HETEROARYL-LINKED ANALOGS AS MGLU5 NEGATIVE ALLOSTERIC MODULATORS AND METHODS OF MAKING AND USING THE SAME

ACKNOWLEDGMENT

[0001] This invention was made with government support under Grant no. 1UG3NS116218 awarded by the National Institute of Health (NIH). The United States government has certain rights in the invention.

BACKGROUND

[0002] Glutamate (L-glutamic acid) is the major excitatory transmitter in the mammalian central nervous system, exerting its effects through both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGlus) belong to family C (also known as family 3) of the G-protein-coupled receptors (GPCRs). They are characterized by a seven transmembrane (7TM) α-helical domain connected via a cysteine rich-region to a large bi-lobed extracellular amino-terminal domain (FIG. 1). While the orthosteric binding site is contained in the amino-terminal domain, currently known allosteric binding sites reside in the 7TM domain. The mGlu family comprises eight known mGlu receptor types (designated as mGlu1 through mGlu8). Several of the receptor types are expressed as specific splice variants, e.g. mGlu5a and mGlu5b or mGlu8a, mGlu8b and mGlu8c. The family has been classified into three groups based on their structure, preferred signal transduction mechanisms, and pharmacology. Group I receptors (mGlu1 and mGlu5) are coupled to $G_{\alpha q}$, a process that results in stimulation of phospholipase C and an increase in intracellular calcium and inositol phosphate levels. Group II receptors (mGlu2 and mGlu3) and group III receptors (mGlu4, mGlu6, mGlu7, and mGlu8) are coupled to $G_{\alpha i}$, which leads to decreases in cyclic adenosine monophosphate (cAMP) levels. While the Group I receptors are predominately located postsynaptically and typically enhance postsynaptic signaling, the group II and III receptors are located presynaptically and typically have inhibitory effects on neurotransmitter release. Without wishing to be bound by theory, increasing evidence indicates mGlus play an important role in lasting changes in synaptic transmission, and studies of synaptic plasticity in the *Fmr1* knockout mouse have identified a connection between the Fragile X phenotype and mGlu signaling.

[0003] The identification of small molecule mGlu antagonists that bind at the orthosteric site has greatly increased the understanding of the roles played by these receptors and their corresponding relation to disease. Because the majority of these antagonists were designed as analogs of glutamate, they typically lack desired characteristics for drugs targeting mGlu such as oral bioavailability and/or distribution to the central nervous system (CNS). Moreover, because of the highly conserved nature of the glutamate binding site, most orthosteric antagonists lack selectivity among the various mGlus.

[0004] A more recent strategy that has been able to successfully deal with the aforementioned issues has been the design of compounds that bind the mGlu at a site that is topographically distinct from the othosteric binding site, or an allosteric binding site. Selective negative allosteric modulators (NAMs) are compounds that do not directly deactivate receptors by themselves, but decrease the affinity of a glutamate-site agonist at its extracellular N-terminal binding site. Negative allosteric modulation is thus an attractive mechanism for inhibiting appropriate physiological receptor activation. Among the most studied and characterized small molecules are the mGlu5 NAMs, 2-methyl-6-(phenylethynyl) pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP). Both MPEP and MTEP have proven efficacious in numerous rodent models of disease, including those for drug addiction and pain as well as anxiety. The compounds were also able to inhibit transient lower esophageal sphincter relaxation (TLESD), the major cause of gastroesophageal reflux disease (GERD), in dogs and ferrets. In addition, MPEP was efficacious in mouse models of Fragile X syndrome (FXS) and Parkinson's disease (PD) as well as a baboon model of binge-eating disorder.

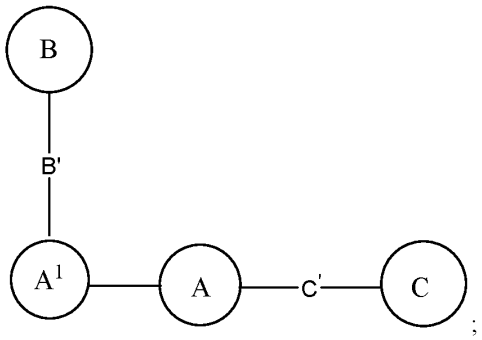
[0005] Although the utility of MPEP and MTEP as tool compounds has been clearly demonstrated, both molecules have issues that complicate or prevent their further development as therapeutic molecules. MPEP has been shown to directly inhibit the *N*-methyl-D-aspartate (NMDA) receptor activity at higher concentrations and is a positive allosteric modulator of mGlu4. While these selectivity issues are mitigated with MTEP, it is a potent inhibitor of cytochrome P450 1A2 and is efficiently cleared following intravenous administration to rhesus monkeys.

[0006] Potential adverse effects of known mGlu5 NAMs, however, could reduce their ultimate therapeutic utility. Further, conventional mGlu5 receptor modulators which target the orthosteric binding site can lack satisfactory aqueous solubility, exhibit poor oral bioavailability, and/or exhibit adverse effects. Therefore, there remains a need for methods and compositions that overcome these deficiencies and that effectively provide selective negative allosteric modulators for the mGlu5 receptor.

SUMMARY

[0007] In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in one aspect, relates to compounds useful as negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGlu5), methods of making same, pharmaceutical compositions comprising same, and methods of treating disorders associated with glutamate dysfunction using same.

[0008] Disclosed are compounds, or pharmaceutically acceptable salts thereof, having a structure represented by a formula:

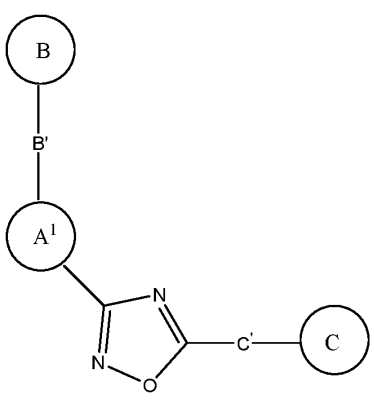


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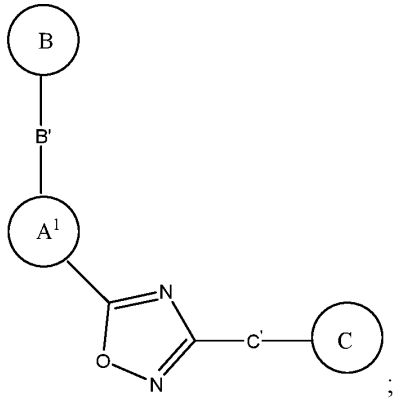
wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted

pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

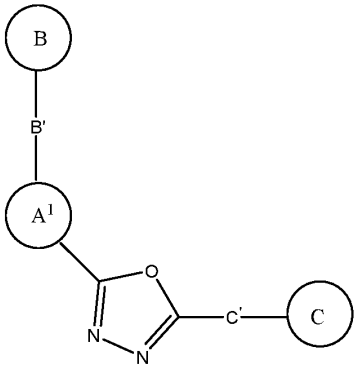
[0009] Other examples include a compound of the following formula:



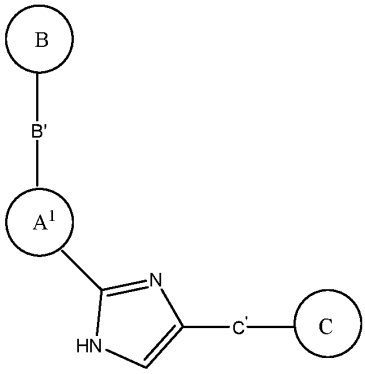
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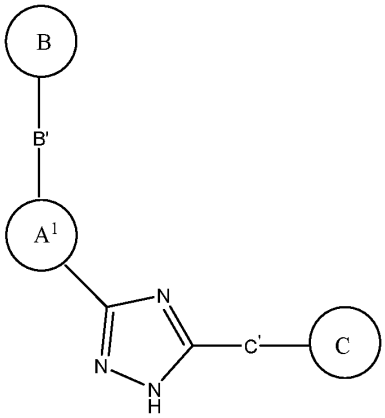
;



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; or



;

or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

[0010] Also disclosed are pharmaceutical compositions comprising an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0011] Also disclosed are methods for manufacturing a medicament comprising combining at least one disclosed compound with a pharmaceutically acceptable carrier or diluent.

[0012] Also disclosed are methods for the treatment of a disorder associated with metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0013] Also disclosed are methods for decreasing metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0014] Also disclosed are methods for inhibition of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0015] Also disclosed are methods for negative allosteric modulation of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0016] Also disclosed are methods for partial antagonism of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0017] Also disclosed are methods for modulating metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0018] Also disclosed are methods for modulating metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting said at least one cell with an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0019] Also disclosed are methods for inhibiting metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting said at least one cell with at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0020] Also disclosed are uses of at least one disclosed compound, or pharmaceutically acceptable salt, solvate, or polymorph thereof, in the manufacture of a medicament for the treatment of a disorder associated with glutamate dysfunction in a mammal.

[0021] Also disclosed are kits comprising at least one compound of any of the below listed exemplary claims, or pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent known to increase mGlu5 activity; (b) at least one agent known to decrease mGlu5 activity; (c) at least one agent known to treat a neurological and/or psychiatric disorder; or (d) instructions for treating a disorder associated with glutamate dysfunction.

[0022] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from

grammatical organization or punctuation, or the number or type of aspects described in the specification.

BRIEF DESCRIPTION OF THE FIGURES

[0023] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0024] **FIG. 1** shows a schematic representation of an mGlu.

[0025] **FIG. 2** shows a representative illustration of allosteric modulation of mGlu5.

[0026] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DESCRIPTION

[0027] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples and Figures included herein.

[0028] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0029] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

[0030] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein may be different from the actual publication dates, which can require independent confirmation.

A. DEFINITIONS

[0031] As used herein, nomenclature for compounds, including organic compounds, can be given using common names, IUPAC, IUBMB, or CAS recommendations for nomenclature. When one or more stereochemical features are present, Cahn-Ingold-Prelog rules for stereochemistry can be employed to designate stereochemical priority, *E*/*Z* specification, and the like. One of skill in the art can readily ascertain the structure of a compound if given a name, either by systemic reduction of the compound structure using naming conventions, or by commercially available software, such as CHEMDRAW™ (Cambridgesoft Corporation, U.S.A.).

[0032] As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a functional group," "an alkyl," or "a residue" includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[0033] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, a further aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0034] References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

[0035] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

[0036] As used herein, the terms "optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0037] As used herein, the term "mGlu5 receptor negative allosteric modulator" refers to any exogenously administered compound or agent that directly or indirectly inhibits the activity of the mGlu5 receptor in the presence of the endogenous ligand (such as glutamate) in an animal, in particular a mammal, for example a human. The term is synonymous with the terms "mGlu5 receptor allosteric inhibitor," "mGlu5 receptor noncompetitive inhibitor," "mGlu5 receptor allosteric antagonist," and "mGlu5 receptor noncompetitive antagonist."

[0038] As used herein, the term "subject" can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects. In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of one or more neurological and/or psychiatric disorders associated with glutamate dysfunction prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for negative allosteric modulation of metabotropic glutamate receptor activity prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for partial antagonism of metabotropic glutamate receptor activity prior to the administering step.

[0039] As used herein, the term "treatment" refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific

therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term "subject" also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.).

[0040] As used herein, the term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0041] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein. For example, "diagnosed with a disorder treatable by modulation of mGlu5" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by a compound or composition that can modulate mGlu5. As a further example, "diagnosed with a need for modulation of mGlu5" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition characterized by mGlu5 activity. Such a diagnosis can be in reference to a disorder, such as a neurodegenerative disease, and the like, as discussed herein. For example, the term "diagnosed with a need for negative allosteric modulation of metabotropic glutamate receptor activity" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by negative allosteric modulation of metabotropic glutamate receptor activity. For example, "diagnosed with a need for partial antagonism of metabotropic glutamate receptor activity" means having been subjected to a physical examination by a person of skill, for

example, a physician, and found to have a condition that can be diagnosed or treated by partial antagonism of metabotropic glutamate receptor activity. For example, "diagnosed with a need for treatment of one or more neurological and/or psychiatric disorders associated with glutamate dysfunction" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have one or more neurological and/or psychiatric disorders associated with glutamate dysfunction.

[0042] As used herein, the phrase "identified to be in need of treatment for a disorder," or the like, refers to selection of a subject based upon need for treatment of the disorder. For example, a subject can be identified as having a need for treatment of a disorder (e.g., a disorder related to mGlu5 activity) based upon an earlier diagnosis by a person of skill and thereafter subjected to treatment for the disorder. It is contemplated that the identification can, in one aspect, be performed by a person different from the person making the diagnosis. It is also contemplated, in a further aspect, that the administration can be performed by one who subsequently performed the administration.

[0043] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0044] The term "contacting" as used herein refers to bringing a disclosed compound and a cell, target metabotropic glutamate receptor, or other biological entity together in such a manner that the compound can affect the activity of the target (e.g., spliceosome, cell, etc.), either

directly; i.e., by interacting with the target itself, or indirectly; i.e., by interacting with another molecule, co-factor, factor, or protein on which the activity of the target is dependent.

[0045] As used herein, the term "effective amount" refers to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a "prophylactically effective amount"; that is, an amount effective for prevention of a disease or condition.

[0046] As used herein, "EC_{50}," is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% agonism of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an EC_{50} can refer to the concentration of a substance that is required for 50% agonism *in vivo*, as further defined elsewhere herein. In a further aspect, EC_{50} refers to the concentration of agonist that provokes a response halfway between the baseline and maximum response.

[0047] As used herein, "IC_{50}," is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an IC_{50} can refer to the concentration of a substance that is required for 50% inhibition *in vivo*, as further defined elsewhere herein. In a further aspect, IC_{50} refers to the half maximal (50%) inhibitory concentration (IC) of a substance.

[0048] The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[0049] As used herein, the term "derivative" refers to a compound having a structure derived from the structure of a parent compound (e.g., a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0050] As used herein, the term "pharmaceutically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the

like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0051] A residue of a chemical species, as used in the specification and concluding claims, refers to the moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $-OCH_2CH_2O-$ units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a sebacic acid residue in a polyester refers to one or more $-CO(CH_2)_8CO-$ moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

[0052] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is

not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0053] In defining various terms, "A^1," "A^2," "A^3," and "A^4" are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0054] The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *s*-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can be cyclic or acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (e.g., from one to four) carbon atoms.

[0055] Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" or "haloalkyl" specifically refers to an alkyl group that is substituted with one or more halide, *e.g.*, fluorine, chlorine, bromine, or iodine. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "alkylamino" specifically refers to an alkyl group that is substituted with one or more amino groups, as described below, and the like. When "alkyl" is used in one

instance and a specific term such as "alkylalcohol" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "alkylalcohol" and the like.

[0056] This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, *e.g.*, an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, *e.g.*, a "halogenated alkoxy," a particular substituted alkenyl can be, *e.g.*, an "alkenylalcohol," and the like. Again, the practice of using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is not meant to imply that the general term does not also include the specific term.

[0057] The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term "heterocycloalkyl" is a type of cycloalkyl group as defined above, and is included within the meaning of the term "cycloalkyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0058] The term "polyalkylene group" as used herein is a group having two or more CH_2 groups linked to one another. The polyalkylene group can be represented by the formula —$(CH_2)_a$—, where "a" is an integer of from 2 to 500.

[0059] The terms "alkoxy" and "alkoxyl" as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an "alkoxy" group can be defined as —OA^1 where A^1 is alkyl or cycloalkyl as defined above. "Alkoxy" also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as —OA^1—OA^2 or —OA^1—

$(OA^2)_a$—OA^3, where "a" is an integer of from 1 to 200 and A^1, A^2, and A^3 are alkyl and/or cycloalkyl groups.

[0060] The term "alkenyl" as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(A^1A^2)C=C(A^3A^4)$ are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0061] The term "cycloalkenyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bond, *i.e.*, C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term "heterocycloalkenyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkenyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0062] The term "alkynyl" as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0063] The term "cycloalkynyl" as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bond. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononynyl, and the like. The term "heterocycloalkynyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkynyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0064] The term "aryl" as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, phenoxybenzene, and the like. The term "aryl" also includes "heteroaryl," which is defined as a group that contains an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Likewise, the term "non-heteroaryl," which is also included in the term "aryl," defines a group that contains an aromatic group that does not contain a heteroatom. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term "biaryl" is a specific type of aryl group and is included in the definition of "aryl." Biaryl refers to two aryl groups that are bound together *via* a fused ring structure, as in naphthalene, or are attached *via* one or more carbon-carbon bonds, as in biphenyl.

[0065] The term "aldehyde" as used herein is represented by the formula —C(O)H. Throughout this specification "C(O)" is a short hand notation for a carbonyl group, *i.e.*, C=O.

[0066] The terms "amine" or "amino" as used herein are represented by the formula —NA^1A^2, where A^1 and A^2 can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0067] The term "alkylamino" as used herein is represented by the formula —NH(-alkyl) where alkyl is a described herein. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, and the like.

[0068] The term "dialkylamino" as used herein is represented by the formula —$N(\text{-alkyl})_2$ where alkyl is a described herein. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, *N*-ethyl-*N*-methylamino group, *N*-methyl-*N*-propylamino group, *N*-ethyl-*N*-propylamino group and the like.

[0069] The term "carboxylic acid" as used herein is represented by the formula —C(O)OH.

[0070] The term "ester" as used herein is represented by the formula —$OC(O)A^1$ or —$C(O)OA^1$, where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "polyester" as used herein is represented by the formula —$(A^1O(O)C\text{-}A^2\text{-}C(O)O)_a$— or —$(A^1O(O)C\text{-}A^2\text{-}OC(O))_a$—, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer from 1 to 500. "Polyester" is as the term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[0071] The term "ether" as used herein is represented by the formula A^1OA^2, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term "polyether" as used herein is represented by the

formula —(A^1O-A^2O)$_a$—, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[0072] The term "halide" as used herein refers to the halogens fluorine, chlorine, bromine, and iodine.

[0073] The term "heterocycle," as used herein refers to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Heterocycle includes pyridinde, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like.

[0074] The term "hydroxyl" as used herein is represented by the formula —OH.

[0075] The term "ketone" as used herein is represented by the formula $A^1C(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0076] The term "azide" as used herein is represented by the formula —N_3.

[0077] The term "nitro" as used herein is represented by the formula —NO_2.

[0078] The term "nitrile" as used herein is represented by the formula —CN.

[0079] The term "silyl" as used herein is represented by the formula —$SiA^1A^2A^3$, where A^1, A^2, and A^3 can be, independently, hydrogen or an alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0080] The term "sulfo-oxo" as used herein is represented by the formulas —$S(O)A^1$, —$S(O)_2A^1$, —$OS(O)_2A^1$, or —$OS(O)_2OA^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification "S(O)" is a short hand notation for S=O. The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by the formula —$S(O)_2A^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfone" as used herein is represented by the formula $A^1S(O)_2A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfoxide" as used herein is represented by the formula $A^1S(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0081] The term "thiol" as used herein is represented by the formula —SH.

[0082] "R^1," "R^2," "R^3," "R^n," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

[0083] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified

group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e. further substituted or unsubstituted). The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0084] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $–(CH_2)_{0–4}R°$; $–(CH_2)_{0–4}OR°$; $-O(CH_2)_{0-4}R°$, $–O–(CH_2)_{0–4}C(O)OR°$; $–(CH_2)_{0–4}CH(OR°)_2$; $–(CH_2)_{0–4}SR°$; $–(CH_2)_{0–4}Ph$, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $–(CH_2)_{0–4}O(CH_2)_{0–1}$-pyridyl which may be substituted with R°; $–NO_2$; –CN; $–N_3$; $-(CH_2)_{0–4}N(R°)_2$; $–(CH_2)_{0–4}N(R°)C(O)R°$; $–N(R°)C(S)R°$; $–(CH_2)_{0–4}N(R°)C(O)NR°_2$; $-N(R°)C(S)NR°_2$; $–(CH_2)_{0–4}N(R°)C(O)OR°$; $–N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $–(CH_2)_{0–4}C(O)R°$; $–C(S)R°$; $–(CH_2)_{0–4}C(O)OR°$; $–(CH_2)_{0–4}C(O)SR°$; $-(CH_2)_{0–4}C(O)OSiR°_3$; $–(CH_2)_{0–4}OC(O)R°$; $–OC(O)(CH_2)_{0–4}SR–$, SC(S)SR°; $–(CH_2)_{0–4}SC(O)R°$; $–(CH_2)_{0–4}C(O)NR°_2$; $–C(S)NR°_2$; –C(S)SR°; –SC(S)SR°, $-(CH_2)_{0–4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $–C(O)C(O)R°$; $–C(O)CH_2C(O)R°$; $–C(NOR°)R°$; $-(CH_2)_{0–4}SSR°$; $–(CH_2)_{0–4}S(O)_2R°$; $–(CH_2)_{0–4}S(O)_2OR°$; $–(CH_2)_{0–4}OS(O)_2R°$; $–S(O)_2NR°_2$; $-(CH_2)_{0–4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $–N(R°)S(O)_2R°$; $–N(OR°)R°$; $–C(NH)NR°_2$; $–P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $–OP(O)(OR°)_2$; $SiR°_3$; $–(C_{1–4}$ straight or branched alkylene)O–$N(R°)_2$; or $–(C_{1–4}$ straight or branched alkylene)C(O)O–$N(R°)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, $C_{1–6}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono–

or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0085] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $–(CH_2)_{0–2}R^•$, –(haloR•), $–(CH_2)_{0–2}OH$, $–(CH_2)_{0–2}OR^•$, $–(CH_2)_{0–2}CH(OR^•)_2$; -O(haloR•), –CN, $–N_3$, $–(CH_2)_{0–2}C(O)R^•$, $–(CH_2)_{0–2}C(O)OH$, $–(CH_2)_{0–2}C(O)OR^•$, $–(CH_2)_{0–2}SR^•$, $–(CH_2)_{0–2}SH$, $–(CH_2)_{0–2}NH_2$, $–(CH_2)_{0–2}NHR^•$, $–(CH_2)_{0–2}NR^•_2$, $–NO_2$, $–SiR^•_3$, $–OSiR^•_3$, -C(O)SR•, –($C_{1–4}$ straight or branched alkylene)C(O)OR•, or –SSR• wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from $C_{1–4}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0086] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, =NNHC(O)R*, =NNHC(O)OR*, $=NNHS(O)_2R^*$, =NR*, =NOR*, $–O(C(R^*_2))_{2–3}O–$, or $–S(C(R^*_2))_{2–3}S–$, wherein each independent occurrence of R* is selected from hydrogen, $C_{1–6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $–O(CR^*_2)_{2–3}O–$, wherein each independent occurrence of R* is selected from hydrogen, $C_{1–6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0087] Suitable substituents on the aliphatic group of R* include halogen, –R•, -(haloR•), -OH, –OR•, –O(haloR•), –CN, –C(O)OH, –C(O)OR•, $–NH_2$, –NHR•, $–NR^•_2$, or $–NO_2$, wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently $C_{1–4}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, or a 5–6–

membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0088] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $–R^{\dagger}$, $–NR^{\dagger}_2$, $–C(O)R^{\dagger}$, $–C(O)OR^{\dagger}$, $–C(O)C(O)R^{\dagger}$, $–C(O)CH_2C(O)R^{\dagger}$, $–S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $–C(S)NR^{\dagger}_2$, $–C(NH)NR^{\dagger}_2$, or $–N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, $C_{1–6}$ aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

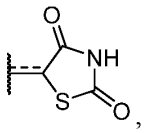
[0089] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $–R^{\bullet}$, $-(haloR^{\bullet})$, –OH, $–OR^{\bullet}$, $–O(haloR^{\bullet})$, –CN, –C(O)OH, $–C(O)OR^{\bullet}$, $–NH_2$, $–NHR^{\bullet}$, $–NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently $C_{1–4}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0090] The term "leaving group" ("LG") refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include halides and sulfonate esters, including, but not limited to, triflate, mesylate, tosylate, brosylate, and halides.

[0091] The terms "hydrolysable group" and "hydrolysable moiety" refer to a functional group capable of undergoing hydrolysis, e.g., under basic or acidic conditions. Examples of hydrolysable residues include, without limitation, acid halides, activated carboxylic acids, and various protecting groups known in the art (see, for example, "Protective Groups in Organic Synthesis," T. W. Greene, P. G. M. Wuts, Wiley-Interscience, 1999).

[0092] The term "organic residue" defines a carbon containing residue, i.e., a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited alkyl or substituted alkyls, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15 carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15 carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms.

[0093] A very close synonym of the term "residue" is the term "radical," which as used in the specification and concluding claims, refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure:



regardless of whether thiazolidinedione is used to prepare the compound. In some embodiments the radical (for example an alkyl) can be further modified (i.e., substituted alkyl) by having bonded thereto one or more "substituent radicals." The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[0094] "Organic radicals," as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some

embodiments, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

[0095] "Inorganic radicals," as the term is defined and used herein, contain no carbon atoms and therefore comprise only atoms other than carbon. Inorganic radicals comprise bonded combinations of atoms selected from hydrogen, nitrogen, oxygen, silicon, phosphorus, sulfur, selenium, and halogens such as fluorine, chlorine, bromine, and iodine, which can be present individually or bonded together in their chemically stable combinations. Inorganic radicals have 10 or fewer, or preferably one to six or one to four inorganic atoms as listed above bonded together. Examples of inorganic radicals include, but not limited to, amino, hydroxy, halogens, nitro, thiol, sulfate, phosphate, and like commonly known inorganic radicals. The inorganic radicals do not have bonded therein the metallic elements of the periodic table (such as the alkali metals, alkaline earth metals, transition metals, lanthanide metals, or actinide metals), although such metal ions can sometimes serve as a pharmaceutically acceptable cation for anionic inorganic radicals such as a sulfate, phosphate, or like anionic inorganic radical. Inorganic radicals do not comprise metalloids elements such as boron, aluminum, gallium, germanium, arsenic, tin, lead, or tellurium, or the noble gas elements, unless otherwise specifically indicated elsewhere herein.

[0096] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

[0097] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[0098] Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Inglod-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

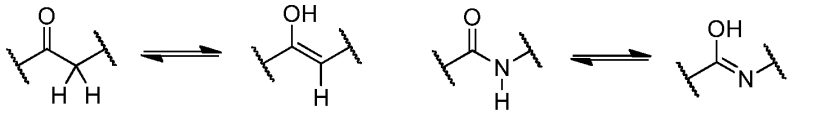
[0099] Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labeled or isotopically-substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labeled reagent for a non- isotopically labeled reagent.

[00100] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvate or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

[00101] The term “co-crystal” means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest

molecules are incorporated in the crystalline lattice as anhydrates or solvates, see e.g. "Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?" Almarasson, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

[00102] It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an α-hydrogen can exist in an equilibrium of the keto form and the enol form.

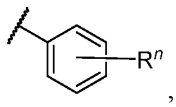


keto form enol form amide form imidic acid form

Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. Unless stated to the contrary, the invention includes all such possible tautomers.

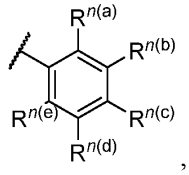
[00103] It is known that chemical substances form solids which are present in different states of order which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

[00104] In some aspects, a structure of a compound can be represented by a formula:



,

which is understood to be equivalent to a formula:



,

wherein n is typically an integer. That is, R^n is understood to represent five independent substituents, $R^{n(a)}$, $R^{n(b)}$, $R^{n(c)}$, $R^{n(d)}$, $R^{n(e)}$. By "independent substituents," it is meant that each R substituent can be independently defined. For example, if in one instance $R^{n(a)}$ is halogen, then $R^{n(b)}$ is not necessarily halogen in that instance.

[00105] Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Acros Organics (Morris Plains, N.J.), Fisher Scientific (Pittsburgh, Pa.), or Sigma-Aldrich Corporation (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[00106] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

[00107] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[00108] It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

B. mGLU5 NEGATIVE ALLOSTERIC MODULATORS

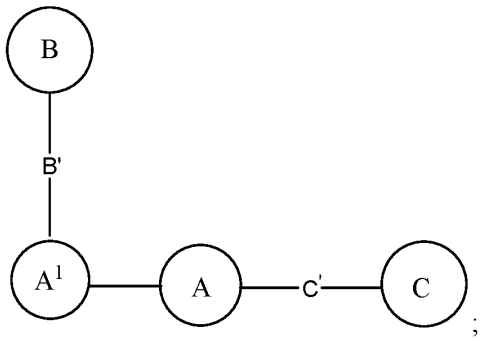
[00109] In one aspect, the invention relates to compounds useful as negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGlu5). Negative allosteric modulators are non-competitive antagonists and can include a range of maximal antagonist activity from partial antagonists to inverse agonists. In one aspect, the present invention relates to compounds that allosterically modulate mGlu5 receptor activity, affecting the sensitivity of

mGlu5 receptors to agonists without acting as orthosteric agonists themselves. The compounds can, in one aspect, exhibit subtype selectivity. The compounds of the invention can be useful in the treatment of neurological and psychiatric disorders associated with glutamate dysfunction and other diseases in which metabotropic glutamate receptors are involved, as further described herein. Generally, the disclosed compounds exhibit negative allosteric modulation of mGlu5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, the human embryonic kidney cells are transfected with mGlu5 of a mammal. In a still further aspect, human embryonic kidney cells are transfected with human mGlu5.

[00110] It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

1. STRUCTURE

[00111] In one aspect, the invention relates to compounds, or pharmaceutically acceptable salts thereof, having a structure represented by a formula:

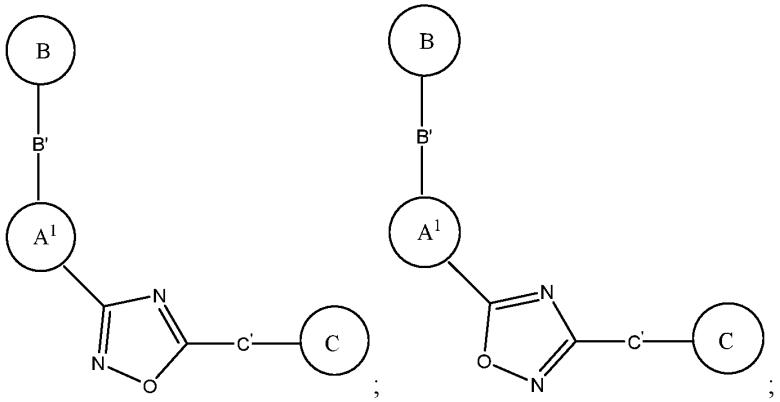


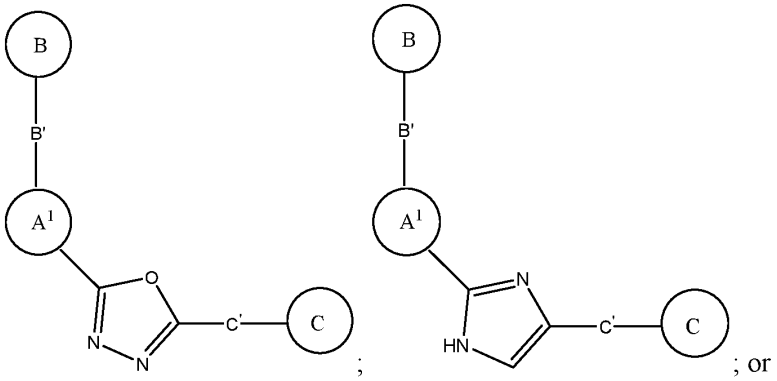
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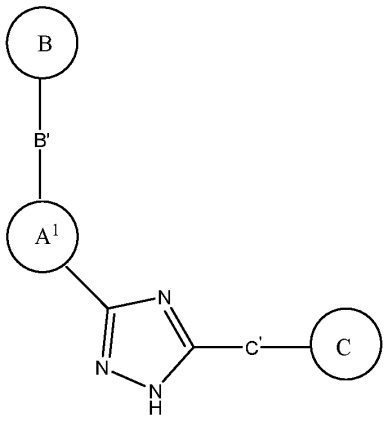
wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran,

oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine; C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00112] In another embodiment, the invention relates to a compound of the following formula:



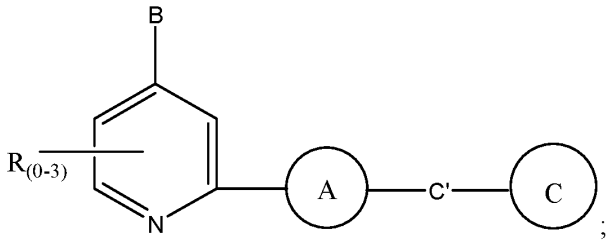




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or a pharmaceutically acceptable salt thereof.

[00113] In another embodiment, the invention relates to a compound of the following formula:

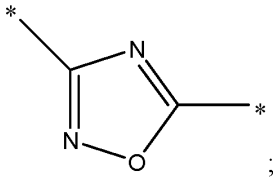
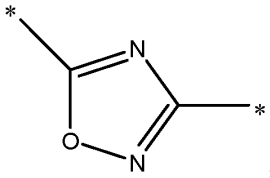
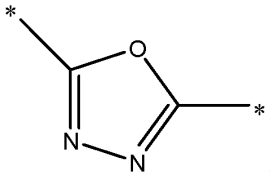


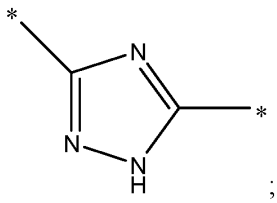
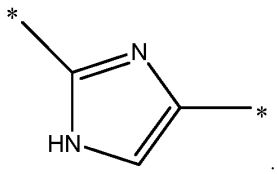
;

wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy; R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3.

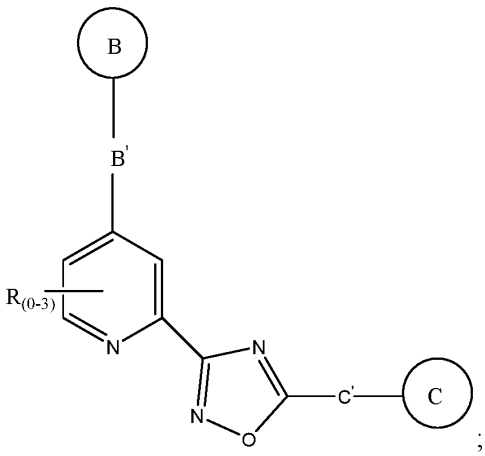
[00114] In another embodiment, A is chosen from 1,2,4-oxadiazole or 1,3,4-oxadiazole.

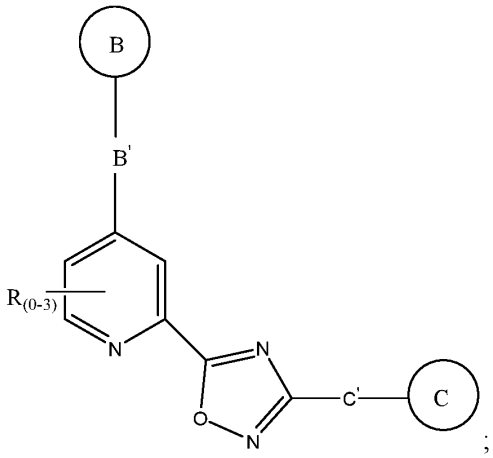
[00115] In another embodiment, A is chosen from:

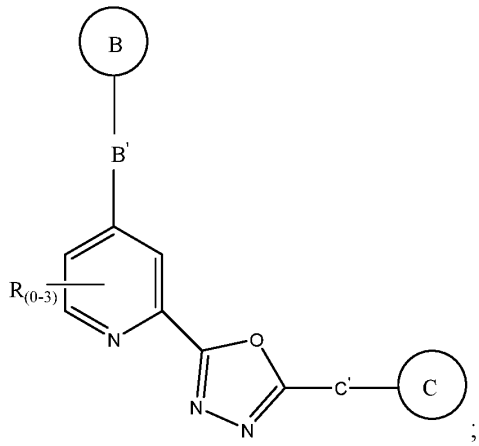
(i)  ; (ii)  ; (iii)  ;

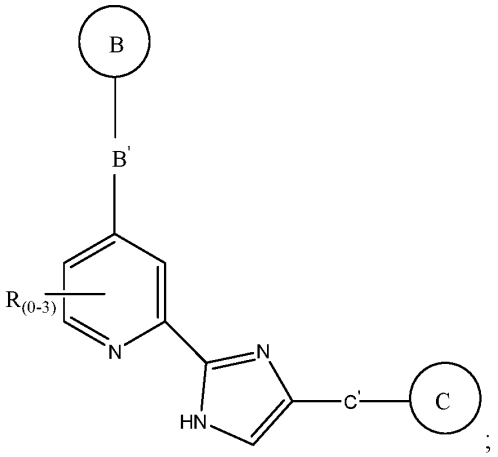
(iv)  ; or (v)  .

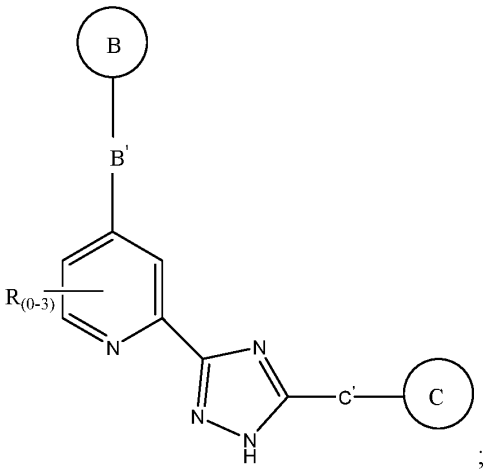
[00116] Another embodiment of the present invention is a compound of the following formula:

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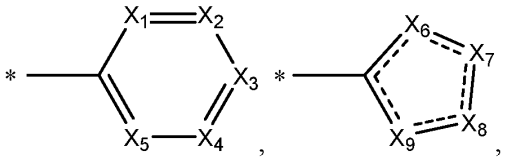
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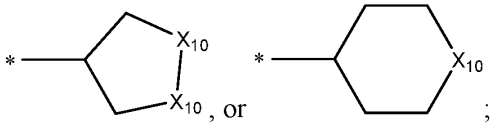
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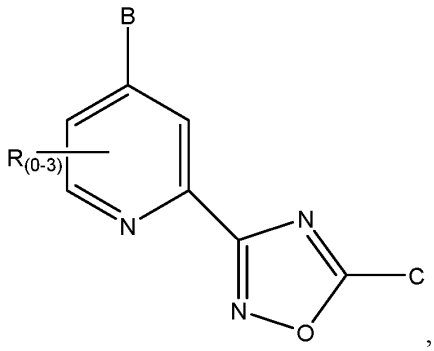
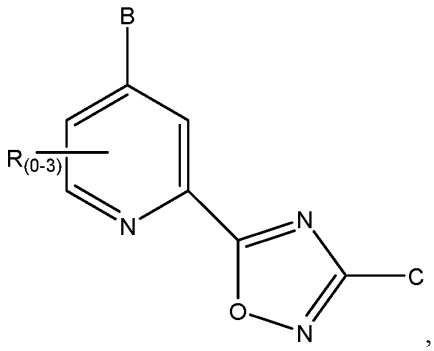
wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy; R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3; or a pharmaceutically acceptable salt thereof.

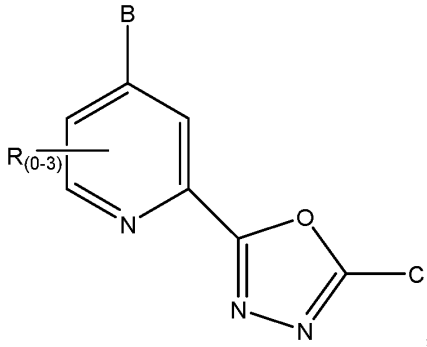
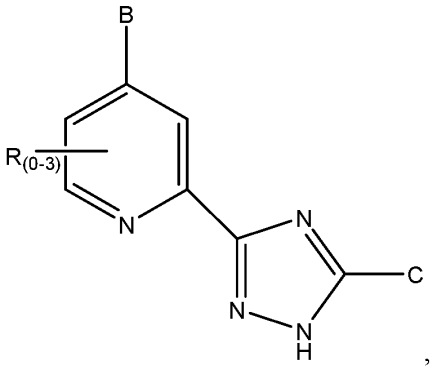
[00117] In another embodiment, B is 

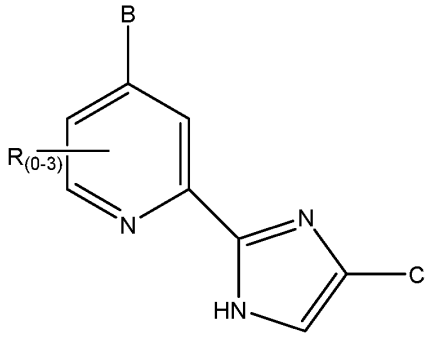
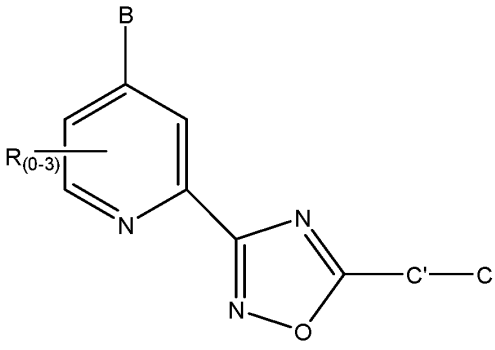
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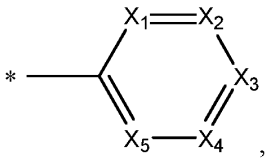
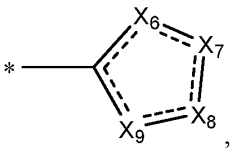
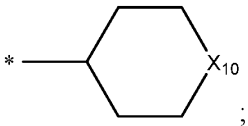
, or ; wherein X_1 is CH, C-R_1, or N; X_2 is CH, C-R_1, or N; X_3 is CH, C-R_1, or N; X_4 is CH, C-R_1, or N; X_5 is CH, C-R_1, or N; X_6 is CH, CR_1, S, NR_1, or N; X_7 is CH, CR_1, S, NR_1, or N; X_8 is CH, CR_1, S, NR_1, or N; X_9 is CH, CR_1, S, NR_1, or N; X_{10} is CH_2 or O; each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

[00118] Another embodiment of the present invention is a compound of claim 1, of the following formula:

(i)  , (ii)  ,

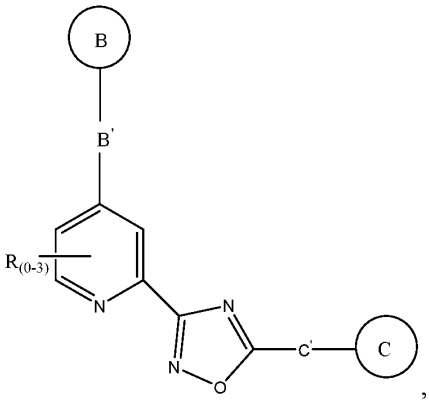
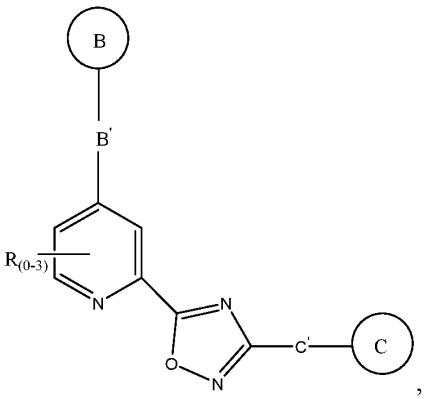
(iii)  , (iv)  , or

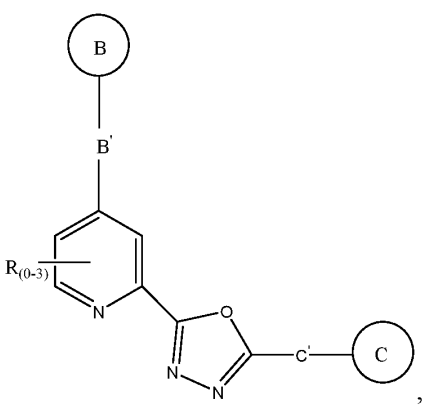
(v)  . (vi)  ; or a pharmaceutically acceptable salt thereof.

