lansoprazol o 2D6:propanolol; 10uM final disuelto en dH_2O) se añadió a las cavidades control del fármaco.

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3. 200 nL de 500mM K^+ de buffer fosfato (pH 8,4) se añadió en las cavidades al 100% de control de actividad, control de fármaco y compuesto.

4. 600 nL de Control Insect Baculosomes (PanVera P2315) en 500mM K^+ de Buffer fosfato (pH 8,4) se añadió a las cavidades de control de fondo. El cálculo para este reactivo se basó en la concentración de proteína para las cavidades control con 100% de actividad.

5. La placa se analizó para el compuesto fluorescente usando un NanoPlate™ Fluorescence Plate Reader (NPR™).

6. 200 nL de $NADP^+$ (Sigma, 100 µM final) y sustrato en 100mM K^+ de buffer fosfato (50mM K^+ de buffer fosfato para 2C9 y 2C19) se añadió a todas las cavidades. Se añadió sustrato fluorogénico (3A4:5 µM Vivid™ 3A4 Red, 2C9:1µM Vivid™ 2C9 Green, 1A2:2µM Vivid™ 1A2 Blue, 2C19:10µM Vivid™ 2C19 Blue y 2D6: 10µM Vivid™ 2D6 Blue) hasta una concentración final correspondiente al K_m del sustrato para la pertinente isozima CYP450.

7. 400 nL de la isozima deseada CYP450 y buffer de reciclado (3,3mM glucosa-6-fosfato, 0,4 unidades/ml glucosa-6-fosfatodeshidrogenasa, 100mM $MgCl_2$ y 0,00025% Antifoam 289; reactivos obtenidos de Sigma) en 100mM K^+ de Buffer fosfato (50mM K^+ buffer fosfato para 2C9 y 2C19) a las cavidades de control de 100% de control de actividad, control de fármaco y

compuesto. La isozima deseada se añadió para obtener las siguientes concentraciones finales de la isozima deseada: 5nM CYP3A4, 10nM CYP2C9, 5nM CYP1A2, 5nM CYP2C19 o 20nM CYP2D6.

8. La placa se incubó durante 60 minutos a temperatura ambiente.

9. La placa se analizó para fluorescencia de la solución usando un NanoPlate™ Fluorescence Plate Reader (NPR™).

10. Los datos NPR™ se convirtieron en un formato compatible con la importación en un visualizador de datos y completó el análisis de los datos adquiridos.

[002279] Los compuestos de la presente invención exhiben una actividad deseablemente baja contra una o más de las isozimas CYP450.

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[002280] La actividad de los compuestos seleccionados de la presente invención contra el canal NaV 1.8 se muestra a continuación en la **Tabla 4**. En la **Tabla 4**, los símbolos tienen el siguiente significado:

"+++" significa < 2 μM; "++" significa entre 2 μM y 10 μM; y "+" significa > 10μM.

[002281] **Tabla 4**

Comp. N.°	IC50	Comp. N.°	IC50	Comp. N.°	IC50	Comp. N.°	IC50	Comp. N.°	IC50
101	+++	114	++	127	+++	140	+	153	++
102	++	115	+	128	++	141	+	154	+
103	+	116	++	129	+	142	++	155	+
104	+	117	++	130	+	143	++	156	++
105	++	118	++	131	+	144	++	157	++
106	+	119	+	132	++	145	+	158	+
107	++	120	++	133	++	146	+	159	++
108	++	121	++	134	++	147	++	160	+
109	++	122	++	135	+++	148	++	162	++
110	+	123	+	136	+	149	+	163	++
111	+	124	+	137	++	150	+	164	+
112	+	125	+	138	+	151	+	165	++
113	++	126	+	139	++	152	+	166	+

Comp. N.°	IC50
167	+
168	++
169	+
170	+
172	+
173	+
174	++
175	+
176	+
177	++
178	+
179	+
180	++
181	+
182	++
183	++
184	++
185	++
201	++
203	+

Comp. N.°	IC50
204	+
205	+
206	++
207	+++
208	+++
210	++
211	+
212	+
213	+
214	+
215	+
216	+
217	+
218	++
219	+++
220	+
221	+
222	+
223	+
224	+

Comp. N.°	IC50
225	+
226	+
227	+
228	+
229	+
230	++
231	++
232	++
233	+
234	+
235	++
236	+
237	+
238	+
239	+
240	+
241	+
242	++
243	+
244	+

Comp. N.°	IC50
245	+
246	+
247	+
248	++
249	++
250	+++
251	++
252	+
253	+
254	++
255	+
256	++
257	++
258	+++
259	+++
260	+++
261	++
262	++
264	+
265	+

Comp. N.°	IC50
266	++
267	+
268	+
269	+
270	++
271	+
272	++
273	++
274	++
275	++
276	++
277	++
278	+
279	++
301	++
302	+
303	++
304	+
305	++
306	+

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Comp. N.°	IC50
307	+
308	+
309	+++
310	++
311	+++
312	++
314	++
315	+
316	+
317	++
318	+
319	++
320	++
321	+
322	+
323	+
324	+
325	+
326	+
327	+

Comp. N.°	IC50
328	+
329	++
335	++
337	++
338	+
339	++
340	+++
342	+
345	++
346	++
347	+
348	+
349	+
350	+
351	++
352	+
353	+
354	++
355	+
356	+

Comp. N.°	IC50
357	+
358	+
359	+
360	+
361	++
362	+
363	++
364	+++
365	+++
366	++
367	+++
368	++
369	+++
370	+++
371	+++
372	+++
373	++
374	+
375	+
376	+

Comp. N.°	IC50
377	++
401	+
402	+
403	+
404	+
405	+
406	+
407	+
408	+
409	+
410	+
411	++
412	+
413	++
414	++
415	++
416	+
417	+
418	++
419	++

Comp. N.°	IC50
420	+++
501	++
502	++
503	++
504	++
505	++
506	++
507	++
508	++
509	+
510	++
511	++
512	++
513	+
514	++

