HU000029733T2

(19) **HU** (11) Lajstromszám: **E 029 733** (13) **T2**

MAGYARORSZÁG
Szellemi Tulajdon Nemzeti Hivatala

EURÓPAI SZABADALOM
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 06 788851**
(22) A bejelentés napja: **2006. 07. 28.**

(96) Az európai bejelentés bejelentési száma:
EP 20060788851
(97) Az európai bejelentés közzétételi adatai:
EP 1910348 A2 **2007. 02. 08.**
(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 1910348 B1 **2016. 04. 13.**

(51) Int. Cl.: ***C07D 417/04*** *(2006.01)*
A61K 314/28 *(2006.01)*
C07D 513/04 *(2006.01)*

(86) A nemzetközi (PCT) bejelentési szám:
PCT/US 06/029520
(87) A nemzetközi közzétételi szám:
WO 07016392

(30) Elsőbbségi adatok:

494234	**2006. 07. 27.**	**US**
704351 P	**2005. 08. 01.**	**US**

(72) Feltaláló(k):
LIU, Chunjian, Pennington, New Jersey 08534 (US)
LEFTHERIS, Katerina, Skillman, New Jersey 08558 (US)
LIN, James, Lawrenceville, NJ 08648 (US)

(73) Jogosult(ak):
Bristol-Myers Squibb Company, Princeton, NJ 08543 (US)

(74) Képviselő:
SWORKS Nemzetközi Szabadalmi Ügyvivői Iroda Kft., Budapest

(54) **Benzotiazol és azabenzotiazol vegyületek kinázinhibitorokként**

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

A fordítást a szabadalmas az 1995. évi XXXIII. törvény 84/H. §-a szerint nyújtotta be. A fordítás tartalmi helyességét a Szellemi Tulajdon Nemzeti Hivatala nem vizsgálta.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 1 910 348 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
13.04.2016 Bulletin 2016/15

(21) Application number: **06788851.1**

(22) Date of filing: **28.07.2006**

(51) Int Cl.:
C07D 417/04 $^{(2006.01)}$ *C07D 513/04* $^{(2006.01)}$
A61K 31/428 $^{(2006.01)}$

(86) International application number:
PCT/US2006/029520

(87) International publication number:
WO 2007/016392 (08.02.2007 Gazette 2007/06)

(54) BENZOTHIAZOLE AND AZABENZOTHIAZOLE COMPOUNDS USEFUL AS KINASE INHIBITORS

BENZOTHIAZOL- UND AZABENZOTHIAZOL-VERBINDUNGEN ALS KINASEHEMMER

COMPOSES DE BENZOTHIAZOLE ET D'AZABENZOTHIAZOLE UTILES EN TANT QU'INHIBITEURS DE KINASE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

(30) Priority: **27.07.2006 US 494234**
01.08.2005 US 704351 P

(43) Date of publication of application:
16.04.2008 Bulletin 2008/16

(60) Divisional application:
10184708.5 / 2 266 981

(73) Proprietor: **Bristol-Myers Squibb Company**
Princeton, NJ 08543 (US)

(72) Inventors:
- **LIU, Chunjian**
  Pennington, New Jersey 08534 (US)
- **LEFTHERIS, Katerina**
  Skillman, New Jersey 08558 (US)
- **LIN, James**
  Lawrenceville, NJ 08648 (US)

(74) Representative: **Reitstötter Kinzebach**
Patentanwälte
Sternwartstrasse 4
81679 München (DE)

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Printed by Jouve, 75001 PARIS (FR)

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

FIELD OF THE INVENTION

[0001] This invention relates to benzothiazole and azabenzothiazole compounds, more particularly, to benzothiazole and azabenzothiazole compounds useful for treating kinase-associated conditions, such as p38 kinase-associated conditions. The invention further pertains to pharmaceutical compositions containing at least one compound according to the invention useful for treating kinase-associated conditions, such as p38 kinase-associated conditions, and methods of inhibiting the activity of kinase in a mammal.

BACKGROUND OF THE INVENTION

[0002] A large number of cytokines participate in the inflammatory response, including IL-1, IL-6, IL-8 and TNF-α. Overproduction of cytokines such as IL-1 and TNF-α are implicated in a wide variety of diseases, including inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis, endotoxin shock, osteoporosis, Alzheimer's disease, and congestive heart failure, among others [Henry et al., Drugs Fut., 24:1345-1354 (1999); Salituro et al., Curr. Med. Chem., 6:807-823 (1999)]. Evidence in human patients indicates that protein antagonists of cytokines are effective in treating chronic inflammatory diseases, such as, for example, monoclonal antibody to TNF-α (Enbrel) [Rankin et al., Br. J. Rheumatol., 34:334-342 (1995)], and soluble TNF-α receptor-Fc fusion protein (Etanercept) [Moreland et al., Ann. Intern. Med., 130:478-486 (1999)].

[0003] The biosynthesis of TNF-α occurs in many cell types in response to an external stimulus, such as, for example, a mitogen, an infectious organism, or trauma. Important mediators of TNF-α production are the mitogen-activated protein (MAP) kinases, and in particular, p38 kinase. These kinases are activated in response to various stress stimuli, including, but not limited to, proinflammatory cytokines, endotoxin, ultraviolet light, and osmotic shock.

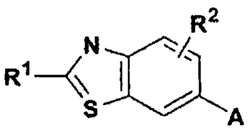
[0004] One important MAP kinase is p38 kinase, also known as cytokine suppressive anti-inflammatory drug binding protein (CSBP) or IK. Activation of p38 requires dual phosphorylation by upstream MAP kinase kinases (MKK3 and MKK6) on threonine and tyrosine within a Thr-Gly-Tyr motif characteristic of p38 isozymes. There are four known isoforms of p38, *i.e.*, p38α, p38β, p38γ, and p38δ. The α and β isoforms are expressed in inflammatory cells and are key mediators of TNF-α production. Inhibiting the p38α and β enzymes in cells results in reduced levels of TNF-α expression. Also, administering p38α and β inhibitors in animal models of inflammatory disease has proven that such inhibitors are effective in treating those diseases. Accordingly, the p38 enzymes serve an important role in inflammatory processes mediated by IL-1 and TNF-α.

[0005] Compounds that reportedly inhibit p38 kinase and cytokines, such as IL-1 and TNF-α for use in treating inflammatory diseases, are disclosed in U.S. Pat. Nos. 6,277,989 and 6,130,235 to Scios, Inc; U.S. Pat. Nos. 6,147,080 and 5,945,418 to Vertex Pharmaceuticals Inc; U.S. Pat. Nos. 6,251,914, 5,977,103 and 5,658,903 to Smith-Kline Beecham Corp.; U.S. Pat. Nos. 5,932,576 and 6,087,496 to G.D. Searle & Co.; WO 00/56738 and WO 01/27089 to Astra Zeneca; WO 01/34605 to Johnson & Johnson; WO 00/12497 (quinazoline derivatives as p38 kinase inhibitors); WO 00/56738 (pyridine and pyrimidine derivatives for the same purpose); WO 00/12497 (discusses the relationship between p38 kinase inhibitors); WO 00/12074 (piperazine and piperidine compounds useful as p38 inhibitors); WO 2004/014900 (benzimidazoles and benzothiazoles as inhibitors of map kinase); WO 01/01986 (reduction of neuronal injury or apoptosis); WO 97/25045 (substituted imidazole componds for treating cytokine mediated diseases) and BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 13, no. 15, 2003, pages 2587-2590 (2-amino-heteroaryl-benzothiazole-6-anilides as potent p56lck inhibitors.

[0006] The present invention provides certain benzothiazole compounds useful as kinase inhibitors, particularly kinases p38α and β.

SUMMARY OF THE INVENTION

[0007] The instant invention generally pertains to compounds of Formula (I),



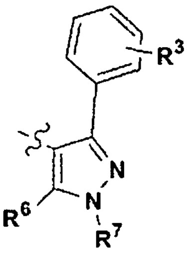
(I), or

an enantiomer, diastereomer or a pharmaceutically-acceptable salt thereof, wherein:

R^1 is $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NH(CH_2)_2CH_3$, $-NH(CH)_2OCH_3$,$-NH(CH_2)_2N(CH_3)_2$, (R)-NH-$CH(CH_3)CH_2CH_3$, (S)-$NHCH(CH_3)CH_2CH_3$, (R)-$NHCH(CH_3)CH_2CH_2OCH_3$, (S)-$NHCH(CH_3)CH_2CH_2OCH_3$, (R)-tetrahydrofuran-3-ylamino, (S)-tetrahydrofuran-3-ylamino, 4-morpholinoethylarnino, 4-morpholinopropylamino, 1-piperidinoethylamino, 1-piperidinopropylamino or cyclopropylamino;

R^2 is hydrogen; and

A is



wherein

R^3 is fluoro at the ortho-position;

R^6 is amino, amino substituted with 1 or 2 C_1-C_6 alkyl, hydroxy or C_1-C_6 alkoxy;

R^7 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with 1 to 4 hydroxy groups, C_3-C_8 cycloalkyl, phenyl, naphthyl, anthracenyl, or saturated, partially unsaturated or fully unsaturated 3 to 7 membered monocyclic heterocyclo containing 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms.

[0008] The invention further pertains to pharmaceutical compositions containing compounds of Formula (I), and to said compounds for use in methods of treating conditions associated with the activity of kinase, such as p38 (α and β), comprising administering to a mammal a pharmaceutically-acceptable amount of a compound of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

[0009] Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

[0010] The terms "alkyl" and "alk" refer to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 6 carbon atoms. Exemplary groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, and the like.

[0011] "Substituted alkyl" refers to an alkyl group substituted with 1 to 4 substituents, at any available point of attachment on the alkyl straight or branched chain. The term "cycloalkyl" refers to a fully saturated cyclic hydrocarbon group containing from 1 to 3 rings and 3 to 8 carbons per ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The term "cycloalkyl" also includes groups having a carbon-carbon bridge of one to two bridgehead carbon atoms, and bicyclic and tricyclic groups in which at least one of the rings is a saturated, carbon-containing ring, in which case the second or third ring may be carbocyclic or heterocyclic, provided that the point of attachment is to the cycloalkyl group. The further rings may be attached to the saturated, carbon-containing ring in a spiro or fused fashion. "Substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, alkyl, substituted alkyl, oxo(=O), and those groups recited above as exemplary alkyl substituents.

[0012] The term "alkoxy" refers to an alkyl group as described above bonded through an oxygen linkage (-O-).

[0013] The term "heterocyclo" refers to fully saturated, partially unsaturated, or fully unsaturated, including aromatic (i.e., "heteroaryl") cyclic groups (for example, 3 to 7 membered monocyclic) which have at least one heteroatom in at least one carbon atom-containing ring. Thus, the term "heteroaryl" is a subset of heterocyclo groups. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. (The term "heteroarylium" refers to a heteroaryl group bearing a quaternary nitrogen atom and thus a positive charge.) Additionally, one or more (preferably one) carbon ring atoms of the heterocyclo ring may, as valence allows, be replaced with carbonyl group, i.e., -C(=O)-. The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system.

[0014] Exemplary monocyclic heterocyclic groups include ethylene oxide, azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, hexahydrodiazepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like.

[0015] The term "heteroaryl" refers to five and six membered monocyclic aromatic heterocyclo groups in which the point of attachment of the ring system to another group is via a five or six membered aromatic ring of the ring system. Thus, for example, the term heteroaryl includes groups such as five or six membered heteroaryl groups, such as thienyl, pyrrolyl, oxazolyl, pyridyl, pyrazinyl, and the like

[0016] Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, and the like.

[0017] When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

[0018] When a functional group is termed "protected", this means that the group is in modified form to mitigate, especially preclude, undesired side reactions at the protected site. Suitable protecting groups for the methods and compounds described herein include, without limitation, those described in standard textbooks, such as Greene, T. W. et al., Protective Groups in Organic Synthesis, Wiley, N.Y. (1991).

[0019] Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

[0020] The compounds of the present invention may form salts which are also within the scope of this invention. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolating or purifying the compounds of this invention.

[0021] The compounds of the present invention may form salts with alkali metals such as sodium, potassium, and lithium; with alkaline earth metals such as calcium and magnesium; and with organic bases such as dicyclohexylamine, tributylamine, pyridine, and amino acids such as arginine, lysine, and the like. Such salts can be formed as known to those skilled in the art.

[0022] The compounds of the present invention may form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, oxalic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid, and various others (e.g., nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates, and the like). Such salts can be formed as known to those skilled in the art. Salt forms of the compounds may be advantageous for improving the compound dissolution rate and oral bioavailability.

[0023] In addition, zwitterions ("inner salts") may be formed.

[0024] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures; it also embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation, or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

PREFERRED COMPOUNDS

[0025] In a preferred embodiment of Formula (I R^6 is $-NN_2$, $-N(CH_2CH_3)_2$,$-NHCH_2CH_3$, $-NH(CH_2)_2CH_3$ or-OH; and R^7 is hydrogen, $-CH_3$, hydroxylethyl or $-CH_2CH_3$.