[00119] In another embodiment, C is  ,  , or  ; wherein X_1 is CH, C-R_2, or N; X_2 is CH, C-R_2, or N; X_3 is CH, C-R_2, or N; X_4 is CH, C-R_2, or N; X_5 is CH, C-R_2, or N; X_6 is CH, CR_2, S, NR_2, or N; X_7 is CH, CR_2, S, NR_2, or N; X_8 is CH, CR_2, S, NR_2, or N; X_9 is CH, CR_2, S, NR_2, or N; X_{10} is CH_2 or O; each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

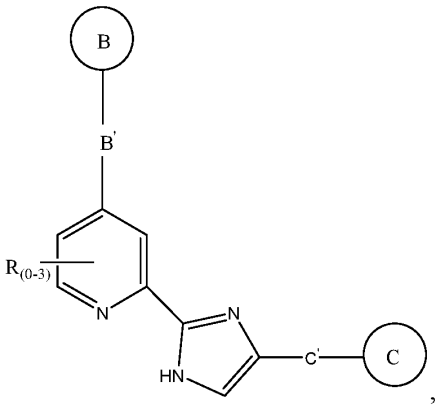
[00120] In yet another embodiment of the present invention,

(i) A^1 and A together form:

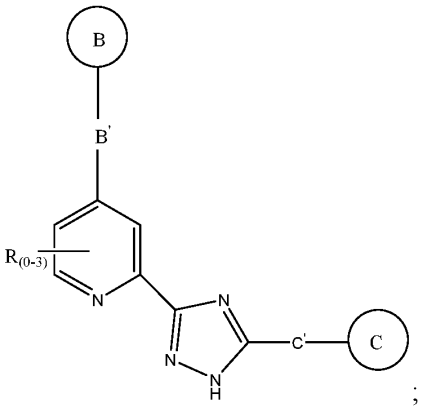
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,

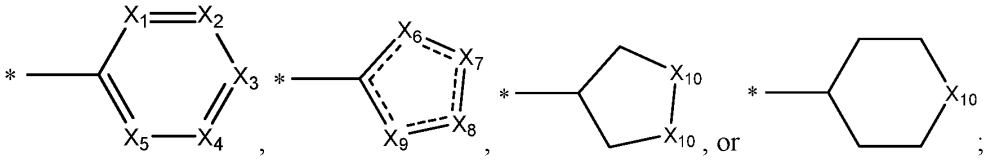


,or



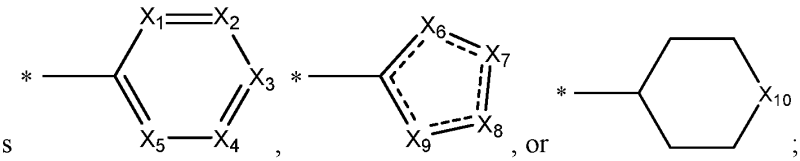
;

wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy; R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3;

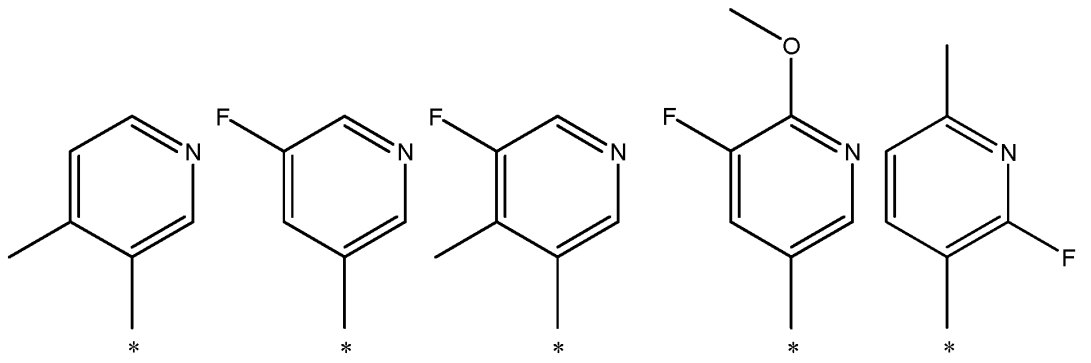
(ii) B is 

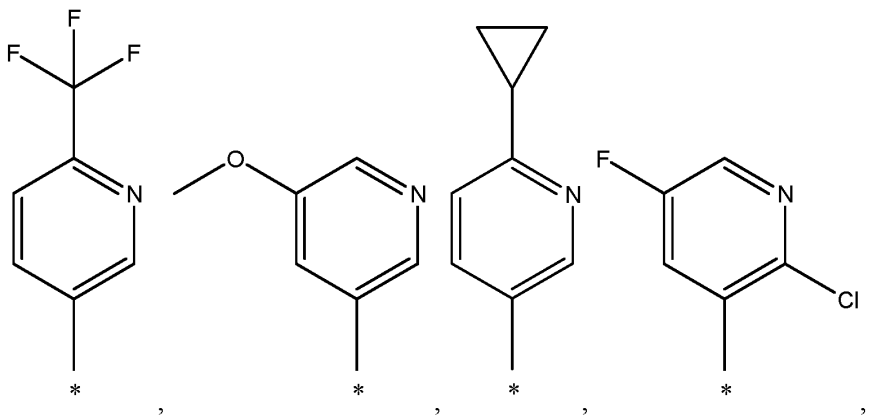
, , , or ;

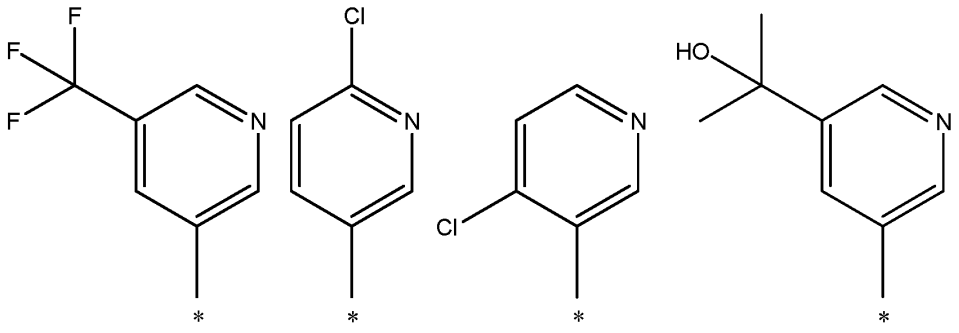
X_1 is CH, C-R_1, or N; X_2 is CH, C-R_1, or N; X_3 is CH, C-R_1, or N; X_4 is CH, C-R_1, or N; X_5 is CH, C-R_1, or N; X_6 is CH, CR_1, S, NR_1, or N; X_7 is CH, CR_1, S, NR_1, or N; X_8 is CH, CR_1, S, NR_1, or N; X_9 is CH, CR_1, S, NR_1, or N; X_{10} is CH_2 or O; each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; and

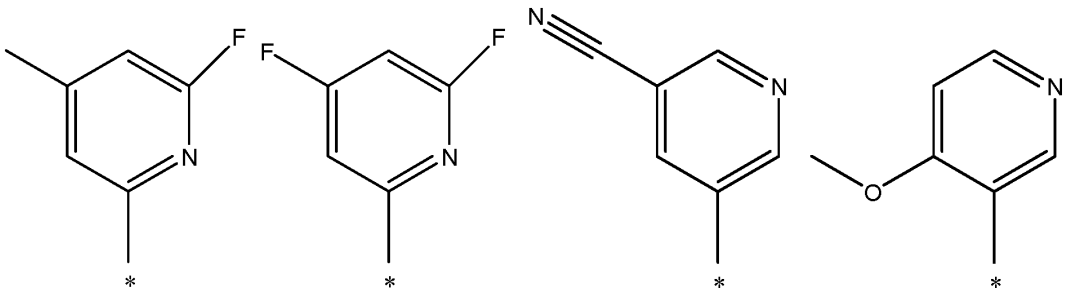
(iii) C is  ; X_1 is CH, C-R_2, or N; X_2 is CH, C-R_2, or N; X_3 is CH, C-R_2, or N; X_4 is CH, C-R_2, or N; X_5 is CH, C-R_2, or N; X_6 is CH, CR_2, S, NR_2, or N; X_7 is CH, CR_2, S, NR_2, or N; X_8 is CH, CR_2, S, NR_2, or N; X_9 is CH, CR_2, S, NR_2, or N; X_{10} is CH_2 or O; each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

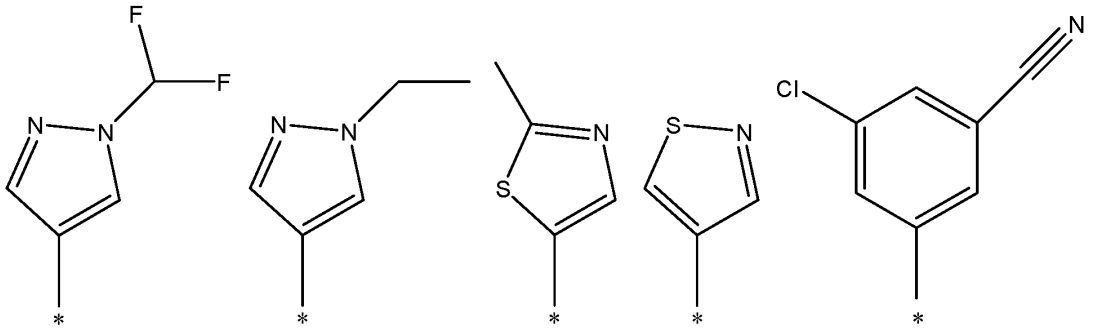
[00121] In another embodiment, B chosen from:

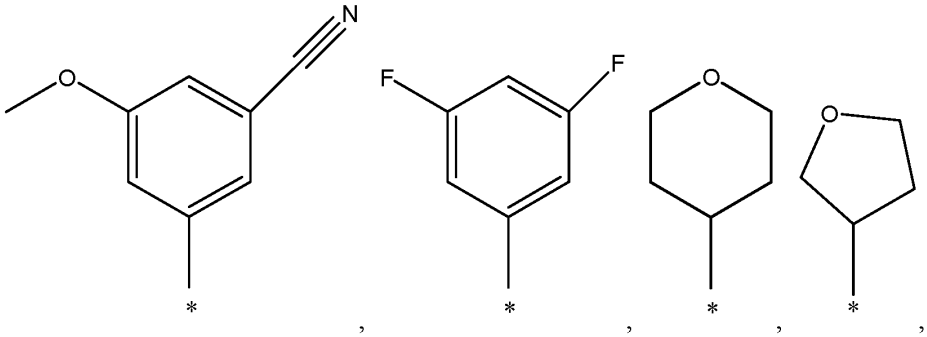


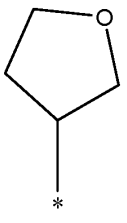






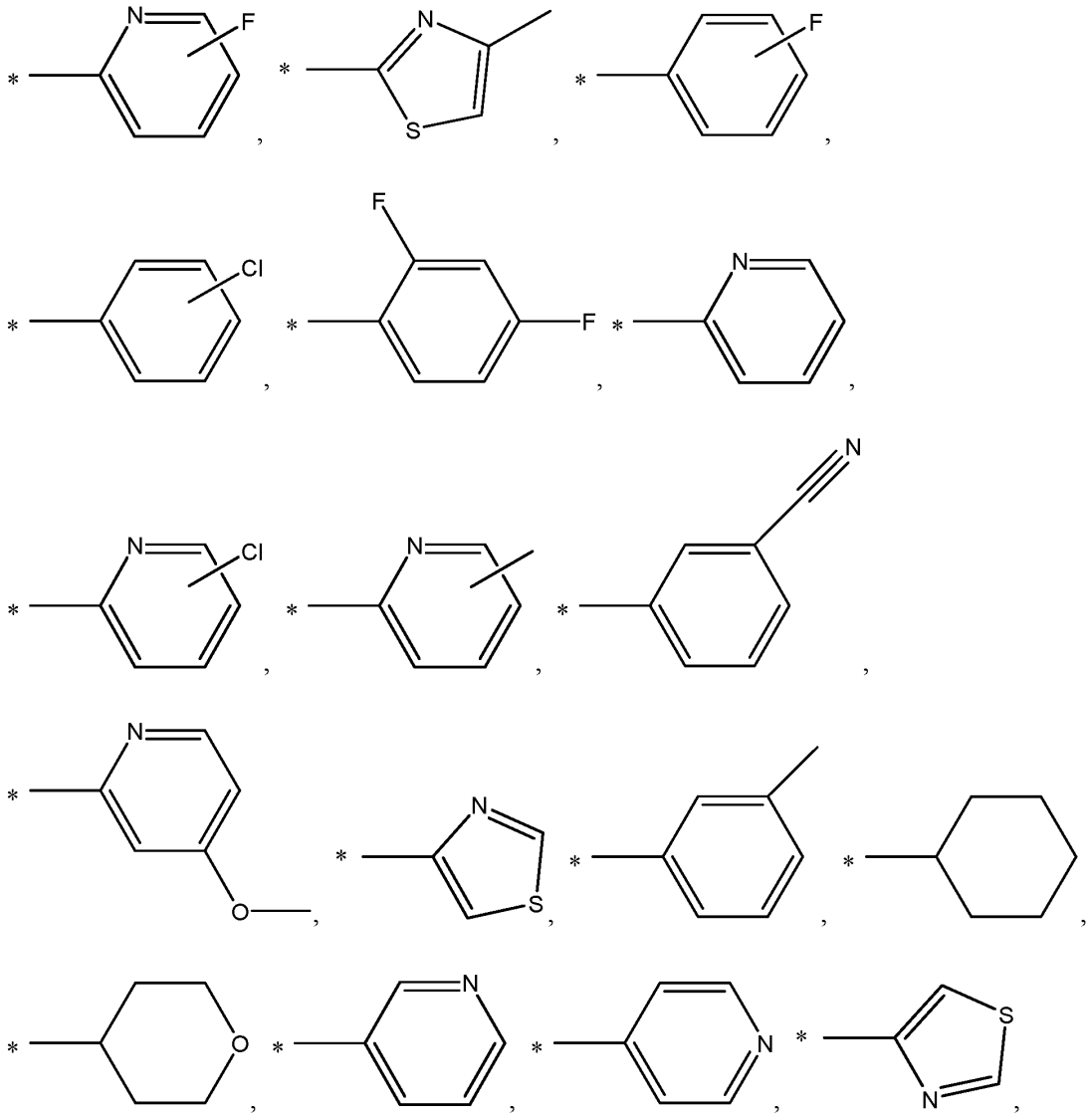


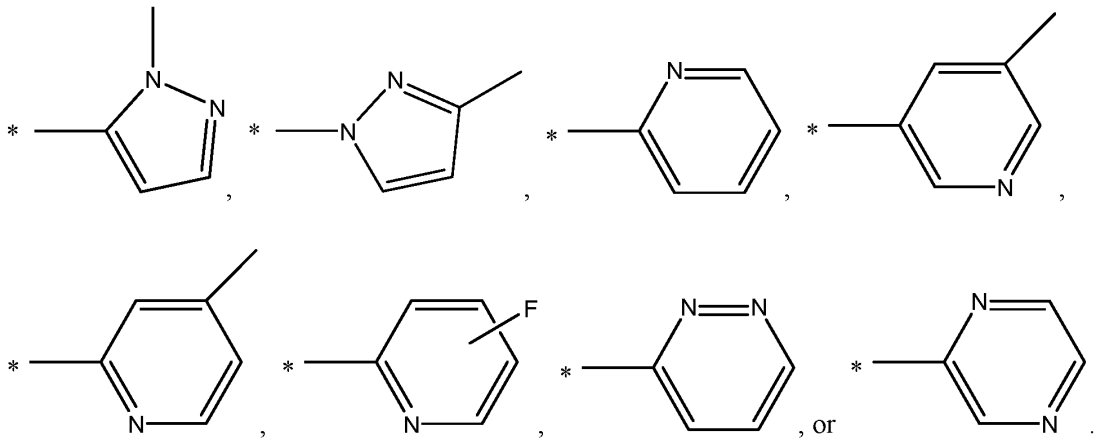




.

[00122] In another embodiment, C is chosen from:

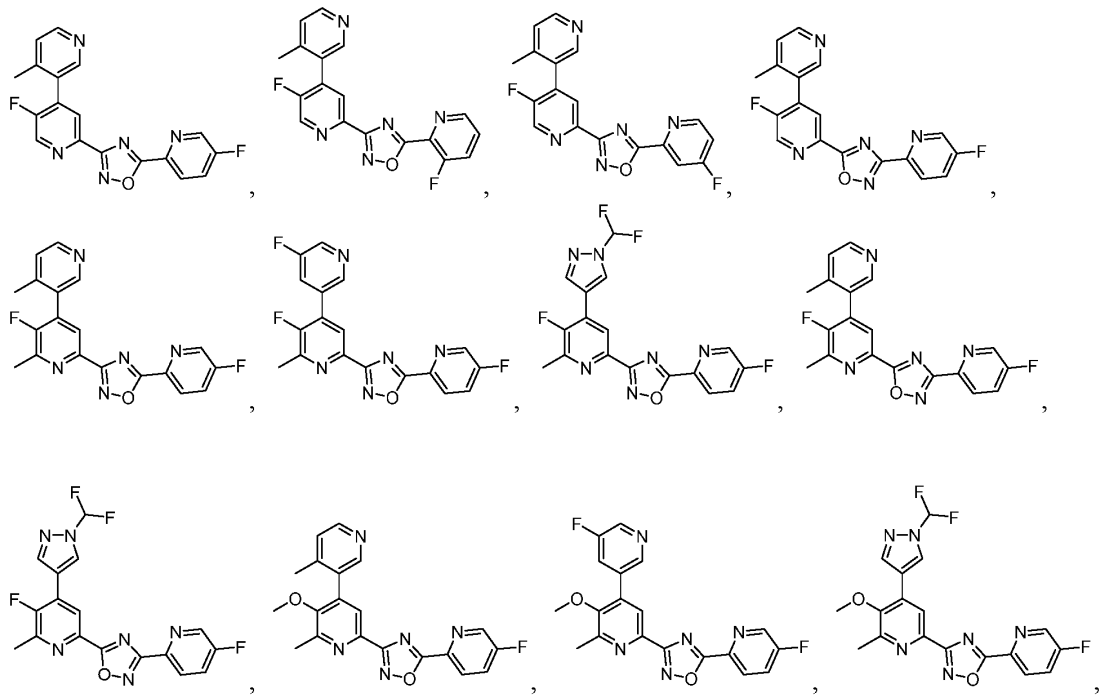


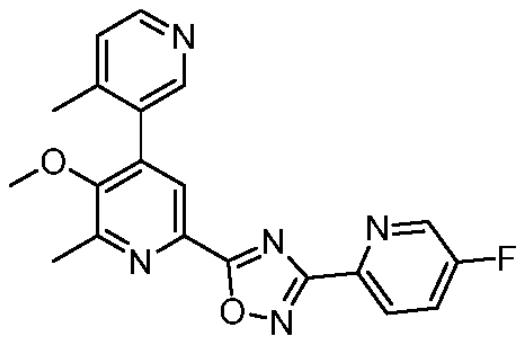
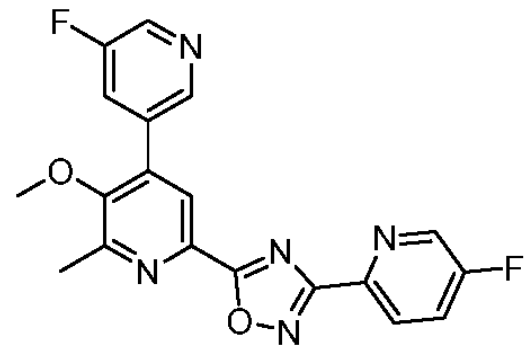
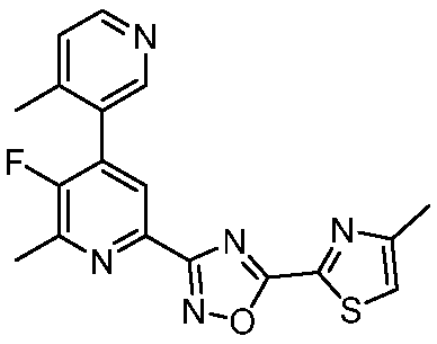
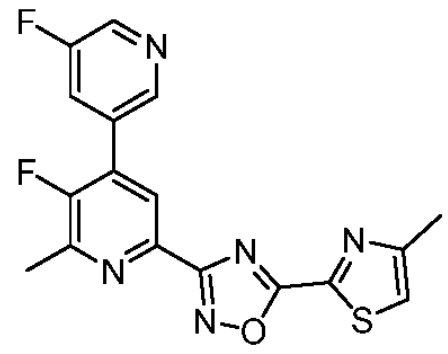


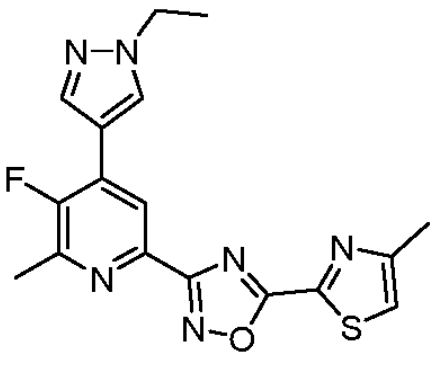
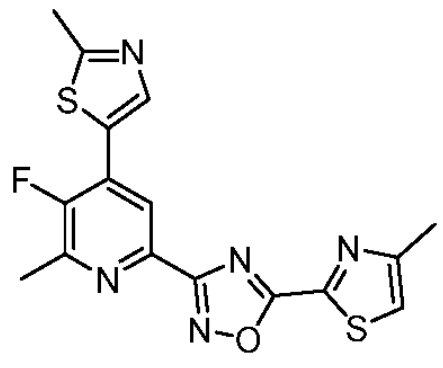
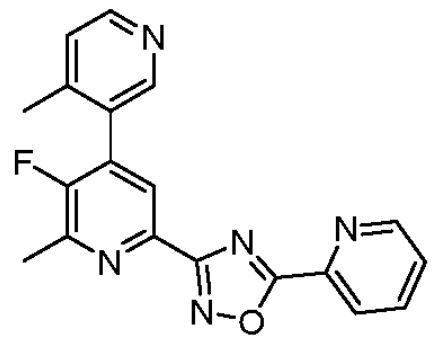
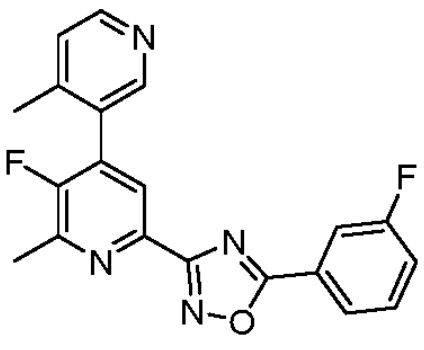
[00123] It is contemplated that the disclosed compounds can be used in connection with the disclosed methods, compositions, products, uses, and kits.

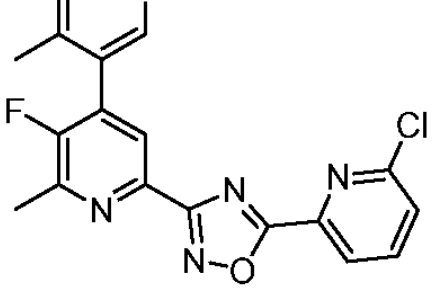
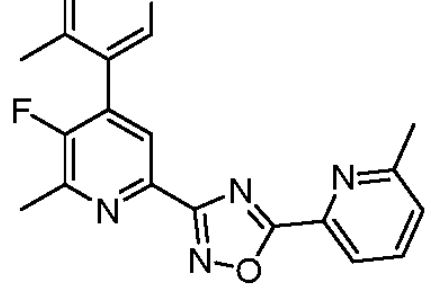
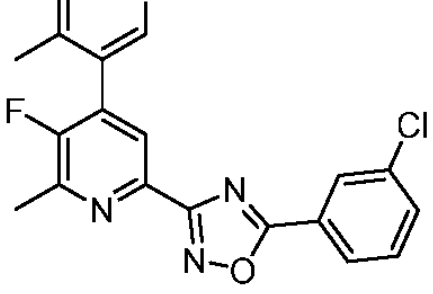
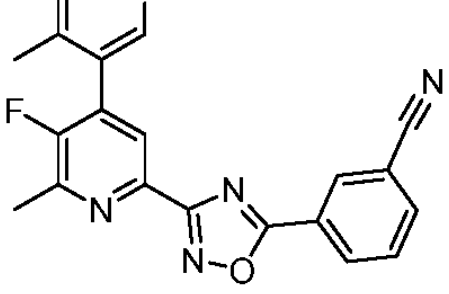
2. EXAMPLE STRUCTURES

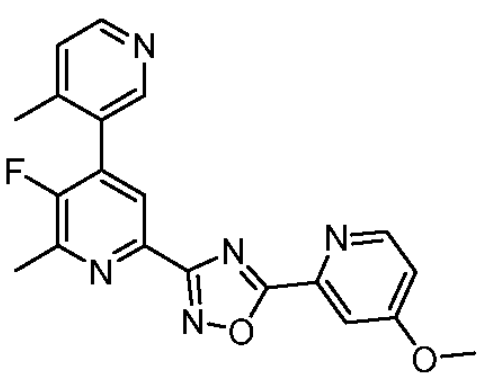
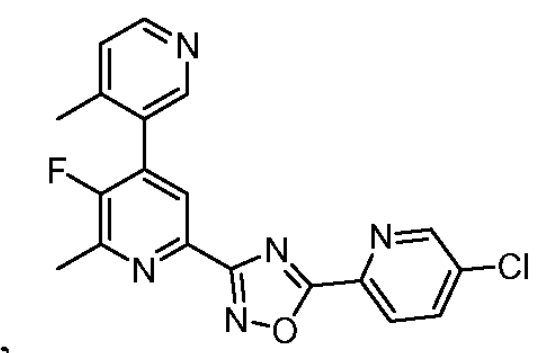
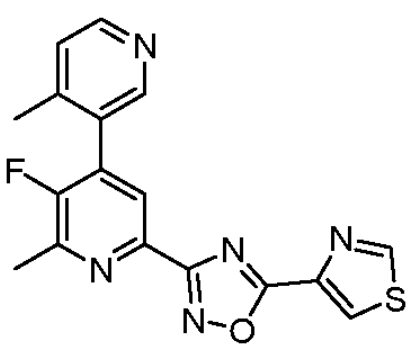
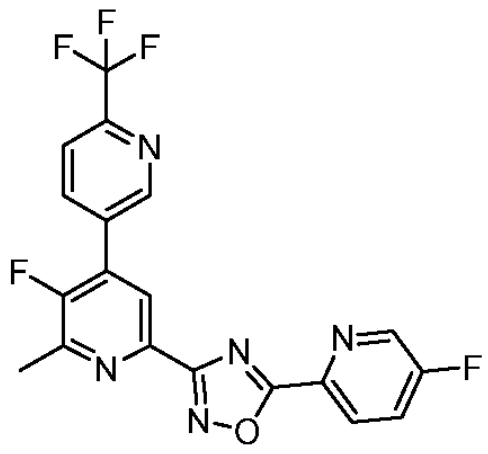
[00124] In one aspect, a compound is selected from:

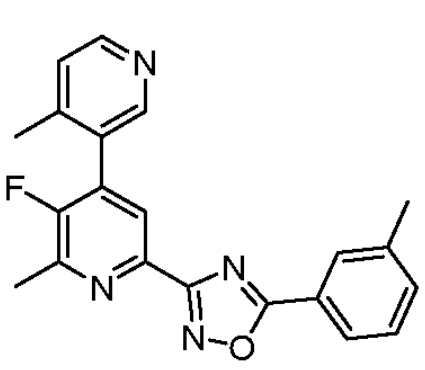
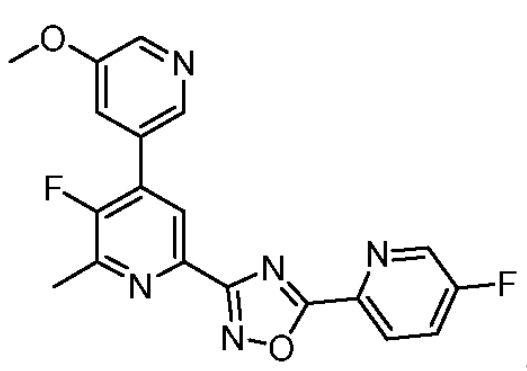
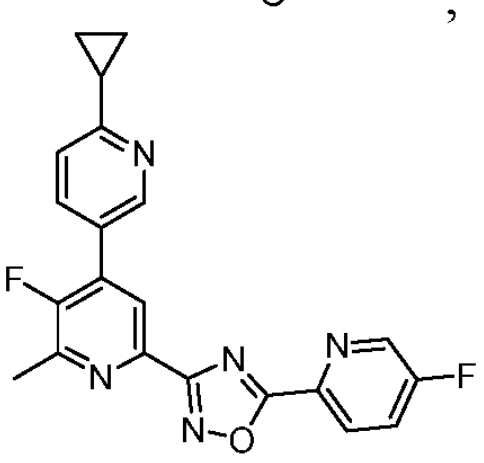
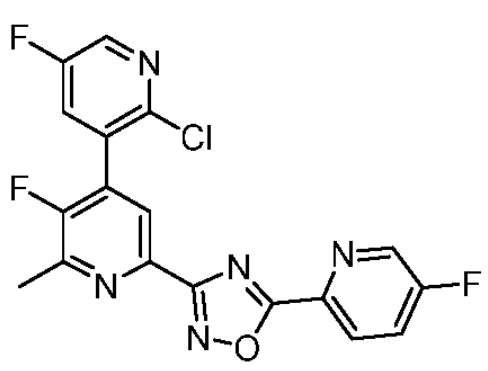


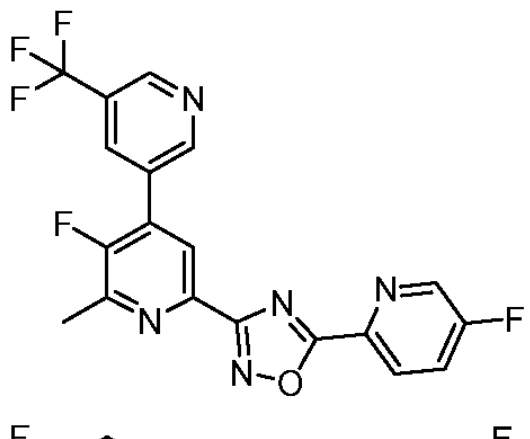
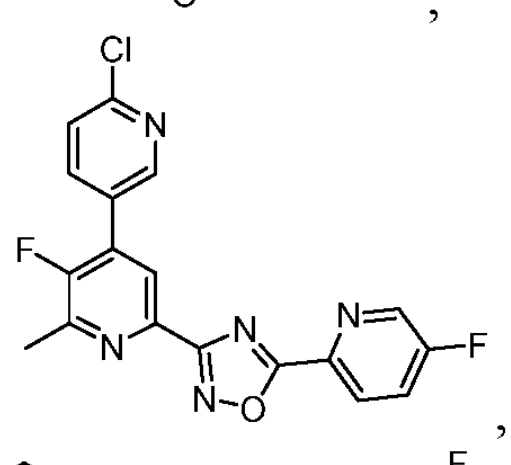
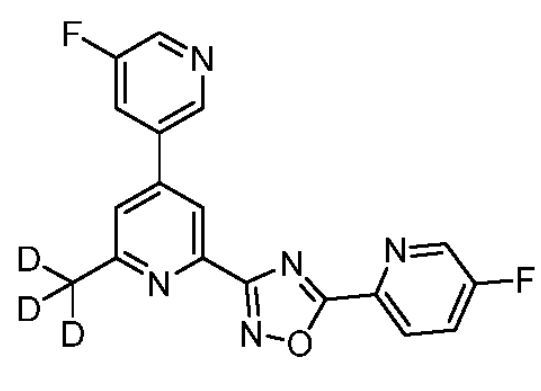
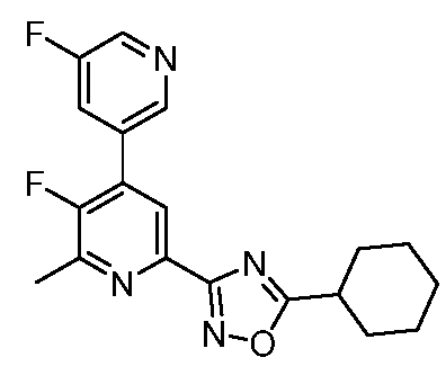
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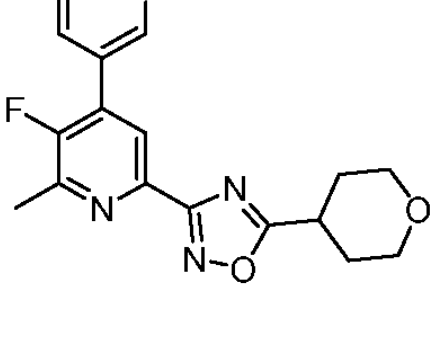
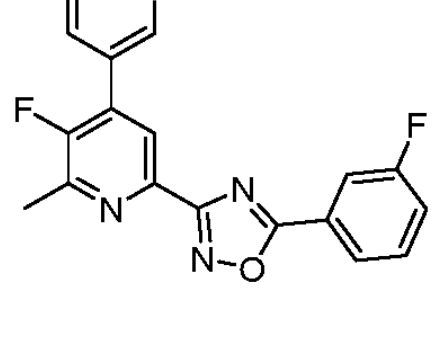
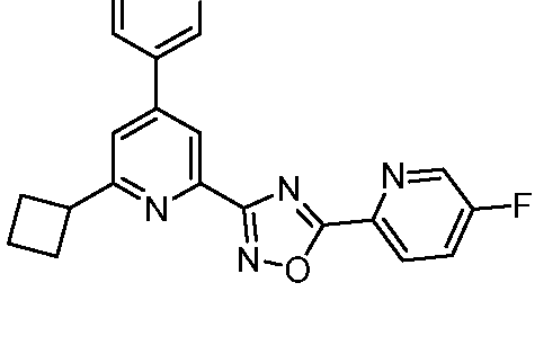
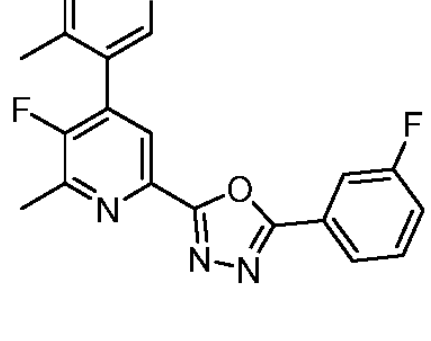
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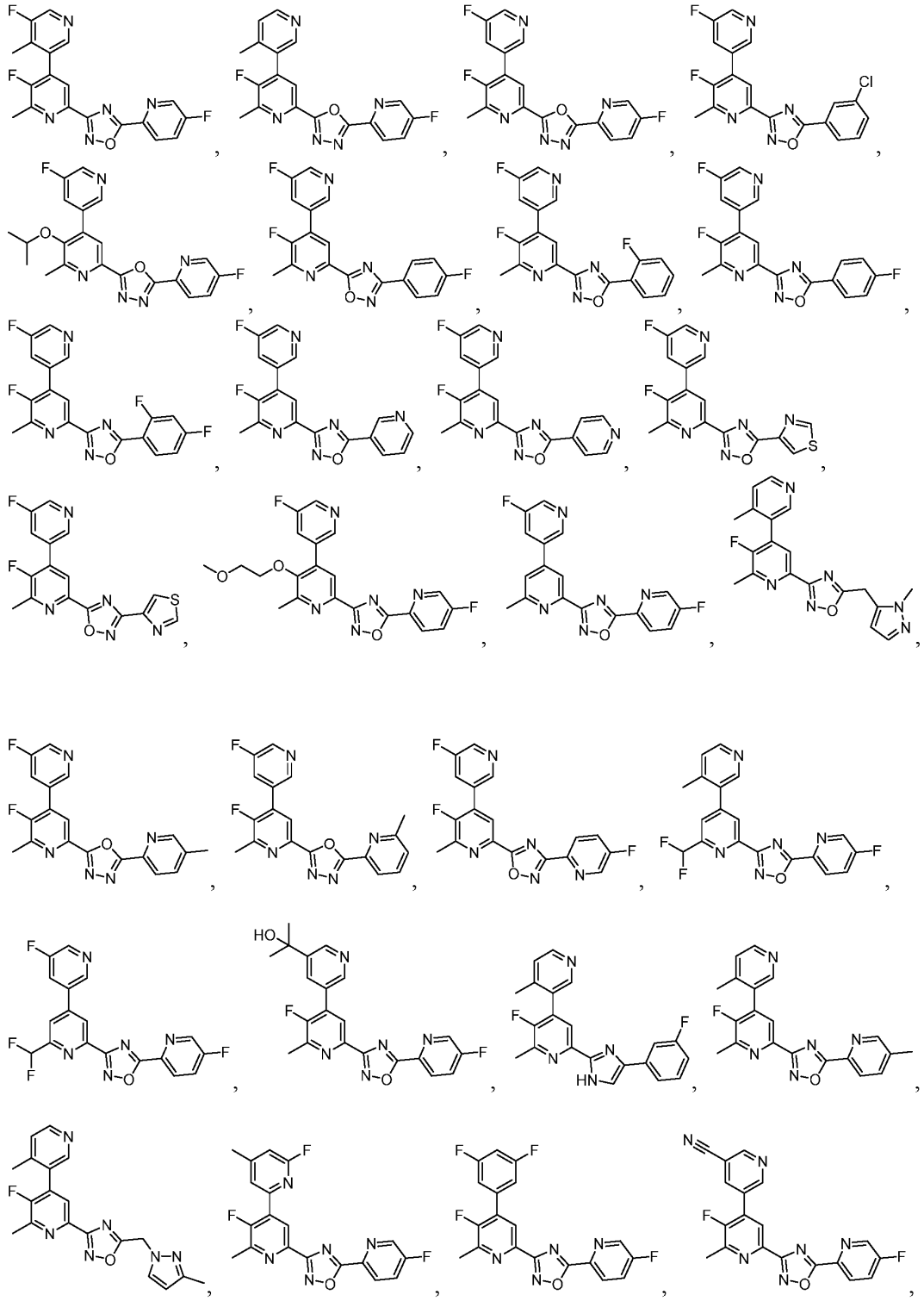
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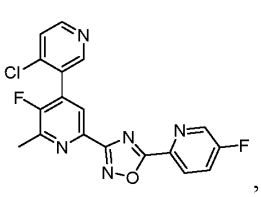
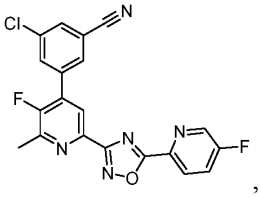
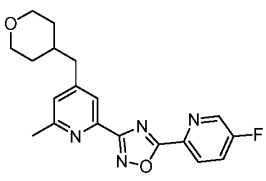
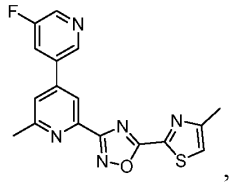
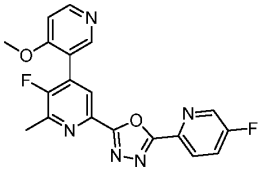
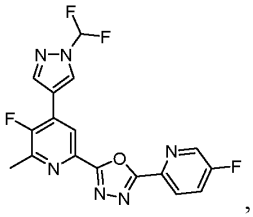
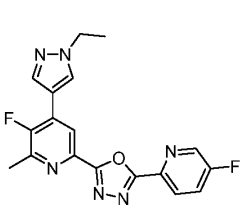
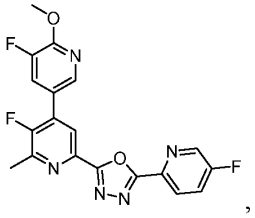
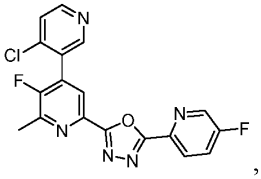
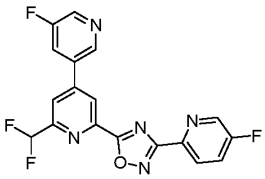
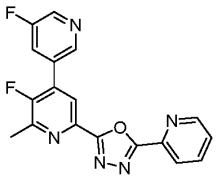
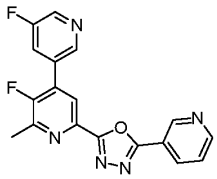
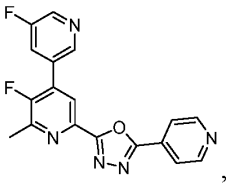
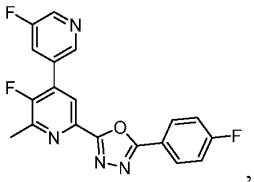
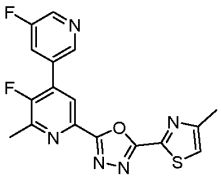
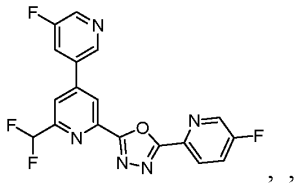
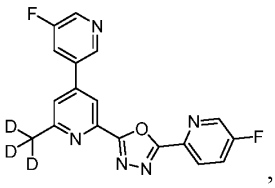
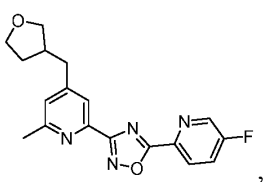
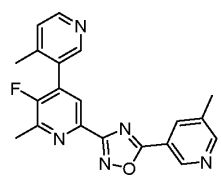
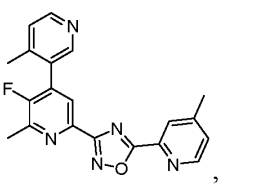
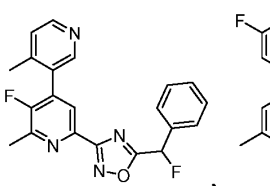
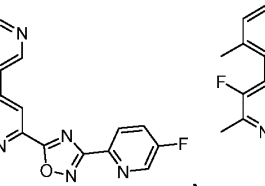
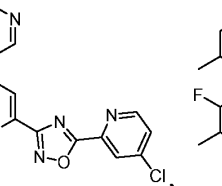
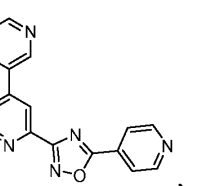
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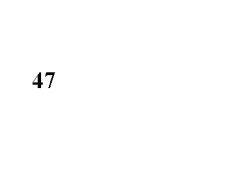
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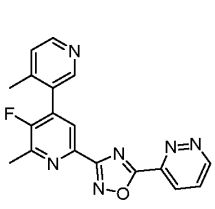
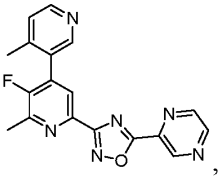
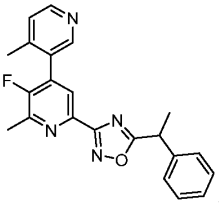
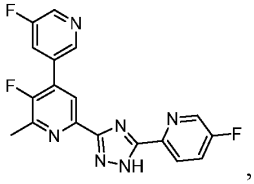
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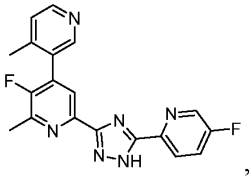
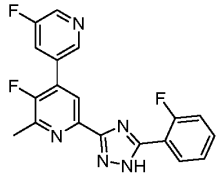
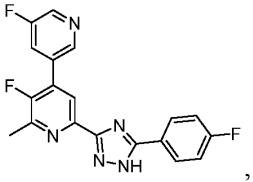
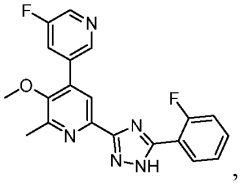
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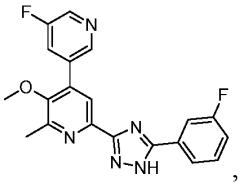
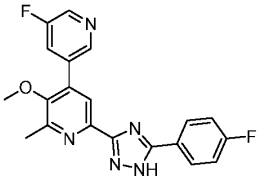
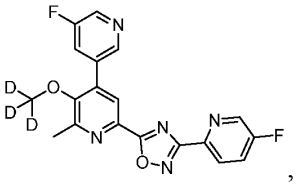
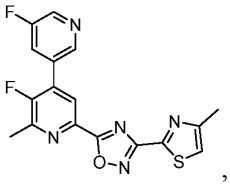
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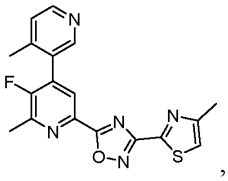
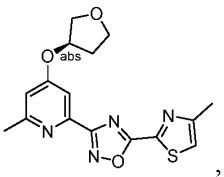
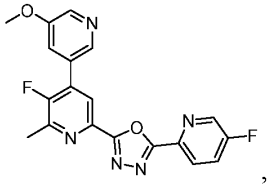
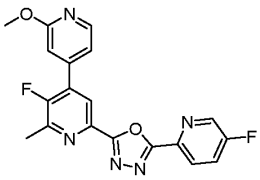
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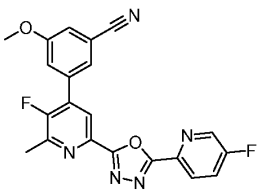
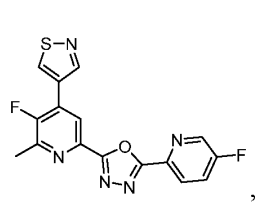
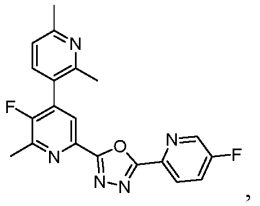
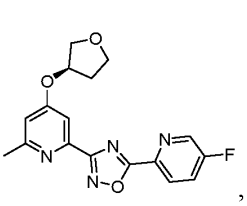
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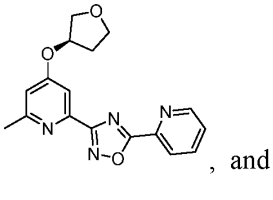
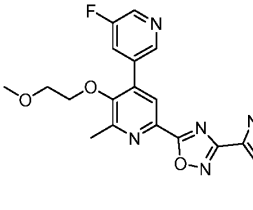
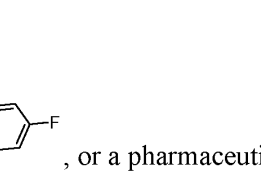
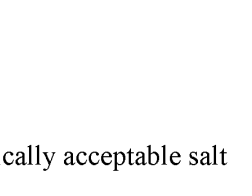
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, and , or a pharmaceutically acceptable salt thereof.

