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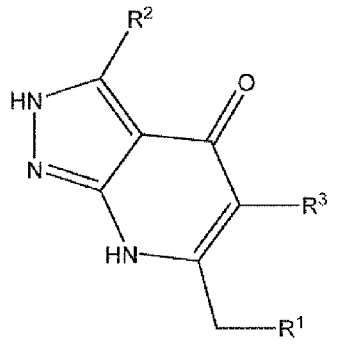
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(54) **Title**: PYRAZOLO [3,4-b] PYRIDIN-4-ONE KINASE INHIBITORS



(I)

(57) **Abstract**: The present invention is directed to novel kinase inhibitors of general formula (I) and pharmaceutically acceptable salts thereof, and to the use of the kinase inhibitors of general formula (I) for treating diseases or disorders in which tau phosphorylation and cell cycle regulation is implicated, such as Alzheimer's Disease and cancer.

TITLE OF THE INVENTION

PYRAZOLO [3,4-b] PYRIDIN-4-ONE KINASE INHIBITORS

The invention is directed to tau phosphorylation and cell cycle regulation kinase inhibitors, which are useful for the treatment of Alzheimer's Disease and cancer.

BACKGROUND OF THE INVENTION

Alzheimer's Disease is a common neurodegenerative disease affecting the elderly. Alzheimer's Disease results in progressive memory impairment, loss of language and visuospatial skills, and behavior deficits. Alzheimer's Disease is characterized by loss of mental ability severe enough to interfere with normal activites of daily living, and a marked decline in cognitive functions such as remembering, reasoning and planning. It is estimated that more than 25 million people worldwide presently suffer from Alzheimer's Disease. The number of Alzheimer's Disease patients may exceed 100 million by 2050.

Current FDA approved treatments for Alzheimer's Disease offer limited symptomatic benefits. These existing treatments target diseased neurons that release insufficient or excessive amounts of particular neurotransmitters, and seek to increase neurotransmitter levels or reduce excessive nerve cell stimulation. There are no approved pharmaceutical treatments that provide a significant delay or halt the progression of Alzheimer's Disease. Consequently, Alzheimer's Disease represents a serious unmet medical need, and many institutions are actively searching for pharmaceutical interventions for the disease.

While the cause and progression of Alzheimer's disease are not fully understood, Alzheimer's Disease is characterized by the deposition of amyloid beta (Aβ) in the brain in the form of extra-cellular plaques. This observation has led to the amyloid hypothesis, which postulates that Aβ deposits are the fundamental cause of the disease. Potential pharmaceutical interventions under the amyloid hypothesis include the prevention of Aβ formation, blocking the aggregation of amyloid into plaques, reducing amyloid solubility in the brain, and disassembling existing amyloid plaques. See Rafii et al, *BMC Medicine* 2 009, 7:7-11.

Typically, tau pathologies are characterized by the deposit of phosphorylated tau in the brain, abnormal conformations of tau and the presence of aggregations of tau, or "neurofibrillary tangles." A particular characteristic of Alzheimer's Disease is the formation in the brain of neurofibrillary tangles of the tau protein. Tangles of tau are formed when hyperphosphorylated tau begins to pair with other threads of tau. The hyperphosphorylated tau forms the neurofibrillary tangles inside nerve cell bodies.

The precise role that tau plays in the pathogenesis of Alzheimer's Disease neurodegeneration is uncertain. However, tau generally promotes microtubule assembly and stabilization, and has a key role in neurogenesis, axonal maintenance and axonal transport. F.

Hernandez et al, *Cell Mol. Life Sci* 64 (2007), 2219-2233. Tau is chiefly expressed in nerve cells.

In Alzheimer's Disease, the degree of dementia correlates more closely to the frequency of neurofibrillary tangles than to the frequency of senile plaques. Arriagada et al, *Neurology* 1992, 42: 631-639. In addition, tau mutations and neurofibrillary tangles are found in other dementias in which the Aβ pathology is absent, such as frontotemporal dementia, Pick's Disease and Parkinsonism linked to chromosome 17. Gong et al, *J Neural Transform* 2005, 112:813-838. Further, significant amounts of amyloid plaques have been found in the brains of non-demented elderly people, suggesting that amyloid pathology on its own is insufficient to cause dementia.

One potential method of inhibiting abnormal tau phosphorylation is through kinase inhibition. Cyclin dependent kinase 5 (CDK5) is a proline-directed protein kinase, which phosphorylates serine and threonine residues. CDK5 is located in the brain, and is involved in brain development. Camins et al, *Drug News & Persp* 2006, 8: 453-460. CDK5 has been implicated in the phosphorylation of tau. In particular, CDK5 interacts with p35, a protein which is expressed in potmitotic neurons, resulting in proteolytic products such as p25. The presence of p25 in transgenic mice is associated with hyperphosphorylation of tau. Iqbal et al, *J Cell Mol Med* 2008, 12:1, 38-55. Increased CDK5 activity and the accumulation of p25 is found in Alzheimer's Disease and other neurodegenerative diseases. Cruz et al, *Neuron* 2003, 40:471-483.

In addition to the hyperphopshorylation of tau, it is postulated that the CDK5/p25 complex induces cytoskeletal disruption, morphological degeneration and apotptosis. Thus, CDK5/p25 activation contributes to neuronal death and consequently, to neurodegenerative diseases. Camins. *See also* Noble et al, *Neuron* 2003, 40:471-483. CDK5 phosphorylation of the transient receptor potential vanilloid 1 (TRPV1) postulates a role for CDK5 in the treatment of pain. Pareek et al, *PNAS* 2007, 104:660-665.

Glycogen synthase kinase 3 (GSK3) is a serine/threonine protein kinase, which phosphorylates glycogen synthase. Embi, et al., *Eur. J. Biochem.* 1980: 107:519-527. GSK3 has also been implicated in the Alzheimer's Disease cascade, via the insulin receptor. Binding to the insulin receptor results in the activation of second messengers, including activiation of the AKT protein. The AKT protein phosphorylates GSK3, leading to inactivity of GSK3.

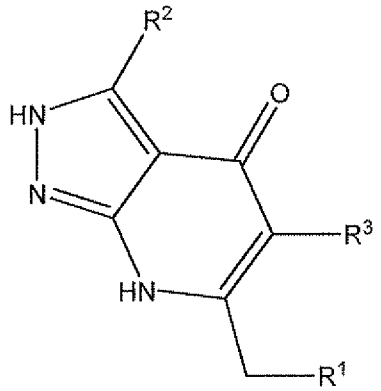
GSK 3 exists in two isomeric forms, GSK3α and GSK3β. In addition to its role in tau phophorylation, GSK3β regulates protection of amyloid beta in cells. Watson et al, *Neurology* 2003; 60(12):1899-1903. Inhibition of GSK3β is a recognized therapeutic target for Alzheimer's Dieasea and other neurodegenerative diseases.

The CDK2 kinase has a role in normal cell cycling. For disorders characterized by abnormal cell cycling, such as tumors, inhibition of CDK2 may help reduce tumor growth,

Inhibitors of CDK2 are therefore useful for the treatment of various types of cancer and other diseases or conditions related to abnormal cell growth *See, e.g,* Fischer, *Cell Cycle* 2004:,3(6):742-6.

SUMMARY OF THE INVENTION

The present invention is directed to pyrazolo [3,4-*b*] pyridin-4-one kinase inhibitors of general formula (I)

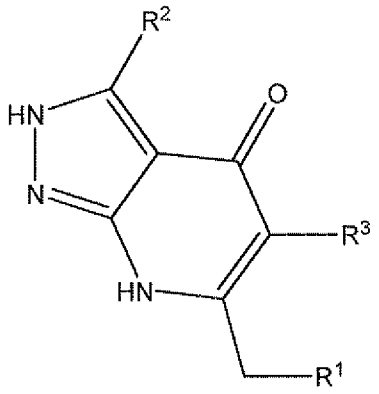


and pharmaceutically acceptable salts thereof. The compounds have been shown to inhibit tau phophorylation kinase activity, such as CDK5 and GSK3β activity, and to inhibit cell cycle regulation activity, such as CDK2 activity.

The invention is also directed to the use of the kinase inhibitors of general formula (I) for treating diseases or disorders in which tau phosphorlyation kinase inhibition and cell cycle regulation inhibition is implicated, such as Alzheimer's Disease and cancer.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention is directed to pyrazolo [3,4-*b*] pyridin-4-one kinase inhibitors of general formula (I)

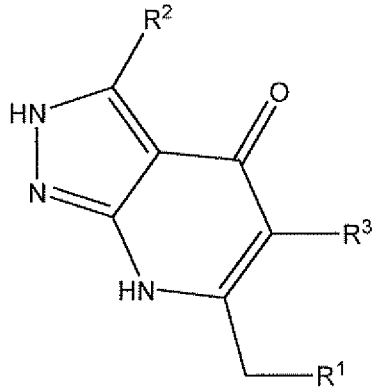


(I)

and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention is directed to pyrazolo [3,4-*b*] pyridin-4-one CDK5 inhibitors of general formula (I)



(I)

and pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from the group consisting of

(1) –C_{6-10} aryl, optionally substituted with one or more fluoro, or

(2) –C_{3-8} cycloalkyl;

wherein said alkyl or aryl is optionally substituted with one or more

(a) halogen,

(b) –C_{6-10} aryl,

(c) $-C_{1-6}$ alkyl,

R^2 is selected from the group consisting of

(1) $-C_{3-8}$ cycloalkyl, or

(2) a heterocyclic group having 4 to 8 ring atoms selected from C, (C=O), N, O or S, wherein at least one ring atom is a heteroatom selected from the group consisting of N, O or S,

wherein said cycloalkyl and heterocyclic are selected from the group consisting of

(a) halogen,

(b) hydroxyl,

R^3 is selected from the group consisting of

(1) hydrogen,or

(2) $-C_{1-6}$ alkyl.

The invention is also directed to pharmaceutical compositions which include an effective amount of a compound of formula (I), or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

The invention is also directed to methods of treating diseases or disorders in which tau phophorylation kinases are implicated, such as Alzheimer's Disease, and diseases or disorders in which cell cycle regulation kinases are implicated, such as cancer, by administering a compound of formula (I), or pharmaceutically acceptable salts thereof, to a patient in need thereof.

