NOVEL FUSED PYRIDINE COMPOUNDS AS CASEIN KINASE INHIBITORS

FIELD OF THE INVENTION

This invention relates generally to pharmaceutical agents useful in the treatment and/or prevention of diseases and disorders associated with the central nervous system. More particularly, the present invention comprises compounds for the treatment of a patient suffering from a disease or disorder ameliorated by inhibition of casein kinase I delta (CK1δ) or CK1 epsilon (CK1ε) activity through the administration of a series of substituted fused pyridine compounds. More specifically the invention relates to aryl substituted 5-membered heteroaryls substituted with optionally substituted (2,3-fusedpyridin-4-yls) and related analogs which are inhibitors of human CK1δ or CK1ε phosphorylation.

BACKGROUND OF THE INVENTION

The circadian clock links our daily cycles of sleep and activity to the external environment. Deregulation of the clock is implicated in a number of human disorders, including depression, seasonal affective disorder, and metabolic disorders. Circadian rhythms are controlled in mammals by the master clock located in the suprachiasmatic nucleus of the hypothalamus (Antle and Silver, Trends Neurosci 28: 145-151). At the cellular level, the molecular events behind clock cycling are described by the regular increase and decrease in mRNAs and proteins that define feedback loops, resulting in approximately 24 hour cycles. The suprachiasmatic nucleus is primarily regulated, or entrained, directly by light via the retinohypothalamic tract. The cycling outputs of the suprachiasmatic nucleus, not fully identified, regulate multiple downstream rhythms, such as those in sleep and awakening, body temperature, and hormone secretion (Ko and Takahashi, Hum Mol Gen 15: R271-R277.). Furthermore, diseases such as depression, seasonal affective disorder, and metabolic disorders, may have a circadian origin (Barnard and Nolan, PLoS Genet. 2008 May; 4(5): e1000040.).

Phosphorylation of circadian clock proteins is an essential element in controlling the cyclical rhythm of the clock. CK1ε and CK1δ are closely related Ser-Thr protein kinases that serve as key clock regulators as demonstrated by mammalian mutations in each that dramatically alter the circadian period. (Lowrey *et al.*, Science 288: 483-492). Therefore, inhibitors of CK1δ/ε have utility in treating

wherein said aryl, heteroaryl, cycloalkyl, and heterocycloalkyl of R^2 may be substituted with up to two substituents independently selected from halogen, OH, cyano, C_{1-6}alkyl, C(O)-O-C_{1-3}alkyl, or C_{1-6}alkyl-O-C_{1-6}alkyl,

and wherein any alkyl, cycloalkyl, and heterocycloalkyl of R^2 may be further substituted with oxo where valency allows;

Each R^3 is independently absent, C_{1-3}alkyl, halogen, oxo, -NR^5R^6, or –OR^5;

Each R^4 is independently halogen, -CF_3, C_{1-3}alkyl, -$(CH_2)_t$-C_{3-4}cycloalkyl, -$(CH_2)_t$-O-C_{1-3}alkyl, -$(CH_2)_t$-cyano, or -$(CH_2)_t$-hydroxy;

Each R^5 is independently H or C_{1-6}alkyl;

Each R^6 is independently H or C_{1-6}alkyl;

R^7 is H, halogen, or C_{1-3}alkyl;

n is 0, 1, or 2;

Each t is independently 0, 1 or 2;

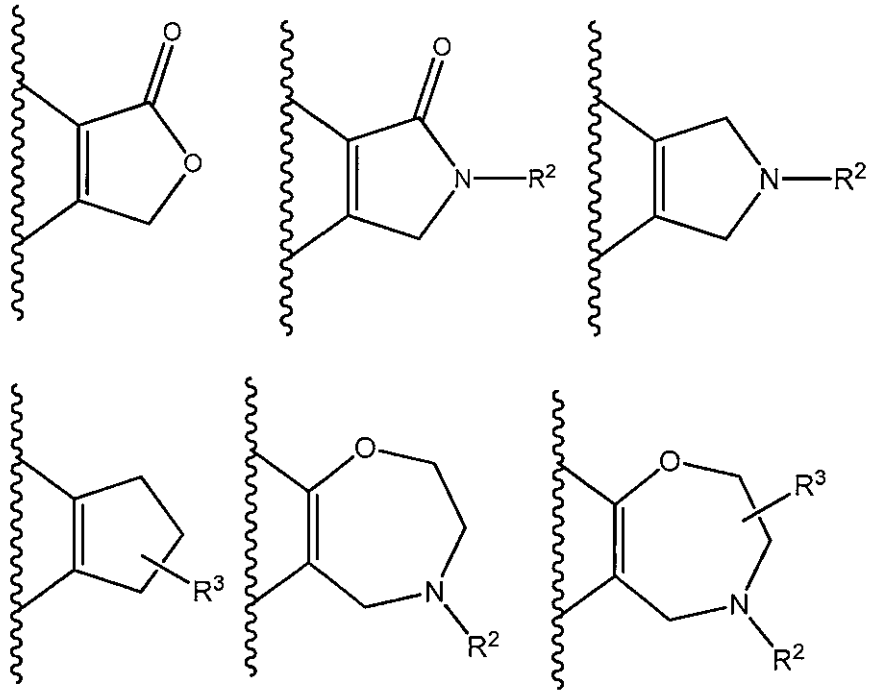
Each u is independently 0 or 1;

and pharmaceutically acceptable salts thereof.

This invention also includes pharmaceutically acceptable salts, hydrates, solvates, isomers, crystalline and non-crystalline forms, isomorphs, polymorphs, and metabolites of compounds of Formula I. This invention also includes all tautomers and stereochemical isomers of these compounds.

This invention relates generally to pharmaceutical agents and pharmaceutically acceptable salts thereof useful in the treatment and/or prevention of diseases and disorders associated with the central nervous system. More particularly, the present invention comprises compounds for the treatment of a patient suffering from a disease or disorder ameliorated by inhibition of CK1δ or CK1ε activity through the administration of a series of substituted fused pyridine compounds of Formula I.

When introducing elements of the present invention or the exemplary embodiment(s) thereof, the articles “a,” “an,” “the” and “said” are intended to mean that there are one or more of the elements. The terms “comprising,” “including” and “having” are intended to be inclusive and mean that there may be additional elements other than the listed elements. Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be



wherein R^2 and R^3 are as defined for embodiment of Formula I or any group of definitions described herein, with the understanding that there can be as many R^3 substituents as valency allows although only one is drawn above for simplicity. Furthermore, when there is no substitution on a carbon of A, then R^3 is absent.

Another embodiment of compounds of Formula I includes compounds where A of Formula I is substituted on an available nitrogen by R^2 wherein R^2 is independently H, $-CH_3$, or SO_2CH_3; and where A of Formula I is substituted on an available carbon by R^3 wherein R^3 is independently absent or oxo. Another embodiment is where A of Formula I is further substituted on at least one carbon with R^3 as described herein of any embodiment of Formula I.

Another embodiment of the invention includes compounds of Formula I wherein X is NR^1 where R^1 is C_{1-4} alkyl or C_{3-4}cycloalkyl; Y is CR^1 where R^1 is H or CH_3; A a lactone, lactam, or isoindolinyl substituted as allowed in any embodiment of Formula I; R^4 is F, and R^7 is H. Using moieties for A, another way to present this embodiment of the invention is wherein X is NR^1 where R^1 is C_{1-4} alkyl or C_{3-4}cycloalkyl; Y is CR^1 where R^1 is H or CH_3; A is:

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-1-methyl-1H-pyrazolo[3,4-b]pyridine;

7-acetyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-7-(methylsulfonyl)-6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5,6,7,8-tetrahydro-1,6-naphthyridine;

ethyl 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-7,8-dihydro-1,6-naphthyridin-5(6H)-one; and

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-methyl-7,8-dihydro-1,6-naphthyridin-5(6H)-one; or as a pharmaceutically acceptable salt thereof.

In another embodiment, the invention relates to methods for inhibiting casein kinase 1 CK1 delta or CK1 epsilon activity in a patient comprising the administration of a therapeutically effective amount of an inhibitor of casein kinase1 CK1 delta or CK1 epsilon.

In another embodiment, the invention relates to methods of inhibiting casein kinase CK1 delta or CK1 epsilon activity which result in a lengthening of the circadian rhythm period.

In another embodiment, the invention relates to a method of treating or preparation of a medicament to treat a mood disorder or a sleep disorder comprising the administration of a therapeutically effective amount of an inhibitor of casein kinase1 CK1 delta or CK1 epsilon. In one embodiment, the invention relates to a method of treating a sleep disorder. In a further embodiment, the sleep disorder is a circadian rhythm sleep disorder. In yet another embodiment, the circadian rhythm sleep disorder is selected from the group consisting of shift work sleep disorder, jet lag syndrome, advanced sleep phase syndrome and delayed sleep phase syndrome.

In a further embodiment, the invention relates to a method of treating or preparation of a medicament to treat a mood disorder selected from the group

comprising administering a compound of Formula I to the mammal. The mammal is preferably a mammal in need of such treatment.

As examples, the invention provides a method for treating or preparation of a medicament to treat attention deficit/hyperactivity disorder, schizophrenia and Alzheimer's Disease.

In another embodiment the present invention provides methods of treating neurological and psychiatric disorders comprising: administering to a patient in need thereof an amount of a compound of Formula I effective in treating such disorders. The compound of Formula I is optionally used in combination with another active agent. Such an active agent may be, for example, an atypical antipsychotic, a cholinesterase inhibitor, Dimebon, or NMDA receptor antagonist. Such atypical antipsychotics include, but are not limited to, ziprasidone, clozapine, olanzapine, risperidone, quetiapine, aripiprazole, paliperidone; such NMDA receptor antagonists include but are not limited to memantine; and such cholinesterase inhibitors include but are not limited to donepezil and galantamine.

The invention is also directed to a pharmaceutical composition comprising a compound of Formula I, and a pharmaceutically acceptable carrier. The composition may be, for example, a composition for treating a condition selected from the group consisting of neurological and psychiatric disorders, including but not limited to: acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia, AIDS-induced dementia, vascular dementia, mixed dementias, age-associated memory impairment, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, including cognitive disorders associated with schizophrenia and bipolar disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine, migraine headache, urinary incontinence, substance tolerance, substance withdrawal, withdrawal from opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, and hypnotics, psychosis, mild cognitive impairment, amnestic cognitive impairment, multi-domain cognitive impairment, obesity, schizophrenia, anxiety, generalized anxiety disorder, social anxiety disorder,

gastrointestinal, for example, esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), gastric, 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, for example, kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and/or 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, for example, hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, pancreatic endocrine tumors (such as pheochromocytoma, insulinoma, vasoactive intestinal peptide tumor, islet cell tumor and glucagonoma);

bone, for example, 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, for example, neoplasms of the central nervous system (CNS), primary CNS lymphoma, skull cancer (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain cancer (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma);

reproductive system, for example, gynecological, 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,

SCLC), breast cancer, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, or a combination of one or more of the foregoing cancers.

In one embodiment of the present invention the non-cancerous conditions include such hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH).

As noted above, the compounds of the invention may be used in combination with one or more additional anti-cancer agents which are described below. When a combination therapy is used, the one or more additional anti-cancer agents may be administered sequentially or simultaneously with the compound of the invention. In one embodiment, the additional anti-cancer agent is administered to a mammal (e.g., a human) prior to administration of the compound of the invention. In another embodiment, the additional anti-cancer agent is administered to the mammal after administration of the compound of the invention. In another embodiment, the additional anti-cancer agent is administered to the mammal (e.g., a human) simultaneously with the administration of the compound of the invention.

The invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, which comprises an amount of a compound of Formula I, as defined above (including hydrates, solvates and polymorphs of said compound or pharmaceutically acceptable salts thereof), in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of anti-angiogenesis agents and signal transduction inhibitors and a pharmaceutically acceptable carrier, wherein the amounts of the active agent and the combination anti-cancer agents when taken as a whole is therapeutically effective for treating said abnormal cell growth.

Definitions

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; in one embodiment from one to twelve carbon atoms; in another embodiment, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including *n*-propyl and isopropyl), butyl (including *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl), pentyl, isoamyl, hexyl and the like. In some instances, the

more substituents, the one or more substituents, unless otherwise specified, are each bound to a carbon atom of the cycloalkyl group. The fused C_6-C_{10} aromatic ring or 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, or =O.

The term "aryl" refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term "aryl" may refer to substituents such as phenyl, naphthyl and anthracenyl. The term "aryl" also includes substituents such as phenyl, naphthyl and anthracenyl that are fused to a C_{4-10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4- to 10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such a fused aryl group is substituted with one more substituents, the one or more substitutents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused C_{4-10} carbocyclic or 4- to 10-membered heterocyclic ring may be optionally substituted with halogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, or =O. Examples of aryl groups include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as "phenalenyl"), and fluorenyl.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (i.e., heteroaryl or heterocycloalkyl) is indicated by the prefix "A-B-membered", wherein wherein A is the minimum and B is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, 5- to 8-membered heterocycloalkyl refers to a heterocycloalkyl containing from 5 to 8 atoms, including one or more heteroatoms, in the cyclic moiety of the heterocycloalkyl.

The term "hydrogen" refers to a hydrogen substituent, and may be depicted as -H.

The term "hydroxy" or "hydroxyl" refers to –OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents.

specified, are each bound to a heteroatom of the heterocycloalkyl group or to a carbon atom of the heterocycloalkyl group. The fused C_6-C_{10} aromatic ring or 5- to 10-membered heteroaromatic ring may be optionally substituted with halogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{1-6}alkoxy, or =O.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include but are not limited to: 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused ring substituents such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. In a group that has a heteroaryl substituent, the ring atom of the heteroaryl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heteroaryl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. The term "heteroaryl" also includes pyridyl *N*-oxides and groups containing a pyridine *N*-oxide ring.

Examples of single-ring heteroaryls and heterocycloalkyls include but are not limited to furanyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl,

isobenzothienyl (also known as "isobenzothiophenyl," "isothionaphthenyl," or "isobenzothiofuranyl"), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl, 1,4,2-benzoxazinyl, 2,3,1-benzoxazinyl, or 3,1,4-benzoxazinyl), benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl), tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl.

The term "heteroaryl" also includes substituents such as pyridyl and quinolinyl that are fused to a C_{4-10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused heteroaryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one or more substituents, the one or more substitutents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. The fused C_{4-10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, or =O.