[00125] In yet a further aspect, the compound exhibits negative allosteric modulation of mGlu5 response to glutamate as a decrease in response to non-maximal concentrations of

glutamate in human embryonic kidney cells transfected with rat mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, human embryonic kidney cells are transfected with human mGlu5. In yet a further aspect, human embryonic kidney cells are transfected with mammalian mGlu5. In a further aspect, the compound exhibits partial or total inhibition of mGlu5 in response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with human, rat or mammalian mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In yet a further aspect, the compound exhibits negative allosteric modulation of mGlu5 after contacting a cell expressing mGlu5. In a further aspect, the compound produced exhibits partial or total inhibition of mGlu5 after contacting a cell expressing mGlu5.

[00126] It is contemplated that one or more example structures can be optionally omitted from the disclosed invention.

3. NEGATIVE ALLOSTERIC MODULATION OF MGLU5 RESPONSE

[00127] In one aspect, the compounds exhibit negative allosteric modulation of mGlu5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, the compound exhibits partial inhibition of mGlu5 response. In a further aspect, the compound exhibits total inhibition of mGlu5 response. In a still further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 1×10^{-7} M. In yet a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 5×10^{-8} M. In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1×10^{-7} M. In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 5×10^{-8} M. In yet a further aspect, the human embryonic kidney cells are transfected with human mGlu5. In an even further aspect, human embryonic kidney cells are transfected with mGlu5 of a mammal.

C. METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

[00128] The utility of the compounds in accordance with the present invention as negative allosteric modulators of metabotropic glutamate receptor activity, in particular mGlu5 activity, can be demonstrated by methodology known in the art. HEK 293A cells stably expressing either rat or human mGlu5 were plated in black-walled, clear-bottomed, poly-D-lysine coated 384-well plates in 20 μL of assay medium (DMEM containing 10% dialyzed FBS, 20 mM HEPES, 100 units/mL penicillin/streptomycin plus 250 ng/mL Fungizone, and 1 mM sodium pyruvate) at a density of 20K cells/well. The cells were grown overnight at 37 ºC in the presence of 5% CO_2. The next day, medium was removed and the cells incubated with 20 μL of 2.3 μM Fluo-4, AM prepared as a 2.3 mM stock in DMSO and mixed in a 1:1 ratio with 10% (w/v) pluronic acid F-127 and diluted in assay buffer (Hank's balanced salt solution, 20 mM HEPES, and 2.5 mM probenecid) for 45 minutes at 37 °C. Dye was removed, 20 μL of assay buffer was added, and the plate was incubated for 5 minutes at room temperature.

[00129] Ca^{2+} flux was measured using the Functional Drug Screening System (FDSS7000, Hamamatsu, Japan). After establishment of a fluorescence baseline for about 3 seconds, the compounds of the present invention were added to the cells, and the response in cells was measured. 2.3 minutes later an EC_{20} concentration of the mGlu5 receptor agonist glutamate was added to the cells, and the response of the cells was measured for 1.9 minutes; an EC_{80} concentration of agonist was added and readings taken for an additional 1.7 minutes. All test compounds were dissolved and diluted to a concentration of 10 mM in 100% DMSO. Compounds were then serially diluted 1:3 in DMSO into 10 point concentration response curves, transferred to daughter plates, and further diluted into assay buffer to a 2x stock. Calcium fluorescence measures were recorded as fold over basal fluorescence; raw data was then normalized to the maximal response to glutamate. Antagonism of the agonist response of the mGlu5 receptor in the present invention was observed as a decrease in response to nearly maximal concentrations of glutamate in the presence of compound compared to the response to glutamate in the absence of compound.

[00130] The raw data file containing all time points was used as the data source in the analysis template. This was saved by the FDSS as a tab-delimited text file. Data were normalized using a

static ratio function (F/F_0) for each measurement of the total 360 values per well divided by each well's initial value. Data were then reduced to peak amplitudes (Max – Initial Min) using a time range that starts approximately 3 seconds prior to the glutamate EC_{20}/EC_{80} addition and continues for approximately 90-120 seconds. This is sufficient time to capture the peak amplitude of the cellular calcium response. Individual amplitudes were expressed as % E_{Max} by multiplying each amplitude by 100 and then dividing the product by the mean of the amplitudes derived from the glutamate EC_{Max}-treated wells. IC_{50} values for test compounds were generated by fitting the normalized values versus the log of the test compound concentration (in mol/L) using a 4 parameter logistic equation where none of the parameters were fixed. Each of the three values collected at each concentration of test compound were weighted evenly.

[00131] A compound was designated as a negative allosteric modulator (NAM) if the compound showed a concentration-dependent decrease in the glutamate EC_{80} addition. For NAMs with a CRC that plateaus at a Glu Max (i.e., the amplitude of response in the presence of compound as a percentage of the maximal response to glutamate) below 10%, IC_{50} values are reported. For NAMs with a CRC that plateaus above 10% Glu Max, the IC_{50} values are reported, the compound is designated a "partial NAM" and the % Glu Max is reported. For NAMs that show a decrease in the EC_{80} response, but do not hit a plateau, the average of the Glu Max at a single concentration (30 μM) was determined (% Glu Max), reported, and IC_{50} values are reported as ">10,000 nM". Compounds without measurable activity are designated as ">30,000 nM" since the top concentration of compound tested in the assay is 30 μM. Exemplary data are provided in Tables 1 and 2 below.

[00132] In particular, the disclosed compounds had activity in modulating the mGlu5 receptor in the aforementioned assays, generally with an IC_{50} for modulation of less than about 30 μM. Preferred compounds within the present invention had activity in modulating the mGlu5 receptor with an IC_{50} for negative allosteric modulation of less than about 500 nM. Preferred compounds reduced the response to an EC_{80} concentration of glutamate to less than 50% of the maximal response and also induced a rightward and downward shift of the glutamate concentration response curve. These compounds are negative allosteric modulators of human and rat mGlu5

and were selective for mGlu5 compared to the other six subtypes of metabotropic glutamate receptors.

D. METHODS OF MAKING THE COMPOUNDS

[00133] In one aspect, the invention relates to methods of making compounds useful as negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGlu5), which can be useful in the treatment neurological and/or psychiatric disorders associated with glutamate dysfunction and other diseases in which metabotropic glutamate receptors are involved.

[00134] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

[00135] The disclosed compounds can be prepared by various routes known to one of ordinary skill in the art, including the schemes disclosed herein.

[00136] In a further aspect, a compound comprises the product of the disclosed methods. In a still further aspect, the invention comprises a pharmaceutical composition comprising a therapeutically effective amount of the product of the disclosed methods and a pharmaceutically acceptable carrier. In a still further aspect, the invention comprises a method for manufacturing a medicament comprising combining at least one compound of any of the disclosed compounds or at least one product of the disclosed methods with a pharmaceutically acceptable carrier or diluent.

[00137] In a further aspect, a compound comprises the product of the disclosed methods. In a still further aspect, the invention comprises a pharmaceutical composition comprising a therapeutically effective amount of the product of the disclosed methods and a pharmaceutically acceptable carrier. In a still further aspect, the invention comprises a method for manufacturing a medicament comprising combining at least one compound of any of disclosed compounds or at least one product of the disclosed methods with a pharmaceutically acceptable carrier or diluent.

[00138] In a further aspect, the compound produce can further undergo functional group transformation of the remaining substituents to yield additional analogs.

[00139] In a further aspect, the compound produced exhibits partial or total inhibition of mGlu5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a still further aspect, human embryonic kidney cells are transfected with human mGlu5. In yet a further aspect, human embryonic kidney cells are transfected with mammalian mGlu5.

[00140] In a further aspect, the compound produced exhibits partial or total inhibition of mGlu5 in response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with human, rat or mammalian mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a still further aspect, the compound produced exhibits negative allosteric modulation of mGlu5 after contacting a cell expressing mGlu5. In yet a further aspect, the compound produced exhibits partial or total inhibition of mGlu5 after contacting a cell expressing mGlu5.

[00141] It is contemplated that each disclosed method can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step, manipulation, and/or component can be optionally omitted from the invention. It is understood that a disclosed methods can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed methods of using.

E. PHARMACEUTICAL COMPOSITIONS

[00142] In one aspect, the invention relates to pharmaceutical compositions comprising the disclosed compounds. That is, a pharmaceutical composition can be provided comprising an effective amount of a disclosed compound, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a further aspect, the effective amount is a therapeutically

effective amount. In a still further aspect, the effective amount is a prophylactically effective amount.

[00143] In certain aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00144] As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (-ic and -ous), ferric, ferrous, lithium, magnesium, manganese (-ic and -ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, *N*,*N*'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[00145] As used herein, the term "pharmaceutically acceptable non-toxic acids", includes inorganic acids, organic acids, and salts prepared therefrom, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

[00146] In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, and/or pharmaceutically acceptable salt(s) thereof, can also be administered by controlled release means and/or delivery devices. The compositions can be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[00147] Thus, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[00148] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[00149] In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets can be coated by standard aqueous or nonaqueous techniques

[00150] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[00151] The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00152] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[00153] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[00154] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[00155] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

[00156] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

[00157] In the treatment conditions which require negative allosteric modulation of metabotropic glutamate receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day and can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably 0.5 to 100 mg/kg per day. A suitable dosage level can be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5.0 or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900 and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage of the patient to be treated. The compound can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosing regimen can be adjusted to provide the optimal therapeutic response.

[00158] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the type and severity of the particular disease undergoing therapy.

[00159] The present invention is further directed to a method for the manufacture of a medicament for modulating glutamate receptor activity (*e.g.*, treatment of one or more neurological and/or psychiatric disorders associated with glutamate dysfunction) in mammals (*e.g.*, humans) comprising combining one or more disclosed compounds, products, or

compositions with a pharmaceutically acceptable carrier or diluent. Thus, in one aspect, the invention relates to a method for manufacturing a medicament comprising combining at least one disclosed compound or at least one disclosed product with a pharmaceutically acceptable carrier or diluent.

[00160] The disclosed pharmaceutical compositions can further comprise other therapeutically active compounds, which are usually applied in the treatment of the above mentioned pathological conditions.

[00161] It is understood that the disclosed compositions can be prepared from the disclosed compounds. It is also understood that the disclosed compositions can be employed in the disclosed methods of using.

[00162] In a further aspect, the compound exhibits partial or total inhibition of mGlu5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a still further aspect, the human embryonic kidney cells are transfected with rat mGlu5. In yet a further aspect, the human embryonic kidney cells are transfected with human mGlu5.

F. METHODS OF USING THE COMPOUNDS AND COMPOSITIONS

[00163] The amino acid L-glutamate (referred to herein simply as glutamate) is the principal excitatory neurotransmitter in the mammalian central nervous system (CNS). Within the CNS, glutamate plays a key role in synaptic plasticity (*e.g.*, long term potentiation (the basis of learning and memory)), motor control and sensory perception. It is now well understood that a variety of neurological and psychiatric disorders are associated with dysfunctions in the glutamatergic system. Thus, modulation of the glutamatergic system is an important therapeutic goal. Glutamate acts through two distinct receptors: ionotropic and metabotropic glutamate receptors. The first class, the ionotropic glutamate receptors, is comprised of multi-subunit ligand-gated ion channels that mediate excitatory post-synaptic currents. Three subtypes of ionotropic glutamate receptors have been identified, and despite glutamate serving as agonist for all three receptor

subtypes, selective ligands have been discovered that activate each subtype. The ionotropic glutamate receptors are named after their respective selective ligands: kainite receptors, AMPA receptors and NMDA receptors.

[00164] The second class of glutamate receptor, termed metabotropic glutamate receptors, (mGlus), are G-protein coupled receptors (GPCRs) that modulate neurotransmitter release or the strength of synaptic transmission, based on their location (pre-or post-synaptic). The mGlus are family C GPCRs, characterized by a large (~560 amino acid) "venus fly trap" agonist binding domain in the amino-terminal domain of the receptor. This unique agonist binding domain distinguishes family C GPCRs from family A and B GPCRs wherein the agonist binding domains are located within the 7-strand transmembrane spanning (7TM) region or within the extracellular loops that connect the strands to this region. To date, eight distinct mGlus have been identified, cloned and sequenced. Based on structural similarity, primary coupling to intracellular signaling pathways and pharmacology, the mGlus have been assigned to three groups: Group I (mGlu1 and mGlu5), Group II (mGlu2 and mGlu3) and Group III (mGlu4, mGlu6, mGlu7 and mGlu8). Group I mGlus are coupled through $G_{\alpha q}$/11 to increase inositol phosphate and metabolism and resultant increases in intracellular calcium. Group I mGlus are primarily located post-synaptically and have a modulatory effect on ion channel activity and neuronal excitability. Group II (mGlu2 and mGlu3) and Group III (mGlu4, mGlu6, mGlu7 and mGlu8) mGlus are primarily located pre-synaptically where they regulate the release of neurotransmitters, such as glutamate. Group II and Group III mGlus are coupled to $G_{\alpha i}$ and its associated effectors such as adenylate cyclase.

[00165] Post-synaptic mGlus are known to functionally interact with post-synaptic ionotropic glutamate receptors, such as the NMDA receptor. For example, activation of mGlu5 by a selective agonist has been shown to increase post-synaptic NMDA currents (Mannaioni et al. (2001) *J. Neurosci.* **21**, 5925-5934). Therefore, modulation of mGlus is an approach to modulating glutamatergic transmission. Numerous reports indicate that mGlu5 plays a role in a number of disease states including anxiety (Spooren et al. (2000) *J. Pharmacol. Exp. Therapeut.* **295**, 1267-1275 ; Tatarczynska et al. (2001) *Br. J. Pharmaol.* **132**, 1423-1430), addiction to cocaine (Chiamulera et al. (2001) *Nature Neurosci.* **4**, 873-874), Parkinson's disease (Awad et al.

(2000) *J. Neurosci.* **20**, 7871-7879 ; Ossowska et al. (2001) *Neuropharmacol.* **41**, 413-420), pain (Salt and Binns (2001) *Neurosci.* **100**, 375-380), and Fragile X syndrome (FXS) (see, *i.e.*, de Vrij, F. M. S., et al. (2008) *Neurobiol. Disease* **31**, 127-132; Yan, Q. J., et al. (2005) *Neuropharmacol* **49**, 1053-1066).

[00166] The disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions for which compounds of formula I or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound is preferred. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound will be more efficacious than either as a single agent.

[00167] In one aspect, the subject compounds can be coadministered with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, muscarinic agonists, muscarinic potentiators, HMG-CoA reductase inhibitors, NSAIDs and anti-amyloid antibodies.

[00168] In a further aspect, the subject compounds can be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics, anti-epileptics, selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), tricyclic antidepressant drugs, monoamine oxidase inhibitors (MAOIs), 5-HT2 agonists or antagonists, GlyT1 inhibitors and the like such as, but not limited to: risperidone, clozapine, olanzapine, haloperidol, fluoxetine, prazepam, xanomeline, lithium, phenobarbitol, and salts thereof and combinations thereof.

[00169] In a further aspect, the subject compound can be used in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor), anti-cholinergics such as

biperiden, COMT inhibitors such as entacapone, A2a adenosine antagonists, cholinergic agonists, NMDA receptor agonists or antagonists and dopamine agonists.

[00170] In a further aspect, the subject compound can be administered in combination with opiate agonists or antagonists, calcium channel antagonists, sodium channel antagonists, COX-2 selective inhibitors, NK1 antagonists, non-steroidal anti-inflammatory drugs ("NSAID"), GABA-A receptor modulators, dopamine agonists or antagonists, norepinephrine modulators, nicotinic agonists or antagonists including nicotine, and muscarinic agonists or antagonists. In a yet further aspect, the subject compound can be administered in combination with heroin substituting drugs such as methadone, levo-alpha-acetylmethadol, buprenorphine and naltrexone, and disulfiram and acamprosate. In a further aspect, the subject compound can be administered in combination with L-DOPA, buspirone, valproate, and gabapentin.

[00171] The pharmaceutical compositions and methods of the present invention can further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

1. TREATMENT METHODS

[00172] The compounds disclosed herein are useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with glutamate dysfunction. Thus, provided is a method of treating or preventing a disorder in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[00173] Also provided is a method for the treatment of one or more neurological and/or psychiatric disorders associated with glutamate dysfunction in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[00174] Examples of disorders associated with glutamate dysfunction include: acute and chronic 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 (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, addictive behavior, including addiction to substances (including opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), withdrawal from such addictive substances (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), obesity, psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic pain states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

[00175] Anxiety disorders that can be treated or prevented by the compositions disclosed herein include generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder. Addictive behaviors include addiction to substances (including opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), withdrawal from such addictive substances (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.) and substance tolerance.

[00176] Also provided is a method for treating or preventing anxiety, comprising: administering to a subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject. At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.),

provides a diagnostic tool including anxiety and related disorders. These include: panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified.

[00177] Further disorders that can be treated or prevented by the compositions disclosed herein include Autism spectrum disorders, which are neuropsychiatric conditions characterized by widespread abnormalities of social interactions and communication, as well as severely restricted interests and highly repetitive behavior. Autism spectrum disorders include Autism, Asperger syndrome, Childhood Disintegrative Disorders, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, and Rett Syndrome. Fragile X syndrome (FXS) is a single gene disorder almost universally associated with symptoms of autism spectrum disorder, the most common form of inherited mental retardation, and the most common known cause of autism, affecting 1 in 6,000 births. Therapeutic agents for treatment of patients with FXS are among the most critical of unmet medical needs, and there are very few proven effective treatment strategies for this patient population. Again, without wishing to be bound by theory, increasing evidence has identified a connection between the Fragile X phenotype and mGlu signaling

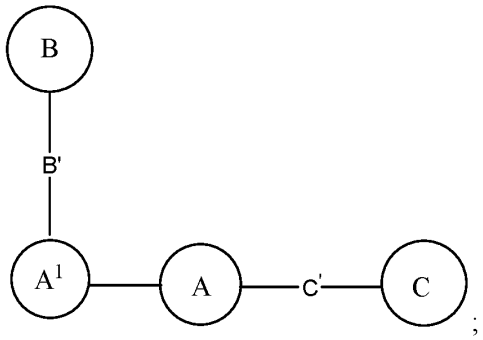
[00178] Compounds of the invention can be used, for example, for the treatment of Fragile X syndrome and autism spectrum disorder in a manner that can improve symptoms (e.g., reduce anxiety and irritability; increase cognitive function, communication and/or social interaction). Thus, the methods of the invention can provide an effective manner to treat a subject having Fragile X syndrome or autism spectrum disorder.

a. TREATING A DISORDER

[00179] In one aspect, the invention relates to a method for the treatment of a disorder associated with metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal at least one disclosed compound or at least one disclosed product in a dosage and amount effective to treat the disorder in the mammal. In a further aspect, the

mammal is a human. In a further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of treatment of the disorder.

[00180] In one aspect, the invention relates to a method for the treatment of a disorder associated with metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound having a structure represented by a formula:



;

[00181] wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;

[00182] C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00183] In a further aspect, the compound administered is any disclosed compound or a product of a disclosed method.

[00184] In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00185] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In yet a further aspect, the treatment of the disorder further comprises the step of identifying a mammal in need of treatment of the disorder. In an even further aspect, the disorder is a neurological and/or psychiatric disorder associated with metabotropic glutamate receptor dysfunction. In a further aspect, the neurological and/or psychiatric disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, and depression.

[00186] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

[00187] In a further aspect, the disorder is a disease of uncontrolled cellular proliferation. In a still further aspect, the uncontrolled cellular proliferation is cancer. In yet a further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung cancer, pancreatic cancer, breast cancer, and malignant melanoma.

[00188] In one aspect, the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a further aspect, the disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, depression, affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman syndrome, Asperger syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, paranoia, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma

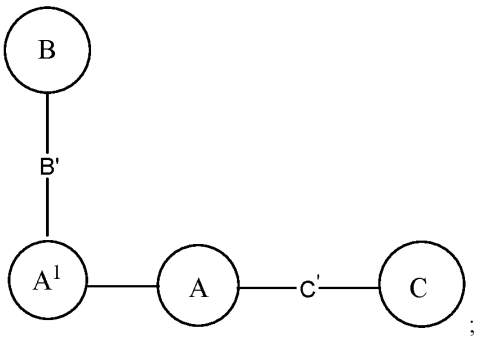
syndrome, senile dementia, sleep disorder, substance-related disorder, post-traumatic stress disorder (PTSD), or unipolar depression.

[00189] In a further aspect, the compound exhibits partial inhibition of mGlu5 response. In a still further aspect, the compound exhibits total inhibition of mGlu5 response. In yet a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 1 x 10^{-7} M. In an even further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 5 x 10^{-8} M. In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1 x 10^{-7} M. In yet a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 5 x 10^{-8} M.

b. DECREASING MGLU5 ACTIVITY

[00190] In one aspect, the invention relates to a method for decreasing metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal at least one disclosed compound or at least one disclosed product in a dosage and amount effective to decrease metabotropic glutamate receptor activity in the mammal. In a further aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of treatment of the disorder.

[00191] In one aspect, the invention relates to a method for decreasing metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00192] In a further aspect, the compound administered is any disclosed compound or a product of a disclosed method.

[00193] In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00194] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In yet a further aspect, the treatment of the disorder further comprises the step of identifying a mammal in need of treatment of the disorder. In an even further aspect, the disorder is a neurological and/or psychiatric disorder associated with metabotropic glutamate receptor dysfunction. In a further aspect, the neurological and/or psychiatric disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, and depression.

[00195] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical

autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

[00196] In a further aspect, the disorder is a disease of uncontrolled cellular proliferation. In a still further aspect, the uncontrolled cellular proliferation is cancer. In yet a further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung cancer, pancreatic cancer, breast cancer, and malignant melanoma.

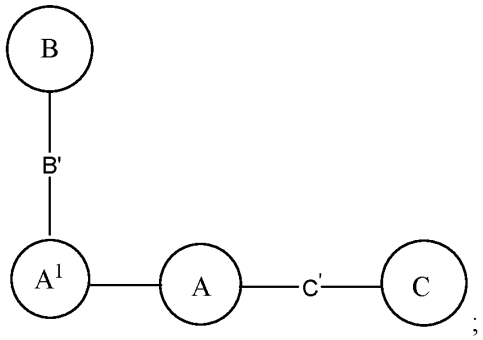
[00197] In one aspect, the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a further aspect, the disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, depression, affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman syndrome, Asperger syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, paranoia, , post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, post-traumatic stress disorder (PTSD), or unipolar depression.

[00198] In a further aspect, the compound exhibits partial inhibition of mGlu5 response. In a still further aspect, the compound exhibits total inhibition of mGlu5 response. In yet a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 1×10^{-7} M. In an even further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 5×10^{-8} M. In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1×10^{-7} M. In yet a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 5×10^{-8} M.

c. INHIBITING MGLU5 ACTIVITY

[00199] In one aspect, the invention relates to a method for inhibiting metabotropic glutamate receptor activity in a mammal, comprising the step of contacting the mammal with at least one disclosed compound or at least one disclosed product in an amount effective to inhibit metabotropic glutamate receptor activity in the mammal.

[00200] In one aspect, the invention relates to a method for inhibiting metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00201] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00202] In a further aspect, the metabotropic glutamate receptor is mGlu5.

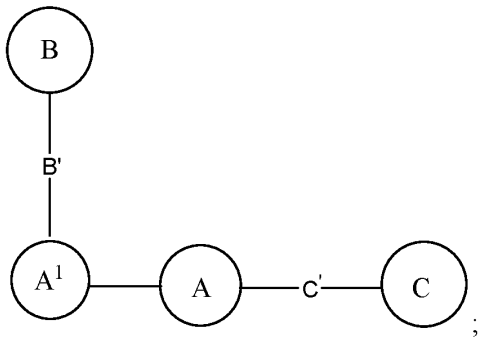
[00203] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In yet a further aspect, the treatment of the disorder further comprises the step of identifying a mammal in need of treatment of the disorder. In an even further aspect, the disorder is a neurological and/or psychiatric disorder associated with metabotropic glutamate receptor dysfunction. In a further aspect, the neurological and/or psychiatric disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, and depression.

[00204] In a further aspect, the compound exhibits partial inhibition of mGlu5 response. In a still further aspect, the compound exhibits total inhibition of mGlu5 response. In yet a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 1 x 10^{-7} M. In an even further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 5 x 10^{-8} M. In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1 x 10^{-7} M. In yet a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 5 x 10^{-8} M.

d. NEGATIVE ALLOSTERIC MODULATION OF MGLU5 ACTIVITY

[00205] In one aspect, the invention relates to a method for negative allosteric modulation of metabotropic glutamate receptor activity in a mammal, comprising the step of contacting the mammal with at least one disclosed compound or at least one disclosed product in an amount effective to negatively allosterically modulate metabotropic glutamate receptor activity in the mammal.

[00206] In one aspect, the invention relates to a method for negative allosteric modulation of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00207] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

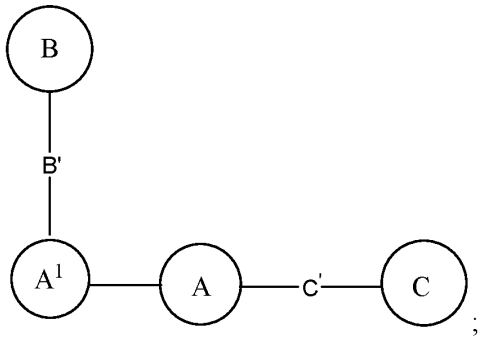
[00208] In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00209] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In yet a further aspect, the treatment of the disorder further comprises the step of identifying a mammal in need of treatment of the disorder. In an even further aspect, the disorder is a neurological and/or psychiatric disorder associated with metabotropic glutamate receptor dysfunction. In a further aspect, the neurological and/or psychiatric disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, and depression.

e. PARTIAL ANTAGONISM OF MGLU5 ACTIVITY

[00210] In one aspect, the invention relates to a method for partial antagonism of metabotropic glutamate receptor activity in a mammal, comprising the step of contacting the mammal with at least one disclosed compound or at least one disclosed product in an amount effective to partially antagonize metabotropic glutamate receptor activity in the mammal.

[00211] In one aspect, the invention relates to a method for partial antagonism of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00212] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

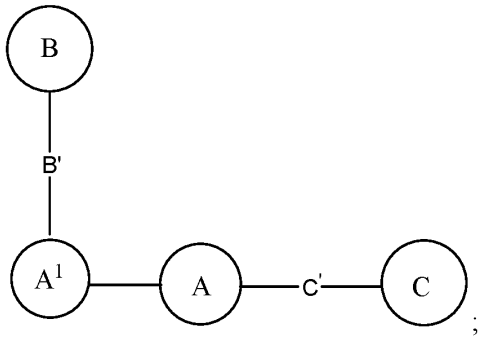
[00213] In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00214] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In yet a further aspect, the treatment of the disorder further comprises the step of identifying a mammal in need of treatment of the disorder. In an even further aspect, the disorder is a neurological and/or psychiatric disorder associated with metabotropic glutamate receptor dysfunction. In a further aspect, the neurological and/or psychiatric disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, and depression.

f. MODULATING MGLU5 ACTIVITY

[00215] In one aspect, the invention relates to a method for modulating metabotropic glutamate receptor activity in a mammal, comprising the step of contacting the mammal with at least one disclosed compound or at least one disclosed product in an amount effective to modulate metabotropic glutamate receptor activity in the mammal.

[00216] In one aspect, the invention relates to a method for modulating metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or

unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00217] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00218] In a further aspect, modulating is inhibition. In a still further aspect, modulating is noncompetitive inhibition. In yet a further aspect, modulating is noncompetitive antagonism. In an even further aspect, modulating is negative allosteric modulation.

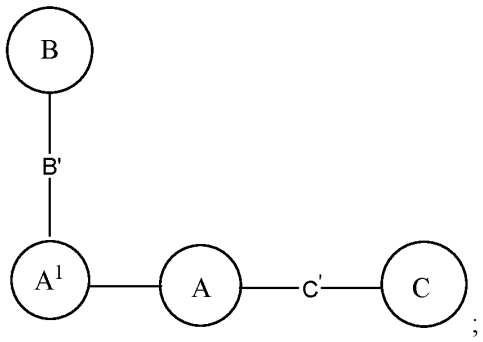
[00219] In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00220] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In yet a further aspect, the treatment of the disorder further comprises the step of identifying a mammal in need of treatment of the disorder. In an even further aspect, the disorder is a neurological and/or psychiatric disorder associated with metabotropic glutamate receptor dysfunction. In a further aspect, the neurological and/or psychiatric disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, and depression.

g. INHIBITING MGLU5 ACTIVITY IN CELLS

[00221] In one aspect, the invention relates to a method for inhibiting metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting at least one cell with at least one disclosed compound or at least one disclosed product in an amount effective to inhibit metabotropic glutamate receptor activity in at least one cell.

[00222] In one aspect, the invention relates to a method for inhibiting metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting at least one cell with at least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00223] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00224] In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00225] In a further aspect, the cell is mammalian. In a still further aspect, the cell is human. In yet a further aspect, the cell has been isolated from a mammal prior to the contacting step. In an even further aspect, contacting the cell is via administration to a mammal. In a still further aspect, inhibiting metabotropic glutamate receptor activity in at least one cell decreases metabotropic glutamate receptor activity in the mammal. In yet a further aspect, the decrease in metabotropic glutamate receptor activity in the mammal treats a disorder associated with metabotropic glutamate receptor activity in the mammal.

[00226] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical

autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

[00227] In a further aspect, the disorder is a disease of uncontrolled cellular proliferation. In a still further aspect, the uncontrolled cellular proliferation is cancer. In yet a further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung cancer, pancreatic cancer, breast cancer, and malignant melanoma.

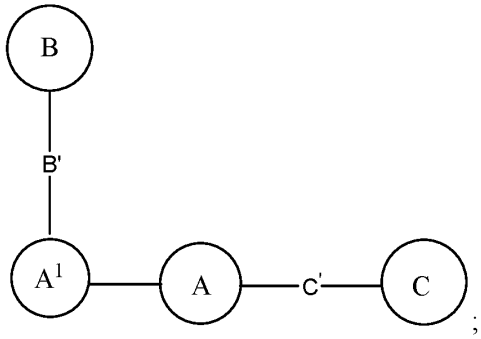
[00228] In one aspect, the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a further aspect, the disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, depression, affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman syndrome, Asperger syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, paranoia, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

[00229] In a further aspect, the compound exhibits partial inhibition of mGlu5 response. In a still further aspect, the compound exhibits total inhibition of mGlu5 response. In yet a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 1 x 10^{-7} M. In an even further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 5 x 10^{-8} M. In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1 x 10^{-7} M. In yet a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 5 x 10^{-8} M.

h. MODULATING MGLU5 ACTIVITY IN CELLS

[00230] In one aspect, the invention relates to a method for modulating metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting at least one cell with at least one disclosed compound or at least one disclosed product in an amount effective to modulate metabotropic glutamate receptor activity in at least one cell.

[00231] In one aspect, the invention relates to a method for modulating metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting at least one cell with at least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00232] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00233] In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00234] In a further aspect, modulating is inhibition. In a still further aspect, modulating is noncompetitive inhibition. In yet a further aspect, modulating is noncompetitive antagonism. In an even further aspect, modulating is negative allosteric modulation.

[00235] In a further aspect, the cell is mammalian. In a still further aspect, the cell is human. In yet a further aspect, the cell has been isolated from a mammal prior to the contacting step. In an even further aspect, contacting the cell is via administration to a mammal. In a still further aspect, inhibiting metabotropic glutamate receptor activity in at least one cell decreases metabotropic glutamate receptor activity in the mammal. In yet a further aspect, the decrease in metabotropic glutamate receptor activity in the mammal treats a disorder associated with metabotropic glutamate receptor activity in the mammal.

2. MANUFACTURE OF A MEDICAMENT

[00236] In one aspect, the invention relates to a method for manufacturing a medicament comprising combining at least one disclosed compound with a pharmaceutically acceptable carrier or diluent. In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound. In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00237] In a further aspect, the compound exhibits partial or total inhibition of mGlu5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a still further aspect, the human embryonic kidney cells are transfected with rat mGlu5. In yet a further aspect, the human embryonic kidney cells are transfected with human mGlu5.

[00238] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

[00239] In a further aspect, the disorder is a disease of uncontrolled cellular proliferation. In a still further aspect, the uncontrolled cellular proliferation is cancer. In yet a further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung cancer, pancreatic cancer, breast cancer, and malignant melanoma.

[00240] In one aspect, the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a further aspect, the disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, depression, affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman syndrome, Asperger syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, paranoia, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, post-traumatic stress disorder (PTSD), or unipolar depression.

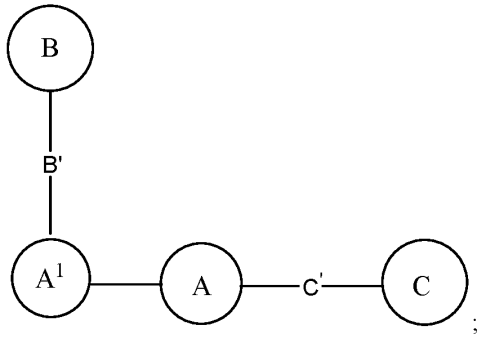
[00241] In a further aspect, the compound exhibits partial inhibition of mGlu5 response. In a still further aspect, the compound exhibits total inhibition of mGlu5 response. In yet a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 1×10^{-7} M. In an even further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 5×10^{-8} M. In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1×10^{-7} M. In yet a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 5×10^{-8} M.

3. USE OF COMPOUNDS

[00242] Also provided are the uses of the disclosed compounds and products. In one aspect, the use relates to a treatment of a disorder in a mammal. In one aspect, the use is characterized in

that the mammal is a human. In one aspect, the use is characterized in that the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In one aspect, the use relates to negative allosteric modulation of metabotropic glutamate receptor activity in a mammal.

[00243] In one aspect, the invention relates to use of at least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof.

[00244] In a further aspect, the compound is any disclosed compound or product of a disclosed method. In a further aspect, the metabotropic glutamate receptor is mGlu5.

[00245] In a further aspect, the compound exhibits partial or total inhibition of mGlu5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGlu5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a still further aspect,

the human embryonic kidney cells are transfected with rat mGlu5. In yet a further aspect, the human embryonic kidney cells are transfected with human mGlu5.

[00246] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

[00247] In a further aspect, the disorder is a disease of uncontrolled cellular proliferation. In a still further aspect, the uncontrolled cellular proliferation is cancer. In yet a further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung cancer, pancreatic cancer, breast cancer, and malignant melanoma.

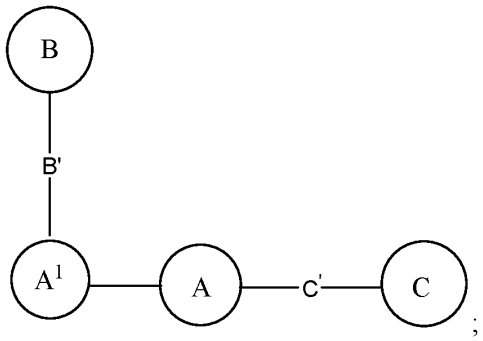
[00248] In one aspect, the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a further aspect, the disorder is selected from addiction, anxiety, Fragile X syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, pain, depression, affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman syndrome, Asperger syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, paranoia, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, post-traumatic stress disorder (PTSD), or unipolar depression.

[00249] In a further aspect, the compound exhibits partial inhibition of mGlu5 response. In a still further aspect, the compound exhibits total inhibition of mGlu5 response. In yet a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 1 x

10^{-7} M. In an even further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 5 x 10^{-8} M. In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1 x 10^{-7} M. In yet a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 5 x 10^{-8} M.

4. KITS

[00250] In one aspect, the invention relates to a kit comprising at least one compound having a structure represented by a formula:



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine, C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl; or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent known to increase mGlu5 activity; (b) at least one agent known to decrease mGlu5 activity; (c) at least one agent known to treat a neurological and/or psychiatric disorder; or (d) instructions for treating a disorder associated with glutamate dysfunction.

[00251] In a further aspect, the at least one compound and the at least one agent are co-formulated. In a further aspect, the at least one compound and the at least one agent are co-packaged.

[00252] In a further aspect, the kit, wherein the compound present is any disclosed compound or at least one product of a disclosed method of making.

[00253] In a further aspect, the kit comprises a disclosed compound or a product of a disclosed method.

[00254] The kits can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another component for delivery to a patient.

[00255] It is contemplated that the disclosed kits can be used in connection with the disclosed methods of making, the disclosed methods of using, and/or the disclosed compositions.

5. NON-MEDICAL USES

[00256] Also provided are the uses of the disclosed compounds and products as pharmacological tools in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of the effects of potentiators of mGlu related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents of mGlu. In a further aspect, the invention relates to the use of a disclosed compound or a disclosed product as pharmacological tools in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of the effects of potentiators of mGlu5 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents of mGlu5.

G. EXPERIMENTAL

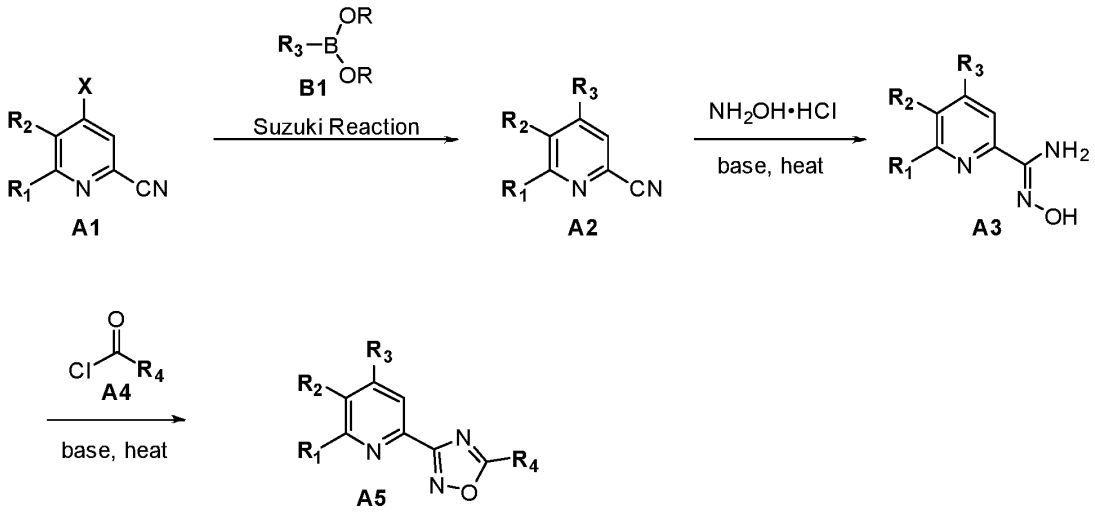
[00257] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless

indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

[00258] Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein. All ^{1}H NMR spectra were obtained on instrumentation at a field strength of 300 to 500 MHz.

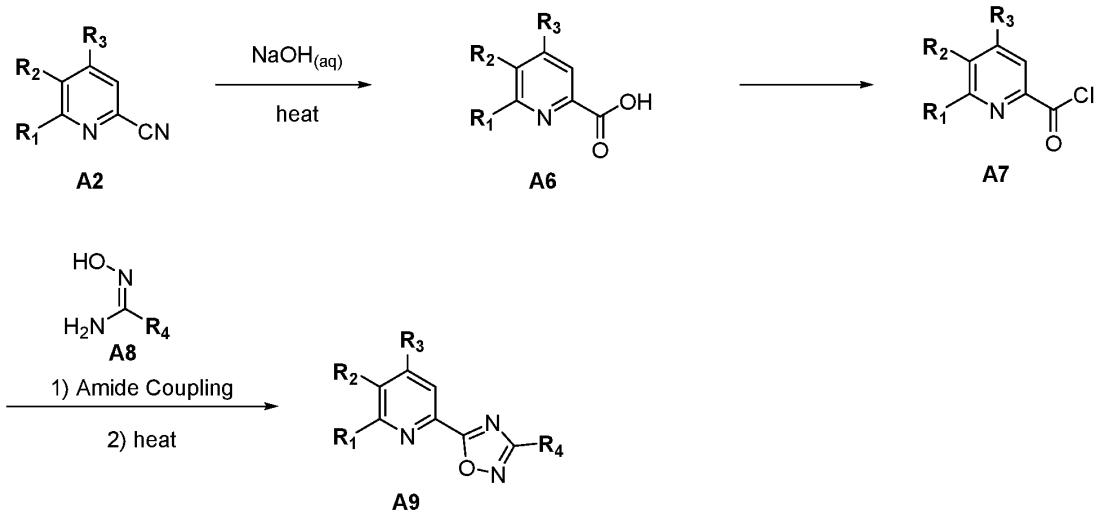
1. General Schemes

General Scheme I



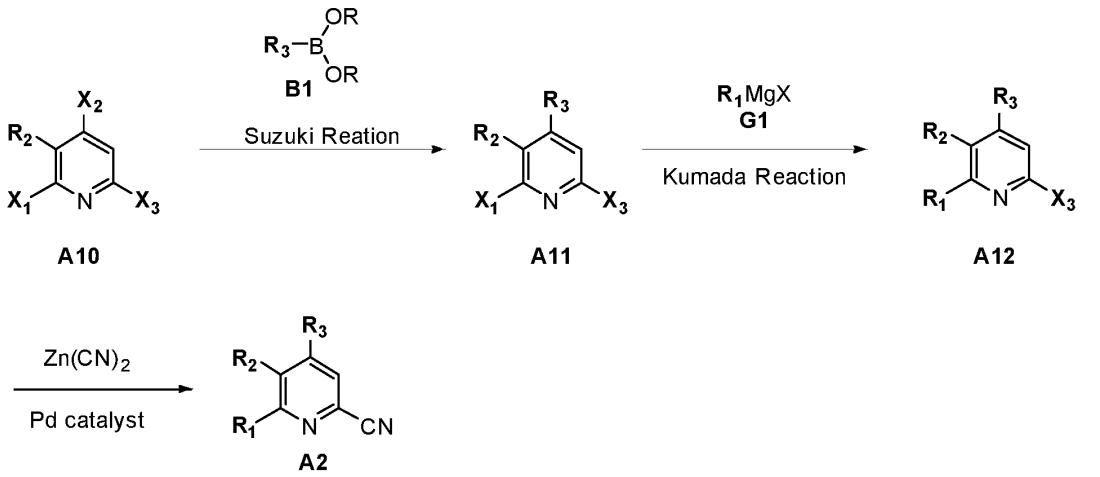
General Scheme I shows a method for preparing intermediates of the invention. Reaction of intermediates **A1** (e.g. X is halogen) with boronic acids or boronic esters (**B1**) under standard Suzuki reaction conditions may provide intermediates **A2**. Intermediates **A2** may be transformed into the amidoxime intermediates **A3** (e.g. $NH_2OH{\cdot}HCl$, Et_3N, EtOH, microwave irradiation at 150°C). Intermediates **A3** may then undergo an amide formation with intermediates **A4**, which may then be further transformed into compounds **A5** upon heating (e.g. 100 °C).

