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(54) Benævnelse: **PYRAZOLO[1,5-]PYRIMIDINFORBINDELSE SOM TRK-KINASEHÆMMER**

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WO-A1-2006/115452

Description

[0001] The present invention relates to a novel compound and to pharmaceutical compositions comprising the compound. More particularly, it relates to a certain substituted pyrazolo[1,5-a]pyrimidine compound which exhibits Trk family protein tyrosine kinase inhibition, and which is useful in the treatment of pain, inflammation, cancer, and certain infectious diseases.

[0002] The current treatment regimes for pain conditions utilize several classes of compounds. The opioids (such as morphine) have several drawbacks including emetic, constipatory and negative respiratory effects, as well as the potential for addictions. Non-steroidal anti-inflammatory analgesics (NSAIDs, such as COX-1 or COX-2 types) also have drawbacks including insufficient efficacy in treating severe pain. In addition, COX-1 inhibitors can cause ulcers of the mucosa. Accordingly, there is a continuing need for new and more effective treatments for the relief of pain, especially chronic pain.

[0003] Trk's are the high affinity receptor tyrosine kinases activated by a group of soluble growth factors called neurotrophins (NT). The Trk receptor family has three members --TrkA, TrkB and TrkC. Among the neurotrophins are (i) nerve growth factor (NGF) which activates TrkA, (ii) brain-derived neurotrophic factor (BDNF) and NT-4/5 which activate TrkB and (iii) NT3 which activates TrkC. Trk's are widely expressed in neuronal tissue and are implicated in the maintenance, signaling and survival of neuronal cells (Patapoutian, A. et al., Current Opinion in Neurobiology, 2001, 11, 272-280).

[0004] Inhibitors of the Trk/neurotrophin pathway have been demonstrated to be effective in numerous pre-clinical animal models of pain. For example, antagonistic NGF and TrkA antibodies (for example, RN-624) have been shown to be efficacious in inflammatory and neuropathic pain animal models and in human clinical trials (Woolf, C.J. et al. (1994) Neuroscience 62,327-331; Zahn, P.K. et al. (2004) J. Pain 5, 157-163; McMahon, S. B. et al., (1995) Nat. Med. 1, 774-780; Ma, Q. P. and Woolf, C. J. (1997) Neuroreport 8, 807-810; Shelton, D. L. et al. (2005) Pain 116, 8-16; Delafoy, L. et al. (2003) Pain 105, 489-497; Lamb, K. et al. (2003) Neurogastroenterol. Motil. 15, 355-361; Jaggar, S. I. et al. (1999) Br. J. Anaesth. 83, 442-448). Additionally, recent literature indicates after inflammation, BDNF levels and TrkB signaling is increased in the dorsal root ganglion (Cho, L. et al. Brain Research 1997, 749, 358) and several studies have show antibodies that decrease signaling through the BDNF/TrkB pathway inhibit neuronal hypersensitization and the associated pain (Chang-Qi, L et al. Molecular Pain 2008, 4:27).

[0005] In addition, it has been shown that tumor cell sand tumor invading macrophages directly stimulates TrkA located on peripheral pain fibers. Using various tumor models in both mice and rats it was demonstrated that neutralizing NGF with a monoclonal antibody inhibits cancer related pain to a degree similar or superior to the highest tolerated dose of morphine. In addition, activation of the BDNF/TrkB pathway has been implicated in numerous studies as a modulator of various types of pain including inflammatory pain (Matayoshi, S., J. Physiol. 2005,

569:685-95), neuropathic pain (Thompson, S.W., Proc. Natl. Acad. Sci USA 1999, 96:7714-18) and surgical pain (Li, C.-Q. et al., Molecular Pain, 2008, 4(28), 1-11). Because TrkA and TrkB kinases may serve as a mediator of NGF driven biological responses, inhibitors of TrkA and/or other Trk kinases may provide an effective treatment for chronic pain states.

[0006] Recent literature has also shown that overexpression, activation, amplification and/or mutation of Trk's are associated with many cancers including neuroblastoma (Brodeur, G. M., Nat. Rev. Cancer 2003, 3, 203-216), ovarian cancer (Davidson. B., et al., Clin. Cancer Res. 2003, 9, 2248-2259), breast cancer (Kruettgen et al, Brain Pathology 2006, 16: 304-310), prostate cancer (Dionne et al, Clin. Cancer Res. 1998, 4(8): 1887-1898), pancreatic cancer (Dang et al, Journal of Gastroenterology and Hepatology 2006, 21(5): 850-858), multiple myeloma (Hu et al, Cancer Genetics and Cytogenetics 2007, 178: 1-10), astrocytoma amd medulloblastoma (Kruettgen et al, Brain Pathology 2006, 16: 304-310) glioma (Hansen et al, Journal of Neurochemistry 2007, 103: 259-275), melanoma (Truzzi et al, Journal of Investigative Dermatology 2008, 128(8): 2031-2040, thyroid carcinoma (Brzezianska et al, Neuroendocrinology Letters 2007, 28(3), 221-229.), lung adenocarcinoma (Perez-Pinera et al, Molecular and Cellular Biochemistry 2007, 295(1&2), 19-26), large cell neuroendocrine tumors (Marchetti et al, Human Mutation 2008, 29(5), 609-616), and colorectal cancer (Bardelli, A., Science 2003, 300, 949). In preclinical models of cancer, Trk inhibitors are efficacious in both inhibiting tumor growth and stopping tumor metastasis. In particular, non-selective small molecule inhibitors of Trk A, B and C and Trk/Fc chimeras were efficacious in both inhibiting tumor growth and stopping tumor metastasis (Nakagawara, A. (2001) Cancer Letters 169:107-114; Meyer, J. et al. (2007) Leukemia, 1-10; Pierottia, M.A. and Greco A., (2006) Cancer Letters 232:90-98; Eric Adriaenssens, E. et al. Cancer Res (2008) 68:(2) 346-351) (Truzzi et al, Journal of Investigative Dermatology 2008, 128(8): 2031-2040. Therefore, an inhibitor of the Trk family of kinases is expected to have utility in the treatment of cancer.

[0007] In addition, inhibition of the neurotrophin/Trk pathway has been shown to be effective in treatment of pre-clinical models of inflammatory diseases. For example, inhibition of the neurotrophin/Trk pathway has been implicated in pre-clinical models of inflammatory lung diseases including asthma (Freund-Michel, V; Frossard, N.; Pharmacology & Therapeutics (2008), 117(1), 52-76), interstitial cystitis (Hu Vivian Y; et. al. The Journal of Urology (2005), 173(3), 1016-21), inflammatory bowel diseases including ulcerative colitis and Crohn's disease (Di Mola, F. F, et. al., Gut (2000), 46(5), 670-678) and inflammatory skin diseases such as atopic dermatitis (Dou, Y.-C.; et. al. Archives of Dermatological Research (2006), 298(1), 31-37), eczema and psoriasis (Raychaudhuri, S. P.; et. al. Journal of Investigative Dermatology (2004), 122(3), 812-819).

[0008] The neurotrophin/Trk pathway, particularly BDNF/TrkB, has also been implicated in the etiology of neurodegenerative diseases including multiple sclerosis, Parkinson's disease and Alzheimer's disease (Sohrabji, Farida; Lewis, Danielle K. Frontiers in Neuroendocrinology (2006), 27(4), 404-414). Modulation of the neutrophin/Trk pathway may have utility in treatment of these and related diseases.

[0009] The TrkA receptor is also thought to be critical to the disease process in the

infection of the parasitic infection of Typanosoma cruzi (Chagas disease) in human hosts (de Melo-Jorge, M. et al. Cell Host & Microbe (2007), 1(4), 251-261). Thus, TrkA inhibition my have utility in treating Chagas disease and related protozoan infections.