The invention is also directed to a method for the manufacture of a medicament or a composition for the treatment of diseases or disorders in which tau phophorylation kinases are implicated, such as Alzheimer's Disease, or for the treatment of diseases or disorders in which cell cycle regulation kinases are implicated, such as cancer, by combining a compound of the present invention with a pharmaceutical carrier or diluent.

In particular embodiments of compounds of formula (I), R^1 is $-C_{6-10}$ aryl, *e.g.* phenyl or naphthyl. The aryl group is optionally substituted by one or more

(a) halogen (for example, fluoro or chloro),

(b)–C_{6-10} aryl, or

(c)–C_{1-6} alkyl.

In other embodiments of compounds of formula (I), R^1 is C_{3-8} cycloalkyl, for example cyclohexyl. The cycloalkyl group is optionally substituted by one or more

(a) halogen (for example, fluoro or chloro),

(b) $-C_{6-10}$ aryl, or

(c) $-C_{1-6}$ alkyl.

In particular embodiments of compounds of formula (I), R^2 is C_{3-8} cycloalkyl (for example, cyclobutyl or oxocyclobutyl). The cyclolalkyl group is optionally substituted with one or more

(a) halogen (for example, fluoro or chloro), or

(b) hydroxyl.

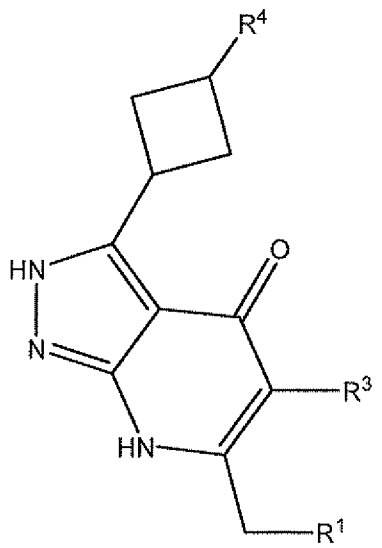
In particular embodiments of compounds of formula (I), R^2 is a heterocyclic group having 4 to 8 ring atoms selected from C, (C=O), N, O or S, wherein one ring atom is a heteroatom selected from the group consisting of N, O or S nitrogen, oxygen or sulfur. The cyclolalkyl group is optionally substituted with one or more

(a) halogen (for example, fluoro or chloro), or

(b) hydroxyl.

In particular embodiments of compounds of formula (I), R^3 is hydrogen.

In one subgenus, the compounds of formula (I) are compounds of formula (II):



(II)

and pharmaceutically acceptable salts thereof, wherein R^1 and R^3 are as described above, and R^4 is selected from the group consisting of

(a) halogen (for example, fluoro or chloro), or

(b) hydroxyl.

In particular embodiments of the compounds of formula (II), R^1 is $-C_{6-10}$ aryl, *e.g.* phenyl or naphthyl. The aryl group is optionally substituted by one or more

(a) halogen (for example, fluoro or chloro),

(b) $-C_{6-10}$ aryl, or

(c)–C_{1-6} alkyl.

In other embodiments of compounds of formula (II), R^1 is–C_{3-8} cycloalkyl, for example cyclohexyl. The cycloalkyl group is optionally substituted by one or more

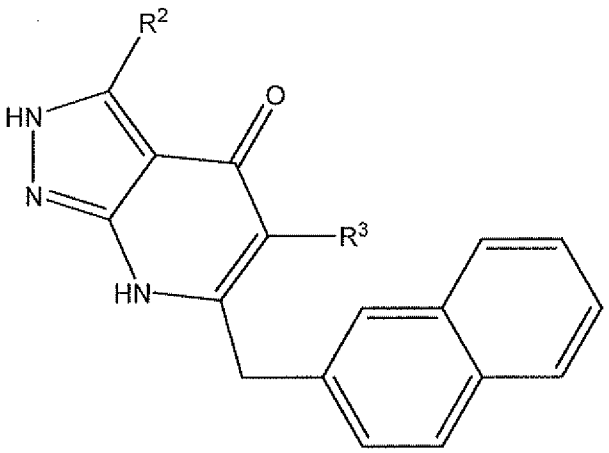
(a) halogen (for example, fluoro or chloro),

(b)–C_{6-10} aryl, or

(c)–C_{1-6} alkyl.

In particular embodiments of compounds of formula (II), R^3 is hydrogen.

In another subgenus, the compounds of formula (I) are compounds of formula (III):



(III)

and pharmaceutically acceptable salts thereof, wherein R^2 and R^3 are described above.

In particular embodiments of compounds of formula (III), R^2 is C_{3-8} cycloalkyl (for example, cyclobutyl or oxocyclobutyl). The cyclolalkyl group is optionally substituted with one or more

(a) halogen (for example, fluoro or chloro), or

(b) hydroxyl.

In particular embodiments of compounds of formula (III), R^2 is a heterocyclic group having 4 to 8 ring atoms selected from C, (C=O), N, O or S, wherein at least one ring atom is a heteroatom selected from the group consisting of N, O or S. The heterocyclic group is optionally substituted with one or more

(a) halogen (for example, fluoro or chloro), or

(b) hydroxyl,

In particular embodiments of compounds of formula (I), R^3 is hydrogen.

The invention is also directed to pharmaceutical compositions which include an effective amount of a compound of formulas (II) or (III), or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

The invention is also directed to methods of treating diseases or disorders in which tau phophorylation kinases are implicated, such as Alzheimer's Disease, and diseases or disorders in which cell cycle regulation kinases are implicated, such as cancer, by administering a compound of formulas (II) or (III), or pharmaceutically acceptable salts thereof, to a patient in need thereof.

The invention is also directed to a method for the manufacture of a medicament or composition for the treatment of diseases or disorders in which tau phophorylation kinases are implicated, such as Alzheimer's Disease, or diseases or disorders in which cell cycle regulation kinases are implicated, such as cancer, by combining a compound of one of formulas (II) or (III) with a pharmaceutical carrier or diluent.

In one embodiment, the compounds of formula (I) are selected from the group consisting of Examples 1-12:

3-cyclobutyl-6-(2-naphthylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(2-chloro-6-fluorobenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(biphenyl-4-ylmethyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(4-*tert*-butylbenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(biphenyl-2-ylmethyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

3-cyclobutyl-6-(3,4-dichlorobenzyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

3-cyclobutyl-6-(cyclohexylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(3-chloro-5-fluorobenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

3-(3,3-difluorocyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

3-(*trans*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

3-(*cis*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one; and

6-(naphthalen-2-ylmethyl)-3-(3-oxocyclobutyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

and pharmaceutically acceptable salts thereof.

As used herein, the term "alkyl," by itself or as part of another substituent, means a saturated straight or branched chain hydrocarbon radical having the number of carbon atoms designated (*e.g.*, C_{1-10} alkyl means an alkyl group having from one to ten carbon atoms).

Preferred alkyl groups for use in the invention are C_{1-6} alkyl groups, having from one to six carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like.C_0 alkyl means a bond.

As used herein, the term "cycloalkyl," by itself or as part of another substituent, means a saturated cyclic hydrocarbon radical having the number of carbon atoms designated (*e.g.*, C_{3-12} cycloalkyl means a cycloalkyl group having from three to twelve carbon atoms). The term cycloalkyl as used herein includes mono-, bi- and tricyclic saturated carbocycles, as well as bridged and fused ring carbocycles, such as spiro fused ring systems.

Preferred cycloalkyl groups for use in the invention are monocyclic C_{3-8} cycloalkyl groups, having from three to eight carbon atoms. Exemplary monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, oxocyclobutyl, cyclopentyl, cyclohexyl and the like. Exemplary bridged cycloalkyl groups include adamantly and norbornyl. Exemplary fused cycloalkyl groups include decahydronaphthalene.

When a non-aromatic heterocyclic group as defined herein is substituted, the substituent may be bonded to a ring carbon atom of the heterocyclic group, or on a ring heteroatom (*i.e.,* a nitrogen, oxygen or sulfur), which has a valence which permits substitution. Preferably, the substituent is bonded to a ring carbon atom. Similarly, when a non-aromatic heterocyclic group is defined as a substituent herein, the point of attachment may be at a ring carbon atom of the heterocyclic group or on a ring heteroatom (i.e., a nitrogen, oxygen or sulfur), which has a valence which permits substitution. Preferably, the attachment is at a ring carbon atom.

As used herein, the term "aryl," by itself or as part of another substituent, means an aromatic cyclic hydrocarbon radical having the number of carbon atoms designated (e.g., C_{6-10} aryl means an aryl group having from six to ten carbons atoms). The term "aryl" includes multiple ring systems as well as single ring systems. Preferred aryl groups for use in the invention include phenyl and naphthyl.

The term "aryl" also includes fused cyclic hydrocarbon rings which are partially aromatic (i.e., one of the fused rings is aromatic and the other is non-aromatic). An exemplary aryl group which is partially aromatic is indanyl.

The term "halo" or "halogen" includes fluoro, chloro, bromo and iodo.

As used herein, the term "heterocyclic," by itself or as part of another substituent, means a cycloalkyl group as defined above, in which one or more of the ring carbon atoms is replaced with a heteroatom (such as N, S or O). Suitable non-aromatic heterocyclic groups for use in the

invention include piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, pyrazolidinyl and imidazolildinyl. Preferred heterocyclic groups for use in the invention have four to eight ring atoms and a single nitrogen or oxygen heteroatom.

When a heterocyclic group as defined herein is substituted, the substituent may be bonded to a ring carbon atom of the heterocyclic group, or to a ring heteroatom (*i.e.*, a nitrogen, oxygen or sulfur), which has a valence which permits substitution. Preferably, the substituent is bonded to a ring carbon atom. Similarly, when a heterocyclic group is defined as a substituent herein, the point of attachment may be at a ring carbon atom of the heterocyclic group, or on a ring heteroatom (*i.e.*, a nitrogen, oxygen or sulfur), which has a valence which permits attachment. Preferably, the attachment is at a ring carbon atom.