General Scheme II



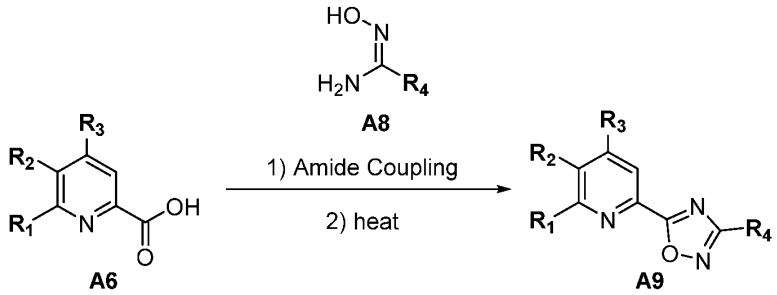
General Scheme II shows a method for preparing compounds of the invention. Intermediates **A2** under basic hydrolysis conditions (e.g. NaOH) and heat (e.g., 100 °C) may provide intermediates **A6**. Intermediates **A6** may then be transformed in to the acid chloride intermediates **A7** under standard conditions (e.g. oxalyl chloride, DMF (catalytic), DCM). Intermediates **A7** may then undergo an amide formation with amidoxime intermediates **A8**, which may then be further transformed into compounds **A9** upon heating (e.g. 100 °C).

General Scheme III



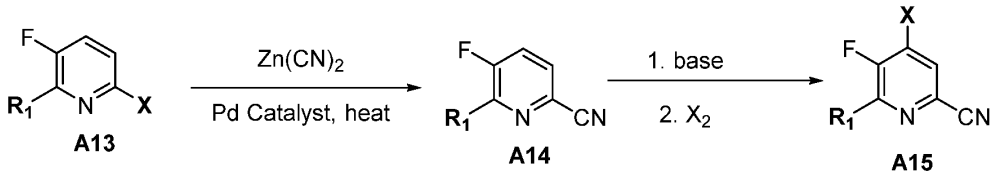
General Scheme III shows a method for preparing intermediates of the invention. Reaction of intermediates **A10** (e.g. X_1, X_2, and X_3 are halogens) with boronic acids or boronic esters (**B1**) under standard Suzuki reaction conditions may provide intermediates **A11**. Reaction of intermediates **A11** with Grignard reagents (**G1**) under Kumada coupling reaction conditions (e.g. $Fe(acac)_3$) may provide intermediates **A12**. Intermediates **A12** in the presence of palladium catalyst (e.g. $Pd(PPh_3)_4$), zinc cyanide and heat (e.g. 100 °C) may provide an alternative route to intermediates **A2.**

General Scheme IV



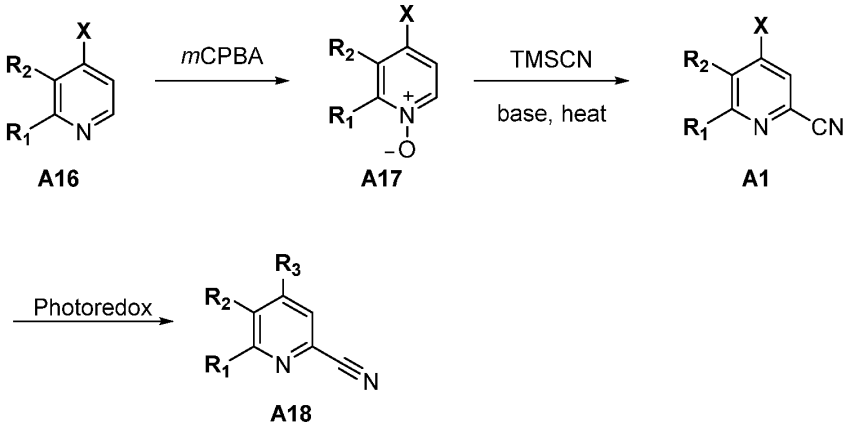
General Scheme IV shows an alternative method for preparing intermediates **A9**. Intermediates **A6** may directly undergo an amide formation with amidoxime intermediates **A8**, which may then be further transformed into compounds **A9** upon heating (e.g. 100 °C).

General Scheme V



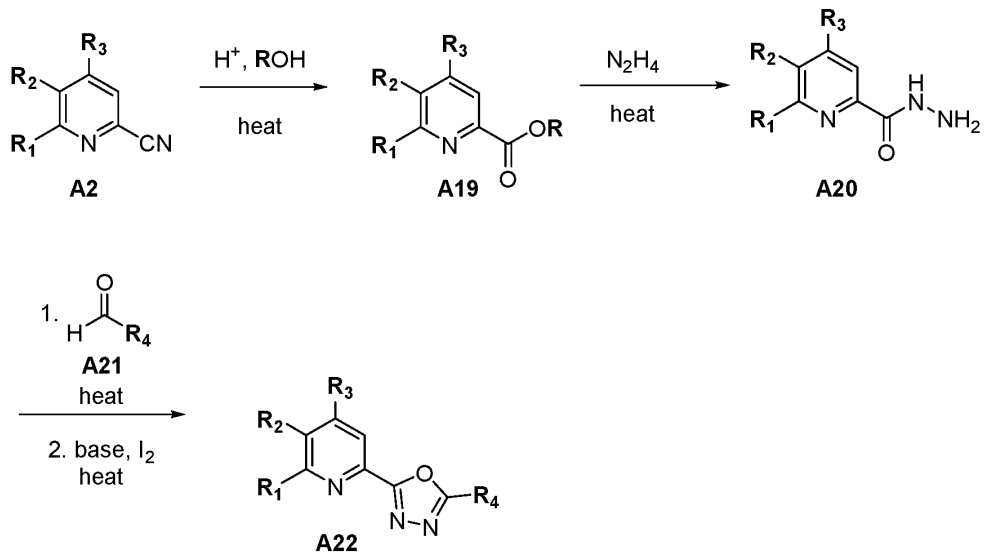
General Scheme V shows a method for preparing intermediates of the invention. Intermediates **A13** (e.g. X is halogen) with a palladium catalyst (e.g. $Pd(PPh_3)_4$), zinc cyanide and heat (e.g. 140 °C) may provide intermediates **A14**. Intermediates **A14** may then be subjected to base (e.g. LDA) followed by a halide source (e.g. I_2) to provide intermediates **A15**.

General Scheme VI



Shown in General Scheme VI is a method for preparing intermediates of the invention. Intermediates **A16** (e.g., X is halogen) may be transformed to intermediates **A17** by an oxidizing agent (e.g., *m*CPBA). Intermediates **A17** may be transformed into intermediates **A1** (e.g. TMSCN, Et_3N, and EtCN). Intermediates **A1** may be subjected to photoredox conditions (e.g. $Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$, TTMSS, LiOH, $(4,4'\text{-dtbbpy})NiCl_2$, monoglyme, and blue LED light) to provide intermediates **A18**.

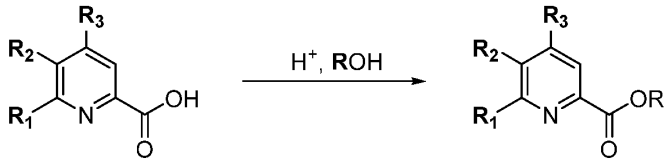
General Scheme VII



Shown in General Scheme VII is a method for preparing intermediates of the invention.

Intermediates **A2** may be transformed into ester intermediates **A19** by standard procedures (e.g. HCl, EtOH, 65 °C). Intermediates **A19** with hydrazine and heat (e.g. μW irradiation at 120 °C) may then provide intermediates **A20**. Following a 2-step sequence, intermediates **A20** may be transformed into compounds **A22**.

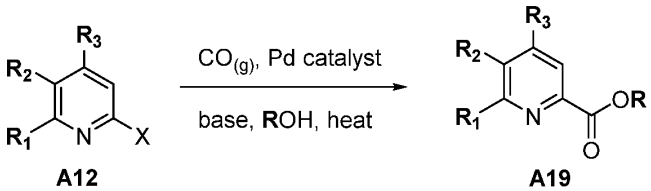
General Scheme VIII



A6 **A19**

General Scheme VIII shows an alternative method for preparing intermediates **A19**. Intermediates **A6** may be transformed under standard acidic esterification conditions (e.g. H_2SO_4, EtOH, 110 °C) to provide intermediates **A19**.

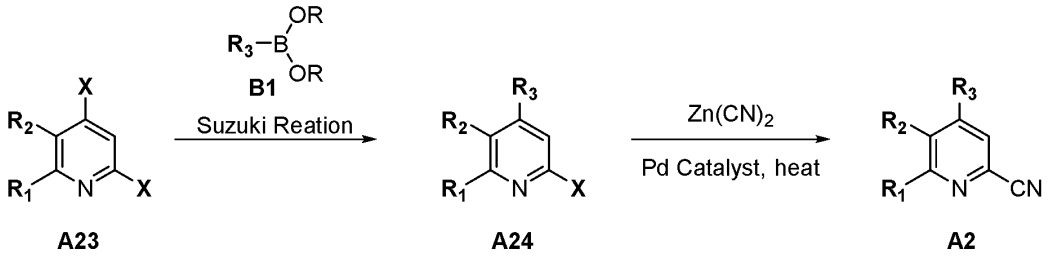
General Scheme IX



A12 **A19**

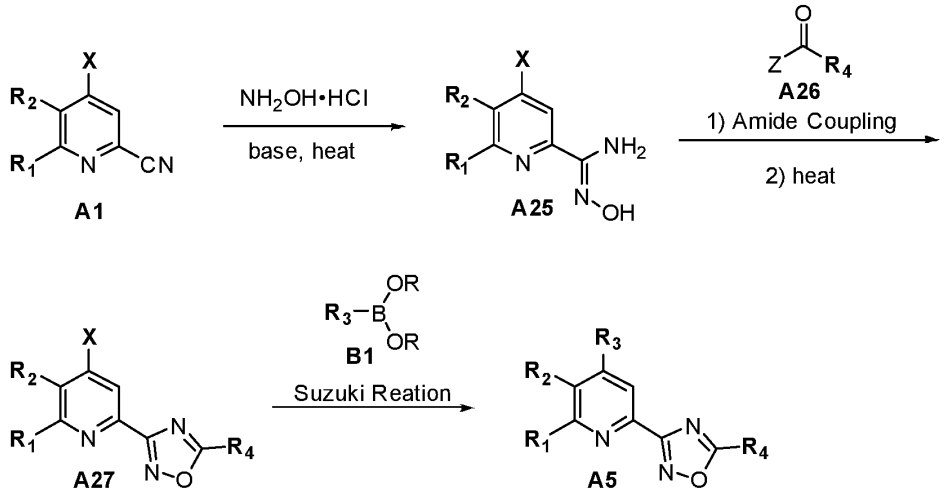
General Scheme IX shows an alternative method for preparing intermediates **A19**. Intermediates **A12** (e.g. X is halogen) with a palladium catalyst (e.g., (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride, complex with DCM), base (e.g. sodium acetate), carbon monoxide and solvent (e.g., DMF/EtOH) may provide intermediates **A19**.

General Scheme X



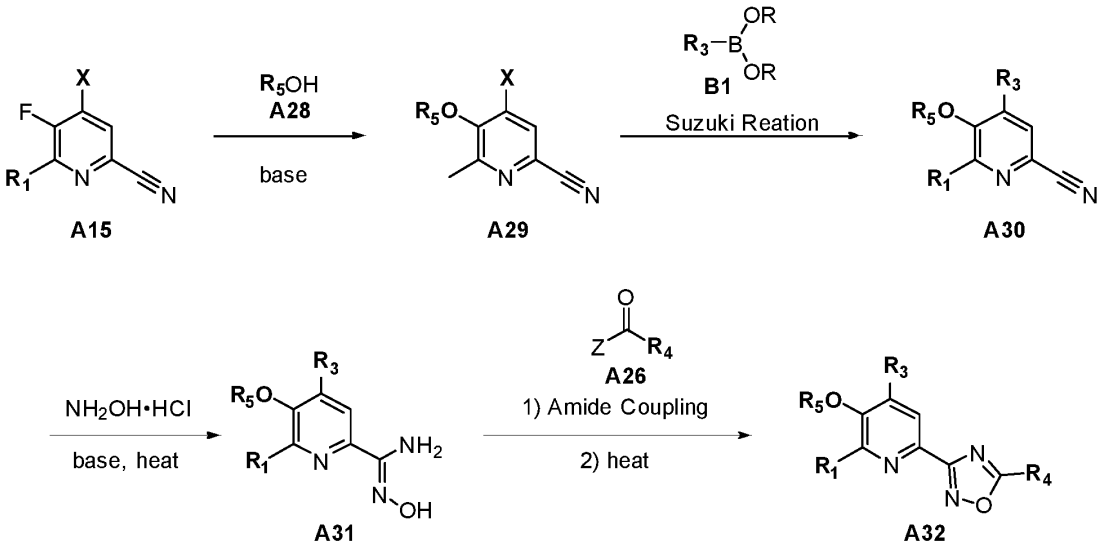
General Scheme X shows an alternative method for preparing intermediates **A2**. Reaction of intermediates **A23** (e.g. X is halogen) with boronic acids or boronic esters (**B1**) under standard Suzuki reaction conditions may provide intermediates **A24**. Intermediates **A24** with a palladium catalyst (e.g. $Pd(PPh_3)_4$), zinc cyanide and heat (e.g. 140 °C) may provide intermediates **A2**.

General Scheme XI



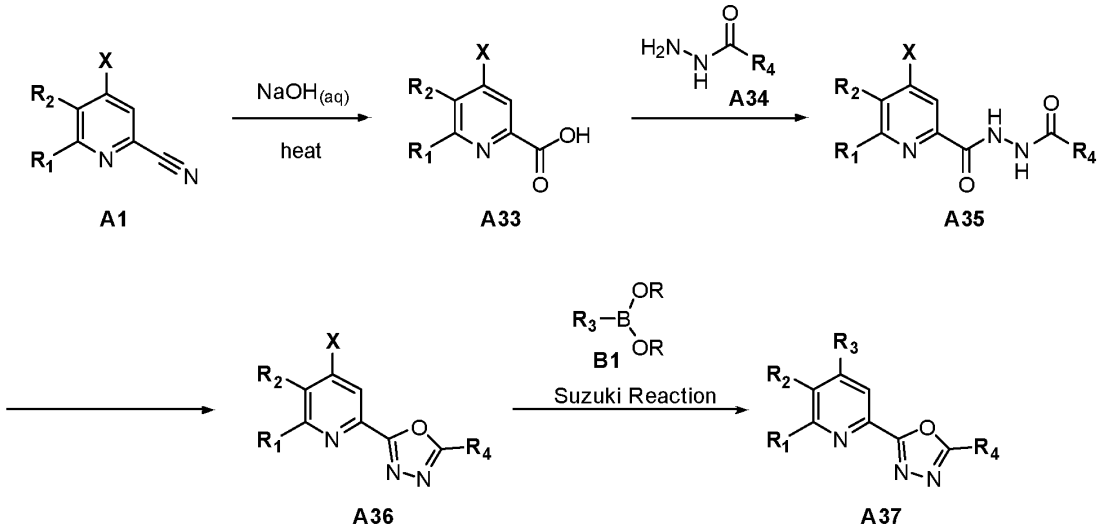
General Scheme XI shows a method for preparing intermediates of the invention. Intermediates **A1** (e.g. X is halogen) may be transformed into the amidoxime intermediates **A25** (e.g. $NH_2OH{\cdot}HCl$, Et_3N, EtOH, microwave irradiation at 150°C). Intermediates **A25** may then undergo an amide formation with intermediates **A26** (e.g. Z is halogen or OH), which may then be further transformed into compounds **A27** upon heating (e.g. 100 °C). Reaction of intermediates **A27** with boronic acids or boronic esters (**B1**) under standard Suzuki reaction conditions may provide compounds **A5**.

General Scheme XII



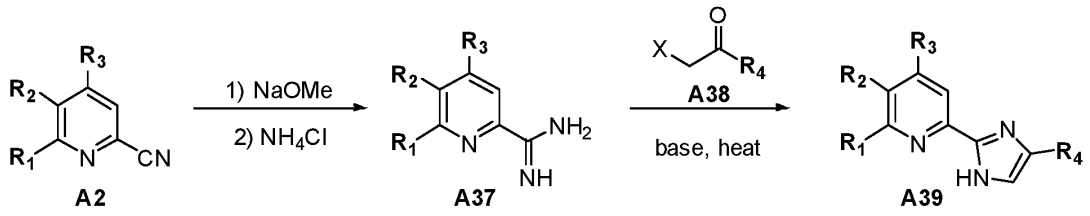
General Scheme XII shows a method for preparing intermediates of the invention. Intermediates **A15** (e.g. X is halogen) with alcohol (**A28**) and base (e.g. NaH) may provide intermediates **A29**. Reaction of intermediates **A29** with boronic acids or boronic esters (**B1**) under standard Suzuki reaction conditions may provide intermediates **A30**. Intermediates **A30** may be transformed into the amidoxime intermediates **A31** (e.g. $NH_2OH{\cdot}HCl$, Et_3N, EtOH, microwave irradiation at 150°C). Intermediates **A31** may then undergo an amide formation with intermediates **A26** (e.g. Z is halogen or OH), which may then be further transformed into compounds **A32** upon heating (e.g. 100 °C).

General Scheme XIII



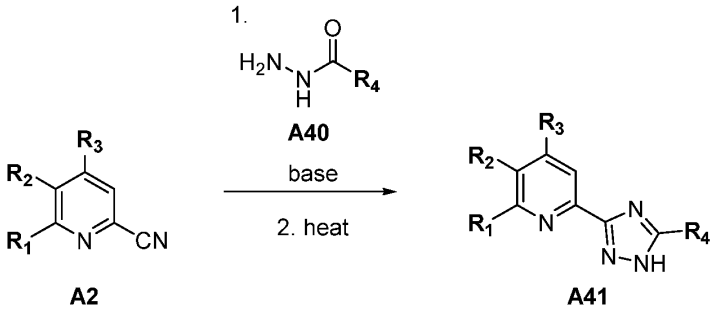
General Scheme XIII shows a method for preparing intermediates of the invention. Intermediates **A1** (e.g., X is halogen) under basic hydrolysis conditions (e.g. NaOH) and heat (e.g. 100 °C) may provide intermediates **A33**. Intermediates **A33** may then undergo an amide formation (e.g. HBTU) with hydrazide intermediates **A34** to provide intermediates **A35**. Intermediates **A35** may be transformed into intermediates **A36** (e.g. Burgess reagent). Reaction of intermediates **A36** (e.g. X is halogen) with boronic acids or boronic esters (**B1**) under standard Suzuki reaction conditions may provide compounds **A37**.

General Scheme XIV



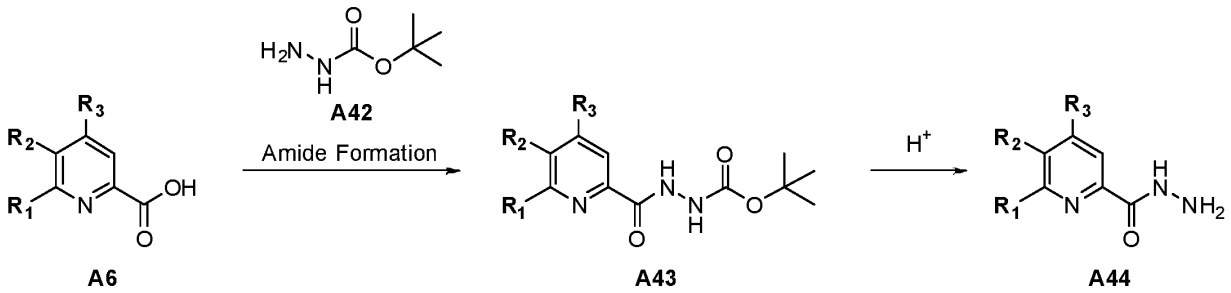
General Scheme XIV shows a method for preparing intermediates of the invention. In a 2-step sequence, intermediates **A2** may be transformed into amidine intermediates **A37**. Intermediates **A37** in the presence of intermediates **A38** (e.g. X is halogen) and base (e.g. DIEA) with heat (e.g. 85 °C) can provide compounds **A39**.

General Scheme XV



General Scheme XV shows a method for preparing intermediates of the invention. Intermediates **A2** in the presences of hydrazide intermediates **A40** and base (e.g. NaOMe) with heat (e.g. 150 °C) may provide compounds **A41**.

General Scheme XVI



General Scheme XVI shows a method for preparing intermediates of the invention. Intermediates **A6** may undergo an amide formation with intermediates **A42** under standard coupling conditions (e.g. HATU, DIEA) to provide intermediate **A43**. Intermediates **A43** may then be transformed into intermediates **A44** under acidic conditions (e.g. HCl).

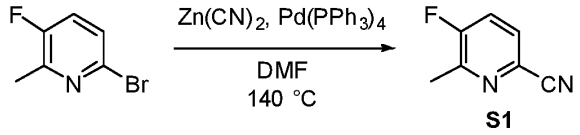
List of Abbreviations:

(4,4'-dtbbpy)$NiCl_2$	[4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine] nickel (II) dichloride
Ac	acetyl
ACN	acetonitrile
aq	aqueous
atm	atmosphere(s)
$CDCl_3$	chloroform-d
CD_3OD	methanol-d_4
Celite®	diatomaceous earth
$(CH_2OH)_2$	ethylene glycol
conc.	concentrated
d	doublet
δ	chemical shift in parts per million
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DIEA	*N,N*-diisopropylethylamine
DIPA	diisopropylamine
DIPEA	*N,N*-diisopropylethylamine
DMCC	dimethylcarbamoyl chloride
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	dimethylsulfoxide-d_6 (deuterated dimethylsulfoxide)
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dt	doublet of triplets
ES-MS	electrospray mass spectrometry
Et	ethyl
EtCN	Propionitrile
EtOH	ethanol
EtOAc	ethyl acetate
eq./equiv	equivalents
$Fe(acac)_3$	iron(III) acetylacetonate
g	gas
h or hr	hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HCTU	*N,N,N′,N′*-Tetramethyl-*O*-(6-chloro-1*H*-benzotriazol-1-yl)uronium hexafluorophosphate

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IPA	*iso*-propyl alcohol
$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	[4,4′-*Bis*(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]*bis*[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate
J	Coupling constant in Hertz
KOAc	potassium acetate
LCMS	liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
M	molarity (for concentration)
m	multiplet
*m*CPBA	3-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
min	minute(s)
μW	microwave
*n*Bu	*n*-butyl
NMR	nuclear magnetic resonance
$Pd(dppf)Cl_2$	(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
ppm	parts per million
RP	reverse phase
r.t./rt/RT	room temperature
s	singlet
sat.	saturated
soln.	solution
t	triplet
tBu	*tert*-butyl
^{t}BuOH	*tert*-butanol
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCN	trimethylsilyl cyanide
TTMSS	Tris(trimethylsilyl)silane

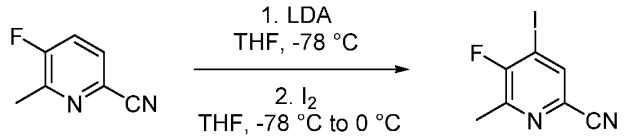
2. EXEMPLARY SCHEMES

Synthesis of intermediates:



S1

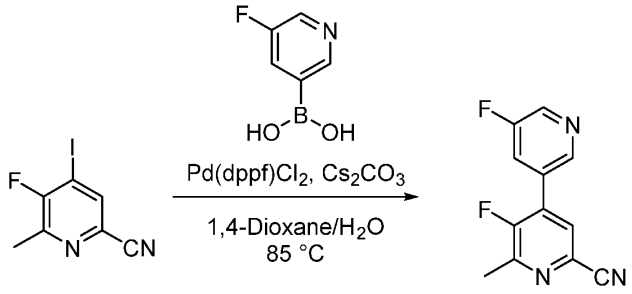
5-Fluoro-6-methylpicolinonitrile (S1). 6-Bromo-3-fluoro-2-methylpyridine (9.0 g, 47 mmol, 1.0 eq), zinc cyanide (3.33 g, 28 mmol, 0.60 eq), and $Pd(PPh_3)_4$ (2.74 g, 2.4 mmol, 0.05 eq) were dissolved in degassed DMF (30 mL) and heated to 140 °C for 3 hours. The reaction mixture was diluted with saturated aqueous sodium bicarbonate and extracted with EtOAc (3x). Combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-10% EtOAc/hexanes afforded 6.22 g of the title compound as a white solid (96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (ddd, J = 8.4, 3.7, 0.6 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 2.58 (s, 3H); ES-MS $[M+1]^+$: 136.9.



S1 **S2**

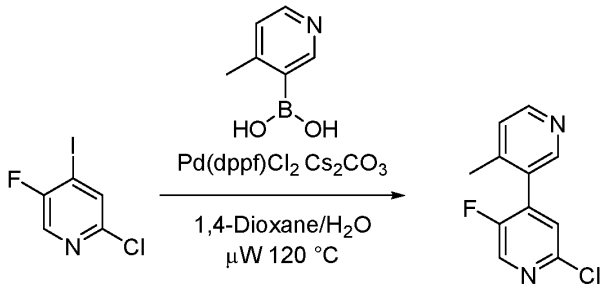
5-Fluoro-4-iodo-6-methylpicolinonitrile (S2). *N,N*-Diisoproylamine (2.97 mL, 21 mmol, 1.2 eq) was dissolved in THF (35 mL) and cooled to -78 °C. *n*BuLi (7.76 mL, 19 mmol, 2.5*M* in hexanes, 1.1 eq) was added dropwise and the reaction stirred at -78 °C for 15 minutes. A solution of intermediate **S1** (2.40 g, 18 mmol, 1.0 eq) in THF (25 mL) was added to the freshly prepared LDA solution dropwise via cannula and stirred at -78 °C for 30 minutes. A solution of iodine (5.37 g, 21 mmol, 1.2 eq) in THF (35 mL) was added dropwise via cannula and the reaction was stirred at -78 °C for 15 minutes and then warmed to 0 °C and stirred an additional 30 minutes. Saturated aqueous $Na_2S_2O_3$ was added and the reaction stirred 15 minutes then extracted with EtOAc (3x). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-35% EtOAc/hexanes afforded 3.20 g of the title compound as a beige solid (69% yield). ^{1}H NMR (400 MHz, CH_3OD) δ 8.25 (dd, J = 4.1, 0.6 Hz, 1H), 2.57 (dd, J = 3.2, 0.6 Hz, 3H); ES-

MS $[M+1]^+$: 263.0.



S2 **S3**

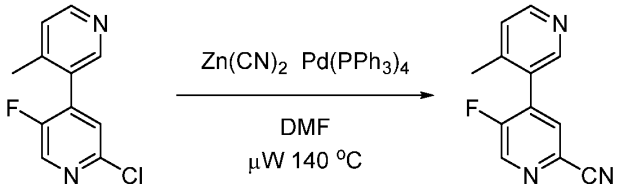
5,5'-Difluoro-6'-methyl-[3,4'-bipyridine]-2'-carbonitrile (S3). Intermediate **S2** (1.00 g, 3.8 mmol, 1.0 eq), 5-fluoropyridine-3-boronic acid (807 mg, 5.7 mmol, 1.5 eq), cesium carbonate (3.75 g, 12 mmol, 3.0 eq) and $Pd(dppf)Cl_2$ (312 mg, 0.38 mmol, 0.10 eq) were dissolved in 1,4-dioxane (14 mL) and water (2 mL). The reaction was placed under inert atmosphere of nitrogen and heated to 85 °C for 16 hours. The reaction was cooled to ambient temperature and then filtered through Celite, washing with DCM/MeOH. The filtrate was concentrated *in vacuo*. Purification by flash chromatography using 0-50% EtOAc/hexanes afforded 660 mg of the title compound as a white solid (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.56 (m, 2H), 7.71 – 7.61 (m, 2H), 2.67 (d, J = 3.4 Hz, 3H); ES-MS $[M+1]^+$: 232.0.



S4

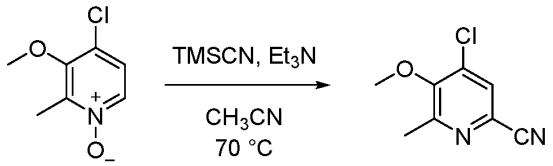
2'-Chloro-5'-fluoro-4-methyl-3,4'-bipyridine (S4). 2-Chloro-5-fluoro-4-iodopyridine (1.50 g, 5.8 mmol, 1.0 eq), 4-picoline-3-boronic acid (958 mg, 7.0 mmol, 1.2 eq), $Pd(dppf)Cl_2$ (428 mg, 0.58 mmol, 0.1 eq) and cesium carbonate (5.73 g, 18 mmol, 3.0 eq) were dissolved in 1,4-dioxane (15 mL) and water (3 mL). The reaction was irradiated in a microwave at 120 °C for 15 minutes. Additional 4-picoline-3-boronic acid (479 mg, 3.5 mmol, 0.60 eq) was added and the reaction was irradiated in a microwave at 120 °C for an additional 15 minutes. After cooling to

ambient temperature, the reaction was filtered through Celite, concentrated *in vacuo* and purified by flash chromatography on silica gel using 0-5% MeOH/DCM. Subsequent purification by flash chromatography on silica gel using 0-65% EtOAc/DCM afforded 636 mg of the title compound as a brown solid (49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 5.1 Hz, 1H), 8.42 (s, 1H), 8.36 (d, J = 1.0 Hz, 1H), 7.31 – 7.24 (m, 2H), 2.26 (d, J = 1.5 Hz, 3H); ES-MS $[M+1]^+$: 223.0.



S4 **S5**

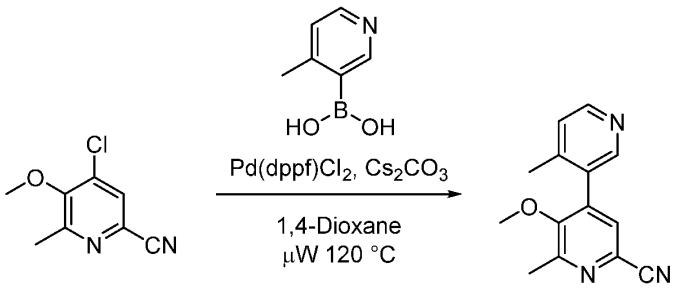
5'-Fluoro-4-methyl-[3,4'-bipyridine]-2'-carbonitrile (S5). Intermediate **S4** (636 mg, 2.9 mmol, 1.0 eq), zinc cyanide (252 mg, 2.1 mmol, 0.75 eq) and $Pd(PPh_3)_4$ (330 mg, 0.29 mmol, 0.10 eq) were dissolved in DMF (10 mL). The reaction was irradiated in a microwave at 140 °C for 15 minutes. After cooling to ambient temperature, the reaction was diluted with EtOAc and washed with saturated aqueous sodium bicarbonate. The aqueous wash was back extracted with EtOAc (2x) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-3% MeOH/DCM afforded 520 mg of the title compound as an off-white solid (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.1 Hz, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.44 (s, 1H), 7.70 (d, J = 5.5 Hz, 1H), 7.32 (d, J = 5.1 Hz, 1H), 2.27 (d, J = 1.5 Hz, 3H); ES-MS $[M+1]^+$: 214.2.



S6

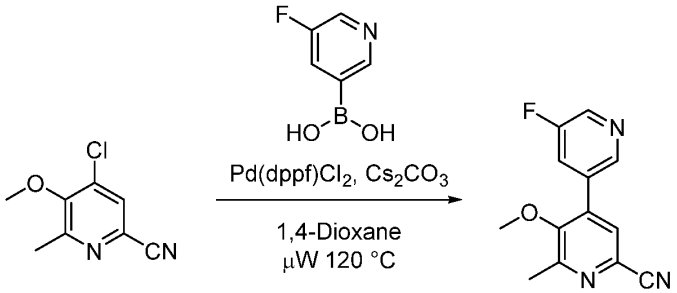
4-Chloro-5-methoxy-6-methylpicolinonitrile (S6). 4-Chloro-3-methoxy-2-methyl-1-oxido-pyridin-1-ium (500 mg, 2.9 mmol, 1.0 eq) and triethylamine (400 μL, 2.9 mmol, 1.0 eq) were dissolved in acetonitrile (14.4 mL). Trimethylsilyl cyanide (1.44 mL, 12 mmol, 4.0 eq) was added dropwise and the reaction was heated to 85 °C for 24 hours and then to 70 °C for 5 days. After cooling to ambient temperature, a solution of 10% aqueous potassium carbonate was added

and the mixture was stirred for 15 minutes. The reaction was diluted with water and extracted with 3:1 $CHCl_3$:IPA (3x). The combined organic layers were passed through a phase separator and concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-30% EtOAc/hexanes afforded 245 mg of the title compound as a white solid (47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 3.94 (s, 3H), 2.57 (s, 3H); ES-MS $[M+1]^+$: 182.9.



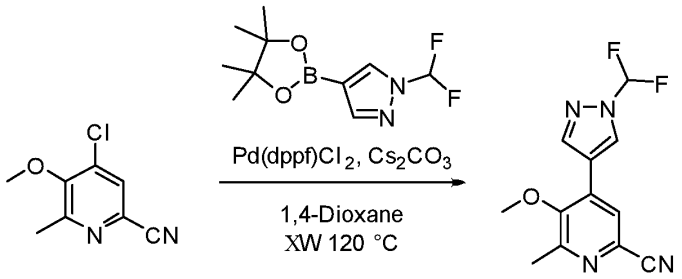
S6 **S7**

5'-Methoxy-4,6'-dimethyl-[3,4'-bipyridine]-2'-carbonitrile (S7). Intermediate **S6** (75 mg, 0.41 mmol, 1.0 eq), 4- picoline-3-boronic acid (84.4 mg, 0.62 mmol, 1.5 eq), cesium carbonate (404 mg, 1.2 mmol, 3.0 eq) and $Pd(dppf)Cl_2$ (30.1 mg, 0.040 mmol, 0.10 eq) were dissolved in 1,4-dioxane (4.1 mL) and placed under inert atmosphere. The reaction was irradiated in a microwave at 120 °C for 30 minutes. Additional $Pd(dppf)Cl_2$ (30.1 mg, 0.040 mmol, 0.10 eq) was added and the reaction was irradiated in a microwave at 120 °C an additional 15 minutes. After cooling to ambient temperature, the reaction was filtered through Celite, washing with MeOH/DCM and the filtrate concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-5% MeOH/DCM afforded 69 mg of the title compound as an off-white solid (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 52.0 Hz, 2H), 7.42 (s, 1H), 7.30 (s, 1H), 3.42 (s, 3H), 2.61 (s, 3H), 2.21 (s, 3H); ES-MS $[M+1]^+$: 240.0.



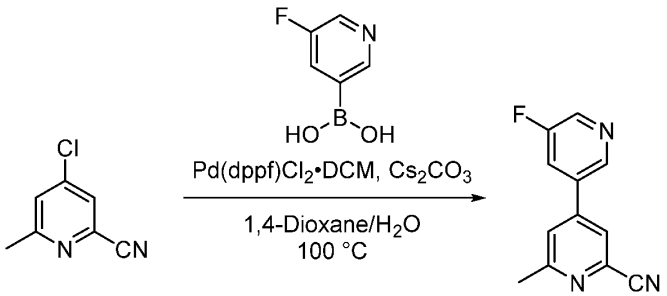
S6 **S8**

5-Fluoro-5'-methoxy-6'-methyl-[3,4'-bipyridine]-2'-carbonitrile (S8). Title compound was prepared in a similar manner as intermediate **S7** to afford 96 mg of the title compound as an off-white solid (96% yield). ES-MS $[M+1]^+$: 244.0.



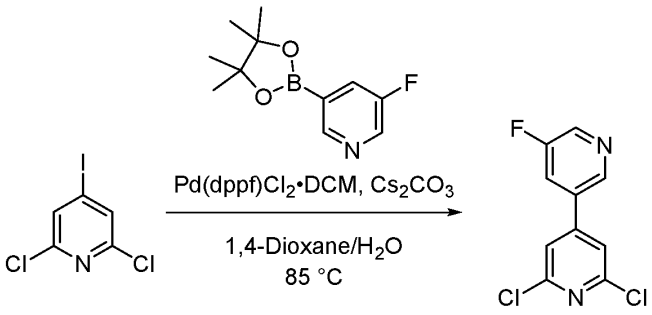
S6 **S9**

4-(1-(Difluoromethyl)-1H-pyrazol-4-yl)-5-methoxy-6-methylpicolinonitrile (S9). Title compound was prepared in a similar manner as intermediate **S7** to afford 41.8 mg of the title compound as a white solid (39% yield). ES-MS $[M+1]^+$: 265.0.



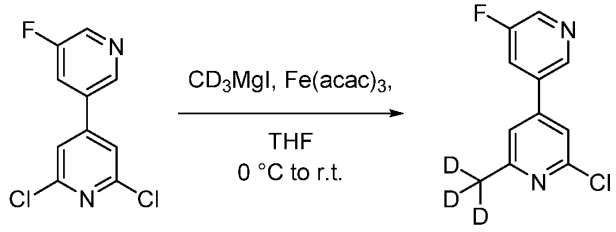
S10

5-Fluoro-6'-methyl-[3,4'-bipyridine]-2'-carbonitrile (S10). 4-Chloro-6-methylpicolinonitrile (500 mg, 3.3 mmol, 1.0 eq), 5-fluoropyridine-3-boronic acid (693 mg, 4.9 mmol, 1.5 eq), cesium carbonate (3.22 g, 9.8 mmol, 3.0 eq) and $Pd(dppf)Cl_2 \cdot DCM$ (268 mg, 0.33 mmol, 0.10 eq) were dissolved in 1,4-dioxane (9 mL) and water (1 mL). The reaction was placed under inert atmosphere and heated to 100 °C for 5 hours. The reaction was cooled to ambient temperature and then filtered through Celite, washing with DCM/MeOH. The filtrate was concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-5% MeOH/DCM afforded 357 mg of the title compound as an off-white solid (51% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (t, J = 1.7 Hz, 1H), 8.62 (d, J = 2.7 Hz, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.56 (d, J = 1.6 Hz, 1H), 2.71 (s, 3H); ES-MS $[M+1]^+$: 214.0.



S11

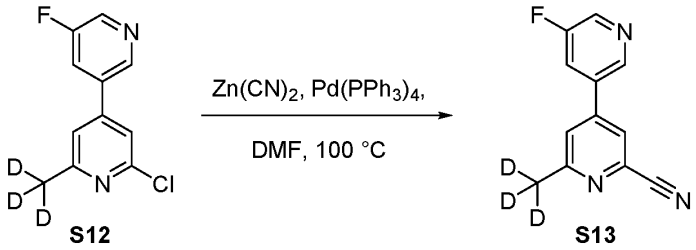
2',6'-Dichloro-5-fluoro-3,4'-bipyridine (S11). 2,6-Dichloro-4-iodopyridine (736 mg, 2.7 mmol, 1.0 eq), 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (659 mg, 3.0 mmol, 1.1 eq), cesium carbonate (2.64 g, 8.1 mmol, 3.0 eq) and Pd(dppf)Cl_2·DCM (220 mg, 0.27 mmol, 0.10 eq) were combined in a vial and 10:1 1,4-dioxane/H_2O solution (20 mL total, degassed under vacuum) was then added via syringe. The resulting reaction mixture was stirred under an inert atmosphere at 85 °C for 1 h, after which time the reaction mixture was cooled to r.t. and diluted with DCM and H_2O. The aqueous layer was extracted with DCM, and combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the crude residue by flash chromatography on silica gel using 3-100% EtOAc/hexanes afforded 466 mg of the title compound as a tan solid (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.62 (d, J = 2.7 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.47 (s, 2H); ES-MS $[M+1]^+$ = 243.0.



S11 **S12**

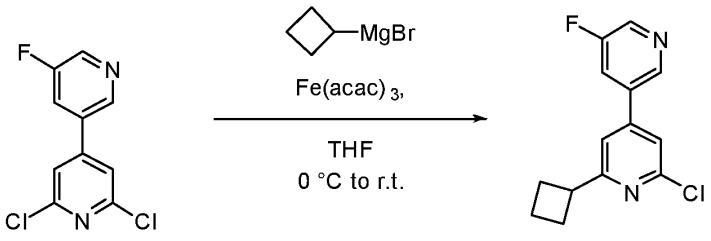
2'-Chloro-5-fluoro-6'-(methyl-d_3)-3,4'-bipyridine (S12). Intermediate **S11** (250 mg, 1.0 mmol, 1.0 eq) and $Fe(acac)_3$ (37 mg, 0.10 mmol, 0.10 eq) were taken up in THF (5 mL), and cooled to 0 °C under an inert atmosphere of nitrogen. Trideuteromethylmagnesium iodide (1.13 mL, 1.1 mmol, 1.1 eq, 1*M* in diethyl ether) was then added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour, after which time it was cooled to 0 °C where an

additional trideuteromethylmagnesium iodide (1.1 eq) was added. The reaction mixture was warmed to room temperature and stirred for an additional 1 hour, after which time the reaction mixture was cooled back to 0 °C and water was added. The aqueous layer was extracted with DCM (3x) and the combined organics were filtered through a phase separator and concentrated. Purification of the crude residue by flash chromatography on silica gel using 3-70% EtOAc/hexanes afforded 57 mg of the title compound as a white solid (24% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (t, J = 1.7 Hz, 1H), 8.57 (d, J = 2.7 Hz, 1H), 7.61 (ddd, J = 9.0, 2.7, 1.9 Hz, 1H), 7.35 (d, J = 1.4 Hz, 1H), 7.27 (d, J = 1.4 Hz, 1H); ES-MS $[M+1]^+$ = 226.0.



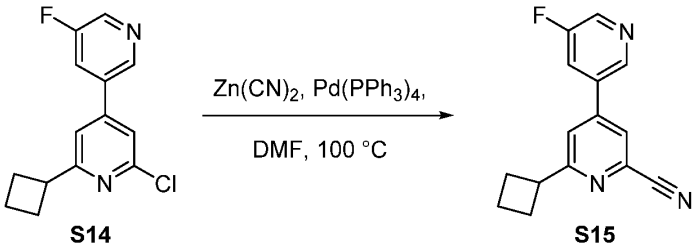
S12 S13

5-Fluoro-6'-(methyl-d_3)-[3,4'-bipyridine]-2'-carbonitrile (S13). Intermediate **S12** (55.0 mg, 0.24 mmol, 1.0 eq), zinc cyanide (34.0 mg, 0.29 mmol, 1.2 eq), and $Pd(PPh_3)_4$ (28.0 mg, 0.024 mmol, 0.10 eq) were taken up in DMF (2 mL), degassed under vacuum, and placed under an inert atmosphere of nitrogen. The resulting reaction mixture was stirred at 100 °C for 2 hours, after which time the reaction mixture was cooled to room temperature and diluted with a saturated aqueous $NaHCO_3$ solution and DCM. The aqueous layer was extracted with DCM (3x), the combined organic extracts were filtered through a phase separator, and the solvents were concentrated. Purification of the crude residue by flash chromatography on silica gel using 0-4% MeOH/DCM afforded 18 mg of the title compound as a white solid (34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 1.6 Hz, 1H), 8.62 (d, J = 2.7 Hz, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.64 (dt, J = 9.1, 2.3 Hz, 1H), 7.56 (d, J = 1.6 Hz, 1H); ES-MS $[M+1]^+$ = 217.1.



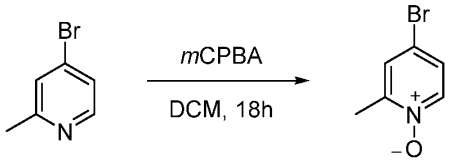
S11 S14

2'-Chloro-6'-cyclobutyl-5-fluoro-3,4'-bipyridine (S14). Prepared in a similar manner as intermediate **S12** to give 68 mg of the title compound as a tan solid (30% yield). ES-MS $[M+1]^+$ = 262.9.