[0010] Trk inhibitors may also find use in treating disease related to an imbalance of the requlation of bone remodeling, such as osteoporosis, rheumatoid arthritis, and bone metastases. Bone metastases are a frequent complication of cancer, occurring in up to 70 percent of patients with advanced breast or prostate cancer(1) and in approximately 15 to 30 percent of patients with carcinoma of the lung, colon, stomach, bladder, uterus, rectum, thyroid, or kidney. Osteolytic metastases can cause severe pain, pathologic fractures, life-threatening hypercalcemia, spinal cord compression, and other nerve-compression syndromes. For these reasons, bone metastasis is a serious and costly complication of cancer. Therefore, agents that can induce apoptosis of proliferating osteoblasts would be highly advantageous. Expression of TrkA and TrkC receptors has been observed in the bone forming area in mouse models of bone fracture (K. Asaumi, et al., Bone (2000) 26(6) 625-633). In addition, localization of NGF was observed in almost all bone forming cells (K. Asaumi, et al.). Recently, it was demonstrated that a pan-Trk inhibitor inhibits the tyrosine signaling activated by neurotrophins binding to all three of the Trk receptors in human hFOB osteoblasts (J. Pinski, et al., (2002) 62, 986-989). These data support the rationale for the use of Trk inhibitors for the treatment of bone remodeling diseases, such as bone metastases in cancer patients.

[0011] Several classes of small molecule inhibitors of Trk kinases said to be useful for treating pain or cancer are known (Expert Opin. Ther. Patents (2009) 19(3)).

[0012] International Patent Application Publications WO 2006/115452 and WO 2006/087538 describe several classes of small molecules said to be inhibitors or Trk kinases which could be useful for treating pain or cancer.

[0013] Pyrazolo[1,5-a]pyrimidine compounds are known. For example, International Patent Application Publication WO 2008/037477 discloses pyrazolo[1,5-a]pyrimidine compounds bearing an alkyl, aryl or heterocyclic group at the 3-position. These compounds are asserted to be PI3K and/or mTOR Lipid Kinase inhibitors.

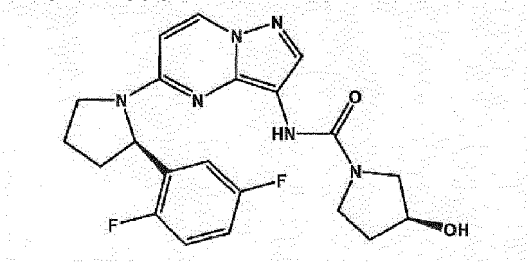
[0014] International Patent Application Publication WO 2008/058126 discloses pyrazolo[1,5-a]pyrimidine compounds bearing a phenyl group at the 3-position. These compounds are asserted to be Pim-kinase inhibitors.

[0015] U.S. Publication US 2006/0094699 discloses pyrazolo[1,5-a]pyrimidine compounds bearing a -C(=O)NH-phenyl, -C(=O)(4-methylpiperidinyl) or -C(=O)NMe(CH_2-trimethylpyrazolyl) group at the 3-position for use in combination therapy with a glucocorticoid receptor agonist.

[0016] Certain compounds which are dual inhibitors of TrkA and TrkB may be useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, surgical pain, and pain associated with cancer, surgery and bone fracture. Selectivity for TrkA and/or TrkB is particularly desirable in compounds for use in treating pain. In addition, the compound of the invention

may be useful for treating cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

[0017] Accordingly, one embodiment of this invention provides a compound which is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide:



or a pharmaceutically acceptable salt thereof.

[0018] In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

[0019] The compound of the invention includes pharmaceutically acceptable salts thereof. Examples of particular salts include hydrogen sulfate salts, hydrochloride salts and trifluoroacetate salts.

[0020] It will further be appreciated that the compound of the invention and its salts may be isolated in the form of solvates, and accordingly that any such solvate is included within the scope of the present invention.

[0021] The compound of the invention also includes compounds that differ only in the presence of one or more isotopically enriched atoms. For example, the compound of the invention includes compounds wherein one or more hydrogen atoms are replaced by deuterium or tritium, or one or more carbon atoms are replaced by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0022] Further described herein is a process for the preparation of the compound of the invention or a pharmaceutically acceptable salt thereof.

[0023] The ability of compounds to act as TrkA inhibitors may be demonstrated by the assays described in Examples A and B. The ability of compounds to act as TrkB inhibitors may be demonstrated by the assay described in Example B.

[0024] The compound of the invention is useful for treating chronic and acute pain, including pain associated with cancer, surgery, and bone fracture. Certain compounds which are inhibitors of TrkA and/or TrkB may be useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, and bone fracture.

[0025] The compound of the invention is also useful for treating cancers including neuroblastoma, ovarian, pancreatic and colorectal cancer.

[0026] The compound of the invention is also useful for treating inflammation and certain infectious diseases.

[0027] In addition, the compound of the invention may also be used to treat interstitial cystitis (IC), painful bladder syndrome (PBS), urinary incontinence, asthma, anorexia, atopic dermatitis, and psoriasis.

[0028] The compound of the invention may also be used to treat demyelination and dysmyelination by promoting myelination, neuronal survival, and oligodendrocyte differentiation via blocking Sp35-TrkA interaction.

[0029] The compound of the invention may be of therapeutic value for use in the treatment of bone-related diseases (such as those involving bone resorption). Examples of bone-related diseases include metastatic bone disease, treatment induced bone loss, osteoporosis, rheumatoid arthritis, ankylosing spondylitis, Paget's disease, and periodontal disease. The osteoporosis may be attributed to (1) menopause in women, (2) aging in men or women, (3) suboptimal bone growth during childhood and adolescence that resulted in failure to reach peak bone mass, and/or (4) bone loss secondary to other disease conditions, eating disorders, medications and/or medical treatments.

[0030] The compound of the present invention can be used for treating other osteolytic diseases that are more localized. A particular example is metastatic tumor-induced osteolysis. In this condition, bone cancers or bone metastases induce localized osteolysis that causes pain, bone weakness and fractures. Such localized osteolysis also permits tumors to grow larger by creating more space for them in the bone and releasing growth factors from the bone matrix. Cancers presently known to cause tumor-induced osteolysis include hematological malignancies (e.g., myeloma and lymphoma) and solid tumors (e.g., breast, prostate, lung, renal and thyroid), all of which the present invention contemplates treating.

[0031] As used herein, the term treatment includes prophylaxis as well as treatment of an existing condition.

[0032] Described herein is a compound of the invention for use in treating diseases or medical conditions in a mammal, wherein said disease or condition is treatable with an inhibitor of TrkA and/or TrkB. In a particular embodiment, provided is a compound of the invention for use in treating pain, cancer, inflammation,
neurodegenerative disease or Typanosoma cruzi infection in a mammal, which comprises administering to said mammal.

[0033] Described herein is a compound of the invention for use in treating osteolytic disease in a mammal.

[0034] The compound of the present invention can be used in combination with one or more additional drugs that work by the same or a different mechanism of action. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Examples include anti-inflammatory compounds, steroids (e.g.,

dexamethasone, cortisone and fluticasone), analgesics such as NSAIDs (e.g., aspirin, ibuprofen, indomethacin, and ketoprofen), and opioids (such as morphine), and chemotherapeutic agents.

[0035] In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to compositions of the present invention may be, for example, surgery, radiotherapy, chemotherapy, signal transduction inhibitors and/or monoclonoal antibodies.

[0036] Accordingly, the compound of the invention may be administered in combination with one or more agents selected from mitotic inhibitors, alkylating agents, antimetabolites, antisense DNA or RNA, intercalating antibiotics, growth factor inhibitors, signal transduction inhibitors, cell cycle inhibitors, enzyme inhibitors, retinoid receptor modulators, proteasome inhibitors, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, cytostatic agents anti-androgens, targeted antibodies, HMG-CoA reductase inhibitors, and prenyl-protein transferase inhibitors.