Some of the compounds of the instant invention have at least one asymmetric center. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Compounds with asymmetric centers give rise to enantiomers (optical isomers), diastereomers (configurational isomers) or both, and it is intended that all of the possible enantiomers and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention. The present invention is meant to encompass all such isomeric forms of these compounds.

Compounds described herein may contain one or more double bonds, and may thus give rise to *cis*/*trans* isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

Formulas (I) to (III) are shown above without a definite stereochemistry at certain positions. The present invention includes all stereoisomers of formulas (I) to (III) and pharmaceutically acceptable salts thereof.

In the compounds of formulas (I) to (III), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic formulas (I) to (III). For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic formulas (I) to (III) can be prepared without

undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the schemes and examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The term "substantially pure" means that the isolated material is at least 90% pure, and preferably 95% pure, and even more preferably 99% pure as assayed by analytical techniques known in the art.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. The compounds of the invention may be mono, di or tris salts, depending on the number of acid functionalities present in the free base form of the compound. Free bases and salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, trifluoroacetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

The subject or patient to whom the compounds of the present invention is administered is generally a human being, male or female, in whom inhibition of tau phosphrylation or cell cycle regulation kinase activity is desired, but may also encompass other mammals, such as dogs, cats, mice, rats, cattle, horses, sheep, rabbits, monkeys, chimpanzees or other apes or primates, for which inhibition of kinase activity or treatment of the above noted disorders is desired.

The compounds of the invention are useful for treating diseases or disorders in which tau phosphorylation and cell cycle regulation kinases are implicated, such as Alzheimer's Disease and other neurodegenerative diseases. Neurodegenerative diseases in which CDK5 is implicated include mild cognitive impairment; age-related cognitive decline; corticobasal degeneration; dementia pugilistica; Down's Syndrome; frontotemporal dementia; Parkinson's Disease and Parkinsonism linked to chromosome 17; Parkinsonian-ALS demential complex; cerebral ischemia and other strokes; spinal cord injury; traumatic brain injury; viral induced dementia, such as HIV and AIDS induced dementia; excitotoxicity; epilepsy; amyotrophic lateral sclerosis; Niemann-Pick type C disease; neurodegeneration due to myocardial infarction and oxidative stresses; Huntington's Disease and dementia due to Huntington's disease; myotonic dystrophy; prion disease with tangles; progressive supranuclear palsy; lower lateral sclerosis; sucabcute sclerosing panencephalistis; multiple sclerosis; neurodegeneration associated with bacterial infection, migraine, hypoglycemia, urinary incontinece, brain ischemia, and emesis. The compounds of the invention are also useful in the treatment of pain.

In addition, the compounds of the invention may be useful for treating schizophrenia; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; personality disorder of the schizoid type; drug addiction, including narcotic (e.g. heroin, opium, and morphine), cocaine and alcohol addiction; drug withdrawal, including narcotic, cocaine and alcohol withdrawal; obsessive compulsive disorder; Tourette's syndrome; depression; a major depressive episode, a manic or mixed mood episode, a hypomanic mood episode, a depressive episode with atypical features or with melancholic features or catatonic features, a mood episode with postpartum onset; post-stroke depression, major depressive disorder, dysthymic disorder, minor depressive disorder, premenstrual dysphoric disorder, post-psychotic depressive disorder of schizophrenia, a major depressive disorder superimposed on a psychotic disorder such as delusional disorder or schizophrenia, a bipolar disorder, for example bipolar I disorder, bipolar II disorder, cyclothymic disorder; anxiety; attention deficit and hyperactivity disorder; and attention deficit disorder.

Other disorders and conditions for which the compounds of the invention may be useful include male fertility and sperm motility; diabetes mellitus; impaired glucose tolerance; metabolic syndrome or syndrome X; polycystic ovary syndrome; adipogenesis and obesity; myogenesis and frailty, for example age-related decline in physical performance; acute

sarcopenia, for example muscle atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery; sepsis; hair loss, hair thinning, and balding; and immunodeficiency

For example, the compounds may be useful for the prevention of dementia of the Alzheimer's type, as well as for the treatment of early stage, intermediate stage or late stage dementia of the Alzheimer's type. In general, Alzheimer's Disease symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and the general withdrawal of the sufferer as their senses decline. The language problems associated with Alzheimer's Disease include a shrinking vocabulary and decreased word fluency. Alzheimer's Disease also includes impairment of fine motor tasks, such as writing, drawing, dressing and other coordinated movements. Alzheimer's Disease symptoms include apraxia (difficulties in movement planning).

Early stage Alzheimer's Disease is characterized by confusion, memory loss and changes in other cognitive abilities. Symptoms may include getting lost, trouble handling money and paying bills, repeating questions, taking longer to complete normal daily tasks, poor judgment, and mood and personality changes.

Intermediate stage Alzheimer's Disease is manifested by problems with reasoning, sensory processing, and conscious thought. Intermediate stage symptoms include continuing memory loss and confusion. Intermediate stage patients typically begin to have problems recognizing family and friends. Symptoms include the inability to learn new things, carry out tasks that involve multiple steps (such as getting dressed), or coping with new situations. Intermediate stage patients may have hallucinations, delusions, and paranoia, and may behave impulsively.

Patients suffering from severe Alzheimer's Disease are typically unable to communicate and are completely dependent on others for their care.

The compounds of the invention are used to treat or prevent cellular proliferation diseases. Cellular proliferation disease states include, but are not limited to, cancer (further discussed below), autoimmune disease, arthritis, graft rejection, inflammatory bowel disease, proliferation induced after medical procedures, including, but not limited to, surgery, angioplasty, and the like. It is appreciated that in some cases the cells may not be in a hyper- or hypoproliferation state (abnormal state) and still require treatment. Thus, in one embodiment, the invention herein includes application to cells or individuals which are afflicted or may eventually become afflicted with any one of these disorders or states.

The compounds, compositions and methods provided herein are particularly useful for the treatment and prevention of cancer, such as angiogenesis and tumorigenesis, and including the treatment of solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, and the like. Particular cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to cardiac sarcomas: angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma and teratoma; lung sarcomas: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; gastrointestinal sarcomas: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); genitourinary tract sarcomas: kidney (adenocarcinoma, Wilm's tumor or nephroblastoma, lymphoma, leukemia,), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); liver sarcomas: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; bone sarcomas: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; nervous system sarcomas: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord (neurofibroma, meningioma, glioma, sarcoma); gynecological sarcomas: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial

carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); hematologic sarcomas: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); skin sarcomas: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. The term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

In another embodiment, the compounds of the instant invention are useful for treating or preventing cancer selected from head and neck squamous cell carcinomas, histiocytic lymphoma, lung adenocarcinoma, small cell lung cancer, non-small cell lung cancer, pancreatic cancer, papillary renal cell carcinoma, liver cancer, gastric cancer, colon cancer, multiple myeloma, glioblastomas and breast carcinoma. In another embodiment, the compounds of the instant invention are useful for the prevention or modulation of the metastases of cancer cells and cancer.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment of diseases or conditions for which the compounds of the present invention have utility, where the combination of the drugs together are safer or more effective than either drug alone. Additionally, the compounds of the present invention may be used in combination with one or more other drugs that treat, prevent, control, ameliorate, or reduce the risk of side effects or toxicity of the compounds of the present invention. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with the compounds of the present invention. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to the compounds of the present invention. The combinations may be administered as part of a unit dosage form combination product, or as a kit or treatment protocol wherein one or more additional drugs are administered in separate dosage forms as part of a treatment regimen.

Examples of combinations of the compounds of the present invention include combinations with anti-Alzheimer's Disease agents, for example other CDK5 inhibitors; beta-secretase inhibitors; alpha 7 nicotinic agonists; ADAM 10 ligands or activators; gamma-secretase

inhibitors; gamma secretase modulators; tau phosphorylation inhibitors; glycine transport inhibitors; LXR β agonists; ApoE4 conformational modulators; NR2B antagonists; androgen receptor modulators; blockers of Aβ oligomer formation; 5-HT4 agonists; 5-HT6 antagonists; 5-HT1a antagonists, such as lecozotan; NK1/NK3 receptor antagonists; COX-2 inhibitors; HMG-CoA reductase inhibitors; NSAIDs including ibuprofen; vitamin E; anti-amyloid antibodies (including anti-amyloid humanized monoclonal antibodies); anti-inflammatory compounds such as (R)-flurbiprofen, nitroflurbiprofen; PPAR gamma agonists, such as pioglitazone and rosiglitazone; CB-1 receptor antagonists or CB-1 receptor inverse agonists; antibiotics such as doxycycline and rifampin; N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine, neramexane; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, tacrine, phenserine and ladostigil; growth hormone secretagogues such as ibutamoren, ibutamoren mesylate, and capromorelin; histamine H_3 receptor antagonists; AMPA agonists or AMPA modulators; PDE 4 inhibitors; PDE 10A inhibitors; $GABA_A$ inverse agonists; GSK3β inhibitors; neuronal nicotinic agonists; selective M1 agonists; HDAC inhibitors; and microtubule affinity regulating kinase (MARK) ligands; or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the compounds of the present invention.

The instant compounds are also useful in combination with known anti-cancer agents. For example, the compounds are useful in combination with known anti-cancer agents. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (2001). Suitable anti-cancer agents include, but are not limited to, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, and apoptosis inducing agents and agents that interfere with cell cycle checkpoints.

The instant compounds are also useful when co-administered with radiation therapy.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopro poxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-

2H-l-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate and 4,4'- dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, trans-N-(4'-hydroxyphenyl) retinamide and N-4- carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of histone deacetylase, inhibitors of kinases involved in mitotic progression, antimetabolites, biological response modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors. Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl- pyridine)platinum, benzylguanine, glufosfamide, GPXlOO, (trans, trans, trans)-bis-mu-(hexane-l,6-diamine)-mu-[diamine-platinum(π)]bis[diamine(chloro)platinu πi (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(1 l-dodecylamino-10-hydroxyundecyl)-3,7- dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755 and 4-demethoxy-3- deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin.