Additional examples of heteroaryls and heterocycloalkyls include but are not limited to: 6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one, 6,7-dihydro-5H-pyrrolo[3,4-b]pyridyl, furo[3,4-b]pyridin-5(7H)-one, 2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine, 6,7-dihydro-5H-cyclopenta[b]pyridyl, 5,6,7,8-tetrahydro-1,7-naphthyridyl, furo[3,4-b]pyridin-7(5H)-one, 7,8-dihydro-1,7-naphthyridin-6(5H)-one, 5H-pyrrolo[3,4-b]pyridin-7(6H)-one, 7,8-dihydro-1,6-naphthyridin-5(6H)-one, 1H-pyrazolo[3,4-b]pyridyl, 5,6,7,8-tetrahydro-1,6-naphthyridyl, 2H-pyrazolo[4,3-b]pyridyl, 6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine, oxazolo[4,5-b]pyridyl, oxazolo[5,4-b]pyridyl, 3-1*H*-benzimidazol-2-one, (1-substituted)-2-oxo-benzimidazol-3-yl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, diazolonyl, *N*-substituted diazolonyl, 1-phthalimidinyl, benzoxanyl, benzo[1,3]dioxine, benzo[1,4]dioxine, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, 4,5,6,7-tetrahydropyrazol[1,5-a]pyridine, benzothianyl,

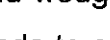
carbon (to the extent there are any) may separately and/or together be replaced with an independently selected optional substituent. If a nitrogen of a substituent is described as being optionally substituted with one or more of a list of substituents, one or more of the hydrogens on the nitrogen (to the extent there are any) may each be replaced with an independently selected optional substituent. One exemplary substituent may be depicted as –NR'R", wherein R' and R" together with the nitrogen atom to which they are attached may form a heterocyclic ring comprising 1 or 2 heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said heterocycloalkyl moiety may be optionally substituted. The heterocyclic ring formed from R' and R" together with the nitrogen atom to which they are attached may be partially or fully saturated, or aromatic. In one embodiment, the heterocyclic ring consists of 4 to 10 atoms. In another embodiment, the heterocyclic ring is selected from the group consisting of piperidinyl, morpholinyl, azetidinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl and thiazolyl.

This specification uses the terms "substituent," "radical," and "group" interchangeably.

If a group of substituents are collectively described as being optionally substituted by one or more of a list of substituents, the group may include: (1) unsubstitutable substituents, (2) substitutable substituents that are not substituted by the optional substituents, and/or (3) substitutable substituents that are substituted by one or more of the optional substituents.

If a substituent is described such that it "may be substituted" or as being optionally substituted with up to a particular number of non-hydrogen substituents, that substituent may be either (1) not substituted; or (2) substituted by up to that particular number of non-hydrogen substituents or by up to the maximum number of substitutable positions on the substituent, whichever is less. Thus, for example, if a substituent is described as a heteroaryl optionally substituted with up to 3 non-hydrogen substituents, then any heteroaryl with less than 3 substitutable positions would be optionally substituted by up to only as many non-hydrogen substituents as the heteroaryl has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) would be optionally substituted with up to one non-hydrogen substituent. To illustrate further, if an amino nitrogen is described as

included are complexes of Formula I containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J. Pharm. Sci., *64* (8), 1269-1288 by Haleblian (August 1975).

The compounds of Formula I may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of Formula I may be depicted herein using a solid line (——), a solid wedge (), or a dotted wedge (). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g. specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of Formula I may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. For example, unless stated otherwise, it is intended that the compounds of Formula I can exist as enantiomers and diastereomers or as racemates and mixtures thereof. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of Formula I and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

Stereoisomers of Formula I include cis and trans isomers, optical isomers such as R and S enantiomers, diastereomers, geometric isomers, rotational isomers, conformational isomers, and tautomers of the compounds of Formula I, including compounds exhibiting more than one type of isomerism; and mixtures thereof (such as racemates and diastereomeric pairs). Also included are acid addition or base addition salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate

compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound of Formula I with an acid whose anion, or a base whose cation, is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the methods of the present invention because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the compounds of this invention are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include but are not limited to aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include but are not limited to acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, stearate, salicylate, *p*-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate,

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above. The term "treating" also includes adjuvant and neo-adjuvant treatment of a subject.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

In another embodiment, the compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

In another embodiment, the compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. In another embodiment, the compounds of the invention can also be administered intranasally or by inhalation. In another embodiment, the compounds of the invention may be administered rectally or vaginally. In another embodiment, the compounds of the invention may also be administered directly to the eye or ear.

The dosage regimen for the compounds and/or compositions containing the compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regimen may vary widely. Dosage levels of the order from about 0.01 mg to about 100 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions. In one embodiment, the total daily dose of a compound of the invention (administered in single or divided doses) is typically from about 0.01 to about 100 mg/kg. In another embodiment, the total daily dose of the compound of the invention is from about 0.1 to about 50 mg/kg, and in another

of the active compounds. A compound of the invention may be coupled with suitable polymers as targetable drug carriers. Other pharmacologically active substances can also be present.

The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and compositions, for example, may be administered orally, rectally, parenterally, or topically.

Oral administration of a solid dose form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention. In another embodiment, the oral administration may be in a powder or granule form. In another embodiment, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of Formula I are ordinarily combined with one or more adjuvants. Such capsules or tablets may contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (i.e., water). Such compositions also may comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In another embodiment, the present invention comprises a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneal injections, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (i.e., sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing, wetting, and/or suspending agents.

In another embodiment, the present invention comprises a topical dose form. "Topical administration" includes, for example, transdermal administration, such as via transdermal patches or iontophoresis devices, intraocular administration, or

particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the present invention comprises a rectal dose form. Such rectal dose form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman *et al.*, Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe *et al.*, Eds., Handbook of Pharmaceutical Excipients (3^{rd} Ed.), American Pharmaceutical Association, Washington, 1999.

The compounds of the present invention can be used, alone or in combination with other therapeutic agents, in the treatment of various conditions or disease states. The compound(s) of the present invention and other therapeutic agent(s) may be administered simultaneously (either in the same dosage form or in separate dosage forms) or sequentially. An exemplary therapeutic agent may be, for example, a metabotropic glutamate receptor agonist.

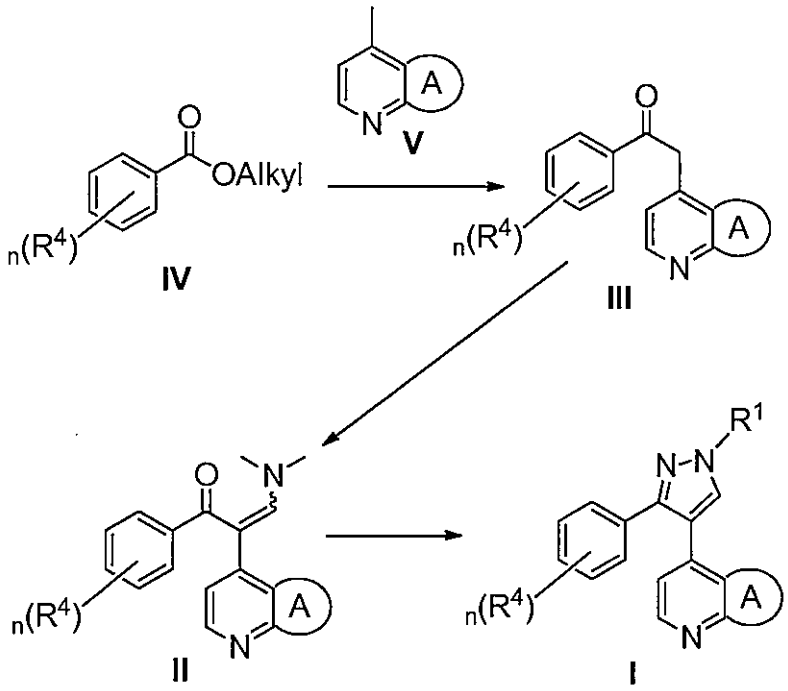
The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds may be administered simultaneously, concurrently or sequentially. Additionally, simultaneous administration may be carried out by mixing the compounds prior to

otherwise indicated, the substituents in the Schemes are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

It will be understood by one skilled in the art that the various symbols, superscripts and subscripts used in the schemes, methods and examples are used for convenience of representation and/or to reflect the order in which they are introduced in the schemes, and are not intended to necessarily correspond to the symbols, superscripts or subscripts in the appended claims. The schemes are representative of methods useful in synthesizing the compounds of the present invention. They are not to constrain the scope of the invention in any way.

Experimental Procedures and Working Examples

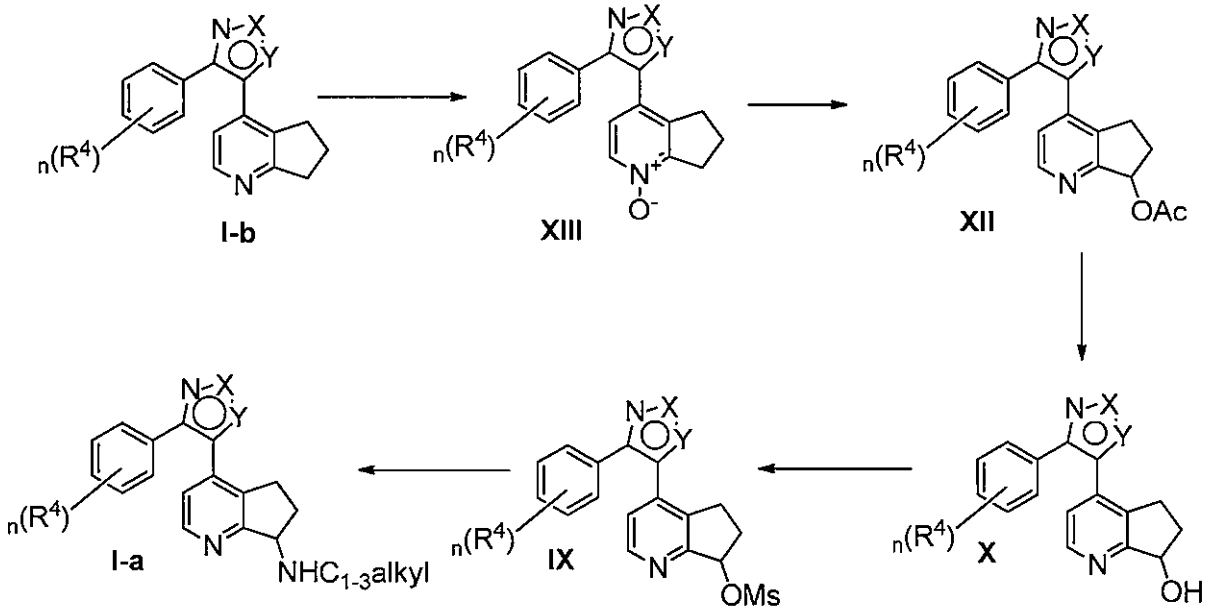
Scheme 1



Compounds of Formula **I** may be synthesized following the general procedure shown in Scheme 1. Picolines of formula **V** may be treated with suitably strong, non-nucleophilic bases such as LDA, NaHMDS or LiHMDS in tetrahydrofuran (THF) or ethyl ether and then reacted with benzoates of Formula **IV** to yield ketone **III**.

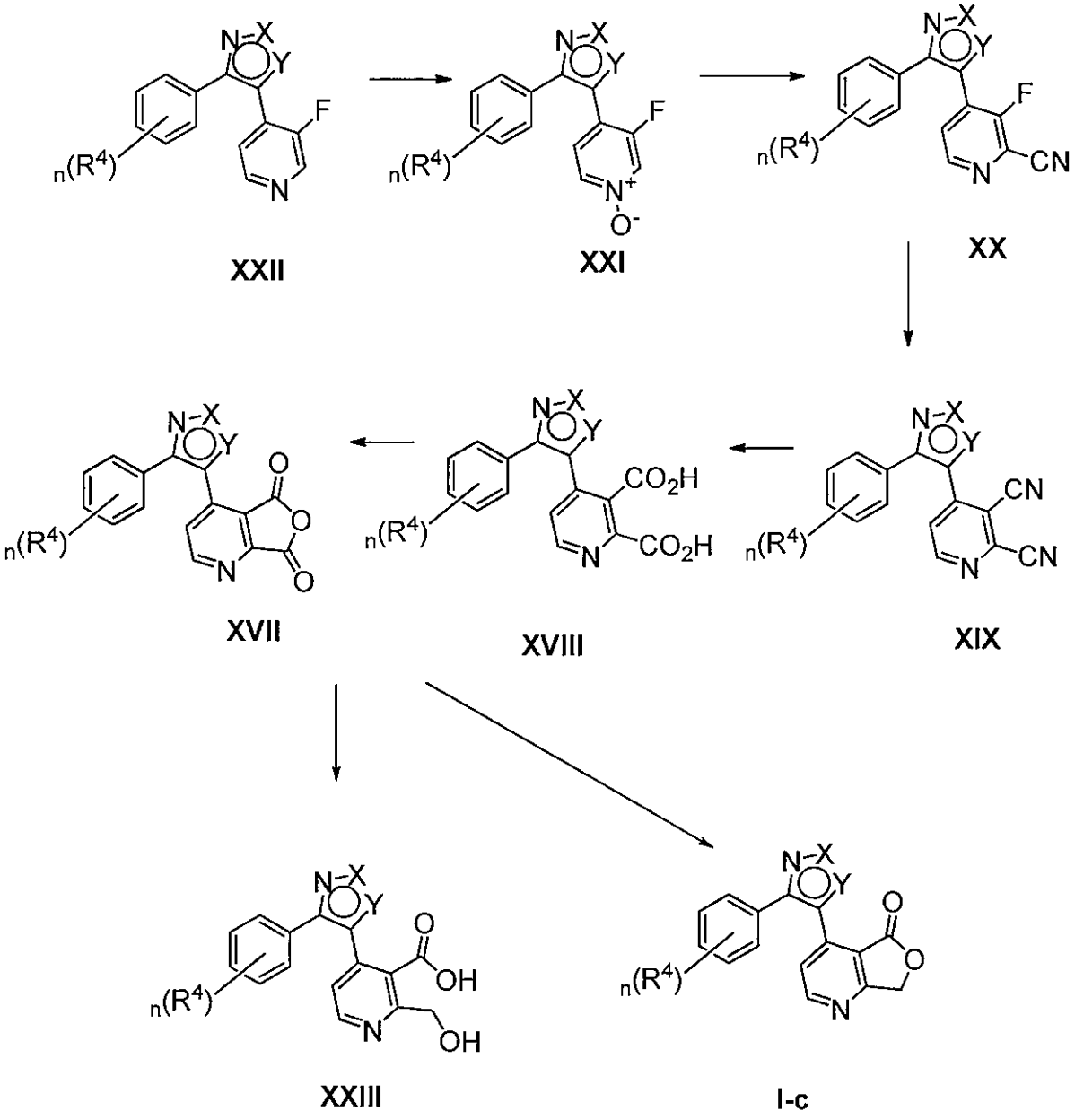
prepared from the corresponding halide **VIII** via coupling with bis(pinacolato)diboron in the presence of a palladium catalyst preferably $Pd(dppf)Cl_2$ in the presence of a base such as KF, K_2CO_3, K_3PO_4 or preferably Cs_2CO_3 in a polar solvent such as dimethyl acetamide or preferably dimethylformamide (DMF) at temperatures ranging from 50 °C to 120 °C where 80 °C -100 °C is preferred. The boronic acid or pinacol borane **VI** may be coupled with halide/triflate **VII** under standard palladium catalyzed cross-coupling reaction conditions well known to one of ordinary skill in the art to provide the compound of Formula I. [Suzuki, A., Journal of Organometallic Chemistry, 576, 147-169 (1999), Miyaura and Suzuki, Chemical Reviews, 95, 2457-2483 (1995).] More specifically, the aryl iodinate, bromate or triflate of Formula **VII** is combined with 1 to 3 equivalents of aryl pinacol borane and a suitable base, such as 2 to 5 equivalents of Cs_2CO_3, in a suitable organic solvent such as DMF. A palladium catalyst is added, such as 0.02 equivalents of tris(dibenzylidineacetone)dipalladium (0), and the reaction mixture is heated to temperatures ranging from 60 °C to 100 °C for 1 to 24 hr. The reaction is not limited to the employment of this solvent, base, or catalyst as many other conditions may be used.