[0037] The phrase "effective amount" means an amount of compound that, when administered to a mammal in need of such treatment, is sufficient to (i) treat or prevent a particular disease, condition, or disorder which can be treated with an inhibitor of TrkA and/or TrkB, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) prevent or delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

[0038] The amount of a compound of the invention that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

[0039] As used herein, the term "mammal" refers to a warm-blooded animal that has or is at risk of developing a disease described herein and includes, but is not limited to, guinea pigs, dogs, cats, rats, mice, hamsters, and primates, including humans.

[0040] The compound of the invention may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or vasculature, or transdermally or dermally. Compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. If parenteral administration is desired, the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

[0041] According to another aspect, the present invention provides a pharmaceutical composition, which comprises the compound of the invention or a pharmaceutically acceptable salt thereof, as defined hereinabove. In one

embodiment, the pharmaceutical composition includes the compound of the invention together with a pharmaceutically acceptable diluent or carrier.

[0042] Described herein is the compound of the invention or a pharmaceutically acceptable salt thereof, for use in therapy, such as the treatment of a condition treatable with an inhibitor or TrkA and/or TrkB, such as a TrkA and/or TrkA mediated condition, such as one or more conditions described herein.

[0043] Described herein is the compound of Formula I or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition that can be treated with an inhibitor of TrkA and/or TrkB, such as a TrkA and/or TrkB mediated condition, such as a condition as defined hereinabove. In one embodiment, described herein is the compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, cancer, inflammation, neurodegenerative disease or Typanosoma cruzi infection.

[0044] The compound of the invention is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide or pharmaceutically acceptable salts thereof.

[0045] Particular examples of salts of the above compounds include hydrogen sulfate salts, hydrochloride salts and trifluoroacetate salts.

Examples

[0046] The following examples illustrate the invention. In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge, and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), dichloromethane (DCM, methylene chloride), toluene, and dioxane were purchased from Aldrich in Sure/Seal™ bottles and used as received.

[0047] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[0048] Column chromatography was done on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel or C-18 reverse phase column, or on a silica SepPak cartridge (Waters).

[0049] Acronyms found in the examples have the following meanings:

CDI	carbonyldiimidazole
DIEA	diisopropylethylamine
DCM	dichloromethane
DME	dimethoxyethane

DMF	dimethylformamide
DMSO	dimethylsulfoxide
HATU	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
PS-DMAP	polystyrene-bound dimethylaminopyridine
TFA	trifluoroacetic acid

Example A

TrkA ELISA assay

[0050] An enzyme-linked immunosorbant assay (ELISA) was used to assess TrkA kinase activity in the presence of inhibitors. Immulon 4HBX 384-well microtiter plates (Thermo part #8755) were coated with a 0.025 mg/mL solution of poly (Glu, Ala, Tyr; 6:3:1; Sigma P3899). Various concentrations of test compound, 2.5 nM TrkA (Invitrogen Corp., histidine-tagged recombinant human TrkA, cytoplasmic domain), and 500 µM ATP were incubated for 25 minutes at ambient temperature in the coated plates while shaking. The assay buffer consisted of 25 mM MOPS pH 7.5, 0.005% (*v/v*) Triton X-100 and 5 mM $MgCl_2$. The reaction mixture was removed from the plate by washing with PBS containing 0.1 % (v/v) Tween 20. The phosphorylated reaction product was detected using 0.2 µg/mL of a phosphotyrosine specific monoclonal antibody (clone PY20) conjugated to horseradish peroxidase in conjunction with the TMB Peroxidase Substrate System (KPL). After the addition of 1M phosphoric acid, the chromogenic substrate color intensity was quantitated via absorbance at 450 nm. IC_{50} values were calculated using either a 4 or 5-parameter logistic curve fit.

[0051] Table 1 provides specific IC_{50} values for the compound of the invention when tested in this assay. Compounds marked with an asterisk (*) are included for reference.

Table 1

Example No.	TrkA Elisa Enzyme IC_{50} (nM)
8*	**13.7**
9*	**820.8**
11*	**171**
13*	**32.2**
14	**9.7**
15*	**13.3**
22*	**11.5**
23*	**41.7**

Example No.	TrkA Elisa Enzyme IC_{50} (nM)
24*	55
25*	82.3
26*	45
27*	106.7
28*	57.4
29*	98
30*	153.7
31*	88.3
35*	20.2
36*	18
37*	8.7
38*	85.5
39*	25.7
40*	30.8
41*	4.1
42*	28.3
43*	11.7
44*	13.4
81*	8
84*	3.2
85*	5.7
86*	14
87*	14.6
88*	156.1
89*	896.1
90*	11.3
91*	10.2
92*	107.4
93*	28.5

Example B

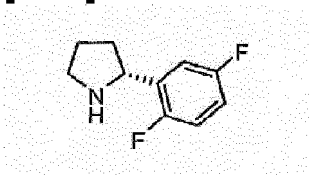
TrkA and TrkB Omnia Assay

[0052] Trk enzymatic selectivity was assessed using Omnia™ Kinase Assay reagents from Invitrogen Corp. Enzyme (either TrkA or TrkB from Invitrogen Corp.) and test compound (various concentrations) were incubated for 10 minutes at ambient temperature in a 384-well white polypropylene plate (Nunc catalog# 267462). Omnia Tyr Peptide #4 (for TrkA) or#5 (for TrkB), as well as ATP, were then added to the plate. Final concentrations were as follows: 20 nM enzyme, 500 μM of ATP for TrkA assay or 1 mM ATP for TrkB assay, 10 μM peptide substrate. The assay buffer consisted of 25 mM MOPS pH 7.5, 0.005% (v/v) Triton X-100 and 5 mM $MgCl_2$. The production of phosphorylated peptide was monitored continuously for 70 minutes using a Molecular Devices FlexStation II^{384} microplate reader (excitation = 360 nm; emission = 485 nm). Initial rates were calculated from the progress curves. IC_{50} values were then calculated from these rates using either a 4 or 5-parameter logistic curve fit.

[0053] In this assay, compounds of the invention had an average IC_{50} below 1000 nM. Certain compounds had an average IC_{50} below 100 nM.

Preparation A

[0054]



Preparation of (R)-2-(2,5-difluorophenyl)pyrrolidine

[0055]

Step A: Preparation of (R)-tert-butyl 2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate: A solution of tert-butylpyrrolidine-1-carboxylate (20 g, 116.8 mmol) and (-)sparteine (32.9, 140 mmol) in MTBE (360 mL) was cooled to -78 °C, and *sec*-BuLi (100 mL, 140 mmol, 1.4 M in cyclohexane) was introduced dropwise via cannula, keeping the internal temperature under -70 °C. The resulting solution was stirred for 3 hours at -78 °C, followed by addition of a solution of $ZnCl_2$ (93.4 mL, 93.4 mmol, 1M in Et_2O) drop-wise with rapid stirring, keeping the internal temperature below -65 °C. The resulting light suspension was stirred at -78 °C for 30 minutes and then warmed to ambient temperature. The resulting mixture was charged with 2-bromo-1,4-difluorobenzene (14.5 mL, 128 mmol), followed by $Pd(OAc)_2$ (1.31 g, 5.8 mmol) and *t*-Bu_3P-HBF_4 (2.03 g, 7.0 mmol) in one portion. After stirring overnight at ambient temperature, 10.5 mL of NH_4OH solution was added and the reaction was stirred for another hour. The resulting slurry was filtered through CELITE and washed with Et_2O (1 L). The filtrate was washed with HCl (0.5 L, 1M aq.) and brine. The organic layer was filtered and concentrated, and the crude product was purified by silica column chromatography, eluting with 5-10% EtOAc/hexanes to give product (R)-

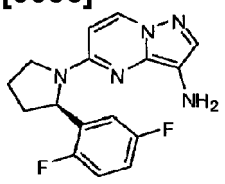
tert-butyl 2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate as yellow oil (23.9 g, 72% yield).