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin and bortezomib.

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, vinflunine, cryptophycin, 2,3,4,5 6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide and epothilones.

Examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-0-exo-benzylidene-chartreusin, 9-methoxy-N,N- dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3- dihydro-9-hydroxy-4-methyl- 1H,12H-benzo [de]pyrano[3',4':b,7]-indolizino [1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, etoposide phosphate, teniposide, sobuzoxane, T -dimethyiamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-l-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5 5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-l,3-dioxol-6-one, 2,3-(methylenedioxy)-5- methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2- aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,l-de]acridin-6-one, N-[I-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,l-c] quinolin-7-one and dimesna.

Examples of inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLPl, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kifl4, inhibitors of Mphosphl and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to SAHA, TSA, oxamflatin, PXDlOl, MG98, valproic acid and scriptaid. Further reference to other histone deacetylase inhibitors are described in Miller, T.A. et al. *J. Med. Chem.* 46(24):5097-51 16 (2003).

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (in particular inhibitors of PLK-I), inhibitors of bub-1 and inhibitors of bub-Rl.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4- dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl -L-glutarnic acid, aminopterin, 5-flurouracil, alanosine, ll-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-l,ll-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-l-B-D- arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include, but are not limited to lovastatin, simvastatin, pravastatin, fluvastatin and atorvastatin . The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (1996). The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (*i.e.*, where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open- acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-H, also called Rab GGPTase).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-I (VEGFRl) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal antiinflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib, steroidal antiinflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagi πol, thalidomide, angiostatin, troponin- 1, angiotensin II antagonists and antibodies to VEGF.

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin, low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chkl and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7- hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

"Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs as described by Bume-Jensen et al, *Nature* 2001;4 11-.355-365.

"Inhibitors of cell proliferation and survival signaling pathway" refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR, inhibitors of cytokine

receptors, inhibitors of MET, inhibitors of PDK, serine/threonine kinases (including but not limited to inhibitors of Akt, inhibitors of Raf kinase, inhibitors of MEK and inhibitors of mTOR. Such agents include small molecule inhibitor compounds and antibody antagonists.

"Apoptosis inducing agents" include activators of TNF receptor family members (including the TRAIL receptors).

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification, NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC50 for COX-2 over IC50 for COX-1 evaluated by cell or microsomal assays. Inhibitors of COX-2 that are particularly useful in the instant method of treatment are 3-phenyl-4-(4-(memylsulfonyl)phenyl)-2-(5/0-furanone; 5-chloro-3-(4-methylsulfonyl)-phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX and BEXTRA or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-l-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-l-[[3,5-dichloro-4- (4-chlorobenzoyl)-phenyl]methyl]-IH-1,2,3-triazole-4-carboxamide,CM 101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino] -bis-(1,3-naphthalene disulfonate) and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αv β3 integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ5 integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the αyβ3 integrin and the αv β5 integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the αv β6, αγβ8 cti βi, 2βl <*5βl α6βl and α β4 integrins. The

term also refers to antagonists of ariy combination of α β3 αv β5, cx v β6, ctv β8 αi βi , α2βl , αs βl, αββl and 6β4 integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5- yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin >4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)pro poxyl]quinazoline, N-(3- ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, 2,3,9,10,1 1,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyI-9,12-epoxy-lH-diindolo[l,2,3-fg :3',2',r- kl]pyrrolo[3,4-i][l,6]benzodiazocin-l-one, SH268, genistein, imatinib, 4-(3-chlorophenylamino)-5,6-dirnethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo- 4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7- dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-l-phthalazinamine and EMD 12 1974.

The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound, which is a compound of formulas (I) to (III), is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable

for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds represented by formulas (I) to (III), or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule preferably containing from about 0.1 mg to about 500 mg of the active ingredient.

Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Other pharmaceutical compositions include aqueous suspensions, which contain the active materials in admixture with excipients suitable for the manufacture of aqueous

suspensions. In addition, oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Oily suspensions may also contain various excipients. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions, which may also contain excipients such as sweetening and flavoring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension, or in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can also be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individual's body in a therapeutically useful form and therapeutically useful amount, including, but not limited to: oral dosage forms, such as tablets, capsules, syrups, suspensions, and the like; injectable dosage forms, such as IV, IM, or IP, and the like; transdermal dosage forms, including creams, jellies, powders, or patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal suppositories.

The terms "effective amount" or "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system,

animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treatment" or "treating" means any administration of a compound of the present invention and includes (1) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or (2) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

The compositions containing compounds of the present invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The term "unit dosage form" is taken to mean a single dose wherein all active and inactive ingredients are combined in a suitable system, such that the patient or person administering the drug to the patient can open a single container or package with the entire dose contained therein, and does not have to mix any components together from two or more containers or packages. Typical examples of unit dosage forms are tablets or capsules for oral administration, single dose vials for injection, or suppositories for rectal administration. This list of unit dosage forms is not intended to be limiting in any way, but merely to represent typical examples of unit dosage forms.

The compositions containing compounds of the present invention may conveniently be presented as a kit, whereby two or more components, which may be active or inactive ingredients, carriers, diluents, and the like, are provided with instructions for preparation of the actual dosage form by the patient or person adminstering the drug to the patient. Such kits may be provided with all necessary materials and ingredients contained therein, or they may contain instructions for using or making materials or components that must be obtained independently by the patient or person administering the drug to the patient.

When treating or ameliorating Alzheimer's disease or cancer, or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per kg of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. The total daily dosage is from about 1.0 mg to about 2000 mg, preferably from about 0.1 mg to about 20 mg per kg of body weight. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 1,400 mg. This dosage regimen may be adjusted to provide the optimal

therapeutic response. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.005 mg to about 2.5 g of active agent, compounded with an appropriate and convenient amount of carrier materia. Unit dosage forms will generally contain between from about 0.005 mg to about 1000 mg of the active ingredient, typically 0.005, 0.01 mg, 0.05 mg, 0.25 mg, 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg, administered once, twice or three times a day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The independent syntheses of the enantiomerically or diastereomerically enriched compounds, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates that are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

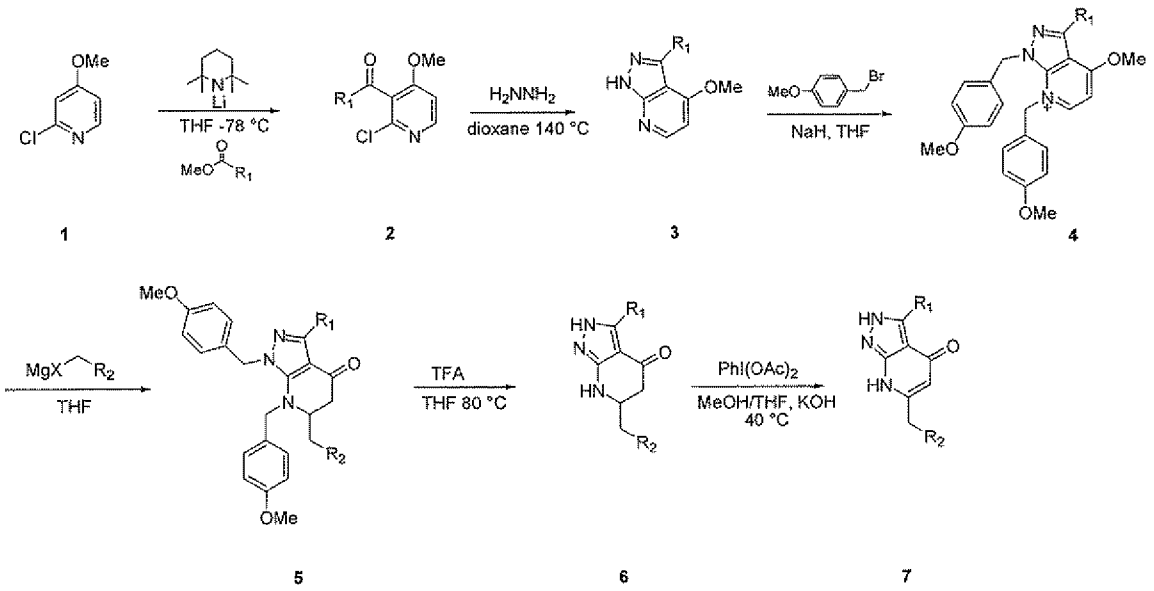
If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

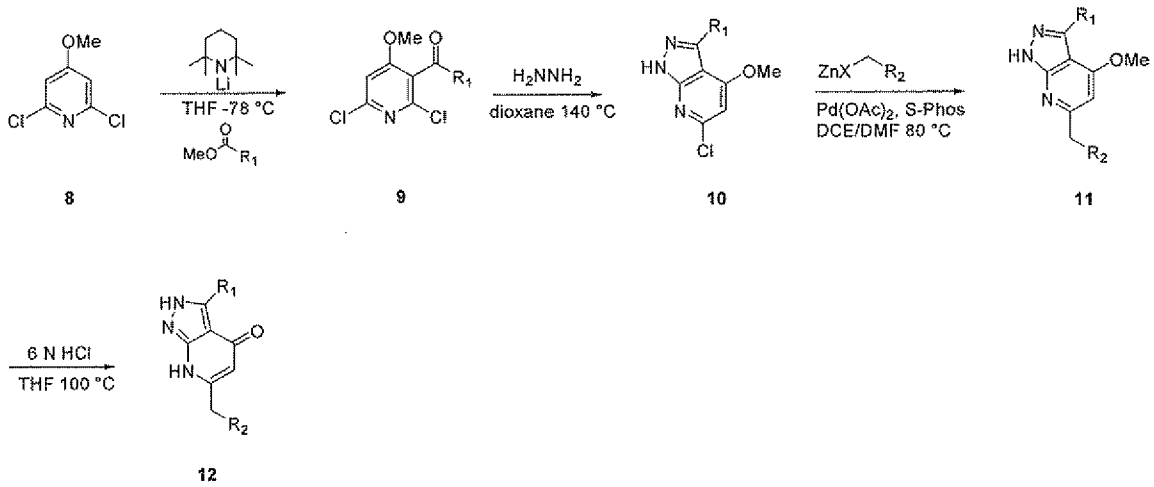
In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. Additionally, various protecting group strategies may be employed to facilitate the reaction or to avoid unwanted reaction products.