Scheme 3



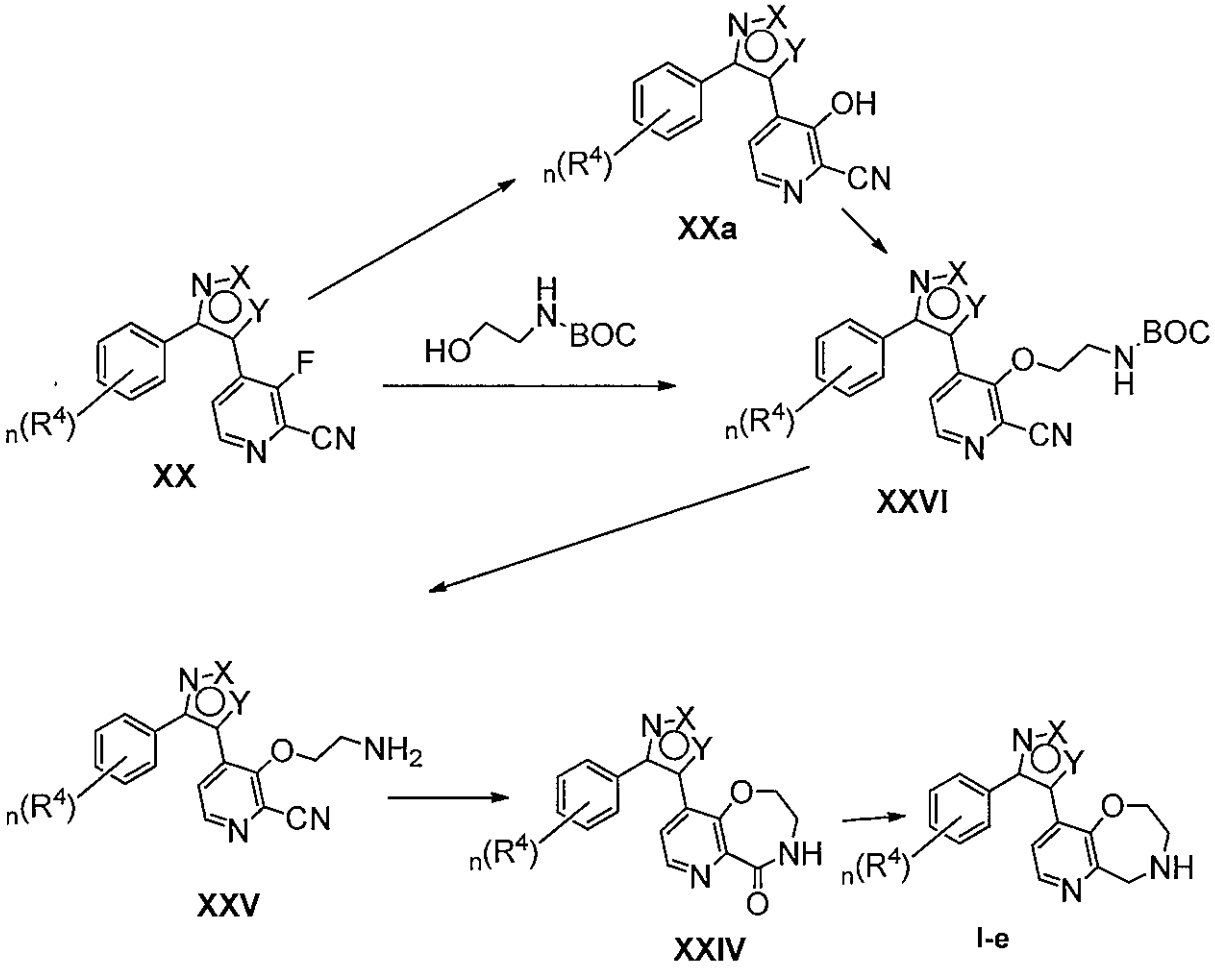
7-Amino-6,7-dihydro-5H-cyclopenta[b]pyridine of Formula I-**a** may be prepared as described in Scheme 3. Compound **I-b** (prepared following general procedures described in Schemes 1 or 2) may be converted to N-oxide **XIII** using

Scheme 4



reduction of **XVI** with zinc in acetic acid at 25 °C to 100 °C where 50 °C to 80 °C is preferred affords lactam of Formula **I-d**. **I-d** may also be prepared by stepwise reduction of **XVI** with hydride reagents such as sodium borohydride in alcoholic solvents such as MeOH to yield mixtures of alcohols of formula **XIV** and **XV**. These may be separated chromatographically and then **XIV** may be reduced further to afford **I-d** using a hydride source such as triethylsilane in a suitable strong acid such as trifluoroacetic acid (TFA) either neat or with CH_2Cl_2 as co-solvent. This transformation may be accomplished at from rt to reflux temperatures.

Scheme 5

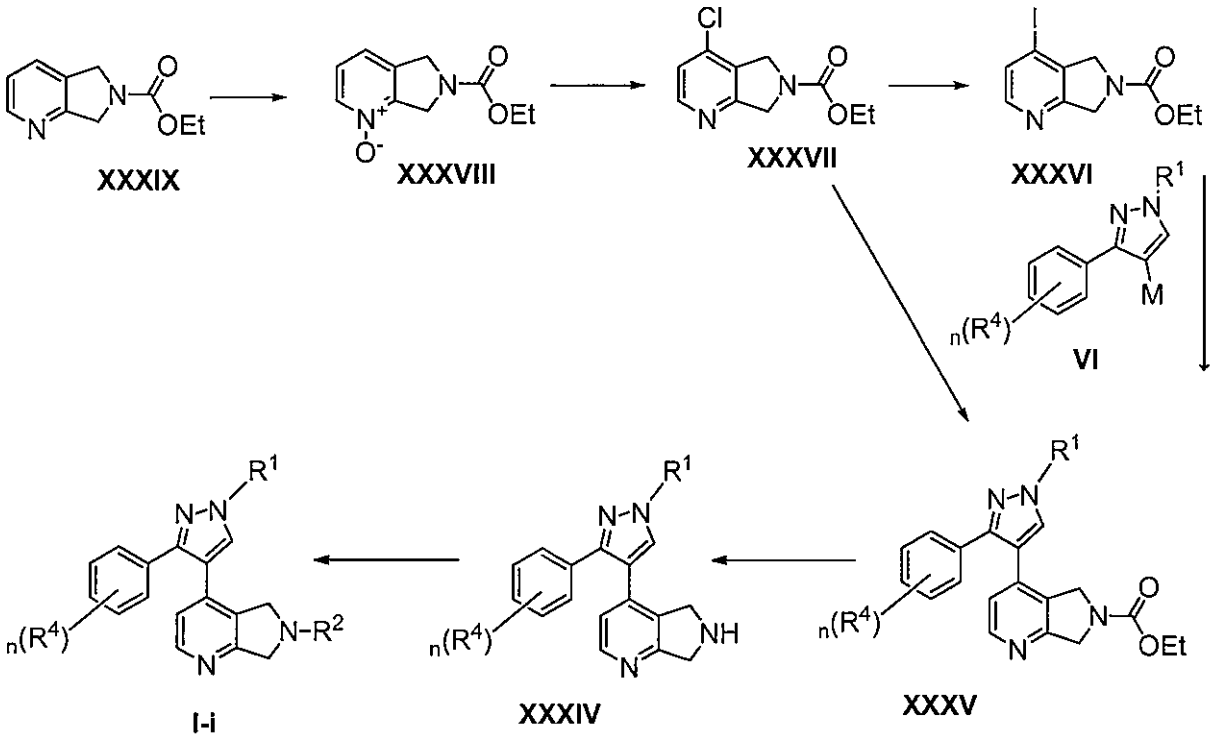


Oxazepine of Formula **I-e** is prepared as shown in Scheme 5. Fluorocyano compound **XX** is treated with the anion of N-Boc ethanolamine generated with lithium or sodium hexamethyldisilazide or preferably sodium hydride in a non-nucleophilic, non-reactive solvent such as THF or dioxane at temperatures ranging from 0°C to 50°C where 10 °C to 25 °C is preferred, to afford ether **XXVI**. Compound of formula **XXVI** may also be prepared by treatment of compound **XX** with 2-

inert solvent such as dimethylacetamide, 1-methyl-2-pyrrolidinone (NMP) or preferably DMF at from 0 °C to 50°C, preferably at rt. Intermediate **XXVIII** may be reacted further to provide compounds of Formula **I-f** following the general procedures described in Schemes 3-5.

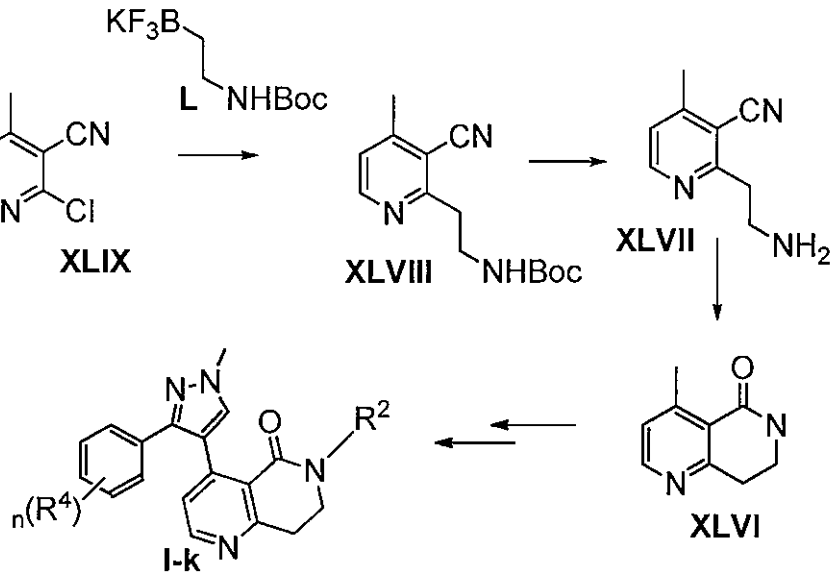
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Scheme 8



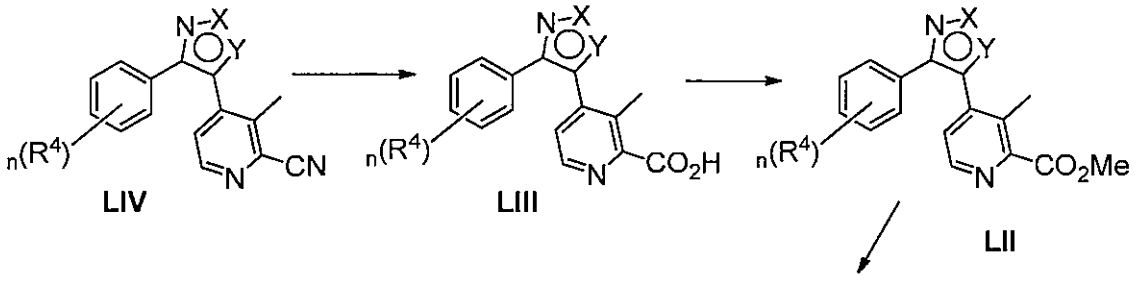
Compound of Formula **I-i** may be prepared as described in Scheme 8. Ethyl 5H-pyrrolo[3,4-b]pyridine-6(7H)-carboxylate **XXXIX** may be treated with an oxidizing agent such as *m*-chloroperbenzoic acid or hydrogen peroxide/ acetic acid to give N-oxide **XXXVIII**. Chlorination using phosphorus oxychloride or preferably oxalyl chloride in a suitably polar but inert solvent such as DMF or NMP at temperatures ranging from 0°C to 50°C where 0°C to rt is preferred gives a mixture of 2-chloro and 4-chloro (formula **XXXVII**) derived products. Intermediate **XXXVII** may be coupled with metallopyrazole **VI** following the general procedures described in Scheme 2 to afford compound of formula **XXXV**. Intermediate **XXXVII** may also be converted to the corresponding iodide **XXXVI** by refluxing in acetonitrile with sodium iodide. The iodide **XXXVI** may also be coupled with metallopyrazole **VI** following the general procedures described in Scheme 2 to afford compound of formula **XXXV**. Treatment of carbamate **XXXV** with aqueous potassium or sodium hydroxide in an alcohol solvent such as EtOH or MeOH at rt to reflux, where reflux is preferred, affords amine **XXXIV**. This material may be converted into N-alkyl amines, amides and sulfonamides of compounds of Formula **I-i**. For example, compounds of Formula **I-i** where R^2 is a substituted carbonyl (amide), may be prepared by coupling of substituted carboxylic acids with **XXXIV** using amide coupling agents where

Scheme 10



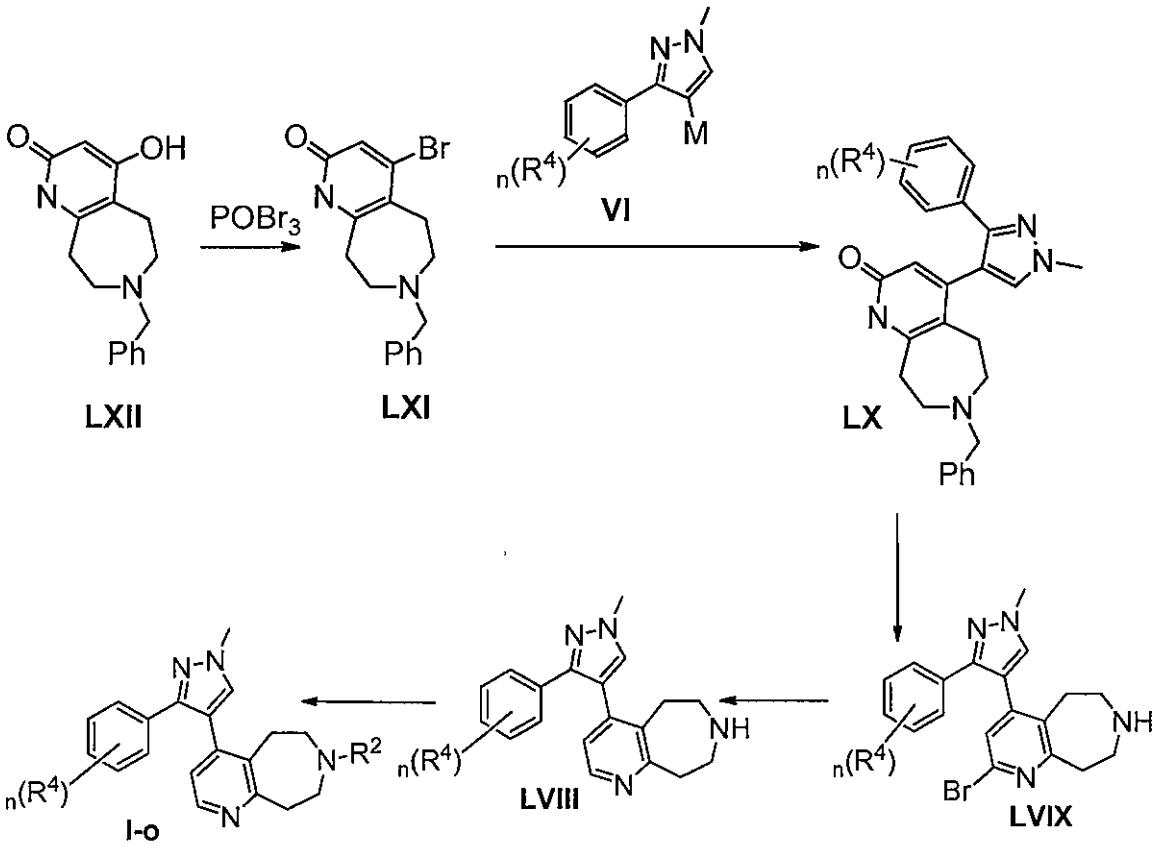
Lactam of Formula **I-k** is prepared as described in Scheme 10. Chlorocyanopicoline **XLIX** is treated with 1 to 2 equivalents of potassium trifluoroborate salt **L** in the presence of 2 to 5 equivalents of Cs_2CO_3 and a catalytic amount (0.01 to 0.10 equivalents) of $Pd(dppf)Cl_2$ in a mixture of toluene and water at temperatures from about 75 °C to about 125 °C in a sealed tube or by microwave heating to give compound **XLVIII**. Removal of the Boc protecting group with TFA, neat or in CH_2Cl_2 solution, or with HCl in MeOH or EtOH provides compound **XLVII** which may then be cyclized to form lactam **XLVI** by heating in aqueous NaOH from 50 °C to 100°C. Compound **XLVI** may be converted into compound of Formula **I-k** following the general procedures detailed in Scheme 1 that were used to prepare compound of Formula I.