Step B: Preparation of (R)-2-(2,5-difluorophenyl)pyrrolidine: To (R)-tert-butyl 2-(2,5-difluorophenyl)pyrrolidine-1-carboxylate (23.9 g, 84.4 mmol) was added 56.2 mL 4N HCl (dioxane). After stirring at ambient temperature for 2 hours, 200 mL of ether was added and the mixture was stirred for 10 minutes. The resulting slurry was filtered, yielding the hydrochloride salt of the product as a white solid (17.2 g). To obtain the free base, the HCl salt product was dispersed in a mixture of EtOAc (200 mL) and NaOH solution (100 mL, 2 N aq.) The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were filtered and concentrated to give the desired product as a liquid (13.2g, 85% yield).

Step C: Determination of Enantiomeric Excess (ee%) of (R)-2-(2,5-difluorophenyl)pyrrolidine: To an ethanol solution of (R)-2-(2,5-difluorophenyl)pyrrolidine was added excess N-(2,4-dinitro-5-fluorophenyl)-L-alanine amide (FDAA, Marfey's reagent). The mixture was heated to reflux for approximately two minutes. After cooling to ambient temperature, the reaction mixture was diluted with acetonitrile and injected onto HPLC (YMC ODS-AQ 4.6 × 50 mm 3 µm 120Å column; mobile phase: 5-95% solvent B in A; solvent A: H_2O/1% IPA/ 10 mM ammonium acetate, and solvent B: ACN/1% IPA/10 mM ammonium acetate; flow rate: 2 mL/min) to determine the enantiomeric excess of the product by calculating the peak areas of the two diastereomeric derivatives formed. A1:1 racemic sample was prepared according the same procedure described herein, replacing (R)-2-(2,5-difluorophenyl)pyrrolidine with (rac)-2-(2,5-difluorophenyl)pyrrolidine. The ee% of the product obtained as described above was determined to be > 93%.

Preparation B

[0056]



Preparation of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine

[0057]

Step A: Preparation of (R)-5-(2-(2.5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine: In a pressure reaction tube was added 5-chloropyrazolo[1,5-a]pyrimidine (4.2 g, 27 mmol), (R)-2-(2,5-

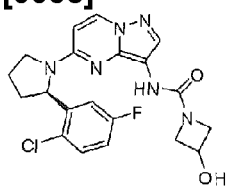
difluorophenyl)pyrrolidine (Preparation A; 5.3 g, 29 mmol), anhydrous n-butanol (5 ml, 55 mmol), and DIEA (9.5 ml, 55 mmol). The yellowish suspension was sealed and heated in an oil bath (160 °C) overnight. The reaction was cooled to ambient temperature, diluted with EtOAc (250 mL), and filtered, rinsing the solid with EtOAc. The filtrate (330 mL) was washed with water (2 × 150 mL), brine (100 mL), concentrated, and purified by silica chromatography, eluting with 2:1 EtOAc/hexanes to give the product as a bright yellowish solid (5.6 g, 68% yield).

Step B: Preparation of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-nitropyrazolo[1,5-a]pyrimidine: (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine (3.3 g, 10.99 mmol), was dissolved in 25 mL TFA at ambient temperature to give a clear yellowish solution, then nitric acid (3.434 mL, 54.94 mmol) was added drop-wise to the solution with rapid stirring. After addition, the reaction mixture was stirred for another 15 minutes at ambient temperature, then quenched by pouring onto ice with rapid stirring. The resulting yellowish suspension was filtered, rinsed with water, then the solid was triturated with MeOH (50 mL, with brief sonication), and vacuum-filtered, giving the pure product as a fine off-white powder (2.2 g, 58% yield).

Step C: Preparation of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: To a yellowish solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-3-nitropyrazolo[1,5-a]pyrimidine (2.3 g, 6.66 mmol), in a 1:1 mixture of MeOH/DCM (30 mL/30 mL) was added Zn dust (4.36 g, 66.6 mmol) [<10 micron, Aldrich] while stirring. Saturated NH_4Cl aqueous solution (30 mL) was added drop-wise to this suspension with rapid stirring. After NH_4Cl addition was complete, the reaction mixture was allowed to cool to ambient temperature and stirred for another 15 minutes. The reaction was diluted with DCM (50 mL) and filtered through a GF/F paper, rinsing the wet cake with DCM. The organic layer of the filtrate was separated, and the aqueous layer was extracted with DCM (2 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, and concentrated, to provide the basically pure product as a brownish foamy solid (2.08 g, 99% yield), which was used without further purification.

Reference Example 8

[0058]



(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide

[0059]

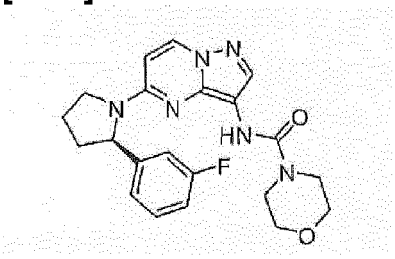
Step A: Preparation of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-2-(2-chloro-5-fluorophenyl)pyrrolidine.

Step B: Preparation of (R)-2-(2-chloro-5-fluorophenyl)pyrrolidine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 2-bromo-1-chloro-4-fluorobenzene in Step A.

Step C: Preparation of (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide: To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (30 mg, 0.090 mmol) was added CDI (29 mg, 0.18 mmol) at ambient temperature in one portion. After stirring two hours, azetidin-3-ol hydrochloride (20 mg, 0.18 mmol) was added in one portion, followed by addition of DIEA (0.047 mL, 0.27 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 50% acetonitrile/water to yield the final product as a yellowish foamy powder (33 mg, 85% yield). MS (apci) m/z = 431.1 (M+H).

Reference Example 9

[0060]



(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)morpholine-4-carboxamide

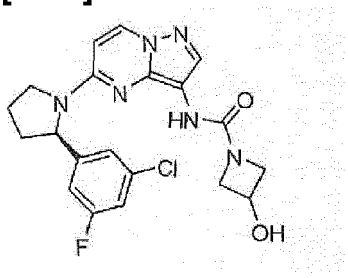
[0061]

Step A: Preparation of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step A with (R)-2-(3-fluorophenyl)pyrrolidine.

Step B: Preparation of (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)morpholine-4-carboxamide: To a DCM (0.8 mL) solution of (R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (50 mg, 0.17 mmol) was added CDI (41 mg, 0.25 mmol) at ambient temperature in one portion. After stirring two hours, morpholine (22 mg, 0.25 mmol) was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 54% acetonitrile/water to yield the final product as a yellowish foamy powder (69 mg, 100% yield). MS (apci) m/z = 411.2 (M+H).

Reference Example 11

[0062]



(R)-N-5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide

[0063]

Step A: Preparation of (R)-5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step A with (R)-2-(3-chloro-5-fluorophenyl)pyrrolidine.

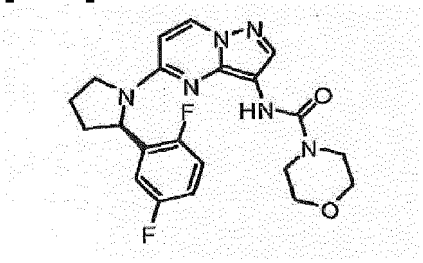
Step B: Preparation of (R)-2-(3-chloro-5-fluorophenyl)pyrrolidine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 1-bromo-3-chloro-5-fluorobenzene in step A.

