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20 selected patent documents

prepared by Michael Thormann
26 January 2016
**PYRIMIDINE COMPOUNDS, COMPOSITIONS AND METHODS OF USE**

**First Priority:** 20080731  -  **Published:** 20100204

**Exemplars:**

![Exemplar 1](image1)

![Exemplar 2](image2)

![Exemplar 3](image3)

![Exemplar 4](image4)

**Inventors:**
BERGERON, PHILIPPE; COHEN, FREDERICK; ESTRADA, ANTHONY; KOEHLER, MICHAEL F. T.; LAU, KEVIN HON LUEN; LY, CUONG; LYSSIKATOS, JOSEPH P.; ORTWINE, DANIEL FRED; PEI, ZHONGHUA; ZHAO, XIANRUI

**Applicants:**
GENETECH, INC.

**Abstract:**

Disclosed are compounds of Formula I, including stereoisomers, geometric isomers, tautomers, solvates, metabolites and pharmaceutically acceptable salts thereof, that are useful in modulating PIKK related kinase signaling, e.g., mTOR, and for the treatment of diseases (e.g., cancer) that are mediated at least in part by the dysregulation of the PIKK signaling pathway (e.g., mTOR).
Disclosed are compounds of Formula I, including stereoisomers, geometric isomers, tautomers, solvates, metabolites and pharmaceutically acceptable salts thereof, that are useful in modulating PIKK related kinase signaling, e.g., mTOR, and for the treatment of diseases (e.g., cancer) that are mediated at least in part by the dysregulation of the PIKK signaling pathway (e.g., mTOR).

Description: More specifically, the components of the PI3K-AKT . . . include, activation mutations of growth factor receptors and the amplification and overexpression of PI3K and AKT.

The above suggests that inhibitors of mTOR kinase can be effective therapeutics for . . . the hyperactivity of the mTOR kinase signalling.

mTORC1, also known as the "mTOR-Raptor complex" . . . complex" because it binds to and is inhibited by the small molecule inhibitor rapamycin.

Rapamycin, itself, is a macrolide and was discovered as the first small molecule inhibitor of mTOR kinase.

The formation of rapamycin-FKBP12 complex results . . . because the complex binds directly to mTOR and inhibits the function of mTOR.

[0011] The discovery of a second mTOR protein complex (mTORC2) that is not inhibited by rapamycin or its analogs suggest that inhibition of mTOR by rapamycin is incomplete and that a direct mTOR kinase inhibitor which can inhibit both mTORC 1 and mTORC2 at the catalytic ATP . . . analogs. [0012] Recently, small molecule mTOR inhibitors have disclosed, including in U.S.

[0013] In view of the increased knowledge of the . . . cancer). it is desirable to have small molecule inhibitors of mTOR (including mTORC 1 and mTORC2) that can . . . is observed, such as, for example, in cancer.

In addition, it can be desirable to have small molecule inhibitors of related enzymes (e.g., PI3K, AKT) that functions upstream or downstream of the mTOR signaling pathway.

[0017] In another aspect, the present invention provides for method for inhibiting the activity of mTOR kinase in a mammal using . . . I or a subformula thereof as described herein.

For example, prodrugs can be slowly converted to . . . in a transdermal patch reservoir with a suitable enzyme or chemical reagent.


Such products can result for example from the . . . deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

Positron emitting isotopes such as 150, 13N, 11C, . . . tomography (PET) studies to examine substrate receptor occupancy.

inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth;
Topoisomerase I inhibitors: camptothecin, topotecan, irinotecan, rubitecan; 

Enzymes: L-asparaginase, RNAse A; 

Hormones and antagonists: adrenocorticosteroids/antagonists, prednisone and equivalents, dexamethasone, . . . me-droxyprogesterone acetate, megestrol acetate; 

EGFR inhibitors, and Proteasome inhibitors. 

Active compounds can also be used CA 02729045 . . . PCT/US2009/052469 as cell culture additives to inhibit mTOR, for example, in order to sensitize cells . . . agents or ionising radiation treatments in vitro. 

[00132] As a general proposition, the initial pharmaceutically effective amount of an inhibitor compound of the invention administered . . . range of compound used being 0.3 to 15 mg/kg/day. 

[00154] In another aspect, the present invention . . . acceptable salt, prodrug thereof that inhibits the activity of mTOR kinase. 

In one embodiment, a compound of the invention . . . acceptable salt, prodrug thereof inhibits the activity of mTORC1 and mTORC2. 

In another embodiment, a compound of the . . . acceptable salt, prodrug thereof, inhibits the activity of mTORC1. 

In another embodiment, a compound of the . . . acceptable salt, prodrug thereof, inhibits the activity of mTORC2. 

[00155] The present invention further provides for a method of inhibiting the activity of mTOR in a cell, comprising . . . acceptable salt or prodrug thereof. 

Accordingly, another aspect of this invention . . . diseases or conditions that can be treated by inhibiting mTOR kinase. 

For local immunosuppressive treatment, the . . . otherwise contacting the graft with the inhibitor before transplan-tation. 

In one embodiment, a human patient is treated . . . invention is present in an amount to detectably inhibit mTOR kinase activity. 

[00168] A method of inhibiting the activity of mTOR kinase in a mammal . . . a compound of Formula I or a sub-formula thereof. 

antimitotic agents (for example vinca alkaloids . . . taxoids like taxol and taxotere and polokinase inhibitors); and topoisoromerase inhibitors (for example epipodophyllotoxins like etoposide . . . amsacrine, topotecan and camptothecin); 

(b) cytostatic agents such as antioestrogens (for . . . nilutamide and cyproterone acetate), LHRH agonists or LHRH antagonists (for example goserelin, leuprorelin and . . . (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5-alpha- reductase such as finasteride; 

(c) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6- . . . PCT/US2009/052469 4- yloxyquinazoline (AZD0530); 

Chem., 2004, 47, 6658- 6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase). (d) inhibitors of growth factor function; for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody . . . C225] and any growth factor or growth factor receptor antibodies disclosed by Stem et al.
such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-... amme (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as famesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through P13K (GDC-0941, GDC0980), MEK (e.g.

PD 325901, GDC-0973) AKT and/or mTOR kinase (rapamycin), inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors: aurora kinase inhibitors (for example AZD1 152, PH739358, VX-680, ... VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(h) gene therapy approaches, including for ... or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme pro drug therapy) approaches such as those using ... thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to ... such as multi drug resistance gene therapy;

(jj) proteosome inhibitors, such as Velcade; and (k) Bcl-2 family protein inhibitors (e.g., ABT-263, ABT-737, obatoclax).

[00176] The chemical reactions in the Examples ... adapted to prepare a number of other mTOR inhibitors of the invention, and alternative methods for ... deemed to be within the scope of this invention.

**Claims:** A method of inhibiting the activity of mTOR kinase in a mammal ... acceptable amount of a compound of claims 1.

The method of claim 35, wherein said compound of claim 1 selectively inhibits mTORC1 over mTORC2.

The method of claim 28, wherein said compound of claim 1 selectively inhibits mTORC2 over mTORC1.
Disclosed are compounds of Formula (I), including stereoisomers, geometric isomers, tautomers, solvates, metabolites and pharmaceutically acceptable salts thereof, that are useful in modulating PIKK related kinase signaling, e.g., mTOR, and for the treatment of diseases (e.g., cancer) that are mediated at least in part by the dysregulation of the PIKK signaling pathway (e.g., mTOR).

Inventors:
BERGERON, PHILIPPE; COHEN, FREDERICK; ESTRADA, ANTHONY; KOEHLER, MICHAEL F.T.; LEE, WENDY; LY, CUONG; LYSSIKATOS, JOSEPH P.; PEI, ZHONGHUA; ZHAO, XIANRUI

Applicants:
GENENTECH, INC.; BERGERON, PHILIPPE; COHEN, FREDERICK; ESTRADA, ANTHONY; KOEHLER, MICHAEL F.T.; LEE, WENDY; LY, CUONG; LYSSIKATOS, JOSEPH P.; PEI, ZHONGHUA; ZHAO, XIANRUI

Abstract:
Disclosed are compounds of Formula (I), including stereoisomers, geometric isomers, tautomers, solvates, metabolites and pharmaceutically acceptable salts thereof, that are useful in modulating PIKK related kinase signaling, e.g., mTOR, and for the treatment of diseases (e.g., cancer) that are mediated at least in part by the dysregulation of the PIKK signaling pathway (e.g., mTOR). Formula (I).

L’invention concerne des composés représentés par la formule (I), comprenant des stéréo-isomères, des isomères géométriques, des tautomères, des solvats, des métabolites et des sels pharmaceutiquement acceptables de ceux-ci, qui sont utilisés pour moduler une signalisation de kinase relative à PIKK, par exemple mTOR, et pour traiter des maladies (par exemple, le cancer) qui sont induites au moins partiellement par la dérégulation de la voie de signalisation de PIKK (par exemple, mTOR).
Disclosed are compounds of Formula (I), including stereoisomers, geometric isomers, tautomers, solvates, metabolites and pharmaceutically acceptable salts thereof, that are useful in modulating PIKK related kinase signaling, e.g., mTOR, and for the treatment of diseases (e.g., cancer) that are mediated at least in part by the dysregulation of the PIKK signaling pathway (e.g., mTOR). Formula (I).
Positron emitting isotopes such as $^{15}$O, $^{13}$N, ... tomography (PET) studies to examine substrate receptor occupancy.

Inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth;

topoisomerase inhibitor RFS 2000;

[0062] Also included in the definition of ... (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX(R));

(ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production ... (megestrol acetate), AROMASIN(R) (exemestane);

(iv) protein kinase inhibitors, for example a PBK inhibitor, a MEK inhibitor, etc; (v) lipid kinase inhibitors,

(vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways ... H-Ras;
(vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME(R)) and HER2 expression inhibitors;

a topoisomerase 1 inhibitor such as LURTOTEACAN(R);

[0114] As a general proposition, the initial pharmaceutically effective amount of an inhibitor compound of the invention administered ... range of compound used being 0.3 to 15 mg/kg/day.

[0136] In another aspect, the present invention ... acceptable salt, prodrug thereof that inhibits the activity of mTOR kinase.

In one embodiment, a compound of the invention ... acceptable salt, prodrug thereof inhibits the activity of mTORC1 and mTORC2.

In another embodiment, a compound of the ... acceptable salt, prodrug thereof, inhibits the activity of mTORC1.

In another embodiment, a compound of the ... acceptable salt, prodrug thereof, inhibits the activity of mTORC2.

In certain embodiments, a compound of Formula I ... 60Ox, 70Ox, 800x, 90Ox, 100Ox more selective at inhibiting the actively of mTORC1 over mTORC2.

In certain other embodiment, a compound of ... 60Ox, 70Ox, 800x, 90Ox, 100Ox more selective at inhibiting the actively of mTORC2 over mTORC1.

[0137] The present invention further provides for a method of inhibiting the activity of mTOR kinase in a cell, ... acceptable salt or prodrug thereof.

The present invention further provides for a method of inhibiting cell proliferation comprising contacting the ... a compound of Formula I or a subgenus thereof.

Accordingly, another aspect of this invention ... diseases or conditions that can be treated by inhibiting mTOR kinase and use of a compound of Formula I ... disorders caused by dysregulated mTOR activity.