Scheme 11



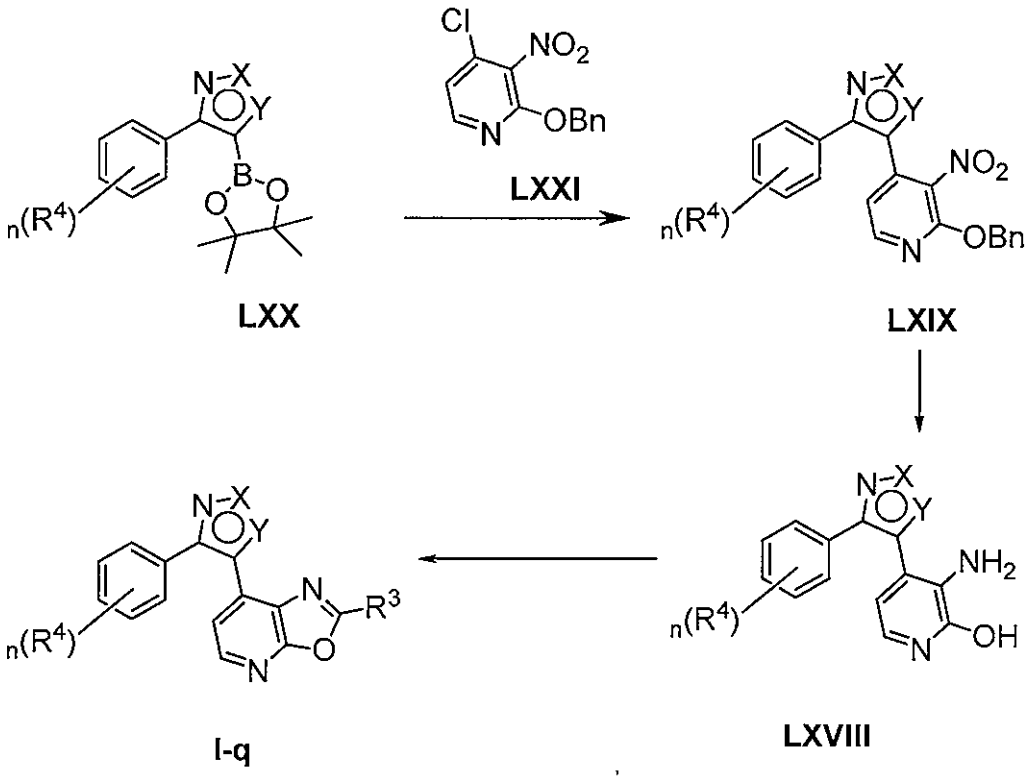
100 °C with 1 to 1.5 equivalents of lithium chloride in DMSO and 2 equivalents of water to give ester **LV**. Hydrogenolysis of **LV** in acetic acid with palladium on activated carbon gives lactam **I-m** which may be converted to compound of Formula **I-n** by treatment with hydride reducing agents such as borane-THF complex or lithium aluminum hydride in THF at from rt to reflux.

Scheme 13



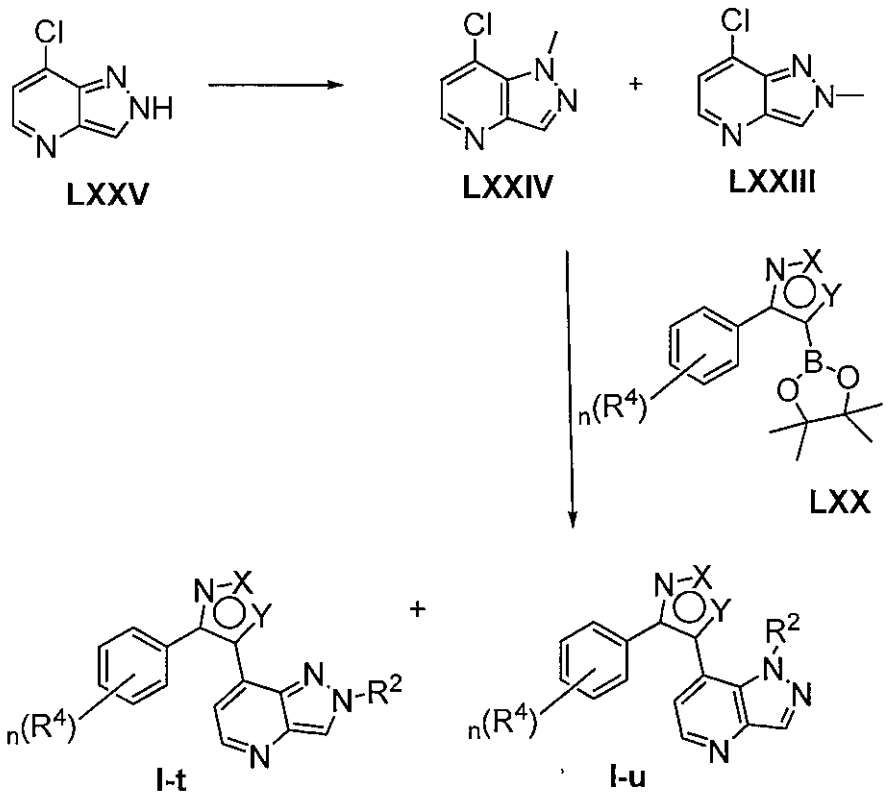
6,7,8,9-Tetrahydro-5H-pyrido[2,3-d]azepine of Formula **I-o** is prepared as shown in Scheme 13. Compound **LXII** (prepared following general procedures described in WO 2007140213 substituting N-benzyl-4-piperidone for N-Boc-4-piperidone) is treated with a brominating agent such as phosphorus tribromide or phosphorus oxybromide neat or in a suitably non-reactive solvent such as CH_2Cl_2 to yield compound **LXI**. Compound **LX** may be prepared with bromide **LXI** and pinacol borane of formula **VI** following the general procedures shown in Scheme 2. Conversion of **LX** to bromopyridine **LVIX** may be accomplished by reaction with a brominating agent such as phosphorus tribromide or phosphorus oxybromide neat or in a suitably non-reactive solvent such as CH_2Cl_2. Hydrodehalogenation to form compound of formula **LVIII** is performed by hydrogenation with Raney nickel or

Scheme 15



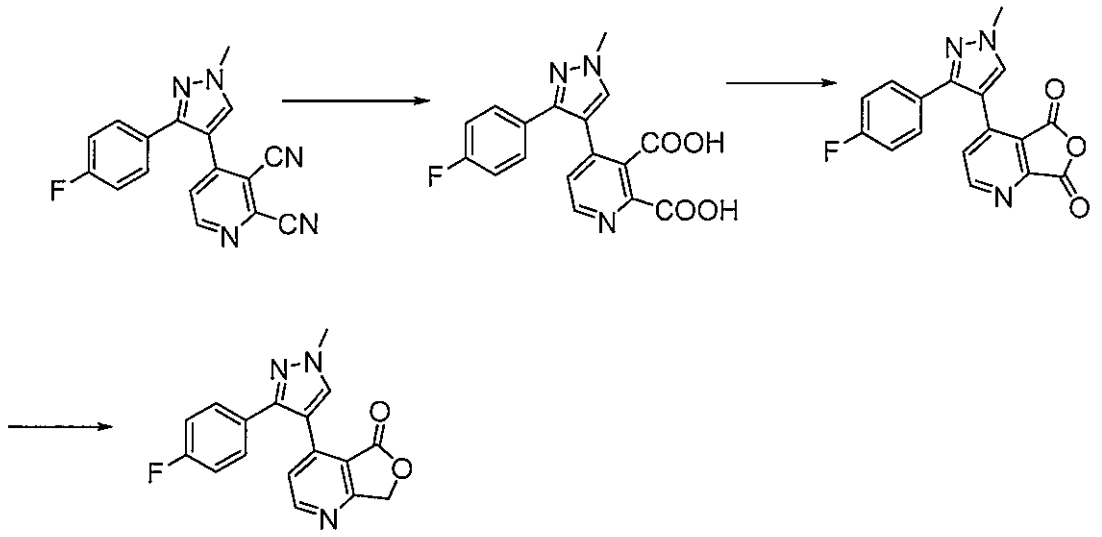
The regioisomeric oxazole **I-q** can be prepared as described in Scheme 15. Suzuki coupling of known chloropyridine **LXXI** (Bioorg.Med.Chem. Lett. 125 (2003)) with a boronate of type **LXX** (prepared following the general methods shown in Scheme 2) in the presence of a Pd(0) catalyst such as palladiumtetrakistriphenylphosphine(0) and a base such as potassium fluoride in a solvent such as MeOH at temperatures ranging from rt to 100 °C, preferably at reflux, will yield nitro derivative **LXIX**. Conversion of **LXIX** to the aminoalcohol **LXVIII** can be accomplished via hydrogenation in the presence of a suitable catalyst such as Pd on carbon or palladium hydroxide in solvents such as MeOH or EtOH. Finally condensation of **LXVII** with an appropriately R^3 substituted orthoformate as solvent in the presence of an acid such as toluene sulfonic acid will yield the desired target oxazolo[5,4-b]pyridine **I-q**.

Scheme 17



Compounds of Formula **I-t/I-u** can be prepared as described in Scheme 17. Alkylation of the known chloro-indazole **LXXV** (prepared as in EP151962) with appropriate alkylhalide or tosylate in the presence of a base such as sodium hydride or Cs_2CO_3, preferably Cs_2CO_3 in a solvent such as THF or DMF, preferably THF, at temperatures ranging from rt to reflux, preferably 50 °C, will yield regiosiomeric alkyl derivatives **LXXIII** and **LXXIV** which can be separated by either normal or reverse phase column chromatography methods. Suzuki coupling of **LXXIII** and **LXXIV** with boronates of type **LXX** in the presence of a Pd(0) catalyst such as bis dibenzylidenepalladium(0) and an added phosphine ligand such as tricyclohexylphosphine and base such as potassium phosphate in a solvent such as DMF at temperature ranging from rt to 120 °C, preferably at 100 °C to 120 °C, will yield compounds of Formula **I-t/I-u.**

The following illustrate the synthesis of various compounds of the present invention. Additional compounds within the scope of this invention may be prepared using the methods illustrated in these Examples, either alone or in combination with techniques generally known in the art.



Step 1: ***Preparation of 3-(4-fluorophenyl)-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole***

A solution of 4-bromo-3-(4-fluorophenyl)-1-methyl-1H-pyrazole (700 g, 2.74 mol) in THF (1.4 L) was cooled to 15 °C and isopropylmagnesium chloride lithium chloride complex (1.3M in THF, 3.8 L, 4.94 mol) was added slowly while maintaining the reaction temperature below 25 °C. The mixture was stirred for 3hr at 20 °C and a 10 °C solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (610 g, 3.28 mol) in THF (1.4L) was added added dropwise while maintaining an internal temperature below 20°C. The resulting green/brown hazy solution as stirred for 1hr between 10 °C and 20 °C after which time it was cooled to 10 °C. Water (5.6 L) cooled to 10 °C was added slowly to the reaction mixture so that the reaction temperature stayed below 25 °C. Celite (1.4 kg) was added followed by 2-methyltetrahydrofuran (7 L) and the mixture was stirred for 15 min at 20 °C. The mixture was filtered through Celite and the filter pad was rinsed with 2-methyltetrahydrofuran (8 L). The organic phase was separated and washed with brine (5.6 L) then concentrated under vacuum to a low stir volume. The material was diluted with EtOH (3 L) and reconcentrated. This material was re-dissolved in EtOH (3.5 L) and water (4.2 L) was added over 30 min with strong stirring. The resulting slurry was stirred at 15 °C for 1hr, filtered and washed with 4 volumes of water. The resulting cake was blown dry then further dried in a vacuum oven at 40 °C to yield 0.4 kg (48%) of Ex 1 - Step 1 product as a white solid: APCI MS m/z 303.2 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.9, 5.6, 2H), 7.70 (s, 1H), 7.03 (dd, *J* = 8.8, 8.8, 2H), 3.90 (s, 3H), 1.29 (s, 12H).

Heated a mixture of Ex 1 - Step 3 product (10.34 g, 34.1 mmol) and aqueous KOH (28.3 g, 504 mmol, dissolved in 100 mL water) at 100 °C for 24 hr. The mixture was cooled in ice to precipitate a thick white solid. The material was warmed back to rt, filtered and air dried to yield 12.47 g (88%) of Ex 1 - Step 4 product as a cream colored solid: LCMS m/z 342.1 (M+1).

Step 5: ***Preparation of 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]furo[3,4-b]pyridin-5(7H)-one, as a monohydrochloride*** Ex 1 - Step 4 Product (5.00 g, 12.0 mmol) was slurried with acetic acid (35 mL) and acetic anhydride (12.5 mL) and heated to 110 °C for 3hrs. The resulting homogeneous mixture was cooled and concentrated, slurried with 50 mL diethyl ether and re-concentrated to yield 4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)-6-methyl-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione as a sticky yellow solid. This material was slurried in THF (70 mL), sodium borohydride (568 mg, 15.0 mmol) was added and acetic acid (1.7 mL, 2.5 mmol) was added dropwise over one minute. After stirring for 90 min, the reaction was concentrated to a thick yellow paste, acetic acid (90 mL) and acetic anhydride (45 mL) were added and the mixture was heated at 110°C for two hr to give a homogeneous solution. The heat was removed and the mixture was stirred overnight at rt and concentrated. The residue was partitioned between EtOAc and water, the organics were separated organics,and the aqueous phase was re-extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to a thick yellow oil. Purification by silica gel chromatography eluting with 50% EtOAc/heptanes yielded 2.06 g (55%) of Ex 1 – Step 5 product as a waxy white solid. This material was dissolved in EtOAc (100 mL) and treated with 1.2 equivalents of 2 N HCl/diethylether to yield 1.91 g of Ex 1- Step 5 product as a yellow solid: MS (APCI) 310.0 m/z (M+1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, *J* = 5.3,1H), 8.17 (s, 1H), 7.32 (dd, *J* = 8.8, 5.5, 2H), 7.11 (dd, *J* = 9.0, 9.0, 2H), 7.08 (d, *J* = 5.0, 1H), 5.32 (s, 2H), 3.92 (s, 3H).