Step C: Preparation of (R)-N-(5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide: To a DCM (0.7 mL) solution of (R)-5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (20 mg, 0.06 mmol, prepared as described in the following paragraph), was added CDI (20 mg, 0.12 mmol) at ambient temperature in one portion. After stirring two hours, azetidin-3-ol hydrochloride (20 mg, 0.18 mmol) was added in one portion, followed by addition of DIEA (0.032 mL, 0.18 mmol). The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column

chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a solid (29 mg, 74% yield). MS (apci) m/z = 431.2 (M+H).

Reference Example 13

[0064]

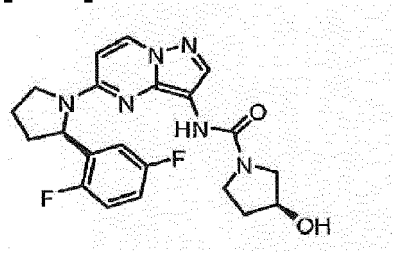


(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)morpholine-4-carboxamide

[0065] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, morpholine (17 mg, 0.19 mmol) was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 55% acetonitrile/water to yield the final product as a yellowish foamy powder (37 mg, 91% yield). MS (apci) m/z = 429.2 (M+H).

Example 14

[0066]



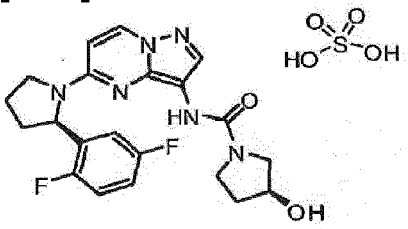
(S)-N-(5-((R)-2-(2.5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1.5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0067] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was

added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (17 mg, 0.19 mmol) [purchased from Suven Life Sciences] was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 50% acetonitrile/water to yield the final product as a yellowish foamy powder (30 mg, 74% yield). MS (apci) m/z = 429.2 (M+H).

Example 14A

[0068]

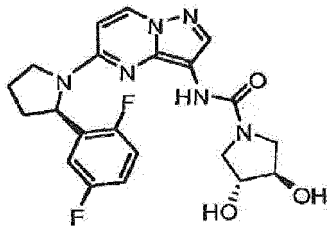


(S)-N-(5-((R)-2-(2,5-difluorophenyl)-pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate

[0069] To a solution of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide (4.5 mg, 0.011 mmol) in methanol (1 mL) at ambient temperature was added sulfuric acid in MeOH (105 µL, 0.011 mmol). The resulting solution was stirred for 30 minutes then concentrated to provide (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (5.2 mg, 0.0099 mmol, 94 % yield) as a yellow solid.

Reference Example 15

[0070]



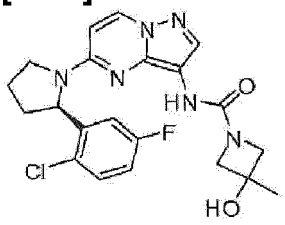
(3R,4R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1.5-a]pyrimidin-3-yl)-3,4-dihydroxypyrrolidine-1-carboxamide

[0071] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 26 mg, 0.08 mmol) was added CDI (27 mg, 0.16 mmol) at ambient temperature in one portion. After stirring two

hours, (3R,4R)-pyrrolidine-3,4-diol (17.3 mg, 0.16 mmol) [obtained from benzyl deprotection of commercially available (3R,4R)-1-benzylpyrrolidine-3,4-diol] was added in one portion. A few drops of DMSO were added to obtain a clear reaction solution. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 45% acetonitrile/water to yield the final product as a yellowish foamy powder (27 mg, 74% yield). MS (apci) m/z = 445.2 (M+H).

Reference Example 22

[0072]

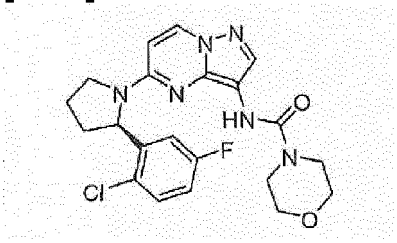


(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide

[0073] To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Reference Example 8, Step A; 22 mg, 0.066 mmol) was added CDI (22 mg, 0.13 mmol) at ambient temperature in one portion. After stirring two hours, 3-methoxyazetidine 3-methylazetidin-3-ol hydrochloride (18 mg, 0.13 mmol) was added in one portion, followed by addition of DIEA (0.035 mL, 0.20 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 50% acetonitrile/water to yield the final product as a yellowish foamy powder (21 mg, 71 % yield). MS (apci) m/z = 445.2 (M+H).

Reference Example 23

[0074]

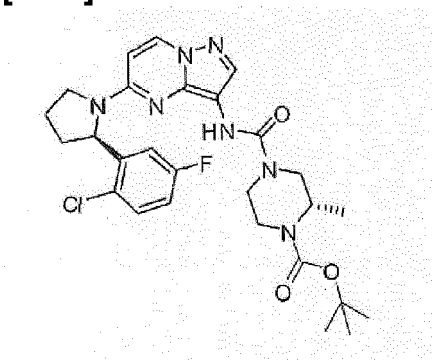


(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)morpholine-4-carboxamide

[0075] Prepared according to the method of Reference Example 22, replacing (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine with morpholine to yield the product as a yellowish foamy powder (26 mg, 76% yield). MS (apci) m/z = 445.1 (M+H).

Reference Example 24

[0076]

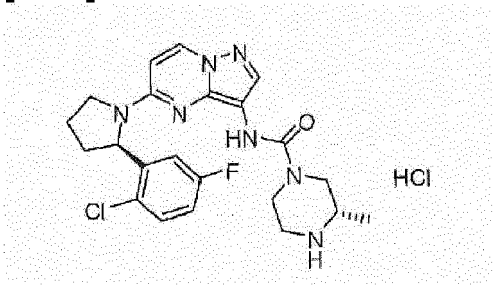


(S)-tert-butyl4-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate

[0077] Prepared according to the method of Reference Example 22, replacing (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine with (S)-tert-butyl2-methylpiperazine-1-carboxylate to yield the product as a yellowish foamy powder (47 mg, 80% yield). MS (apci) m/z = 558.1 (M+H).

Reference Example 25

[0078]



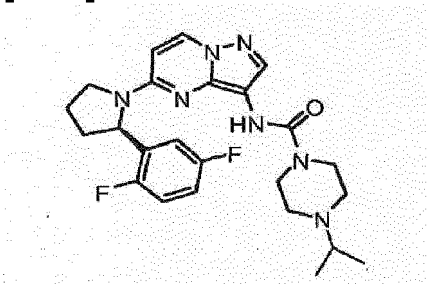
(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1.5-a]pyrimidin-3-yl)-3-methylpiperazine-1-carboxamide hydrochloride

[0079] To (S)-tert-butyl4-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate

(Example 24; 47 mg, 0.084 mmol), was added 1 mL 4 N HCl (dioxane) solution and stirred at ambient temperature for 10 minutes. The reaction was concentrated, treated with ether, and filtered, giving the final product HCl salt as a fine beige powder. MS (apci) m/z = 458.1 (M+H).

Reference Example 26

[0080]

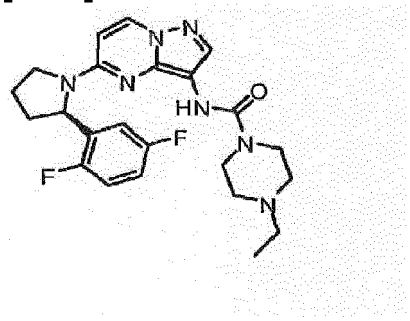


(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-isopropylpiperazine-1-carboxamide

[0081] To a DCM (0.8 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 30 mg, 0.095 mmol) was added CDI (31 mg, 0.19 mmol) at ambient temperature in one portion. After stirring two hours, 1-isopropylpiperazine (24 mg, 0.19 mmol) was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 45% acetonitrile/water to yield the final product as a yellowish foamy powder (40 mg, 90% yield). MS (apci) m/z = 470.1 (M+H).