UTILITY

[0026] The compounds of the invention are selective inhibitors of p38 kinase, and in particular, isoforms p38α, and p38β. Accordingly, compounds of Formula (I) have utility in treating conditions associated with p38 kinase activity. Such conditions include diseases or disorders in which cytokine levels are modulated as a consequence of intracellular signaling via p38, and in particular, diseases that are associated with an overproduction of cytokines IL-1, IL-4, IL-8, and TNF-α. As used herein, the terms "treating" or "treatment" encompass responsive and/or prophylaxis measures addressed to the disease state and/or its sypmtoms, e.g., measures designed to inhibit or delay the onset of the disease or disorder, achieve a full or partial reduction of the symptoms or disease state, and/or alleviate, lessen, or cure the disease and/or its symptoms. When reference is made herein to inhibition of "p-38α/β kinase," this means that either or both p38α and p38β kinase are inhibited.

[0027] In view of their activity as inhibitors of p-38α/β kinase, compounds of Formula (I) are useful in treating inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, angiogenic disorders, infectious diseases, neurodegenerative diseases, viral diseases, and ischemia reperfusion conditions.

[0028] More particularly, the inventive compounds may be used to treat inflammatory diseases including, but not limited to, arthritis (*e.g.*, rheumatoid arthritis, lyme disease arthritis, osteoarthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, gouty arthritis, and other arthritic conditions), glomerulonephritis, pancreatitis (acute or chronic), diabetes, diabetic retinopathy, macular degeneration, conjunctivitis, aplastic anemia, thrombocytopenia, gastritis, chronic thyroiditis, chronic active hepatitis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, cachexia (including cachexia secondary to infection, cancer, or heart disease), periodontal disease, Alzheimer's disease, Parkinson's disease, keloid formation, pulmonary sarcoidosis, myasthenia gravis, inflammatory reaction induced by endotoxin, Reiter's syndrome, gout, acute synovitis, diseases characterized by massive neutrophil infiltration, ankylosing spondylitis, influenze, cerebral malaria, silicosis, bone resorption disease, fever, myalgias due to infection, osteoporosis, multiple myeloma-related bone disorder, neurodegenerative disease caused by traumatic injury, and traumatic brain injury.

[0029] The inventive compounds may also be used to treat acute or chronic graft vs. host reactions (e.g., pancreatic islet allograft), acute or chronic transplant rejection (e.g., kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts, heterografts, and/or cells derived from such organs), and skin conditions including, but not limited to scar tissue formation, eczema, atopic dermatitis, contact dermatitis, urticaria, schleroderma, scleraclerma, and psoriasis. The inventive compounds also may be used to treat allergies and respiratory conditions, including asthma, acute respiratory distress syndrome, hayfever, allergic rhinitis, and any chronic pulmonary inflammatory disease such as chronic obstructive pulmonary disease. The compounds further may be used to treat steroid resistance in asthma and allergies.

[0030] Additionally, the inventive compounds may be used to treat inflammation associated with autoimmune diseases including, but not limited to, systemic lupus erythematosis, Addison's disease, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), and Graves' disease. The inventive compounds may be used to infectious diseases such as sepsis, septic shock, Shigellosis, and Heliobacter Pylori.

[0031] The compounds may be used to treat viral diseases including herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), cytomegalovirus, Epstein-Barr, human immunodeficiency virus (HIV), acute hepatitis infection (including hepatitis A, hepatits B, and hepatitis C), HIV infection and CMV retinitis, AIDS< ARC or malignancy, and herpes.

[0032] The inventive compounds also may be used to treat angiogenic disorders including solid tumors, ocular neovasculization, and infantile haemangiomas.

[0033] In addition, p38 inhibitors of this invention inhibit the expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxide synthase-2 (PGHS-2), also referred to as cyclooxygenase-2 (COX-2). Accordingly, additional conditions that may be treated with the inventive compounds include edema, analgesia and pain, such as neuromuscular pain, headache, pain caused by cancer or surgery, dental pain and arthritis pain. In view of their COX-2 inhibitory activity, the inventive compounds also may be used to treat cancer, including, without limitation, epithelial cancer and adenocarcinoma.

[0034] Additionally, the compounds of this invention are useful to treat ischemia, including ischemia resulting from vascular occlusion, cerebral infarction, stroke, and related cerebral vascular diseases (including cerebrovascular accident and transient ischemic attack). Accordingly, the compounds may be used to treat myocardial infarction, coronary artery disease, non-Q wave MI, congestive heart failure, ventricular hypertrophy, cardiac arrhythmias, unstable angina, chronic stable angina, Prinzmetal's angina, high blood pressure, intermittent claudication, silent ischemia, cardiac hypertrophy, and peripheral occlusive arterial disease (e.g., peripheral arterial disease, critical leg ischemia, prevention of amputation, and prevention of cardiovascular morbidity such as MI, stroke or death).

[0035] Additionally, in view of their activity in treating ischemia, the compounds of the invention may be useful to treat symptoms or consequences occurring from thrombosis, atherosclerosis, peripheral arterial disease, and thrombotic or thromboembolic symptoms or consequences associated with and/or caused by one or more of the following: thromboembolic stroke (including that resulting from atrial fibrillation or from ventricular or aortic mural thrombus), venous thrombosis (including deep vein thrombosis), arterial thrombosis, cerebral thrombosis, pulmonary embolism, cerebral embolism, thrombophilia (e.g., Factor V Leiden, and homocystinenimia), coagulation syndromes and coagulopathies (e.g., disseminated intravascular coagulation), restenosis (e.g., following arterial injury induced endogenously or exogenously), atrial fibrillation, and ventricular enlargement (including dilated cardiac myopathy and heart failure). The compounds of the invention also may be used to treat symptoms or consequences of atherosclerotic diseases and disorders, such as atherosclerotic vascular disease, atherosclerotic plaque rupture, atherosclerotic plaque formation, transplant atherosclerosis, and vascular remodeling atherosclerosis. The compounds of the invention further may be used to treat symptoms or consequences of thrombotic or thromboembolic conditions associated with cancer, surgery, inflammation, systematic infection, artificial surfaces (such as stents, blood oxygenators, shunts, vascular access ports, vascular grafts, artificial valves, etc.), interventional cardiology such as percutaneous transluminal coronary angioplasty (PTCA), immobility, medication (such as oral contraceptives, hormome replacement therapy, and heparin), pregnancy and fetal loss, and diabetic complications including retinopathy, nephropathy, and neuropathy.

[0036] The compounds of the present invention may be used for the preservation of tissue, for example, the preservation of tissue as relates to organ transplantation and surgical manipulation. The compounds may be used to treat diseases or disorders in other tissues or muscles that are associated with ischemic conditions and/or to enhance the strength or stability of tissue and muscles. For example, the compounds may be used to treat muscle cell damage and necrosis and/or to enhance athletes' performance.

[0037] Additional diseases and disorders that may be treated with the inventive compounds include irritable bowel syndrome, leukemia, CNS disorders associated with cerebral ischemia, such as cerebral infarction, cerebral edema and the like, and diseases associated with proliferation of smooth muscle cells, mesangial cells, and fibroblasts. Such diseases include renal fibrosis, hepatic fibrosis, prostate hypertrophy, and pulmonary fibrosis.

[0038] The inventive compounds also may be used to treat veterinary viral infections, such as lentivirus infections, including, but not limited to, equine infectious anemia virus; or repro virus infections, including feline immunodeficiency virus, bovine immunodeficiency virus, and canine immunodeficiency virus.

[0039] When the terms "p38 associated condition" or "p38 associated disease or disorder" are used herein, each is intended to encompass all of the conditions identified above as if repeated at length, as well as any other condition that is modulated by p38 kinase activity.

[0040] The present invention thus provides the compounds of the invention for use in methods for treating such conditions, comprising administering to a subject in need thereof an effective amount of at least one compound of Formula (I), or a pharmaceutically-acceptable salt, hydrate, or prodrug thereof. The methods of treating p38 kinase-associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents such as anti-inflammatory drugs, antibiotics, anti-viral agents, anti-oxidants, cholesterol/lipid lowering agents, anti-tumor agents including antiproliferative agents, and agents used to treat ischemia.

[0041] Examples of suitable other anti-inflammatory agents with which the inventive compounds may be used include aspirin, cromolyn, nedocromil, theophylline, zileuton, zafirlukast, monteleukast, pranleukast, indomethacin, and lipoxygenase inhibitors; non-steroidal antiinflammatory drugs (NSAIDs) (such as ibuprofen and naproxin); TNF-α inhibitors (such as tenidap and rapamycin or derivatives thereof), or TNF-α antagonists (e.g., infliximab, enbrel, D2E7, OR1384), cytokine modulators (e.g. TNF-alpha converting enzyme [TACE] inhibitors, Interleukin-1 converting enzyme (ICE) inhibitors, Interleukin-1 receptor antagonists), prednisone, dexamethasone, Enbrel®, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as Naproxen®, Celebrex®, or Vioxx®), CTLA4-Ig agonists/antagonists (LEA29Y), CD40 ligand antagonists, IMPDH inhibitors (such as mycophenolate [CellCept®] and VX-497), integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), other p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, therapies for the treatment of irritable bowel syndrome (e.g., Zelmac®, Zelnorm®, and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1), or other NF-κB inhibitors (such calphostin, CSAIDs, and quinoxalines as disclosed in U.S. Patent No. 4,200,750); corticosteroids (such as beclomethasone, triamcinolone, budesonide, fluticasone, flunisolide, dexamethasone, prednisone, and dexamethasone); disassociated steroids; chemokine receptor modulators (including CCR1, CCR2, CCR3, CCR4, and CXCR2 receptor antagonists); secretory and cytosolic phospholipase A2 inhibitors, VLA4 antagonists, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; and nuclear translocation inhibitors, such as deoxyspergualin (DSG).

[0042] To treat pain, the inventive compounds may be used in combination with aspirin, NSAIDs, or with 5-HT 1 receptor agonists such as buspirone, sumitriptan, eletriptan or rizatriptan.

[0043] Examples of suitable antibiotics with which the inventive compounds may be used include β-lactams (e.g., penicillins, cephalosporins and carbopenams); β-lactam and lactamase inhibitors (e.g., augamentin); aminoglycosides (e.g., tobramycin and streptomycin); macrolides (e.g., erythromycin and azithromycin); quinolones (e.g., cipro and tequin); peptides and deptopeptides (e.g. vancomycin, synercid and daptomycin); metabolite-based anti-biotics (e.g., sulfonamides and trimethoprim); polyring systems (e.g., tetracyclins and rifampins); protein synthesis inhibitors (e.g., zyvox, chlorophenicol, clindamycin, etc.); and nitro-class antibiotics (e.g., nitrofurans and nitroimidazoles).

[0044] Examples of suitable antiviral agents for use with the inventive compounds include nucleoside-based inhibitors, protease-based inhibitors, and viral-assembly inhibitors.

[0045] Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH fragment, raloxifene, calcitonin, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM) and AP-1 inhibitors.

[0046] Examples of suitable anti-oxidants for use in combination with the compounds of the present invention include lipid peroxidation inhibitors such as probucol, BO-653, Vitamin A, Vitamin E, AGI-1067, and α-lipoic acid.

[0047] A further use of the compounds of this invention is in combination with steriodal or non-steroidal progesterone receptor agonists, ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA).

[0048] The inventive compounds also may be used in combination with antidiabetic agents, such as biguanides (e.g.

metformin), glucosidase inhibitors (e.g. acarbose), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g. repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/glyburide combinations (e.g., glucovance), thiazolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Patent No. 6,548,529 and assigned to the present assignee, glucagon-like peptide-1 (GLP-1), glucagon phosphorylase, and dipeptidyl peptidase IV (DP4) inhibitors.

[0049] In addition, the compounds may be used with agents that increase the levels of cAMP or cGMP in cells for a therapeutic benefit. For example, the compounds of the invention may have advantageous effects when used in combination with phosphodiesterase inhibitors, including PDE1 inhibitors (such as those described in Journal of Medicinal Chemistry, Vol. 40, pp. 2196-2210 [1997]), PDE2 inhibitors, PDE3 inhibitors (such as revizinone, pimobendan, or olprinone), PDE4 inhibitors (such as rolipram, cilomilast, or piclamilast), PDE7 inhibitors, or other PDE inhibitors such as dipyridamole, cilostazol, sildenafil, denbutyline, theophylline (1,2-dimethylxanthine), ARIFLO™ (i.e., cis-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid), arofyline, roflumilast, C-11294A, CDC-801, BAY-19-8004, cipamfylline, SCH351591, YM-976, PD-189659, mesiopram, pumafentrine, CDC-998, IC-485, and KW-4490.

[0050] The inventive compounds may also be useful in combination with anticancer strategies and chemotherapies such as taxol and/or cisplatin. The compounds may be used in conjunction with antitumor agents such as paclitaxel, adriamycin, epithilones, cisplatin, and carboplatin.