3-Fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinonitrile (see step 2) was also prepared via the following route:

of the crude product showed a mixture of two N-methyl pyrazole regiosomers which were separated by silica gel chromatography using a 1:1 mixture of heptanes and 7:2:1 heptane:diethylamine:MeOH for elution. Ex 1 – Step 8 product was isolated as a light yellow solid (900 mg, 60%): LCMS m/z 272.5 (M+1); ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.41 (d, *J* = 2.5, 1H), 8.20 (d, *J* = 5.1, 1H), 8.01 (d, *J* = 1.7, 1H), 7.39 (dd, *J* = 8.8, 5.3, (2H), 7.19 (dd, *J* = 6.7, 5.1, 1H), 7.09 (dd, *J* = 8.8, 8.8, 2H), 3.98 (s, 3H).

Step 9: Preparation of 3-fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)pyridine 1-oxide

Ex 1 – Step 8 product (900 mg, 3.32 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with *m*-chloroperbenzoic acid (85%, 1.35g, 6,64 mmol) and stirred at rt for 5 hr. The mixture was concentrated and purified by silica gel chromatography. The column was flushed with CH_2Cl_2 then 0-50% EtOAc/ CH_2Cl_2 and finally EtOAc, then the desired N-oxide was removed using 20% MeOH/EtOAc with 1% triethylamine. The desired N-oxide was obtained as a yellow oil (1.06 g, quantitative yield): LCMS m/z 288.5 (M+1); ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.42 (dd, *J* = 5.4, 1.7, 1H), 8.04-8.06 (ddd , *J* = 6.7, 1.8, 0.8,1H), 8.02 (d, *J* = 2.1, 1H), 7.42 (dd, *J* = 8.8, 5.3, 2H), 7.24 (dd, *J* = 8.7, 6.8, 1H), 7.12 (dd, *J* = 8.7, 8.7, 2H), 3.97 (s, 3H).

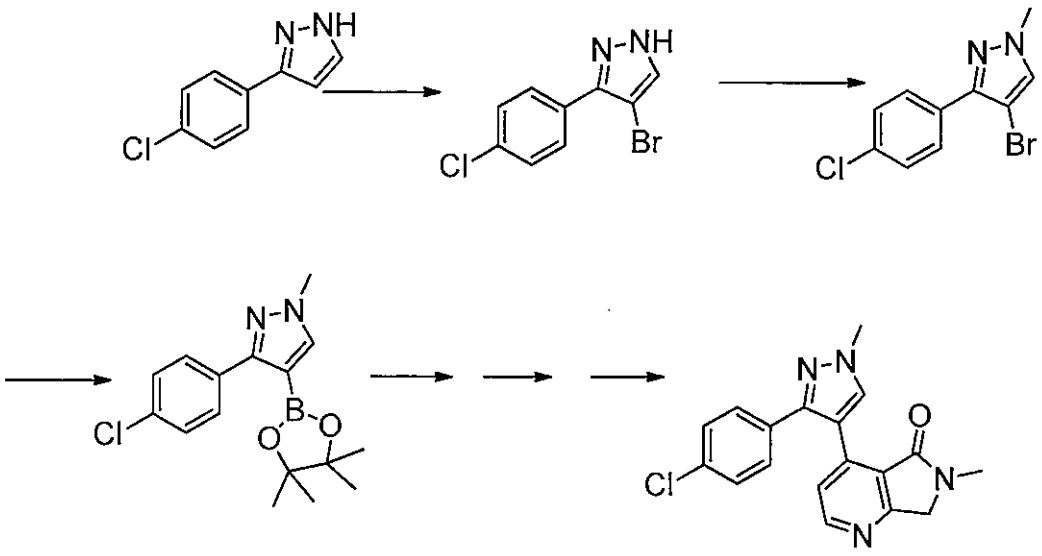
Step 10: Preparationof 3-Fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinonitrile

Ex 1 – Step 9 product (1.06 g, 3.69 mmol), triethylamine (1.03 mL, 7.38 mmol) and trimethylsilyl cyanide (0.615 mL, 4.61 mmol) were stirred in acetonitrile (10 mL) at 70 °C for 3 days. LCMS indicated N-oxide was still present, so an additional 1.5 mL of trimethylsilyl cyanide and 2.5 mL triethylamine were added and the heating was continued for another 24 hr. The mixture was cooled, concentrated and purified by silica gel chromatography using 10-100% EtOAc/heptanes with 1% triethylamine modifier to yield 600 mg (55%) of Ex 1 – Step 10 as a yellow solid. Spectral data are consistent with that of the material prepared using the procedure in step 2 above.

Example 2 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

collected, rinsed with water, and dried under vacuum overnight to give 103.23 g (53%) of Example 2 as a solid: LCMS m/z 323.2 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.5, 1H), 8.28 (s, 1H), 7.41 (dd, *J* = 8.8, 5.5, 2H), 7.03 (dd, *J* = 8.6, 8.6, 2H), 6.96 (d, *J* = 5.2, 1H), 4.44 (s, 2H), 4.01 (s, 3H), 3.24 (s, 3H).

Example 3: 4-[3-(4-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one



Step 1: Preparation of 4-bromo-3-(4-chlorophenyl)-1H-pyrazole

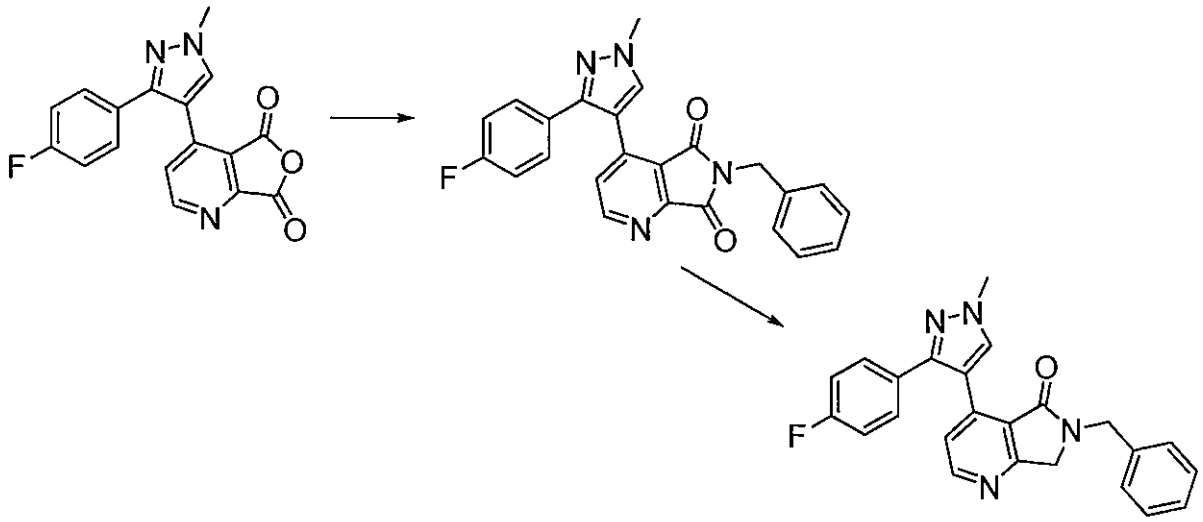
N-Bromosuccinimide (10.4 g, 56.0 mmol) was added portionwise to a solution of 3-(4-chlorophenyl)-1H-pyrazole (10.0 g, 56.0 mmol) in CH_2Cl_2 (140 mL). The mixture was stirred for 10 min, water and an additional portion of CH_2Cl_2 were added and the mixture was stirred for 5 min. The organic phase was separated, washed with brine, dried ($MgSO_4$) and concentrated to yield 15.0 g of Ex 3 – Step 1 product as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.6, 2H), 7.59 (s, 1H), 7.35-7.39 (m, 2H).

Step 2: Preparation of 4-bromo-3-(4-chlorophenyl)-1-methyl-1H-pyrazole

Cs_2CO_3 (38.0 g, 116.0 mmol) was added to a solution of Ex 3 – Step 1 product (15.0 g, 58.0 mmol) in DMF (63 mL). Methyl iodide (3.74 mL, 58.2 mmol) was added and the resulting pink colored solution was stirred at rt for 2hr. The mixture was concentrated and the residue was partitioned between EtOAc and water. The organic phase was separated and washed with brine, dried ($MgSO_4$) and concentrated. Silica gel chromatography using 40% heptane / CH_2Cl_2 yielded 10.1 g (64%) of Ex 3 – Step 2 product as a white solid. ^{1}H NMR (CDCl3) showed ~5% of

Example 4 was prepared in 71% yield from Ex 4 – Step 1 product following the general procedure described in Example 2, step 2 using 5 equivalents of zinc dust and heating for 1.5 hr: LCMS m/z 309.1 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.4, 1H), 8.21 (s, 1H), 7.37-7.49 (m, 2H), 6.95-7.03 (m, 3H), 6.14 (br s, 1H), 4.74 (s, 2H), 3.98 (s, 3H).

Example 5: 6-benzyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one



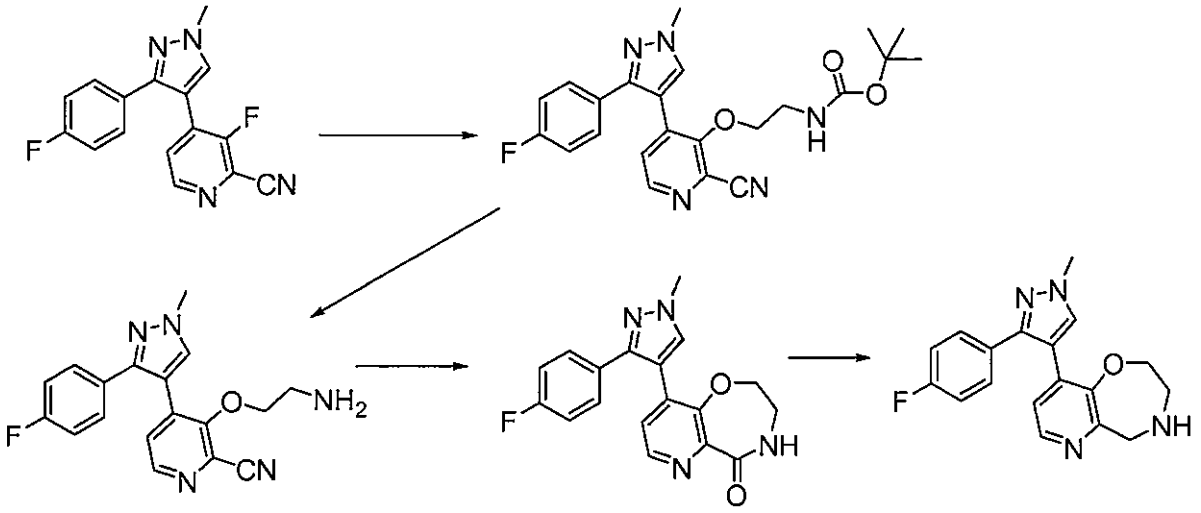
Step 1 Preparation of 6-benzyl-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione

4-[3-(4-Fluorophenyl)-1-methyl-1H-pyrazol-4-yl]furo[3,4-b]pyridin-5(7H)-one (Example 1, step 5, 472 mg, 1.46 mmol) and benzyl amine (0.167 mL, 1.53 mmol) in acetic acid (4.7 mL) were heated at reflux for 18 hr, cooled and then concentrated to a brown solid. This material was stirred with diethyl ether (20 mL) for 10 min and then filtered to yield 450 mg (75%) of Ex 5 - Step 1 product as a tan colored solid: LCMS m/z 413.5 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.2, 1H), 8.15 (s, 1H), 7.26-7.42 (m, 7H), 7.13 (d, *J* = 5.3, 1H), 7.01 (dd, *J* = 8.6, 8.6, 2H), 4.87 (s, 2H), 4.00 (s, 3H).

Step 2 Preparation of 6-benzyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

Boron trifluoride-diethyl etherate (0.18 mL, 1.45 mmol) was added to a solution of Ex 5 - Step 1 product (100 mg, 0.242 mmol) in THF (2.4 mL). After stirring 30 min at rt, borane THF complex (1.0M/THF, 1.21 mL, 1.21 mmol) was added and the mixture was heated to 40 °C overnight. A few drops of 6N HCl were added and

Example 7: 9-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine

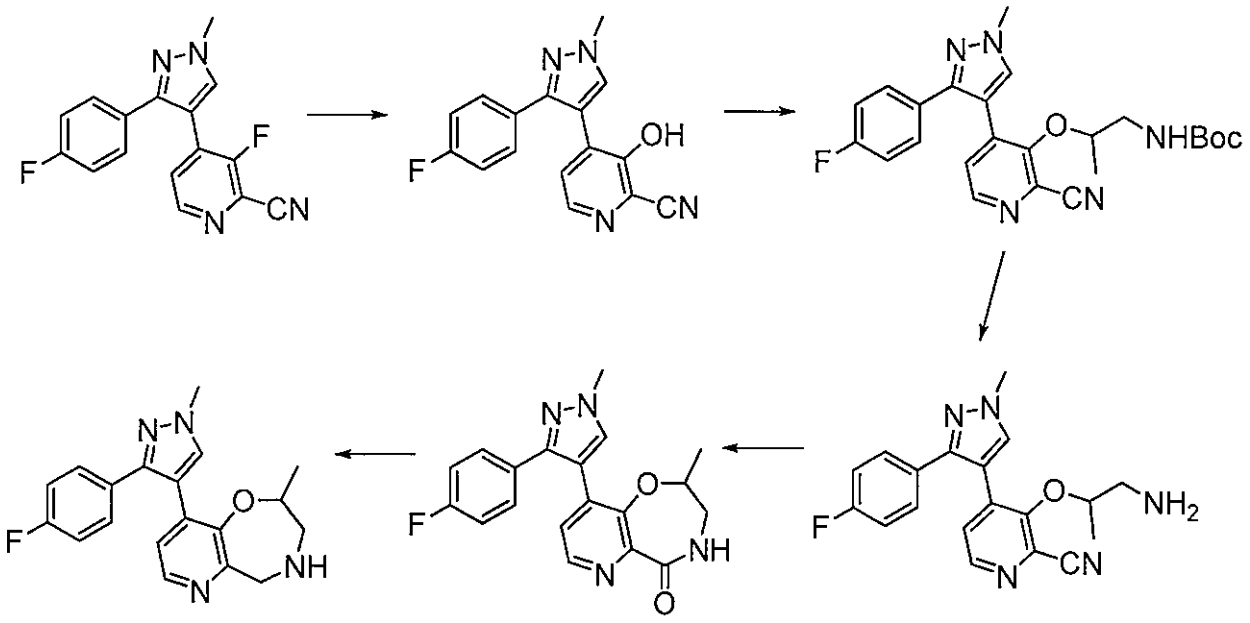


Step 1: Preparation of tert-butyl 2-(2-cyano-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yloxy)ethylcarbamate

60% Sodium hydride (1.35 g, 33.8 mmol) was added to a solution of of N-Boc-ethanolamine (2.62 mL, 16.9 mmol) in THF (85 mL). After stirring 5 min at rt, Example 1- Step 2 product (5.0 g, 17.0 mmol) was added with stirring. The mixture was stirred for 30 min then quenched with saturated aqueous NH_4Cl and diluted with EtOAc (100mL). The organic phase was separated, dried ($MgSO_4$) and concentrated to yield 1.4 g of a viscous oil. Purification by silica gel chromatography using 40-60%% EtOAc /heptane gave 3.35 g (45%) of Ex 7 – Step 1 product as a white solid: LCMS m/z 438.6 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 5.1, 1H), 7.76 (s, 1H), 7.30 (dd, *J* = 8.8, 5.5, 2H), 7.14 (d, *J* = 4.9, 1H), 6.95 (dd, *J* = 8.8, 8.8, 2H), 5.01 (br s, 1H), 3.94 (s, 3H), 3.91 (t, *J* = 5.3, 2H), 3.30 (q, *J* = 5.5, 2H), 1.33 (s, 9H).