For local immunosuppressive treatment, the ... or otherwise contacting the graft with the inhibitor before transplantation.

In one embodiment, a human patient is treated ... invention is present in an amount to detectably inhibit mTOR kinase activity.

[0153] The chemical reactions in the Examples ... adapted to prepare a number of other mTOR inhibitors of the invention, and alternative methods for ... deemed to be within the scope of this invention.
The kinase activity of mTOR enzyme is assessed by incubating purified recombinant enzyme (mTOR(1360-2549)+GBL, prepared in-house) in an ATP regeneration system, e.g., GFP-4E-BP1 (Invitrogen, product PR8808A).

Enzymatic activity is measured as an increase in TR-FRET signal using a Perkin Elmer Envision plate reader.

The reaction mixture (8 uls) containing 0.25 nM mTOR+GBL enzyme, 400 nM GFP-4E-BP1, 8 uM ATP, 50 mM Hepes pH 7.4 is incubated at room temperature for 30 minutes.

The assay measures a test compound’s inhibition of AKT serine-473 phosphorylation in human cells stimulated with epidermal growth factor (EGF).

After 10 minutes, compounds and stimulation media are added with 25 µl lysis buffer containing protease inhibitors and phosphatase inhibitors.

Claims: A method of inhibiting the activity of mTOR kinase in a mammal accepts an acceptable amount of a compound of claim 1.29.
PYRAZOLOPYRIDINES AS INHIBITORS OF THE KINASE LRRK2

First Priority: 20100514 - Published: 20111117

Exemplars:

Inventors:
CHAN, BRAYN; ESTRADA, ANTHONY; SWEENEY, ZACHARY; MCIVER, EDWARD GILES

Applicants:
MEDICAL RESEARCH COUNCIL TECHNOLOGY; CHAN, BRAYN; ESTRADA, ANTHONY; SWEENEY, ZACHARY; MCIVER, EDWARD GILES

Abstract:
A compound of formula la or formula lb, or a pharmaceutically acceptable salt or ester thereof, wherein R1 is selected from: aryl; heteroaryl; -NHR3; fused aryl-C4-7-heterocycloalkyl; - CONR4R5; -NHCOR6; -C3-7-cycloalkyl; -0-C3-7-cycloalkyl; -NR3R6; and optionally substituted -C1-6 alkyl; wherein said aryl, heteroaryl, fused aryl-C4-7-heterocycloalkyl and C4-7- heterocycloalkyl are each optionally substituted; Q is CN, halogen, or is selected from C1-6-alkyl, C3-7-cycloalkyl, heterocycloalkyl, aryl and heteroaryl, each of which is optionally substituted with one or more substituents A; R2 is selected from hydrogen, aryl, C1-6-alkyl, C2-6-alkenyl, C3-7-cycloalkyl, heteroaryl, C4-7 heterocycloalkyl and halogen, wherein said C1-6-alkyl, C2-6-alkenyl, aryl, heteroaryl and C4-7-heterocycloalkyl are each optionally substituted; R3 is selected from aryl, heteroaryl, C4-7-heterocycloalkyl, C3-7 cycloalkyl, fused aryl-C heterocycloalkyl and C1-6-alkyl, each of which is optionally substituted; R4 and R5 are each independently hydrogen, or optionally substituted C3-7 cycloalkyl, aryl, heteroaryl, C1-6-alkyl or C3-6-heterocycloalkyl; or R4 and R5 together with the N to which they are attached form a C3-6-heterocycloalkyl ring; each R6 is independently selected from C1-6-alkyl, C3-7 cycloalkyl, C-heterocycloalkyl, aryl
A compound of formula Ia or formula Ib, or a pharmaceutically acceptable salt or ester thereof, wherein R1 is selected from: aryl; heteroaryl; -NR3; fused aryl-C4-7-heterocycloalkyl; -CONR4R5; -NHCOR6; -C3-7-cycloalkyl; -NR3R6; and optionally substituted -C1-6 alkyl; wherein said aryl, heteroaryl, fused aryl-C4-7-heterocycloalkyl and C4-7-heterocycloalkyl are each optionally substituted; Q is C=O, halogen, or is selected from C1-6-alkyl, C3-7-cycloalkyl, heterocycloalkyl, aryl and heteroaryl, each of which is optionally substituted with one or more substituents A; R2 is selected from hydrogen, aryl, C1-6-alkyl, C2-6-alkenyl, C3-7-cycloalkyl, heteroaryl, C4-7 heterocycloalkyl and halogen, wherein said C1-6-alkyl, C2-B-alkenyl, aryl, heteroaryl and C4-7-heterocycloalkyl are each optionally substituted; R3 is selected from aryl, heteroaryl, C4-7-heterocycloalkyl, C3-7 cycloalkyl, fused aryl-C heterocycloalkyl and C1-6 alkyl, each of which is optionally substituted; R4 and R5 are each independently hydrogen, or optionally substituted C3-7 cycloalkyl, arylic cycloalkyl, aryl and heteroaryl, each of which is optionally substituted; R7 is selected from hydrogen, optionally substituted C1-6-alkyl and C3-7-cycloalkyl; each of R8 and R9 is independently hydrogen or optionally substituted C1-6-alkyl; or R8 and R9 together with the N to which they are attached form a C4-6-heterocycloalkyl; each R10 is selected from C3-7 cycloalkyl and optionally substituted C1-6 alkyl; each R11 is independently selected from C1-6-alkyl, C3-7-cycloalkyl, C1-6-alkyl-C3-7-cycloalkyl, C4-7-heterocycloalkyl, aryl and heteroaryl, each of which is optionally substituted; A is selected from halogen, -NR4SOR5, -CN, -OR6, -NR4R5, -NR7R11, hydroxyl, -CF3, -CONR4R5, -NR4COR5, -NR7(CO)NR4R5, -NO2, -CO2H, -CO2R6, -SO2R6, -SO2NR4R5, -NR4COR5, -NR4COOR5, 6-alkyl and -COR6. Further aspects relate to pharmaceutical compositions, therapeutic uses and process for preparing compounds of formulae la and lb. La présente invention concerne un composé de formule la ou de formule lb, ou l’un de ses sels pharmaceutiquement acceptables ou esters, dans laquelle R1 est choisi parmi les groupes : aryle ; hétéroatyle ; -NR3 ; aryl-hétérocycloalkyle en C4 à C7 condensé ; -CONR4R5 ; -NHCOR6 ; cycloalkyle en C3 à C7 ; -O-cycloalkyle en C3 à C7 ; -NR3R6 ; et alkyne en C1 à C6 éventuellement substitué ; lesdits groupes aryle, hétéroatyle, aryl-hétérocycloalkyle en C4 à C7 condensé, hétérocycloalkyle en C4 à C7 étant chacun éventuellement substitué ; Q représente CN, un atome d’halogène ou est choisi parmi les groupes alkyle en C1 à C6, cycloalkyle en C3 à C7, hétérocycloalkyle, aryle et hétéroatyle, chacun étant éventuellement substitué par un ou plusieurs substituents A ; R2 est choisi parmi un atome d’hydrogène, un groupe aryle, alkyne en C1 à C6, alcèneyle en C2 à C6, cycloalkyle en C3 à C7, hétéroatyle, hétérocycloalkyle en C4 à C7 et un atome d’halogène, lesdits groupes alkyle en C1 à C6, Cz-B-alcèneyle, aryle, hétéroatyle et hétérocycloalkyle en C4 à C7 chacun étant éventuellement substitué ; R3 est choisi parmi les groupes aryle, hétéroatyle, hétérocycloalkyle en C4 à C7, cycloalkyle en C3 à C7, aryl-C-hétérocycloalkyl condensé et alkyne en C1 à C6, chacun étant éventuellement substitué ; R4 et R5 représentent chacun indépendamment un atome d’hydrogène ou un groupe éventuellement substitué, cycloalkyle en C3 à C7, aryle, hétéroatyle, alkyne en C1 à C6 ou hétérocycloalkyle en C3 à C6 ; ou R4 et R5 conjointement avec le N auquel ils sont fixés forment un cycle hétérocycloalkyle en C3 à C6 ; chaque R6 est choisi indépendamment parmi les groupes alkyle en C1 à C6, cycloalkyle en C3 à C7, C-hétérocycloalkyle, aryle et hétéroatyle, chacun étant éventuellement substitué ; chaque R7 est choisi parmi un atome d’hydrogène, les groupes alkyle en C1 à C6 et cycloalkyle en C3 à C7 ; chacun de R8 et R9 représente indépendamment un atome d’hydrogène ou un groupe alkyle en C1 à C6 ; ou R8 et R9 conjointement avec le N auquel ils sont fixés forment un groupe hétérocycloalkyle en C4 à C6 ; chaque R10 est choisi parmi le groupe cycloalkyle en C3 à C7 et le groupe alkyle en C1 à C6 éventuellement substitué ; chaque R11 est choisi indépendamment parmi les groupes alkyle en C1 à C6, cycloalkyle en C3 à C7, alkyl en C1 à C6-cycloalkyle en C3 à C7, hétéroatyle, hétérocycloalkyle en C4 à C7, aryle et hétéroatyle, chacun étant éventuellement substitué ; A est choisi parmi un atome d’halogène, les groupes -NR4S0R5, -CN,-OR6, -NR4R5, -NR7R11, hydroxyle, -CF3, -CONR4R5, -NR4COR5, -NR7(CO)NR4R5, -NO2, -CO2H, -CO2R6, -SO2R6, -SO2NR4R5, -NR4COR5, -NR4COOR5, alkyne en C1 à C6 et -COR6. D’autres aspects concernent des compositions pharmaceutiques, des utilisations thérapeutiques et un procédé de préparation des composés des formules la et lb.

fulltext score : 9.06e-2 , cippix score : 86

Query-specific Abstract:

**Title:** PYRAZOLOPYRIDINES AS INHIBITORS OF THE KINASE LRRK2
Description: PYRAZOLOPYRIDINES AS INHIBITORS OF THE KINASE LRRK2. The present invention . . . pyrazolopyridine compounds that are capable of inhibiting one or more kinases, more particularly, LRRK2.

The defining feature of the LRRK2 enzyme is a Leucine Rich Repeat (LRR) motif (residues . . . and a C-terminal WD40 motif (2231-2276) [6, 7].

The protein kinase domain of LRRK2 belongs to the . . . kinases and is most similar to the kinase RIP (Receptor Interacting Protein), which play key roles in innate immunity signalling pathways.

These observations suggest that over-activation . . . humans to develop PD, implying that drugs which inhibited LRRK2, could be utilised to halt progression or even perhaps reverse symptoms of some forms of PD.

The study of LRRK2 has been hampered by the difficulty in expressing active recombinant enzyme and by the lack of a robust quantitative assay.

The present invention seeks to provide compounds that are capable of inhibiting one or more kinases, more particularly, LRRK, even more preferably LRRK2.

A seventh aspect of the invention relates to a . . . a mammal having a disease state alleviated by inhibition of a kinase (preferably LRRK, more preferably . . . amount of a compound as described above.

An eighth aspect of the invention relates to the . . . further candidate compounds capable of inhibition of a kinase, preferably LRRK, more preferably LRRK2.