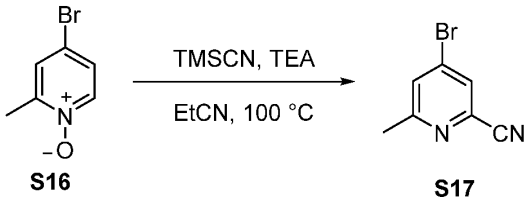
S14 S15

6'-Cyclobutyl-5-fluoro-[3,4'-bipyridine]-2'-carbonitrile (S15). Prepared in a similar manner to intermediate **S13** give 16 mg of the title compound as a white solid (24% yield). ES-MS $[M+1]^+$ = 254.1.

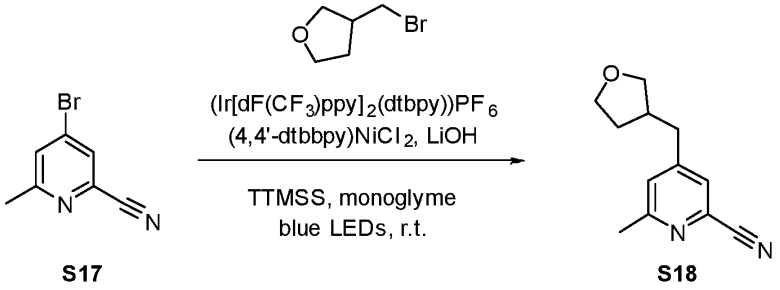


S16

4-Bromo-2-methylpyridine 1-oxide (S16). A solution of 4-bromo-2-methylpyridine (15.0 g, 87 mmol, 1.0 eq) in DCM (436 mL) was cooled to 0 °C where 3-chloroperoxybenzoic acid (23.5 g, 105 mmol, 1.2 eq) was added portionwise. The reaction was then stirred at ambient temperature for 18 hours. An aqueous 10% $Na_2S_2O_3$ solution was added (~200 mL) and the mixture was stirred for 2 hours. The organic layer was isolated and the aqueous layer was further extracted with DCM (3x). The organics were pooled, washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford title compound as a white solid that was carried forward without further purification (99% yield). ES-MS $[M+1]^+$: 187.9/189.9.

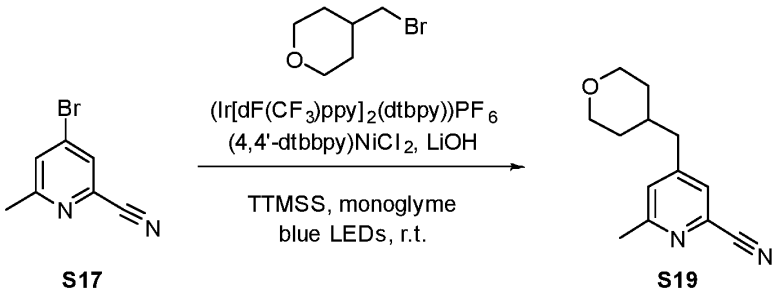


4-Bromo-6-methylpicolinonitrile (S17). To a solution of intermediate **S16** (286 mg, 1.5 mmol, 1.0 eq) in propionitrile (6.4 mL) was added triethylamine (1.12 mL, 8.1 mmol, 5.3 eq) followed by trimethylsilyl cyanide (571 µL, 4.6 mmol, 3.0 eq) and the mixture was stirred at 100 °C for 24 hours. After cooling to room temperature, additional triethylamine (5.3 eq) and trimethylsilyl cyanide (3.0 eq) were added and the mixture was heated to 100 °C for an additional 24 hours. After cooling to room temperature, an aqueous 10% K_2CO_3 solution (20 mL) was added to the reaction mixture. The aqueous layer was extracted with EtOAc (3x) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Purification of the crude residue by flash chromatography on silica gel using 0 - 10% EtOAc/hexanes to afford 276 mg of title compound (92% yield). ES-MS $[M+1]^+$: 196.9/198.9.



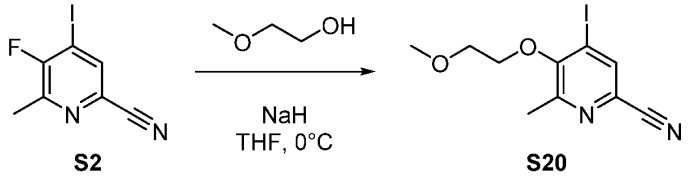
6-Methyl-4-((tetrahydrofuran-3-yl)methyl)picolinonitrile (S18). Intermediate **S17** (200 mg, 1.02 mmol, 1.0 eq), lithium hydroxide (73 mg, 3.05 mmol, 3.0 eq), $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (57 mg, 0.051 mmol, 0.050 eq), 3-(bromomethyl)tetrahydrofuran (0.34 mL, 3.05 mmol, 3.0 eq), and tris(trimethylsilyl)silane (0.47 mL, 1.52 mmol, 1.5 eq) were combined in a vial and monoglyme (8 mL) was added. The vial was sealed and placed under vacuum, followed immediately by degassing under N_2 (bubbled through solution) for 5-10 minutes. Next, (4,4′-dtbbpy)$NiCl_2$ (20 mg, 0.051 mmol, 0.050 eq) was then added to the mixture and the vial was sealed and purged under vacuum and then filled with N_2. The reaction mixture was sonicated for 5-10 minutes, after which time it was sealed with Parafilm, placed under blue LEDs

(EvoluChem™ PhotoRedOx Box equipped with Kessil® LED lamp (HepatoChem)) and stirred at ambient temperature overnight. The reaction mixture was diluted with a saturated aqueous $NaHCO_3$ solution and DCM. The aqueous layer was extracted with DCM (3x), the combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. Purification of the crude residue by flash chromatography on silica gel using 3-100% EtOAc/hexanes gave 113 mg of title compound as a yellow oil that solidified upon standing (55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.18 (s, 1H), 3.91 (td, J = 8.3, 5.0 Hz, 1H), 3.83 (dd, J = 8.6, 6.8 Hz, 1H), 3.79 – 3.75 (m, 1H), 3.43 (dd, J = 8.6, 6.1 Hz, 1H), 2.76 – 2.65 (m, 2H), 2.58 (s, 3H), 2.55 – 2.48 (m, 1H), 2.07 – 1.99 (m, 1H), 1.62 – 1.54 (m, 1H); ES-MS $[M+1]^+$ = 203.1.



S17 S19

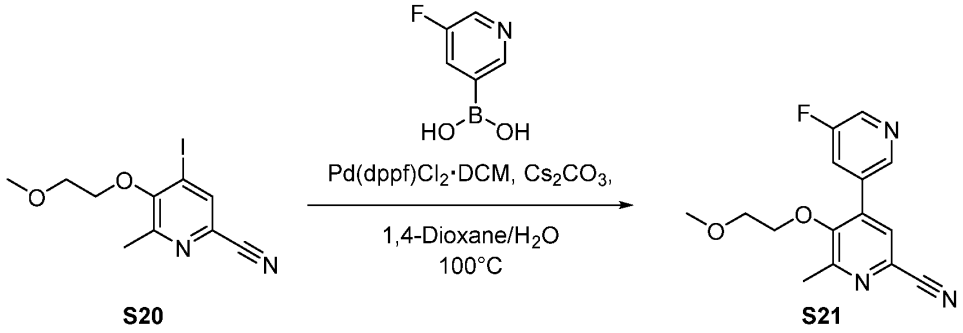
6-Methyl-4-((tetrahydro-2*H*-pyran-4-yl)methyl)picolinonitrile (S19). Prepared in a similar manner to intermediate **S18** to give 56 mg of the title compound as a yellow oil (51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 1.6 Hz, 1H), 7.15 (d, J = 1.5 Hz, 1H), 4.97 – 3.93 (m, 2H), 3.37 – 3.31 (m, 2H), 2.58 (s, 3H), 2.56 (d, J = 7.3 Hz, 2H), 1.85 – 1.73 (m, 1H), 1.54 – 1.49 (m, 2H), 1.40 – 1.30 (m, 2H); ES-MS $[M+1]^+$ = 217.1.



S2 S20

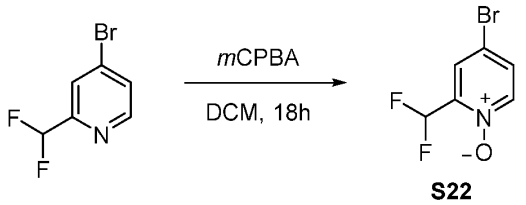
4-Iodo-5-(2-methoxyethoxy)-6-methylpicolinonitrile (S20). To a solution of sodium hydride (73.2 mg, 1.8 mmol, 1.6 eq, 60% dispersion in mineral oil) in THF (3 mL) at 0 °C was added 2-methoxyethan-1-ol (131 mg, 1.7 mmol, 1.5 eq). After 15 minutes at 0 °C, a solution of intermediate **S2** (300 mg, 1.2 mmol, 1.0 eq) in THF (2 mL) was added dropwise. After 45 minutes at 0°C, an additional solution of sodium hydride (36.6 mg, 0.92 mmol, 0.80 eq, 60% dispersion in mineral oil) and 2-methoxyethan-1-ol (65.3 mg, 0.86 mmol, 0.75 eq) in THF (1

mL) was added dropwise. After an additional 10 minutes at 0 °C, a saturated aqueous ammonium chloride solution and an aqueous 2*M* HCl solution were added to the mixture and organics were concentrated. The aqueous layer was basified by the addition of a saturated aqueous $NaHCO_3$ solution and extracted with DCM (3x). The combined organic extracts were passed through a phase separator and concentrated. Purification of the crude residue by flash chromatography on silica gel using 0-80% EtOAc/hexanes afforded 167 mg of the title compound as a white solid (46% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 4.22 – 4.18 (m, 2H), 3.81 – 3.77 (m, 2H), 3.42 (s, 3H), 2.57 (s, 3H); ES-MS $[M+H]^+$ = 318.9.



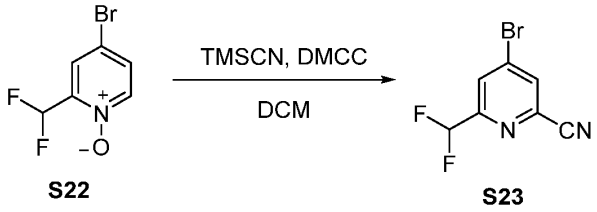
S20 **S21**

5-Fluoro-5'-(2-methoxyethoxy)-6'-methyl-[3,4'-bipyridine]-2'-carbonitrile (S21). Intermediate **S20** (78 mg, 0.25 mmol, 1.0 eq), Pd(dppf)Cl_2·DCM (30.1 mg, 0.037 mmol, 0.15 eq), (5-fluoropyridin-3-yl)boronic acid (51.8 mg, 0.37 mmol, 1.5 eq), and cesium carbonate (241 mg, 0.74 mmol, 3.0 eq) in 1,4-dioxane (2 mL) and water (0.4 mL) were sealed in a vial and placed under an inert atmosphere of N_2. After stirring at 100 °C overnight, the reaction mixture was cooled to ambient temperature then diluted with water and extracted with DCM (3x). The combined organics were dried over $MgSO_4$, filtered, and concentrated. Purification of the crude residue by flash chromatography on silica gel using 3-80% EtOAc/hexanes afforded 58 mg of the title compound as a colorless oil (82% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 – 8.69 (m, 1H), 8.58 (d, *J* = 2.8 Hz, 1H), 8.00 (ddd, *J* = 9.5, 2.8, 1.8 Hz, 1H), 7.89 (s, 1H), 3.82 – 3.79 (m, 2H), 3.47 – 3.44 (m, 2H), 3.20 (s, 3H), 2.62 (s, 3H); ES-MS $[M+H]^+$ = 288.0.



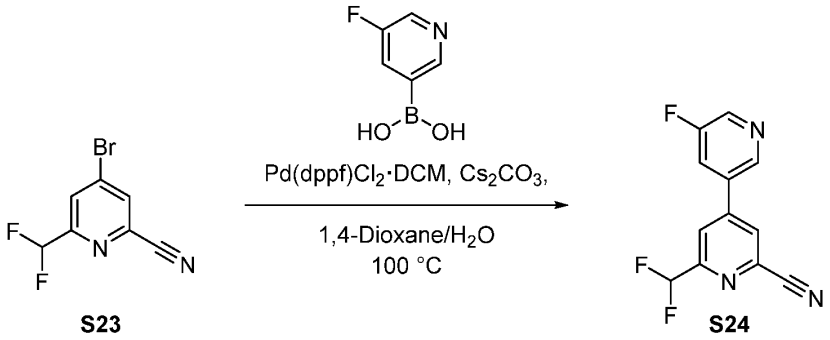
S22

4-Bromo-2-(difluoromethyl)pyridine 1-oxide (S22). Prepared in a similar manner to intermediate **S16** to afford 351 mg of the title compound as a white solid (49% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (dt, J = 7.0, 1.2 Hz, 1H), 7.98 (d, J = 2.8 Hz, 1H), 7.82 (dd, J = 7.0, 2.8 Hz, 1H), 7.13 (t, J = 53.1 Hz, 1H); ES-MS $[M+1]^+$ = 223.9/225.9.



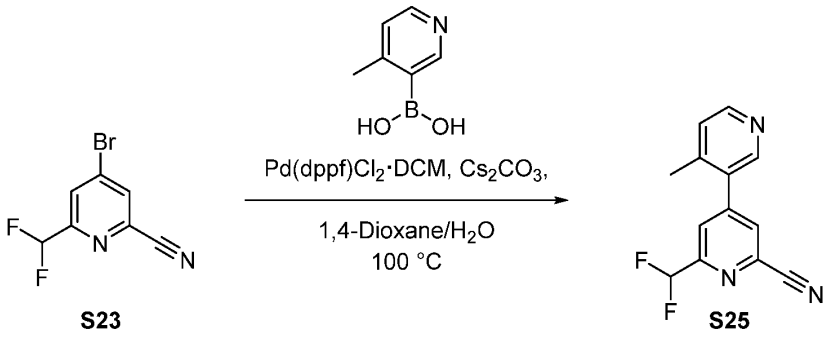
S22 S23

4-Bromo-6-(difluoromethyl)picolinonitrile (S23). Intermediate **S22** (350 mg, 1.6 mmol, 1.0 eq) was dissolved in DCM (4.7 mL) and dimethylcarbamoyl chloride (173 µL, 1.9 mmol, 1.2 eq) was added over 5 minutes. Next, trimethylsilyl cyanide (235 µL, 1.9 mmol, 1.2 eq) was added and the reaction was stirred for 18 hours. Additional dimethylcarbamoyl chloride (173 µL, 1.9 mmol, 1.2 eq) and trimethylsilyl cyanide (235 µL, 1.9 mmol, 1.2 eq) were added and stirred for an additional 18 hours. After the addition of an aqueous 10% K_2CO_3 solution (50 mL), the mixture was allowed to stir for 15 minutes then diluted further with water (50mL) and extracted with DCM (3x). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the crude residue by flash chromatography on silica gel using 0-20% EtOAc/hex afforded 164 mg of title compound (45% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (dt, J = 1.7, 0.8 Hz, 1H), 8.21 (d, J = 1.7 Hz, 1H), 6.77 (t, J = 54.6 Hz, 1H); ES-MS $[M+1]^+$ = 233.9.



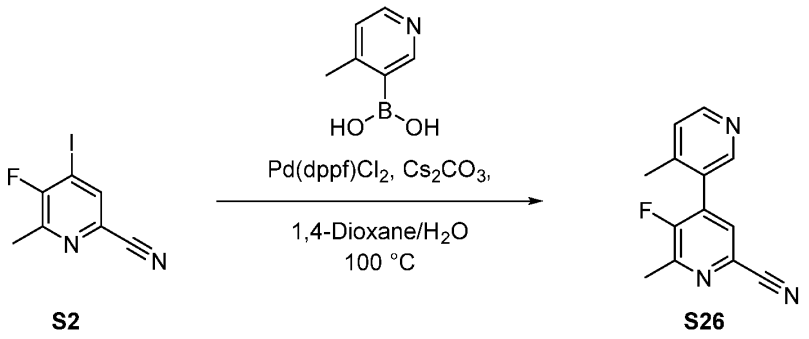
S23 **S24**

6'-(Difluoromethyl)-5-fluoro-[3,4'-bipyridine]-2'-carbonitrile (S24). Prepared in a similar manner to intermediate **S3** to afford 80 mg of the title compound as a tan solid (92% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.94 (t, J = 1.6 Hz, 1H), 8.68 (d, J = 2.7 Hz, 1H), 8.48 (dt, J = 1.6, 0.8 Hz, 1H), 8.35 (d, J = 1.7 Hz, 1H), 8.22 (ddd, J = 9.5, 2.7, 1.9 Hz, 1H), 6.87 (t, J = 54.7 Hz, 1H); ES-MS $[M+1]^+$ = 250.0.

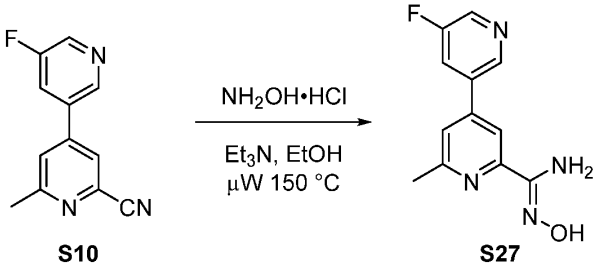


S23 **S25**

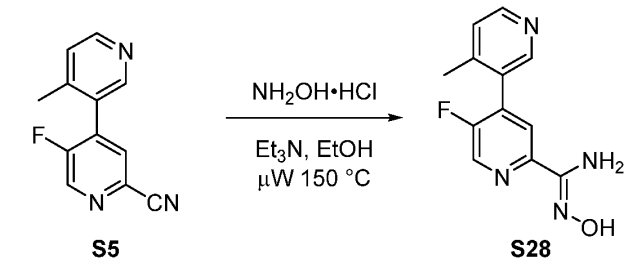
6'-(Difluoromethyl)-4-methyl-[3,4'-bipyridine]-2'-carbonitrile (S25). Prepared in a similar manner to intermediate **S3** to afford 55 mg of the title compound as a tan solid (64% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 5.2 Hz, 1H), 8.45 (s, 1H), 8.15 (dt, J = 1.6, 0.8 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 7.47 (dt, J = 5.2, 0.7 Hz, 1H), 6.85 (t, J = 54.7 Hz, 1H), 2.38 (s, 3H); ES-MS $[M+1]^+$ = 246.1.



5'-Fluoro-4,6'-dimethyl-[3,4'-bipyridine]-2'-carbonitrile (S26). Prepared in a similar manner to intermediate **S3** to afford 610 mg of the title compound as a tan solid (70% yield). ES-MS $[M+1]^+ = 228.0$.

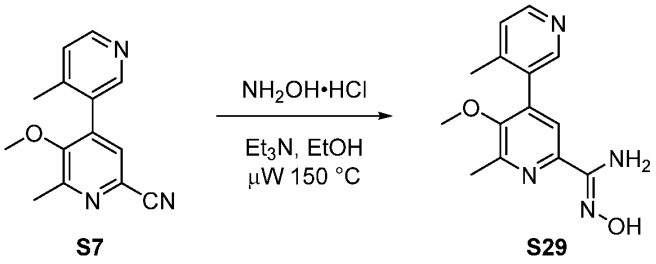


(*Z*)-5-Fluoro-*N*'-hydroxy-6'-methyl-[3,4'-bipyridine]-2'-carboximidamide (S27). Intermediate **S10** (150 mg, 0.70 mmol, 1.0 eq), and hydroxylamine hydrochloride (97.8 mg, 1.4 mmol, 2.0 eq) were dissolved in EtOH (3.5 mL). Triethylamine (0.12 mL, 0.84 mmol, 1.2 eq) was added and the reaction was irradiated in a microwave at 150 °C for 5 minutes. After cooling to ambient temperature, the reaction was concentrated, dissolved in $CHCl_3$:IPA (3:1) and washed with water. The organic layer was passed through a phase separator and concentrated *in vacuo*. Purification by flash chromatography on silica gel using 1% MeOH/DCM afforded 116.4 mg of the title compound as a white solid (99% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 (t, J = 1.7 Hz, 1H), 8.56 (d, J = 2.7 Hz, 1H), 8.04 (ddd, J = 9.6, 2.7, 1.8 Hz, 1H), 8.01 (dd, J = 1.7, 0.7 Hz, 1H), 7.63 (dd, J = 1.6, 0.6 Hz, 1H), 2.65 (s, 3H); ES-MS $[M+1]^+$: 247.1.



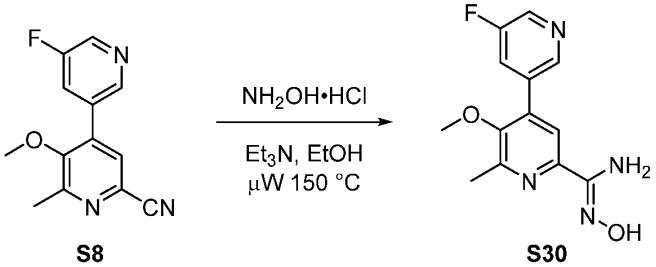
S5 **S28**

(*Z*)-5'-Fluoro-*N*'-hydroxy-4-methyl-[3,4'-bipyridine]-2'-carboximidamide (S28). Intermediate **S5** (50 mg, 0.23 mmol, 1.0 eq), and hydroxylamine hydrochloride (25 mg, 0.35 mmol, 1.5 eq) were dissolved in EtOH (2.3 mL). Triethylamine (6.5 μL, 0.47 mmol, 2 eq) was added and the reaction stirred at ambient temperature for 18 hours. After cooling to ambient temperature, the reaction was concentrated, dissolved in EtOAc and washed with water. The organic layer was dried over Na_2SO_3, filtered, and concentrated to afford 52 mg of the title compound as an off-white solid that was used without further purification (91% yield). ES-MS $[M+1]^+$: 247.2.



S7 **S29**

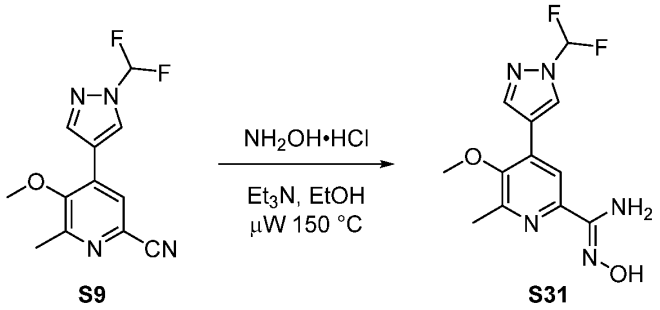
(*Z*)-*N*'-Hydroxy-5'-methoxy-4,6'-dimethyl-[3,4'-bipyridine]-2'-carboximidamide (S29). Prepared in a similar manner to intermediate **S27** to afford 22.6 mg of the title compound as a brown oil that was used without further purification (99% yield). ES-MS $[M+1]^+$: 273.3.



S8 **S30**

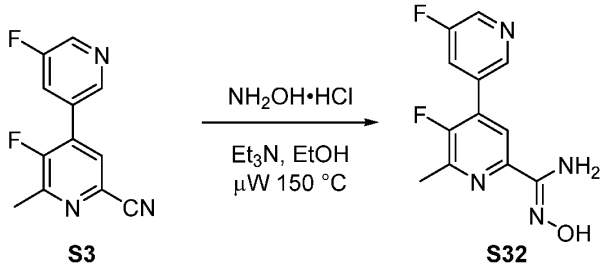
(*Z*)-5-Fluoro-*N*'-hydroxy-5'-methoxy-6'-methyl-[3,4'-bipyridine]-2'-carboximidamide (S30).

Prepared in a similar manner to intermediate **S27** to afford 22.4 mg of the title compound as a brown oil that was used without further purification (99% yield). ES-MS $[M+1]^+$: 277.2.



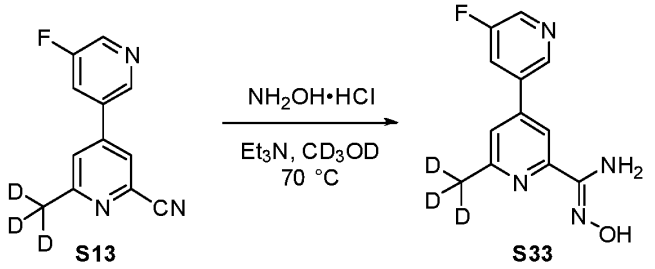
S9 **S31**

(*Z*)-4-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-*N*'-hydroxy-5-methoxy-6-methylpicolinimidamide (S31). Prepared in a similar manner to intermediate **S26** to afford 14.0 mg of the title compound as a brown oil that was used without further purification (62% yield). ES-MS $[M+1]^+$: 298.2.



S3 **S32**

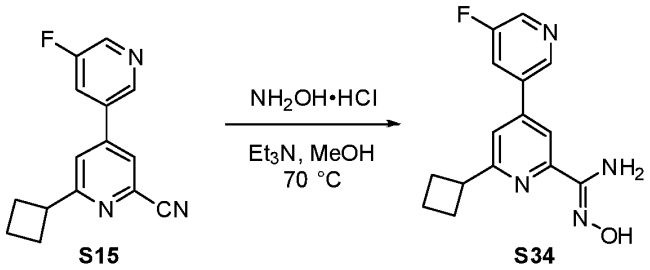
(*Z*)-5,5'-Difluoro-*N*'-hydroxy-6'-methyl-[3,4'-bipyridine]-2'-carboximidamide (S32). Prepared in a similar manner to intermediate **S27** to afford 731 mg of the title compound as a white solid that was used without further purification (99% yield). ES-MS $[M+1]^+$: 265.0.



S13 **S33**

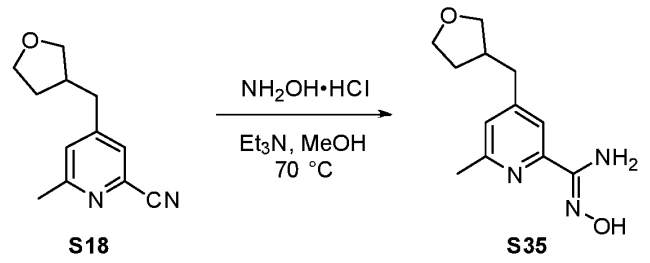
(*Z*)-5-fluoro-*N*'-hydroxy-6'-(methyl-d_3)-[3,4'-bipyridine]-2'-carboximidamide (S33). To a solution of intermediate **S13** (18 mg, 0.083 mmol, 1.0 eq) in CD_3OD (1 mL) was added

hydroxylamine hydrochloride (12 mg, 0.17 mmol, 2.0 eq), followed by triethylamine (14 µL, 0.10 mmol, 1.2 eq). The resulting reaction mixture was stirred at 70 °C for 1 hour, after which time the reaction mixture was cooled to room temperature and solvents were concentrated. The resulting residue was taken up in 3:1 chloroform/IPA (*v/v*) and water and the aqueous layer was extracted with 3:1 chloroform/IPA (3x). Combined organic extracts were filtered through a phase separator and concentrated to give 15 mg of title compound as a tan solid, which was dried under vacuum and used without further purification (74% yield). ES-MS $[M+1]^+ = 250.1$.



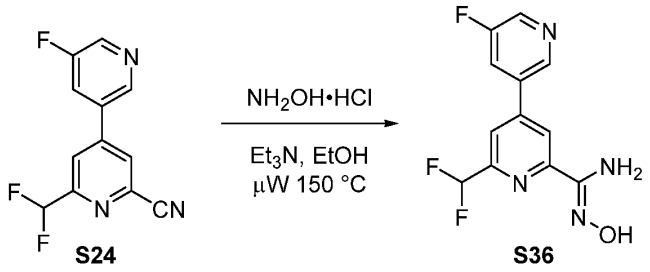
S15 S34

(*Z*)-6'-cyclobutyl-5-fluoro-*N*'-hydroxy-[3,4'-bipyridine]-2'-carboximidamide (S34). Prepared in a similar manner to intermediate **S33** to afford 18 mg of title compound as a tan solid that was used without further purification (100% yield). ES-MS $[M+1]^+ = 287.1$.

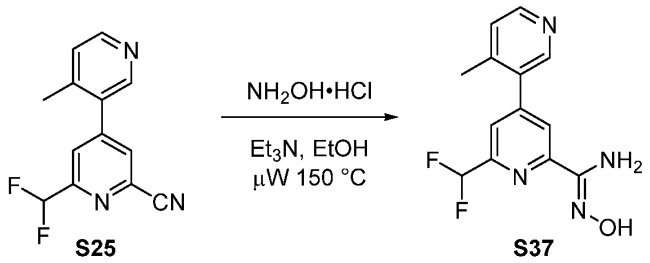


S18 S35

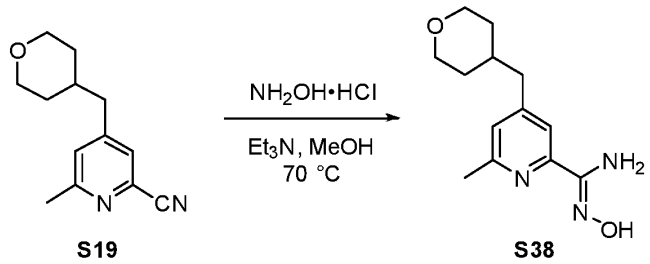
(*Z*)-*N*'-Hydroxy-6-methyl-4-((tetrahydrofuran-3-yl)methyl)picolinimidamide (S35). Prepared in a similar manner to intermediate **S33** to afford 116 mg of title compound as a yellow oil that was used without further purification (93% yield). ES-MS $[M+1]^+ = 236.2$.



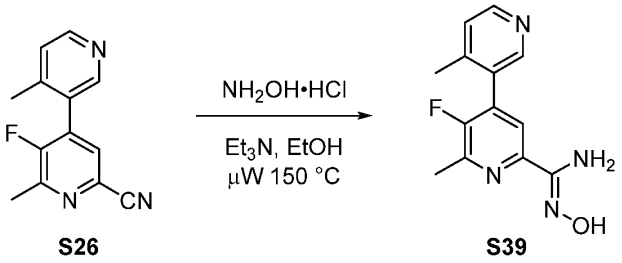
(*Z*)-6'-(Difluoromethyl)-5-fluoro-*N*'-hydroxy-[3,4'-bipyridine]-2'-carboximidamide (S36). Prepared in a similar manner to intermediate **S27** to afford 16 mg of title compound as a pale yellow solid that was used without further purification (95% yield). ES-MS $[M+1]^+ = 283.0$.



(*Z*)-6'-(Difluoromethyl)-*N*'-hydroxy-4-methyl-[3,4'-bipyridine]-2'-carboximidamide (S37). Prepared in a similar manner to intermediate **S27** to afford 12 mg of title compound as a pale yellow solid that was used without further purification (72% yield). ES-MS $[M+1]^+ = 279.0$.

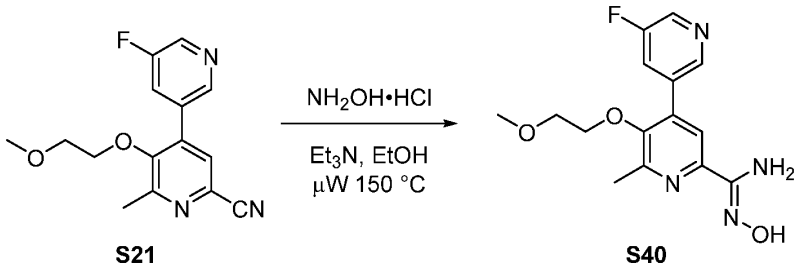


(*Z*)-*N*'-hydroxy-6-methyl-4-((tetrahydro-2*H*-pyran-4-yl)methyl)picolinimidamide (S38). Prepared in a similar manner to intermediate **S33** to afford 54 mg of title compound as a yellow oil that was used without further purification (92% yield). ES-MS $[M+1]^+ = 250.1$.



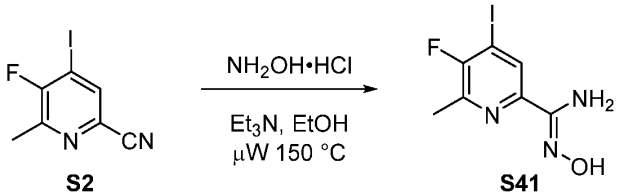
S26 S39

(*Z*)-5'-Fluoro-*N*'-hydroxy-4,6'-dimethyl-[3,4'-bipyridine]-2'-carboximidamide (S39). Prepared in a similar manner to intermediate **S27** to afford 286 mg of title compound as an off-white solid that was used without further purification (99% yield). ES-MS $[M+1]^+ = 261.1$.



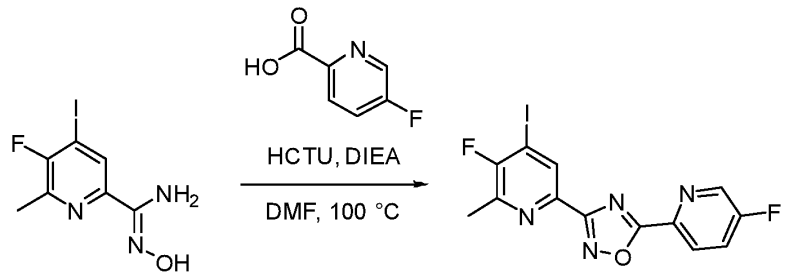
S21 S40

(*Z*)-5-Fluoro-N'-hydroxy-5'-(2-methoxyethoxy)-6'-methyl-[3,4'-bipyridine]-2'-carboximidamide (S40). Prepared in a similar manner to intermediate **S27** to afford 29 mg of title compound as a white solid (99% yield). ES-MS $[M+H]^+ = 321.1$.



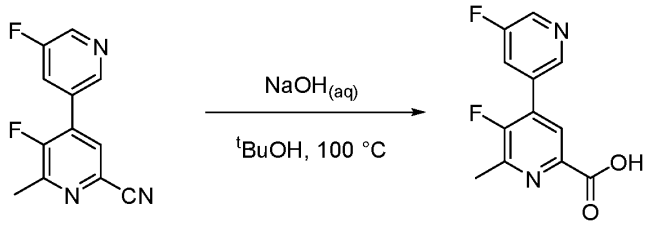
S2 S41

(*Z*)-5-Fluoro-*N*'-hydroxy-4-iodo-6-methylpicolinimidamide (S41). Prepared in a similar manner to intermediate **S27** to afford 1.099 g of the title compound as a white solid that was used without further purification (98%). ES-MS $[M+1]^+$: 295.9.



S41 S42

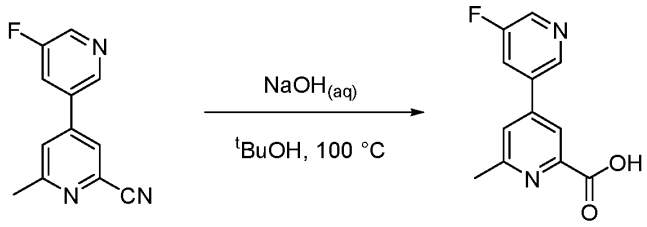
5-(5-Fluoro-4-iodo-6-methylpyridin-2-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (S42). Intermediate **S41** (1.0 g, 3.4 mmol, 1.0 eq) and 5-fluoropicolinic acid (478 mg, 3.4 mmol, 1.0 eq) and HCTU (2.10 g, 5.1 mmol, 1.5 eq) were dissolved in DMF (17 mL) and *N,N*-diisopropylethylamine (1.18 mL, 6.8 mmol, 2.0 eq) was added. The reaction was stirred for 1 hour at room temperature then heated to 100 °C for 4 hours. After cooling to ambient temperature, water was added and the reaction extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-30% EtOAc/hexanes afforded 246 mg of the title compound as a white solid (18% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 2.8 Hz, 1H), 8.56 (dd, J = 4.2, 0.6 Hz, 1H), 8.41 (ddd, J = 8.7, 4.4, 0.6 Hz, 1H), 7.66 (ddd, J = 8.7, 7.7, 2.8 Hz, 1H), 2.72 – 2.66 (m, 3H); ES-MS $[M+1]^+$: 400.9.



S3 S43

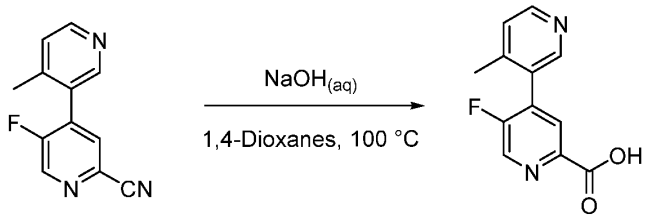
5,5'-Difluoro-6'-methyl-[3,4'-bipyridine]-2'-carboxylic acid (S43). To a solution of intermediate **S43** (400 mg, 1.7 mmol, 1.0 eq) in *tert*-butanol (3 mL) was added an aqueous solution of 3*M* sodium hydroxide (2.9 mL, 8.7 mmol, 5.0 eq). The flask was equipped with a reflux condenser and heated at 100 °C for 48 hours. After cooling to ambient temperature, the reaction mixture was brought to pH 4-5 using 1*M* aqueous HCl and the mixture was concentrated *in vacuo*. The residue was dissolved in 10% MeOH/DCM then filtered to remove insoluble salts. The organic solvents were concentrated *in vacuo* to afford 432 mg of the title compound as an

off-white solid which was used without further purification (99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J = 1.8 Hz, 1H), 8.74 (d, J = 2.8 Hz, 1H), 8.16 (ddt, J = 9.8, 2.7, 1.2 Hz, 1H), 8.09 (d, J = 5.6 Hz, 1H), 7.73 (s, 1H), 2.59 (d, J = 3.3 Hz, 3H); ES-MS $[M+1]^+$: 251.0.



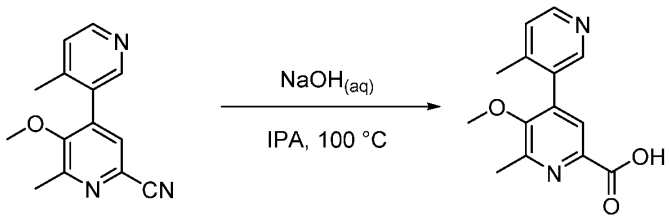
S10 **S44**

5-Fluoro-6'-methyl-[3,4'-bipyridine]-2'-carboxylic acid (S44). Prepared in a similar manner to intermediate **S43** to afford 217 mg of title compound (99% yield). ES-MS $[M+1]^+$: 233.1.



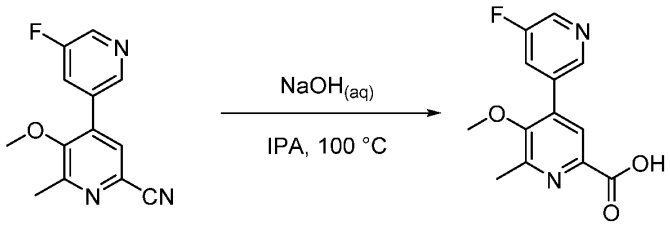
S5 **S45**

5'-Fluoro-4-methyl-[3,4'-bipyridine]-2'-carboxylic acid (S45). Intermediate **S5** (520 mg, 2.4 mmol, 1.0 eq) and 2*M* aqueous sodium hydroxide (12.2 mL, 24 mmol, 10 eq) were dissolved in 1,4-dioxane (4.9 mL) and heated to 100 °C for 15 minutes. After cooling to ambient temperature the reaction was washed with DCM (2x) and the aqueous layer was brought to pH 4-5 with 2*M* aqueous HCl and concentrated *in vacuo*. The resulting residue was dissolved in 10% MeOH/DCM and filtered to remove salts. The filtrate was concentrated *in vacuo* to afford 561 mg of the title compound as a yellow solid that was used without further purification (99% yield). ES-MS $[M+1]^+$: 233.4.



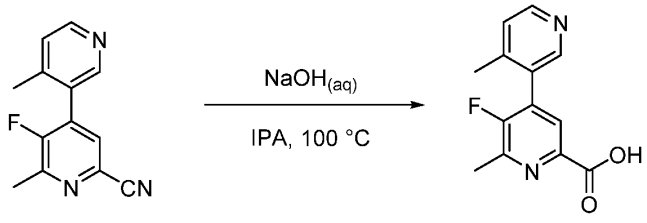
S7 S46

5'-Methoxy-4,6'-dimethyl-[3,4'-bipyridine]-2'-carboxylic acid (S46). Intermediate **S7** (20 mg, 0.084 mmol, 1.0 eq) and 2*M* aqueous sodium hydroxide (0.42 mL, 0.84 mmol, 10.0 eq) were dissolved in IPA (0.17 mL) and heated to 100 °C for 2 hours. The reaction was cooled to ambient temperature and was brought to pH 4-5 with 2*M* aqueous HCl and concentrated *in vacuo*. The resulting residue was dissolved in 10% MeOH/DCM and filtered to remove insoluble salts. The filtrate was concentrated *in vacuo* to afford 21.3 mg of the title compound as an off-white solid that was used without further purification (99% yield). ES-MS $[M+1]^+$: 259.1.



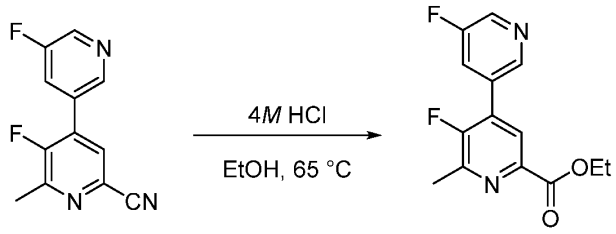
S8 S47

5-Fluoro-5'-methoxy-6'-methyl-[3,4'-bipyridine]-2'-carboxylic acid (S47). Prepared in a similar manner to intermediate **S46** to afford 21.3 mg of the title compound as an off-white solid (97% yield). ES-MS $[M+1]^+$: 263.0.



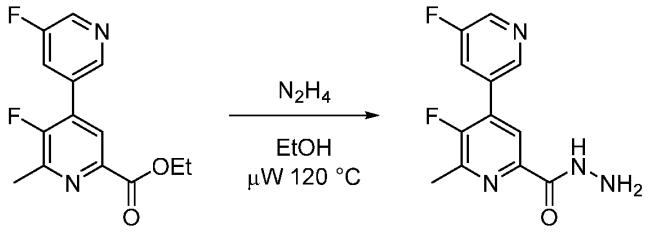
S26 S48

5'-fluoro-4,6'-dimethyl-[3,4'-bipyridine]-2'-carboxylic acid (S48). Prepared in a similar manner to intermediate **S46** to afford 123 mg of the title compound as an off-white solid (98% yield). ES-MS $[M+1]^+$: 247.1.



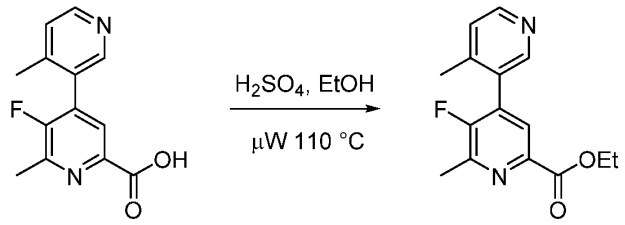
S3 S49

Ethyl 5,5'-difluoro-6'-methyl-[3,4'-bipyridine]-2'-carboxylate (S49). Intermediate **S3** (300 mg, 1.3 mmol, 1.0 eq) was dissolved in EtOH (13 mL). Hydrochloric acid (3.2 mL, 4*M* in 1,4-dioxane, 13 mmol, 10 eq) was added and the reaction heated to 65 °C for 72 hours. After cooling to ambient temperature the reaction was concentrated *in vacuo*. The resulting residue was dissolved in EtOAc and washed successively with saturated aqueous sodium bicarbonate, water, and brine. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-50% EtOAc/hexanes afforded 209 mg of the title compound as a white solid (58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (q, J = 1.6 Hz, 1H), 8.59 (d, J = 2.7 Hz, 1H), 8.11 (d, J = 5.4 Hz, 1H), 7.70 (dt, J = 9.1, 1.4 Hz, 1H), 4.50 (q, J = 7.1 Hz, 2H), 2.70 (d, J = 3.5 Hz, 3H), 1.45 (d, J = 14.2 Hz, 3H); ES-MS $[M+1]^+$: 279.0.