[0051] In view of their usefulness in treating ischemia, the inventive compounds may be used in combination with agents for inhibiting F1F0-ATPase, including efrapeptin, oligomycin, autovertin B, azide, and compounds described in U.S. Publication No. 2004-0039033A1, published February 26, 2004, and assigned to the present assignee; alpha- or beta- adrenergic blockers (such as propranolol, nadolol, carvedilol, and prazosin), or β-adrenergic agonists (such as albuterol, terbutaline, formoterol, salmeterol, bitolterol, pilbuterol, and fenoterol); antianginal agents such as nitrates, for example, sodium nitrates, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, and nitrovasodilators; antiarrhythmic agents including Class I agents (such as propafenone); Class II agents (propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide and ibutilide); Class IV agents (such as ditiazem and verapamil); K^+ channel modulators such as IAch inhibitors and inhibitors of the Kv1 subfamily of K^+ channel openers such as IKur inhibitors (*e.g.*, compounds disclosed in U.S. Patent No. 6,706,720, assigned to the present assignee); and gap-junction modulators such as connexions; anticoagulant or antithrombotic agents including aspirin, warfarin, ximelagtran, low molecular weight heparins (such as lovenox, enoxaparain, and dalteparin), anti-platelet agents such as GPIIb/GPIIIa blockers (*e.g.*, abciximab, eptifibatide and tirofiban), thromboxane receptor antagonists (e.g., ifetroban), P2Y1 and P2Y12 antagonists (e.g., clopidogrel, ticlopidine, CS-747, and aspirin/clopidogrel combinations), and Factor Xa inhibitors (e.g., fondaprinux); and diuretics such as sodium-hydrogen exchange inhibitors, chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide; trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene and amiloride.

[0052] Additionally, the inventive compounds may be used in combination with lipid profile modulators and antiatherosclerotic agents including HMG-CoA reductase inhibitors (e.g., pravastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, AZ4522, itavastatin [Nissan/Kowa]), ZD-4522 (a.k.a. rosuvastatin, atavastatin or visastatin), pravachol, squalene synthetase inhibitors, fibrates, bile acid sequestrants (such as questran), niacin and niacin/statin combinations, lipooxygenase inhibitors, ileal Na+/bile acid cotransporter inhibitors, ACAT1 inhibitors, ACAT2 inhibitors, dual ACAT1/2 inhibitors, microsomal triglyceride transport protein inhibitors (such as disclosed in U.S. Patent Nos. 5,739,135, 5,712,279 and 5,760,246), cholesterol absorption inhibitors (such as Zetia®), cholesterol ester transfer protein inhibitors (e.g., CP-529414), PPAR-delta agonists, PPAR-alpha agonists, dual PPAR-alpha/delta agonists, LXR-alpha agonists, LXR-beta agonists, LXR dual alpha/beta agonists, and SCAP modulators.

[0053] The combination of the inventive compounds with other therapeutic agents may prove to have additive and synergistic effects. The combination may be advantageous to increase the efficacy of the administration or decrease the dosage to reduce possible side-effects.

[0054] The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds.

[0055] The present invention also provides pharmaceutical compositions capable of treating p38-kinase associated conditions, including TNF-α, IL-1, and/or IL-8 mediated conditions, as described above. The inventive compositions may contain other therapeutic agents as described above. Pharmaceutical compositions may be formulated by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (e.g., excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulations.

[0056] The compounds of Formula (I) may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques (e.g., as sterile injectable aq. or non-aq. solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

[0057] Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

[0058] Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, e.g., with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (e.g., GANTREZ®); and agents to control release such as polyacrylic copolymer (e.g., CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

[0059] Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

[0060] Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

[0061] Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

[0062] The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like. Thus, when the term "patient" is used herein, this term is intended to include all subjects, most preferably mammalian species, that are affected by mediation of p38 enzyme levels.

[0063] Compounds of Formula (I), including the compounds described in the examples hereof, have been tested in one or more of the assays described below and have shown activity as inhibitors of p38α/β enzymes and TNF-α.

BIOLOGICAL ASSAYS

Generation of p38 Kinases

[0064] cDNAs of human p38α, β, and γ isozymes were cloned by PCR. These cDNAs were subcloned in the pGEX expression vector (Pharmacia). GST-p38 fusion protein was expressed in E. Coli and purified from bacterial pellets by affinity chromatography using glutathione agarose. p38 fusion protein was activated by incubating with constitutively active MKK6. Active p38 was separated from MKK6 by affinity chromatography. Constitutively active MKK6 was generated according to Raingeaud et al. [Mol. Cell. Biol., 1247-1255 (1996)].

TNF-α Production by LPS-Stimulated PBMCs

[0065] Heparinized human whole blood was obtained from healthy volunteers. Peripheral blood mononuclear cells (PBMCs) were purified from human whole blood by Ficoll-Hypaque density gradient centrifugation and resuspended at a concentration of 5 x 10^6/ml in assay medium (RPMI medium containing 10% fetal bovine serum). 50 μl of cell suspension was incubated with 50 μl of test compound (4X concentration in assay medium containing 0.2% DMSO) in 96-well tissue culture plates for 5 minutes at RT. 100 μl of LPS (200 ng/ml stock) was then added to the cell suspension and the plate was incubated for 6 hours at 37°C. Following incubation, the culture medium was collected and stored at -20°C. TNF-α concentration in the medium was quantified using a standard ELISA kit (Pharmingen-San Diego, CA). Concentrations of TNF-α and IC_{50} values for test compounds (concentration of compound that inhibited LPS-stimulated TNF-α production by 50%) were calculated by linear regression analysis.

p38 Assay

[0066] The assays were performed in V-bottomed 96-well plates. The final assay volume was 60 μl prepared from three 20 μl additions of enzyme, substrates (MBP and ATP) and test compounds in assay buffer (50 mM Tris pH 7.5, 10 mM MgCl2, 50 mM NaCl and I mM DTT). Bacterially expressed, activated p38 was pre-incubated with test compounds for 10 min. prior to initiation of reaction with substrates. The reaction was incubated at 25°C for 45 min. and terminated by adding 5 μl of 0.5 M EDTA to each sample. The reaction mixture was aspirated onto a pre-wet filtermat using a Skatron Micro96 Cell Harvester (Skatron, Inc.), then washed with PBS. The filtermat was then dried in a microwave oven for 1 min., treated with MeltilLex A scintillation wax (Wallac), and counted on a Microbeta scintillation counter Model 1450 (Wallac). Inhibition data were analyzed by nonlinear least-squares regression using Prizm (GraphPadSoftware). The final concentration of reagents in the assays are ATP, 1 μM; [γ-^{33}P]ATP, 3 nM,; MBP (Sigma, #M1891), 2μg/well; p38, 10 nM; and DMSO, 0.3%.

TNF-α Production by LPS-Stimulated Mice

[0067] Mice (Balb/c female, 6-8 weeks of age, Harlan Labs; n=8/treatment group) were injected intraperitoneally with 50 μg/kg lipopolysaccharide (LPS; *E coli* strain 0111:B4, Sigma) suspended in sterile saline. Ninety minutes later, mice were sedated by CO_2:O_2 inhalation and a blood sample was obtained. Serum was separated and analyzed for TNF-alpha concentrations by commercial ELISA assay per the manufacturer's instructions (R&D Systems, Minneapolis, MN).

[0068] Test compounds were administered orally at various times before LPS injection. The compounds were dosed either as suspensions or as solutions in various vehicles or solubilizing agents.

ABBREVIATIONS

[0069] For ease of reference, the following abbreviations are employed herein, including the methods of preparation and Examples that follow:

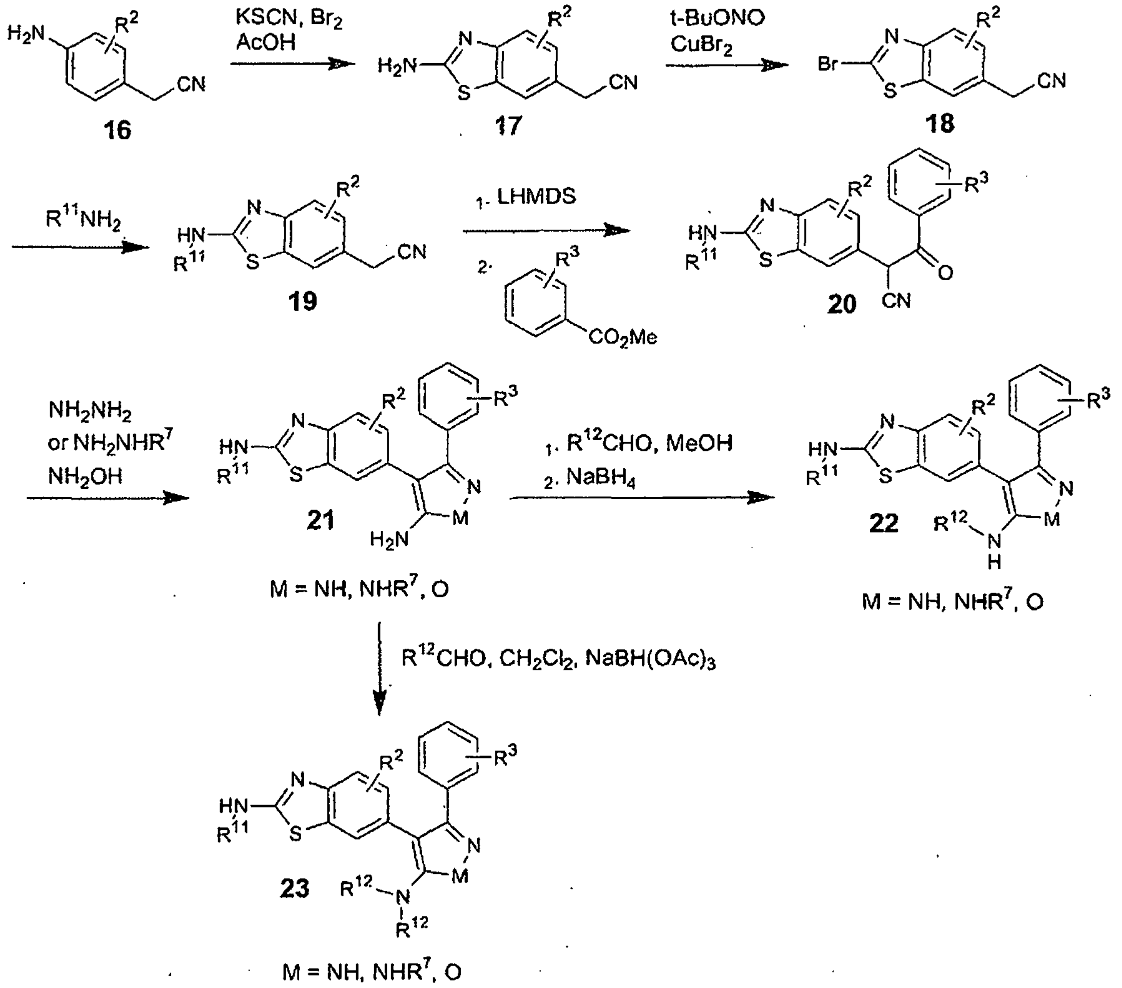
°C = degrees Celsius
μL = microliter
anhyd. = anhydrous
aq. = aqueous
Bn = Benzyl
Boc = tert-butyloxycarbonyl
CBZ = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
CO_2 = carbon dioxide
d = doublet
DCE = 1,2-dichloroethane
DCM = dichloromethane
dd = doublet of doublet
DEAD = diethyl azodicarboxylate
DIPEA = diisopropylethylamine
DMF = dimethyl formamide
DMSO = dimethyl sulfoxide
EDC or EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc = ethyl acetate
EtOH = ethanol

g = gram(s)
h = hour(s)
HATU = O-(7-Azabenzotriazol-1-yl-N,N,N',N'-tetramethyluronim hexafluorophosphate
HCl = hydrogen chloride
HOBt = 1-hydroxybenzotriazole hydrate
HPLC = high performance liquid chromatography
K_2CO_3 = potassium carbonate
KOH = potassium hydroxide
KOtBu = potassium t-butoxide
L = liter
LCMS = high performance liquid chromatography/mass spectrometry
LDA = lithium diisopropylamide
LHMDS = lithium hexamethyldisilazide.
M = Molar
m = multipet
m-CPBA = m-chloroperbenzoic acid
MeOH = methanol
mg = milligram(s)
MHz = megahertz
min = minute(s)
mL = milliliter
mmol = millimole(s)
mol = moles
MS = mass spectrometry
N = Normal
$Na_2S_2O_3$ = sodium thiosulfate
NaH = sodium hydride
NaOEt = sodium ethoxide
NaOH = sodium hydroxide
NMP = N-methylpyrrolidinone
NMR = nuclear magnetic resonance
Pd = palladium
Pd/C = palladium on carbon
PMB = p-methoxybenzyl
$POCl_3$ = phosphorous oxychloride
Ret. time or tR = retention time (minutes)
rt = room temperature
s = singlet
sat or sat'd = saturated
sec = second (s)
TEA = triethylamine
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TMS = trimethylsilyl
X = Br, I