DETAILED DESCRIPTION The present invention . . . pyrazolopyridine compounds that are capable of inhibiting one or more kinases, more particularly LRRK, even more particularly LRRK2.

BIOLOGICAL ACTIVITY The compounds of the present invention are capable of inhibiting one or more kinases, preferably, LRRK, even more preferably LRRK2.

In one preferred embodiment, the compound of the invention is capable of inhibiting LRRK2, as measured by the assay described in the accompanying Examples section.

Preferably, the compound of the invention exhibits an IC50 value of less than 10 [mu][Mu], more preferably . . . more preferably still less than 0.1 [mu][Mu].

Preferably, the compound is administered in an amount sufficient to inhibit one or more kinases, preferably LRRK, even more preferably LRRK2.

Yet another aspect of the invention relates to a . . . a mammal having a disease state alleviated by inhibition of a protein kinase, wherein the method . . . amount of a compound according to the invention.

Preferably, the disease state is alleviated by the inhibition of the protein kinase LRRK, more preferably LRRK2.

The term "administering" as used herein refers to . . . such a manner that the compound can affect the enzyme activity of the protein kinase either directly;

Herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a . . . of clinical symptoms of a disease or disorder.

For example, a dose can be formulated in animal . . . concentration range that includes the IC50 or the IC100 as determined in cell culture.

Thus, the present invention further provides use . . . treatment of diseases where it is desirable to inhibit LRRK2.

The present invention contemplates the use of all . . . stereoisomers and geometric isomers of those inhibitor agents, and mixtures thereof.
Reversion is usually performed by an enzyme naturally present in such subject, though it is ... in order to perform the reversion in vivo.

In accordance with this invention, an effective ... of general formula (I) may be administered to inhibit the kinase implicated with a particular condition or disease.

preferably between 0.1 and 20 mg/kg, in a manner ... in the plasma at a concentration effective to inhibit a kinase.

Beneficial combinations may be suggested by studying the inhibitory activity of the test compounds with agents known ... in the treatment of a particular disorder.

ASSAY A further aspect of the invention relates ... further candidate compounds capable of inhibiting one or more kinases, more preferably LRRK, even more preferably, LRRK2.

The above methods may be used to screen for a ligand useful as an inhibitor of one or more kinases.

Protein kinase assays All assays were carried ... and were linear with respect to time and enzyme concentration under the conditions used.

The enzyme was diluted and assayed in 50mM Tris-HCl pH7.5, 0.1 mM EGTA, 1mM DTT and 10mM MgCl2.

(Perkin Elmer, Shelton CT 06484-4794 USA) IC50 values of inhibitors were determined after carrying out assays at 10 ... concentrations of each compound in duplicate.


Table 1: Potency scores for selected compounds of the invention = LRRK2 IC50 <100nM = LRRK2 IC50 between 100nM and 1 [mu]M = LRRK2 IC50 between 1 [mu]M and 10 [mu]M <EMI ... compounds of the invention = LRRK2 KI <100nM

Claims: A method of treating a mammal having a disease state alleviated by the inhibition of LRRK2, wherein the method comprises ... compound according to any one of claims 1 to 23.

Use of a compound according to any one of claims ... further candidate compounds capable of inhibiting LRRK, more preferably LRRK2.
Exemplars:

Inventors:
BAKER-GLENN CHARLES; BURDICK DANIEL JON; CHAMBERS MARK; CHAN BRYAN K.; CHEN HUIFEN; ESTRADA ANTHONY; GUNZNER-TOSTE JANET; SHORE DANIEL; SWEENEY ZACHARY; WANG SHUMEI; ZHAO GUILING

Applicants:
GENENTECH, INC.; BAKER-GLENN CHARLES; BURDICK DANIEL JON; CHAMBERS MARK; CHAN BRYAN K.; CHEN HUIFEN; ESTRADA ANTHONY; GUNZNER-TOSTE JANET; SHORE DANIEL; SWEENEY ZACHARY; WANG SHUMEI; ZHAO GUILING

Abstract:
Compounds of the formula I: or pharmaceutically acceptable salts thereof, wherein m, n, X, R1, R2, R3, R5, R6 and R7 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson's disease.
Compounds of the formula I or pharmaceutically acceptable salts thereof, wherein m, n, X, R1, R2, R3, R5, R6 and R7 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

fulltext score : 1.83e-1 , cippix score : 705

Query-specific Abstract:

Title: Aminopyrimidine derivatives as LRRK2 inhibitors

Abstract: Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

Description: The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

"Treating" or "treatment" of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

The invention also provides a method for treating a disease or condition mediated by or otherwise associated with the LRRK2 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention.

0.0625 Example 12 In Vitro LRRK2 LabChip Assay This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

Lab Chip 3000 Protocol: The LabChip 3000 was run using the job "LRRK2 IC50" with the following job settings: Pressure: -1.4 psi Downstream voltage: -500 V Upstream voltage: -2350 V Post sample buffer sip time: 75 seconds Post dye buffer sip time: 75 seconds Final delay time: 200 seconds

Example 13 In Vitro LRRK2 Lanthascreen Binding Assay This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.
Compounds and their administration for treating a neurodegenerative disease as well as a method for identifying a...

First Priority: 20100922 - Published: 20131029

Exemplars:

Inventors:
CHAN BRYAN K.; CHEN HUIFEN; ESTRADA ANTHONY; SHORE DANIEL; SWEENEY ZACHARY; MCIVER EDWARD GILES

Applicants:
CHAN BRYAN K.; CHEN HUIFEN; ESTRADA ANTHONY; SHORE DANIEL; SWEENEY ZACHARY; MCIVER EDWARD GILES; MEDICAL RESEARCH COUNCIL TECHNOLOGY; GENENTECH, INC.

Abstract:
The present invention relates to substituted pyrazolopyridine compounds, and pharmaceutically acceptable salts or esters thereof. The present invention further relates to therapeutic uses of pharmaceutical compositions comprising the substituted pyrazolopyridine compounds, for example, in cancer and neurodegenerative diseases.
The present invention relates to substituted pyrazolopyridine compounds, and pharmaceutically acceptable salts or esters thereof. The present invention further relates to therapeutic uses of pharmaceutical compositions comprising the substituted pyrazolopyridine compounds, for example, in cancer and neurodegenerative diseases.
The term "administering" as used herein refers to . . . such a manner that the compound can affect the enzyme activity of the protein kinase either . . . with the protein kinase itself or indirectly;

Herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a . . . of clinical symptoms of a disease or disorder.

For example, a dose can be formulated in . . . concentration range that includes the IC50 or the IC100 as determined in cell culture.

Thus, the present invention further provides use . . . treatment of diseases where it is desirable to inhibit LRRK2.

The present invention contemplates the use of all . . . stereoisomers and geometric isomers of those inhibitor agents, and mixtures thereof.

Reversion is usually performed by an enzyme naturally present in such subject, though it is . . . in order to perform the reversion in vivo.

In accordance with this invention, an effective . . . of general formula (I) may be administered to inhibit the kinase implicated with a particular condition or disease.

preferably between0.1 and 20 mg/kg, in a manner . . . in the plasma at a concentration effective to inhibit a kinase.

Beneficial combinations may be suggested by studying the inhibitory activity of the test compounds with agents known . . . in the treatment of a particular disorder.

Assay A further aspect of the invention relates . . . further candidate compounds capable of inhibiting one or more kinases, more preferably LRRK, even more preferably, LRRK2.

The above methods may be used to screen for a ligand useful as an inhibitor of one or more kinases.

EXAMPLES Materials and Methods In Vitro LRRK2 . . . was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

Lab Chip 3000 Protocol: The LabChip 3000 was run using the job "LRRK2 IC50" with the following job settings: Pressure: -1.4 . . . of striatal dopamine (DA) nerve terminalmarkers.


Claims: A method of treating a disease alleviated by the inhibition of LRRK2, wherein the method comprises . . . to claim 1, thereby treating said disease.

A method for identifying a compound capable of inhibiting LRRK, the method comprising the steps of: . . . the presence of a compound according to claim 1;

and detecting interaction between LRRK and the . . . indicates that the candidate compound is an inhibitor of the LRRK.
PYRAZONE AMINOPYRIMIDINE DERIVATIVES AS LRRK2 MODULATORS

First Priority: 20101110 - Published: 20120518

Exemplars:

Inventors:
BAKER-GLENN, CHARLES; BURDICK, DANIEL JON; CHAMBERS, MARK; CHEN, HUIFEN; ESTRADA, ANTHONY; SWEENEY, ZACHARY KEVIN; CHAN, BRYAN K.

Applicants:
F. HOFFMANN-LA ROCHE AG

Abstract:
Compounds of the formula (I), or pharmaceutically acceptable salts thereof, wherein X, R1, R2, R3, R4 and R5 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.
Bibliographic Data:

CA2812669A1 20120518 ( US41227310P20101110; US201161546613P20111013; EP2011069696W20111109 ) PYRAZOLE AMINOPYRIMIDINE DERIVATIVES AS LRRK2 MODULATORS; DERIVES DE PYRA-ZOLE AMINOPYRIMIDINE EN TANT QUE MODULATEURS DU LRRK2 - BAKER-GLENN, CHARLES; BURDICK, DANIEL JON; CHAMBERS, MARK; CHEN, HUIFEN; ESTRADA, ANTHONY; SWEENEY, ZACHARY KEVIN; CHAN, BRYAN K. - F. HOFFMANN-LA ROCHE AG

Compounds of the formula (I), or pharmaceutically acceptable salts thereof, wherein X, R1, R2, R3, R4 and R5 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson's disease.

fulltext score : 7.43e-3 , cippix score : 1217

Query-specific Abstract:

Abstract: Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson's disease.

Description: The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

The term "half maximal inhibitory concentration" (IC50) denotes the concentration of a particular compound required for obtaining 50% inhibition of a biological process in vitro. IC50 values can be converted logarithmically to pIC50 values (-log IC50), in which higher values indicate exponentially greater potency. The IC50 value is not an absolute value but depends on experimental conditions e.g. concentrations employed. The IC50 value can be converted to an absolute inhibition constant (Ki) using the Cheng-Prusoff equation (Biochem. Pharmacol. (1973) 22:3099). The term "inhibition constant" (Ki) denotes the absolute binding affinity of a particular inhibitor to a receptor.

It is measured using competition binding assays and is equal to the concentration where the particular inhibitor would occupy 50% of the receptors if no competing ligand (e.g.

"Treating" or "treatment" of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

The invention also provides a method for treating a disease or condition mediated by or otherwise associated with the LRRK2 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention.

propionitrile 2-(3-chloro-4-(4-(methylamino)- F 5- N’<, FF (trifluoromethyl) FIN/N NH pyrimidin-2- ci— N methylpropanenit rile CA 02812669 2013-03-26 WO 2012/062783 PCT/EP2011/069696 -195- 2-[4-(4- Ethylamino-5- 3:1)(1 trifluoromethyl- HN N NH pyrimidin-2- 4530.0092 ylamino)-3- N-N methyl-pyrazol- 1-y1]-N-methyl- NH 0 \isobutyramide Example 454: In Vitro LRRK2 Lanthascreen binding assay This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

Binding of the tracer and antibody to a kinase results in a high degree of FRET, whereas displacement of the tracer with a kinase inhibitor results in a loss of FRET.