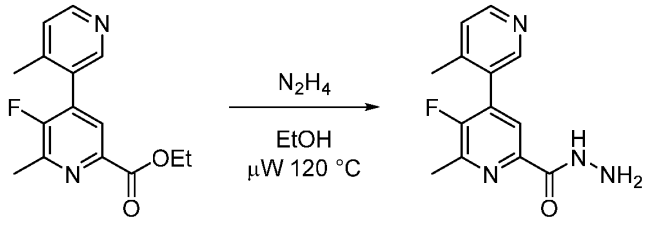
S49 S50

5,5'-Difluoro-6'-methyl-[3,4'-bipyridine]-2'-carbohydrazide (S50). Intermediate **S49** (100 mg, 0.36 mmol, 1.0 eq) was dissolved in EtOH (2 mL). Hydrazine (40 μL, 1.3 mmol, 3.5 eq) was added and the reaction was irradiated in a microwave at 120 °C for 15 minutes. After cooling to ambient temperature the reaction was concentrated *in vacuo* to afford 95 mg of the title compound as a white solid that was used without further purification (100% yield). ES-MS $[M+1]^+$: 265.1.



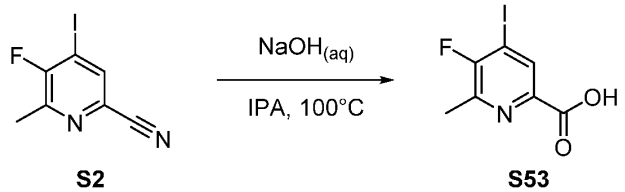
S48 **S51**

Ethyl 5'-fluoro-4,6'-dimethyl-[3,4'-bipyridine]-2'-carboxylate (S51). In a microwave vial was added a solution of intermediate **S48** (146 mg, 0.20 mmol, 1.0 eq) in EtOH (1.1 mL). Next, sulfuric acid (161 μL, 3.1 mmol, 15 eq) was added dropwise over 5-10 minutes (exothermic). Upon complete addition, the vial was sealed and the mixture was irradiated in a microwave reactor at 110 °C for 15 minutes. Additional sulfuric acid (100 μL) was added and the mixture irradiated in a microwave reactor for an additional 15 minutes at 110 °C. After cooling to ambient temperature, the pH was adjusted (pH = 7) with a saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$/IPA (4:1) (3x). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 44.5 mg of title compound that was used without further purification (81% yield). ES-MS $[M+1]^+$: 275.3.



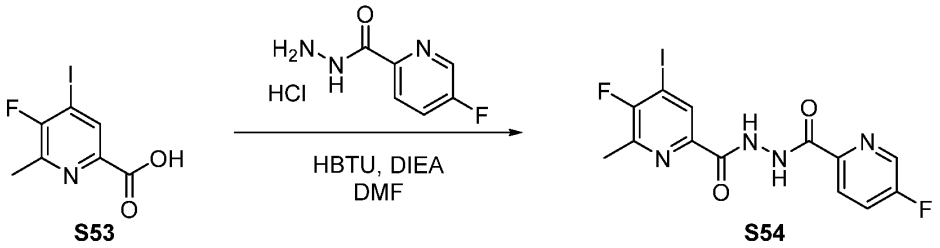
S51 **S52**

5'-Fluoro-4,6'-dimethyl-[3,4'-bipyridine]-2'-carbohydrazide (S52). Prepared in a similar manner to intermediate **S50** to afford 39 mg of the title compound as tan solid (91% yield). ES-MS $[M+1]^+$: 261.1.



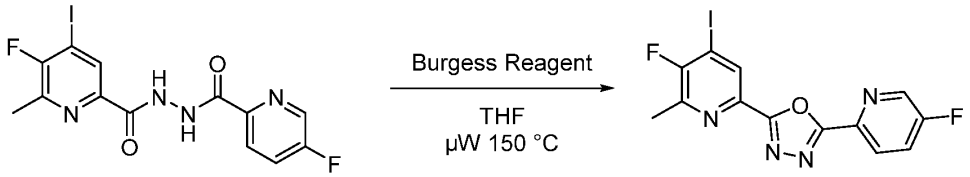
S2 **S53**

5-Fluoro-4-iodo-6-methylpicolinic acid (S53). Prepared in a similar manner to intermediate **S46** to afford 536 mg as an off-white solid (99% yield). ES-MS $[M+1]^+$: 281.9.



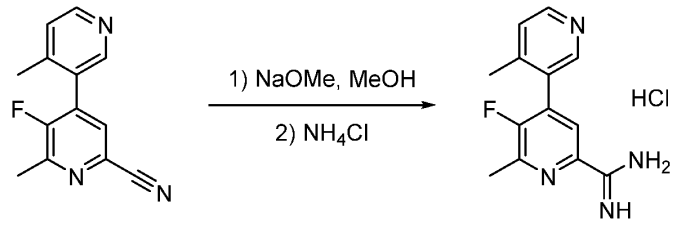
S53 S54

5-Fluoro-*N*'-(5-fluoropicolinoyl)-4-iodo-6-methylpicolinohydrazide (S54). To a solution of **S53** (214 mg, 0.43 mmol, 1.0 eq) and 5-fluoropicolinohydrazide hydrochloride (73.6 mg, 0.38 mmol, 1.5 eq) in DMF (3 mL) and DIEA (0.13 mL, 1.3 mmol, 3 eq) was added HBTU (146 mg, 0.38 mmol, 1.5 eq). After 1 hour at ambient temperature, the solvents were concentrated. Purification by flash chromatography on silica gel using 3-80% EtOAc/hexanes afforded 70 mg of title compound as a white solid (66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 2H), 8.46 (d, J = 2.8 Hz, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.24 (dd, J = 8.5, 4.6 Hz 1H), 7.58 (td, J = 8.3, 2.8 Hz, 1H), 2.59 (d, J = 3.1 Hz, 3H); ES-MS $[M+H]^+$ = 419.0.



S54 S55

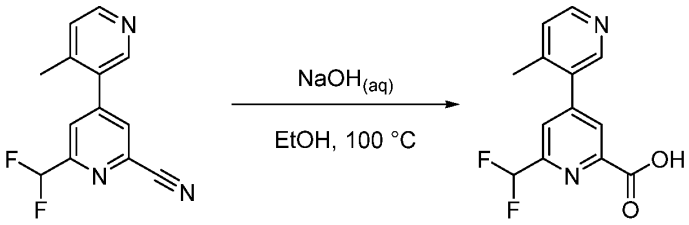
2-(5-Fluoro-4-iodo-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (S55). In a microwave vial was added intermediate **S54** (70.2 mg, 0.17 mmol, 1.0 eq) and Burgess Reagent (400 mg, 1.7 mmol, 10 eq) dissolved in THF (2 mL). The vial was sealed and the mixture was irradiated in a microwave at 150 °C for 2 hours. Solvents were concentrated and the crude residue was diluted with water and extracted in DCM (3x). The combined organic extracts were passed through a phase separator then concentrated. Purification by flash chromatography on silica gel using 3-50% EtOAc/ hexanes afforded 27 mg the title compound as a white solid (40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 2.9 Hz, 1H), 8.55 (d, J = 4.1 Hz, 1H), 8.38 (dd J = 8.5, 4.3 Hz, 1H), 7.63 (td, J = 8.3, 2.8 Hz, 1H), 2.68 (d, J = 3.2 Hz, 3H). ES-MS $[M+H]^+$ = 401.0.



S26 **S56**

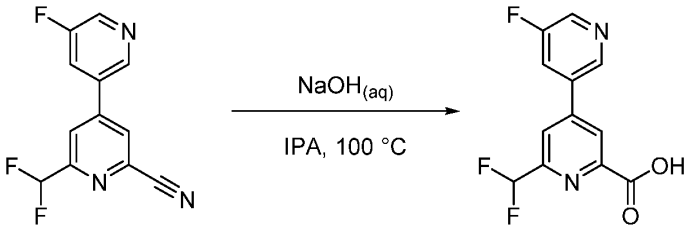
5'-Fluoro-4,6'-dimethyl-[3,4'-bipyridine]-2'-carboximidamide hydrochloride (S56). To a solution of intermediate **S26** (10 mg, 0.044 mmol) in MeOH (0.50 mL) was added sodium methoxide (0.5*M* in MeOH, 106 µL, 0.053 mmol, 1.2 eq) and the mixture was stirred at ambient temperature for 18 hours (ES-MS $[M+H]^+ = 260.1$).

Ammonium chloride (5.2 mg, 0.11 mmol, 2.4 eq) was then added and the reaction mixture was allowed to stir for 18 hours. Unreacted NH_4Cl was removed by filtration and the filtrate was concentrated to give 12 mg of title compound that was carried forward without further purification (97% yield). ES-MS $[M+H\text{-}HCl]^+ = 245.1$.



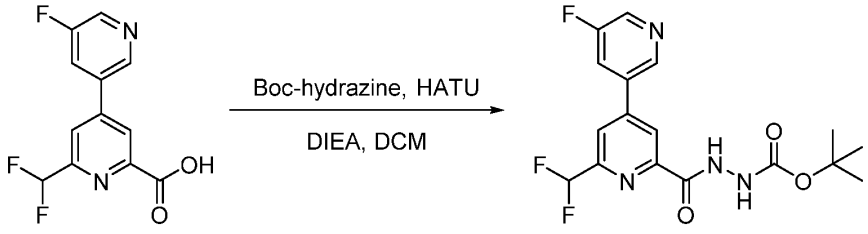
S25 **S57**

6'-(Difluoromethyl)-4-methyl-[3,4'-bipyridine]-2'-carboxylic acid (S57). Prepared in a similar manner to intermediate **S46** to afford 38 mg of title compound as an off-white solid (99% yield). ES-MS $[M+H]^+ = 265.0$.



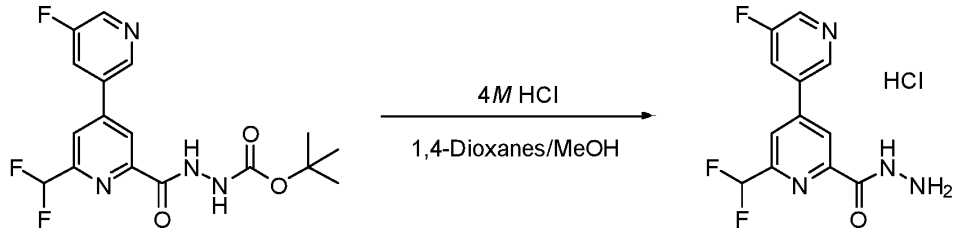
S24 **S58**

6'-(Difluoromethyl)-5-fluoro-[3,4'-bipyridine]-2'-carboxylic acid (S58). Prepared in a similar manner to intermediate **S46** to afford 67 mg of title compound as an off-white solid (98% yield). ES-MS $[M+H]^+ = 269.0$.



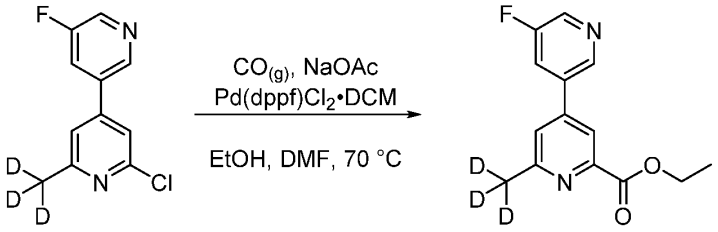
S58 **S59**

***tert*-Butyl 2-(6'-(difluoromethyl)-5-fluoro-[3,4'-bipyridine]-2'-carbonyl)hydrazine-1-carboxylate (S59).** To a solution of Boc-hydrazine (12 µL, 0.089 mmol, 1.2 eq) and intermediate **S58** (20 mg, 0.075 mmol, 1.0 eq) in DCM (0.41 mL) was added DIEA (39 µL, 0.22 mmol, 3.0 eq), followed by HATU (34.0 mg, 0.089 mmol, 1.2 eq). The resulting solution was stirred at ambient temperature for 1 hour. A saturated aqueous $NaHCO_3$ solution was added to the mixture and the organic layer was isolated. The aqueous layer was further extracted with DCM (3x) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel using 3-100% EtOAc/hexanes afforded the title compound as a white solid. ES-MS $[M+H]^+ = 383.2$.



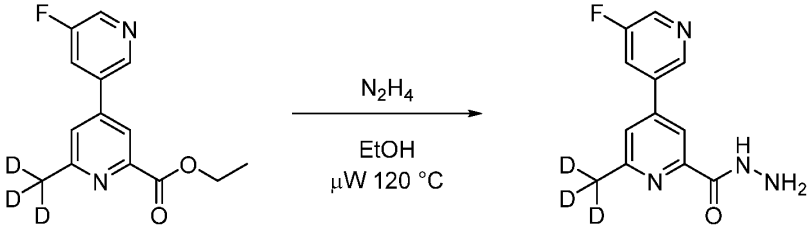
S59 **S60**

6'-(Difluoromethyl)-5-fluoro-[3,4'-bipyridine]-2'-carbohydrazide hydrochloride (S60). To a solution of intermediate **S59** (12.5 mg, 0.033 mmol, 1.0 eq) in1,4-dioxane (0.16 mL) and methanol (0.16 mL) was added hydrochloric acid (4*M* in 1,4-dioxanes, 81.7 µL, 0.33 mmol, 10 eq) and the reaction mixture was stirred for 2 hours. Solvents were concentrated to afford 9 mg of title compound that was carried forward without further purification. ES-MS $[M+H]^+ = 283.1$.



S12 **S61**

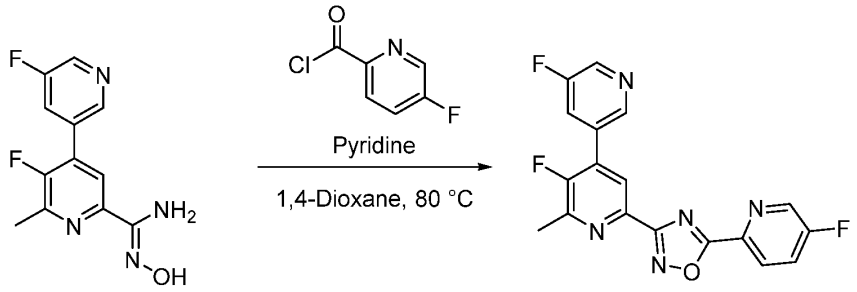
Ethyl 5-fluoro-6'-(methyl-d_3)-[3,4'-bipyridine]-2'-carboxylate (S61). Intermediate **S12** (277 mg, 1.2 mmol, 1.0 eq), sodium acetate (204 mg, 2.5 mmol, 2.0 eq) and $Pd(dppf)Cl_2 \cdot DCM$ (101 mg, 0.12 mmol, 0.1 eq) were combined in a vial with DMF (1 mL) and EtOH (5 mL) and the solvents were degassed under vacuum. The resulting mixture was stirred under a $CO_{(g)}$ atmosphere at 70 °C for 2 hours, after which time the reaction was cooled to room temperature and diluted with DCM and water. The aqueous layer was extracted with DCM (3x), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel using 3-100% EtOAc/hexanes to give 276 mg of title compound as a light brown solid (85% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.58 (d, J = 2.4 Hz, 1H), 8.15 (s, 1H), 7.69 (dt, J = 9.0, 2.2 Hz, 1H), 7.54 (s, 1H), 4.52 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H); ES-MS $[M+1]^+$ = 264.1.



S61 **S62**

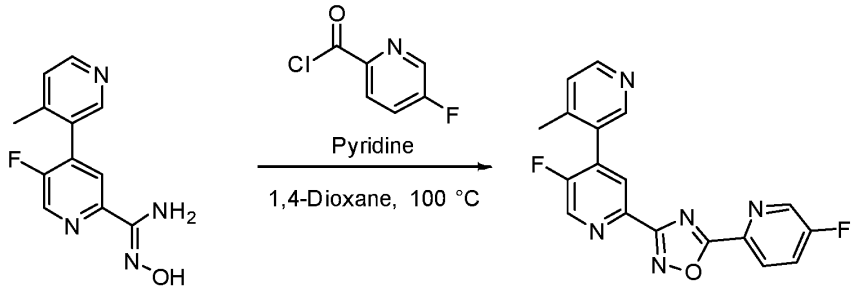
5-Fluoro-6'-(methyl-d_3)-[3,4'-bipyridine]-2'-carbohydrazide (S62). Intermediate **S61** (60 mg, 0.23 mmol, 1.0 eq) was dissolved in EtOH (1.3 mL) then hydrazine (50 μL, 1.6 mmol, 7.0 eq) was added. The resulting solution was irradiated in a microwave reactor at 120 °C for 45 minutes. After cooling to room temperature, the solvents were concentrated to afford 57 mg of title compound which was carried forward without further purification (100% yield). ES-MS $[M+1]^+$ = 250.1.

Synthesis of Compounds:



S32 6

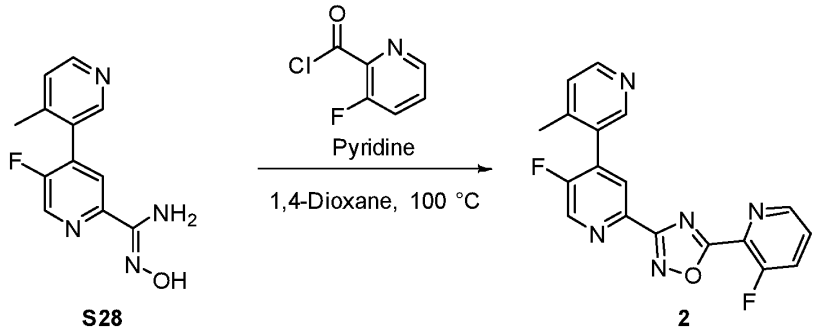
3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (6). Intermediate **S32** (731 mg, 2.8 mmol, 1.0 eq) and 5-fluoropicolinoyl chloride (486 mg, 3.0 mmol, 1.1 eq) were dissolved in 1,4-dioxane (50 mL). Pyridine (0.25 mL, 3.0 mmol, 1.1 eq) was added and the reaction was heated to 80 ℃ for 40 hours. After cooling to ambient temperature the reaction was concentrated *in vacuo*. Purification by flash chromatography on silica gel using 0-50% EtOAc/hexanes and subsequent recrystallization from IPA afforded 631 mg of the title compound as a white solid (62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (q, J = 1.6 Hz, 1H), 8.73 (d, J = 2.8 Hz, 1H), 8.61 (d, J = 2.7 Hz, 1H), 8.43 (dd, J = 8.7, 4.3 Hz, 1H), 8.26 (d, J = 5.3 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.67 (ddd, J = 8.8, 7.7, 2.8 Hz, 1H), 2.76 (d, J = 3.4 Hz, 3H); ES-MS $[M+1]^+$: 370.1.



S28 1

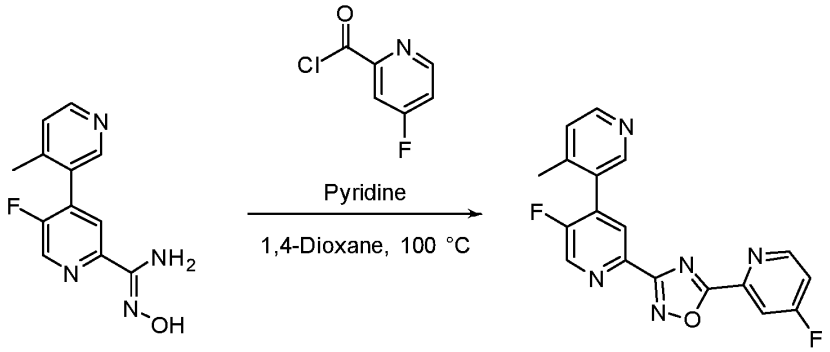
3-(5'-Fluoro-4-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (1). Intermediate **S28** (17 mg, 0.07 mmol, 1.0 eq) was dissolved in 1,4-dioxane (1.5 mL). 5-fluoropicolinoyl chloride (13.2 mg, 0.083, 1.2 eq) and pyridine (6.7 µL, 0.083 mmol, 1.2 eq) were added and the reaction was heated to 100 °C for 18 hours. After cooling to ambient temperature, water was added and the mixture was extracted with EtOAc (3x). The combined

organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was dissolved in DMSO (1 mL), syringe filtered, and purified by RP-HPLC (25-55% MeCN/0.1% aqueous TFA). Fractions containing product were basified with a saturated $NaHCO_3$ solution and extracted with DCM to afford 3.8 mg of the title compound as a white solid (16% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.72 (d, J = 2.8 Hz, 1H), 8.65 (d, J = 5.2 Hz, 1H), 8.59 (s, 1H), 8.45 (dd, J = 8.7, 4.3 Hz, 1H), 8.28 (d, J = 5.7 Hz, 1H), 7.67 (td, J = 8.2, 2.8 Hz, 1H), 7.52 (s, 1H), 2.41 (s, 3H); ES-MS $[M+1]^+$: 352.2.



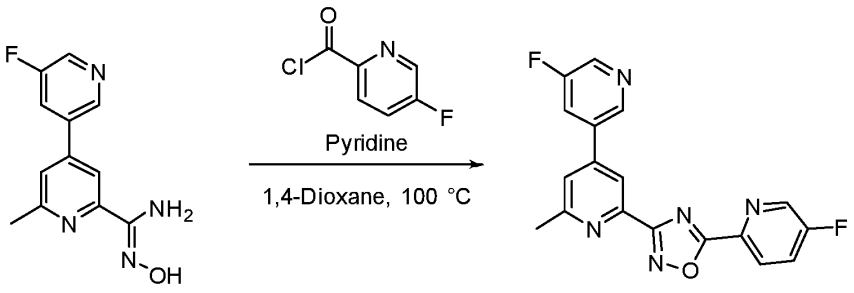
S28 2

3-(5'-Fluoro-4-methyl-[3,4'-bipyridin]-2'-yl)-5-(3-fluoropyridin-2-yl)-1,2,4-oxadiazole (2). Prepared in a similar manner to compound **1** to afford 5.3 mg of the title compound as a white solid (22% yield). ES-MS $[M+1]^+$: 352.3.



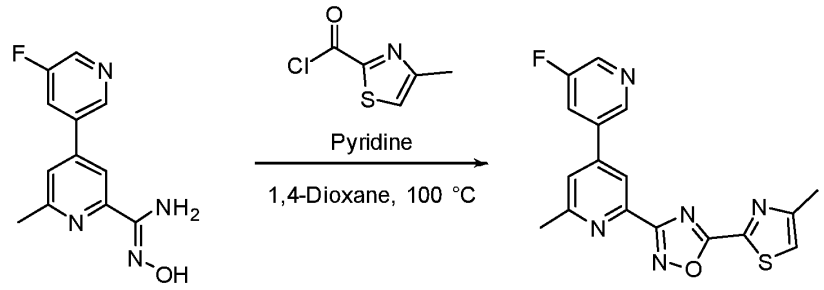
S28 3

3-(5'-Fluoro-4-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-fluoropyridin-2-yl)-1,2,4-oxadiazole (3). Prepared in a similar manner to compound **1** to afford 1.7 mg of the title compound as a white solid (7% yield). ES-MS $[M+1]^+$: 352.3.



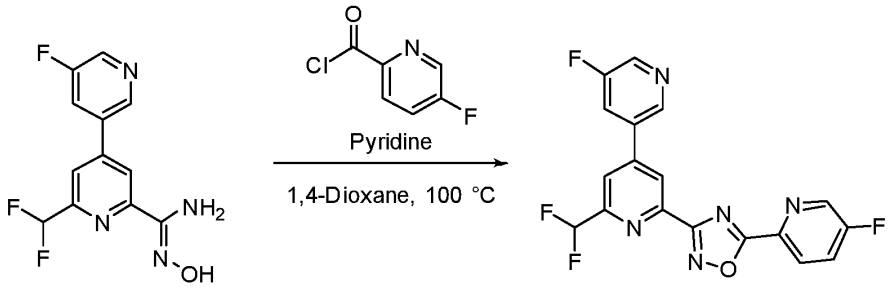
S27 55

3-(5-Fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (55). Prepared in a similar manner to compound **1** to afford 2.6 mg of the title compound as a white solid (12% yield). ES-MS $[M+1]^+$: 352.0.



S27 72

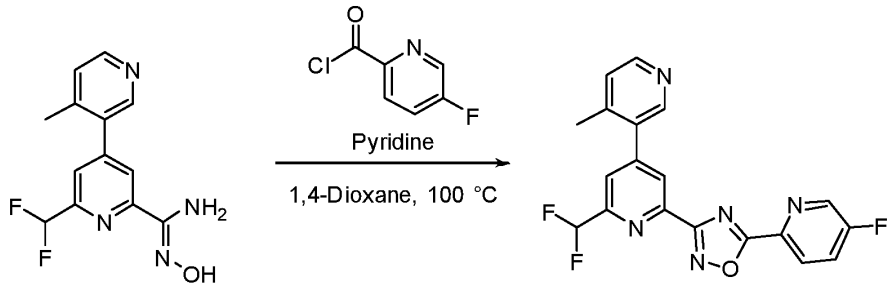
3-(5-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-methylthiazol-2-yl)-1,2,4-oxadiazole (72). Prepared in a similar manner to compound **1** to afford 15.3 mg of the title compound as a white solid (53% yield). ES-MS $[M+1]^+$: 354.1.



S36 61

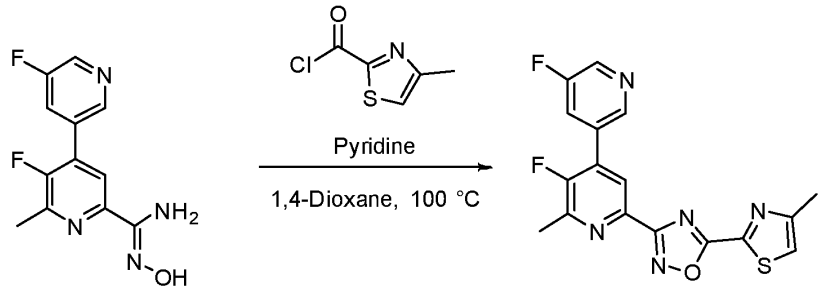
3-(6'-(Difluoromethyl)-5-fluoro-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (61). Prepared in a similar manner to compound **1** to afford 5.1 mg of the title compound as a white solid (40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (t, J = 1.7 Hz, 1H),

8.75 (d, J = 2.7 Hz, 1H), 8.66 (d, J = 2.7 Hz, 1H), 8.61 (dt, J = 1.6, 0.8 Hz, 1H), 8.45 (ddd, J = 8.7, 4.3, 0.6 Hz, 1H), 8.04 (d, J = 1.7 Hz, 1H), 7.81 (ddd, J = 8.9, 2.7, 1.9 Hz, 1H), 7.69 (ddd, J = 8.7, 7.6, 2.8 Hz, 1H), 6.90 (t, J = 54.9 Hz, 1H); ES-MS $[M+1]^+$: 388.1.



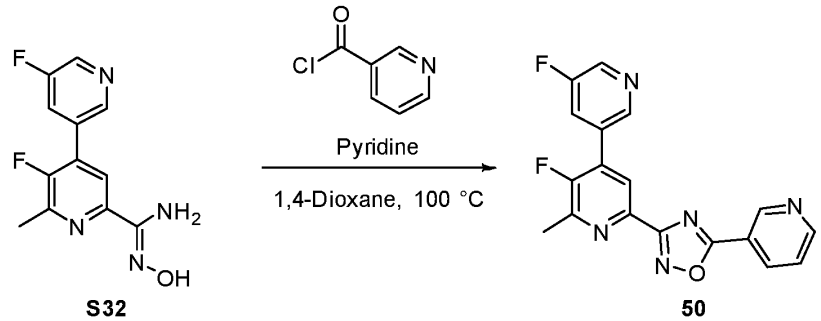
S37 60

3-(6'-(Difluoromethyl)-4-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (60). Prepared in a similar manner to compound **1** to afford 6.7 mg of the title compound as a white solid (40% yield). ES-MS $[M+1]^+$: 384.1.



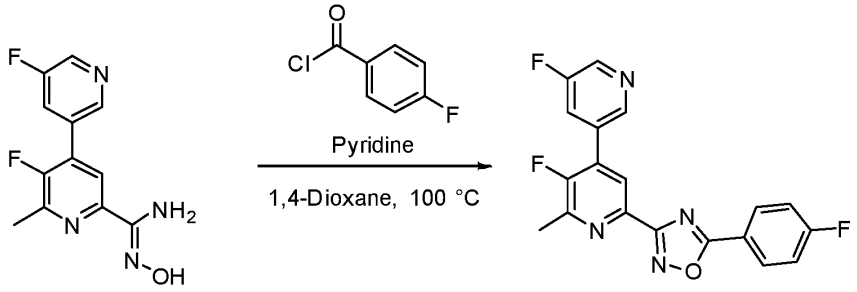
S32 16

3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-methylthiazol-2-yl)-1,2,4-oxadiazole (16). Prepared in a similar manner to compound **1** to afford 2.2 mg of the title compound as a white solid (10% yield). ES-MS $[M+H]^+$: 372.1.



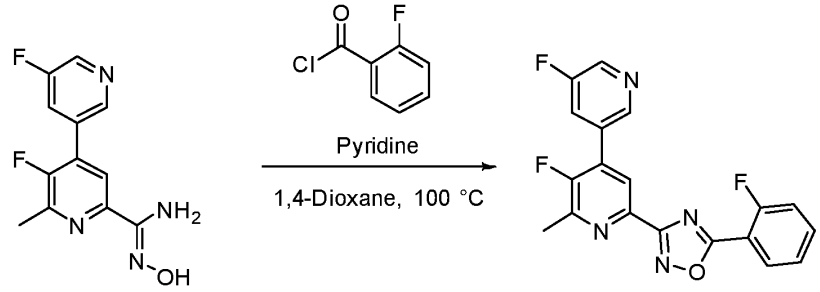
S32 50

3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole (50). Prepared in a similar manner to compound **1** to afford 3.2 mg of the title compound as a white solid (16% yield). ES-MS $[M+H]^+$: 352.1.



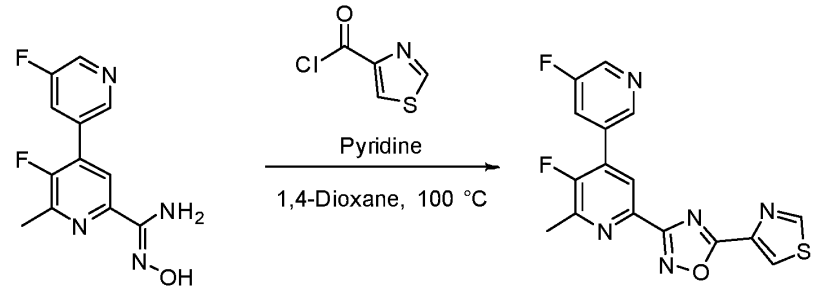
S32 48

3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-fluorophenyl)-1,2,4-oxadiazole (48). Prepared in a similar manner to compound **1** to afford 1.5 mg of the title compound as a white solid (7% yield). ES-MS $[M+H]^+$: 369.1.



S32 47

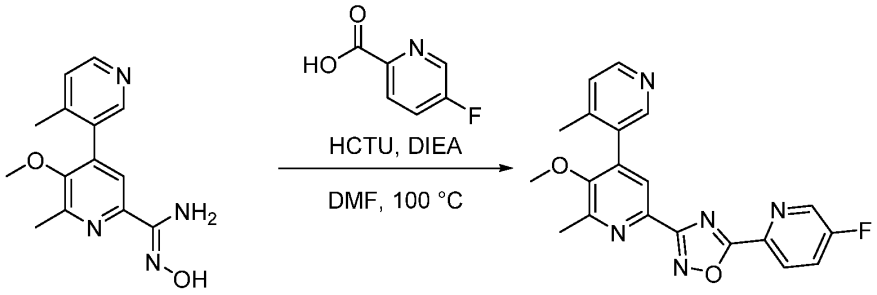
3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(2-fluorophenyl)-1,2,4-oxadiazole (47). Prepared in a similar manner to compound **1** to afford 2.8 mg of the title compound as a white solid (13% yield). ES-MS $[M+H]^+$: 369.1.



S32 52

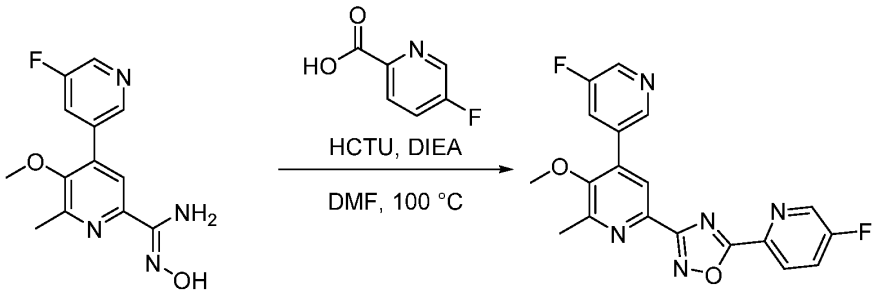
3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(thiazol-4-yl)-1,2,4-oxadiazole (52).

Prepared in a similar manner to compound **1** to afford 1.0 mg of the title compound as a white solid (4% yield). ES-MS $[M+H]^+$: 358.1.



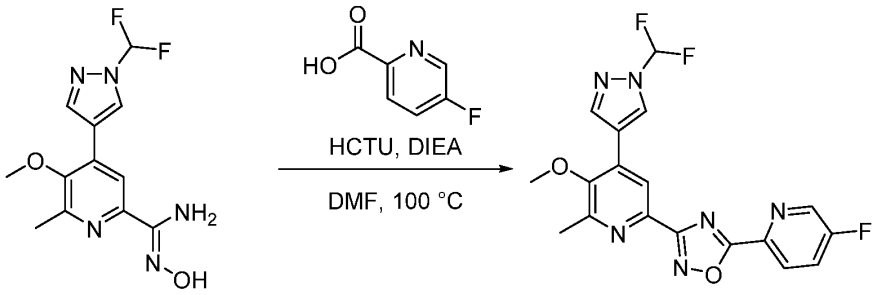
S29 **10**

5-(5-Fluoropyridin-2-yl)-3-(5'-methoxy-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole (10). Intermediate **S29** (22 mg, 0.081 mmol, 1.0 eq), 5-fluoropicolinic acid (11.4 mg, 0.081 mmol, 1.0 eq), HCTU (50.1 mg, 0.12 mmol, 1.5 eq) and *N,N*-diisopropylethylamine (28.1 µL, 0.16 mmol, 2.0 eq) were dissolved in DMF (1.6 mL) and heated to 100 °C for 90 minutes. The reaction was syringe filtered and purified by RP-HPLC (10-40% MeCN/0.1% aqueous TFA). Fractions containing product were basified with a saturated $NaHCO_3$ solution and extracted with DCM to afford 2.3 mg of the title compound as a white solid (8% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 2.8 Hz, 1H), 8.59 (d, J = 5.3 Hz, 1H), 8.56 (s, 1H), 8.42 (ddd, J = 8.7, 4.3, 0.6 Hz, 1H), 8.00 (d, J = 0.6 Hz, 1H), 7.65 (ddd, J = 8.7, 7.7, 2.8 Hz, 1H), 7.42 (s, 1H), 3.47 (s, 3H), 2.74 (s, 3H), 2.32 (s, 3H); ES-MS $[M+1]^+$: 378.1.



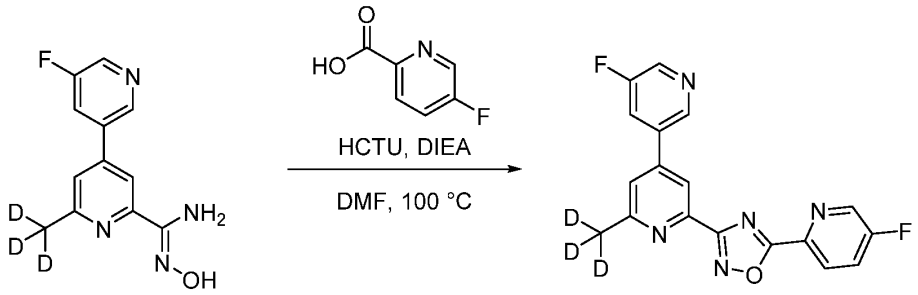
S30 **11**

3-(5-Fluoro-5'-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (11). Prepared in a similar manner to compound **10** to afford 1.9 mg of the title compound as a white solid (6% yield). ES-MS $[M+1]^+$: 382.1.



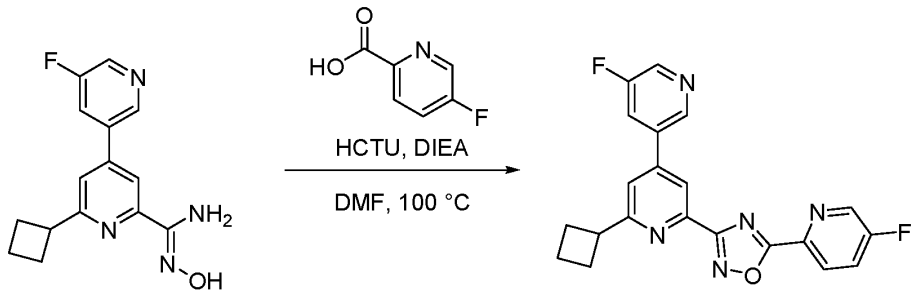
S31 12

3-(4-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-5-methoxy-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (12). Prepared in a similar manner to compound **10** to afford 1.7 mg of the title compound as a white solid (8% yield). ES-MS $[M+1]^+$: 403.1



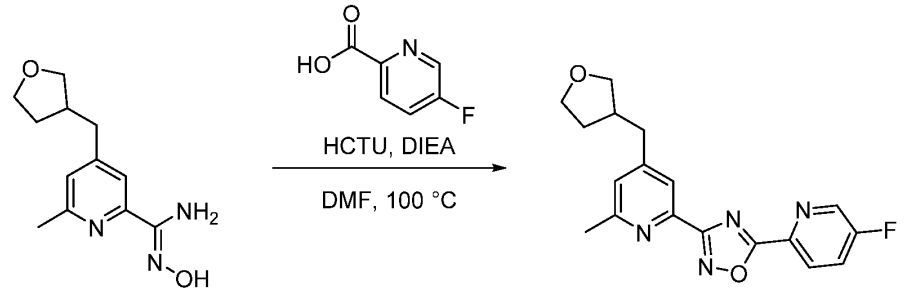
S33 35

3-(5-Fluoro-6'-(methyl-d_3)-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (35). Prepared in a similar manner to compound **10** to afford 8.4 mg of title compound as a white solid (38% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.73 (d, J = 2.8 Hz, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.45 (dd, J = 8.8, 4.3 Hz, 1H), 8.30 (t, J = 1.4 Hz, 1H), 7.77 – 7.73 (m, 1H), 7.69 – 7.64 (m, 1H), 7.54 (t, J = 1.4 Hz, 1H); ES-MS $[M+1]^+$ = 355.2.



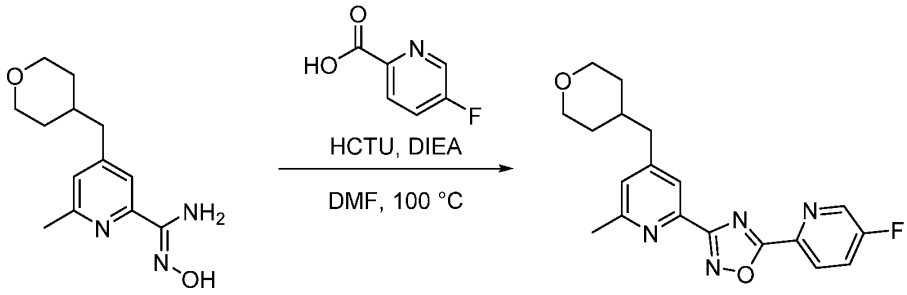
S34 39

3-(6'-Cyclobutyl-5-fluoro-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (39). Prepared in a similar manner to compound **10** to afford 9.6 mg of title compound as a tan solid (40% yield). ES-MS $[M+1]^+ = 392.1$.



S35 **86**

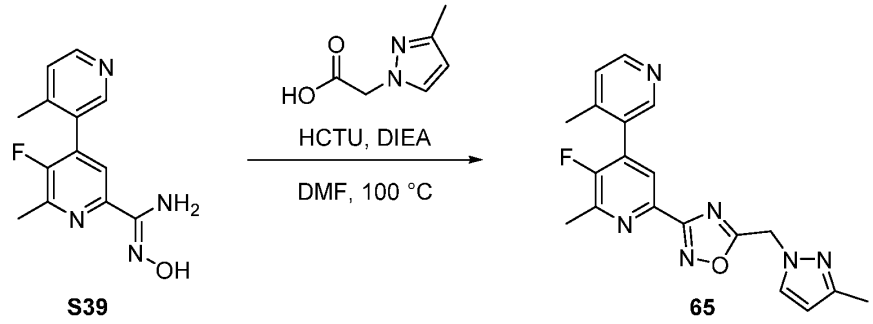
5-(5-fluoropyridin-2-yl)-3-(6-methyl-4-((tetrahydrofuran-3-yl)methyl)pyridin-2-yl)-1,2,4-oxadiazole (86). Prepared in a similar manner to compound **10** to afford 2.5 mg of title compound as a colorless oil (7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 2.8 Hz, 1H), 8.44 (ddd, J = 8.8, 4.4, 0.6 Hz, 1H), 7.94 (s, 1H), 7.65 (ddd, J = 8.7, 7.7, 2.8 Hz, 1H), 7.16 (d, J = 1.1 Hz, 1H), 3.93 (td, J = 8.3, 5.1 Hz, 1H), 3.86 (dd, J = 8.5, 6.8 Hz, 1H), 3.82 – 3.76 (m, 1H), 3.48 (dd, J = 8.5, 6.3 Hz, 1H), 2.81 – 2.73 (m, 2H), 2.69 (s, 3H), 2.66 – 2.56 (m, 1H), 2.08 – 2.00 (m, 1H), 1.70 – 1.59 (m, 1H); ES-MS $[M+1]^+ = 341.2$.



S38 **71**

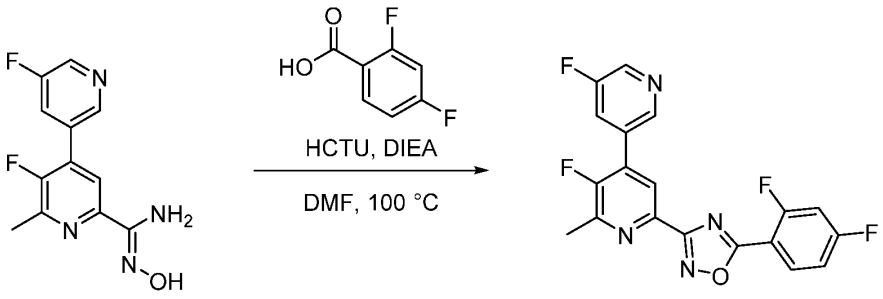
5-(5-Fluoropyridin-2-yl)-3-(6-methyl-4-((tetrahydro-2*H*-pyran-4-yl)methyl)pyridin-2-yl)-1,2,4-oxadiazole (71). Prepared in a similar manner to compound **10** to afford 3.9 mg of title compound as a tan solid (5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 2.8 Hz, 1H), 8.44 (dd, J = 8.7, 4.3 Hz, 1H), 7.91 (s, 1H), 7.65 (ddd, J = 8.7, 7.7, 2.8 Hz, 1H), 7.12 (d, J = 1.5 Hz, 1H), 3.95 (ddd, J = 11.3, 5.2, 1.8 Hz, 2H), 3.35 (td, J = 11.8, 2.1 Hz, 2H), 2.68 (s, 3H), 2.61

(d, J = 7.2 Hz, 2H), 1.93 – 1.82 (m, 1H), 1.58 – 1.54 (m, 2H), 1.43 – 1.33 (m, 2H); ES-MS $[M+1]^+$ = 355.1.



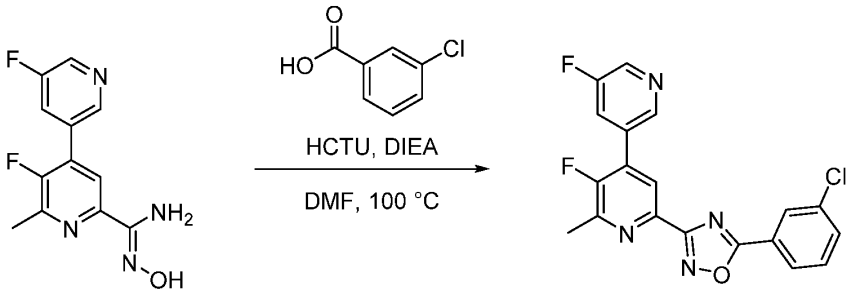
S39 65

3-(5'-Fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-((3-methyl-1*H*-pyrazol-1-yl)methyl)-1,2,4-oxadiazole (65). Prepared in a similar manner to compound **10** to afford 1.5 mg of the title compound as a white solid (7% yield). ES-MS $[M+H]^+$: 365.1.