The compounds claimed in this invention can be prepared according to the following general procedure methods (Schemes 1 and 2). 2-chloro-4-methoxy pyridine can be deprotonated by lithium tetramethy-piperidine at low temperature and quenched with a variety of esters to afford ketone 2. Heating ketone 2 with hydrazine at high temperatures cyclizes to form indazole 3. The indazole is protected as bis 4-methoxy benzyl amines and treatment with Grignard reagents to yield pyridone 5. The 4-methoxy benzyl protecting groups are deprotected under acidic conditions and oxidation with (diacetoxy) iodobenzene provides compounds claimed in this invention.



Scheme 1

Alternatively, compounds in this invention can also be prepared according to the procedure in Scheme 2. 2,6 Dichloro-4-methoxy-pyridine can be deprotonated with lithium tetramethyl-piperidine at low temperature and quench with a variety of esters. Ketone 9 is reacted with hydrazine at elevated temperatures to afford indazole 10. Negishi Reaction with zinc intermediates and palladium acetate and S-Phos produce compound 11. Hydrolysis of the methyl ether under acidic conditions yields compounds also covered in this patent.

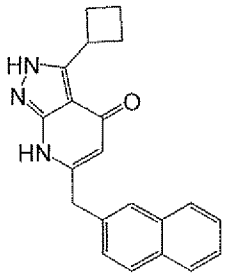


Scheme 2

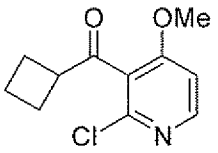
The following Examples are provided so that the invention might be more fully understood. These Examples are illustrative only and should not be construed as limiting the invention in any way.

Method A:

Example 1

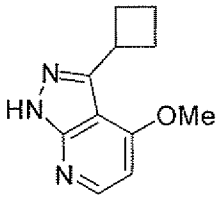


3-cyclobutyl-6-(2-naphthylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one



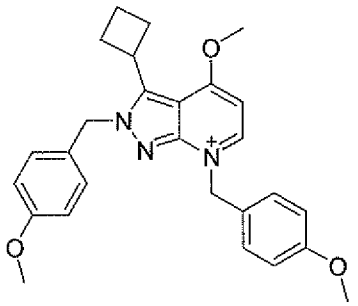
Step 1: (2-chloro-4-methoxypyridin-3-yl)(cyclobutyl)methanone

0.90 M of lithium tetramethyl piperidine was prepared by adding n-BuLi (2.50 M in hexanes, 28.3 mL, 70.8 mmol) to tetramethyl piperidine (10 g, 70.8 mmol) in THF (50 mL) at 0 °C under nitrogen dropwise. The solution was stirred for 30 minutes at 0 °C then lithium tetramethyl piperidine was added dropwise (0.90 M, 70 mL, 63 mmol) to a solution 2-chloro-4-methoxy pyridine (3 g, 28.1 mmol) in THF (40 mL) at -78 °C under nitrogen. The solution was stirred for 1hr then methyl cyclobutanecarboxylate (4.8 g, 42 mmol) was added and the dry ice bath was removed and warmed to room temperature. The solution was quenched with MeOH and worked up with EtOAc and water, dried with $MgSO_4$, filtered, and concentrated to afford orange brown oil. Column chromatography on silica gel 100% Hex to 100% EtOAc afforded (2-chloro-4-methoxypyridin-3-yl)(cyclobutyl)methanone as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 1H), 6.8 (d, 1H), 3.84 (s, 3H), 3.68 (m, 1H), 2.40 (m, 2H), 2.14 (m, 2H), 1.90 (m, 2H), 1.86 (m, 2H). LRMS (APCI) calc'd for ($C_{11}H_{13}ClNO_2^+$) $[M]^+$, 226.0; found 226.0.



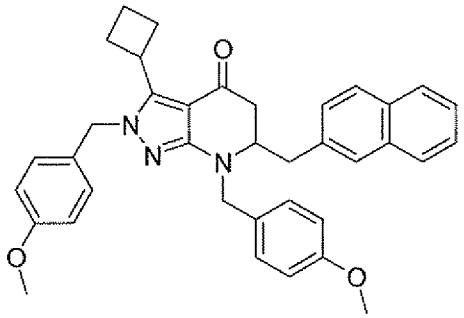
Step 2: 3-cyclobutyl-4-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine

To a solution of -chloro-4-methoxypyridin-3-yl)(cyclobutyl)methanone (3170 mg, 14.1 mmol) in dioxane (50 mL) was added hydrazine (0.880 mL, 28 mmol) and heated to 140 °C for 14 hr. The reaction mixture was concentrated to dryness and triturated with diethyl ether to afford 3-cyclobutyl-4-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, 1H), 6.60 (d, 1H), 3.96 (s, 3H), 3.86 (m, 1H), 2.40-2.20 (m, 4H), 2.00 (m, 1H), 1.84 (m, 1H). LRMS (APCI) calc'd for $(C_{11}H_{13}ClNO_2^+)$ $[M]^+$, 226.0; found 226.0. LRMS (APCI) calc'd for $(C_{11}H_{14}N_3O^+)$ $[M]^+$, 204.1; found 204.1.



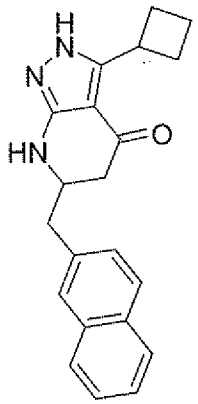
Step 3: 3-cyclobutyl-4-methoxy-2,7-bis(4-methoxybenzyl)-2*H*-pyrazolo[3,4-*b*]pyridin-7-ium

To a solution of 3-cyclobutyl-4-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine (607 mg, 2.99 mmol) in THF (15 mL), was added sodium hydride(131 mg, 3.29 mmol) and stirred for 10 minutes at room temperature followed by 1-(bromomethyl)-4-methoxybenzene (1801 mg, 8.96 mmol) and stirred for an additional 2h. The reaction was diluted with ethyl acetate and extracted with water followed by brine. The organic layer was dried with sodium sulfate, filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica gel eluting with ethylacetate in hexanes(10-100%) followed by MeOH in CH_2Cl_2 (0-8%) to afford 3-cyclobutyl-4-methoxy-2,7-bis(4-methoxybenzyl)-2*H*-pyrazolo[3,4-*b*]pyridin-7-ium. LRMS (APCI) calc'd for $(C_{27}H_{30}N_3O_3^+)$ $[M]^+$, 444.2; found 444.2.



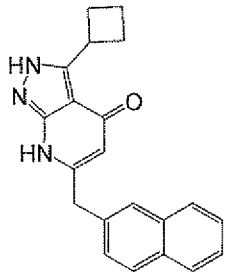
Step 4: 3-cyclobutyl-2,7-bis(4-methoxybenzyl)-6-(2-naphthylmethyl)-2,5,6,7 tetrahydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

To a slurry of 3-cyclobutyl-4-methoxy-2,7-bis(4-methoxybenzyl)-2*H*-pyrazolo[3,4-*b*]pyridin-7-ium. (1050 mg, 2.36 mmol) in THF (12 mL) at room temperature was added bromo(2-naphthylmethyl)magnesium (28.4 mL, 7.1 mmol, 0.5M in THF). The reaction was stirred at room temperature for 1h. The reaction was diluted with ethyl acetate and extracted with water followed by brine. The organic layer was dried with sodium sulfate, filtered, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate in hexanes (0-20%) to afford 3-cyclobutyl-2,7-bis(4-methoxybenzyl)-6-(2-naphthylmethyl)-2,5,6,7-tetrahydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one. LRMS (APCI) calc'd for ($C_{37}H_{38}N_3O_3^+$) $[M+H]^+$, 572.3; found 572.3.



Step 5: (3-cyclobutyl-6-(naphthalen-2-ylmethyl)-2,5,6,7-tetrahydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

To a solution of 3-cyclobutyl-2,7-bis(4-methoxybenzyl)-6-(2-naphthylmethyl)-2,5,6,7-tetrahydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one (617 mg, 1.1 mmol) in TFA (5 mL) was heated to 80 °C for 8h. The reaction was evaporated and the residue was dissolved with ethyl acetate and extracted with saturated aqueous sodium bicarbonate followed by brine. The organic layer was dried with sodium sulfate, filtered, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel eluting with ethylacetate in hexanes(10-100%) followed by MeOH in CH_2CL_2 (0-2%) to afford 3-cyclobutyl-6-(naphthalen-2-ylmethyl)-2,5,6,7-tetrahydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-oneas racemate. LRMS (APCI) calc'd for ($C_{21}H_{22}N_3O^+$) $[M+H]^+$, 332.2; found 332.2.