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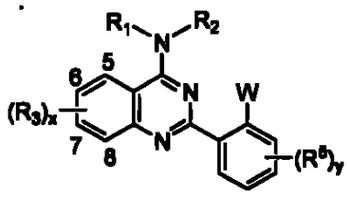
REIVINDICACIONES

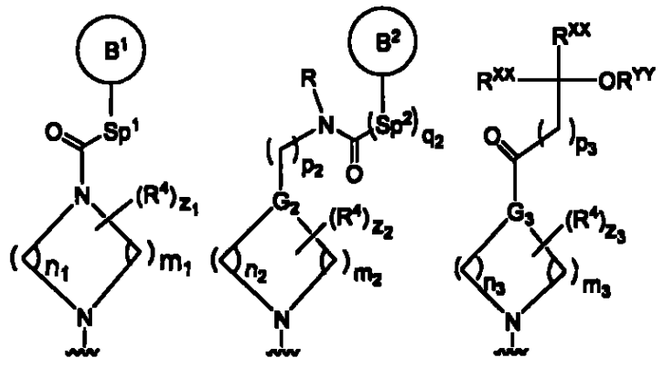
1. Un compuesto de fórmula I:



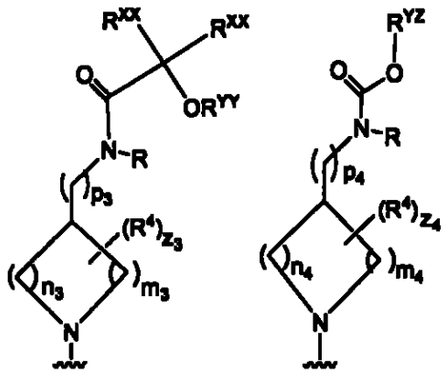
I;

o una de sus sales o derivados farmacéuticamente aceptables, en donde:

R^1 y R^2, junto con el átomo de nitrógeno, forman un anillo sustituido seleccionado de:



(A) (B) (C)



(D) o (E);

en donde, en el anillo (A):

cada uno de m_1 y n_1 es, de modo independiente, 0-3, con la condición de que m_1+n_1 sea 2-6;

z_1 es 0-4;

Sp^1 es -O-, -S-, -NR'- o un ligador de alquilideno C_1-C_6, en donde hasta dos unidades de metileno están opcional e independientemente reemplazadas por -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$ o $-NR'SO_2NR'-$, con la condición de que Sp^1 esté unido al grupo carbonilo a través de un átomo distinto del carbono;

anillo B^1 es un anillo heterocíclico monocíclico, saturado, parcialmente insaturado o aromático de 4-8 miembros que tiene 1-4 heteroátomos seleccionados de O, S o N, en donde el anillo

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B^1 está opcionalmente sustituido con w_1 apariciones independientes de $-R^{11}$, en donde w_1 es 0-4;

en donde, en el anillo (B):

G_2 es -N- o CH;

cada uno de m_2 y n_2 es, de modo independiente, 0-3, con la condición de que $m_2 + n_2$ sea 2-6;

p_2 es 0-2; con la condición de que cuando G_2 es N, entonces p_2 no sea 0;

q_2 es 0 ó 1;

z_2 es 0-4;

Sp^2 es un enlace o un ligador de alquilideno C_1-C_6, en donde hasta dos unidades de metileno están opcional e independientemente reemplazadas por -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$ o $-NR'SO_2NR'-$;

el anillo B^2 es un anillo heterocíclico monocíclico, saturado, parcialmente insaturado o aromático de 4-8 miembros que tiene 1-4 heteroátomos seleccionados de O, S o N, en donde el anillo B está opcionalmente sustituido con w apariciones independientes de $-R^{12}$, en donde w_2 es 0-4;

en donde, en el anillo (C) o el anillo (D):

G_3 es -N-, -CH-NH- o $-CH-CH_2-NH-$;

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cada uno de m_3 y n_3 es, de modo independiente, 0-3, con la condición de que m_3+n_3 sea 2-6;

p_3 es 0-2;

z_3 es 0-4;

cada R^{XX} es hidrógeno, grupo alifático C_1-6, un anillo monocíclico saturado, parcialmente insaturado o totalmente insaturado de 3-8-miembros que tiene 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillos bicíclicos saturados, parcialmente insaturados o totalmente insaturados de 8-12 miembros que tiene 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre; en donde R^{XX} está opcionalmente sustituido con w_3 apariciones independientes de -R^{13}, en donde w_3 es 0-3;

con la condición de que ambos R^{XX} no sean de forma simultánea hidrógeno;

R^{YY} es hidrógeno, -COR', $-CO_2R'$, $-CON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-P(O)(OR')_2$, $-P(O)_2OR'$ o $-PO(R')$, en donde, en el anillo (E):

cada uno de m_4 y n_4 es, de modo independiente, 0-3, con la condición de que $m_4 + n_4$ sea 2-6;

p_4 es 1-2;

z_4 es 0-4;

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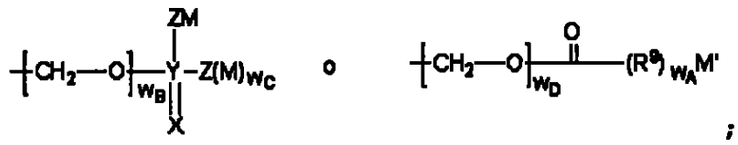
R^{YZ} es grupo alifático C_1-C_6, opcionalmente sustituido con w_4 apariciones independientes de $-R^{14}$, en donde w_4 es 0-3;

x e y, cada uno es, de modo independiente, 0-4;

W es OR^{XY};

R^{XY} es hidrógeno o un grupo seleccionado de:



;

en donde:

cada uno de w_A, w_B, wC y w_D es, de modo independiente, 0 ó 1;

cada M está seleccionado, de modo independiente, de hidrógeno, Li, Na, K, Mg, Ca, Ba, $-N(R^7)_4$, alquilo C_1-C_12, alquenilo C_2-C_12 o $-R^6$; en donde 1 a 4 radicales $-CH_2$ del grupo alquilo o alquenilo distinto de $-CH_2$ que está unido a Z, está opcionalmente reemplazado por un grupo de heteroátomo seleccionado de O, S, S(O), $S(O_2)$ o $N(R^7)$; y en donde cualquier hidrógeno en dicho alquilo, alquenilo o R^6 está opcionalmente reemplazado por un sustituyente seleccionado de oxo, $-OR^7$, $-R^7$, $N(R^7)_2$, $N(R^7)_3$, R^7OH, -CN, $-CO_2R^7$, $-C(O)-N(R^7)_2$, $S(O)_2-N(R^7)_2$, $N(R^7)-C(O)-R^7$, $C(O)R^7$, $-S(O)_n-R^7$, OCF_3, $-S(O)_n-R^6$, $N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$ o $-NO_2$;

n es 0-2;

M' es H, alquilo C_1-C_12, alquenilo C_2-C_12 o $-R^6$; en donde 1 a 4 radicales $-CH_2$ del grupo alquilo o alquenilo están opcionalmente reemplazados por un grupo de heteroátomo

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seleccionado de O, S, S(O), $S(O_2)$ o $N(R^7)$; y en donde cualquier hidrógeno en dicho alquilo, alquenilo o R^6 está opcionalmente reemplazado por un sustituyente seleccionado de oxo, $-OR^7$, $-R^7$, $-N(R^7)_2$, $N(R^7)_3$, $-R^7OH$, -CN, $-CO_2R^7$, $-C(O)-N(R^7)_2$, $-S(O)_2-N(R^7)_2$, $-N(R^7)-C(O)-R^7$, $-C(O)R^7$, $-S(O)_n-R^7$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^7)-S(O)_2(R^7)$, halo, $-CF_3$ o $-NO_2$;

Z es $-CH_2-$, -O-, -S-, $-N(R^7)_2-$; o

cuando M está ausente, Z es hidrógeno, =O o =S;

Y es P o S, en donde cuando Y es S, Z no es S;

X es O o S;

cada R^7 está seleccionado, de modo independiente, de hidrógeno o alifático C_1-C_4, opcionalmente sustituido con hasta dos Q_1;

cada Q_1 está seleccionado, de modo independiente, de un sistema de anillos carbocíclicos saturados, parcialmente saturados o insaturados de 3-7 miembros; o un anillo heterocíclico saturado, parcialmente saturado o insaturado de 5-7 miembros que contiene uno o varios heteroátomos o grupos de heteroátomos seleccionados de O, N, NH, S, SO o SO_2; en donde Q_1 está opcionalmente sustituido con hasta tres sustituyentes seleccionados de oxo, -OH, -O(alifático C_1-C_4), -alifático C_1-C_4, $-NH_2$, NH(alifático C_1-C_4), -N(alifático $C_1-C_4)_2$, -N(alifático C_1-C_4)-C(O)-alifático C_1-C_4, -(alifático C_1-C_4)-OH, -CN, $-CO_2H$, $-CO_2$(alifático C_1-C_4), $-C(O)-NH_2$, -C(O)-NH(alifático C_1-C_4), -C(O)-N(alifático $C_1-C_4)_2$, halo o $-CF_3$;

R^6 es un sistema de anillos carbocíclicos o heterocíclicos saturados, parcialmente saturados o insaturados de 5-6 miembros o un sistema de anillos bicíclicos saturados, parcialmente saturados o insaturados de 8-10 miembros; en donde cualquiera de dichos sistemas de anillos heterocíclicos contiene uno o varios heteroátomos seleccionados de O, N, S, $S(O)_n$ o $N(R^7)$; y en donde cualquiera de dichos sistemas de anillos contiene opcionalmente 1 a 4 sustituyentes independientemente seleccionados de OH, alquilo C_1-C_4, O-alquilo C_1-C_4 u O-C(O)-alquilo C_1-C_4;

R^9 es $C(R^7)_2$, O o $N(R^7)$;

cada aparición de R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4 y R^5 es, de modo independiente, $Q-R^X$; en donde Q es un enlace o es una cadena de alquilideno C_1-C_6, en donde hasta dos unidades de metileno no adyacentes de Q están opcional e independientemente reemplazadas por -NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, -OP(O)(OR)- o -POR-; y cada aparición de R^X está seleccionada, de modo independiente, de -R', halógeno, =O, =NR', $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -NR'COR', $-NR'CON(R')_2$, $-NR'CO_2R'$, -COR', $-CO_2R'$, -OCOR', $-CON(R')_2$, $-OCON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, $-NR'SO_2R'$, $-NR'SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$ u $-OPO(R')_2$; y

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cada aparición de R es, de modo independiente, hidrógeno o grupo alifático C_1-6 que tiene hasta tres sustituyentes; y cada aparición de R' es, de modo independiente, hidrógeno o grupo alifático C_1-6, un anillo monocíclico saturado, parcialmente insaturado o totalmente insaturado de 3-8-miembros que tiene 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillos bicíclicos saturados, parcialmente insaturados o totalmente insaturados de 8-12 miembros que tiene 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde R' tiene hasta cuatro sustituyentes; o R y R', dos apariciones de R o dos apariciones de R', se toman junto con los átomos a los que están unidos para formar un anillo monocíclico o bicíclico opcionalmente sustituido de 3-12 miembros saturado, parcialmente insaturado o totalmente insaturado que tiene 0-4 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre.

2. El compuesto de acuerdo con la reivindicación 1, en donde W es OH.

3. El compuesto de acuerdo con la reivindicación 1, en donde x es 1 y R^3 está presente en la posición 6 ó 7 del anillo quinazolina.