METHODS OF PREPARATION

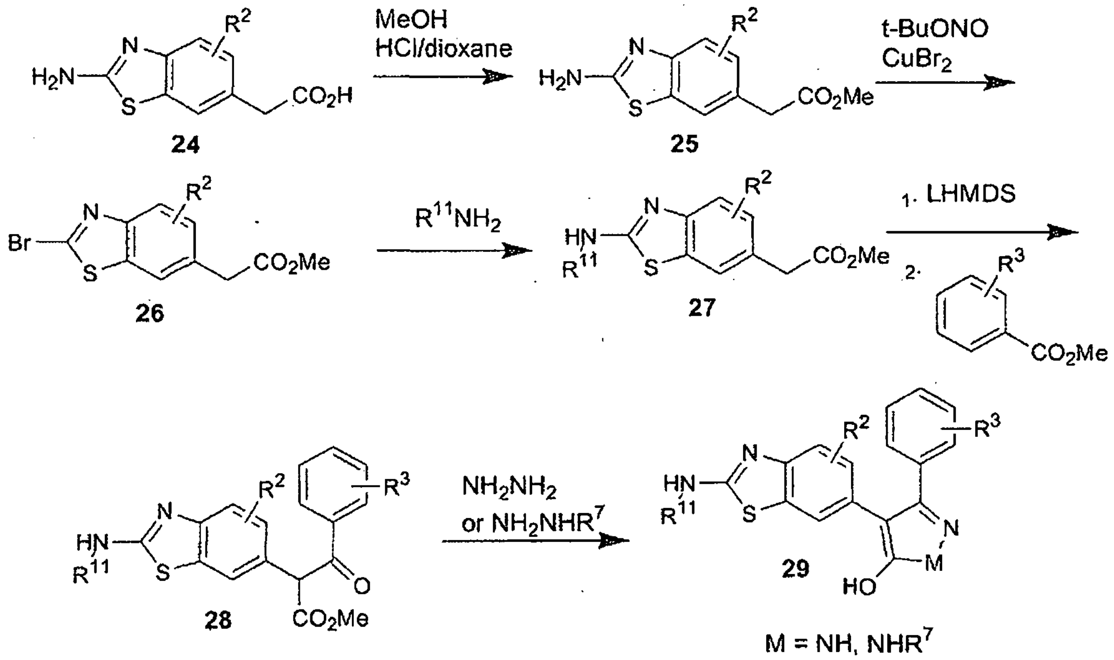
[0070] The compounds of Formula (I) may generally be prepared according to the following schemes and the knowledge of one skilled in the art.

Scheme 1



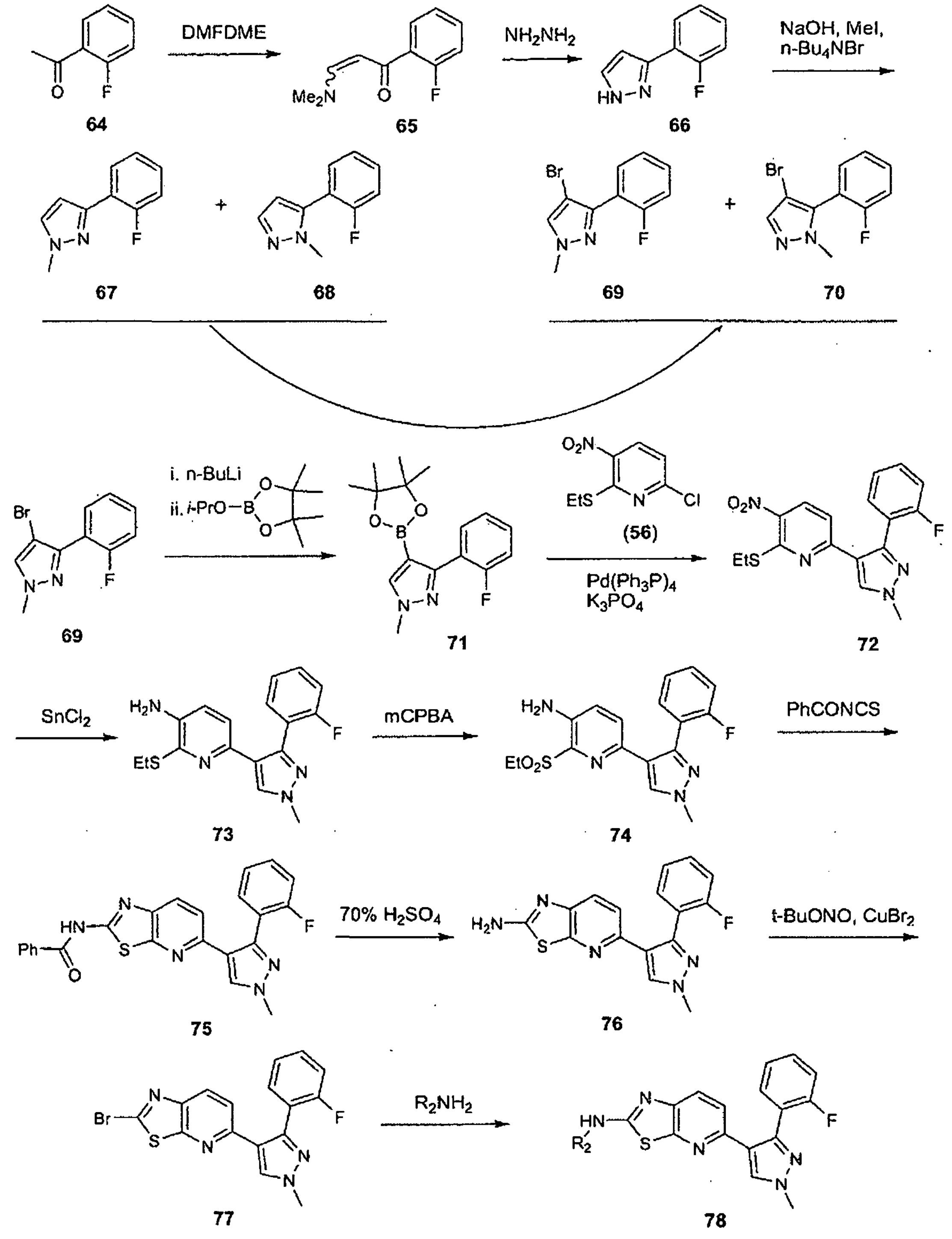
[0071] The preparation of the compound of formula **23** is outlined in Scheme 3. The 2-aminobenzothiazole of formula **17** is made from the 4-aminophenylacetonitrile of formula **16** with potassium thiocyanate and bromine in acetic acid. Conversion of **17** into the compound of formula **19** is performed in a manner known in the art, and shown previously in Scheme 1 for converting the compound of formula **4** to **6**. Treatment of **19** with a strong base, such as LHMDS, followed by a benzoate, affords the compound of formula **20**. Cyclozation of **20** with hydrazine or hydroxylamine provides the compound of formula **21**. Reductive amination at different conditions give the compounds of formulae **22** and **23**.

Scheme 2



[0072] The compound of formula **29** is obtained as depicted in Scheme 4. Esterification of the carboxylic acid of formula **24** supplies the compound of formula **25**. Conversion of **25** into the compound of formula **28** is realized in the same manner as used in Scheme 3 to convert the compound of formulae **17** to **20**. Cyclization of **28** with hydrazine provides the compound of formula **29**.

Scheme 3



[0073] Scheme 10 displays the synthetic route to **78**. The commercially available 2'-fluoroacetophenone (**64**) was treated with DMFDMA to provide **65**, which was reacted with hydrazine to form **66**. N-Methylation of **66** was effected with NaOH and MeI in the presence of n-Bu_4NBr to give a mixture of two isomers **67** and **68**. Without separation, the mixture was reacted with bromine to afford a mixture of **69** and **70**. The isomer **69** was then separated from the mixture by flush chromatography. Treatment of **69** with n-BuLi, followed by 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, supplied **71**. Reaction of **71** with **56** in the presence of $Pd(Ph_3P)_4$ and K_3PO_4 gave rise to **72**. Nitro reduction of **72** with $SnCl_2$ yielded **73**, which was oxidized to sulfone **74** with mCPBA. Reaction of **74** with benzyol isothiocyanate and a subsequent acid hydrolysis of amide **75** led to the formation of **76**. The aminoazabenzothizole **76** was converted to bromoazabenzothiazole **77** with t-butyl nitrite and $CuBr_2$. Analogues **78** were obtained by treating **77** with amines.

EXAMPLES

[0074] In the following examples, HPLC retention times were determined using the following conditions: Ballistic YMC S5 ODS 4.6 x 50 mm column with a binary solvent system where solvent A = 10% methanol, 90% water, 0.2% phosphoric acid and solvent B = 90% methanol, 10% water, and 0.2% phosphoric acid, flow rate = 4 mL / min, linear gradient time = 4 min, start %B = 0, final %B = 100.

[0075] LCMS analyses were performed using the following conditions: Waters Xterra 5 μM 4.6 x 30 mm column with a binary solvent system where solvent A = 10% methanol, 90% water, 0.1% trifluoroacetic acid and solvent B = 90% methanol, 10% water, and 0.1 % trifluoroacetic acid, flow rate = 4 mL/min, linear gradient time = 2 min, start %B = 0, final %B = 100.

[0076] Preparative reverse-phase HPLC purifications were performed using the following conditions: Ballistic YMC S5 ODS 20 x 100 mm column with a binary solvent system where solvent A = 10% methanol, 90% water, 0.1% trifluoroacetic acid and solvent B = 90% methanol, 10% water, and 0.1% trifluoroacetic acid, flow rate = 20 mL/min, linear gradient time = 10 min, start %B = 20, final %B = 100.

[0077] Solvent quantities for the above HPLC retention times, HPLC purifications, and LCMS analyses are reported on volume basis.

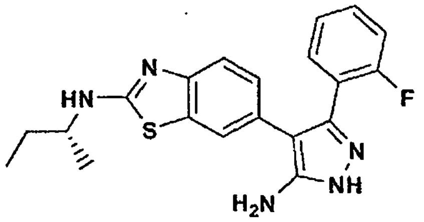
[0078] All reagents were purchased from commercial sources, unless otherwise noted. All reactions were performed under an argon atmosphere. Reactions run in aqueous media were run under an ambient atmosphere unless otherwise noted. Yields are reported as mole %.

Experimental

EXAMPLE 1

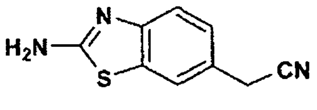
6-(5-Amino-3-(2-fluorophenyl)-1H-pyrazol-4-yl)-N-(R)-sec-butylbenzo[d]thiazol-2-amine

[0079]



1. 2-(2-Aminobenzo[d]thiazol-6-yl)acetonitrile

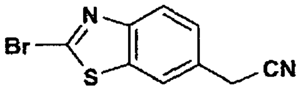
[0080]



[0081] To a solution of 2-(4-aminophenyl)acetonitrile (6.00 g, 45.4 mmol) in AcOH (70 mL) was added potassium thiocyanate (17.6 g, 181 mmol) at rt in one portion. The mixture was stirred at rt until it became a clear solution. To this solution was then added a solution of bromine (2.3 mL, 44.9 mmol) in AcOH (30 mL) at rt over 1 hr. The resulting mixture was stirred at rt for 4 hr. The precipitate that formed during the reaction was collected by suction filtration, and then suspended into water (100 mL). The pH value of the aqueous suspension was adjusted to 8 with concentrated ammonium hydroxide. The insoluble product (7.39 g, 86% yield) was collected as a pale yellow solid by suction filtration and dried over Drierite® under vacuum at 65°C.

2. 2-(2-Bromobenzo[d]thiazol-6-yl)acetonitrile

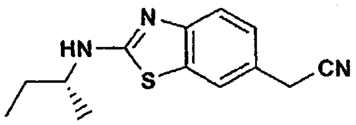
[0082]



[0083] To a mixture of copper (II) bromide (7.63 g, 34.3 mmol) and t-butyl nitrite (5.3 mL, 44.6 mmol) in acetonitrile (120 mL) was added 2-(2-aminobenzo[d]thiazol-6-yl)acetonitrile (5.00 g, 26.4 mmol) at 0°C in one portion. The resulting mixture was stirred at rt for 6 hr before it was poured into a mixture of water (120 mL) and ethyl acetate (300 mL). The whole reaction mixture was stirred at rt for 15 min. The insoluble material was removed by suction filtration through Celite® 545. The organic layer of filtrate was washed successively with water and brine. The combined aqueous layer was extracted with AcOEt. The combined organic phase was dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum provided the title compound (5.53 g, 83% yield) as a tan solid.

3. (R)-2-(2-(sec-Butylamino)benzo[d]thiazol-6-yl)acetonitrile

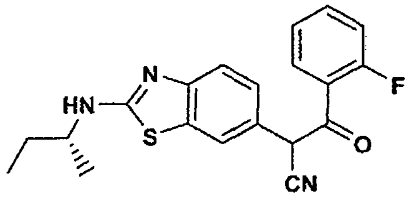
[0084]



[0085] A mixture of 2-(2-bromobenzo[d]thiazol-6-yl)acetonitrile (2.00 g, 7.90 mmol) and (R)-sec-butylamine (4.0 mL, 39.4 mmol) in 1,4-dioxane (30 mL) was heated at 135°C in a sealed bottle for 3.5 hr. The excess (R)-sec-butylamine and 1,4-Dioxane were removed under vacuum. The residue was diluted with AcOEt (150 mL), washed successively with saturated $NaHCO_3$ solution (twice) and brine, and dried over anhydrous $MgSO_4$. The title compound (1.35 g, 70% yield) was isolated as a light orange oil by ISCO (40% AcOEt/hexane).