Reference Example 27

[0082]

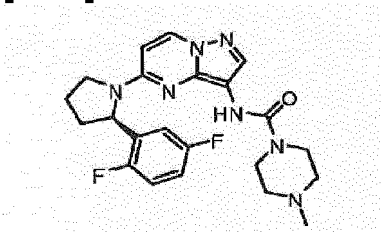


(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-ethylpiperazine-1-carboxamide

[0083] Prepared by the method as described in Example 26, substituting 1-isopropylpiperazine with 1-ethylpiperazine, giving the final product as a yellowish solid (40 mg, 92%). MS (apci) m/z = 456.1 (M+H).

Reference Example 28

[0084]

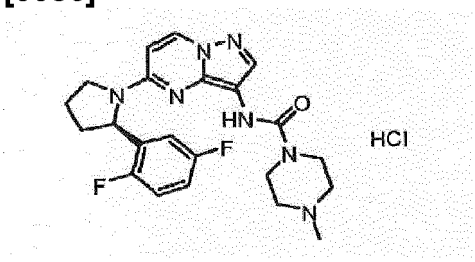


(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)yrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide

[0085] Prepared by the method as described in Example 26, substituting 1-isopropylpiperazine with 1-methylpiperazine, giving the final product as a yellowish solid (38 mg, 90%). MS (apci) m/z = 442.2 (M+H).

Reference Example 28A

[0086]

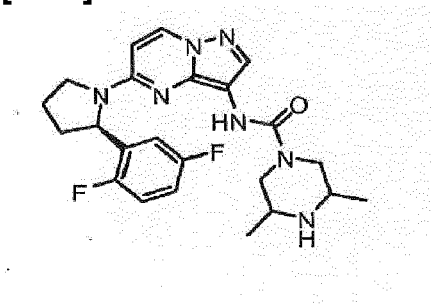


(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide hydrochloride

[0087] To a methanol (1 mL) solution of (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide was added HCl as a solution is dioxane (30 µL). After 30 minutes, the reaction was concentrated to provide (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-methylpiperazine-1-carboxamide hydrochloride as a yellow solid.

Reference Example 29

[0088]

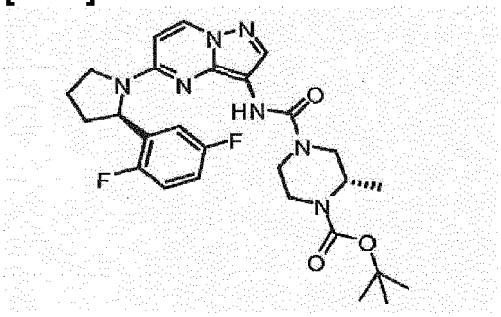


N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3.5-dimethylpiperazine-1-carboxamide

[0089] Prepared by the method as described in Example 26, substituting 1-isopropylpiperazine with 2,6-dimethylpiperazine [predominantly cis, Aldrich], giving the final product as a yellowish solid (34 mg, 78%). MS (apci) m/z = 456.2 (M+H).

Reference Example 30

[0090]

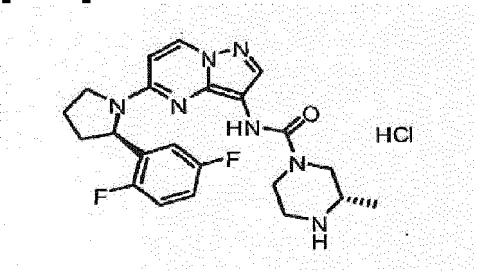


(S)-tert-butyl 4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate

[0091] Prepared by the method as described in Example 26, substituting 1-isopropylpiperazine with (S)-tert-butyl2-methylpiperazine-1-carboxylate, giving the final product as a yellowish solid (47 mg, 90%). MS (apci) m/z = 542.2 (M+H).

Reference Example 31

[0092]

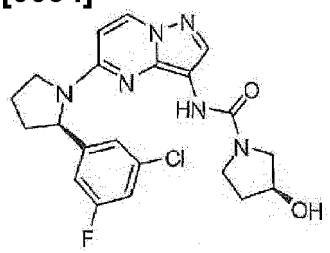


(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpiperazine-1-carboxamide hydrochloride

[0093] To (S)-tert-butyl 4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-ylcarbamoyl)-2-methylpiperazine-1-carboxylate (Example 30; 47 mg, 0.087 mmol), was added 1 mL 4 N HCl (dioxane) solution and stirred at ambient temperature for 1 hour. The reaction was concentrated, treated with ether, and filtered, giving the final product HCl salt as a fine yellowish powder. MS (apci) m/z = 442.2 (M+H).

Reference Example 35

[0094]

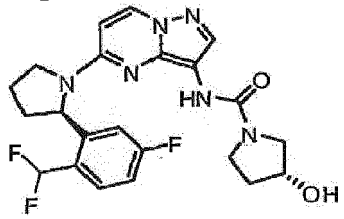


(S)-N-(5-((R)-2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0095] To a DCM (0.6 mL) solution of (R)-5-(2-(3-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Reference Example 11, Step A; 20 mg, 0.06 mmol), was added CDI (20 mg, 0.12 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (16 mg, 0.18 mmol) was added in one portion. The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a solid (50 mg, 83% yield). MS (apci) m/z = 445.2 (M+H).

Reference Example 36

[0096]



(R)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

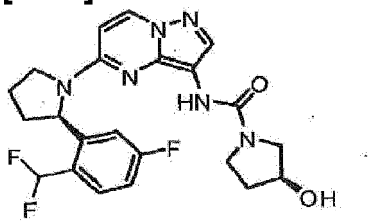
[0097]

Step A: Preparation of (R)-S-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to the method of Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidine.

Step B: Preparation of (R)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide: To a DCM (0.6 mL) solution of (R)-5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (10 mg, 0.028 mmol, prepared as described in the following paragraph), was added CDI (9 mg, 0.056 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (8 mg, 0.084 mmol) was added in one portion. The reaction was stirred overnight, then concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 50% acetonitrile/water to yield the final product as a solid (9 mg, 69%). MS (apci) m/z = 461.2 (M+H).

Reference Example 37

[0098]

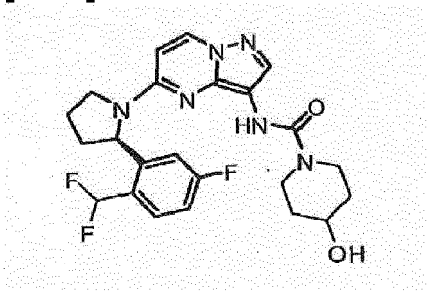


(S)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0099] Prepared by the method as described in Example 36, substituting (S)-pyrrolidin-3-ol with (R)-pyrrolidin-3-ol, giving the final product as a solid (12 mg, 89%). MS (apci) m/z = 461.2 (M+H).

Reference Example 38

[0100]

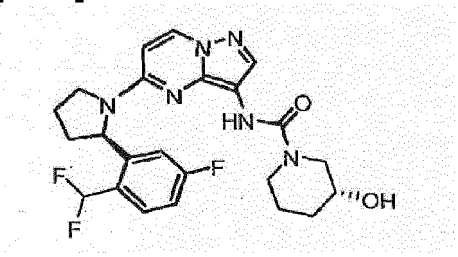


(R)-N-(5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-hdyroxypiperidine-1-carboxamide

[0101] Prepared by the method as described in Example 36, substituting (S)-pyrrolidin-3-ol with piperidin-4-ol, giving the final product as a solid (11 mg, 80%). MS (apci) m/z = 475.2 (M+H).