Step 2: Preparation of 3-(2-aminoethoxy)-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinonitrile

Ethanolic HCl (1.25 M, 33 mL, 41 mmol) was added to Ex 7 – Step 1 product (3.35 g, 7.7 mmol) and the resulting solution was refluxed for 30 min, then concentrated to yield 2.90 g (92%) of Ex 7- Step 2 product, isolated as the di HCl salt as a white solid: MS (APCI) m/z 338.0 (M+1); ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.33 (d, *J* = 4.9, 1H), 8.16 (s, 1H), 7.42 (dd, *J* = 8.8, 5.3, 2H) 7.38 (d, *J* = 5.1, 1H), 7.10 (dd, *J* = 8.7, 2H); 4.14 (t, *J* = 5.2, 2H), 4.03 (s, 3H), 3.22 (t, *J* = 5.1, 2H).



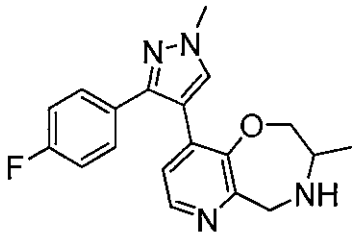
Step 1: Preparation of 4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)-3-hydroxypicolinonitrile

Sodium hydride (60%, 4.05 mg, 10.1 mmol) was added to a 0 °C solution of Example 1, Step 2 product (1.00g, 3.38 mmol) and 2-(methylsulfonyl)ethanol (629 mg, 5.06 mmol) in THF (20 mL). The mixture was warmed to rt and stirred for 18 hr. Saturated aqueous ammonium chloride solution was added to quench the excess sodium hydride and the mixture was extracted into EtOAc. The organic phase was separated, dried ($MgSO_4$) and concentrated. Silica gel chromatography with a 20% to 100% EtOAc/heptanes gradient gave Ex 8 - Step 1 product in quantitative yield: LCMS m/z 295.1 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 4.7, 1H), 7.74 (s, 1H), 7.40 (dd, *J* = 8.8, 5.3, 2H), 7.23 (d, *J* = 4.7, 1H), 7.05 (dd, *J* = 8.6, 8.6, 2H), 4.03 (s, 3H).

Step 2: Preparation of tert-butyl 2-(2-cyano-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)pyridin-3-yloxy)propylcarbamate

Diisopropyl azodicarboxylate (0.78 mL, 3.70 mmol) was added to an ice cold solution of Ex 8 - Step 1 product (990 mg, 3.36 mmol), tert-butyl 2-hydroxypropylcarbamate (590 mg, 3.36 mmol) and triphenylphosphine (1.06g, 4.04 mmol). The mixture was stirred at rt for 3 hr. The reaction was loaded onto silica gel and purified by chromatography using a 10-60% EtOAc/heptanes gradient to yield 1.48g of ~75% pure Ex 8 – Steph 2 product as a yellow gum which was used without further purification: LCMS m/z 452.2 (M+1).

Example 9: 9-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-3-methyl-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine

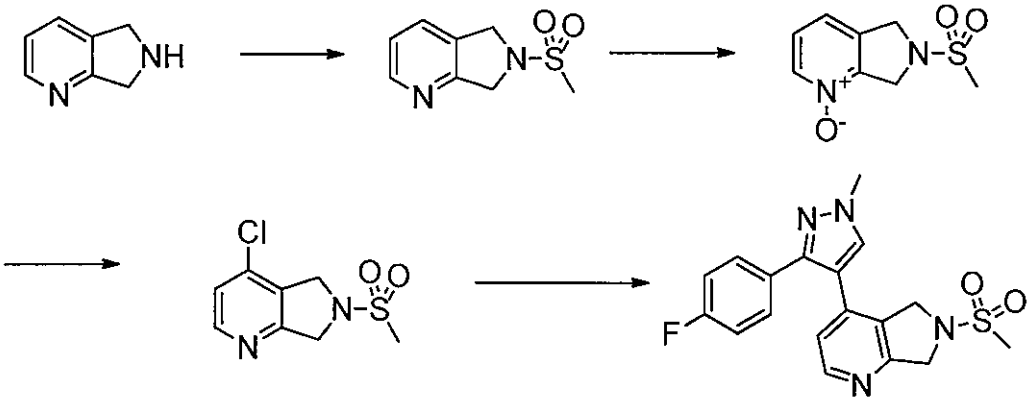


Example 9 was prepared following the same general procedures described in Example 7, substituting tert-butyl 1-hydroxypropan-2-ylcarbamate for tert-butyl 2-hydroxypropylcarbamate in step 2 and the enantiomers were separated by chiral HPLC (Chiralpak AD-H, 10 mm x 250 cm; mobile phase 80/20 carbon dioxide/EtOH; flow 10 mL/min; modifier 0.2% isopropyl amine):

Enantiomer #1: RetT = 4.30 min; LCMS m/z 339.2 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.8, 1H), 7.65 (s, 1H), 7.41 (dd, *J* = 8.8, 5.5, 2H), 7.03 (dd, *J* = 8.8, 8.8, 2H), 6.93 (d, *J* = 5.1, 1H), 4.30 (s, 2H), 4.07 (dd, *J* = 11.9, 2.5, 1H), 4.00 (s, 3H), 3.25-3.30 (m, 1H), 3.17-3.22 (m, 2H), 1.04 (d, *J* = 6.5, 3H).

Enantiomer #2: RetT = 4.73 min; LCMS m/z 339.2 (M+1); ^{1}H NMR same as for enantiomer #1.

Example 10: 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine

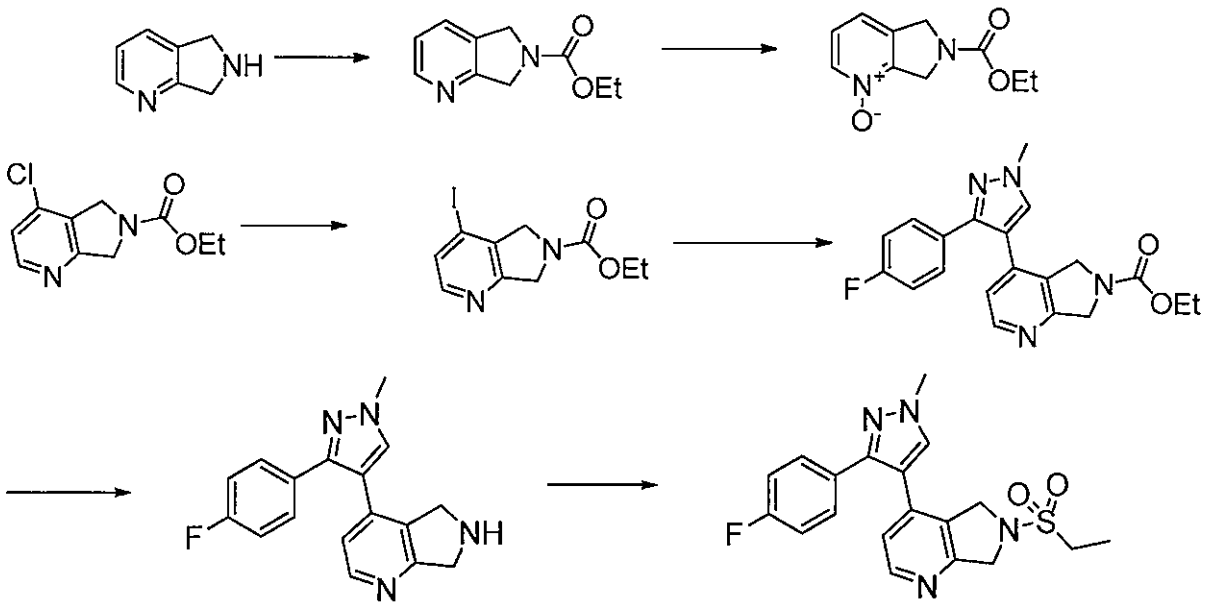


Step1: Preparation of 6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine

Methanesulfonyl chloride (0.97 mL, 12.4 mmol) was added dropwise to a -10 °C solution of diisopropyl-ethylamine (5.16 mL, 31.1 mmol) and 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (2.0g, 10.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred overnight at rt diluted with CH_2Cl_2 (300 mL) and washed with saturated aqueous sodium bicarbonate. The organic phase was separated, dried ($MgSO_4$) and filtered

afforded 102 mg (64%) of Example 10 as a light brown solid:LCMS m/z 373.1 (M+1); ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.47 (d, *J* = 6.4, 1H), 8.28 (s, 1H), 7.42-7.48 (m, 3H), 7.15 (dd, *J* = 8.8, 8.8, 2H), 4.96-4.97 (m, 2H), 4.77-4.79 (m, 2H), 4.02 (s, 3H), 3.00 (s, 3H).

Example 11: 6-(ethylsulfonyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine



Step 1: Preparation of ethyl 4-chloro-5H-pyrrolo[3,4-b]pyridine-6(7H)-carboxylate

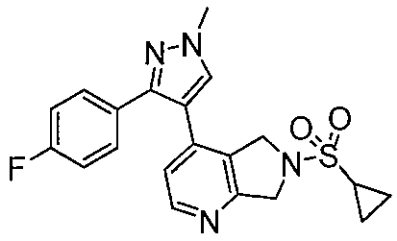
Ex 11- Step 1 product was prepared using the general procedures described in Example 10 (steps 1-3) substituting ethylchloroformate for methanesulfonyl chloride in step 1. The material was obtained as a pink solid: MS (APCI) m/z 226.9 (M+1); ^{1}H NMR shows a mixture of rotamers (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.4, 1H), 7.23-7.26 (m, 1H), 4.75-4.85 (m, 4H), 4.26 (q, *J* = 7.1, 2H), 1.31-1.36 (overlapping triplets, *J* = 7.2, 3H total). This material was converted to the HCl salt for use in the next step.

Step 2: Preparation of ethyl 4-iodo-5H-pyrrolo[3,4-b]pyridine-6(7H)-carboxylate

Sodium iodide (3.93g, 26.2 mmol) and Ex 11- Step 1 product, hydrochloride salt (step 1, 2.30 g, 8.74 mmol) in acetonitrile (20 mL) were refluxed for 3 days. The reaction mixture was cooled, concentrated and partitioned between CH_2Cl_2 and saturated aqueous sodium bicarbonate. The phases were separated and the aqueous phase was re-extracted twice with CH_2Cl_2 (total volume 750 mL). The

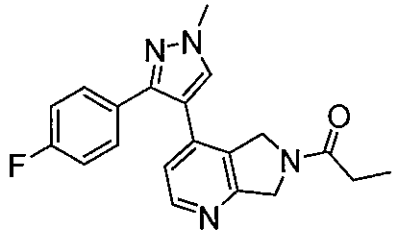
(dd, *J* = 8.2, 5.6, 2H), 7.02-7.06 (m, 3H), 4.76 (br s, 2H), 4.46 (br s, 2H), 4.02 (s, 3H), 3.00 (q, *J* = 7.5, 2H), 1.34 (t, *J* = 7.3, 3H).

Example 12: 6-(cyclopropylsulfonyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine,



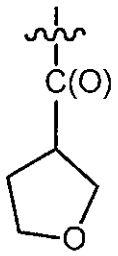
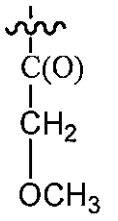
Example 12 was prepared following the general procedure described in Example 11, step 5, substituting cyclopropanesulfonyl chloride for ethanesulfonyl chloride to yield the hydrochloride salt in 88% yield: LCMS m/z 399.1 (M+1); ^{1}H NMR (400 MHz, MeOH-d_4) mixture of rotamers, 8.54 (br s, 1H), 8.31 (brs, 1H), 7.57 (br s, 1H), 7.47 (br s, 2H), 7.19 (br s, 2H), 5.06 (br s, 2H), 4.79 (br s, 2H), 4.05 (br s, 3H),2.70 (br s, 1H),1.14 (br s, 2H), 1.06 (br s, 2H).

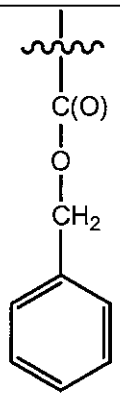
Example 13: 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-propionyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine



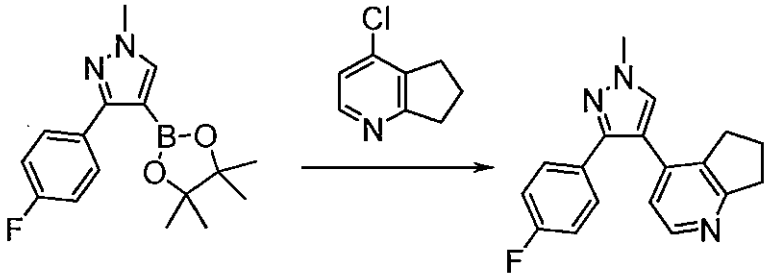
Triethylamine (142 µL, 1.02 mmol), propionic acid (22.9 µL, 0.31 mmol) and propylphosphonic anhydride (T3P) solution (50% wt, 360 µL, 0.60 mmol) were added to a solution of Example 11 (75mg, 0.26 mmol) in EtOAc (4 mL). The resulting slurry was stirred at rt for 2 hr then diluted withCH_2Cl_2, washed with saturated aqueous K_2CO_3, dried (Na_2SO_4) and concentrated. The residue was redissolved in EtOAc and treated with excess 2N HCl in diethyl ether to yield 113 mg of the hydrochloride salt of Example 12 as a solid in quantitative yield: LCMS m/z 351.1 (M+1); ^{1}H NMR (400 MHz, MeOH-d_4) mixture of rotamers, 8.52 (br d, *J* = 6.3, 1H), 8.32/8.36 (singlets, 1H), 7.45-7.54 (m, 3H), 7.15-7.21 (m, 2H), 4.98/5.03/5.20 (3 br singlets, 4H total), 4.06/4.07 (singlets, 3H total), 2.43-2.52 (m, 2H), 1.16-1.21 (2 overlapping triplets, 3H).