Results expressed as a Ki in M. Equation for Ki: Y=V0* (1-((x+Ki * (1+ 5/Km)+Et)/(2*Et)));(x+Ki * (1+ 5/Km)+Et)*2- (4*Et*x))*0.5)/(2*Et)) Where Et = 4nM kd (Tracer) = 8.5nM Tracer concentration (S) = 8.5nM Example 455: In Vitro LRRK2 Assay This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.
Lab Chip 3000 Protocol: The LabChip 3000 was run using the job "LRRK2 IC50" with the following job settings:
Pressure: -1.4 psi Downstream voltage: -500 V Upstream voltage: -2350 V Post sample buffer sip time: 75 seconds Post dye buffer sip time: 75 seconds Final delay time: 200 seconds

Example 456 Parkinson’s disease mouse model Parkinson’s disease can be replicated in mice and in primates by administration of 1-methyl-4-phenyl tetrahydropyridine (MPTP), a selective nigrostriatal dopaminergic neurotoxin that produces a loss of striatal dopamine (DA) nerve terminal markers.
Exemplars:

Inventors:
BAKER-GLENN, CHARLES; BURDICK, DANIEL JON; CHAMBERS, MARK; CHAN, BRYAN K.; CHEN, HUIFEN; ESTRADA, ANTHONY; GUNZNER-TOSTE, JANET; SHORE, DANIEL; SWEENEY, ZACHARY; WANG, SHUMEI; ZHAO, GUILING

Applicants:
F. HOFFMANN-LA ROCHE AG

Abstract:
Specific Compounds of formula (I): or pharmaceutically acceptable salts thereof, wherein m, X, R, R2, R3, R6 and R7 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.
Specific Compounds of formula (I): or pharmaceutically acceptable salts thereof, wherein m, X, R, R2, R3, R6 and R7 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.
Compounds of the formula (I), or pharmaceutically acceptable salts thereof, wherein m, n, X, R1, R2, R3, R4 and R5 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

Inventors:
BAKER-GLENN, CHARLES; CHAMBERS, MARK; CHAN, BRYAN K.; ESTRADA, ANTHONY; SWEENEY, ZACHARY KEVIN

Applicants:
F. HOFFMANN-LA ROCHE AG

Abstract:
Compounds of the formula (I), or pharmaceutically acceptable salts thereof, wherein m, n, X, R1, R2, R3, R4 and R5 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.
Compounds of the formula (I), or pharmaceutically acceptable salts thereof, wherein m, n, X, R1, R2, R3, R4 and R5 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

fulltext score : 7.09e-3 , cippix score : 192

Query-specific Abstract:

Abstract: Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease

Description: The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

"Treating" or "treatment" of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., . . . of the disease state or its clinical symptoms.

The invention also provides a method for treating . . . by or otherwise associated with the LRRK2 receptor, the method comprising administering to a . . . effective amount of a compound of the invention.
Compounds of the formula I: or pharmaceutically acceptable salts thereof, wherein A, X, R1, R2, R3 and R4 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.
Compounds of the formula I: or pharmaceutically acceptable salts thereof, wherein A, X, R1, R2, R3 and R4 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

Fulltext score: 7.74e-3, cippix score: 189

Abstract: Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

Description: The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

"Treating" or "treatment" of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

The invention also provides a method for treating a disease or condition mediated by or otherwise associated with the LRRK2 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention.

\[ \text{[2.2.1]heptan-5-yl(5-chloro-1-methyl-6-(4-(methylamino)-5-(trifluoromethyl) pyrimidin-2-ylamino)-1H-indol-3-yl)methanone 0.003 34 STR00124 4-methoxy-2-methyl-5-(4-(methylamino)-5-(trifluoromethyl) pyrimidin-2-ylamino)isoindolin-1-yl one 35 STR00125(5-methoxy-6-(4-(methylamino)-5-(trifluoromethyl) pyrimidin-2-ylamino)benzofuran-3-yl)(morpholino)methanone 36 STR00126 5-methoxy-N,N-dimethyl-6-(4-(methylamino)-5-(trifluoromethyl) pyrimidin-2-ylamino)benzofuran-3-carboxamide} \]

Example 10 In Vitro LRRK2 LabChip Assay This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

Lab Chip 3000 Protocol: The LabChip 3000 was run using the job "LRRK2 IC50" with the following job settings: Pressure: -1.4 psi Downstream voltage: -500 V Upstream voltage: -2350 V Post sample buffer sip time: 75 seconds Post dye buffer sip time: 75 seconds Final delay time: 200 seconds Example 11 In Vitro LRRK2 Lanthascreen Binding Assay This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.
Compounds of the formula (I), or pharmaceutically acceptable salts thereof, wherein m, n, X, R1, R2, R3, R4 and R5 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

Compounds of the formula (I), or pharmaceutically acceptable salts thereof, wherein m, n, X, R1, R2, R3, R4 and R5 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

L'invention concerne des composés de formule (I) : Formule (I) ou des sels pharmaceutiquement acceptables de ceux-ci, où m, n, X, R1, R2, R3, R4 et R5 sont tels que défini présentement. L'invention concerne également des procédés de fabrication des composés et d'utilisation des composés pour le traitement de maladies associées à un récepteur de LRRK2, telle que la maladie de Parkinson.
WO2013079493A1

Bibliographic Data:

WO2013079493A1 20130606 ( US201161564753P20111129 ) DÉRIVÉS AMINOPYRIDINES EN TANT QUE MODULATEURS DE LRRK2; AMINOPYRIMIDINE DERIVATIVES AS LRRK2 MODULATORS - BAKER-GLENN, CHARLES; CHAMBERS, MARK; CHAN, BRYAN K.; CHEN, HUIFEN; ESTRADA, ANTHONY; SHORE, DANIEL; SWEENEY, ZACHARY - F. HOFFMANN-LA ROCHE AG; BAKER-GLENN, CHARLES; CHAMBERS, MARK; CHAN, BRYAN K.; CHEN, HUIFEN; ESTRADA, ANTHONY; SHORE, DANIEL; SWEENEY, ZACHARY

Compounds of the formula (I), or pharmaceutically acceptable salts thereof, wherein m, n, X, R1, R2, R3, R4 and R5 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

L’invention concerne des composés de formule (I) : Formule (I) ou des sels pharmaceutiquement acceptables de ceux-ci, où m, n, X, R1, R2, R3, R4 et R5 sont tels que défini présentement. L’invention concerne également des procédés de fabrication des composés et d’utilisation des composés pour le traitement de maladies associées à un récepteur de LRRK2, telle que la maladie de Parkinson.

fulltext score: 5.71e-3, cippix score: 164

Query-specific Abstract:

Abstract: Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

L’invention concerne également des procédés de fabrication des composés et d’utilisation des composés pour le traitement de maladies associées à un récepteur de LRRK2, telle que la maladie de Parkinson.

Description: The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

“Treating” or “treatment” of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

The invention also provides a method for treating a disease or condition mediated by or otherwise associated with the LRRK2 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention.

Table 3 Example 30 In Vitro LRRK2 LabChip Assay
This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

Lab Chip 3000 Protocol: The LabChip 3000 was run using the job “LRRK2 IC50” with the following job settings:
Pressure: -1.4 psi Downstream voltage: -500 V Upstream voltage: -2350 V Post sample buffer sip time: 75 seconds Post dye buffer sip time: 75 seconds Final delay time: 200 seconds Example 31 In Vitro LRRK2 Lanthascreen binding Assay This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

Binding of the tracer and antibody to a kinase results in a high degree of FRET, whereas displacement of the tracer with a kinase inhibitor results in a loss of FRET.
A method for positron emission tomography (PET) imaging of LRRK2 in the tissue of a subject, the method comprising: administering a compound of formula (I), formula (II) or formula (III), or a pharmaceutically acceptable salt thereof to the subject, wherein the compound includes at least one C11 or F18 label thereon; allowing the compound to penetrate into the tissue of the subject; and collecting a PET image of the CNS or brain tissue of the subject.
WO2013079496A1 20130606 ( US201161565324P20111130; US201261720870P20121031 ) FLUORINE-18 AND CARBON-11 LABELED RADIOLIGANDS FOR POSITRON EMISSION TOMOGRAPHY (PET) IMAGING FOR LRRK2; RADIOLIGANDS MARQUÉS PAR LE FLUOR 18 ET LE CARBONE 11 POUR UNE IMAGERIE PAR TOMOGRAPHIE PAR ÉMISSION DE POSITONS (PET) POUR LRRK2 - CHAN, BRYAN, K.; ESTRADA, ANTHONY; MARIK, JAN; SWEENEY, ZACHARY, KEVIN - F. HOFFMANN-LA ROCHE AG; CHAN, BRYAN, K.; ESTRADA, ANTHONY; MARIK, JAN; SWEENEY, ZACHARY, KEVIN

L'invention concerne un procédé pour l'imagerie par tomodigraphie par émission de positons (PET) de LRRK2 dans le tissu d'un sujet, le procédé comprenant : l'administration d'un composé de formule (I), de formule (II) ou de formule (III), ou un sel pharmaceutiquement acceptable de celui-ci au sujet, le composé comprenant au moins un marqueur C11 ou F18 sur celui-ci ; la pénétration du composé à l'intérieur du tissu du sujet ; et la collecte d'une image de PET du SNC ou du tissu cérébral du sujet.; A method for positron emission tomography (PET) imaging of LRRK2 in the tissue of a subject, the method comprising: administering a compound of formula (I), formula (II) or formula (III), or a pharmaceutically acceptable salt thereof to the subject, wherein the compound includes at least one C11 or F18 label thereon; allowing the compound to penetrate into the tissue of the subject; and collecting a PET image of the CNS or brain tissue of the subject.

fulltext score : 4.08e-5 , cippix score : 367

Query-specific Abstract:

Description: The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

"Treating" or "treatment" of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.
Inventors:
CHAN, BRYAN; ESTRADA, ANTHONY; SHORE, DANIEL; SWEENEY, ZACHARY

Applicants:
F. HOFFMANN-LA ROCHE AG; GENENTECH, INC.