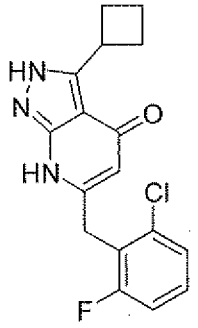
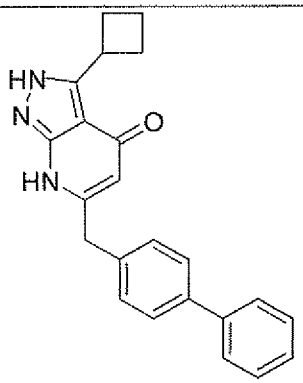
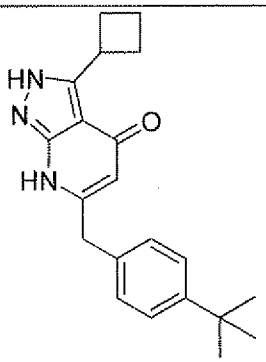
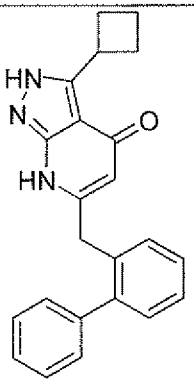


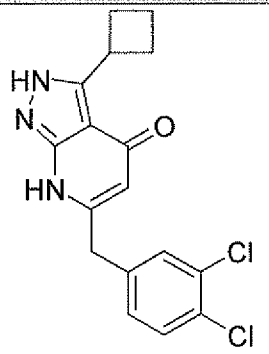
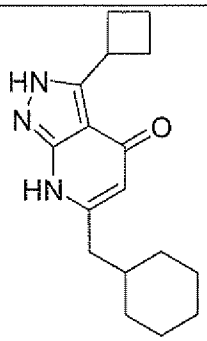
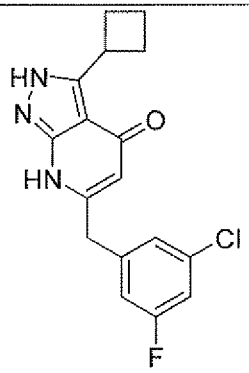
Step 6: 3-cyclobutyl-6-(2-naphthylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4- *b*]pyridin-4-one

To a solution of 5-{[2,6-dichloro-4-(1*H*-pyrazol-5-yl)phenyl]amino}-9-(3-hydroxy-3-methylbut-1-yn-1-yl)benzo[*c*]-2,6-naphthyridin-1(2*H*)-one (1000 mg, 3.02 mmol) in a mixture of MeOH/THF (8 mL) was added KOH (677 mg, 12.1 mmol) and stirred the reaction for 20 min at 40 °C. The reaction was cooled to RT and added bis(acetyloxy)(phenyl)-iodane (972 mg, 3.02 mmol) and the reaction was stirred at RT for 30 minutes. The reaction was evaporated and the residue was dissolved with ethyl acetate and extracted with water followed by brine. The organic layer was dried with sodium sulfate, filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica gel eluting with MeOH in CH_2Cl_2 (0-7%) to afford 3-cyclobutyl-6-(2-naphthylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one. Two tautomers were seen by H NMR. ^{1}H NMR (500 MHz, DMSO-D6) δ 13.18 (s, 0.6H), 12.75 (s, 0.4H), 11.64 (s, 0.6H), 11.40 (s, 0.4H), 7.88 – 7.75 (m, 4H), 7.50-7.38 (m, 3H), 6.30 (s, 0.4H), 5.53 (s, 0.6H), 4.17 (s, 0.8H), 4.04-3.88 (m, 1.8H), 3.88-3.78 (m, 0.4H), 2.42-2.30 (m, 2H), 2.30-

2.16(m, 2H), 2.02-1.88 (m, 1H), 1.84-1.78 (m, 1H). LRMS (APCI) calc'd for ($C_{21}H_{20}N_3O^+$) $[M+H]^+$, 330.2; found 330.1.

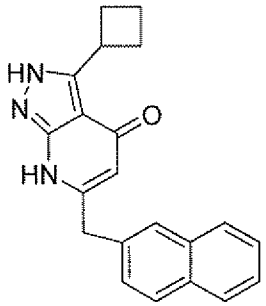
The following compounds were prepared utilizing the preceeding general methods which will be evident to those with ordinary skill in the art of organic synthesis.

Example	Structure	Name	LRMS (M+H)
2		6-(2-chloro-6-fluorobenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one	Calc'd: 332.1, found: 332.0
3		6-(biphenyl-4-ylmethyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one	Calc'd: 356.2, found: 356.1
4		6-(4-*tert*-butylbenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one	Calc'd: 336.2, found: 336.1
5		6-(biphenyl-2-ylmethyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one	Calc'd: 356.2, found: 356.1

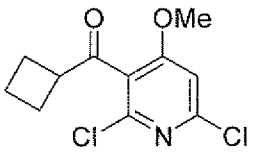
Example	Structure	Name	LRMS (M+H)
6		3-cyclobutyl-6-(3,4-dichlorobenzyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one	Calc'd: 348.1, found: 348.0
7		3-cyclobutyl-6-(cyclohexylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one	Calc'd: 286.2, found: 286.0
8		6-(3-chloro-5-fluorobenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one	Calc'd: 332.1, found: 332.0

Method B

Example 1

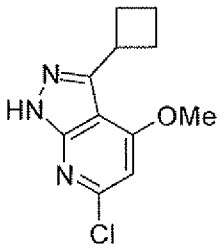


3-cyclobutyl-6-(2-naphthylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one



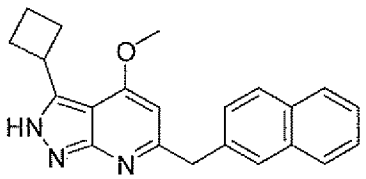
Step 1: cyclobutyl(2,6-dichloro-4-methoxypyridin-3-yl)methanone

0.84 M of lithium tetramethyl piperidine was prepared by adding n-BuLi (2.50 M in hexanes, 28.3 mL, 70.8 mmol) to tetramethyl piperidine (10g, 70.8 mmol) in THF (56 mL) at 0 °C under nitrogen dropwise. The solution was stirred for 30 minutes at 0 ^{0}C then LTMP was added dropwise (0.84 M, 84 mL, 70.2 mmol) to a solution 2,6 dichloro-4-methoxy pyridine (5g, 28.1 mmol) in THF (30 mL) at -78 °C under nitrogen. The solution was stirred for 1hr then methyl cyclobutanecarboxylate (4.8 g, 42 mmol) was added and the dry ice bath was removed and warmed to room temperature. The solution was quenched with MeOH and worked up with EtOAc and water, dried with $MgSO_4$, filtered, and concentrated to afford orange brown oil. Column chromatography on silica gel 100% Hex to 100% EtOAc afforded the product as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (s, 1H), 3.89 (s, 3H), 3.64 (m, 1H), 2.40 (m, 2H), 2.15 (m, 2H), 2.0 (m, 1H), 1.9 (m, 1H). LRMS (APCI) calc'd for ($C_{11}H_{12}Cl_2NO_2^+$) $[M+H]^+$, 260.0 ; found 260.0.



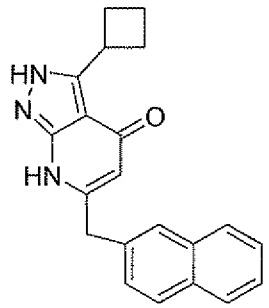
Step 2: 6-chloro-3-cyclobutyl-4-methoxy-2*H*-pyrazolo[3,4-*b*]pyridine

To as solution of cyclobutyl(2,6-dichloro-4-methoxypyridin-3-yl)methanone (3680 g, 14.2 mmol) in dioxane (25 mL) was added hydrazine (0.5 mL, 17 mmol) and heated to 140 °C overnight. The solution was concentrated to dryness and triturated with diethyl ether to afford 6-chloro-3-cyclobutyl-4-methoxy-2*H*-pyrazolo[3,4-*b*]pyridine as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.9 (s, 1H), 6.5 (s, 1H), 4.1 (s, 3H), 3.9 (t, 1H), 2.5-2.3 (m, 4H), 2.1 (m, 1H), 1.9 (m, 1H). LRMS (APCI) calc'd for ($C_{11}H_{13}N_3O^+$) $[M+H]^+$, 238.1 ; found 238.1.



Step 3: 3-cyclobutyl-4-methoxy-6-(2-naphthylmethyl)-2*H*-pyrazolo[3,4-*b*]pyridine

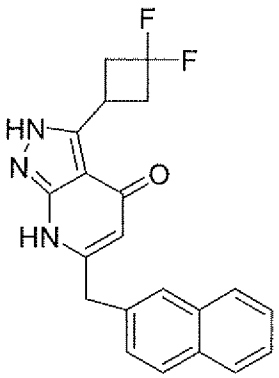
To a microwave vial under N_2 added $Pd(OAc)_2$ (14.2 mg, 0.021 mmol), S-Phos (17.3 mg, 0.042 mmol), dichloroethane(0.2 mL) and DMF (1.3 mL). The mixture was stirred for 20 min and added 6-chloro-3-cyclobutyl-4-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine (50 mg, 0.21 mmol) followed by bromo(2-naphthylmethyl)zinc (1.3 mL, 0.63 mmol, 0.5 M solution in THF). The reaction was stirred in a sealed tube at 80 °C for 16h. The reaction was filtered and purified by HPLC to afford 3-cyclobutyl-4-methoxy-6-(2-naphthylmethyl)-2*H*-pyrazolo[3,4-*b*]pyridine. LRMS (APCI) calc'd for ($C_{22}H_{22}N_3O^+$) $[M+H]^+$, 344.1; found 344.2.



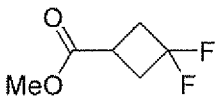
Step 4: 3-cyclobutyl-6-(2-naphthylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

To a solution of 3-cyclobutyl-4-methoxy-6-(2-naphthylmethyl)-2*H*-pyrazolo[3,4-*b*]pyridine (462 mg, 1.3 mmol) in a THF (5 mL) was added HCl (5 mL, 30 mmol, 6N HCl) and the reaction was stirred for 48 h at 100 °C. The reaction was diluted with ethyl acetate and extracted with saturated aqueous sodium bicarbonate followed by brine. The organic layer was dried with sodium sulfate, filtered, and the filtrate was evaporated. The residue was purified by HPLC to afford 3-cyclobutyl-6-(2-naphthylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one. Two tautomers were seen by ^{1}H NMR. ^{1}H NMR (500 MHz, DMSO-D6) δ 13.18 (s, 0.6H), 12.75 (s, 0.4H), 11.64 (s, 0.6H), 11.40 (s, 0.4H), 7.88 – 7.75 (m, 4H), 7.50-7.38 (m, 3H), 6.30 (s, 0.4H), 5.53 (s, 0.6H), 4.17 (s, 0.8H), 4.04-3.88 (m, 1.8H), 3.88-3.78 (m, 0.4H), 2.42-2.30 (m, 2H), 2.30-2.16(m, 2H), 2.02-1.88 (m, 1H), 1.84-1.78 (m, 1H). LRMS (APCI) calc'd for ($C_{21}H_{20}N_3O^+$) $[M+H]^+$, 330.2; found 330.1.