4. El compuesto de acuerdo con la reivindicación 3, en donde R^3 está seleccionado de -Cl, $-CH_3$, $-CH_2CH_3$, -F, $-CF_3$, $-OCF_3$, $-CONHCH_3$, $-CONHCH_2CH_3$, -CONH(ciclopropilo), $-OCH_3$, $-NH_2$, $-OCH_2CH_3$ o -CN.

5. El compuesto de acuerdo con la reivindicación 4, en donde x es 1 y R^3 está en la posición 7 del anillo quinazolina y es $-CH_3$.

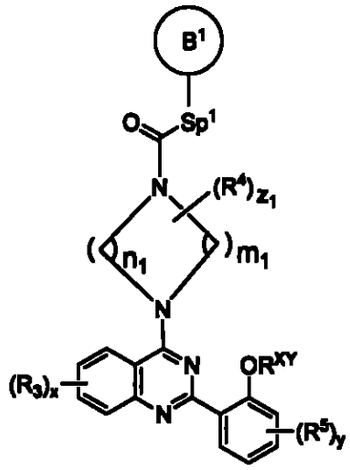
6. El compuesto de acuerdo con la reivindicación 1, en donde y es 0.

7. El compuesto de acuerdo con la reivindicación 1, en donde y es 1 y R^5 es halo.

8. El compuesto de acuerdo con la reivindicación 7, en donde R^5 es halo en la posición 6.

9. El compuesto de acuerdo con la reivindicación 1, en donde z_1, z_2, z_3 y z_4 es cada uno 0.

10. El compuesto de acuerdo con la reivindicación 1, en donde dicho compuesto tiene la fórmula **I-A**:



I-A.

11. El compuesto de acuerdo con la reivindicación 10, en donde Sp^1 es -O-, $-O-CH_2-$, -S- o -NH- o $-NH-CH_2-$.

12. El compuesto de acuerdo con la reivindicación 10, en donde cada uno de m_1 y n_1 es 2.

13. El compuesto de acuerdo con la reivindicación 10, en donde el anillo B^1 es un anillo heterocíclico monocíclico saturado de 5-6 miembros que tiene 1-2 heteroátomos seleccionados de O, S o N, en donde el anillo B^1 está opcionalmente sustituido con w apariciones independientes de $-R^{11}$, en donde w_1 es 0-4.

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14. El compuesto de acuerdo con la reivindicación 13, en donde el anillo B1 es tetrahidrofuranilo, tetrahidro-[*2H*]-piranilo, piridilo o fenilo.

15. El compuesto de acuerdo con la reivindicación 10, en donde Sp^1 es un enlace, O u $-O-CH_2-$; R es hidrógeno; y n_1 y m_1 son ambos de forma simultánea 2.

16. El compuesto de acuerdo con la reivindicación 10, en donde:

n_1 y m_1 es cada uno 2;

R^{xy} es hidrógeno;

y es 0 ó 1 y R^5 es flúor;

x es 1 y R^3 es Me en la posición 7 o flúor en la posición 6;

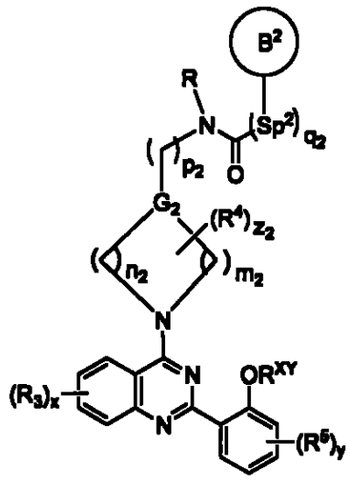
z_1 es 0;

Sp^1 es $-O-CH_2-$;

w_1 es 0; y

el anillo B^1 es tetrahidrofuran-3-ilo, fenilo, piridin-3-ilo, piridin-4-ilo o tetrahidro[2H]-piran-4-ilo.

17. El compuesto de acuerdo con la reivindicación 1, en donde dicho compuesto tiene la fórmula I-B:



I-B.

18. El compuesto de acuerdo con la reivindicación 17, en donde G_2 es CH y p_2 es 1 ó 2.

19. El compuesto de acuerdo con la reivindicación 17, en donde m_2 y n_2 es cada uno 1 ó 2.

20. El compuesto de acuerdo con la reivindicación 17, en donde m_2 es 1 y n_2 es cada uno 2.

21. El compuesto de acuerdo con la reivindicación 17, en donde n_2 es 1 y m_2 es 3.

22. El compuesto de acuerdo con la reivindicación 17, en donde Sp^2 es -O- u $-O-CH_2-$.

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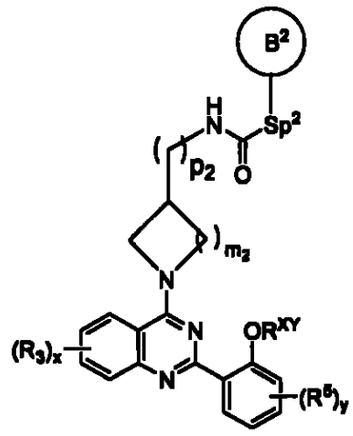
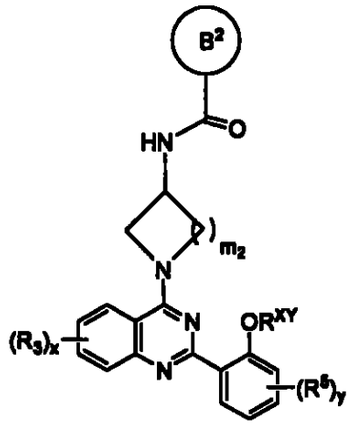
23. El compuesto de acuerdo con la reivindicación 17, en donde el anillo B^2 es un anillo heterocíclico monocíclico saturado de 5-6 miembros que tiene 1-2 heteroátomos seleccionados de O, S o N, en donde el anillo B^2 está opcionalmente sustituido con w apariciones independientes de $-R^{12}$, en donde w_2 es 0-4.