Abstract:
L'invention porte sur un composé de formule (1A) ou (1B), ou un sel pharmaceutiquement acceptable de celui-ci, dans laquelle formule R1 représente un groupe choisi parmi un groupe alkyle, un groupe hétérocycloalkyle monocyclique, un groupe hétérocycloalkyle bicyclique et un groupe cycloalkyle, chacun de ceux-ci étant éventuellement substitué par un ou plusieurs groupes choisis parmi un groupe alkyle, un atome d’halogène et un groupe cycloalkyle ; pour la formule (1A) : un, deux ou trois groupes parmi X1, X2, X3 et X4 représentent N et les autres représentent chacun indépendamment CR2 ; ou pour la formule (1B) : X4 représente C ou N ; et un ou deux des groupes X1, X2 et X3 sont indépendamment choisis entre N et NR8 et les autres représentent chacun indépendamment CR2 ; de façon à ce que X1, X2, X3, X4 et N forment un groupe hétéroatyle ; chaque R2 est indépendamment choisi parmi H, un groupe alkyle, CN, un atome d’halogène, un groupe hétéroatyle, un groupe hétérocycloalkyle, un groupe cycloalkyle, OR4, CONR5R6 et SO2R7, lesdits groupes alkyle, hétéroatyle, hétérocycloalkyle et cycloalkyle étant chacun éventuellement en outre substitués par un ou plusieurs groupes choisis parmi un groupe alkyle, un atome d’halogène et OR9 ; chaque R8 est indépendamment choisi entre H et un groupe alkyle, ledit groupe alkyle étant éventuellement...
The invention relates to a compound of formula (1A) or (1B), or a pharmaceutically acceptable salt thereof, where R1 is a group selected from alkyl, monocyclic heterocycloalkyl, bicyclic heterocycloalkyl and cycloalkyl, each of which is optionally substituted by one or more groups selected from alkyl, halo and cycloalkyl; for formula (1A): one, two or three of X1, X2, X3 and X4 are N, and the remainder are each independently CR2; or for formula (1B): X4 is C or N; and one or two of X1, X2 and X3 are independently selected from N and NR8, and the remainder are each independently CR2; such that X1, X2, X3, X4 and N form a heteroaryl group; each R2 is independently selected from H, alkyl, CN, halo, heteroaryl, heterocycloalkyl, cycloalkyl, OR4, CONR5R6 and SO2R7, wherein said alkyl, heteroaryl, heterocycloalkyl and cycloalkyl groups are each optionally further substituted by one or more groups selected from alkyl, halo and OR9; each R8 is independently selected from H and alkyl, wherein said alkyl group is optionally further substituted by one or more groups selected from CN, halo, heteroaryl, heterocycloalkyl, cycloalkyl OR4, CONR5R6 and SO2R7, wherein said alkyl group is optionally further substituted by one or more groups selected from CN, halo, heteroaryl, heterocycloalkyl, cycloalkyl OR4, CONR5R6 and SO2R7, wherein said alkyl group is optionally further substituted by one or more groups selected from CN, halo, heteroaryl, heterocycloalkyl, cycloalkyl OR4, CONR5R6 and SO2R7; each R5 and R6 together with the nitrogen to which they are attached are linked to form a cyclic group which optionally further comprises one or more heteroatoms selected from O, N and S; with the proviso that when the compound is of formula (1B), the compound is other than 3-(5-isopropyl-4H-1,2,4-triazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[4,3-c]pyridin-4-amine or 3-(5-cyclopropyl-4H-1,2,4-triazol-3-yl)-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[4,3-c]pyridin-4-amine. Further aspects relate to pharmaceutical compositions, therapeutic uses and process for preparing compounds of formula (1A) and (1B).

fulltext score : 2.42e-3 , cippix score : 208

Query-specific Abstract:

**Description:** PYRAZOLOPYRIDINES FOR TREATMENT OF PARKINSONS... pyrazolopyridine compounds that are capable of inhibiting one or more kinases, more particularly LRRK2.

The defining feature of the LRRK2 enzyme is a Leucine Rich Repeat (LRR) motif (residues ... and a C-terminal WD40 motif (2231-2276) [6, 7].

The protein kinase domain of LRRK2 belongs to the ... kinases and is most similar to the kinase RIP (Receptor Interacting Protein), which play key roles in innate immunity signalling pathways.
These observations suggest that over-activation of kinases in humans to develop PD, implying that drugs which inhibit LRRK2, could be utilised to halt progression or even perhaps reverse symptoms of some forms of PD.

The study of LRRK2 has been hampered by the difficulty in expressing active recombinant enzyme and by the lack of a robust quantitative assay.

Small molecule inhibitors of LRRK are described in WO 2010/106333 and WO ... the name of Medical Research Council Technology.

The present invention seeks to provide further compounds that are capable of inhibiting one or more kinases, more particularly, LRRK, even more preferably LRRK2.

A seventh aspect of the invention relates to a mammal having a disease state alleviated by inhibition of a kinase (preferably LRRK, more preferably ... amount of a compound as described above.

An eighth aspect of the invention relates to the further candidate compounds capable of inhibition of a kinase, preferably LRRK, more preferably LRRK2.

DETAILED DESCRIPTION The present invention pyrazolopyridine compounds that are capable of inhibiting one or more kinases, more particularly LRRK, even more particularly LRRK2.

Advantageously, the claimed compounds exhibit surprisingly good inhibition of LRRK2 (see Table 1), compared to compounds ... example, in WO 2010/106333 and WO 2011/141756.

Preferably, the compound is administered in an amount sufficient to inhibit one or more kinases, preferably LRRK, even more preferably LRRK2.

Yet another aspect of the invention relates to a mammal having a disease state alleviated by inhibition of a protein kinase, wherein the method ... amount of a compound according to the invention.

Preferably, the disease state is alleviated by the inhibition of the protein kinase LPvRK, more preferably LRRK2.

The term "administering" as used herein refers to ... such a manner that the compound can affect the enzyme activity of the protein kinase either directly;

Herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a ... of clinical symptoms of a disease or disorder.

For example, a dose can be formulated in animal ... concentration range that includes the IC50 or the IC100 as determined in cell culture.

Thus, the present invention further provides use ... treatment of diseases where it is desirable to inhibit LRRK2.

The present invention contemplates the use of all ... stereoisomers and geometric isomers of those inhibitor agents, and mixtures thereof.

Reversion is usually performed by an enzyme naturally present in such subject, though it is ... in order to perform the reversion in vivo.

In accordance with this invention, an effective ... of general formula (I) may be administered to inhibit the kinase implicated with a particular condition or disease.

preferably between 0.1 and 20 mg/kg, in a manner ... in the plasma at a concentration effective to inhibit a kinase.

Beneficial combinations may be suggested by studying the inhibitory activity of the test compounds with agents known ... in the treatment of a particular disorder.
A further aspect of the invention relates to further candidate compounds capable of inhibiting one or more kinases, more preferably LRRK, even more preferably, LRRK2.

The above methods may be used to screen for a ligand useful as an inhibitor of one or more kinases.

Protein kinase assays: All assays were carried out and were linear with respect to time and enzyme concentration under the conditions used.

The enzyme was diluted and assayed in 50mM Tris-HCl pH7.5. . . of magnesium chloride in the assay was 10mM.

(Perkin Elmer, Shelton CT 06484-4794 USA) IC50 values of inhibitors were determined after carrying out assays at 10 . . . concentrations of each compound in duplicate.


424, 47-60 Table 1: Structures and [Kappa][iota] . . . compounds according to the prior art = LRRK2 IC50 100nM = LRRK2 IC50 between 100nM and [iota][mu][Mu] = LRRK2 IC50 between [iota][mu][Mu] and 10 [mu][Mu] Compound . . . WO 2010106333 ** Example 160 WO 2010106333 **

Claims: A method of treating a mammal having a disease state alleviated by the inhibition of LRRK2, wherein the method comprises . . . compound according to any one of claims 1 to 16.

Use of a compound according to any one of claims . . . further candidate compounds capable of inhibiting LRRK, more preferably LRRK2.
Pyrazole compounds that are modulators of LRRK2, methods of making the compounds, and methods for using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

Inventors:
BAKER-GLENN CHARLES; BURDICK DANIEL JON; CHAN BRYAN K.; CHAMBERS MARK; CHEN HUIFEN; ESTRADA ANTHONY; SWEENY ZACHARY KEVIN

Applicants:
GENENTECH, INC.

Abstract:
Pyrazole compounds that are modulators of LRRK2, methods of making the compounds, and methods for using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.
Pyrazole compounds that are modulators of LRRK2, methods of making the compounds, and methods for using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson's disease.

**Abstract:** Pyrazole compounds that are modulators of LRRK2, methods of making the compounds, and methods for using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson's disease.

**Description:** The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

[0142] "Treating" or "treatment" of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

[0262] The invention also provides a method for treating a disease or condition mediated by or otherwise associated with the LRRK2 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0425] This assay was used to determine a compound's potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

Binding of the tracer and antibody to a kinase results in a high degree of FRET, whereas displacement of the tracer with a kinase inhibitor results in a loss of FRET.

[0441] This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

[0460] The LabChip 3000 was run using the job “LRRK2 IC50” with the following job settings: TABLE-US-00010 Pressure: -1.4 psi Downstream voltage: -500 V Upstream voltage: -2350 V Post sample buffer sip time: 75 seconds Post dye buffer sip time: 75 seconds Final delay time: 200 seconds Example 53 Parkinson’s Disease Mouse Model
Compounds of formula I: or pharmaceutically acceptable salts thereof, wherein X, R1, R2, R3 and A are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.
Compounds of formula I: or pharmaceutically acceptable salts thereof, wherein X, R1, R2, R3 and A are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease.

**Query-specific Abstract:**

**Title:** BICYCLIC PYRAZOLE LRRK2 SMALL MOLECULE INHIBITORS

**Abstract:** Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson’s disease

**Description:** The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

[0105] “Treating” or “treatment” of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

[0367] The invention also provides a method for treating a disease or condition mediated by or otherwise associated with the LRRK2 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0518] This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

Binding of the tracer and antibody to a kinase results in a high degree of FRET, whereas displacement of the tracer with a kinase inhibitor results in a loss of FRET.

[0551] This assay was used to determine a compound’s potency in inhibiting activity of LRRK2 by determining, Kiapp, IC50, or percent inhibition values.

[0596] The LabChip 3000 was run using the job “LRRK2 IC50” with the following job settings:
The invention is concerned with the compounds of formula (I), and salts thereof, wherein X, Y, Z, R1, R2, R3, R4, R5 and R6 are defined in the detailed description and claims. In addition, the present invention relates to methods of manufacturing and using the compounds of Formula (I) as well as pharmaceutical compositions containing such compounds. The compounds may be useful in treating diseases and conditions mediated by TRPA1, such as pain.
The invention is concerned with the compounds of formula (I), and salts thereof, wherein X, Y, Z, R1, R2, R3, R3, R4, R5 and R6 are defined in the detailed description and claims. In addition, the present invention relates to methods of manufacturing and using the compounds of Formula (I) as well as pharmaceutical compositions containing such compounds. The compounds may be useful in treating diseases and conditions mediated by TRPA1, such as pain.

Fulltext score: 6.17e-4, cippix score: 545

Query-specific Abstract:

**Description:** [0001] The present invention relates to ... containing them and their use as Transient Receptor Potential (TRP) channel antagonists.

[0003] Many of the known TRPA1 agonists are irritants that cause pain, irritation and ... Therefore, it would be expected that TRPA1 antagonists or agents that block the biological effect of ... for the treatment of acute and chronic pain.

This finding provides additional rationale for the utility of small molecule TRPA1 antagonists in the treatment of diseases related to tissue ... asthma, and virally-induced lung inflammation.

Wei et al., Neurosci Lett 479 (2010) 253-256)) ... for the utility of small molecule TRPA1 inhibitors in the treatment of pain disorders.

[0089] Substitution with positron emitting ... Topography (PET) studies for examining substrate receptor occupancy.

For example, prodrugs can be slowly converted to ... in a transdermal patch reservoir with a suitable enzyme or chemical reagent.


Such products can result for example from the ... deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

The compositions of the invention can be used to selectively inhibit TRPA1 in patients (e.g., humans).

The compositions of the invention can be used to selectively inhibit TRPA1 in patients (e.g., humans).