Reference Example 39

[0102]

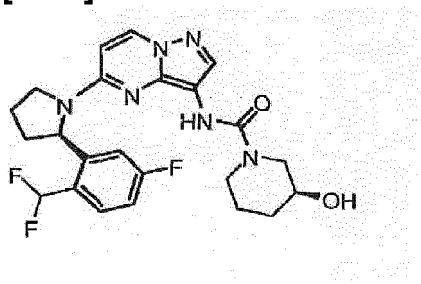


(R)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[0103] Prepared by the method as described in Example 36, substituting (S)-pyrrolidin-3-ol with (R)-piperidin-3-ol hydrochloride (followed by addition of 3 equivalents of DIEA), giving the final product as a solid (10 mg, 74%). MS (apci) m/z = 475.2 (M+H).

Reference Example 40

[0104]

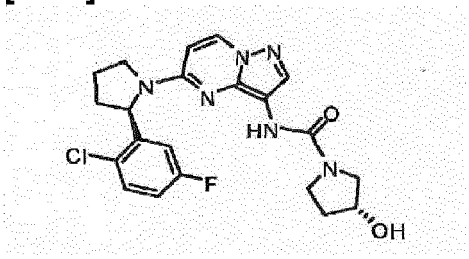


(S)-N-(5-((R)-2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[0105] Prepared by the method as described in Example 36, substituting (S)-pyrrolidin-3-ol with (S)-piperidin-3-ol hydrochloride (followed by addition of 3 equivalents of DIEA), giving the final product as a solid (11 mg, 80%). MS (apci) m/z = 475.2 (M+H).

Reference Example 41

[0106]

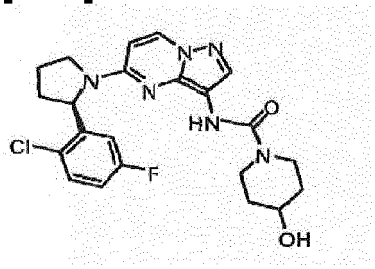


(R)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0107] To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (10 mg, 0.030 mmol, prepared as described in Example 8) was added CDI (10 mg, 0.06 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (5 mg, 0,06 mmol) was added in one portion. The reaction was stirred at ambient temperature for 20 hours before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 50% acetonitrile/water to yield the final product as a solid (9 mg, 67% yield). MS (apci) m/z = 445.2 (M+H).

Reference Example 42

[0108]

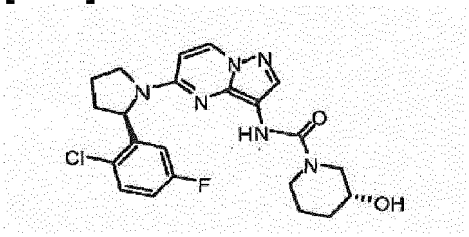


(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-4-hydroxypiperidine-1-carboxamide

[0109] Prepared by the method as described in Example 41, substituting (S)-pyrrolidin-3-ol with piperidin-4-ol, giving the final product as a solid (8 mg, 60%). MS (apci) m/z = 459.2 (M+H).

Reference Example 43

[0110]

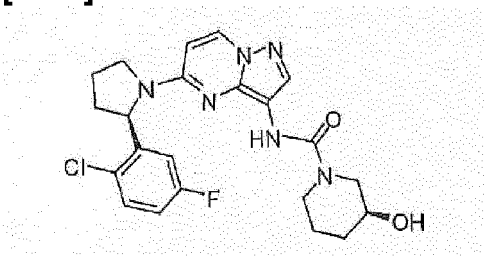


(R)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[0111] Prepared by the method as described in Example 41, substituting (S)-pyrrolidin-3-ol with (R)-piperidin-3-ol hydrochloride (followed by addition of 3 equivalents of DIEA), giving the final product as a solid (9.4 mg, 69%). MS (apci) m/z = 459.1 (M+H).

Reference Example 44

[0112]

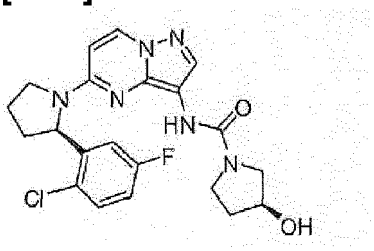


(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[0113] Prepared by the method as described in Example 41, substituting (S)-pyrrolidin-3-ol with (S)-piperidin-3-ol hydrochloride (followed by addition of 3 equivalents of DIEA), giving the final product as a solid (9.3 mg, 68%). MS (apci) m/z = 459.2 (M+H).

Reference Example 81

[0114]

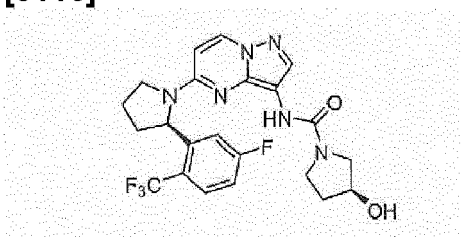


(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0115] To a DCM (0.8 mL) solution of (R)-5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Reference Example 8, Step A; 30 mg, 0.09 mmol) was added CDI (29 mg, 0.18 mmol) at ambient temperature in one portion. After stirring two hours, (S)-pyrrolidin-3-ol (15.8 mg, 0.181 mmol) was added in one portion. The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 5 to 53% acetonitrile/water to yield the final product as a yellowish foamy powder (33 mg, 81% yield). MS (apci) m/z = 445.2 (M+H).

Reference Example 84

[0116]



(S)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0117]

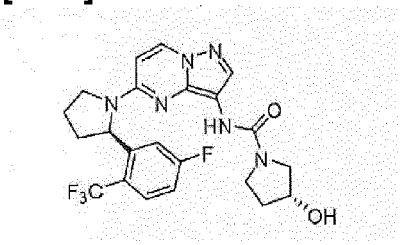
Step A: Preparation of (R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine: Prepared according to Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-2-(5-fluoro-2-(trifluoromethyl)phenyl) pyrrolidine.

Step B: Preparation of (R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolldine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 2-bromo-4-fluoro-1-(trifluoromethyl)benzene in Step A.

Step C: Preparation of (S)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide: To a DCM (1 mL) solution of (R)-S-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (25 mg, 0.068 mmol) was added CDI (22 mg, 0.14 mmol) at ambient temperature in one portion. After stirring for two hours, (S)-pyrrolidin-3-ol (18 mg, 0.21 mmol) was added in one portion. The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a yellowish solid (28 mg, 86% yield). MS (apci) m/z = 479.2 (M+H).

Reference Example 85

[0118]

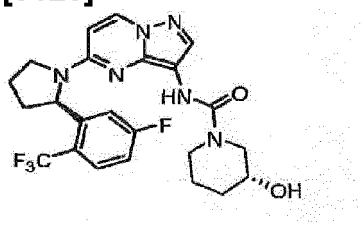


(R)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0119] Prepared by the method as described in Example 84, substituting (S)-pyrrolidin-3-ol in Step C with (R)-pyrrolidin-3-ol, giving the final product as a yellowish solid (26 mg, 79%). MS (apci) m/z = 479.2 (M+H).

Reference Example 86

[0120]

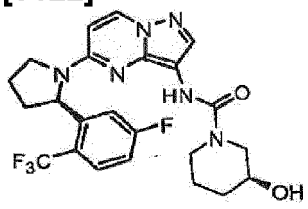


(R)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[0121] Prepared by the method as described in Example 84, substituting (S)-pyrrolidin-3-ol in Step C with (R)-piperidin-3-ol, giving the final product as a yellowish solid (37 mg, 91%). MS (apci) m/z = 493.2 (M+H).

Reference Example 87

[0122]

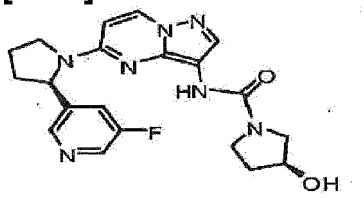


(S)-N-(5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[0123] Prepared by the method as described in Example 84, substituting (S)-pyrrolidin-3-ol in Step C with (S)-piperidin-3-ol, giving the final product as a yellowish solid (39 mg, 97%). MS (apci) m/z = 493.2 (M+H).