Examples 14-22:

16		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(tetrahydro-furan-3-ylcarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine, HCl salt	393.2	(MeOH-d4) ~1.5:1 mixture of rotamers, 8.50-8.53 (m, 1H), 8.36/8.30 (singlets, 1H), 7.44-7.56 (m, 3H), 7.15-7.21 (m, 2H), 5.28/5.02 (br singlets, 4H total), 4.06/4.05 (singlets, 3H total), 3.82-4.03 (m , 4H), 3.40 (br s, 1H), 2.07-2.15 (m, 2H).
17		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(methoxy-acetyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine, HCl salt	367.2	(MeOH-d4) ~1:1 mixture of rotamers, 8.47-8.55 (m, 1H), 8.28-8.35 (m, 1H), 7.37-7.56 (m, 3H), 7.14-7.21 (m, 2H), 5.22/5.08/4.95/4.91 (br singlets, 4H total), 4.25/4.21 (br singlets, 2H total), 4.07/4.06 (singlets, 3H), 3.47/3.45 (singlets, 3H).
18	C(O)-$CH(CH_3)_2$	4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-isobutyryl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine, HCl salt	365.2	(MeOH-d4) ~1:1 mixture of rotamers, 8.47-8.59 (m, 1H), 8.37/8.31 (br singlets, 1H total), 7.55-7.60 (m, 1H), 7.41-7.54 (m, 2H), 7.13-7.25 (m, 2H), 5.28/5.02/4.98 (br singlets, 4H total), 4.07/4.06 (singlets, 3H), 2.85 (br singlet, 1H), 1.20/1.15 (br doublets, *J* = 6.4, 6H).

				4H).
22		benzyl 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate	429.2	(DMSO-d6) ~1:1 mixture of rotamers,8.39-8.43 (2 over-lapping doublets, 1H total), 8.21/8.25 (singlets, 1H), 7.33-7.43 (m, 7H), 7.16-7.22 (m, 2H), 7.05/7.01 (2 doublets, *J* = 5.6, 1H total), 5.17/5.14 (singlets, 2H total), 4.80/4.71 (singlets, 2H total), 4.64/4.62 (singlets, 2H total), 3.96/3.94 (singlets, 3H total)

Example 23: 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-cyclopenta[b]pyridine



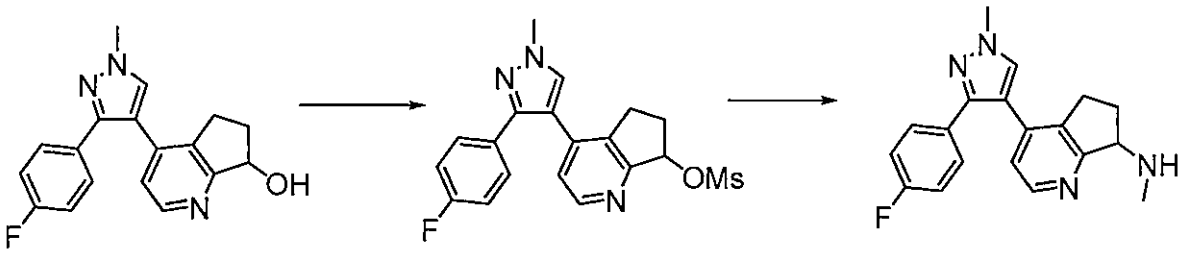
4-Chloro-6,7-dihydro-5H-cyclopenta[b]pyridine (350 mg, 2.28 mmol), Ex 1 Step 1 product (688 mg, 2.28 mmol), K_2CO_3 (661 mg, 4.78 mmol), 1,1-bis(diphenylphosphino)ferrocene palladium dichloride (84 mg, 0.144 mmol) in DMF (5 mL) were placed in a microwave vial and microwaved at 150 °C for 10 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and water (5 mL). The layers were separated and the aqueous phase was extracted again withCH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated to yield a brown solution. Chromatography on 40g of silica gel eluting with 9:1, 4:1 and 1:1 heptane:EtOAc yielded Example 23 as a light brown oil that solidified on standing

10%-90% EtOAc/heptanes gradient yielded 109 mg (62%) of Ex 24 – Step 2 product as a white solid: LCMS *m/z* 352.5 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.1, 1H), 7.49 (s, 1H), 7.36 (dd, *J* = 8.2, 5.4, 2H), 6.95 - 7.04 (m, 3H), 6.11 (dd, *J* = 7.2, 5.3,1H), 3.99 (s, 3H), 2.69-2.79 (m, 1H), 2.49 - 2.59 (m, 2H), 2.13 (s, 3H), 1.89 – 1.97 (m, 1H).

Step 3: *Example 24:*

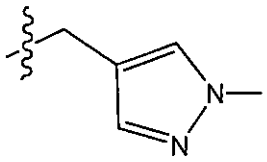
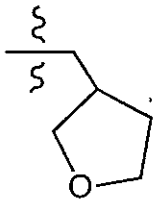
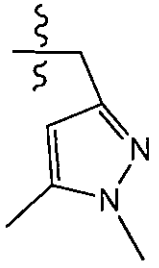
Partially dissolved Ex 24 – Step 2 product (105 mg, 0.299 mmol) in 1.5 mL of MeOH. Added 1.5 mL of 10% aqueous K_2CO_3 solution and stirred at rt for 3 days. Concentrated the reaction, re-dissolved in EtOAc and washed with saturated sodium bicarbonate solution and brine. Dried over Na_2SO_4, filtered and concentrated to yield Example 24 as a brown solid (95 mg, quantitative yield) LCMS m/z 310.5 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 5.1,1H), 7.48 (s, 1H), 7.32 - 7.39 (m, 2H), 6.95 – 7.01 (m, 3H), 5.19 (dd, *J* = 7.0, 7.0, 1H), 3.98 (s, 3H), 3.76 (br s, 1H), 2.70-2.79 (m, 1H), 2.40 - 2.52 (m, 2H), 1.86 - 1.97 (m, 2H).

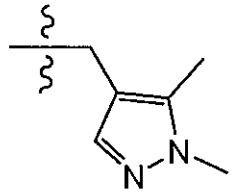
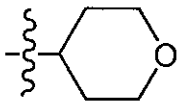
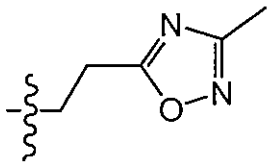
Example 25: 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-N-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-amine

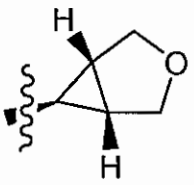
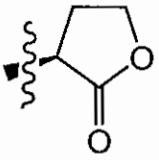
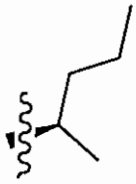
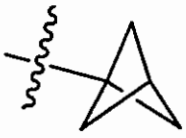


Example 23 (50 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C. Triethylamine (0.027 mL, 0.194 mmol) was added followed by methanesulfonyl chloride (0.013 mL, 0.170 mmol). The resulting mixture was stirred at 0 °C for 30 min. LCMS showed starting alcohol was still present so additional portions of triethylamine and methanesulfonyl chloride were added and stirring was continued until LCMS indicated the starting material was consumed.Water was added and the organic phase was separated, dried and concentrated to afford crude 4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-cyclopenta[b]pyridin-7-yl methanesulfonate (62 mg, 99%) as a purple solid. THF (1 mL) was added to his crude mesylate followed by 1 mL of methylamine (2M in THF, 2 mmol) to give a brown solution. The reaction was stirred for 16 hours at rt and then purified by silica gel chromatography. Elution with 1:3, 1:1, and 1:3 heptane/EtOAc then EtOAc and

Table 2

Ex#	R^2	IUPAC NAME	Ret. Time (min) [HPLC in foot-notes]	Calc'd Exact Mol. Wt.	Mass spec, Observed ion *m/z* (M+1) or (M+2)/2
26		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1-methyl-1H-pyrazol-4-yl)methyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.32	402.1604	403.1109
27		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(tetrahydrofuran-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.34	392.1649	393.1183
28		6-[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.48	416.1761	417.1566
29	$-(CH_2)_3-O-CH_3$	4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(3-methoxypropyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.4	380.1649	381.148

35		6-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.34	416.1761	417.1088
36		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(tetrahydro-2H-pyran-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.37	392.1649	393.1505
37	-CH_2-cyclopropyl	6-(cyclopropylmethyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.67	362.1543	363.1586
38		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.44	418.1554	419.107
39	-CH_2-i-propyl	4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-isobutyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.75	364.17	365.1593

45		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1R,5S,6r)-3-oxabicyclo[3.1.0]hex-6-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.37	390.1492	391.1226
46		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(3S)-2-oxotetrahydrofuran-3-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.34	392.1285	393.0993
47		4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1R)-1-methylbutyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.94	378.1856	379.1638
48		6-bicyclo[1.1.1]pent-1-yl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one	2.88	374.1543	375.1468

4% DMSO. The reaction was incubated for 85 min at 25 °C; detection was carried out as described for the Kinase-Glo Assay (Promega). Luminescent output was measured on the Perkin Elmer Envision plate reader (PerkinElmer, Waltham, MA).

The CK1ε kinase assay was performed in a 40-µl final volume in buffer containing 50 mM Tris, pH 7.5, 10 mM $MgCl_2$, 1 mM dithiothreitol, 100 µg/mL BSA with 10 µM ATP, 2.5 nM CKI ε wild type, and 42 µM peptide substrate PLSRTLpSVASLPGL (Flotow et al., 1990) in the presence of 1 µl of CKI ε inhibitor or 4% DMSO. The reaction was incubated for 70 min at 25 °C; detection was carried out as described for the Kinase-Glo Assay (Promega). Luminescent output was measured on the Perkin Elmer Envision plate reader (PerkinElmer, Waltham, MA).

CK1 WCA HCS Nuclear Translocation Assay. Cos7 cells were maintained at 37 °C in 5% CO_2 in Dulbecco's Modified Eagle Medium (Gibco 11995) supplemented with 10% fetal bovine serum. Log-phase cells were dislodged with 5 min treatment of TrypLE Express (Gibco 12605) and viable cell count was determined with Cedex cell counter. Cells were diluted in DMEM medium to a density of 1.5e5 viable cells/mL in 2/3 of the final volume of final transfected cell mix. Cells were cotransfected with two plasmid DNAs, mouse Per3-GFP (green fluorescent protein) in pd2EGFP-N1 vector and human CKI in pcDNA4/hisA vector (for CK1Epsilon at a ratio of 1:5 respectively ; for CK1δ at a ratio of 1:11 respectively), using Lipofectamine 2000 reagent (Invitrogen) according to the manufacturer's recommendations. The transfection mix contained approximately 0.83 µg/mL of DNA and 6 µL/mL of Lipofectamine 2000, in a total of 1/3 of the final transfection volume in Opti-MEM I medium (Invitrogen). After 20 min at rt, the cell mix was combined with the DNA transfection mix, per manufacturer instructions. 50 µL of the transfected cell suspension was dispensed per well by multidrop dispenser into Greiner 384-well Cellcoat (PDL) plates (Greiner # 781946).

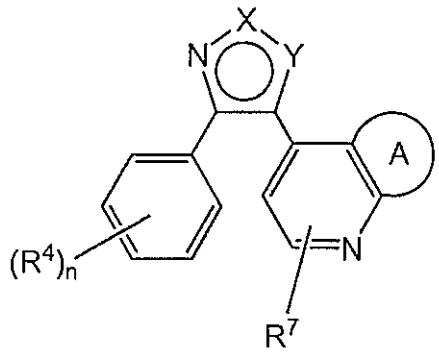
Compounds were solubilized in 100% DMSO, diluted with Opti-MEM I to a 4x concentration before addition to plated cells. After overnight exposure at 37 °C in a CO_2 incubator, cells were fixed by the addition of 12% paraformaldehyde (Electron Microscopy Sciences, Hatfield, PA) in phosphate-buffered saline (PBS) with 20% sucrose to a final concentration of 4%, and then the cells were incubated for 30 min at rt. Fixative was removed, and cells were washed with PBS and then stained with 0.4 µg/ml Hoechst dye (Invitrogen) in blocking buffer containing 4% goat serum

11			**103**	**668**
12			**202**	**882**
13			**16.2**	**124**
14			**40.2**	**150**
15			**12.6**	**75.4**
16			**38.1**	**218**
17			**47.5**	**210**
18			**39.5**	**195**
19			**54.8**	**566**
20			**84.7**	**361**
21			**18.3**	**82.3**
22			**51.6**	**275**
23	**25.4**	**157**	**214**	
24	**28.5**	**149**	**266**	
25	**17.4**	**83.7**	**59.8**	
26	**22.6**	**123**	**125**	
27	**35.3**	**210**	**369**	
28	**15.7**	**86.4**	**66.4**	

47	**>160**	**>423**	**89.7**	
48	**18.4**	**80.7**	**130**	
49	**108**	**496**	**506**	
50	**21.3**	**145**	**83.6**	
51	**14.6**	**63.8**	**129**	
52	**19**	**127**	**60.7**	

CLAIMS

1. A compound of Formula I:

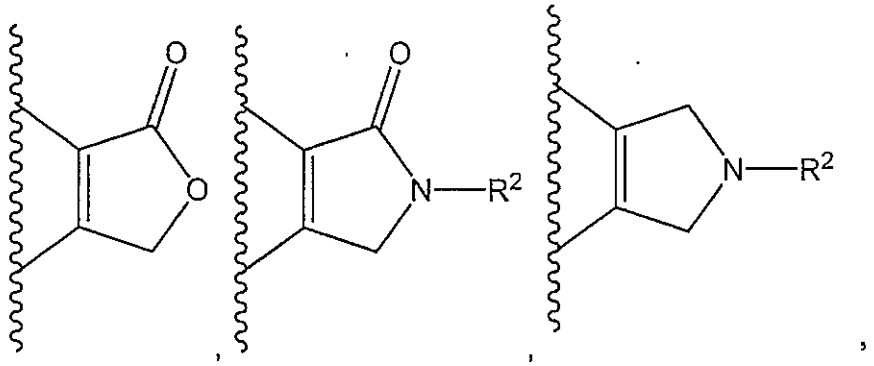


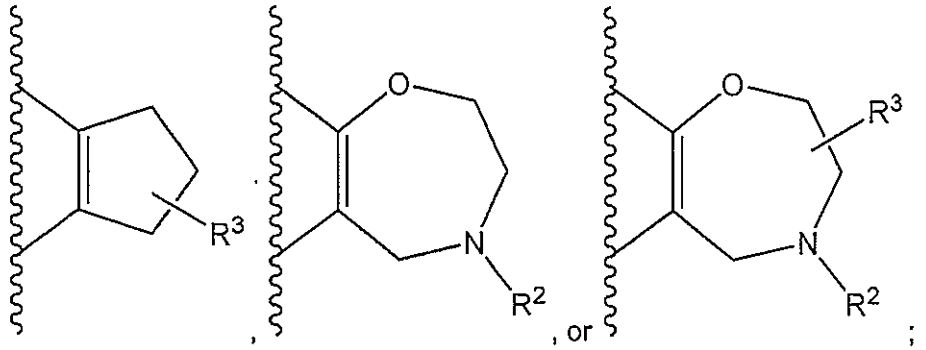
I

wherein:

X is NR^1 and said R^1 off of N is C_{1-4} alkyl or C_{3-4}cycloalkyl;

Y is CR^1 and said R^1 off of C is H or C_{1-4} alkyl;

Ring A is 



Each R^2 is independently H, C_{1-6}alkyl, C_{4-10}-bicycloalkyl, -$(CH_2)_t$-CN, -SO_2C_{1-6}alkyl, -$SO_2(CH_2)_tC_{3-6}$cycloalkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C_{1-6}alkyl-C(O)O-C_{1-6}alkyl, -C_{3-6}cycloalkyl-C(O)O-C_{1-6}alkyl, -C(O)-$(O)_u$-C_{1-6}alkyl, -C(O)-C_{1-6}alkyl-O-C_{1-6}alkyl, -C(O)-$(O)_u$-$(CH_2)_t$-(C_{6-10}aryl), -$(CH_2)_t$-(C_{6-10}aryl), -C(O)-$(O)_u$-$(CH_2)_t$-(5- to 10-membered

heteroaryl), -$(CH_2)_t$-C(O)-NR^5R^6, -$(CH_2)_t$-(5- to 10-membered heteroaryl), -C(O)-$(O)_u$-$(CH_2)_t$-(3- to 10-membered heterocycloalkyl), -$(CH_2)_t$-(4- to 10-membered heterocycloalkyl), -C(O)-$(O)_u$-$(CH_2)_t$-(3- to 10-membered cycloalkyl), or -$(CH_2)_t$-(3- to 10-membered cycloalkyl),

wherein said aryl, heteroaryl, cycloalkyl, and heterocycloalkyl of R^2 may be substituted with up to two substituents independently selected from halogen, OH, cyano, C_{1-6}alkyl, -C(O)-O-C_{1-3}alkyl or C_{1-6}alkyl-O-C_{1-6}alkyl,

and wherein any alkyl, cycloalkyl, and heterocycloalkyl of R^2 may be further substituted with oxo where valency allows;

Each R^3 is independently absent, C_{1-3}alkyl, oxo, -NR^5R^6, or –OR^5;

Each R^4 is independently halogen;

Each R^5 is independently H or C_{1-6}alkyl;

Each R^6 is independently H or C_{1-6}alkyl;

R^7 is H;

n is 0, 1, or 2;

Each t is independently 0, 1 or 2; and

Each u is independently 0 or 1;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is NR^1 and said R^1 off of N is C_{1-4}alkyl and Y is CR^1 and said R^1 off of C is H or CH_3;

Each R^2 is independently H, C_{1-6}alkyl, -SO_2C_{1-6}alkyl, -$SO_2(CH_2)_tC_{3-6}$cycloalkyl, -C_{1-6}alkyl-O-C_{1-6}alkyl, -C(O)-$(O)_u$-C_{1-6}alkyl, -$(CH_2)_t$-(C_{6-10}aryl), -C(O)-$(O)_u$-$(CH_2)_t$-(5- to 10-membered heteroaryl), -$(CH_2)_t$-C(O)-NR^5R^6, -$(CH_2)_t$-(5- to 10-membered heteroaryl), -$(CH_2)_t$-(4- to 10-membered heterocycloalkyl), or -$(CH_2)_t$-(3- to 10-membered cycloalkyl),

wherein said aryl, heteroaryl, cycloalkyl, and heterocycloalkyl of R^2 may be substituted with up to two substituents independently selected from halogen, OH, cyano, -C_{1-6}alkyl, -C(O)-O- C_{1-3}alkyl, or C_{1-6}alkyl-O-C_{1-6}alkyl,

and wherein any alkyl, cycloalkyl, and heterocycloalkyl of R^2 may be further substituted with oxo where valency allows;

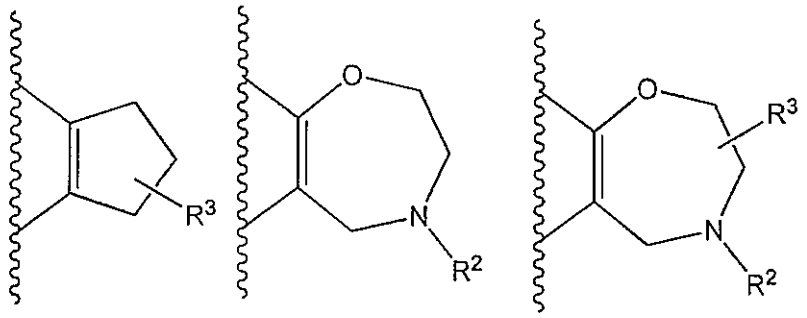
R^4 is F;

Each R^5 is H;

n is 1; and

R^3, R^6, R^7 , t, u and A are as defined in claim 1.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A is one of:



and R^2 and R^3 are as defined in any previous claim.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^2 is independently H, $-CH_3$, or SO_2CH_3; and R^3 is independently absent or oxo.

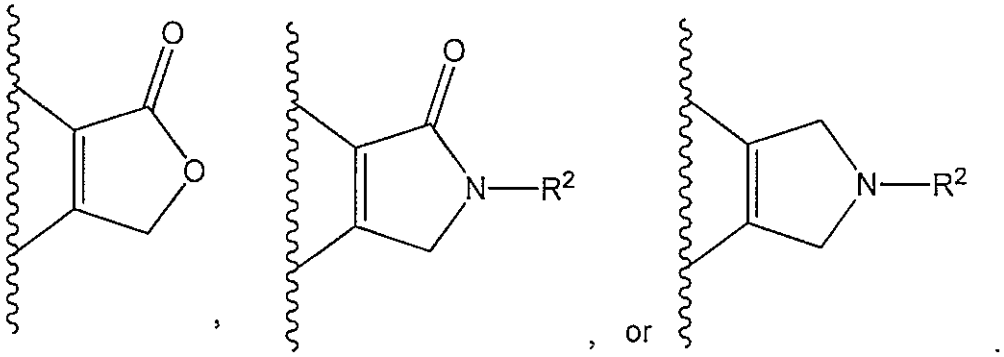
5. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^2 is independently H, $-CH_3$, or SO_2CH_3; and R^3 is independently absent or oxo.

6. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X is NR^1 and said R^1 off of N is C_{1-4} alkyl;

Y is CR^1 and said R^1 off of C is H or CH_3;

R^4 is F;

A is



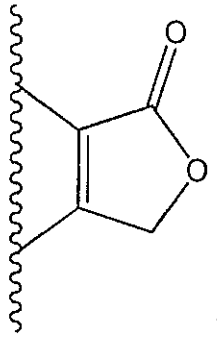
and n is 1.

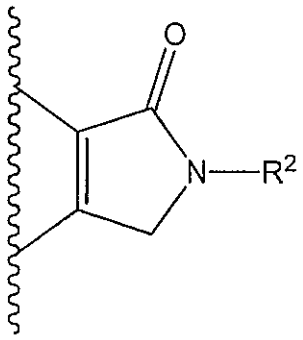
7. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein X is NR^1 and said R^1 off of N is C_{1-4} alkyl;

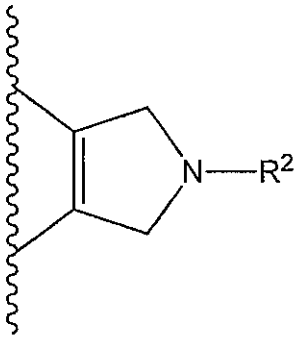
Y is CR^1 and said R^1 off of C is H or CH_3;

R^4 is F;

A is

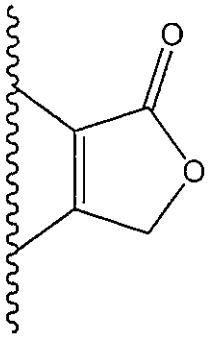


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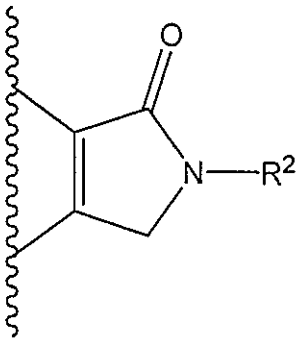
, or


;

and n is 1.

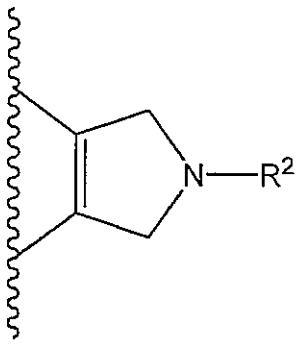
8. A compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein ring A is 

.

9. A compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein ring A is 

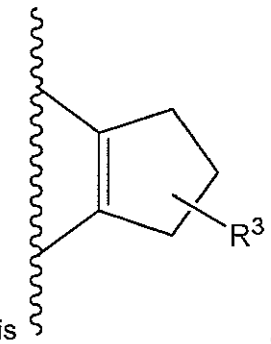
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10. A compound according to claim 7, or a pharmaceutically acceptable salt thereof,

wherein ring A is 

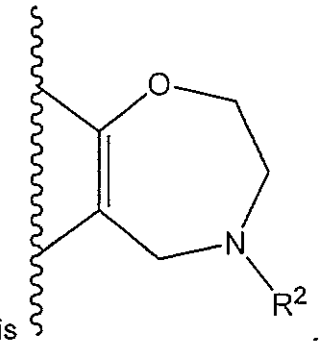
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11. A compound according to claim 3, or a pharmaceutically acceptable salt thereof,

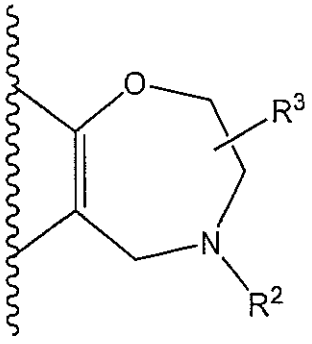
wherein Ring A is 

.

12. A compound according to claim 3, or a pharmaceutically acceptable salt thereof,

wherein Ring A is 

.

13. A compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein is Ring A is 

.

14. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is:

4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)furo[3,4-b]pyridin-5(7H)-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-benzyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

6-(ethylsulfonyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-propionyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1-methyl-1H-pyrazol-4-yl)methyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(tetrahydrofuran-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-cyclopentyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-ethyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;
6-(cyclopropylmethyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;
4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;
3-{4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl}propanenitrile;
3-({4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl}methyl)benzonitrile;
4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1R,5S,6r)-3-oxabicyclo[3.1.0]hex-6-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;
6-bicyclo[1.1.1]pent-1-yl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;
4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(pyridin-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;
6-(3-ethoxypropyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one; or
4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(6-methylpyridin-3-yl)methyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one.

15. A compound according to claim 1 wherein the compound is:

4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)furo[3,4-b]pyridin-5(7H)-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-benzyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-benzyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(methylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

6-(ethylsulfonyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

6-(cyclopropylsulfonyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-propionyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

6-acetyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine

6-(cyclopropylacetyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(tetrahydro-furan-3-ylcarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(methoxy-acetyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-isobutyryl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(tetrahydro-2H-pyran-4-ylcarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(pyrimidin-2-ylacetyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

6-(cyclopropylcarbonyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine;

benzyl 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5,7-dihydro-6H-pyrrolo[3,4-b]pyridine-6-carboxylate;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1-methyl-1H-pyrazol-4-yl)methyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(tetrahydrofuran-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(3-methoxypropyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-(2-tert-butoxyethyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

methyl 1-{4-[3-(4-fluoro-phenyl)-1-methyl-1H-pyrazol-4-yl]-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl}cyclopropanecarboxylate;

6-cyclopentyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[2-(1-methyl-1H-pyrazol-4-yl)ethyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-ethyl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(tetrahydro-2H-pyran-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-(cyclopropylmethyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-isobutyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

3-{4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl}propanenitrile;

3-({4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl}methyl)benzonitrile;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(2-methoxyethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

2-{4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl}-N,N-dimethylacetamide;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1R,2S)-2-(methoxymethyl)cyclopentyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1R,5S,6r)-3-oxabicyclo[3.1.0]hex-6-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(3S)-2-oxotetrahydrofuran-3-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(1R)-1-methylbutyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-bicyclo[1.1.1]pent-1-yl-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

isopropyl {4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl}acetate;

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-(pyridin-3-ylmethyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one;

6-(3-ethoxypropyl)-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one; or

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-6-[(6-methylpyridin-3-yl)methyl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one,

or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1 wherein the compound is:

9-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine;

9-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-methyl-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine;

9-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-3-methyl-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine; or

4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-N-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-7-amine,

or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 1 which is 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]furo[3,4-b]pyridin-5(7H)-one or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 5 which is 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]furo[3,4-b]pyridin-5(7H)-one.

19. The compound or pharmaceutically acceptable salt according to claim 5, which is a pharmaceutically acceptable salt of 4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]furo[3,4-b]pyridin-5(7H)-one.

20. A compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for use as a CK1 delta or CK1 epsilon activity inhibitor.

21. Use of an inhibitor of CK1 delta or CK1 epsilon, wherein the inhibitor is a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a mood disorder or a sleep disorder.

22. The use according to claim 21 wherein the sleep disorder is a circadian rhythm sleep disorder that is selected from the group consisting of shift work sleep disorder, jet lag syndrome, advanced sleep phase syndrome and delayed sleep phase syndrome; and the mood disorder is selected from the group consisting of a depressive disorder and a bipolar disorder.

23. The compound of any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof for use in the treatment of a neurological and psychiatric disease or disorder.

24. Use of a compound of any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a neurological or psychiatric disorder that is selected from the group consisting of cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia, AIDS-induced dementia, vascular dementia, mixed dementias, age-associated memory impairment, Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, including cognitive disorders associated with schizophrenia and bipolar disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine, migraine headache, urinary incontinence, substance tolerance, substance withdrawal, withdrawal from opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, and hypnotics, psychosis, mild cognitive impairment, amnestic cognitive impairment, multi-domain cognitive impairment, obesity, schizophrenia, anxiety, generalized anxiety disorder, social anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive compulsive disorder, mood disorders, depression, mania, bipolar disorders, trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain, acute

and chronic pain states, severe pain, intractable pain, neuropathic pain, post-traumatic pain, tardive dyskinesia, sleep disorders, narcolepsy, attention deficit/hyperactivity disorder, autism, Asperger's disease, and conduct disorder.

25. The use according to claim 23 wherein the disease or disorder is a mood disorder or a sleep disorder.

26. The use according to claim 24 wherein the disease or disorder is a mood disorder or a sleep disorder.

27. The use according to claim 25 wherein the mood disorder is selected from the group consisting of a depressive disorder and a bipolar disorder.

28. The use according to claim 26 wherein the mood disorder is selected from the group consisting of a depressive disorder and a bipolar disorder.

29. A pharmaceutical composition comprising a compound of any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.