The effective amount of the compound to be ... and is the minimum amount necessary to inhibit TRPA1 activity as required to prevent or treat ... disease or disorder, such as for example, pain.

When the blood-brain barrier remains intact, ... to, physical methods, lipid- based methods, and receptor and channel-based methods.

[00132] Lipid-based methods of transporting a ... to antibody binding fragments that bind to receptors on the vascular endothelium of the blood- brain barrier (see, e.g., U.S.

[00133] Receptor and channel-based methods of transporting a ... of the blood-brain barrier (see, e.g., U.S.

2005/0089473), inhibiting ABC drug transporters (see, e.g., U.S.

coating a compound of formula I (or an embodiment ... activity of the one or more transferrin receptors (see, e.g., U.S.
The inhibitors can be administered into the ventricles of the CNS or spinal fluid.

More specifically, the inhibitors can be injected through chronically implanted catheters infused with the help of osmotic minipumps.

Examples of suitable administration protocols and agonists for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer’s disease patients and animal models of Parkinson’s disease, as described by Harbaugh, J. COX-2 selective inhibitors, e.g., celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, and lumiracoxib; tachykinin (NK) antagonists, particularly an NK-3, NK-2 or NK-1 antagonist, e.g., (OR, 9R)- and (2S, 3S); serotonin reuptake inhibitors, e.g., paroxetine, sertraline, norfluoxetine, etc.; noradrenaline (norepinephrine) reuptake inhibitors, e.g., maprotiline, lofepramine, mirtazepine, etc.; especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular duloxetine; neuroleptics sedative/anxiolytics; dual serotonin-noradrenaline reuptake inhibitors, such as venlafaxine, venlafaxine metabolite, etc.; and imipramine; acetylcholinesterase inhibitors such as donepezil; 5-HT3 antagonists such as ondansetron; metabotropic glutamate receptor (mGluR) antagonists; muscarinic antagonists, e.g., tolterodine, propiverine, tropsium, etc.; and ipratropium; cannabinoids; vanilloid receptor antagonists (e.g., resinferatoxin) or antagonists (e.g., capsazepine); anti-histamines or HI antagonist; NMDA receptor antagonists; 5-HT receptor agonists/antagonists; PDEV inhibitors; prostaglandin E2 subtype antagonists; leukotriene B4 antagonists; 5-lipoxygenase inhibitors, and 5-HT3 antagonists.

Example 87 IC50 Determinations of Exemplified Compounds Dose = The cell line doubling rate was -15 hours. Preparation of Cinnamaldehyde (agonist addition): FW = 132.16 - Specific gravity = ... to reflect desired final assay concentrations.

Compound plates were resuspended with 100u1 of buffer/DMSO (bk) column 2A-H: AP-18 (control antagonist for CHOK1 TRP A1 cells) column 1I-P: ATP (control ... CHOK1 teton cells) column 2 I-P: 2APB (control antagonist for CHOK1/TRPM8 cells).

After incubation, both the cell and compound ... to the FLIPR and 20u1 of the diluted compounds/agonist/bk were transferred to the cell plates by the FLIPR.

During the compound addition as well as agonist addition, fluorescence readings were taken ... 384 wells of the cell plate every 1.5 seconds.

The fluorescence was continuously monitored before, during and after sample/agonist addition for a total elapsed time of 100 seconds (compound addition) and 120 seconds (agonist addition).

Responses (increase in peak fluorescence) in each well following agonist addition was determined.

The responses were expressed as % inhibition of the inhibitor control as shown in Table 1 below: Table 1 Example IC50 Example IC50 (FLIPR) (FLIPR) 1 0.081 39 0.051 40 ... 37 0.014 75 0.025 76 0.020 Example 88 IC50 Determinations of Exemplified Compounds IC50s ... using a Hamamatsu FDSS fluorescence plate reader.

Following dye load and plate cool down, compounds ... whether any of the test compounds have TRPA1 agonist activity.

Plates were then incubated with compound for 20 minutes at room temperature prior to adding agonist.
Fixing the Hill coefficient will generally reduce variability of the IC\textsubscript{50} determination.

Table 2 Example hTRP\textsubscript{A1} AUC IC\textsubscript{50} (PM) CA 02885908 2015-03-24 WO 2014/049047 ... Example hTRPA1 Example hTRPA1 AUC IC\textsubscript{50} AUC IC\textsubscript{50} AUC IC\textsubscript{50} (PM) (PM) (PM) 77 0.883 80 0.251 84 0.029 78 1.0 ... fall within the scope of the appended claims.
The present invention provides for compounds of Formula (I) and various embodiments thereof, and compositions comprising compounds of Formula (I) and various embodiments thereof. (I) In compounds of Formula I, the groups R1, R2, R3, R4, R5, R6 and R7 have the meaning as described herein. The present invention also provides for methods of using compounds of Formula I and compositions comprising compounds of Formula (I) as DLK inhibitors and for treating neurodegeneration diseases and disorders.

La présente invention concerne des composés de Formule (I) et divers modes de réalisation associés, et des compositions comprenant les composés de Formule (I) et divers modes de réalisation associés. (I) Dans les composés de Formule I, les groupes R1, R2, R3, R4, R5, R6 et R7 ont la signification telle que décrite ici. La présente invention concerne également des procédés d’utilisation des composés de Formule (I) et des compositions comprenant les composés de Formule (I) en tant qu’inhibiteurs de DLK et pour le traitement de maladies et de troubles de neurodégénérescence.
3-SUBSTITUTED PYRAZOLES AND USE AS DLK INHIBITORS; PYRAZOLES 3 SUBSTITUTE ET UTILISATION EN TANT QU’INHIBITEURS DE DLK - ESTRADA, ANTHONY; LIU, WEN; PATEL, SHAHEL; SIU, MICHAEL - F. HOFFMANN-LA ROCHE AG; GENENTECH, INC.

The present invention provides for compounds of Formula (I) and various embodiments thereof, and compositions comprising compounds of Formula (I) and various embodiments thereof. (I) In compounds of Formula I, the groups R1, R2, R3, R4, R5, R6 and R7 have the meaning as described herein. The present invention also provides for methods of using compounds of Formula I and compositions comprising compounds of Formula (I) as DLK inhibitors and for treating neurodegeneration diseases and disorders.

In another aspect the present invention provides a method for inhibiting or preventing degeneration of a central nervous ... compound of formula I or any embodiment thereof.

In another aspect the present invention provides a method for inhibiting or preventing degeneration of a central nervous ... or a pharmaceutically acceptable salt thereof.

In another aspect the present invention provides ... thereof for the preparation of a medicament for inhibiting or preventing degeneration of a central nervous ... a neurodegenerative disease or condition.

For example, prodrugs can be slowly converted to ... in a transdermal patch reservoir with a suitable enzyme or chemical reagent.


Such products can result for example from the ... deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

Positron emitting isotopes such as <15>O, <13>N, ... tomography (PET) studies to examine substrate receptor occupancy.

This includes administration of the compound to a ... thereof is present, as well as introducing the inhibitor into a medium in which a neuro or portion thereof is cultured.
The phrases "preventing axon degeneration," . . . "preventing CNS neuron degeneration," "inhibiting axon degeneration," "inhibiting neuron degeneration" and "inhibiting CNS neuron degeneration" as used herein include (i) the ability to inhibit or preserve axon or neuron degeneration in . . . disease and (ii) the ability to inhibit or prevent further axon or neuron degeneration . . . or have symptoms of a neurodegenerative disease.

Preventing axon or neuron degeneration includes . . . may be characterized by complete or partial inhibition or neuron or axon degeneration.

Further, the phrases "preventing neuron degeneration" and "inhibiting neuron degeneration" in clued such inhibition with respect to the entire neuron or a portion . . . such as the neuron ell body, axons and dendrites.

The compositions of the invention can be used for inhibiting DLK activity in patients (e.g., humans) The term . . . specified ingredients in the specified amounts.

The effective amount of the compound to be . . . and is the minimum amount necessary to inhibit DLK activity as required to prevent or treat the . . . tangles, or undesired cell growth.

When the blood-brain barrier remains intact, . . . to, physical methods, lipid-based methods, and receptor and channel-based methods.

Lipid-based methods of transporting a compound of . . . to antibody binding fragments that bind to receptors on the vascular endothelium of the blood- brain barrier (see, e.g., U.S.

Receptor and channel-based methods of transporting a . . . of the blood-brain barrier (see, e.g., U.S.

2005/0089473), inhibiting ABC drug transporters (see, e.g., U.S.

coating a compound of formula I or I-I (or an . . . activity of the one or more transferrin receptors (see, e.g., U.S.

The inhibitors can be administered into the ventricles of the . . . introduced into the CNS or spinal fluid.

More specifically, the inhibitors can be injected through chronically implanted . . . infused with the help of osmotic minipumps.

Examples of suitable administration protocols and . . . for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer’s disease patients and animal . . . Parkinson’s disease, as described by Harbaugh, J.

Indications and Methods of Treatment In another aspect, the invention provides for methods of inhibiting the Dual Leucine Zipper Kinase (DLK) in an in . . . thereof. In these methods of the invention, the inhibition of DLK signaling or expression with a compound . . . a decrease in JNK2 and/or JNK3 expression).

Compounds of the invention can be used in methods for inhibiting neuron or axon degeneration. The inhibitors are, therefore, useful in the therapy of, for . . . memory loss, and (vii) psychiatric disorders.

Thus, the inhibitors described herein can be useful as components of . . . media for use in culturing nerve cells in vitro.

Accordingly, in another aspect, the invention provides for a method for inhibiting or preventing degeneration of a central nervous . . . thereof. In one embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . vitro. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . agent. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . .

. . . In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . device. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . or more additional pharmaceutical agents. The inhibitors can be optionally combined with or administered . . . Thus, in the treatment of ALS, for example, inhibitors can be administered in combination with Riluzole . . . growth factor 1 (IGF-1), and/or methylcobalamin.
In another example, in the treatment of Parkinson’s disease, inhibitors can be administered with L-dopa, dopamine agonists (e.g., bromocriptine, pergolide, pramipexole, ... apomorphine, and lisuride), dopa decarboxylase inhibitors (e.g., levodopa, benserazide, and carbidopa), and/or MAO-B inhibitors (e.g., selegiline and rasagiline).

In a further example, in the treatment of Alzheimer’s disease, inhibitors can be administered with acetylcholinesterase inhibitors (e.g., donepezil, galantamine, and rivastigmine) and/or NMDA receptor antagonists (e.g., memantine).

In addition to the combinations noted above, ... included in the invention are combinations of inhibitors of degeneration of different neuronal regions.

Thus, the invention includes combinations of agents that (i) inhibit degeneration of the neuron cell body, and (ii) inhibit axon degeneration. For example, inhibitors of GSK and transcription are found to prevent degeneration of neuron cell bodies, while inhibitors of EGFR and p38 MAPK are found to prevent ... Thus, the invention includes combinations of inhibitors of GSK and EGFR (and/or p38 MAPK), combinations of transcription inhibitors and EGF (and/or p38 MAPK), and further combinations of inhibitors of dual leucine zipper-bearing kinase (DLK), ... kinase (CaMKK), a G-protein, a G-protein coupled receptor, transcription factor 4 (TCF4), and [beta]-catenin. The inhibitors used in these combinations can be any of those described herein, or other inhibitors of these targets as described in WO 2011/050192, incorporated herein by reference.