3. 2-(2-((R)-sec-Butylamino)benzo[d]thiazol-6-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile

[0086]



[0087] To a solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 35.3 mL) in THF (60 mL) was added a solution of (R)-2-(2-(sec-butylamino)benzo[d]thiazol-6-yl)acetonitrile (3.74 g, 15.2 mmol) in THF (60 mL) at -78°C over 40 min. The resulting solution was stirred at -78°C for 10 min before a solution of methyl 2-fluorobenzoate (2.5 mL, 19.6 mmol) in THF (15 mL) was added over 5 min. The mixture was stirred at -78°C for 1 hr and then at rt for 3 hr before it was poured into ice-cold water (100 mL). After its pH value was adjusted to 9 with 6 N HCl, the mixture was extracted with AcOEt (3 x 60 mL). The combined extract was washed with brine and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum, and the residue was subjected to ISCO (2% MeOH/CH2Cl2) to give a mixture (4.09 g) of the title compound and the starting material in a ratio of 1:1.

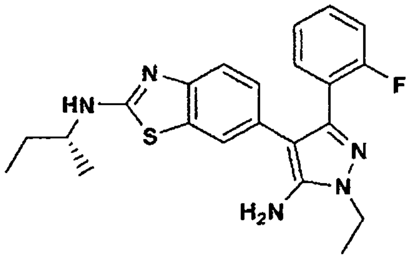
4. 6-(5-Amino-3-(2-fluorophenyl)-1H-pyrazol-4-yl)-N-(R)-sec-butylbenzo[d]thiazol-2-amine

[0088] To a solution of 2-(2-((R)-sec-butylamino)benzo[d]thiazol-6-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile (approximately 50% purity, 2.00 g) in glacial AcOH (30 mL) and EtOH (15 mL) was added anhydrous hydrazine (1.7 mL, 54 mmol) at 0°C. The resulting mixture was heated at 85°C for 16 hr. After it cooled to rt, the mixture was diluted with water (50 mL), basified with concentrated ammonium hydroxide to pH 8, and extracted with AcOEt (3 x 40 mL). The combined extract was washed with brine and dried over anhydrous $MgSO_4$. The title compound (0.518 g, 18% yield over two steps) was isolated by flash chromatography (5% $MeOH/CH_2Cl_2$). $(M + H)^+ = 369.37$.

EXAMPLE 2

6-(5-Amino-1-ethyl-3-(2-fluorophenyl)-1H-pyrazol4-yl)-N-(R)-sec-butylbenzo[d]thiazol-2-amine

[0089]

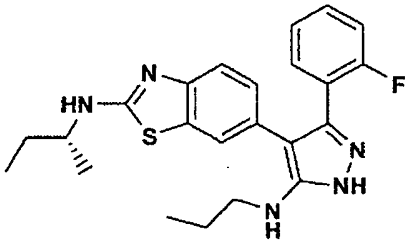


[0090] A mixture of ethyl hydrazine oxalate (0.306 g, 2.04 mmol) and triethylamine (0.34 mL, 2.44 mmol) in EtOH (2 mL) was stirred at rt for 30 min before 2-(2-((R)-sec-butylamino)benzo[d]thiazol-6-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile (example 4) (approximately 50% purity, 0.150 g) and glacial AcOH (4 mL) were successively added. The whole reaction mixture was heated at 80°C for 16 hr. After it cooled to rt, the mixture was diluted with water, basified with concentrated ammonium hydroxide to pH 8, and extracted with AcOEt (3 times). The combined extract was washed with brine and concentrated under vacuum. The title compound (7.5 mg, 3.3% yield over two steps) was isolated as a white solid by preparative HPLC and subsequent flash chromatography (45% $AcOEt/CH_2Cl_2$); 98% purity by LCMS, $(M + H)^+ = 409.52$.

EXAMPLE 3

N-(R)-sec-Butyl-6-(3-(2-fluorophenyl)-5-(propylamino)-1H-pyrazol-4-yl)benzo[d]thiazol-2-amine

[0091]

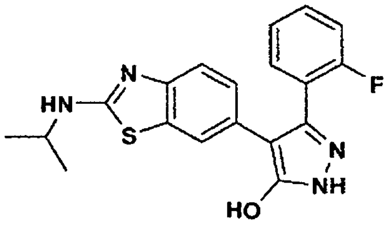


[0092] A mixture of 6-(5-amino-3-(2-fluorophenyl)-1H-pyrazol-4-yl)-N-(R)-sec-butylbenzo[d]thiazol-2-amine (example 4) (0.100 g, 0.262 mmol) and propionaldehyde (34 μL, 0.47 mmol) in methanol (2 mL) was stirred at rt for 4.5 hr before $NaBH_4$ (54 mg, 1.43 mmol) was added. The whole was stirred at rt for 1 hr before it was quenched with water (2 mL). The mixture was diluted with AcOEt (50 mL), washed successively with water and brine, and concentrated under vacuum. The title compound (12.5 mg, 11% yield) was isolated as a white solid by preparative HPLC and subsequent flash chromatography (65% $AcOEt/CH_2Cl_2$); 98% purity by LCMS, $(M + H)^+ = 424.20$.

EXAMPLE 4

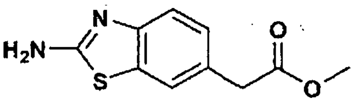
3-(2-Fluorophenyl)-4-(2-(isopropylamino)benzo[d]thiazol-6-yl)-1H-pyrazol-5-ol

[0093]



1. Methyl 2-(2-aminobenzo[d]thiazol-6-yl)acetate

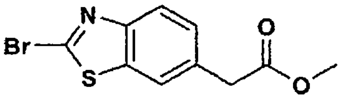
[0094]



[0095] A mixture of 2-(2-aminobenzo[d]thiazol-6-yl)acetic acid (95%, 10.0 g, 45.6 mmol), methanol (50 mL), 4 N HCl/1,4-dioxane (12.0 mL, 48.0 mmol) in 1,4-dioxane (30 mL) was heated at 75°C for 9 hr and then concentrated under vacuum. The residue was suspended into water (50 mL) and basified to pH 9 with IN NaOH solution. The title compound (8.19 g, 81% yield) was collected as a pale solid by suction filtration and dried under vacuum at 50°C.

2. Methyl 2-(2-bromobenzo[d]thiazol-6-yl)acetate

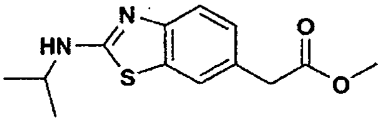
[0096]



[0097] The title compound was prepared in the same manner as 2-(2-bromobenzo[d]thiazol-6-yl)acetonitrile (Example 1, step 2).

3. Methyl 2-(2-(isopropylamino)benzo[d]thiazol-6-yl)acetate

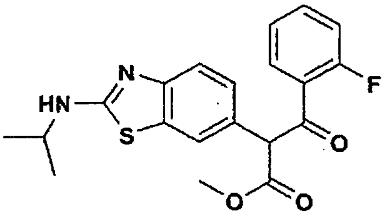
[0098]



[0099] The title compound was prepared in the same manner as (R)-2-(2-(sec-butylamino)benzo[d]thiazol-6-yl)acetonitrile (example 1, step 3).

4. Methyl 3-(2-fluorophenyl)-2-(2-(isopropylamino)benzo[d]thiazol-6-yl)-3-oxopropanoate

[0100]



[0101] To a solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 15.1 mL) in THF (30 mL) was added a solution of methyl 2-(2-(isopropylamino)benzo[d]thiazol-6-yl)acetate (1.60 g, 6.05 mmol) in THF (20 mL) at -78°C over 40 min. The resulting solution was stirred at -78°C for 15 min before a solution of methyl 2-fluorobenzoate (1.08 mL, 8.48 mmol) in THF (10 mL) was added over 5 min. The mixture was stirred at -78°C for 1 hr and then at rt for 3 hr before it was poured into ice-cold water (100 mL). After its pH value was adjusted to 9 with 6 N HCl, the mixture was extracted with AcOEt (3 x 40 mL). The combined extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum give the title compound (2.81 g) as an orange yellowish oil. This product was 63% pure by LCMS, but it was used in the next step without further purification.

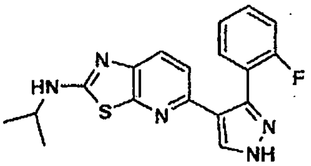
5. 3-(2-Fluorophenyl)-4-(2-(isopropylamino)benzo[d]thiazol-6-yl)-1H-pyrazol-5-ol

[0102] To a solution of methyl 3-(2-fluorophenyl)-2-(2-(isopropylamino)benzo[d]thiazol-6-yl)-3-oxopropanoate(63% purity, 0.260 g) in glacial AcOH (4 mL) and EtOH (2 mL) was added anhydrous hydrazine (0.18 mL, 5.73 mmol) at 0°C. The resulting mixture was heated at 85°C for 4 hr. After it cooled to rt, the mixture was diluted with water (40 mL), basified with concentrated ammonium hydroxide to pH 8, and extracted with AcOEt (3 x 30 mL). The combined extract was washed with brine and dried over anhydrous $MgSO_4$. The title compound (55.0 mg, 27% yield over two steps) was isolated by ISCO (8% $MeOH/CH_2Cl_2$). $(M + H)^+ = 369.21$.

EXAMPLE 5

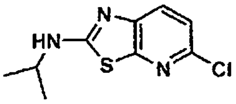
5-(3-(2-fluorophenyl)-1H-pyrazol-4-yl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine

[0103]



1. 5-chloro-N-isopropylthiazolo[5,4-b]pyridin-2-amine

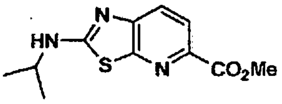
[0104]



[0105] To a solution of 2,6-dichloropyridin-3-amine (3.71 g, 22.8 mmol, 1.0 eq.) and isopropyl isothiocyanate (2.5 mL, 23.5 mmol, 1.0 eq.) in DMF (57 mL) under nitrogen at 0°C was added NaH (95% in mineral oil, 0.77 g, 30.5 mmol, 1.3 eq.). After 10 min., the cold bath was removed, and the reaction mixture was stirred to room temperature for 10 min. It was then heated at 68°C overnight. After cooling to 0°C, isopropyl isothiocyanate (1.5 mL) and NaH (0.44 g) were added, and heating was resumed. After 7.25 h, the reaction was cooled to room temperature. At 0°C, aqueous HCl (1 N), water and EtOAc were added, and the reaction mixture was stirred. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* Trituration with Et_2O afforded 5-chloro-N-isopropylthiazolo[5,4-b]pyridin-2-amine as a white solid (3.43 g, 66% yield).

2. Methyl 2-(isopropylamino)thiazolo[5,4-b]pyridine-5-carboxylate

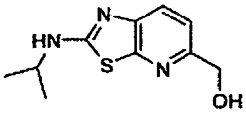
[0106]



[0107] A solution of 5-chloro-N-isopropylthiazolo[5,4-b]pyridin-2-amine (2.06 g, 9.05 mmol, 1.0 eq.), $Pd(OAc)_2$ (0.2084 g, 0.928 mmol, 0.1 eq.), 1,3-bis(diphenylphosphino)propane (0.3775 g, 0.915 mmol, 0.1 eq.) and K_2CO_3 (1.90 g, 13.7 mmol, 1.5 eq.) in MeOH (24 mL) and DMF (12 mL) was stirred under an atmosphere of CO inside a bomb (42 psi) at 92°C overnight. After cooling to room temperature, the reaction mixture was filtered through Celite and rinsed with MeOH. The filtrate was concentrated *in vacuo,* diluted with EtOAc and water. The layers were separated, and the organic layer was washed with brine and 10% aqueous LiCl, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel chromatography using CH_2Cl_2:MeOH (10:0.1) as eluent afforded methyl 2-(isopropylamino)thiazolo[5,4-b]pyridine-5-carboxylate as a white solid (1.67 g, 74% yield).

3. (2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)methanol

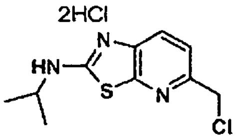
[0108]



[0109] To a solution of methyl 2-(isopropylamino)thiazolo[5,4-b]pyridine-5-carboxylate (1.67 g, 6.64 mmol, 1.0 eq.) in THF (17 mL) under nitrogen at 0°C was added LAH (1M, THF; 10 mL, 10 mmol, 1.5 eq.). After 2.25 hr, ice and EtOAc were added, the cold bath was removed, and the solution was stirred to room temperature. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography using CH_2Cl_2:MeOH (10:0.4) as eluent afforded (2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)methanol as a white solid (1.25 g, 84% yield).