Reference Example 88

[0124]



(S)-N-(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0125]

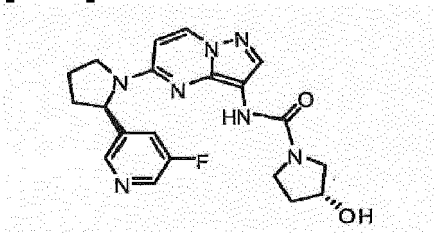
Step A: Preparation of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine:Prepared according to Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-3-fluoro-5-(pyrrolidin-2-yl)pyridine.

Step B: Preparation of (R)-3-fluoro-5-(pyrrolidin-2-yl)pyridine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 3-bromo-5-fluoropyridine in Step A.

Step C: Preparation of (S)-N-(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide: To a DCM (1 mL) solution of (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (25 mg, 0.084 mmol) was added CDI (27 mg, 0.17 mmol) at ambient temperature in one portion. After stirring for two hours, (S)-pyrrolidin-3-ol (15 mg, 0.17 mmol) was added in one portion. The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 40% acetonitrile/water to yield the final product as a solid (27 mg, 78% yield). MS (apci) m/z = 412.2 (M+H).

Reference Example 89

[0126]

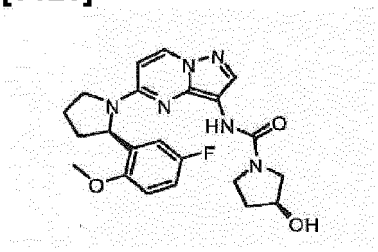


(R)-N-(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0127] Prepared by the method as described in Example 88, substituting (S)-pyrrolidin-3-ol in Step C with (R)-pyrrolidin-3-ol, giving the final product as a solid (28 mg, 81 %). MS (apci) m/z = 412.2 (M+H).

Reference Example 90

[0128]



(S)-N-(5-((R)-2-(5-fluoro-2-methoxyohenyl)pyrrolidin-1-yl)pyrazolo[1,5-alpyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0129]

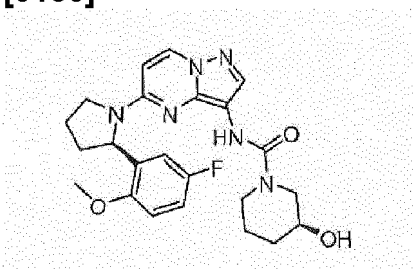
Step A: Preparation of (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazoto[1,5-a]pyrimidin-3-amine: Prepared according to Preparation B, substituting (R)-2-(2,5-difluorophenyl)pyrrolidine in Step 1 with (R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidine.

Step B: Preparation of (R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidine: Prepared by the method of Preparation A, substituting 2-bromo-1,4-difluorobenzene with 2-bromo-4-fluoro-1-methoxybenzene in Step A.

Step C: Preparation of (S)-N-(5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide: To a DCM (5 mL) solution of (R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (25 mg, 0.076 mmol) and DIEA (0.04 mL, 0.23 mmol) was added CDI (25 mg, 0.15 mmol) at ambient temperature in one portion. After stirring for one hour, (S)-pyrrolidin-3-ol (20 mg, 0.23 mmol) was added in one portion. The reaction was stirred overnight before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a yellowish solid (28 mg, 83% yield). MS (apci) m/z = 441.2 (M+H).

I Reference Example 91

[0130]

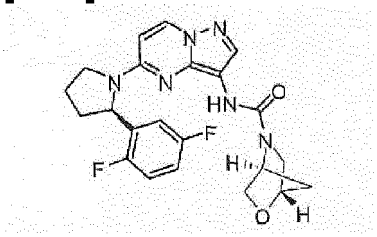


(S)-N-(5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypiperidine-1-carboxamide

[0131] Prepared according to the method as described in Example 90, substituting (S)-pyrrolidin-3-ol in Step C with (S)-piperidin-3-ol, giving the final product as a yellowish solid. MS (apci) m/z = 455.2 (M+H).

Reference Example 92

[0132]

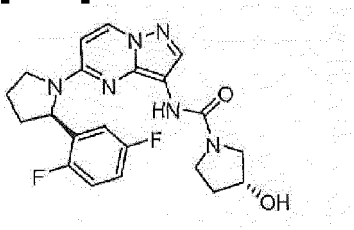


(1S,4S)-N-(5-((R)-2-(2.5-diftuorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxamide

[0133] To a DCM (1.0 mL) solution of (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-amine (Preparation B; 50 mg, 0.16 mmol) was added CDI (51 mg, 0.32 mmol) at ambient temperature in one portion. After stirring 90 minutes, (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (43 mg, 0.32 mmol) was added in one portion, followed by DIEA (0.083 mL, 0.48 mmol). The reaction was stirred for 5 minutes before it was concentrated and directly purified by reverse-phase column chromatography, eluting with 0 to 60% acetonitrile/water to yield the final product as a pale-yellowish powder (60 mg, 86% yield). MS (apci) m/z = 441.2 (M+H).

Reference Example 93

[0134]

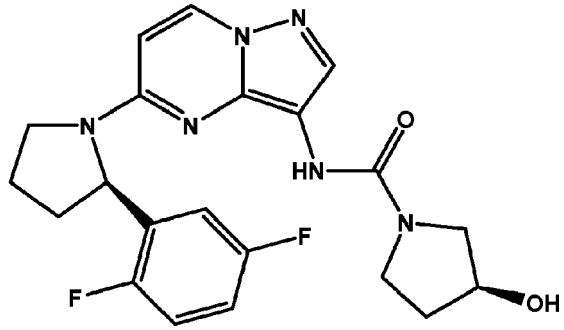


(R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide

[0135] Prepared by the method as described in Reference Example 92, substituting (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride with (R)-pyrrolidin-3-ol. The crude material was purified by reverse-phase column chromatography with 5 to 50% acetonitrile/water eluent, giving the final product as a solid (89 mg, 66% yield). MS (apci) m/z = 429.2 (M+H).

Patentkrav

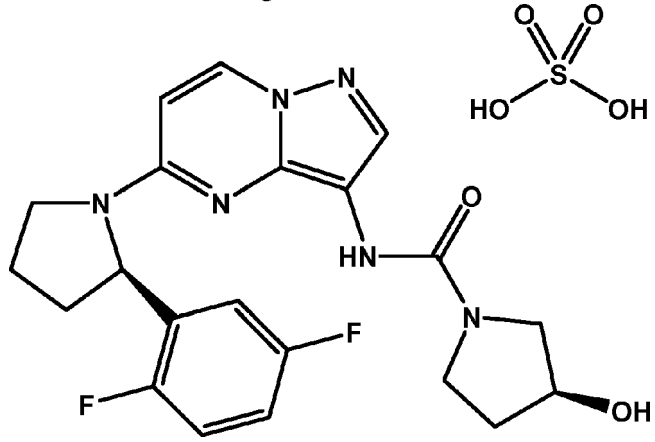
1. Forbindelse, som er:



(S)-N-(5-((R)-2-(2,5-difluorphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidin-1-carboxamid; eller et farmaceutisk acceptabelt salt deraf.

2. Forbindelse ifølge krav 1, hvor forbindelsen er et trifluoracetatsalt, et hydrogensulfatsalt eller et hydrochloridsalt.

3. Forbindelse ifølge krav 1, hvor forbindelsen er:



(S)-N-(5-((R)-2-(2,5-difluorphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidin-1-carboxamidsulfat.

4. Farmaceutisk sammensætning omfattende en forbindelse ifølge et hvilket som helst af kravene 1 til 3 og et farmaceutisk acceptabelt fortyndingsmiddel eller bæremiddel.