24. El compuesto de acuerdo con la reivindicación 23, en donde el anillo B^2 es tetrahidrofuranilo, tetrahidro[2*H*]piranilo o piridilo.

25. El compuesto de acuerdo con la reivindicación 17, en donde Sp^2 es un enlace, O u $-O-CH_2-$;
p_2 es 1;
R es hidrógeno; y
n_2 es 1 y m_2 es 2 ó 3.

26. El compuesto de acuerdo con la reivindicación 17, en donde dicho compuesto tiene la fórmula I-B-i o fórmula I-B-ii:





I-B-i o I-B-ii;

en donde:

m_2 es 2 ó 3; y

Sp^2 es -O- u $-O-CH_2-$.

27. El compuesto de fórmula **I-B-i** de acuerdo con la reivindicación 26, en donde:

p_2 es 1;

m_2 es 3;

Sp^2 es -O-;

y es 0 ó 1 y R^5 es flúor;

x es 1 y R^3 es 7-Me; y

anillo B^2 es tetrahidrofuranilo.

28. El compuesto de fórmula **I-B-i** de acuerdo con la reivindicación 26, en donde:

p_2 es 0 ó 1;

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m_2 es 2;

Sp^2 es -O- u $-O-CH_2-$;

y es 0;

x es 1 y R^3 es 7-Me; y

anillo B^2 es tetrahidrofuranilo, tetrahidro[2H]piranilo, piridilo o fenilo.

29. El compuesto de fórmula **I-B-ii** de acuerdo con la reivindicación 26, en donde:

p_2 es 0;

m_2 es 2;

Sp^2 es un enlace;

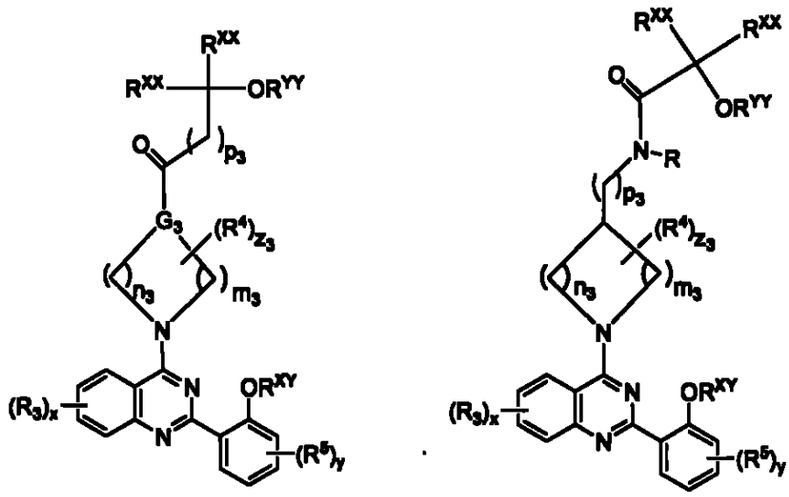
y es 0 ó 1 y R^5 es flúor;

x es 1 y R^3 es 7-Me o 6-F; y

anillo B^2 es ciclopropilo opcionalmente sustituido con alquilo C_1-C_4 o piridilo.

30. El compuesto de fórmula **I-B-i** o fórmula **I-B-ii** de acuerdo con la reivindicación 17, en donde R^{XY} es hidrógeno.

31. El compuesto de acuerdo con la reivindicación 1, en donde dicho compuesto tiene la fórmula **I-C** o fórmula **I-D**:



I-CI-D.

32. El compuesto de acuerdo con la reivindicación 31, en donde un R^{XX} es hidrógeno y el otro R^{XX} no es hidrógeno.

33. El compuesto de acuerdo con la reivindicación 31, en donde un R^{XX} es hidrógeno y el otro R^{XX} es alquilo C_1-C_6 opcionalmente sustituido con halo.

34. El compuesto de acuerdo con la reivindicación 31, en donde ambos R^{XX} son de forma simultánea alquilo C_1-C_6.

35. El compuesto de acuerdo con las reivindicaciones 33 ó 34, en donde dicho alquilo está seleccionado de metilo, etilo, isopropilo, *n*-propilo, *n*-butilo, *sec*-butilo o *t*-butilo.

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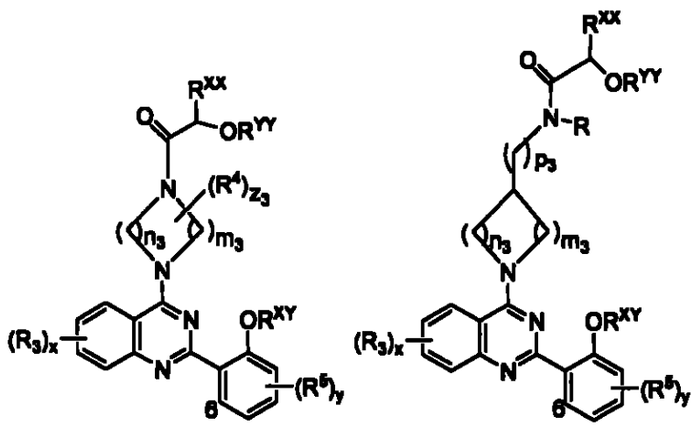
36. El compuesto de acuerdo con la reivindicación 31, en donde p_3 es 0.

37. El compuesto de acuerdo con la reivindicación 31, en donde m_3 y n_3 es cada uno 2.

38. El compuesto de acuerdo con la reivindicación 31, en donde R^{YY} es hidrógeno.

39. El compuesto de acuerdo con la reivindicación 31, en donde dicho compuesto tiene la fórmula I-C-i o fórmula I-D-i:



I-C-iI-D-i.

40. El compuesto de acuerdo con la reivindicación 39, en donde R^{XX} es C_1-C_6 alquilo.

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41. El compuesto de acuerdo con la reivindicación 39, en donde x es 1 y R^3 es alquilo C_1-C_4 en la posición 7.