4. 5-(chloromethyl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine dihydrochloride

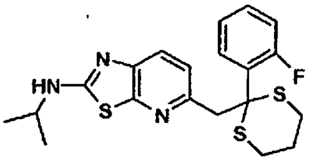
[0110]



[0111] To a solution of (2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)methanol (0.71 g, 3.18 mmol, 1.0 eq.) in CH_2Cl_2 (11 mL) under nitrogen at 0°C was added $SOCl_2$ (1.0 mL, 13.7 mmol, 4.3 eq.). After 5 min., the cold bath was removed, and the reaction mixture was stirred to room temperature for 10 min. and then refluxed for 2.75 hr. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to give 5-(chloromethyl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine dihydrochloride as a white solid (0.90 g, 90% yield).

5. 5-((2-(2-fluorophenyl)-1,3-dithian-2-yl)methyl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine

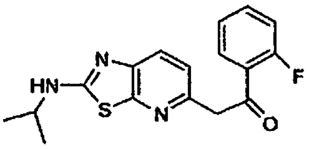
[0112]



[0113] To a solution of 2-(2-fluorophenyl)-1,3-dithiane (2.72 g, 12.7 mmol, 4.4 eq.) in THF (65 mL) under nitrogen at 0°C was added n-BuLi (1.6M/hexane; 7.4 mL, 11.8 mmol, 4.1 eq.) over 0.5 hr. After another 0.5 hr, the 0°C bath was removed and replaced by a -78°C bath. 5-(Chloromethyl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine dihydrochloride (0.90 g, 2.86 mmol, 1.0 eq.) was added in portions after 15 min., and the reaction was stirred for 1.5 hr. Ice, EtOAc and saturated aqueous $NaHCO_3$ were added, and the -78°C bath was removed. After stirring to room temperature, the layers were separated, and the organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography using CH_2Cl_2 followed by CH_2Cl_2:MeOH (40:1) as eluent afforded 5-((2-(2-fluorophenyl)-1,3-dithian-2-yl)methyl)-N-isopropylothiazolo[5,4-b]pyridin-2-amine as a yellow solid (0.95 g, 79% yield).

6. 1-(2-fluorophenyl)-2-(2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)ethanone

[0114]



[0115] To a solution of 5-((2-(2-fluorophenyl)-1,3-dithian-2-yl)methyl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine (0.61 g, 1.45 mmol), 1.0 eq.) in MeOH (73 mL) and water (6 mL) were added HgO (0.83 g, 3.83 mmol, 2.6 eq.) and $HgCl_2$ (1.83 g, 6.74 mmol, 4.6 eq.). After stirring for 15 min., the solution was refluxed for another 15 min. and cooled to room temperature. The precipitate was removed, and the filtrate was concentrated *in vacuo*. The residue was diluted with EtOAc and water, and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Acetone (7 mL), water (0.1 mL, 5.56 mmol, 3.8 eq.), and TsOH•H_2O (0.0342 g, 0.180 mmol, 0.1 eq.) were added, and the reaction was stirred overnight and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 and water, and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel chromatography using CH_2Cl_2:MeOH (15:0.1) as eluent afforded 1-(2-fluorophenyl)-2-(2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)ethanone as a yellow solid (0.1994 g, 42% yield).

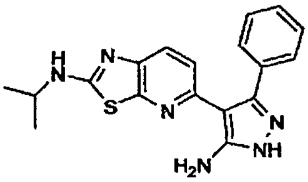
7. 5-(3-(2-fluorophenyl)-1H-pyrazol-4-yl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine

[0116] A solution of 1-(2-fluorophenyl)-2-(2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)ethanone (0.0403 g, 0.122 mmol, 1.0 eq.) in DMF/DMA (1.0 mL) was heated under nitrogen at 80°C for 2 hr. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and dissolved in EtOH (0.5 mL). Hydrazine (0.1 mL, 3.19 mmol, 26.1 eq.) was added, and the reaction was allowed to stand for 2.75 hr and then concentrated *in vacuo*. MeOH was added to the residue, and the mixture was subjected to autoprep. The appropriate fractions were collected, and $NaHCO_3$ (s) was added. The solution was then concentrated *in vacuo* not to dryness and extracted with CH_2Cl_2 (3x). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 5-(3-(2-fluorophenyl)-1H-pyrazol-4-yl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine as a light yellow solid (0.0125 g, 29% yield). LC/MS (MH) = 354.26.

EXAMPLE 6

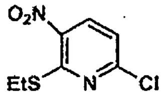
5-(5-amino-3-phenyl-1H-pyrazol-4-yl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine

[0117]



1. 6-chloro-2-(ethylthio)-3-nitropyridine

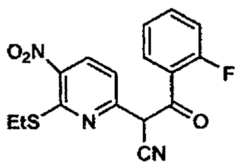
[0118]



[0119] To a solution of 2,b-dichloro-3-nitropyridine (2.24 g, 11.6, 1.0 eq.) and EtSH (0.86 mL, 11.6 mmol, 1.0 eq.) in THF (60 mL) under nitrogen at 0°C was added NaH (95%; 0.33 g, 13.1 mmol, 1.1 eq.). After 2.25 hr, the solution was concentrated *in vacuo.* The residue was dissolved in EtOAc and washed with water, saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered and concentrated in *vacuo.* Silica gel chromatography using hexanes:EtOAc (10:0.05) as eluent afforded 6-chloro-2-(ethylthio)-3-nitropyridine as a yellow solid (1.34 g, 53%).

2. 2-(6-(ethylthio)-5-nitropyridin-2-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile

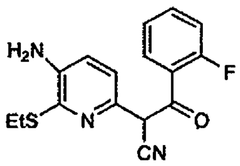
[0120]



[0121] To a solution of 3-(3-fluorophenyl)-3-oxopropanenitrile (1.21 g, 7.42 mmol, 1.2 eq.) in DMF (10 mL) under nitrogen at 0°C was added NaH (95%; 0.37 g, 14.6 mmol, 2.4 eq.). After 1.25 hr, a solution of 6-ehloro-2-(ethylthio)-3-nitropyridine (1.34 g, 6.13 mmol, 1.0 eq.) in DMF (5 mL) was added over 10 min. After 0.5 h, the reaction was heated to 70°C for 1.5 hr, cooled to room temperature, and concentrated *in vacuo.* It was diluted with EtOAc and water, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Silica gel chromatography using hexanes:EtOAc (2:1) as eluent afforded 2-(6-(ethylthio)-5-nitropyridin-2-yl)-3-(2-fluorophenyl)-3-axopropanenitrile as a yellow solid (0.40 g, 19%).

3. 2-(5-amino-6-(ethylthiolpyridin-2-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile

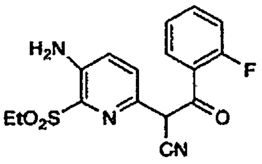
[0122]



[0123] A solution of 2-(6-(ethylthio)-5-nitropyridin-2-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile (0.40 g, 1.16 mmol, 1.0 eq.) and $SnCl_2 \cdot 2H_2O$ (1.35 g, 5.98 mmol, 5.2 eq.) in EtOAc (30 mL) was refluxed for 0.75 hr and cooled to room temperature. At 0°C, aqueous NaOH (1N, 15 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Silica gel chromatography using CH_2Cl_2:MeOH (10:0.2) as eluent afforded 2-(5-amino-6-(ethylthio)pyridin-2-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile as a light brown solid (0.1933 g, 53%).

4. 2-(5-amino-6-(ethylsulfonyl)pyridin-2-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile

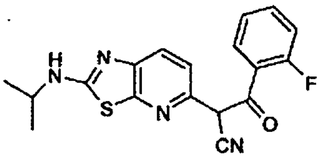
[0124]



[0125] To a solution of 2-(5-amino-6-(ethylthio)pyridin-2-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile (0.30 g, 0.951 mmol, 1.0 eq.) in THF (32 mL) at 0°C was added MCPBA (0.49 g, 2.84 mmol, 3.0 eq.). After 20 min., the solution was concentrated in vacuo and dissolved in CH_2Cl_2. 5% aqueous sodium thiosulfate was added, and the solution was stirred for 5 min. Saturated aqueous $NaHCO_3$ was then added, and the solution was stirred for 5 min. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 2-(5-amino-6-(ethylsulfonyl)pyridin-2-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile as a burgundy solid which was carried to the next step without purification.

5. 3-(2-fluorophenyl)-2-(2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)-3-oxopropane-nitrile

[0126]



[0127] To a solution of 2-(5-amino-6-(ethylsulfonyl)pyridin-2-yl)-3-(2-fluorophenyl)-3-oxopropanenitrile (presumed 0.951 mmol, 1.0 eq.) and iPrNCS (0.15 mL, 1.43 mmol), 1.5 eq.) in DMF (4.8 mL) under nitrogen at 0°C was added NaH (95%; 0.0982 g, 3.89 mmol, 4.1 eq.). After 0.75 hr, the cold bath was removed and the reaction was stirred to room temperature for 0.5 hr. At 0°C, iPrNCS (0.1 mL) and NaH (0.050 g) were added and stirred for 0.25 hr. The cold bath was removed, and the reaction was stirred to room temperature overnight. At 0°C, water and EtOAc were added, and separated. The aqueous layer was washed with EtOAc (2x). The aqueous layer was concentrated in vacuo. Silica gel chromatrography using CH_2Cl_2:MeOH (100:1) as eluent afforded 3-(2-fluorophenyl)-2-(2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)-3-oxopropanenitrile as a burgundy solid (0.10g,29%).

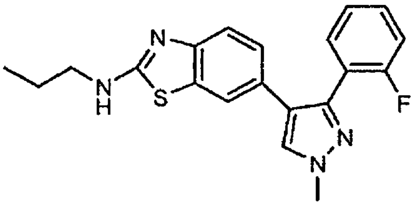
6. 5-(5-amino-3-phenyl-1H-pyrazol-4-yl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine

[0128] To a solution of 3-(2-fluorophenyl)-2-(2-(isopropylamino)thiazolo[5,4-b]pyridin-5-yl)-3-oxopropanenitrile (0.10 g, 0.282 mmol, 1.0 eq.) in EtOH (1 mL) and HOAc (2 mL) at 0°C was added hydrazine (0.1 mL, 3.19 mmol, 11.3 eq.). After 10 min., the cold bath was removed, and the reaction mixture was stirred to room temperature for 10 min. It was then heated at 88°C for 5 hr and at 100°C overnight. After cooling to room temperature and then to 0°C, water was added followed by concentrated aqueous NH_4OH until pH was 10 by litmus paper. The aqueous layer was extracted with EtOAc (3x). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* MeOH was added to the residue, and the mixture was subjected to autoprep. The appropriate fractions were collected, and $NaHCO_3$ (s) was added. The solution was then concentrated *in vacuo* not to dryness and extracted with CH_2Cl_2 (3x). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 5-(5-amino-3-phenyl-1H-pyrazol-4-yl)-N-isopropylthiazolo[5,4-b]pyridin-2-amine as alight yellow solid (0.0014 g, 1.3% yield). LC/MS (MH) = 369.14.

EXAMPLE 7

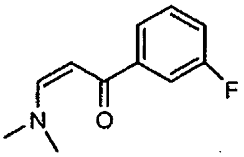
6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)-N-propylbenzo[d]thiazol-2-amine

[0129]



1. (Z)-3-(dimethylamino)-1-(3-fluorophenyl)prop-2-en-1-one

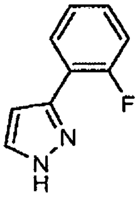
[0130]



[0131] A solution of 1-(3-fluorophenyl)ethanone (21.38 g, 154.8 mmol, 1.0 eq.) in DMF/DMA (150 mL) was heated under nitrogen at 95 °C overnight. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to give (Z)-3-(dimethylamino)-1-(3-fluorophenyl)prop-2-en-1-one as a red oil (30.70 g, 100 % yield).

2. 3-(2-fluorophenyl)-1H-pyrazole

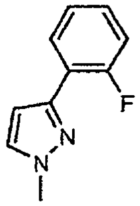
[0132]

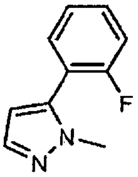


[0133] To a solution of (Z)-3-(dimethylamino)-1-(3-fluorophenyl)prop-2-en-1-one (10.30 g, 53.3 mmol, 1.0 eq.) in ethanol (180 mL) under nitrogen at 0 °C was added hydrazine (10.0 mL, 318.6 mmol, 6.0 eq.). After 10 mim, the cold bath was removed, and the reaction mixture was stirred to room temperature overnight. It was then concentrated *in vacuo* to give 3-(2-fluorophenyl)-1H-pyrazole as an oil (8.62 g, 100 % yield).