DLK TR-FRET inhibition assay: DLK kinase reactions (20 L) containing 5 ... 60 minutes in 384 well OptiPlate (Perkin Elmer).

Compounds of formula I as set forth in Table 1 inhibited the DLK kinase with the KjS in micromolar ([mu][Mu]) as provided in Table 2 below.

**Claims:** A method for inhibiting or preventing degeneration of a central nervous ... I as described in any one of claims 1-29.32.

A method for inhibiting or preventing degeneration of a central nervous ... or a pharmaceutically acceptable salt thereof 42.

The use of a compound of formula I as described ... thereof for the preparation of a medicament for inhibiting or preventing degeneration of a central nervous ... a neurodegenerative disease or condition 49.
A first aspect of the invention relates to a compound of formula (1A) or (1B), or a pharmaceutically acceptable salt thereof, wherein R1 is a group selected from alkyl, monocyclic heterocycloalkyl, bicyclic heterocycloalkyl and cycloalkyl, each of which is optionally substituted, and wherein X1, X2, X3 and X4 are as defined herein. Further aspects relate to pharmaceutical compositions, therapeutic uses and process for preparing compounds of formula (1A) and (1B).
The present invention relates to pyrazolopyridine compounds that are capable of inhibiting one or more kinases, more particularly, LRRK2.

The defining feature of the LRRK2 enzyme is a Leucine Rich Repeat (LRR) motif (residues ... and a C-terminal WD40 motif [2231-2276] [6, 7].

The protein kinase domain of LRRK2 belongs to the ... kinases and is most similar to the kinase RIP (Receptor Interacting Protein), which play key roles in innate immunity signalling pathways.

These observations suggest that over-activation ... humans to develop PD, implying that drugs which inhibited LRRK2, could be utilised to halt progression or even perhaps reverse symptoms of some forms of PD.

The study of LRRK2 has been hampered by the difficulty in expressing active recombinant enzyme and by the lack of a robust quantitative assay.

Small molecule inhibitors of LRRK are described in WO 2010/106333 and WO ... the name of Medical Research Council Technology.

The present invention seeks to provide further compounds that are capable of inhibiting one or more kinases, more particularly LRRK2.

A seventh aspect of the invention relates ... a mammal having a disease state alleviated by inhibition of a kinase such as LRRK2, wherein the method ... amount of a compound as described above.

An eighth aspect of the invention relates ... further candidate compounds capable of inhibition of a kinase such as LRRK2.

The present invention relates to pyrazolopyridine compounds that are capable of inhibiting one or more kinases, more particularly LRRK, even more particularly LRRK2.

Advantageously, the claimed compounds exhibit surprisingly good inhibition of LRRK2 (see Table 1), compared to compounds ... example, in WO 2010/106333 and WO 2011/141756.

The compound is administered in an amount sufficient to inhibit one or more kinases such as LRRK2.

Yet another aspect of the invention ... a mammal having a disease state alleviated by inhibition of a protein kinase, wherein the method ... amount of a compound according to the invention.

The disease state may be alleviated by the inhibition of the protein kinase LRRK, more preferably LRRK2.

The term "administering" as used herein ... such a manner that the compound can affect the enzyme activity of the protein kinase either directly;
Herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a . . . of clinical symptoms of a disease or disorder.

For example, a dose can be formulated in animal . . . concentration range that includes the IC50 or the IC100 as determined in cell culture.

Thus, the present invention further . . . treatment of diseases where it is desirable to inhibit LRRK2.

The present invention contemplates the use of all . . . stereoisomers and geometric isomers of those inhibitor agents, and mixtures thereof.

Reversion is usually performed by an enzyme naturally present in such subject, though it is . . . in order to perform the reversion in vivo.

In accordance with this invention, an . . . of general formula (I) may be administered to inhibit the kinase implicated with a particular condition or disease.

or between 0.1 and 20 mg/kg, in a manner to . . . in the plasma at a concentration effective to inhibit a kinase.

Beneficial combinations may be suggested by studying the inhibitory activity of the test compounds with agents known . . . in the treatment of a particular disorder.

A further aspect of the invention relates . . . further candidate compounds capable of inhibiting one or more kinases, such as LRRK2.

The above methods may be used to screen for a ligand useful as an inhibitor of one or more kinases.

C.) and were linear with respect to time and enzyme concentration under the conditions used.

The enzyme was diluted and assayed in 50 mM Tris-HCl pH7.5, 0.1 mM EGTA, 1 mM DTT and 10 mM MgCl2.

IC50 values of inhibitors were determined after carrying out assays at 10 . . . concentrations of each compound in duplicate.

[3.2.1]octan-3-yl)-3-(6- . . . WO 2011141756 STR00239 *** *** = LRRK2 IC50 < 100 nM ** = LRRK2 IC50 between 100 nM and 1 muM * = LRRK2 IC50 between 1 muM and 10 muM STR00240 . . . Arg Phe Tyr Thr Leu Arg Arg Ala Arg Gin1

**Claims:** A method of treating a mammal having a disease state alleviated by the inhibition of LRRK2, wherein the method comprises . . . amount of a compound according to claim 1.
The present invention provides for compounds of Formula I-I and embodiments and salts thereof for the treatment of diseases (e.g., neurodegenerative diseases). R 1, R 2, R 3, X 1, X 2, A and Cy variable in Formula (I-I) all have the meaning as defined herein.
La présente invention concerne des composés représentés par la formule I-I ainsi que des modes de réalisation et des sels correspondants qui sont destinés au traitement de maladies (notamment, de maladies neurodégénératives). R 1, R 2, R 3, X 1, X 2, A et la variable Cy de la formule I-I possèdent tous la signification telle que définie dans la description. ; The present invention provides for compounds of Formula I-I and embodiments and salts thereof for the treatment of diseases (e.g., neurodegenerative diseases). R 1, R 2, R 3, X 1, X 2, A and Cy variable in Formula (I-I) all have the meaning as defined herein.

fulltext score : 1.80e-3 , cippix score : 259

Query-specific Abstract:

Description: FIELD OF THE INVENTIONThe present invention . . . or prophylaxis in a mammal, and in particular to inhibitors of DLK useful for treating neurodegeneration . . . a traumatic injury to the brain and spinal cord.

There is a great need for the development of . . . injuries, including for example, through the inhibition of DLK in neurons.SUMMARY OF THE INVENTIONIn one . . . Ci-6 alkylthio, =0, -NH2, -CN, -NO2and -SF5;

In another aspect, the present invention provides . . . the present invention provides for a method for inhibiting or preventing degeneration of a central nervous . . . neuron a compound of Formula I-I or Formula I.

In another aspect, the present invention provides for a method for inhibiting or preventing degeneration of a central nervous . . . I or a pharmaceutically acceptable salt thereof.

For example, prodrugs can be slowly converted to . . . in a transdermal patch reservoir with a suitable enzyme or chemical reagent.


Such products can result for example from the . . . deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered . . . the urine, blood or other biological samples.

Positron emitting isotopes such as 1<1>5<J>0, . . . tomography (PET) studies to examine substrate receptor occupancy.

This includes administration of the compound to a . . . thereof is present, as well as introducing the inhibitor into a medium in which a neuro or portion . . . farm animals such as cow, horses, dogs and cats.

Bioavailability is an absolute term that . . . “preventing CNS neuron degeneration,” “inhibiting axon degeneration,” “inhibiting neuron degeneration” “inhibiting CNS neuron degeneration” as used herein include (i) the ability to inhibit or preserve axon or neuron degeneration in . . . disease and (ii) the ability to inhibit or prevent further axon or neuron degeneration . . . or have symptoms of a neurodegenerative disease.

Preventing axon or neuron degeneration includes . . . may be characterized by complete or partial inhibition or neuron or axon degeneration.
Further, the phrases "preventing neuron degeneration" and "inhibiting neuron degeneration" in clued such inhibitors with respect to the entire neuron or a portion . . . such as the neuron cell body, axons and dendrites.

The compositions of the invention can be used for inhibiting DLK activity in patients (e.g., humans).

The effective amount of the compound to be . . . and is the minimum amount necessary to inhibit DLK activity as required to prevent or treat the . . . tangles, or undesired cell growth.

When the blood-brain barrier remains intact, . . . to, physical methods, lipid-based methods, and receptor and channel-based methods.

5,112,596, 5,268,164, 5,506,206, and . . . to antibody binding fragments that bind to receptors on the vascular endothelium of the blood- brain barrier (see, e.g., U.S. 2004/0131692). Receptor and channel-based methods of transporting a . . . of the blood-brain barrier (see, e.g., U.S. 2005/0089473), inhibiting ABC drug transporters (see, e.g., U.S.

coating a compound of Formula I-I or I (or an . . . activity of the one or more transferrin receptors (see, e.g., U.S.

The inhibitors can be administered into the ventricles of the . . . introduced into the CNS or spinal fluid.

More specifically, the inhibitors can be injected through chronically implanted . . . infused with the help of osmotic minipumps.

Examples of suitable administration protocols and . . . for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer’s disease patients and animal . . . Parkinson’s disease, as described by Harbaugh, J.

Indications and Methods of Treatment In another aspect, the invention provides for methods of inhibiting the Dual Leucine Zipper Kinase (DLK) in an in . . . thereof. In these methods of the invention, the inhibition of DLK signaling or expression with a compound . . . a decrease in JNK2 and/or JNK3 expression).

Compounds of the invention can be used in methods for inhibiting neuron or axon degeneration. The inhibitors are, therefore, useful in the therapy of, for . . . memory loss, and (vii) psychiatric disorders.

Thus, the inhibitors described herein can be useful as components of . . . aspect, the invention provides for a method for inhibiting or preventing degeneration of a central nervous . . . thereof. In one embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . vitro. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . agent. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . .

In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . device. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous . . . one or more additional pharmaceutical agents. The inhibitors can be optionally combined with or administered . . . Thus, in the treatment of ALS, for example, inhibitors can be administered in combination with Riluzole . . .

In another example, in the treatment of Parkinson’s disease, inhibitors can be administered with L-dopa, dopamine agonists (e.g., bromocriptine, pergolide, pramipexole, . . . apomorphine, and lisuride), dopa decarboxylase inhibitors (e.g., levodopa, benzerazide, and carbidopa), and/or MAO-B inhibitors (e.g., selegiline and rasagiline).

In a further example, in the treatment of Alzheimer’s disease, inhibitors can be administered with acetylcholinesterase inhibitors (e.g., donepezil, galantamine, and rivastigmine) and/or NMDA receptor antagonists (e.g., memantine).

The invention also includes pharmaceutical . . . included in the invention are combinations of inhibitors of degeneration of different neuronal regions.
Thus, the invention includes combinations of agents that (i) inhibit degeneration of the neuron cell body, and (ii) inhibit axon degeneration. For example, inhibitors of GSK and transcription are found to prevent degeneration of neuron cell bodies, while inhibitors of EGFR and p38 MAPK are found to prevent ... Thus, the invention includes combinations of inhibitors of GSK and EGFR (and/or p38 MAPK), combinations of transcription inhibitors and EGF (and/or p38 MAPK), and further combinations of inhibitors of dual leucine zipper-bearing kinase (DLK), ... kinase (CaMKK), a G-protein, a G-protein coupled receptor, transcription factor 4 (TCF4), and [beta]-catenin. The inhibitors used in these combinations can be any of those described herein, or other inhibitors of these targets as described in WO 2011/050192, ... that results from using the compounds separately.