42. El compuesto de acuerdo con la reivindicación 39, en donde x es 1 y R^3 es F, CN o CF_3 en la posición 6.

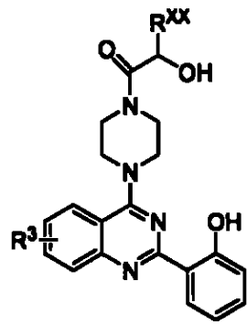
43. El compuesto de acuerdo con la reivindicación 39, en donde R^{XX} es metilo, *n*-propilo, isopropilo, *n*-butilo, *sec*-butilo o *t*-butilo.

44. El compuesto de acuerdo con la reivindicación 41, en donde R^3 es metilo, *n*-propilo, isopropilo, *n*-butilo, *sec*-butilo o *t*-butilo.

45. El compuesto de acuerdo con la reivindicación 39, en donde R^{XY} es hidrógeno e y es 0.

46. El compuesto de acuerdo con la reivindicación 39, en donde R^{XY} es hidrógeno, y es 1 y R^5 es 6-F.

47. El compuesto de acuerdo con la reivindicación 31, en donde dicho compuesto tiene la fórmula I-C-ii:

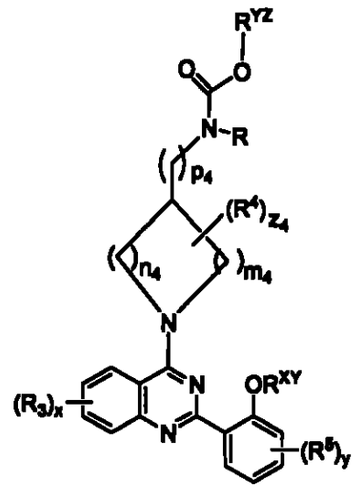


I-C-ii.

48. El compuesto de acuerdo con la reivindicación 47, en donde R^3 es metilo en la posición 7 del anillo quinazolina.

49. El compuesto de acuerdo con la reivindicación 47, en donde R^{XX} es $CH_2C(O)OH$ o $CH_2C(O)NH_2$.

50. El compuesto de acuerdo con la reivindicación 1, en donde dicho compuesto tiene la fórmula I-E:



I-E.

51. El compuesto de acuerdo con la reivindicación 50, en donde p_4 es 1.

52. El compuesto de acuerdo con la reivindicación 50, en donde m_4 y n_4 es cada uno 2.

53. El compuesto de acuerdo con la reivindicación 50, en donde n_4 es 1, m_4 es 3, z_4 es 0, p_4 es 1, y es 0 ó 1 y x es 1.

54. El compuesto de acuerdo con la reivindicación 50, en donde n_4 es 1, m_4 es 2, z_4 es 0, p_4 es 1, y es 0 ó 1 y x es 1.

55. El compuesto de acuerdo con la reivindicación 50, en donde n_4 es 1, m_4 es 3, z_4 es 0, p_4 es 1, y es 0 ó 1, x es 1 y R y R^{xy} son ambos hidrógeno.

56. El compuesto de acuerdo con la reivindicación 50, en donde n_4 es 1, m_4 es 2, z_4 es 0, p_4 es 1, y es 0 ó 1, x es 1 y R y R^{xy} son ambos hidrógeno.

57. El compuesto de acuerdo con la reivindicación 50, en donde R^{yz} es grupo alquilo C_1-C_4 opcionalmente sustituido con w_4 apariciones independientes de $-R^{14}$, en donde w_4 es 0-3.

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58. El compuesto de acuerdo con la reivindicación 50, en donde:

n_4 es 1 y m_4 es 3;

p_4 es 1;

z_4 es 0;

R^{YZ} es alquilo C_1-C_6, en donde hasta dos grupos $-CH_2-$ están opcionalmente reemplazados por -O-;

y es 0 ó 1 y R^5 es 6-flúor; y

x es 1 y R^3 es alquilo C_1-C_4.

59. El compuesto de acuerdo con la reivindicación 50, en donde:

n_4 es 1 y m_4 es 2;

p_4 es 1;

z_4 es 0;

R^YZ es alquilo C_1-C_6, en donde hasta dos grupos $-CH_2-$ están opcionalmente reemplazados por -O-;

y es 0 ó 1 y R^5 es 6-flúor; y

x es 1 y R^3 es alquilo C_1-C_4.

60. El compuesto de acuerdo con la reivindicación 50, en donde:

n_4 es 1 y m_4 es 3;

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p_4 es 1;

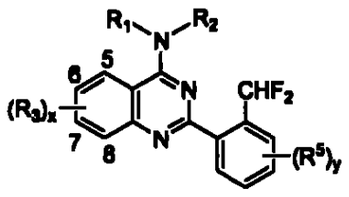
z_4 es 0;

R^YZ es bencilo;

y es 0 ó 1 y R^5 es 6-flúor; y

x es 1 y R^3 es alquilo C_1-C_4.

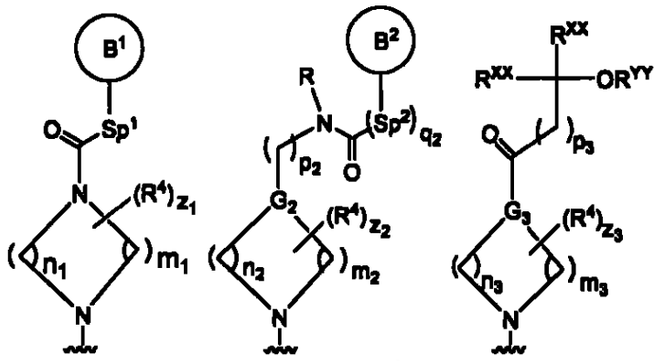
61. Un compuesto que tiene fórmula I-F:



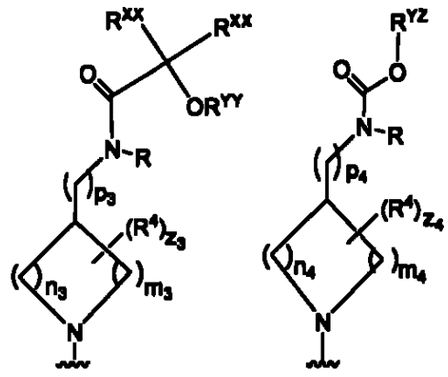
I-F;

en donde:

R^1 y R^2, junto con el átomo de nitrógeno, forman un anillo sustituido seleccionado de:



(A) (B) (C)



(D) o (E);

en donde, en el anillo (A):

cada uno de m_1 y n_1 es, de modo independiente, 0-3, con la condición de que m_1+n_1 sea 2-6;

z_1 es 0-4;

Sp^1 es -O-, -S-, -NR'- o un ligador de alquilideno C_1-C_6, en donde hasta dos unidades de metileno están opcional e independientemente reemplazadas por -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$ o $-NR'SO_2NR'-$, con la condición de que Sp^1 esté unido al grupo carbonilo a través de un átomo distinto del carbono;

anillo B^1 es un anillo heterocíclico monocíclico, saturado, parcialmente insaturado o aromático de 4-8 miembros que tiene 1-4 heteroátomos seleccionados de O, S o N, en donde el anillo

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B^1 está opcionalmente sustituido con w_1 apariciones independientes de $-R^{11}$, en donde w_1 es 0-4;

en donde, en el anillo (B):

G_2 es -N- o CH;

cada uno de m_2 y n_2 es, de modo independiente, 0-3, con la condición de que $m_2 + n_2$ sea 2-6;

p_2 es 0-2; con la condición de que cuando G_2 es N, p_2 no sea 0;

q_2 es 0 ó 1;

z_2 es 0-4;

Sp^2 es un enlace o un ligador de alquilideno C_1-C_6, en donde hasta dos unidades de metileno están opcional e independientemente reemplazadas por -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, $-CO_2-$, -OCO-, $-NR'CO_2-$, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO, $-SO_2-$, -NR'-, $-SO_2NR'-$, $NR'SO_2-$ o $-NR'SO_2NR'-$;

anillo B^2 es un anillo heterocíclico monocíclico, saturado, parcialmente insaturado o aromático de 4-8 miembros que tiene 1-4 heteroátomos seleccionados de O, S o N, en donde el anillo B está opcionalmente sustituido con w apariciones independientes de $-R^{12}$, en donde w_2 es 0-4;

en donde, en el anillo (C) o anillo (D):

G_3 es -N-, -CH-NH- o $-CH-CH_2-NH-$;

cada uno de m_3 y n_3 es, de modo independiente, 0-3, con la condición de que m_3+n_3 sea 2-6;

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p_3 es 0-2;

z_3 es 0-4;

cada R^{XX} es hidrógeno, grupo alifático C_1-6, un anillo monocíclico saturado, parcialmente insaturado o totalmente insaturado de 3-8-miembros que tiene 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillos bicíclicos saturados, parcialmente insaturados o totalmente insaturados de 8-12 miembros que tiene 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre; en donde R^{XX} está opcionalmente sustituido con w_3 apariciones independientes de -R^{13}, en donde w_3 es 0-3;

con la condición de que ambos R^{XX} no sean de forma simultánea hidrógeno;

R^{YY} es hidrógeno, -COR', -CO_2R', -CON(R')$_2$, -SOR', -SO_2R', -SO_2N(R')$_2$, -COCOR', -$COCH_2$COR', -P(O)(OR')$_2$, -$P(O)_2$OR' o -PO(R'), en donde, en el anillo (E):

cada uno de m_4 y n_4 es, de modo independiente, 0-3, con la condición de que m_4 + n_4 sea 2-6;

p_4 es 1-2;

z_4 es 0-4;

R^{YZ} es grupo alifático C_1-C_6, opcionalmente sustituido con w_4 apariciones independientes de -R^{14}, en donde w_4 es 0-3;

x e y, es cada uno, de modo independiente, 0-4;

cada aparición de R^{11}, R^{12}, R^{13}, R^{14}, R^3, R^4 y R^5 es, de modo independiente, $Q-R^X$; en donde Q es un enlace o es una cadena de alquilideno C_1-C_6 en donde hasta dos unidades de metileno no adyacentes de Q están opcional e independientemente reemplazadas por -NR-, -S-, -O-, -CS-, $-CO_2-$, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, $-NRSO_2NR-$, -SO-, $-SO_2-$, -PO-, $-PO_2-$, -OP(O)(OR)- o -POR-; y cada aparición de R^X está seleccionada, de modo independiente, de -R', halógeno, =O, =NR', $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -NR'COR', $-NR'CON(R')_2$, $-NR'CO_2R'$, -COR', $-CO_2R'$, -OCOR', $-CON(R')_2$, $-OCON(R')_2$, -SOR', $-SO_2R'$, $-SO_2N(R')_2$, $-NR'SO_2R'$, $-NR'SO_2N(R')_2$, -COCOR', $-COCH_2COR'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_2OR'$, $-P(O)_2OR'$, $-PO(R')_2$ u $-OPO(R')_2$; y

cada aparición de R es, de modo independiente, hidrógeno o grupo alifático C_1-6 que tiene hasta tres sustituyentes; y cada aparición de R' es, de modo independiente, hidrógeno o grupo alifático C_1-6, un anillo monocíclico saturado, parcialmente insaturado o totalmente insaturado de 3-8-miembros que tiene 0-3 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre o un sistema de anillos bicíclicos saturados, parcialmente insaturados o totalmente insaturados de 8-12 miembros que tiene 0-5 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre, en donde R' tiene hasta cuatro sustituyentes; o R y R', dos apariciones de

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R o dos apariciones de R', se toman junto con los átomos a los que están unidos para formar un anillo monocíclico o bicíclico opcionalmente sustituido de 3-12 miembros saturado, parcialmente insaturado o totalmente insaturado que tiene 0-4 heteroátomos seleccionados, de modo independiente, de nitrógeno, oxígeno o azufre.