3. 3-(2-fluorophenyl)-1-methyl-1H-pyrazole and 5-(2-fluorophenyl)-1-methyl-1H-pyrazole

[0134]

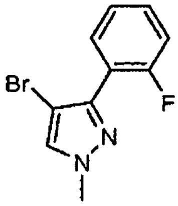




[0135] To a solution of 3-(2-fluorophenyl)-1H-pyrazole (8.62 g, 53.2 mmol, 1.0 eq.) in methanol (133 mL) under nitrogen at 0 °C were added iodomethane (4.3 mL, 68.9 mmol, 1.3 eq.), NaOH (aq., 6 N, 34 mL, 204.0 mmol, 3.8 eq.) and nBu_4NBr (0.68 g, 2.11 mmol, 0.04 eq.). The cold bath was then removed, and the reaction mixture was stirred to room temperature. After 6.5 h, iodomethane was added (4 mL), and the reaction mixture was stirred overnight. More iodomethane (4 mL) and NaOH (aq., 6 N, 20 mL) were added, and the reaction mixture was stirred overnight. It was then concentrated *in vacuo* not to dryness, diluted with EtOAc, and the two layers were separated. The aqueous layer was extracted with EtOAc, and the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Silica gel chromatography using hexanes: EtOAc (15:2) as eluent afforded a mixture of 3-(2-fluorophenyl)-1-methyl-1H-pyrazole and 5-(2-fluorophenyl)-1-methyl-1H-pyrazole (6.78 g, 72 % yield).

4. 4-bromo-3-(2-fluorophenyl)-1-methyl-1H-pyrazole

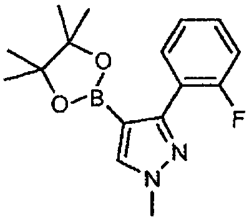
[0136]



[0137] To a solution of a mixture of 3-(2-fluorophenyl)-1-methyl-1H-pyrazole and 5-(2-fluoropbenyl)-1-methyl-1H-pyrazole (6.77 g, 38.4 mmol, 1.0 eq.) in chloroform (10 mL) under nitrogen at 0 °C was added a solution of bromine (2.0 mL, 39.0 mmol, 1.0 eq.) in chloroform (5 mL) over 10 min. After 50 min, the reaction mixture was diluted with chloroform and washed with saturated aqueous $NaHCO_3$ (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Silica gel chromatography using hexanes:EtOAc (10:1) as eluent afforded 4-bromo-5-(2-fluorophenyl)-1-methyl-1H-pyrazole as a white solid (2.70 g, 28 % yield), a mixture (0.65 g, 7 % yield) and 4-bromo-3-(2-fluorophenyl)-1-methyl-1H-pyrazole as a white solid (5.94 g, 61 % yield).

5. 3-(2-fluorophenyl)-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

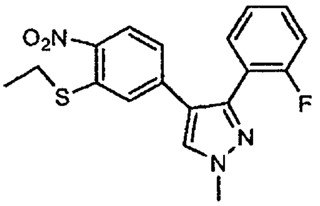
[0138]



[0139] To a solution of 4-bromo-3-(2-fluorophenyl)-1-methyl-1H-pyrazole (3.03 g, 11.9 mmol, 1.0 eq.) in THF (40 mL) under nitrogen at -78 °C was added nBuLi (hexane, 2.5 M, 5.3 mL, 13.2 mmol, 1.1 eq.) over 10 min. After 45 min, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.7 mL, 13.2 mmol), 1.1 eq.) was added. After 1 h 45 min, saturated aqueous NH_4Cl and EtOAc were added. The cold bath was removed, and the reaction mixture was stirred to room temperature. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Silica gel chromatography using hexanes: EtOAc (3:1) as eluent afforded 3-(2-fluorophenyl)-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as a white solid (1.83 g, 51 % yield).

6. 4-(3-(ethylthio)-4-nitrophenyl)-3-(2-fluorophenyl)-1-methyl-pyrazole

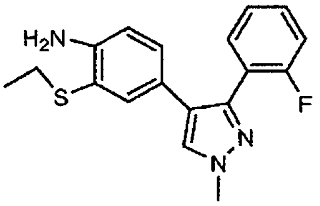
[0140]



[0141] A solution of (5-chloro-2-nitrophenyl)(ethyl)sulfane (0.1267 g, 0.579 mmol, 1.00 eq.) and 3-(2-fluorophenyl)-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.2148 g, 0.711 mmol, 1.2 eq.) in toluene (3.3 mL) was purged with nitrogen for 15 min. Pd(Ph_3P)$_4$ (0.0365 g, 0.0316 mmol, 0.05 eq.), K_3PO_4 (aqueous, 2 M, 0.58 mL, 1.16 mmol, 2.0 eq.) and EtOH (0.42 mL) were added, and the reaction mixture was refluxed overnight. After cooling to room temperature, it was diluted with EtOAc and water. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Silica gel chromatography using hexanes:EtOAc (2:1) as eluent afforded 4-(3-(ethylthio)-4-nitrophenyl)-3-(2-fluorophenyl)-1-methyl-1H-pyrazole as a yellow solid (0.1421 g, 68 % yield).

7. 2-(ethylthio)-4-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)aniline

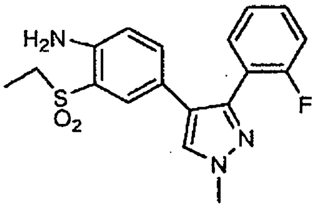
[0142]



[0143] A solution of 4-(3-(ethylthio)-4-nitrophenyl)-3-(2-fluorophenyl)-1-methyl-1H-pyrazole (2.87 g, 8.01 mmol, 1.00 eq.) and $SnCl_2$•$2H_2O$ (9.05 g, 40.1 mmol, 5.0 eq.) in EtOAc (200 mL) was refluxed for 2 h. After cooling to room temperature, the solution was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 2-(ethylthio)-4-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)aniline as a yellow solid (2.31 g, 88 % yield).

8. 2-(ethylsulfonyl)-4-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)aniline

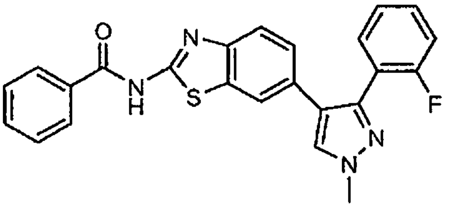
[0144]



[0145] To a solution of 2-(ethylthio)-4-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)aniline (1.00 g, 3.04 mmol, 1.0 eq.) in THF (100 mL) under nitrogen at 0 °C was added MCPBA (77%, 1.60 g, 9.27 mmol, 3.05 eq.). After 3 h 15 min, 5 % aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$ were added, and the solution was stirred for 10 min. CH_2Cl_2 was then added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x), and the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Trituration with EtOAc afforded 2-(ethylsulfonyl)-4-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)aniline as a light tan solid (0.94 g, 85 % yield).

9. N-(6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)benzo[d]thiazol-2-yl)benzamide

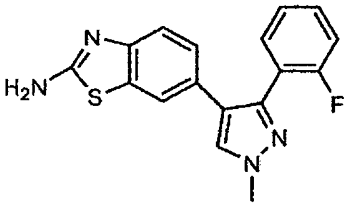
[0146]



[0147] To a solution of 2-(ethylsulfonyl)-4-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)aniline (1.04 g, 2.89 mmol, 1.0 eq.) in THF under nitrogen at 0 °C was added benzoyl isothiocyanate (0.47 mL, 3.50 mmol, 1.2 eq.). The cold bath was removed, and the reaction mixture was stirred to room temperature for 20 min. It was then heated to 70 °C for 6 h. After cooling to room temperature, it was diluted with EtOAc and water. The layers were separated, and the organi layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Trituration with EtOAc afforded N-(6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)benzo[d]thiazol-2-yl)benzamide as a light tan solid (1.05 g, 85 % yield).

10. 6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)benzo[d]thiazol-2-amine

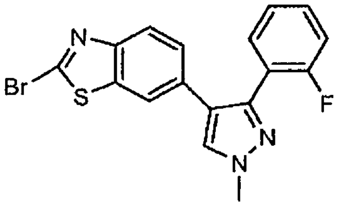
[0148]



[0149] A solution of N-(6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)benzo[d]thiazol-2-yl)benzamide (0.36 g, 0.838 mmol, 1.0 eq.) in 70 % aqueous H_2SO_4 (4.2 mL) was heated at 105 °C for 2 h. After cooling to room temperature, the reaction mixture was added to water. At 0 °C, 30 % aqueous NaOH followed by solid NaOH were added until pH ~ 13 by litmus paper. The precipitate was washed with water and dried to give 6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)benzo[d]thiazol-2-amine as a tan solid (0.1493 g, 55 % yield).

11. 2-bromo-6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)benzo[d]thiazole

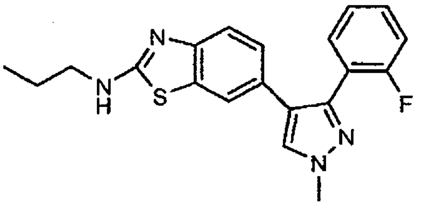
[0150]



[0151] A solution of $CuBr_2$ (0.3251 g, 1.46 mmol, 1.3 eq.) in acetonitrile (8 mL) was purged with N2 for 20 min. At 0 °C, t-butyl nitrite (0.21 mL, 1.77 mmol, 1.5 eq.) and 6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)benzo[d]thiazol-2-amine (0.2578 g, 1.15 mmol, 1.0 eq.) were added. After 15 min, the cold bath was removed, and the reaction mixture was stirred to room temperature overnight. It was then diluted with Et_2O and water. The layers were separated, and the aqueous layer was extracted with Et_2O (2x). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Silica gel chromatography using CH_2Cl_2 as eluent afforded 2-bromo-6-(3-(2-fluorophenyl)-1-methy]-1H-pyrazol-4-yl)benzo[d]thiazole as a yellow foam (0.1584 g, 35 % yield).

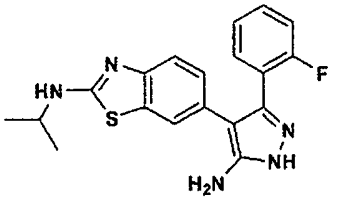
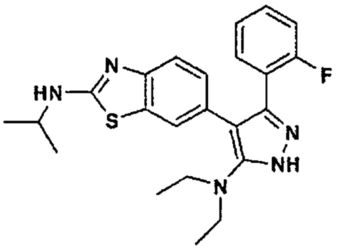
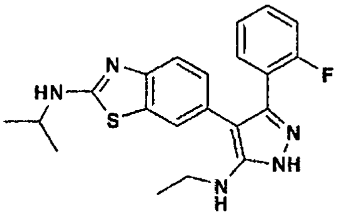
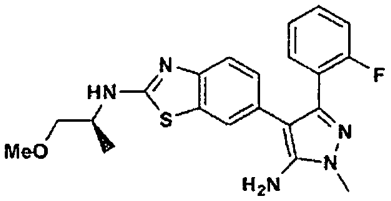
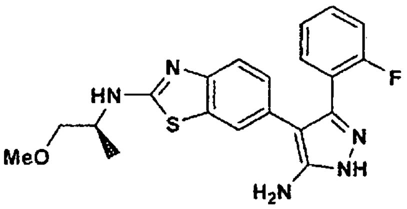
12. 6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)N-propylbenzo[d]thiazol-2-amine

[0152]



[0153] A solution of 2-bromo-6-(3-(2-fluoropbenyl)-1-methyl-1H-pyrazol-4-yl)benzo[d]thiazole (0.0294 g, 0.0755 mmol, 1.0 eq.) and n-propylamine (0.1 mL, 1.22 mmol, 16.1 eq.) in 1,4-dioxane (1.5 mL) was heated at 75 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 6-(3-(2-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)-N-propylbenzo[d]thiazol-2-amine as a light tan solid (0.0270 g, 97 % yield). LC/MS (MH)=368.16.