Example 9

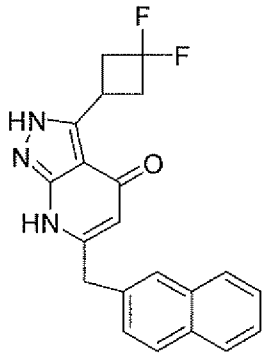


3-(3,3-difluorocyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one



Step 1: methyl 3,3-difluorocyclobutanecarboxylate

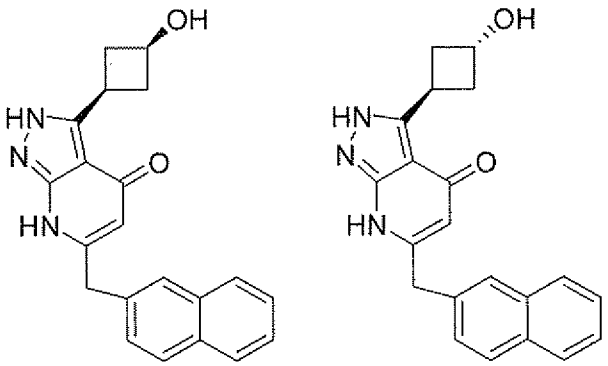
To a solution of 3,3-difluorocyclobutanecarboxylic acid (3000 mg, 22.0 mmol) in 1:1 MeOH/Benzene (10 mL) was added TMS-diazomethane (13.2 mL, 26.5 mmol, 2.0 M in hexanes). The solution was stirred for 30 mintues followed by a few drops of acetic acid to quench the TMS-diazomethane. The solvents were evaporated under redcuded pressure to afford methyl 3,3-difluorocyclobutanecarboxylate a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.96 (m, 1H), 2.80 (m, 4H).



Step 2: 3-(3,3-difluorocyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

3-(3,3-difluorocyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one was synthesized using Method B with methyl 3,3-difluorocyclobutanecarboxylate. LRMS (APCI) calc'd for ($C_{21}H_{18}F_2N_3O^+$) $[M+H]^+$, found 366.1.

Example 10 and 11

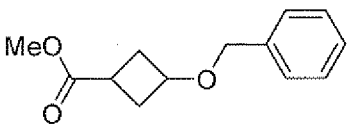


10 11

3-(*trans*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

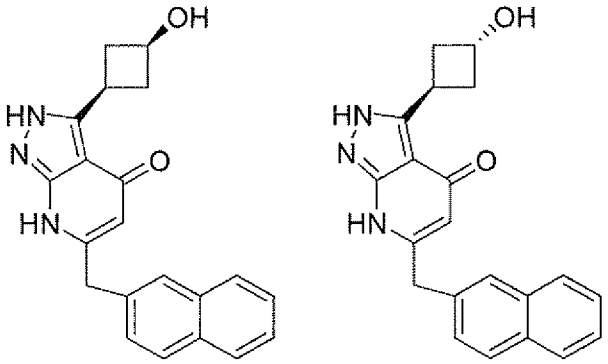
and

3-(*cis*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one



Step 1: methyl 3-(benzyloxy)cyclobutanecarboxylate

To a solution of 3-(benzyloxy)cyclobutanecarboxylic acid (3000 mg, 14.5 mmol) in MeOH (3 mL) and benzene (3 mL) at 0 °C was added trimethyl silyl diazomethane (2.0M in hexanes, 8.0 mL, 16 mmol) dropwise. The solution was concentrated to dryness to afford a yellow oil (mixture of cis/trans isomers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.42 (br s, 2H), 4.30 (m, 0.5H), 3.96 (m, 0.5H), 3.70 (br s, 3H), 3.04 (m, 1H), 2.62 (m, 1H), 2.50 (m, 2H), 2.30 (m, 2H). LRMS (APCI) calc'd for ($C_{13}H_{17}O_3^+$) $[M+H]^+$, 221.1; found 221.1



10 11

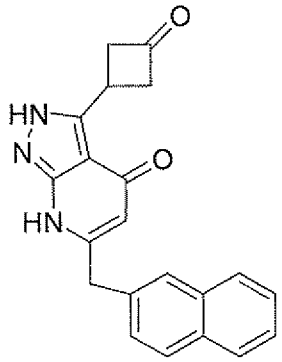
Step 2: 3-(*trans*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

and

3-(*cis*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

3-(*trans*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one and 3-(*cis*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one was synthesized using Method B and methyl 3-(benzyloxy)cyclobutanecarboxylate. The stereoisomers were seperated on silica gel column chromatography 100% CH_2Cl_2 to 90% CH_2Cl_2/10% MeOH. Cis : ^{1}H NMR (500 MHz, CD_3OD) δ 7.80-7.76 (m, 3H), 7.72 (s, 1H), 7.44-7.40 (m, 2H), 7.38 (m, 1H), 5.80 (s, 1H), 4.20 (m, 1H), 4.10 (s, 2H), 3.50 (m, 1H), 2.74 (m, 2H), 2.26 (m, 2H). LRMS (APCI) calc'd for ($C_{21}H_{20}N_3O_2^+$) $[M+H]^+$, 346.1; found 346.1. Trans: 7.80-7.76 (m, 3H), 7.72(s, 1H), 7.46 (m, 2H), 7.7.38 (m, 1H), 5.80 (s, 1H), 4.46(m, 1H), 4.10 (s, 2H), 2.64 (m, 2H), 2.40 (m, 2H). LRMS (APCI) calc'd for ($C_{21}H_{20}N_3O_2^+$) $[M+H]^+$, 346.1; found 346.1.

Example 12



6-(naphthalen-2-ylmethyl)-3-(3-oxocyclobutyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one

To a solution of 3-(*trans*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one (25 mg, 0.072 mmol) in DMF (1 mL) and THF (1 mL) was added Dess-Martin Periodinane (61 mg, 0.15 mmol) and stirred for 2hr. The solution was concentrated to dryness and purified by reverse phase HPLC to afford 6-(naphthalen-2-ylmethyl)-3-(3-oxocyclobutyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one. ^{1}H NMR (500 MHz, MeOD) δ 7.82 (m, 5H), 7.46 (m, 2H), 6.22 (s, 1H), 4.34 (s, 2H), 4.06 (m, 1H), 3.52 (m, 4H). LRMS (APCI) calc'd for ($C_{21}H_{18}N_3O_2^+$) $[M+H]^+$, 344.1; found 344.1.

The utility of the compounds in accordance with the present invention as inhibitors of CDK5 may be demonstrated by methodology known in the art. Enzyme inhibition may be determined as follows.

CDK5-p25 Kinase Enzymatic Assay

CDK5-p25 kinase (Invitrogen PV4677) enzymatic activity was measured using electrophoretic separation and fluorescent detection to monitor phosphorylation of a fluorescently labeled histone H1-derived peptide substrate, FL29 (5-FAM-GGGPATPKKAKKL-CONH2, Caliper #760429)

First, 0.25 uL of serially diluted compound in DMSO at 100 X concentration was transferred into each well of a 384-well polystyrene assay plate. To this was added 15 uL of a 1.67X enzyme

solution (500 pM enzyme, 1 mM DTT (Sigma D9779), 1 X reconstitution buffer with protease inhibitor (Caliper #700329 proprietary formulation)), followed by centrifugation for 1 min at 1000 rpm, and incubation for 5-15 min at room temperature to allow binding of compound to enzyme. To initiate the reaction, 10 uL of substrate/ATP mix (245 mM Hepes pH 7.5, 0.003 % Brij 35, 0.004 % Tween, 12.75 uM ATP, 3.75 uM FL29 peptide) were added to each well, followed by centrifugation at 1000 rpm for 1 min. The reaction was then incubated at room temperature for 30 min. Final assay conditions were: 0.3 nM CDK5-p25, 1.5 uM peptide, 5 uM ATP, 0.6 mM DTT, 1% DMSO, 98 mM HEPES pH 7.5.

After incubation, reactions were quenched by the addition of 45 uL Caliper termination solution (Caliper proprietary formula), followed by centrifugation at 1000 rpm for 1 min. Extent of reaction (percentage conversion of substrate to phosphorylated product) was then measured using the Caliper EZ II reader. Dose-response curves were created by plotting the inhibition of enzyme activity (normalized relative to vehicle treated and no ATP control reactions) as a function of the log of compound concentration. The curve was analyzed using a four parameter logistical fit to calculate IC_{50} values.

The IC50 potencies of the exemplary compounds of the invention were evaluated by the CDK5-p25 kinase enzymatic assay, as shown below:

Example	<50 nM	50 nM – 99 nM	100 nM – 499 nM	500 nM – 3 μM
1	X			
2			X	
3		X		
4		X		
5			X	
6	X			
7			X	
8	X			
9				X
10	X			

Example	<50 nM	50 nM – 99 nM	100 nM – 499 nM	500 nM – 3 μM
11				X
12	X			

CDK5 Tau S235 Phosphorylation Assay in Rat Primary Cortical Neurons

Primary rat cortical neurons were plated at a density of 6000 cells/well in 384-well black/clear bottom Poly D-Lysine coated BD Falcon Biocoat plates using Neurobasal media supplemented with 1X B27 + 2mM L-glutamine and 10% FBS. Cells were maintained at 37°C and 5% CO_2 for 6 days in culture, with a one-half volume media change every 3-4 days. Prediluted compound in medium was added to cells in media at 1:5 dilution to create a 3-fold serial dilution series with 0.5% final DMSO concentration. Cells were incubated with compound for a total of 120 min at 37°C. After compound treatment, cells were washed with phosphate buffered saline (PBS), fixed 30 min at room temperature with 1% PFA diluted in PBS, and then washed three times again with PBS. Next, cells were permeabilized and blocked 1 hr at room temperature using 0.1 % Triton X-100 and 5 % normal goat serum. After permeabilization, the cells were washed 3X with PBS before incubation at 4°C overnight with mouse anti-tau-3R (Upstate 05-803) (1:1000 final) and rabbit anti-tau-pS235 (ABR 38719) (1:500 final). The next day, cells were washed 4X with PBS and further incubated in the dark for 1 hr at room temperature with AlexaFluor goat anti mouse 488 (1:1000 final), AlexaFluor goat anti rabbit 594 (1:1000 final), and Hoechst 33342 dye (1:10000 final). Cells were washed 4X with PBS while protected from light and then imaged on an INCell Analyzer 1000 using a 10X objective. The phospho-S235 tau signal was calculated by measuring the average phospho-S235 signal for all cells expressing tau. The percentage inhibition of the pS235 signal relative to DMSO-treated controls was plotted as a function of the log of the compound dose and IC_{50} values were calculated using a four parameter logistical fit of the data.