The compounds disclosed in Table 1 were tested for DLK inhibitory activity as described in Example 3.

Example 3DLK TR-FRET inhibition assay: DLK kinase reactions (20 [mu][iota]) ... 60 minutes in 384 well OptiPlate (Perkin Elmer).

Compounds of Formula I-I or I as set forth in Table 1 inhibited the DLK kinase with the K;s in micromolar ([mu][Mu])

Claims: A method for inhibiting or preventing degeneration of a central nervous ... neuron a compound of Formula I-I or Formula I.29.

A method for inhibiting or preventing degeneration of a central nervous ... or a pharmaceutically acceptable salt thereof.39.
The invention is concerned with the compounds of formula I or II: and salts thereof. In addition, the present invention relates to methods of manufacturing and methods of using the compounds of formula I or II as well as pharmaceutical compositions containing such compounds. The compounds may be useful in treating diseases and conditions mediated by TRPA1, such as pain.

L'invention concerne des composés de formule I ou II ainsi que des sels de ceux-ci. L'invention concerne également des procédés de fabrication et des procédés d'utilisation des composés de formule I ou II, ainsi que des compositions pharmaceutiques contenant lesdits composés. Les composés peuvent être utiles dans le traitement de maladies et d’états pathologiques médies par TRPA1, tels que la douleur.
The invention is concerned with the compounds of formula I or II: and salts thereof. In addition, the present invention relates to methods of manufacturing and methods of using the compounds of formula I or II as well as pharmaceutical compositions containing such compounds. The compounds may be useful in treating diseases and conditions mediated by TRPA1, such as pain.

**Query-specific Abstract:**

**Description:** [002] The present invention relates to ... containing them and their use as Transient Receptor Potential (TRP) channel antagonists.

[004] Many of the known TRPA1 agonists are irritants that cause pain, irritation and ... Therefore, it would be expected that TRPA1 antagonists or agents that block the biological effect of ... for the treatment of acute and chronic pain.

This finding provides additional rationale for the utility of small molecule TRPA1 antagonists in the treatment of diseases related to tissue ... asthma, and virally-induced lung inflammation.

Wei et al., Neurosci Lett 479 (2010) 253-256)) ... for the utility of small molecule TRPA1 inhibitors in the treatment of pain disorders.

[0328] Substitution with positron emitting ... Topography (PET) studies for examining substrate receptor occupancy.

For example, prodrugs can be slowly converted to ... in a transdermal patch reservoir with a suitable enzyme or chemical reagent.


Such products can result for example from the ... deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

The compositions of the invention can be used to selectively inhibit TRPA1 in patients (e.g., humans).

The effective amount of the compound to be ... and is the minimum amount necessary to inhibit TRPA1 activity as required to prevent or treat ... disease or disorder, such as for example, pain.

When the blood-brain barrier remains intact, ... to, physical methods, lipid-based methods, and receptor and channel-based methods.

[0359] Lipid-based methods of transporting a ... to antibody binding fragments that bind to receptors on the vascular endothelium of the blood-brain barrier (see, e.g., U.S.

[0360] Receptor and channel-based methods of transporting a ... of the blood-brain barrier (see, e.g., U.S.

2005/0089473), inhibiting ABC drug transporters (see, e.g., U.S.
coating a compound of Formula I or II (or an ... activity of the one or more transferrin receptors (see, e.g., U.S.

The inhibitors can be administered into the ventricles of the ... introduced into the CNS or spinal fluid.

More specifically, the inhibitors can be injected through chronically implanted ... infused with the help of osmotic minipumps.

Examples of suitable administration protocols and ... for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer’s disease patients and animal ... Parkinson’s disease, as described by Harbaugh, J.

COX -2 selective inhibitors, e.g., celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, and lumiracoxib;

tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g., (DR, 9R)- ... -methylamino] -2-phenylpiperidine (2S ,3 S).

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Fixing the Hill coefficient will generally reduce variability of the IC50 determination.

Table 5: IC50 Determinations of Exemplified Compounds.
The present invention provides for compounds of formula 0 and various embodiments thereof, and compositions comprising compounds of formula 0 and various embodiments thereof. In compounds of formula 0, the groups R1A, R1B, R1C, R1D, R2, R3, R4, R5 and R6 have the meaning as described herein. The present invention also provides for methods of using compounds of formula 0 and compositions comprising compounds of formula 0 as DLK inhibitors and for treating neurodegeneration diseases and disorders.
The present invention provides for compounds of formula 0 and various embodiments thereof, and compositions comprising compounds of formula 0 and various embodiments thereof. In compounds of formula 0, the groups R1A, R1B, R1C, R1D, R2, R3, R4, R5 and R6 have the meaning as described herein. The present invention also provides for methods of using compounds of formula 0 and compositions comprising compounds of formula 0 as DLK inhibitors and for treating neurodegeneration diseases and disorders.

Query-specific Abstract:

Abstract: The present invention also provides for methods ... comprising compounds of formula 0 as DLK inhibitors and for treating neurodegeneration diseases and disorders

Description: FIELD OF THE INVENTION The present invention ... prophylaxis in a mammal, and in particular to inhibitors of DLK useful for treating neurodegeneration diseases and disorders.

There is a great need for the development of ... including for example, the development of inhibitors of DLK.

In another aspect the present invention provides a method for inhibiting or preventing degeneration of a central nervous ... compound of formula 0 or any embodiment thereof.

In another aspect the present invention provides a method for inhibiting or preventing degeneration of a central nervous ... or a pharmaceutically acceptable salt thereof.

In another aspect the present invention provides ... thereof for the preparation of a medicament for inhibiting or preventing degeneration of a central nervous ... a neurodegenerative disease or condition.

For example, prodrugs can be slowly converted to ... in a transdermal patch reservoir with a suitable enzyme or chemical reagent.


Such products can result for example from the ... deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

Positron emitting isotopes such as 15O, 13N, 11C, ... tomography (PET) studies to examine substrate receptor occupancy.

This includes administration of the compound to a ... thereof is present, as well as introducing the inhibitor into a medium in which a neuron or portion thereof is cultured.

The phrases preventing axon degeneration, ... preventing CNS neuron degeneration, inhibiting axon degeneration, inhibiting neuron degeneration inhibiting CNS neuron degeneration as used herein include (i) the ability to inhibit or prevent axon or neuron degeneration in ... disease and (ii) the ability to inhibit or prevent further axon or neuron degeneration ... or have symptoms of a neurodegenerative disease.

Preventing axon or neuron degeneration includes decreasing or inhibiting axon or neuron degeneration, which may be characterized by complete or partial inhibition or neuron or axon degeneration.

Further, the phrases preventing neuron degeneration and inhibiting neuron degeneration include such inhibition with respect to the entire neuron or a portion ... as the neuron cell body, axons and dendrites.

The compositions of the invention can be used for inhibiting DLK activity in patients (e.g., humans).
The effective amount of the compound to be... and is the minimum amount necessary to inhibit DLK activity as required to prevent or treat the... tangles, or undesired cell growth.

When the blood-brain barrier remains intact,... to, physical methods, lipid-based methods, and receptor and channel-based methods.

Lipid-based methods of transporting a compound of... to antibody binding fragments that bind to receptors on the vascular endothelium of the blood-brain barrier (see, e.g., U.S.

Recipient and channel-based methods of transporting a... of the blood-brain barrier (see, e.g., U.S. 2005/0089473), inhibiting ABC drug transporters (see, e.g., U.S.

coating a compound of formula 0 (or an embodiment... activity of the one or more transferrin receptors (see, e.g., U.S.

The inhibitors can be administered into the ventricles of the... introduced into the CNS or spinal fluid.

More specifically, the inhibitors can be injected through chronically implanted... infused with the help of osmotic minipumps.

Examples of suitable administration protocols and... for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer’s disease patients and animal... Parkinson’s disease, as described by Harbaugh, J.

Indications and Methods of Treatment In another aspect, the invention provides for methods of inhibiting the Dual Leucine Zipper Kinase (DLK) in an... thereof. In these methods of the invention, the inhibition of DLK signaling or expression with a compound... a decrease in JNK2 and/or JNK3 expression).

Compounds of the invention can be used in methods for inhibiting neuron or axon degeneration. The inhibitors are, therefore, useful in the therapy of, for... memory loss, and (vii) psychiatric disorders.

Thus, the inhibitors described herein can be useful as components of... media for use in culturing nerve cells in vitro.

Accordingly, in another aspect, the invention provides for a method for inhibiting or preventing degeneration of a central nervous... thereof. In one embodiment, of the method for inhibiting or preventing degeneration of a central nervous... vitro. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous... agent. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous... In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous...

... In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous... device. In another embodiment, of the method for inhibiting or preventing degeneration of a central nervous... or more additional pharmaceutical agents. The inhibitors can be optionally combined with or administered... Thus, in the treatment of ALS, for example, inhibitors can be administered in combination with Riluzole... growth factor 1 (IGF-1), and/or methylcobalamin.

In another example, in the treatment of Parkinson’s disease, inhibitors can be administered with L-dopa, dopamine agonists (e.g., bromocriptine, pergolide, pramipexole, ... apomorphine, and lisuride), dopa decarboxylase inhibitors (e.g., levodopa, benzerazide, and carbidopa), and/or MAO-B inhibitors (e.g., selegiline and rasagiline).

In a further example, in the treatment of Alzheimer’s disease, inhibitors can be administered with acetylcholinesterase inhibitors (e.g., donepezil, galantamine, and rivastigmine) and/or NMDA receptor antagonists (e.g., memantine).

In addition to the combinations noted above, ... included in the invention are combinations of inhibitors of degeneration of different neuronal regions.
Thus, the invention includes combinations of agents that (i) inhibit degeneration of the neuron cell body, and (ii) inhibit axon degeneration. For example, inhibitors of GSK and transcription are found to prevent degeneration of neuron cell bodies, while inhibitors of EGFR and p38 MAPK are found to prevent ... Thus, the invention includes combinations of inhibitors of GSK and EGFR (and/or p38 MAPK), combinations of transcription inhibitors and EGF (and/or p38 MAPK), and further combinations of inhibitors of dual leucine zipper-bearing kinase (DLK), ... kinase (CaMKK), a G-protein, a G-protein coupled receptor, transcription factor 4 (TCF4), and β-catenin. The inhibitors used in these combinations can be any of those described herein, or other inhibitors of these targets as described in WO 2011/050192, incorporated herein by reference.

Example 4 DLK TR-FRET inhibition assay: DLK kinase reactions (20 L) containing 5 ... 60 minutes in 384 well OptiPlate (Perkin Elmer).

Compounds of formula 0 as set forth in Table A inhibited the DLK kinase with the Kis in micromolar (M) as provided in Table B below.

Claims: A method for inhibiting or preventing degeneration of a central nervous ... as described in claim 1. 42. A method for inhibiting or preventing degeneration of a central nervous ... 1, or a pharmaceutically acceptable salt thereof.