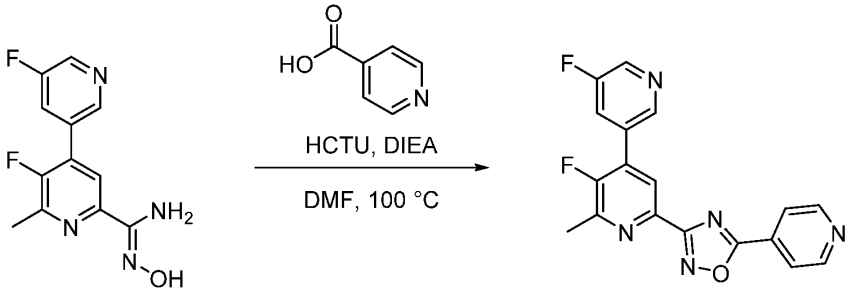
S32 49

3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(2,4-difluorophenyl)-1,2,4-oxadiazole (49). Prepared in a similar manner to compound **10** to afford 6.8 mg of the title compound as a white solid (23% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.80 – 8.78 (m, 1H), 8.64 (d, J = 2.7 Hz, 1H), 8.36 (td, J = 7.9, 6.3 Hz 1H), 8.29 (d, J = 5.4 Hz, 1H), 8.10 – 8.05 (m, 1H), 7.35 – 7.24 (m, 2H), 2.70 (d, J = 3.4 Hz, 3H); ES-MS $[M+H]^+$ = 387.1.



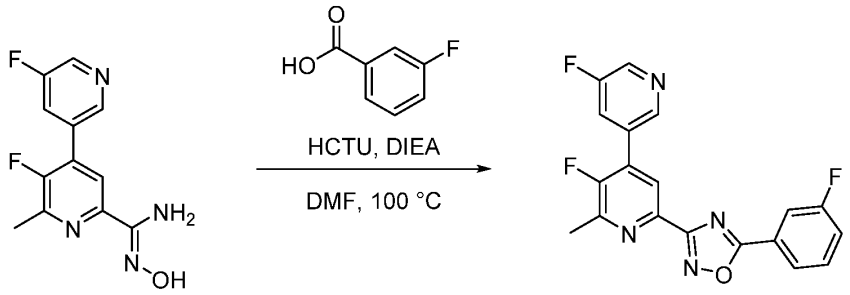
S32 44

5-(3-Chlorophenyl)-3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole (44). Prepared in a similar manner to compound **10** to afford 2.4 mg of the title compound as an off-white solid (8% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.81 – 8.79 (m, 1H), 8.65 (d, J = 2.8 Hz, 1H), 8.33 (d, J = 5.4 Hz, 1H), 8.30 (t, J = 1.9 Hz, 1H), 8.21 (dt, J = 7.8, 1.3 Hz, 1H), 8.12 – 8.07 (m, 1H), 7.75 – 7.72 (m, 1H), 7.67 – 7.63 (m, 1H), 2.72 (d, J = 3.4 Hz, 3H); ES-MS $[M+H]^+$ = 385.1.



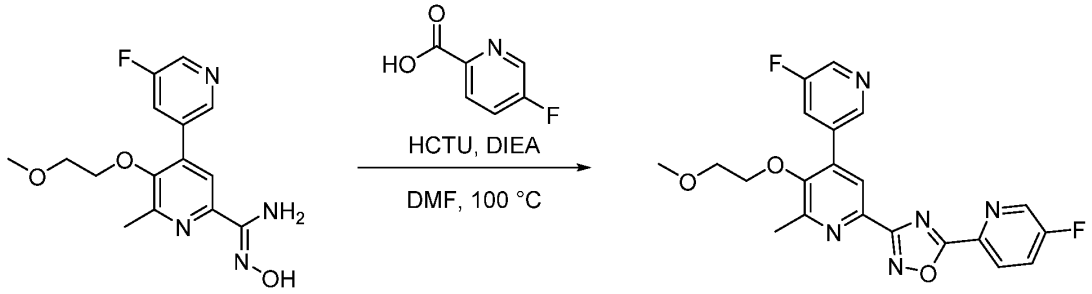
S32 51

3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-4-yl)-1,2,4-oxadiazole (51). Prepared in a similar manner to compound **10** to afford 2.7 mg of the title compound as a white solid (15% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 – 8.90 (m, 2H), 8.79 – 8.77 (m, 1H), 8.62 (d, J = 2.7 Hz, 1H), 8.21 (d, J = 5.3 Hz, 1H), 8.12 – 8.09 (m, 2H), 7.79 – 7.75 (m, 1H), 2.77 (d, J = 3.5 Hz, 3H); ES-MS $[M+H]^+$ = 352.1.



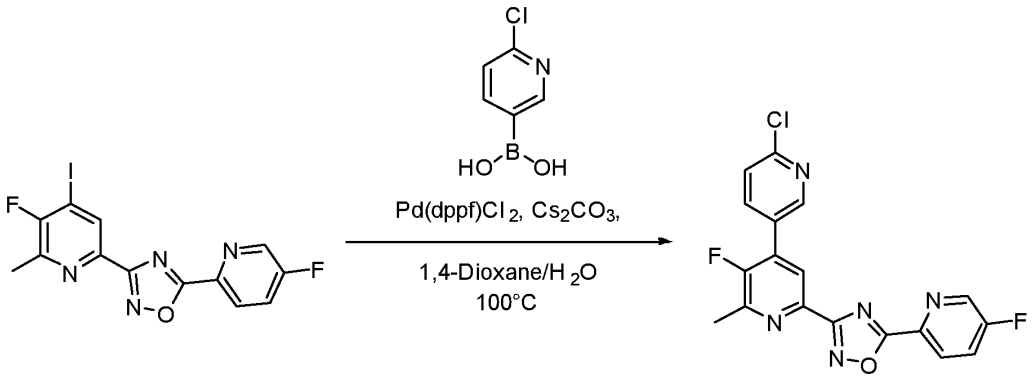
S32 38

3-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(3-fluorophenyl)-1,2,4-oxadiazole (38). Prepared in a similar manner to compound **10** to afford 8.8 mg of the title compound as an off-white solid (32% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 – 8.76 (m, 1H), 8.61 (d, *J* = 2.7 Hz, 1H), 8.20 (d, *J* = 5.3 Hz, 1H), 8.08 – 8.05 (m, 1H), 7.97 (ddd, *J* = 8.9, 2.7, 1.7 Hz, 1H), 7.79 – 7.74 (m, 1H), 7.56 (td, *J* = 8.2, 5.5 Hz, 1H), 7.34 (tdd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 2.76 (d, *J* = 3.5 Hz, 3H); ES-MS $[M+H]^+$ = 369.1.



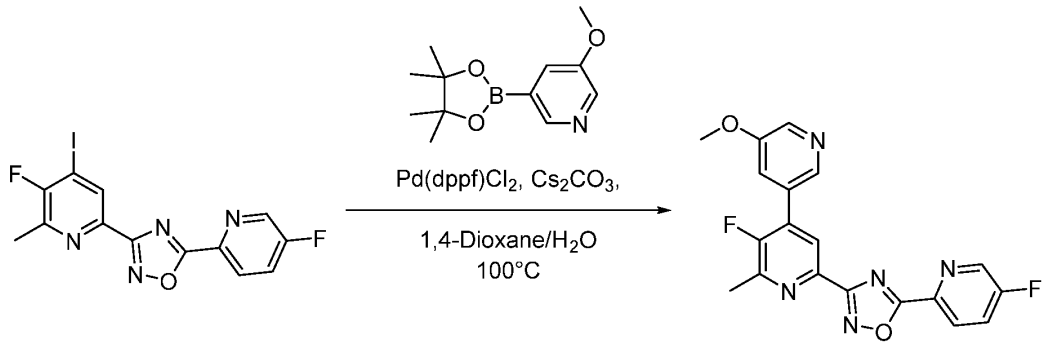
S40 54

3-(5-fluoro-5'-(2-methoxyethoxy)-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (54). Prepared in a similar manner to compound **10** to afford 5.5 mg of title compound as a tan oil (15% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 – 8.77 (m, 1H), 8.73 (d, *J* = 2.8 Hz, 1H), 8.60 (d, *J* = 2.7 Hz, 1H), 8.49 (dd, *J* = 8.7, 4.6, 1H), 8.19 (s, 1H), 8.08 (ddd, *J* = 9.6, 2.8, 1.8 Hz, 1H), 7.92 (td, *J* = 8.4, 2.8 Hz, 1H), 3.84 – 3.80 (m, 2H), 3.50 – 3.47 (m, 2H), 3.23 (s, 3H), 2.70 (s, 3H); ES-MS $[M+H]^+$ = 426.2.



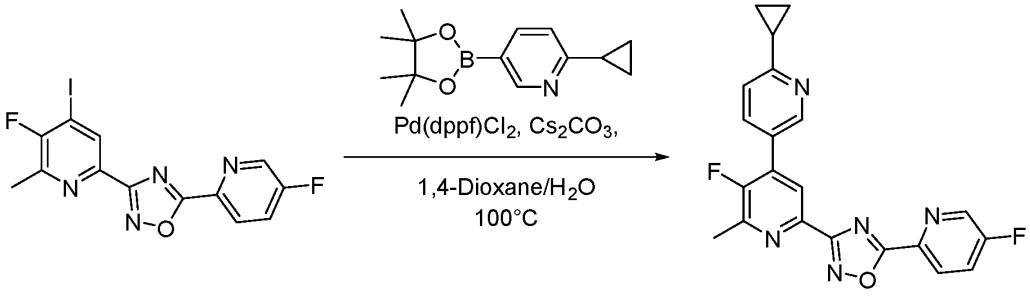
S42 34

3-(6-Chloro-5'-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (34). Intermediate **S42** (15 mg, 0.037 mmol, 1.0 eq) and 2-chloropyridine-5-boronic acid (8.8 mg, 0.056 mmol, 1.5 eq) were dissolved in 1,4-dioxane (0.38 mL). Next, $Pd(dppf)Cl_2$ (2.7506 mg, 0.0038 mmol, 0.10 eq) and cesium carbonate (36.9 mg, 0.11 mmol, 3.0 eq) were added. The mixture was purged with N_2, sealed, and stirred for 2 hours at 85 °C. The mixture was filtered over Celite, washed with 10% DCM/MeOH then the solvents were concentrated. Purification using RP-HPLC (50 – 90% ACN/0.05% aqueous NH_4OH) afforded 3.5 mg of the title compound as a white solid (22% yield). ES-MS $[M+1]^+$: 386.1.



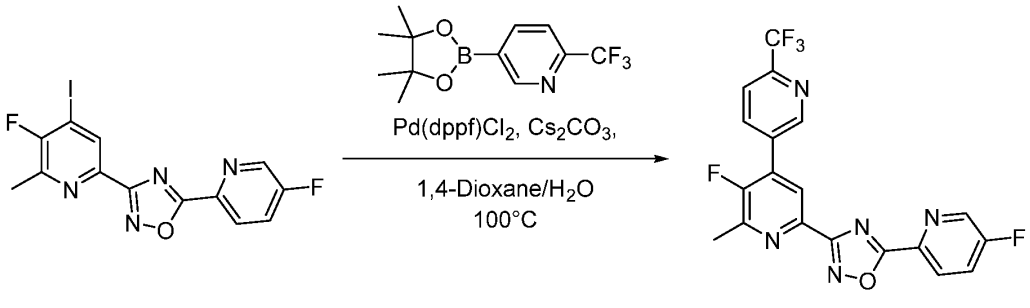
S42 30

3-(5'-Fluoro-5-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (30). Prepared in a similar manner to compound **34** to afford 2.6 mg of the title compound (18% yield). ES-MS $[M+H]^+$: 382.1.



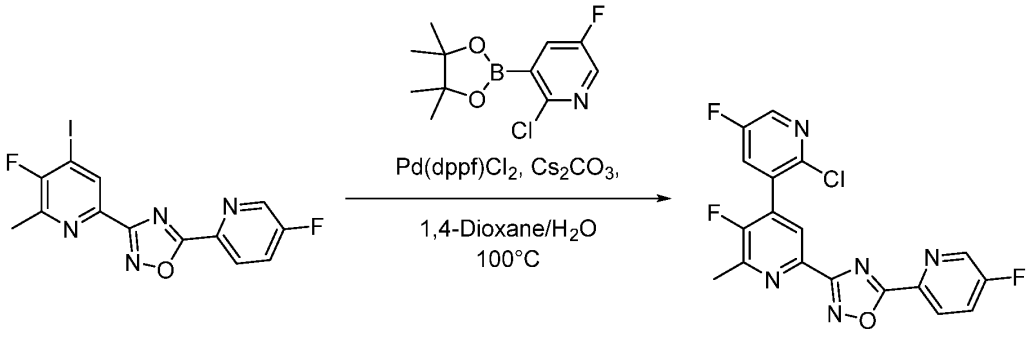
S42 31

3-(6-Cyclopropyl-5'-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (31). Prepared in a similar manner to compound **34** to afford 1.8 mg of the title compound as a white solid (12% yield). ES-MS $[M+H]^+$: 392.1.



S42 29

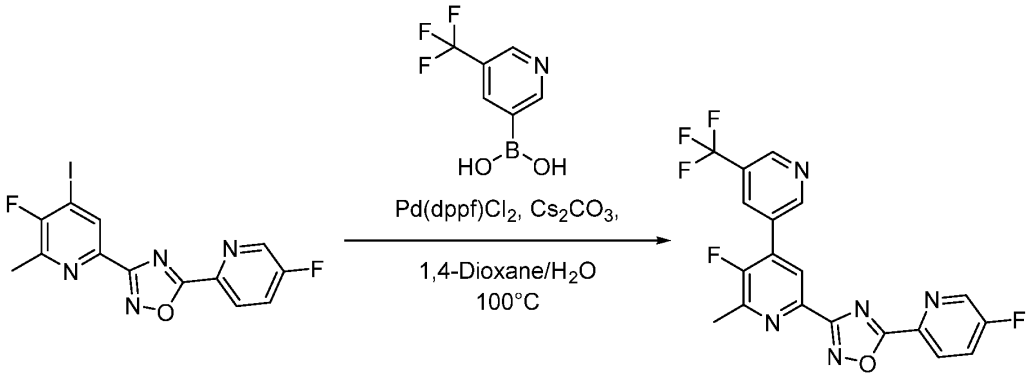
3-(5'-fluoro-6'-methyl-6-(trifluoromethyl)-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (29). Prepared in a similar manner to compound **34** to afford 3.5 mg of the title compound as a white solid (22% yield). ES-MS $[M+H]^+$: 420.1.



S42 32

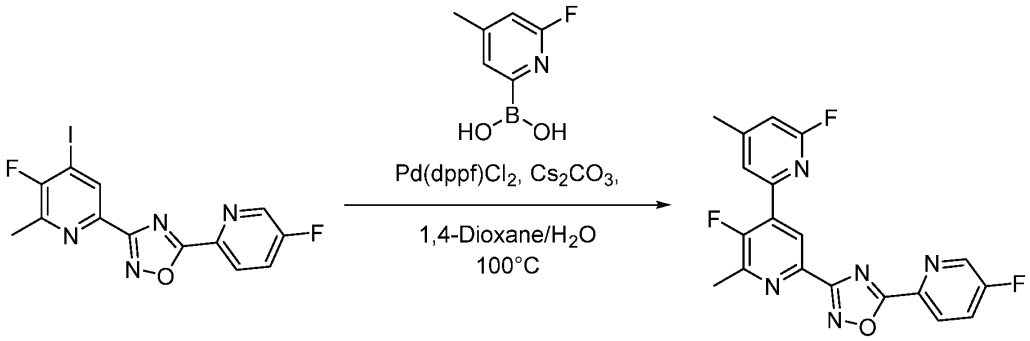
3-(2-Chloro-5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (32). Prepared in a similar manner to compound **34** to afford 4.1 mg of the title

compound as a white solid (27% yield). ES-MS $[M+H]^+$: 404.0.



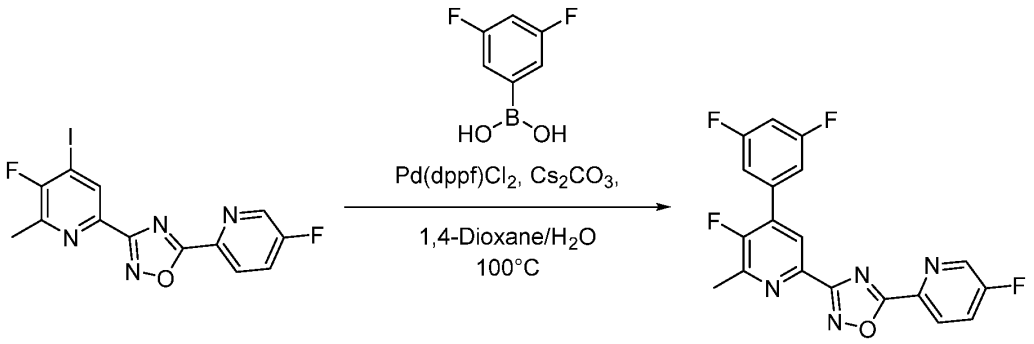
S42 33

3-(5'-fluoro-6'-methyl-5-(trifluoromethyl)-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (33). Prepared in a similar manner to compound **34** to afford 4.9 mg of the title compound as a white solid (31% yield). ES-MS $[M+H]^+$: 419.9.



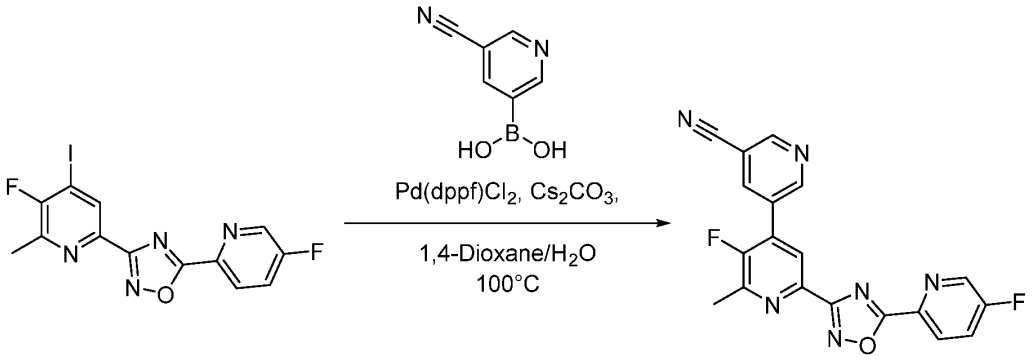
S42 66

3-(5',6-Difluoro-4,6'-dimethyl-[2,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (66). Prepared in a similar manner to compound **34** to afford 1 mg of the title compound as a white solid (7% yield). ES-MS $[M+H]^+$: 384.1.



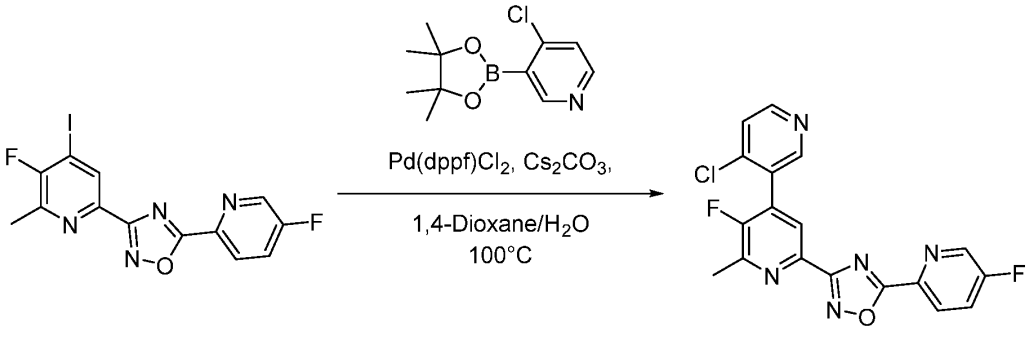
S42 67

3-(4-(3,5-Difluorophenyl)-5-fluoro-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (67). Prepared in a similar manner to compound **34** to afford 3.7 mg of the title compound as a white solid (25% yield). ES-MS $[M+H]^+$: 387.0.



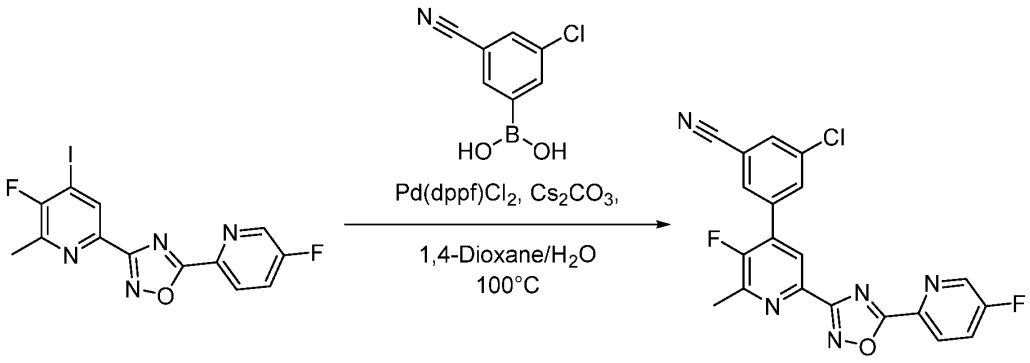
S42 68

3'-Fluoro-6'-(5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl)-2'-methyl-[3,4'-bipyridine]-5-carbonitrile (68). Prepared in a similar manner to compound **34** to afford 2.5 mg of the title compound as a white solid (17% yield). ES-MS $[M+H]^+$: 377.1.



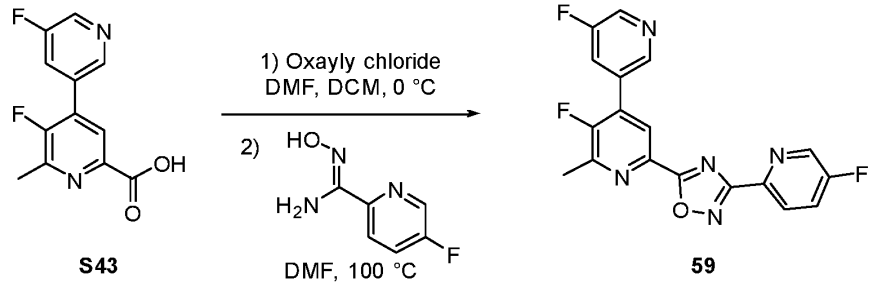
S42 69

3-(4-Chloro-5'-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (69). Prepared in a similar manner to compound **34** to afford 5.7 mg of the title compound as a white solid (39% yield). ES-MS $[M+H]^+$: 384.1.



S42 **70**

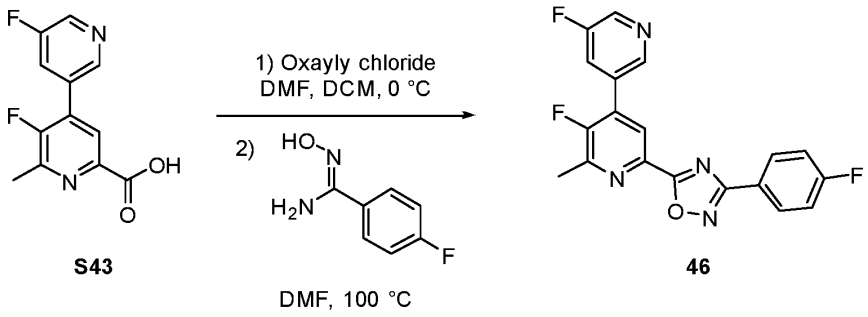
3-chloro-5-(3-fluoro-6-(5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylpyridin-4-yl)benzonitrile (70). Prepared in a similar manner to compound **34** to afford 9.3 mg of the title compound as a white solid (60% yield). ES-MS $[M+H]^+$: 410.1.



S43 **59**

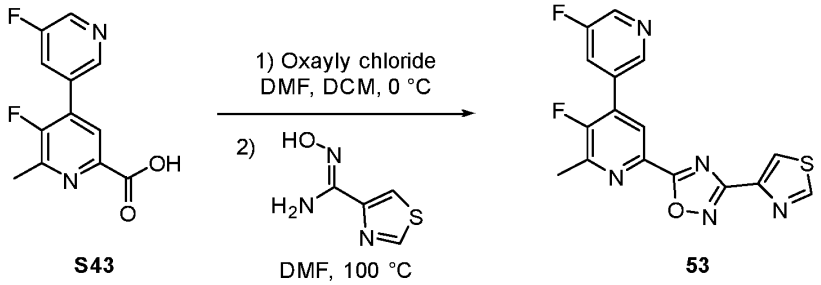
5-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (59). To a solution of intermediate **S43** (45 mg, 0.18 mmol, 1.0 eq) in DCM (0.5 mL) at 0 °C was added DMF (10 µL, 0.018mmol, 0.10 eq) and oxalyl chloride (31.0 µL, 0.36 mmol, 2.0 eq). After 30 minutes, the mixture was azeotroped with toluene and the organic solvents were concentrated *in vacuo*. The crude residue was then dissolved in DMF (1.0 mL) and 5-fluoro-*N*'-hydroxy-pyridine-2-carboxamidine (55.8 mg, 0.36 mmol, 2.0 eq) was added. The reaction stirred at ambient temperature for 1 hour then heated at 100 °C for 16 hours. The reaction was syringe filtered and purified by RP-HPLC (20-50% MeCN/0.1% aqueous TFA). Fractions containing product were basified with a saturated $NaHCO_3$ solution and extracted with DCM to afford 7.6 mg of the title compound as a white solid (11% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J*

= 1.6 Hz, 1H), 8.70 (d, *J* = 2.8 Hz, 1H), 8.63 (d, *J* = 2.7 Hz, 1H), 8.46 – 8.40 (m, 1H), 8.32 (ddd, *J* = 8.7, 4.4, 0.6 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.61 (ddd, *J* = 8.7, 7.8, 2.9 Hz, 1H), 2.79 – 2.77 (m, 3H); ES-MS $[M+1]^+$: 370.1.



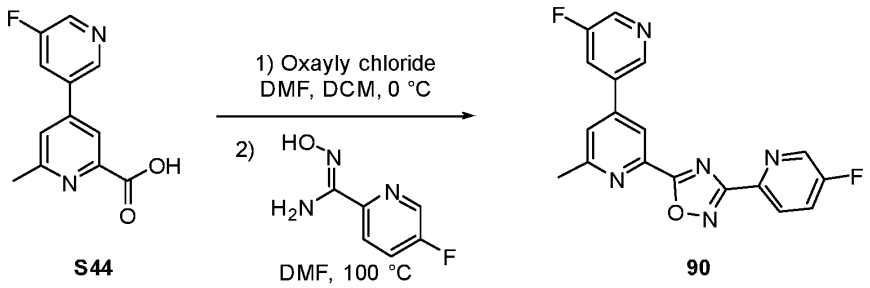
S43 46

5-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (46). Prepared in a similar manner to compound **59** to afford 2.0 mg of title compound (3% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (d, *J* = 1.6 Hz, 1H), 8.67 (d, *J* = 2.7 Hz, 1H), 8.47 (d, *J* = 5.3 Hz, 1H), 8.30 – 8.18 (m, 2H), 8.11 (d, *J* = 9.4 Hz, 1H), 7.33 (t, *J* = 8.8 Hz, 2H), 2.74 (d, *J* = 3.4 Hz, 3H); ES-MS $[M+1]^+$: 369.1.



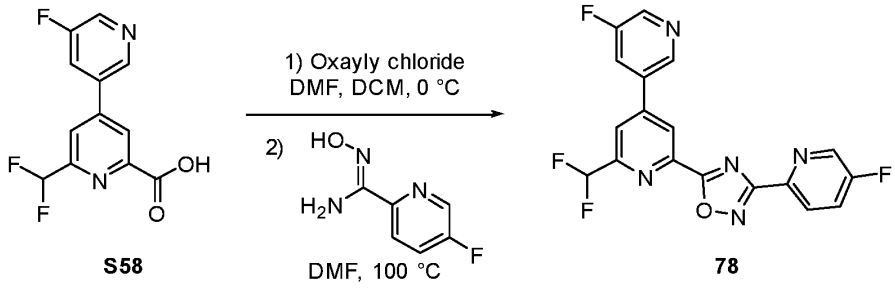
S43 53

5-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(thiazol-4-yl)-1,2,4-oxadiazole (53). Prepared in a similar manner to compound **59** to afford 4.2 mg of title compound (6% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 9.24 (d, *J* = 2.0 Hz, 1H), 8.83 (d, *J* = 1.6 Hz, 1H), 8.67 (d, *J* = 2.7 Hz, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 8.50 (d, *J* = 5.3 Hz, 1H), 8.11 (ddt, *J* = 9.4, 2.9, 1.4 Hz, 1H), 2.75 (d, *J* = 3.4 Hz, 3H); ES-MS $[M+1]^+$: 358.1.



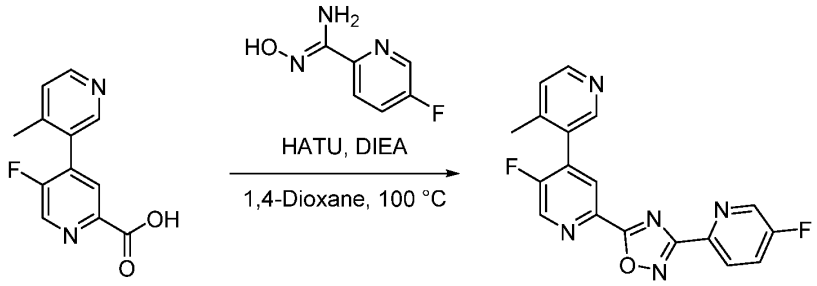
S44 90

5-(5-Fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (90). Prepared in a similar manner to compound **59** to afford 3.8 mg of title compound (6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (t, J = 1.7 Hz, 1H), 8.70 (d, J = 2.9 Hz, 1H), 8.61 (d, J = 2.7 Hz, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.34 (dd, J = 8.7, 4.4 Hz, 1H), 7.76 (ddd, J = 9.0, 2.7, 1.9 Hz, 1H), 7.66 – 7.56 (m, 2H), 2.82 (s, 3H); ES-MS $[M+1]^+$: 352.3.

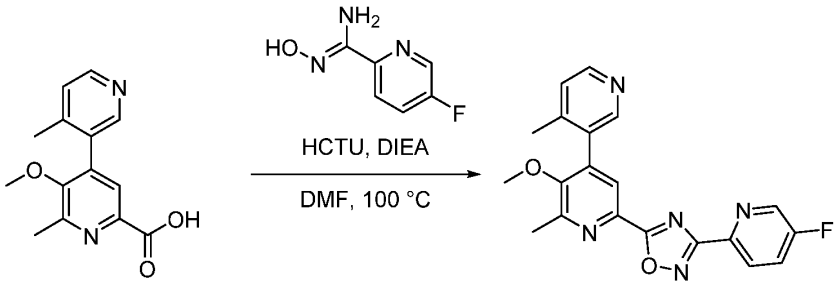


S58 78

5-(6'-(Difluoromethyl)-5-fluoro-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (78). Prepared in a similar manner to compound **59** to afford 2.7 mg of title compound (13% yield). ES-MS $[M+1]^+$: 388.1.

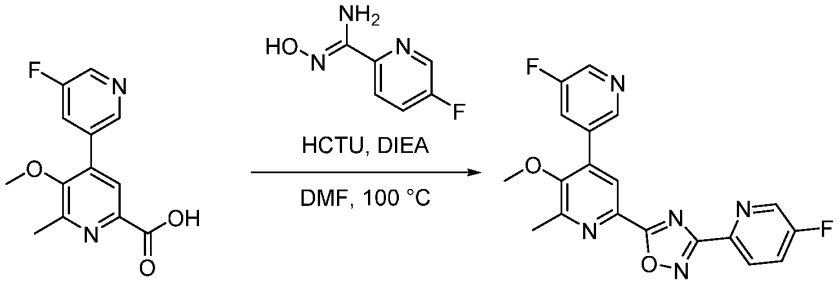


5-(5'-Fluoro-4-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (4). Intermediate **S45** (25.0 mg, 0.11 mmol, 1.0 eq) and 5-fluoro-*N*'-hydroxypicolinimidamide (16.7 mg, 0.11 mmol, 1.0 eq) were dissolved in 1,4-dioxane (1 mL) and HATU (49.1 mg, 0.13 mmol, 1.2 eq) was added. The reaction was stirred for 10 minutes and then *N,N*-diisopropylethylamine (50 µL, 0.27 mmol, 2.5 eq) was added and the reaction was heated to 100 °C for 18 hours. After cooling to ambient temperature, the reaction was concentrated *in vacuo* and the resulting residue dissolved in DMSO, syringe filtered, and purified using RP-HPLC (5-40% ACN/0.1% aqueous TFA). Repurification using RP-HPLC (25-55% ACN/0.05% aqueous NH_4OH) afforded 3.4 mg of the title compound as a white solid (9% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 – 8.79 (m, 1H), 8.68 (d, *J* = 2.8 Hz, 1H), 8.62 (d, *J* = 5.1 Hz, 1H), 8.51 (s, 1H), 8.43 (d, *J* = 5.7 Hz, 1H), 8.31 (ddd, *J* = 8.7, 4.4, 0.6 Hz, 1H), 7.61 (ddd, *J* = 8.7, 7.8, 2.9 Hz, 1H), 7.34 (s, 1H), 2.31 (dd, *J* = 1.5, 0.7 Hz, 3H); ES-MS $[M+1]^+$: 352.0.



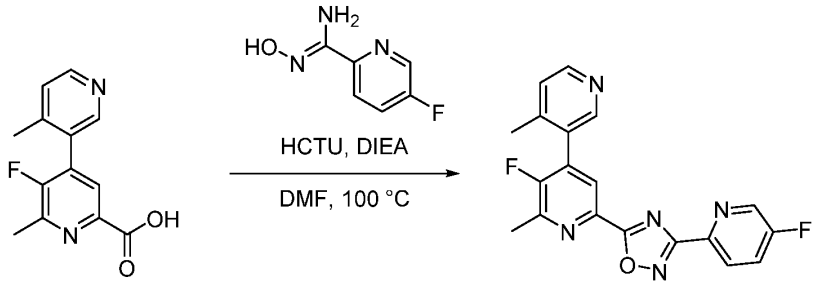
S46 13

3-(5-Fluoropyridin-2-yl)-5-(5'-methoxy-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole (13). Intermediate **S46** (21.3 mg, 0.082 mmol, 1.0 eq), 5-fluoro-*N*'-hydroxypicolinimidamide (12.8 mg, 0.082 mmol, 1.0 eq), HCTU (51.2 mg, 0.12 mmol, 1.5 eq) and *N,N*-diisopropylethylamine (29 µL, 0.16 mmol, 2.0 eq) were dissolved in DMF (1.7 mL) and heated to 100 °C for 4 hours. The reaction was syringe filtered and purification using RP-HPLC (30-60% ACN/0.05% aqueous NH_4OH) afforded 4.9 mg of the title compound as a white solid (16% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 2.8 Hz, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.54 (s, 1H), 8.30 (ddd, J = 8.7, 4.4, 0.6 Hz, 1H), 8.18 – 8.13 (m, 1H), 7.58 (ddd, J = 8.7, 7.8, 2.9 Hz, 1H), 7.39 (s, 1H), 3.48 (s, 3H), 2.74 (s, 3H), 2.30 (s, 3H); ES-MS $[M+1]^+$: 378.2.

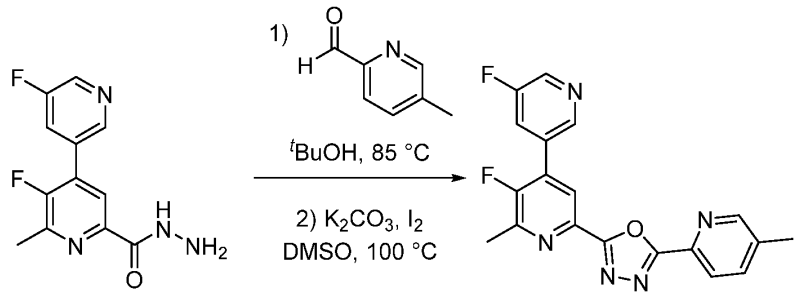


S47 14

5-(5-Fluoro-5'-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (14). Prepared in a similar manner to compound **13** to afford 2.4 mg of the title compound as a white solid (8% yield). ES-MS $[M+1]^+$: 382.1.

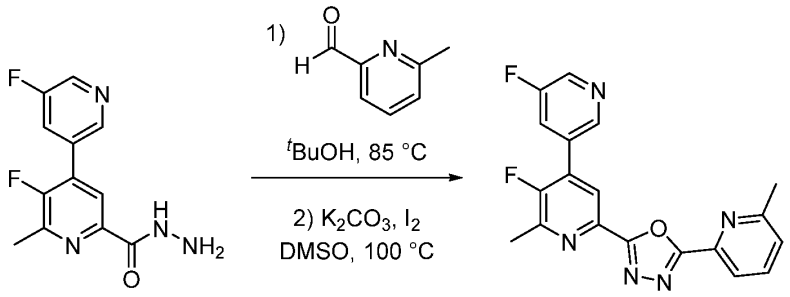


5-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole (8). Prepared in a similar manner to compound **13** to afford 2.4 mg of the title compound as a white solid (12% yield). ES-MS $[M+1]^+$: 366.4.



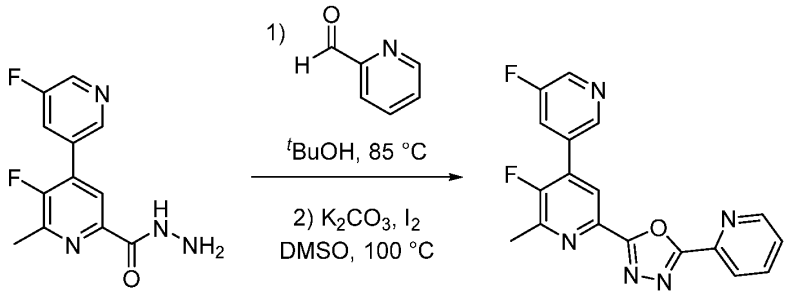
2-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-methylpyridin-2-yl)-1,3,4-oxadiazole (57). Intermediate **S50** (15 mg, 0.06 mmol, 1.0 eq) and 5-methylpicolinaldehyde (7.6 mg, 0.06 mmol, 1.1 eq) were dissolve in *t*BuOH (0.5 mL) and the reaction was heated to 85 °C for 3 hours. After cooling to ambient temperature, the reaction was concentrated *in vacuo*. The resulting residue was dissolved in DMSO (0.5 mL) and following the sequential addition of potassium carbonate (23.9 mg, 0.17 mmol, 3 eq) and iodine (17.3 mg, 0.07 mmol, 1.2 eq) the reaction was heated to 100 °C for 18 hours. After cooling to ambient temperature, saturated aqueous $Na_2S_2O_3$ was added. The reaction was extracted with EtOAc (3x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was dissolved in DMSO (1 mL), syringe filtered, and purified by RP-HPLC (20-55% MeCN/0.1% aqueous TFA). Fractions containing product were basified with a saturated $NaHCO_3$ solution and extracted with DCM to afford 5.8 mg of the title compound as an off-white solid (28% yield). 1H NMR (400 MHz, $CDCl_3$) δ 8.77 (q, J = 1.6 Hz, 1H), 8.66 (dt, J = 2.3, 0.8 Hz, 1H), 8.62 (d, J = 2.7 Hz, 1H), 8.28 (dd, J = 5.2, 0.6 Hz, 1H), 8.25

(d, J = 8.0 Hz, 1H), 7.74 (dddd, J = 14.3, 8.1, 2.6, 1.1 Hz, 2H), 2.75 (dd, J = 3.5, 0.5 Hz, 3H), 2.47 (s, 3H); ES-MS $[M+1]^+$: 366.1.



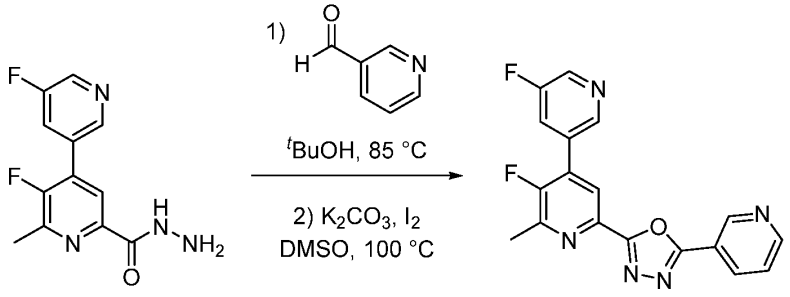
S50 58

2-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(6-methylpyridin-2-yl)-1,3,4-oxadiazole (58). Prepared in a similar manner to compound **57** to afford 1.5 mg of the title compound as a white solid (8% yield). ES-MS $[M+1]^+$: 366.1.



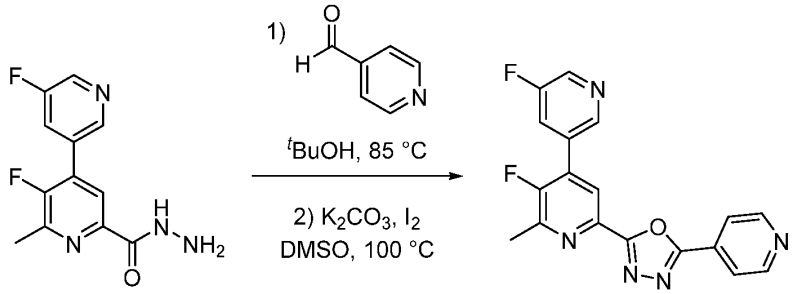
S50 79

2-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-2-yl)-1,3,4-oxadiazole (79). Prepared in a similar manner to compound **57** to afford 2.1 mg of the title compound as a white solid (13% yield). ES-MS $[M+1]^+$: 352.1.



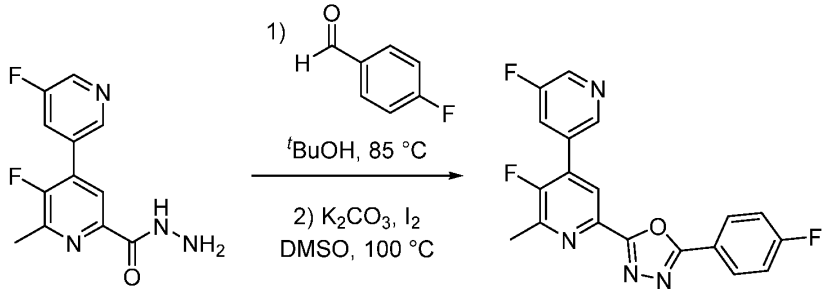
S50 80

2-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (80). Prepared in a similar manner to compound **57** to afford 4.6 mg of the title compound as a white solid (29% yield). ES-MS $[M+1]^+$: 352.1.



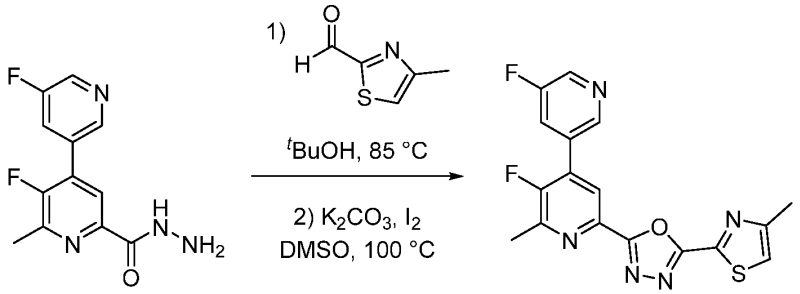
S50 **81**

2-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (81). Prepared in a similar manner to compound **57** to afford 3.3 mg of the title compound as a white solid (21% yield). ES-MS $[M+1]^+$: 352.1.



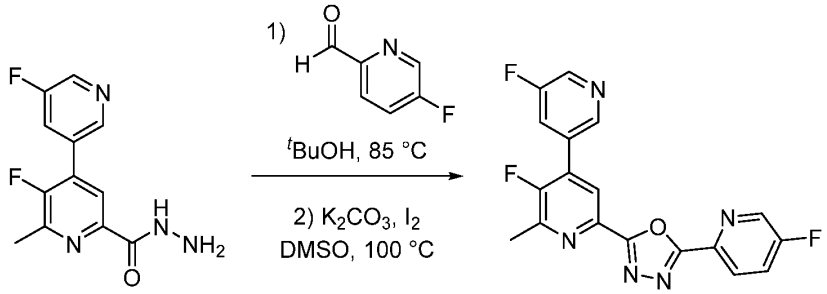
S50 **82**

2-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (82). Prepared in a similar manner to compound **57** to afford 3.4 mg of the title compound as a solid (20% yield). ES-MS $[M+1]^+$: 369.1.