Table 1

Compound	Structure	$(M + H)^+$
1		368.20
2		424.19
3		396.25
4		412.22
5		397.22

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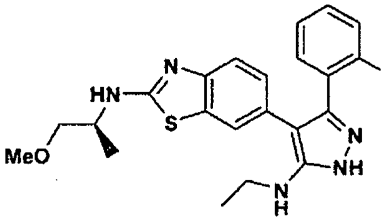
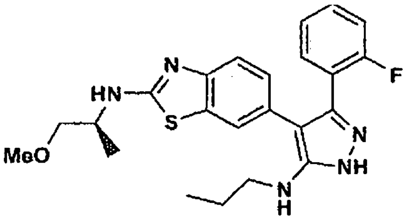
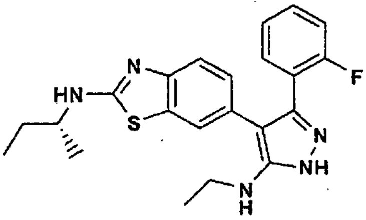
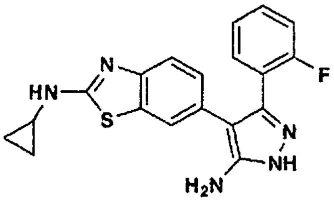
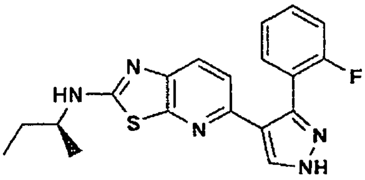
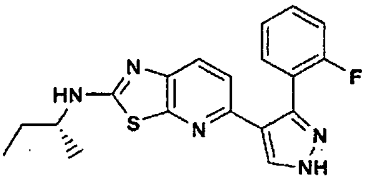
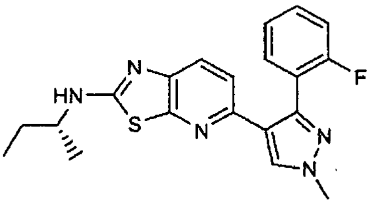
Compound	Structure	(M + H)$^+$
6		426.31
7		440.33
8		410.20
9		366.15
10		368.14
11		368.16
12		382.15

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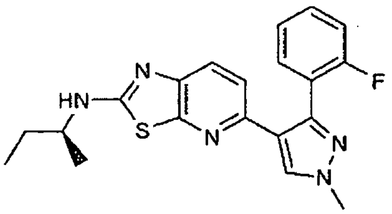
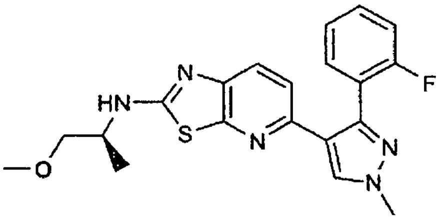
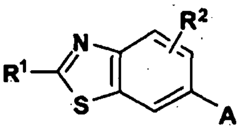
Compound	Structure	$(M + H)^+$
13		382.13
14		398.15

Claims

1. A compound of Formula (I)



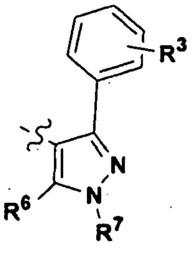
I

an enantiomer, diastereomer or a pharmaceutically-acceptable salt thereof, wherein:

R^1 is $-NHCH_3$, $NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NH(CH_2)_2CH_3$, $-NH(CH)_2OCH_3$,$-NH(CH_2)_2N(CH_3)_2$, (R)-NH-$CH(CH_3)CH_2CH_3$, (S)-$NHCH(CH_3)CH_2CH_3$, (R)-$NHCH(CH_3)CH_2CH_2OCH_3$, (S)-$NHCH(CH_3)CH_2CH_2OCH_3$, (R)-tetrahydrofuran-3-ylamino, (S)-tetrahydrofuran-3-ylamino, 4-morpholinoethylamino, 4-morpholinopropylamino, 1-piperidinoethylamino, 1-piperidinopropylamino or cyclopropylamino;

R^2 is hydrogen; and

A is



wherein

R^3 is fluoro at the ortho-position;

R^6 is amino, amino substituted with 1 or 2 C_1-C_6 alkyl, hydroxy or C_1-C_6 alkoxy;

R^7 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkyl substituted with 1 to 4 hydroxy groups, C_3-C_8 cycloalkyl, phenyl, naphthyl, anthracenyl, or saturated, partially unsaturated or fully unsaturated 3 to 7 membered monocyclic heterocyclo containing 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms.

2. The compound of Claim 1, wherein R^6 is $-NH_2$, $-N(CH_2CH_3)_2$, $-NHCH_2CH_3$, $-NH(CH_2)_2CH_3$ or -OH.

3. The compound of Claim 1, wherein R^7 is hydrogen, $-CH_3$, hydroxylethyl or-CH_2CH_3.

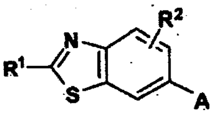
4. A pharmaceutical composition comprising at least one compound according to any one of Claims 1 to 3 and a pharmaceutically-acceptable carrier or diluent.

5. A compound of any one of claims 1 to 3 for use in treating an inflammatory disorder.

6. The compound for use according to Claim 5, wherein the inflammatory disorder is selected from asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, diabetes, inflammatory bowel disease, osteoporosis, psoriasis, graft vs. host rejection, atherosclerosis, multiple myeloma, pain, myocardial ischemia and arthritis including rheumatoid arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, gouty arthritis and osteoarthritis.

Patentansprüche

1. Verbindung der Formel (I)



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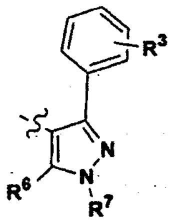
ein Enantiomer, Diastereomer oder ein pharmazeutisch verträgliches Salz davon, wobei:

R^1 $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NH(CH_2)_2CH_3$, $-NH(CH)_2OCH_3$,$-NH(CH_2)_2N(CH_3)_2$, (R)-$NHCH(CH_3)CH_2CH_3$, (S)-$NHCH(CH_3)CH_2CH_3$, (R)-$NHCH(CH_3)CH_2CH_2OCH_3$, (S)-$NHCH(CH_3)CH_2CH_2OCH_3$, (R)-Tetrahydrofuran-3-ylamino, (S)-Tetrahydrofuran-3-ylamino, 4-Morpholinoethylamino, 4-Morpholinopropylamino, 1-Piperidinoethylamino, 1-Piperidinopropylamino oder Cyclopropylamino ist;
R^2 Wasserstoff ist; und
A



ist, wobei

R^3 Fluor an der ortho-Position ist;
R^6 Amino, Amino, substituiert mit 1 oder 2 C_1-C_6-Alkyl, Hydroxy oder C_1-C_6-Alkoxy, ist;
R^7 Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkyl, substituiert mit 1 bis 4 Hydroxygruppen, C_3-C_8-Cycloalkyl, Phenyl, Naphthyl, Anthracenyl oder gesättigter, teilweise ungesättigter oder vollständig ungesättigter 3- bis 7-gliedriger monocyclischer Heterocyclo, enthaltend 1, 2, 3 oder 4 Heteroatome, ausgewählt aus Stickstoffatomen, Sauerstoffatomen und/oder Schwefelatomen, ist.

2. Verbindung nach Anspruch 1, wobei R^6 $-NH_2$, $-N(CH_2CH_3)_2$, $-NHCH_2CH_3$,$-NH(CH_2)_2CH_3$ oder -OH ist.

3. Verbindung nach Anspruch 1, wobei R^7 Wasserstoff, $-CH_3$, Hydroxylethyl oder$-CH_2CH_3$ ist.

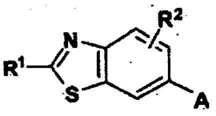
4. Pharmazeutische Zusammensetzung, umfassend mindestens eine Verbindung gemäß einem der Ansprüche 1 bis 3 und einen pharmazeutisch verträglichen Träger oder ein Verdünnungsmittel.

5. Verbindung nach einem der Ansprüche 1 bis 3 zur Verwendung beim Behandeln einer entzündlichen Erkrankung.

6. Verbindung zur Verwendung gemäß Anspruch 5, wobei die entzündliche Erkrankung aus Asthma, Atemnotsyndrom bei Erwachsenen, chronisch-obstruktiver Lungenerkrankung, chronischer Lungenentzündung, Diabetes, entzündlicher Darmkrankheit, Osteoporose, Psoriasis, Transplantat-gegen-Wirt-Abstoßung, Atherosklerose, multiplem Myelom, Schmerz, myokardialer Ischämie und Arthritis einschließlich rheumatoider Arthritis, psoriatischer Arthritis, traumatischer Arthritis, Rubella-Arthritis, Gichtarthritis und Osteoarthritis ausgewählt ist.

Revendications

1. Composé de Formule (I)



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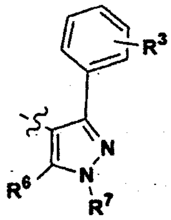
énantiomère, diastéréomère, ou sel pharmaceutiquement acceptable de celui-ci, dans lequel:

R^1 est $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NH(CH_2)_2CH_3$, $-NH(CH)_2OCH_3$, $-NH(CH_2)_2N(CH_3)_2$, (R)-$NHCH(CH_3)CH_2CH_3$, (S)-$NHCH(CH_3)CH_2CH_3$, (R)-$NHCH(CH_3)CH_2CH_2OCH_3$, (S)-$NHCH(CH_3)CH_2CH_2OCH_3$, (R)-tétrahydrofuran-3-ylamino, (S)-tétrahydrofuran-3-ylamino, 4-morpholinoéthylamino, 4-morpholinopropylamino, 1-pipéridinoéthylamino, 1-pipéridinopropylamino ou cyclopropylamino;
R^2 est hydrogène; et
A est



où

R^3 est fluoro à la position ortho;
R^6 est amino, amino substitué par 1 ou 2 C_1-C_6 alkyle, hydroxy ou C_1-C_6 alcoxy;
R^7 est hydrogène, C_1-C_6 alkyle, C_1-C_6 alkyle substitué par 1 à 4 groupes hydroxy, C_3-C_8 cycloalkyle, phényle, naphtyle, anthracényle, ou hétérocyclo monocyclique à 3 à 7 chaînons saturé, partiellement insaturé ou totalement insaturé contenant 1, 2, 3 ou 4 hétéroatomes choisis parmi les atomes d'azote, les atomes d'oxygène et/ou les atomes de soufre.

2. Composé selon la revendication 1, dans lequel R^6 est $-NH_2$, $-N(CH_2CH_3)_2$, $-NHCH_2CH_3$, $-NH(CH_2)_2CH_3$ ou $-OH$.

3. Composé selon la revendication 1, dans lequel R^7 est hydrogène, $-CH_3$, hydroxyléthyle ou $-CH_2CH_3$.

4. Composition pharmaceutique comprenant au moins un composé selon l'une quelconque des revendications 1 à 3 et un véhicule ou diluant pharmaceutiquement acceptable.

5. Composé selon l'une quelconque des revendications 1 à 3 pour l'utilisation dans le traitement d'un trouble inflammatoire.

6. Composé pour l'utilisation selon la revendication 5, dans lequel le trouble inflammatoire est choisi parmi asthme, syndrome de détresse respiratoire de l'adulte, maladie pulmonaire chronique obstructive, maladie inflammatoire pulmonaire chronique, diabète, maladie intestinale inflammatoire, ostéoporose, psoriasis, rejet greffon contre hôte, athérosclérose, myélome multiple, douleur, ischémie myocardique et arthrite incluant polyarthrite rhumatoïde, arthrite psoriasique, arthrite traumatique, arthrite associée à la rubéole, arthrite goutteuse et ostéoarthrite.

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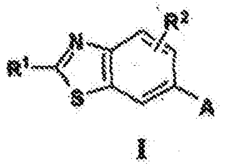
Szabadalmi igénypontok

1. Képlet (I) szerinti vegyület



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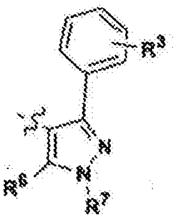
annak enantiomere, diasztereomere vagy gyógyszerészetileg elfogadható sója, ahol:

R^1 $-NHCH_3$, $NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NH(CH_2)_2CH_3$, $-NH(CH)_2OCH_3$,$-NH(CH_2)_2N(CH_3)_2$, (R)-$NHCH(CH_3)CH_2CH_3$, (S)-$NHCH(CH_3)CH_2CH_3$, (R)-$NHCH(CH_3)CH_2CH_2OCH_3$, (S)-$NHCH(CH_3)CH_2CH_2OCH_3$, (R)-tetrahidrofuran-3-ilamino, (S)-tetrahidrofuran-3-ilamino, 4-morfolinoetilamino, 4-morfolinopropilamino, 1-piperidinoetilamino, 1-piperidinopropilamino vagy ciklopropilamino;

R^2 hidrogén; és

A



ahol

R^3 fluor az orto helyzetben;

R^6 amino, amino szubsztituálva 1-el vagy 2-vel a következők közül: C_1-C_6 alkil, hidroxi vagy C_1-C_6 alkoxi;

R^7 hidrogén, C_1-C_6 alkil, C_1-C_6 alkil szubsztituálva 1-4 hidroxi csoporttal, C_3-C_8 cikloalkil, fenil, naftil, antracenil, vagy telített, részben telítetlen vagy teljesen telítetlen 3-7 tagú monociklusos heterociklo, amely 1, 2, 3, vagy 4 heteroatomot tartalmaz, amely ki van választva nitrogén atomok, oxigén atomok és/vagy kénatomok közül.

2. Az 1. igénypont szerinti vegyület, ahol R^6 $-NH_2$, $-N(CH_2CH_3)_2$, $-NHCH_2CH_3$, $-NH(CH_2)_2CH_3$ vagy -OH.

3. Az 1. igénypont szerinti vegyület, ahol R^7 hidrogén, $-CH_3$, hidroxiletil vagy $-CH_2CH_3$.

4. Gyógyszerészeti kompozíció, amely tartalmaz legalább 1-3. igénypontok bármelyike szerinti vegyületet és gyógyszerészetileg elfogadható hordozóanyagot vagy higítót.

5. Az 1-3. igénypontok bármelyike szerinti vegyület felhasználásra gyulladásos betegség kezelésére.

6. Az 5. igénypont szerinti vegyület felhasználásra, ahol a gyulladásos betegség ki van választva a következők közül: asztma, légzési nehézség szindróma felnőtteknél, krónikus obstruktív tüdőbetegség, krónikus tüdőgyulladásos betegség, diabétesz, gyulladásos bélbetegség, oszteoporózis, psoriasis, transzplantátum gazda kilökődés, atherosclerosis, myeloma multiplex, fájdalom, myocardialis ischemia és

arthritis, beleértve a következőket: rheumatoid arthritis, psoriatikus arthritis, traumatikus arthritis, rubella arthritis, köszvény arthritis és osteoarthritis.