62. El compuesto de acuerdo con la reivindicación 1, en donde dicho compuesto está seleccionado de Tabla 2.

63. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1.

64. Un método para tratar o reducir la gravedad de una enfermedad, trastorno o condición patológica seleccionados de dolor agudo, crónico, neuropático o inflamatorio, artritis, migraña, cefaleas acuminadas, neuralgia de trigémino, neuralgia herpética, neuralgias generales, epilepsia o condiciones epilépticas, trastornos neurodegenerativos, trastornos psiquiátricos tales como ansiedad y depresión, miotonía, arritmia, trastornos del movimiento, trastornos neuroendocrinos, ataxia, esclerosis múltiple, síndrome de intestino irritable, incontinencia, dolor visceral, dolor de osteoartritis, neuralgia posherpética, neuropatía diabética,

dolor radicular, ciático, dolor de espalda, dolor de cabeza o cuello, dolor severo o intratable, dolor nociceptivo, dolor intenso, dolor posquirúrgico o dolor por cáncer, en donde dicho método comprende la etapa de administrar a dicho paciente una cantidad efectiva de una composición de acuerdo con la reivindicación 62.

65. El método de acuerdo con la reivindicación 63, en donde la enfermedad, la condición patológica o el desorden está implicado en la activación o hiperactividad de canales de sodio regulados por voltaje.

66. El método de acuerdo con la reivindicación 64, en donde la enfermedad, la condición patológica o el desorden es agudo, crónico, neuropático o inflamatorio.

67. El método de acuerdo con la reivindicación 64, en donde la enfermedad, la condición patológica o el desorden es dolor radicular, ciático, dolor de espalda, dolor de cabeza o dolor de cuello.

68. El método de acuerdo con la reivindicación 64, en donde la enfermedad, la condición patológica o el desorden es un

dolor severo o intratable, dolor agudo, dolor posquirúrgico, dolor de espalda o dolor por cáncer.

69. El método de acuerdo con la reivindicación 64, en donde dicha enfermedad está seleccionada de dolor por cáncer de fémur; dolor óseo crónico no maligno; artritis reumatoide; osteoartritis; estenosis espinal; dolor lumbar neuropático; dolor lumbar neuropático; síndrome de dolor miofascial; fibromialgia; dolor articular temporomandibular; dolor visceral crónico, incluso, abdominal; pancreático; dolor IBS; dolor por cefalea crónica; migraña; cefalea por tensión, incluso cefalea acuminada; dolor neuropático crónico, incluso, neuralgia posherpética; neuropatía diabética; neuropatía asociada con HIV; neuralgia de trigémino; neuropatía de Charcot-Marie Toot; neuropatías sensoriales hereditarias; lesión de nervios periféricos; neuromas dolorosos; descargas ectópicas proximal y distal; radiculopatía; dolor neuropático inducido por quimioterapia; dolor neuropático inducido por radioterapia; dolor posmastectomía; dolor central; dolor por lesión de médula espinal; dolor post-accidente cerebrovascular; dolor talámico; síndrome doloroso de complejo regional; dolor fantasma; dolor intratable; dolor agudo, dolor agudo postoperatorio; dolor musculoesquelético agudo; dolor articular; dolor lumbar mecánico; dolor de cuello; tendinitis; dolor por

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lesión/ejercicio; dolor visceral agudo, incluso dolor abdominal; pielonefritis; apendicitis; colecistitis; obstrucción intestinal; hernias; etc.; dolor torácico, incluso dolor cardiaco; dolor pelviano, dolor cólico renal, dolor obstétrico agudo, incluso, dolor de parto; dolor por cesárea; dolor inflamatorio agudo, por quemadura y traumatismo; dolor intermitente agudo, incluso, endometriosis; dolor agudo por herpes zoster; anemia por célula falciforme; pancreatitis aguda; dolor sistémico; dolor orofacial, incluso dolor por sinusitis, dolor dental; dolor por esclerosis múltiple (MS); dolor en depresión; dolor por lepra; dolor por enfermedad de Behcet; adiposis dolorosa; dolor flebítico; dolor por Guillain-Barre; piernas dolorosas y dedos de los pies movibles; síndrome de Haglund; dolor por eritromelalgia; dolor por enfermedad de Fabri; enfermedad vesical y urogenital, incluso, incontinencia urinaria; vejiga hiperactiva; síndrome de vejiga dolorosa; cistitis intersticial (IC); o prostatitis.

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[002282] **RESUMEN**

La presente invención se refiere a compuestos de utilidad como inhibidores de canales de sodio regulados por voltaje. La invención también provee composiciones farmacéuticamente aceptables que comprenden los compuestos de la invención y métodos para usar las composiciones en el tratamiento de diversos trastornos.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 07-033374- -00000-0000
Fec: 2007-04-02 17:29:09 Dep: 2000 NUEVECREACIONES
Tra: 11 PATENTEYU
Ere: 370 FASENACION/LI
Act 411 PRESENTACION Folios: 1290

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 24,752
FECHA : MARZO 26 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
PARRA RODRIGUEZ & CAVELIECONSIGNACION		BANCO POPULAR	050-00110-6	55012748	26/03/2007	5,479,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Quinto Folio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 07-033374- -00000-0000
Fec: 2007-04-02 17:23:09 Dep: 2020 NUECREACIONES
Tra: 11 PATENTES
Cla: 379 FASERACIONALI
Act 411 PRESENTACION Folios: 1295

1295

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [x]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [x]
- Descripción de la invención [x]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [x]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 02 ABR. 2007

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

1296

Bogotá,
2020

Doctor(a)
PARRA GOMEZ ALVARO

REFERENCIA	Radicación No.	7 33374
	Solicitud internacional	PCT/US2005/031146
	Fecha inicio fase nacional	02/04/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	5039

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, 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, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 04 MAYO 2007
adpall