The compounds of the invention also demonstrated binding in off-target assays to the tau phosphorylation kinases GSKβ and CDK2.

Several methods for preparing the compounds of this invention are illustrated in the schemes and examples herein. Starting materials are made according to procedures known in the art or as illustrated herein. The following examples are provided so that the invention might be

more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

The following abbreviations are used throughout the text:

Me: methyl

Et: ethyl

t-Bu: *tert*-butyl

Ar: aryl

Ph: phenyl

Bn: benzyl

Ac: acetyl

Dba: dibutylamine

THF: tetrahydrofuran

DCE: 1,1-dichloroethene

DCM: dichloromethane

LTMP:lithium tetramethyl piperidine

TMS: trimethylsilyl

EDC: 1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide

HOBt: 1-Hydroxybenzotriazole

rt: room temperature

HPLC: high performance liquid chromatography

X-Phos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

TFA: trifluoroacetic acid

DMF: N,N-dimethylformamide

DMSO: dimethylsulfoxide

NEt_3: triethylamine

Dess Martin Periodinane: 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one

S-Phos:

2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

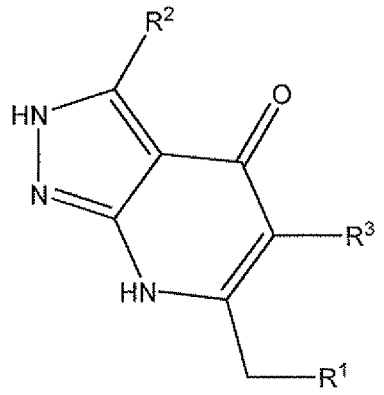
$Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium(0)

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the

invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein R^1 is selected from the group consisting of

(1) $-C_{6-10}$ aryl, optionally substituted with one or more fluoro, or

(2) $-C_{3-8}$ cycloalkyl,

wherein said alkyl or aryl is optionally substituted with one or more

(a) halogen,

(b) $-C_{6-10}$ aryl,

(c) $-C_{1-6}$ alkyl;

R^2 is selected from the group consisting of

(1) $-C_{3-8}$ cycloalkyl, or

(2) a heterocyclic group having 4 to 8 ring atoms selected from C, (C=O), N, O or S, wherein at least one ring atom is a heteroatom selected from N, O or S,

wherein said cycloalkyl and heterocyclic are selected from the group consisting of

(a) halogen,

(b) hydroxyl;

R^3 is selected from the group consisting of

(1) hydrogen, or

(2) $-C_{1-6}$ alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein R^1 is phenyl or naphthyl, optionally substituted with one or more

(a) halogen,

(b)–C_{6-10} aryl, or

(c)–C_{1-6} alkyl.

3. A compound of claim 1 or 2, wherein R^1 is–C_{3-8} cycloalkyl, which is optionally substituted by one or more

(a) halogen,

(b)–C_{6-10} aryl, or

(c)–C_{1-6} alkyl.

4. A compound of any of claims 1 to 3, wherein R^2 is C_{3-8} cycloalkyl, which is optionally substituted with one or more

(a) halogen, or

(b) hydroxyl.

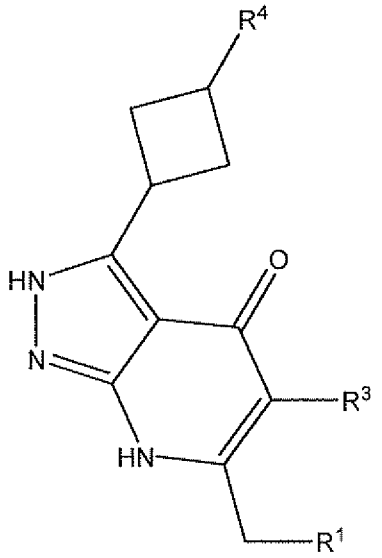
5. A compound of any of claims 1 to 3, wherein R^2 is a heterocyclic group having 4 to 8 ring atoms selected from C, (C=O), N, O or S, wherein at least one ring atom is a heteroatom selected from N, O or S, wherein the heterocyclic group is optionally substituted with one or more

(a) halogen, or

(b) hydroxyl.

6. A compound of any of claims 1 to 5, wherein R^3 is hydrogen.

7. A compound of claim 1, wherein the compound of formula (I) is a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of

(a) halogen, or

(b) hydroxyl.

8. A compound of claim 7, wherein R^1 is phenyl or napthyl, which is optionally substituted by one or more

(a) halogen,

(b) $-C_{6-10}$ aryl, or

(c) $-C_{1-6}$ alkyl.

9. A compound of claim 7, wherein R^1 is C_{3-8} cycloalkyl, which is optionally substituted by one or more

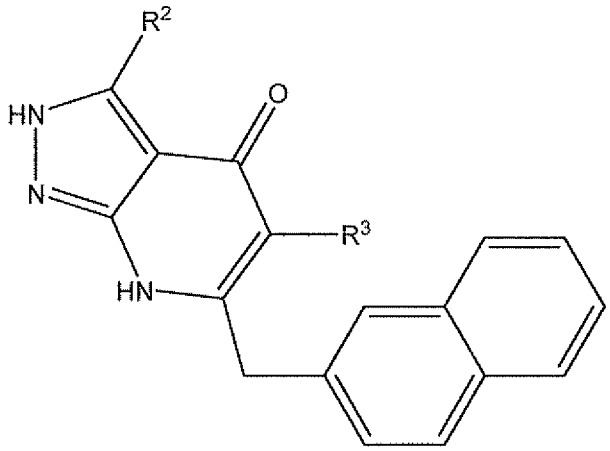
(a) halogen,

(b) $-C_{6-10}$ aryl, or

(c) $-C_{1-6}$ alkyl.

10. A compound of any of claims 7 to 9, wherein R^3 is hydrogen.

11. A compound of claim 1, wherein the compound of formula (I) is a compound of formula (III):



(III)

or a pharmaceutically acceptable salt thereof.

12. A compound of claim 11, wherein R^2 is $-C_{3-8}$ cycloalkyl, which is optionally substituted with one or more

(a) halogen, or

(b) hydroxyl.

13. A compound of claim 11, wherein R^2 is a heterocyclic group having 4 to 8 ring atoms selected from C, (C=O), N, O or S, wherein at least one ring atom is a heteroatom selected from N, O or S, wherein the heterocyclic group is optionally substituted with one or more

(a) halogen, or

(b) hydroxyl.

14. A compound of any of claims 12 to 14, wherein R^3 is hydrogen.

15. A compound of claim 1, which is selected from the group consisting of:

3-cyclobutyl-6-(2-naphthylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(2-chloro-6-fluorobenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(biphenyl-4-ylmethyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(4-*tert*-butylbenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(biphenyl-2-ylmethyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

3-cyclobutyl-6-(3,4-dichlorobenzyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

3-cyclobutyl-6-(cyclohexylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;

6-(3-chloro-5-fluorobenzyl)-3-cyclobutyl-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;
3-(3,3-difluorocyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;
3-(*trans*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one;
3-(*cis*-3-hydroxycyclobutyl)-6-(naphthalen-2-ylmethyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one; and
6-(naphthalen-2-ylmethyl)-3-(3-oxocyclobutyl)-2,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one
or a pharmaceutically acceptable salts thereof.

16. A pharmaceutical composition which comprises a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. A method of treating Alzheimer's Disease in a patient, comprising the step of administering to the patient an effective amount of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof.

18. Use of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Alzheimer's Disease.

19. Use of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for the treatment of Alzheimer's Disease.

20. A method of treating a disease or disorder in which tau phophorylation kinases are implicated, comprising the step of administering to the patient an effective amount of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof.

21. Use of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease or disorder in which tau phophorylation kinases are implicated.

22. Use of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for the treatment of a disease or disorder in which tau phophorylation kinases are implicated.

23. Use of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt

thereof, for the treatment of cancer.

24. A method of treating a disease or disorder in which cell cycle regulation kinases are implicated, comprising the step of administering to the patient an effective amount of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof.

25. Use of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease or disorder in which cell cycle regulation are implicated.

26. Use of a compound of any of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for the treatment of a disease or disorder in which cell cycle regulation kinases are implicated.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/50689

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/542; A61K 31/53; A61P 35/00 (2010.01)
USPC - 514/222.8;514/243;544/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC-514/222.8;514/243;544/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-514/222.8;514/243;544/10 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT,PGPB,EPAB,JPAB); Google, USPC
Search terms used: bicyclic, pyrazole, pyridinone, kinase inhibitors, heterocyclic, pyrazolo pyridin-4-one

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,038,281 A (Denzel et al.) 26 July 1977 (26.07.1977), entire document esp. col. 1, ln 9-20 , col. 3, ln 42-45 , col. 7, ln 10, 12	1-3, 7-15
Y	US 3,891,630 A (Swett) 24 June 1975 (24.06.1975), entire document esp. col. 1, ln 24-30, 34, 39	1-3, 7-15
Y	US 2009/0137582 A1 Pettus et al. (Pettus) 28 May 2009 (28.05.2009), entire document esp. para[0038], [0042], [0021], [0269]	1-3, 7-15
Y	US 7,235,566 B2 Hickey et al. (Hickey et al) 26 June 2007 (26 June 2007), entire document esp. col. 3, ln 45-46, col. 5, ln 43-46	11-14

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 November 2010 (06.11.2010)	18 NOV 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/50689

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: Claims 4-6, 16-26
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.