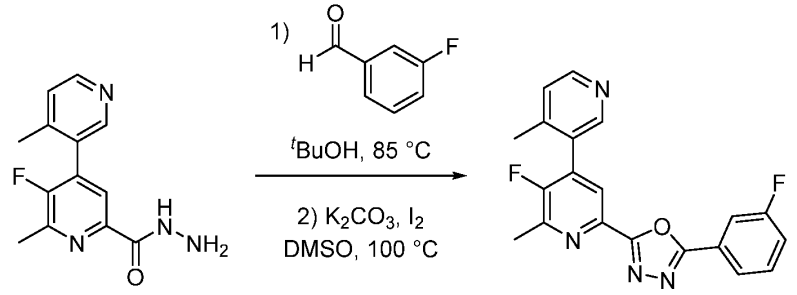
S50 **83**

2-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-methylthiazol-2-yl)-1,3,4-oxadiazole (83). Prepared in a similar manner to compound **57** to afford 5.7 mg of the title compound as a white solid (34% yield). ES-MS $[M+1]^+$: 372.1.



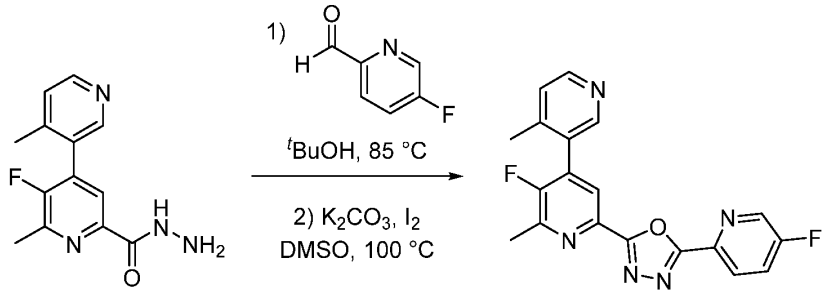
S50 **43**

2-(5,5'-Difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (43). Prepared in a similar manner to compound **57** to afford 8.1 mg of the title compound as a white solid (28% yield). ES-MS $[M+1]^+$: 370.0.



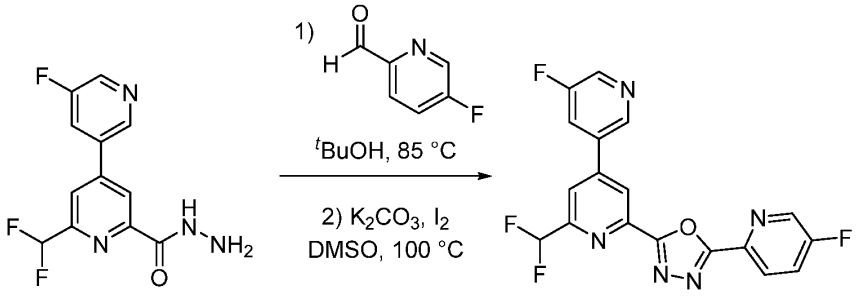
S52 **40**

2-(5'-Fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(3-fluorophenyl)-1,3,4-oxadiazole (40). Prepared in a similar manner to compound **57** to afford 5.5 mg of the title compound as a white solid (31% yield). ES-MS $[M+1]^+$: 365.1.



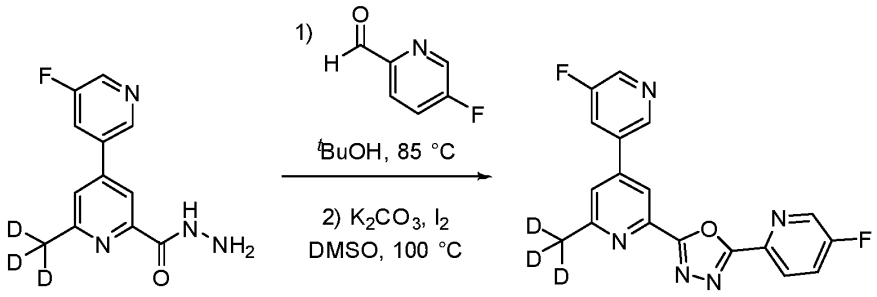
S52 **42**

2-(5'-Fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (42). Prepared in a similar manner to compound **57** to afford 8.5 mg of the title compound as a white solid (47% yield). ES-MS $[M+1]^+$: 366.0.



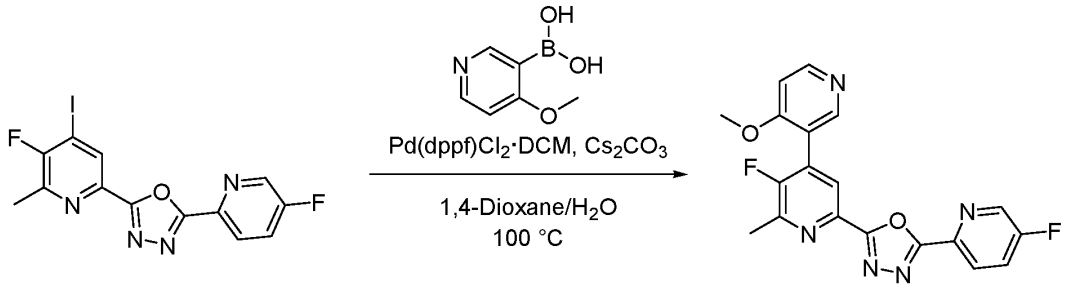
S60 84

2-(6'-(Difluoromethyl)-5-fluoro-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (84). Prepared in a similar manner to compound **57** to afford 4.5 mg of the title compound as an off-white solid (36% yield). ES-MS $[M+1]^+$: 388.0.

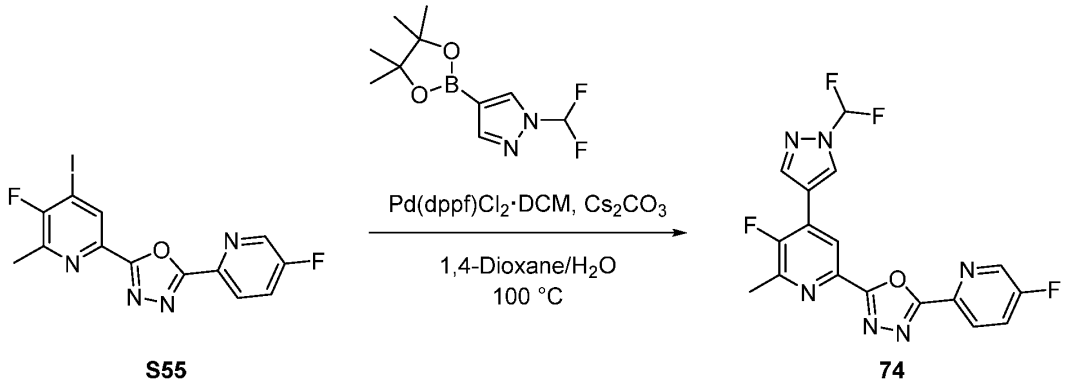


S62 85

2-(5-Fluoro-6'-(methyl-d_3)-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (85). Prepared in a similar manner to compound **57** to afford 8.3 mg of title compound as a white solid (10% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (t, J = 1.7 Hz, 1H), 8.69 (d, J = 2.8 Hz, 1H), 8.60 (d, J = 2.7 Hz, 1H), 8.41 (dd, J = 8.4, 4.0 Hz, 1H), 8.33 (d, J = 1.6 Hz, 1H), 7.75 (ddd, J = 9.0, 2.7, 1.9 Hz, 1H), 7.64 (ddd, J = 8.8, 7.8, 2.8 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H); ES-MS $[M+1]^+$ = 355.1.

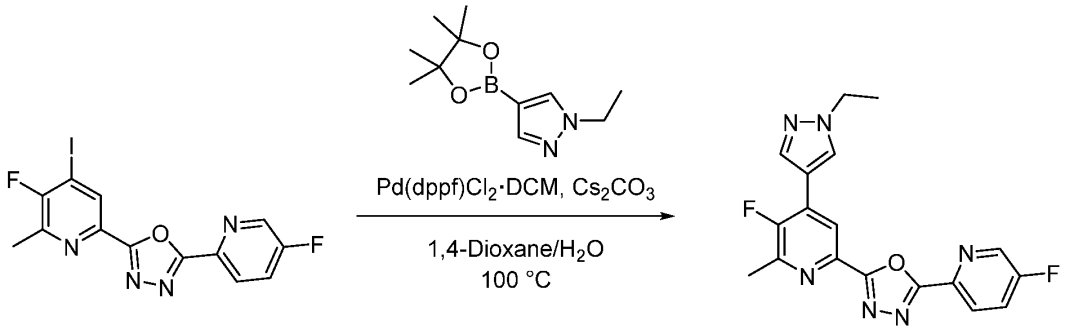


2-(5'-Fluoro-4-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (73). A mixture of intermediate **S55** (13 mg, 0.32 mmol, 1.0 eq), (4-methoxypyridin-3-yl)boronic acid (7.5 mg, 0.049 mmol, 1.5 eq), cesium carbonate (32 mg, 0.097 mmol, 3 eq), and Pd(dppf)Cl_2·DCM (4 mg, 0.0049 mmol, 0.15 eq) in 1,4-dioxane (1 mL) and water (0.2 mL) was placed under an inert atmosphere. After 1.5 hours at 100 °C, the solvents were concentrated and the crude was suspended in water and extracted with DCM (3x). The combined organic extracts were passed through a phase separator then concentrated. The crude residue was dissolved in DMSO (1 mL) and purified by RP-HPLC (5-45% MeCN/0.1% aqueous TFA). Fractions containing product were basified with saturated $NaHCO_3$ solution and extracted with DCM to yield 3.7 mg of title compound as an off-white solid (30% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (d, J = 2.8 Hz, 1H), 8.58 (d, J = 6.0 Hz, 1H), 8.47 (s, 1H), 8.42 (dd, J = 8.7, 4.4 Hz, 1H), 8.25 (d, J = 5.0 Hz, 1H), 7.90 (td, J = 8.6, 2.9 Hz, 1H), 7.30 (d, J = 6.0 Hz, 1H), 3.98 (s, 3H), 2.69 (d, J = 3.3 Hz, 3H); ES-MS $[M+H]^+$ = 382.1.



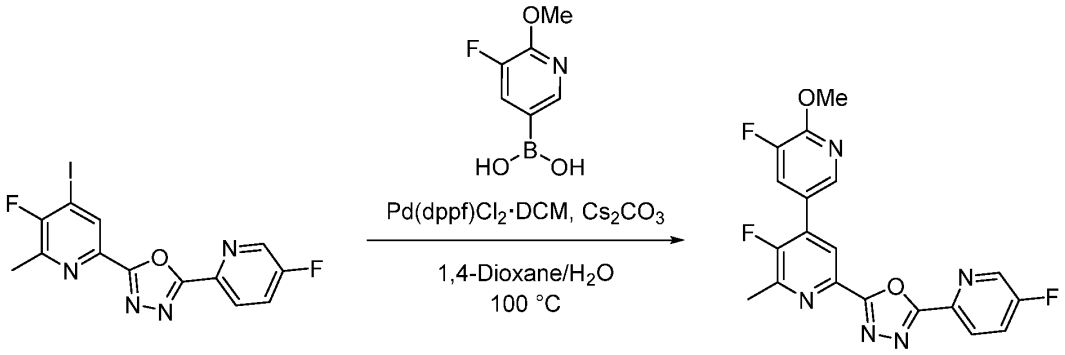
2-(4-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-5-fluoro-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (74). Prepared in a similar manner to compound **73** to

afford 5.1 mg of the title compound as an off-white solid (26% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.8 Hz, 1H), 8.43 (d, J = 1.6 Hz, 1H), 8.39 (dd, J = 8.5, 4.2, Hz, 1H), 8.36 (d, J = 5.1 Hz, 1H), 8.22 (s, 1H), 7.64 (td, J = 8.4, 3.0 Hz, 1H), 7.28 (t, J = 60.5 Hz, 1H), 2.71 (d, J = 3.5 Hz, 3H); ES-MS $[M+H]^+$ = 391.0.



S55 **75**

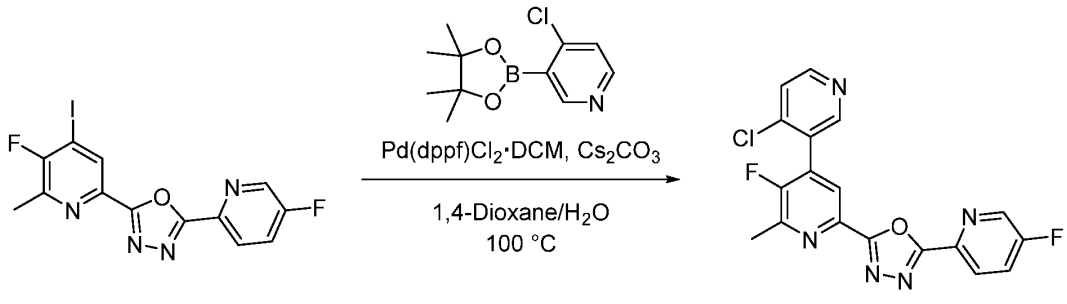
2-(4-(1-Ethyl-1*H*-pyrazol-4-yl)-5-fluoro-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (75). Prepared in a similar manner to compound **73** to afford 9.6 mg of the title compound as an off-white solid (52% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (d, J = 2.8 Hz, 1H), 8.41 – 8.37 (m, 2H), 8.34 – 8.32 (m, 1H), 8.12 – 8.10 (m, 1H), 7.88 (td, J = 8.8, 3.0 Hz, 1H), 4.28 (q, J = 7.3 Hz, 2H), 2.61 (d, J = 3.4 Hz, 3H), 1.53 (t, J = 7.3 Hz, 3H); ES-MS $[M+H]^+$ = 369.1.



S55 **76**

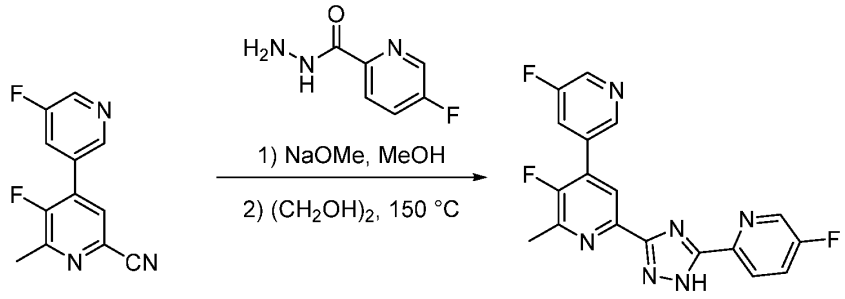
2-(5,5'-Difluoro-6-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (76). Prepared in a similar manner to compound **73** to afford 1.3 mg of the title compound as an off-white solid (7% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 2.8 Hz, 1H), 8.39 (dd, J = 8.7, 4.3 Hz, 1H), 8.32 –8.30 (m, 1H), 8.25 (d, J = 5.4 Hz, 1H), 7.73 – 7.68 (m,

1H), 7.64 (td, *J* = 8.2, 2.9 Hz, 1H), 4.12 (s, 3H), 2.73 (d, *J* = 3.7 Hz, 3H); ES-MS $[M+H]^+$ = 400.1.



S55 **77**

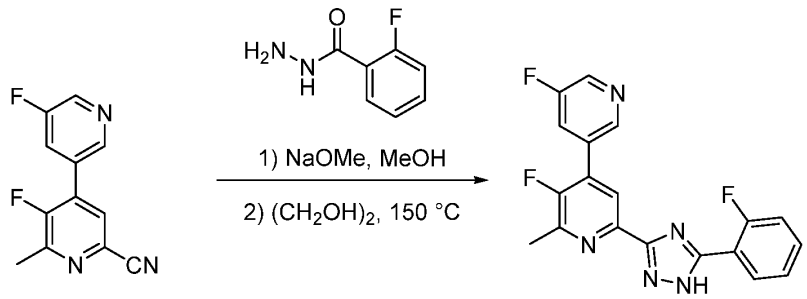
2-(4-Chloro-5'-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole (77). Prepared in a similar manner to compound **73** to afford 5.1 mg of the title compound as an off-white solid (26% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.8 Hz, 1H), 8.64 (d, *J* = 5.4 Hz, 1H), 8.61 (s, 1H), 8.39 (ddd, *J* = 8.7, 4.3, 1H), 8.17 (d, *J* = 4.8 Hz, 1H), 7.63 (td, *J* = 8.2, 2.9 Hz, 1H), 7.52 (d, *J* = 5.5, 1H), 2.75 (d, *J* = 3.2 Hz, 3H); ES-MS $[M+H]^+$ = 386.0.



S3 **96**

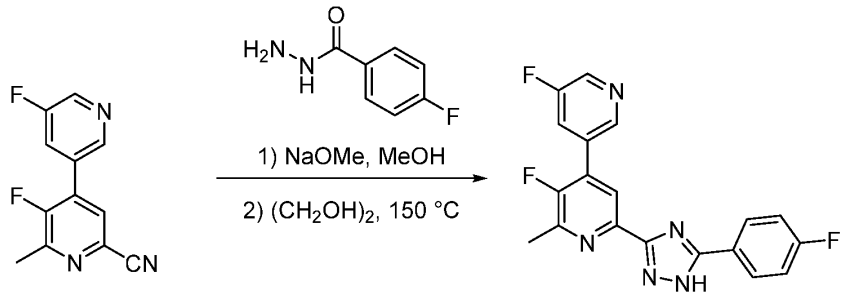
3',5-Difluoro-6'-(5-(5-fluoropyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-2'-methyl-3,4'-bipyridine (96). Intermediate **S3** (20 mg, 0.087 mmol, 1.0 eq) was dissolve in MeOH (0.87 mL) and sodium methoxide (0.5*M* in MeOH, 0.21 mL, 0.10 mmol, 1.2 eq) was added. The reaction stirred for 1 hour after which time 5-fluoropicolinohydrazide (16.1 mg, .010 mmol, 1.2 eq) was added and the reaction stirred an additional hour. The reaction was concentrated *in vacuo* and the resulting residue dissolved in ethylene glycol (0.87 mL) and heated to 150 °C for 2 hours. After cooling to ambient temperature, DMSO (1 mL) was added and the reaction mixture syringe filtered, and the crude residue was purified by RP-HPLC (25-55% MeCN/0.1% aqueous TFA). Fractions

containing product were basified with saturated $NaHCO_3$ solution and extracted with DCM to afford 1.3 mg of the title compound as a white solid (4% yield). ^1H NMR (400 MHz, CD_3OD) δ 8.81 (t, J = 1.6 Hz, 1H), 8.62 (dd, J = 10.0, 2.8 Hz, 2H), 8.31 (dd, J = 8.9, 4.7 Hz, 2H), 8.08 (ddt, J = 9.6, 2.9, 1.4 Hz, 1H), 7.79 (td, J = 8.6, 2.9 Hz, 1H), 2.70 (d, J = 3.3 Hz, 3H); ES-MS $[M+1]^+$: 369.1.



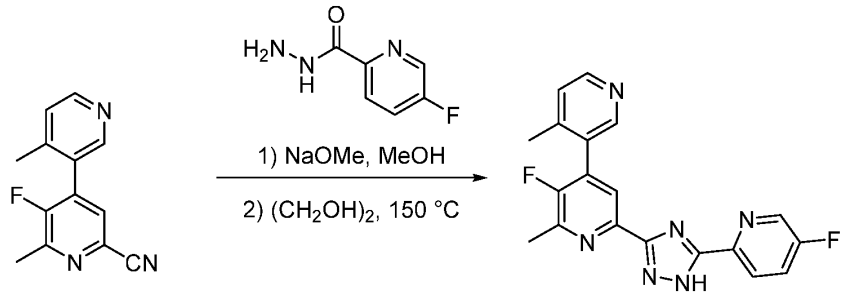
S3 **98**

3',5-Difluoro-6'-(5-(2-fluorophenyl)-1*H*-1,2,4-triazol-3-yl)-2'-methyl-3,4'-bipyridine (98). Prepared in a similar manner to compound **96** to afford 7.8 mg of title compound as a white solid (25% yield). ES-MS $[M+1]^+$: 368.1.



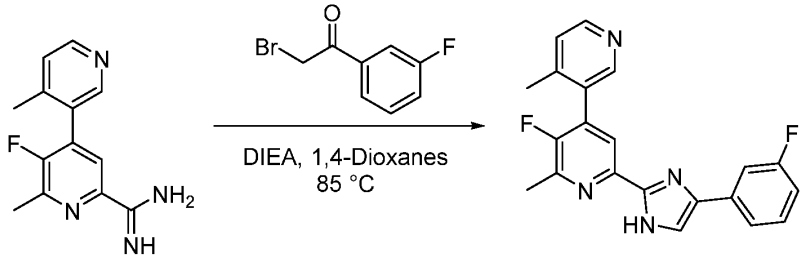
S3 **99**

3',5-Difluoro-6'-(5-(4-fluorophenyl)-1*H*-1,2,4-triazol-3-yl)-2'-methyl-3,4'-bipyridine (99). Prepared in a similar manner to compound **96** to afford 1 mg of title compound as a white solid (3% yield). ES-MS $[M+1]^+$: 368.1.



S26 97

3'-Fluoro-6'-(5-(5-fluoropyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-2',4-dimethyl-3,4'-bipyridine (97). Prepared in a similar manner to compound **96** to afford 5.1 mg of title compound as a white solid (16% yield). ES-MS $[M+1]^+$: 365.1.



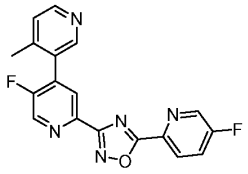
S56 63

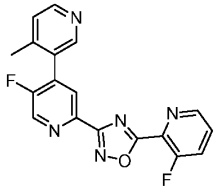
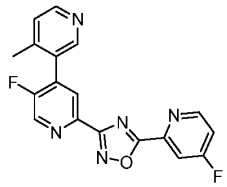
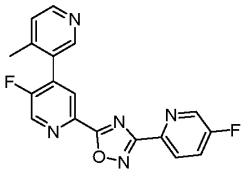
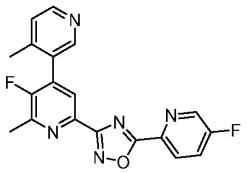
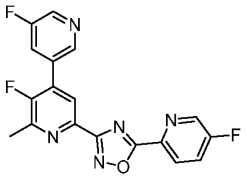
3'-Fluoro-6'-(4-(3-fluorophenyl)-1*H*-imidazol-2-yl)-2',4-dimethyl-3,4'-bipyridine (63). To a solution of intermediate **S56** (11 mg, 0.044 mmol, 1.0 eq) and DIEA (23 µL, 0.13 mmol, 3.0 eq) in 1,4-dioxane (0.50 0mL) was added 2-bromo-1-(3-fluorophenyl)ethan-1-one (14 mg, 0.066 mmol, 1.5 eq) and the mixture was heated to 85 °C for 5 hours. After cooling to room temperature, the solvents were concentrated and the resulting residue was dissolved in DMSO (1 mL). The crude residue was purified by RP-HPLC (5-55% MeCN/0.1% aqueous TFA). Fractions containing product were basified with saturated $NaHCO_3$ solution and extracted with 3:1 chloroform/IPA. The combined organics were passed through a phase separator and concentrated. Repurification by flash chromatography on silica gel using 20-40% EtOAc/DCM afforded 1.4 mg of title compound as a tan solid (9% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (d, *J* = 5.1 Hz, 1H), 8.48 (s, 1H), 8.00 (s, 1H), 7.70 – 7.61 (m, 2H), 7.62 – 7.54 (m, 1H), 7.53 – 7.47 (m, 1H), 7.42 (s, 1H), 7.00 (s, 1H), 2.68 (d, *J* = 3.2 Hz, 3H), 2.36 (s, 3H); ES-MS $[M+1]^+$: 363.2.

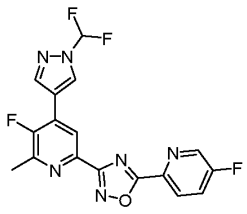
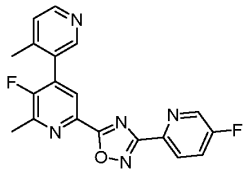
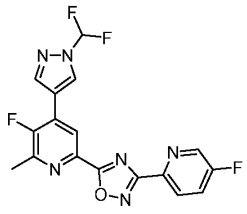
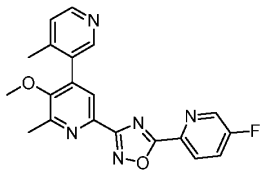
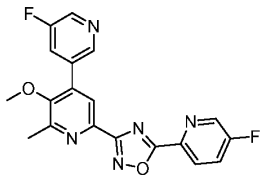
1. CHARACTERIZATION OF EXEMPLARY COMPOUNDS

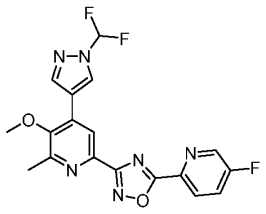
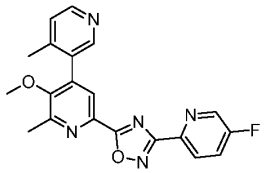
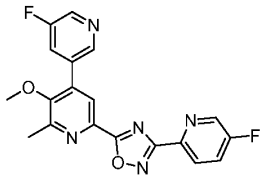
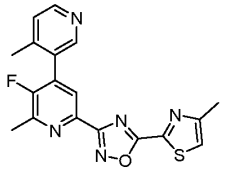
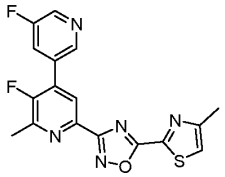
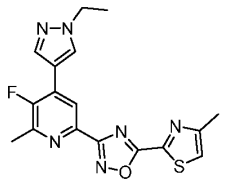
[00259] Tables 1 and 2 below lists specific compounds, experimentally determined molecular mass, and mGlu5 activity determined in a cell-based assay. The mGlu5 activity was determined using the metabotropic glutamate receptor activity assays in human embryonic kidney cells as described herein, wherein the human embryonic kidney cells were transfected with rat mGlu5. The mGlu5 activity data for some compounds are shown as the average of at least three experiments with the standard error in these cases. If no error is indicated for the mGlu5 activity, the values given represent the results from a single experiment or the average of two experiments. The compounds in Table 1 were synthesized with methods identical or analogous to those shown herein. The requisite starting materials were commercially available, described in the literature, or readily synthesized by one skilled in the art of organic synthesis.

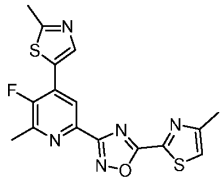
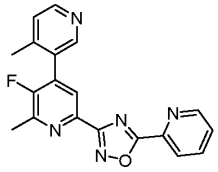
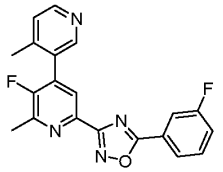
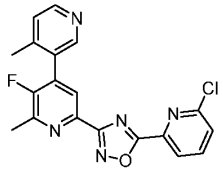
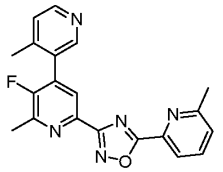
Table 1.

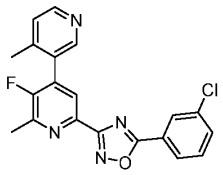
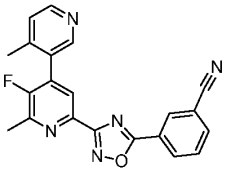
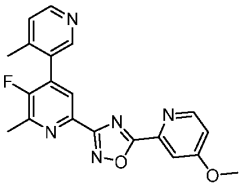
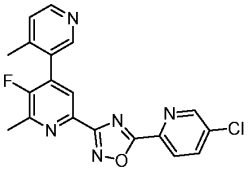
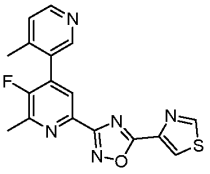
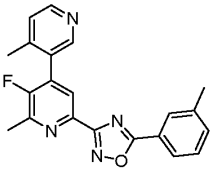
Compound	Structure	Chemical Name	ES-MS LCMS
1		3-(5'-fluoro-4-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	352.2

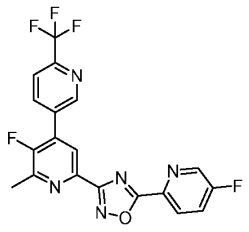
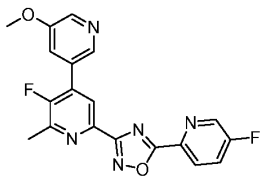
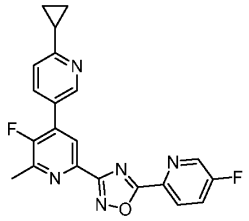
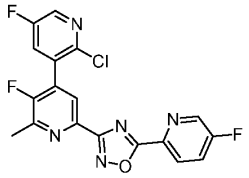
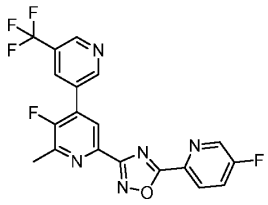
2		3-(5'-fluoro-4-methyl-[3,4'-bipyridin]-2'-yl)-5-(3-fluoropyridin-2-yl)-1,2,4-oxadiazole	352.3
3		3-(5'-fluoro-4-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-fluoropyridin-2-yl)-1,2,4-oxadiazole	352.3
4		5-(5'-fluoro-4-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	352.0
5		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	366.1
6		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	370.0

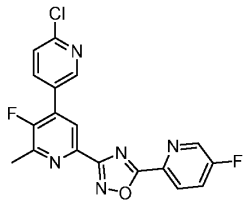
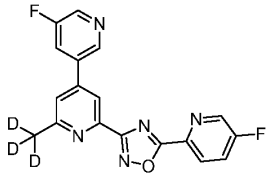
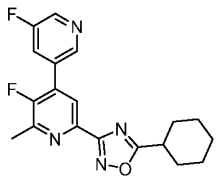
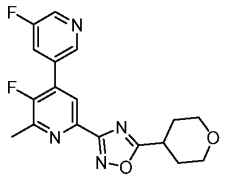
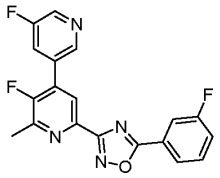
7		3-(4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-fluoro-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	391.0
8		5-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	366.4
9		5-(4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-fluoro-6-methylpyridin-2-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	391.0
10		5-(5-fluoropyridin-2-yl)-3-(5'-methoxy-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	378.1
11		3-(5-fluoro-5'-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	382.1

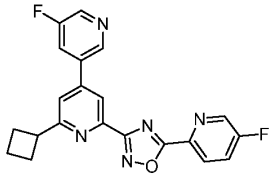
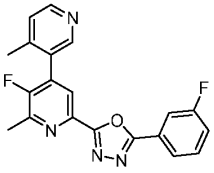
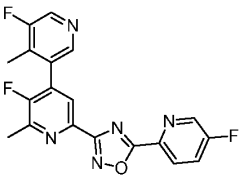
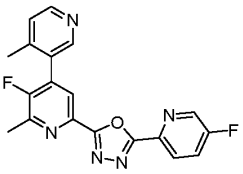
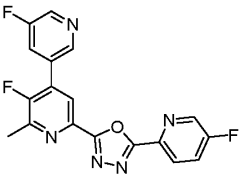
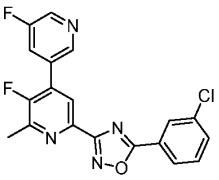
12		3-(4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-methoxy-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	403.1
13		3-(5-fluoropyridin-2-yl)-5-(5'-methoxy-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	378.2
14		5-(5-fluoro-5'-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	382.1
15		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(4-methylthiazol-2-yl)-1,2,4-oxadiazole	368.1
16		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-methylthiazol-2-yl)-1,2,4-oxadiazole	372.1
17		3-(4-(1-ethyl-1*H*-pyrazol-4-yl)-5-fluoro-6-methylpyridin-2-yl)-5-(4-methylthiazol-2-yl)-1,2,4-oxadiazole	371.1

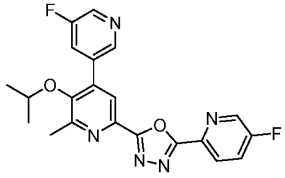
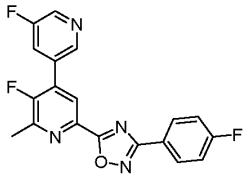
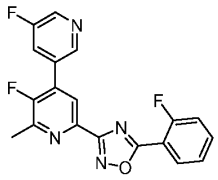
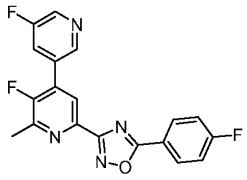
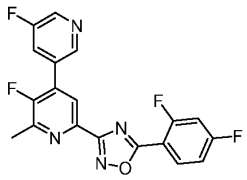
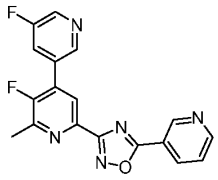
18		3-(5-fluoro-6-methyl-4-(2-methylthiazol-5-yl)pyridin-2-yl)-5-(4-methylthiazol-2-yl)-1,2,4-oxadiazole	374.0
19		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-2-yl)-1,2,4-oxadiazole	348.1
20		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(3-fluorophenyl)-1,2,4-oxadiazole	365.1
21		5-(6-chloropyridin-2-yl)-3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	382.1
22		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(6-methylpyridin-2-yl)-1,2,4-oxadiazole	362.1

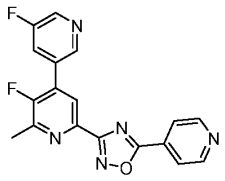
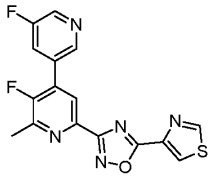
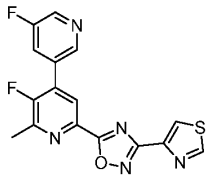
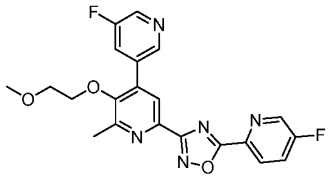
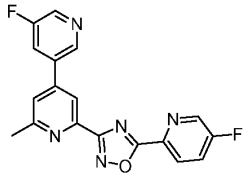
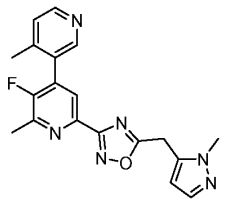
23		5-(3-chlorophenyl)-3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	381.1
24		3-(3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazol-5-yl)benzonitrile	372.1
25		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(4-methoxypyridin-2-yl)-1,2,4-oxadiazole	378.1
26		5-(5-chloropyridin-2-yl)-3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	382.1
27		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(thiazol-4-yl)-1,2,4-oxadiazole	354.1
28		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(*m*-tolyl)-1,2,4-oxadiazole	361.1

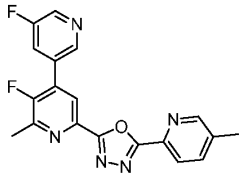
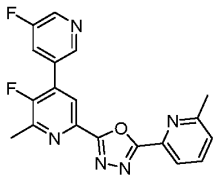
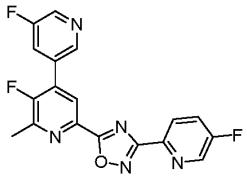
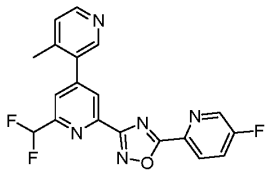
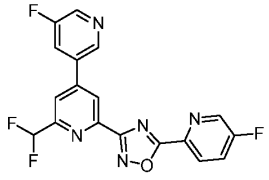
29		3-(5'-fluoro-6'-methyl-6-(trifluoromethyl)-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	420.1
30		3-(5'-fluoro-5-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	382.1
31		3-(6-cyclopropyl-5'-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	392.1
32		3-(2-chloro-5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	404.0
33		3-(5'-fluoro-6'-methyl-5-(trifluoromethyl)-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	419.9

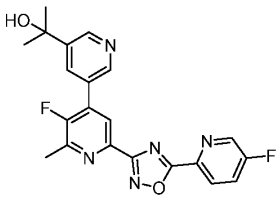
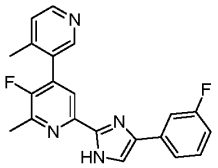
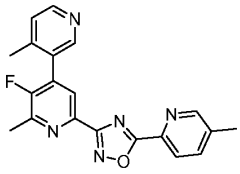
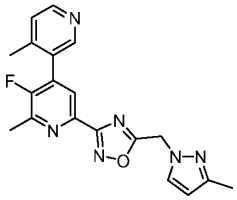
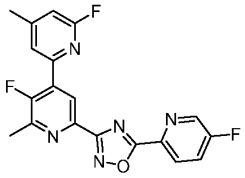
34		3-(6-chloro-5'-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	386.1
35		3-(5-fluoro-6'-(methyl-d_3)-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	355.2
36		5-cyclohexyl-3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	357.2
37		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(tetrahydro-2*H*-pyran-4-yl)-1,2,4-oxadiazole	359.1
38		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(3-fluorophenyl)-1,2,4-oxadiazole	369.7

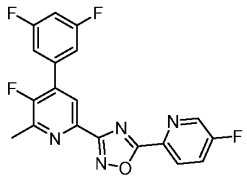
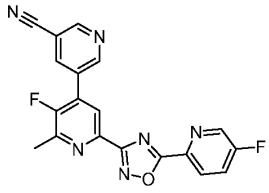
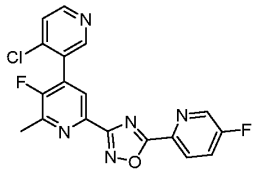
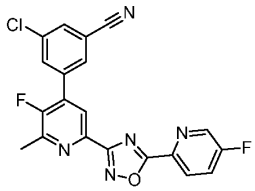
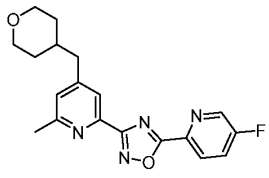
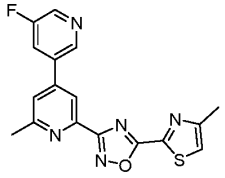
39		3-(6'-cyclobutyl-5-fluoro-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	392.1
40		2-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(3-fluorophenyl)-1,3,4-oxadiazole	365.1
41		3-(5,5'-difluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	384.1
42		2-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	366.0
43		2-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	370.0
44		5-(3-chlorophenyl)-3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	385.1

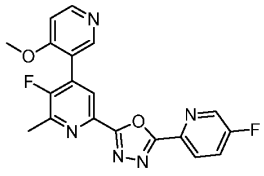
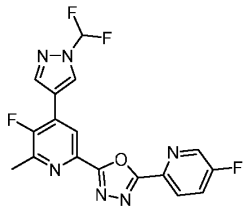
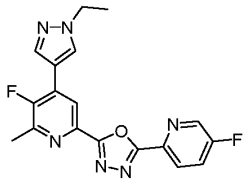
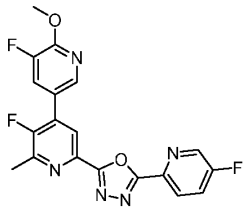
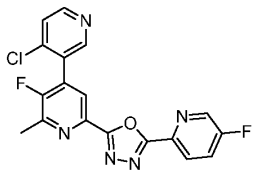
45		2-(5-fluoro-5'-isopropoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	410.0
46		5-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(4-fluorophenyl)-1,2,4-oxadiazole	369.1
47		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(2-fluorophenyl)-1,2,4-oxadiazole	369.2
48		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-fluorophenyl)-1,2,4-oxadiazole	369.1
49		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(2,4-difluorophenyl)-1,2,4-oxadiazole	387.1
50		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-3-yl)-1,2,4-oxadiazole	352.1

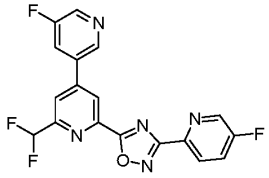
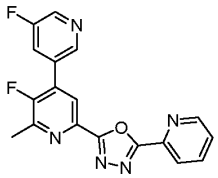
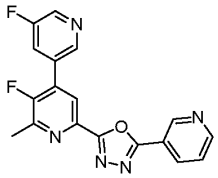
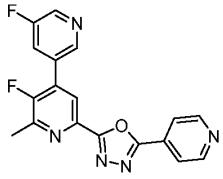
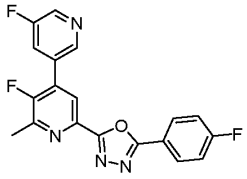
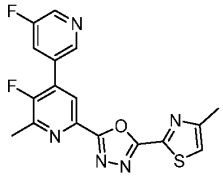
51		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-4-yl)-1,2,4-oxadiazole	352.1
52		3-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(thiazol-4-yl)-1,2,4-oxadiazole	358.1
53		5-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(thiazol-4-yl)-1,2,4-oxadiazole	358.1
54		3-(5-fluoro-5'-(2-methoxyethoxy)-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	426.2
55		3-(5-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	352.0
56		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-((1-methyl-1*H*-pyrazol-5-yl)methyl)-1,2,4-oxadiazole	365.2

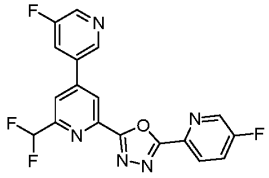
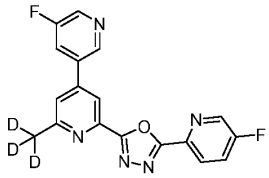
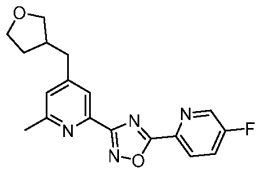
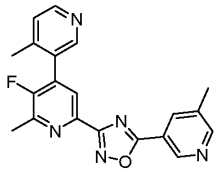
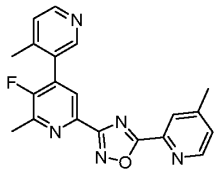
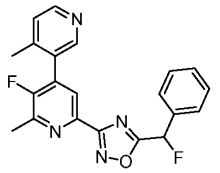
57		2-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-methylpyridin-2-yl)-1,3,4-oxadiazole	366.1
58		2-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(6-methylpyridin-2-yl)-1,3,4-oxadiazole	366.1
59		5-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	370.1
60		3-(6'-(difluoromethyl)-4-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	384.1
61		3-(6'-(difluoromethyl)-5-fluoro-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	388.1

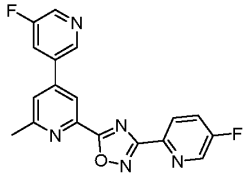
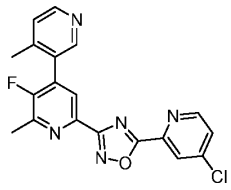
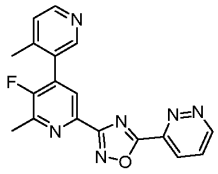
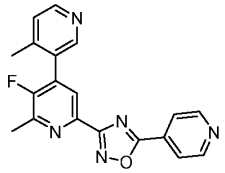
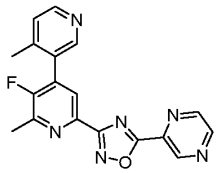
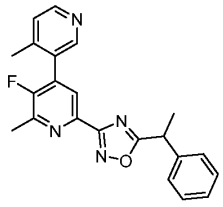
62		2-(3'-fluoro-6'-(5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl)-2'-methyl-[3,4'-bipyridin]-5-yl)propan-2-ol	410.1
63		3'-fluoro-6'-(4-(3-fluorophenyl)-1*H*-imidazol-2-yl)-2',4-dimethyl-3,4'-bipyridine	363.2
64		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(5-methylpyridin-2-yl)-1,2,4-oxadiazole	362.1
65		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-((3-methyl-1*H*-pyrazol-1-yl)methyl)-1,2,4-oxadiazole	365.1
66		3-(5',6-difluoro-4,6'-dimethyl-[2,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	384.1

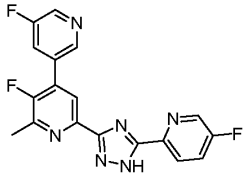
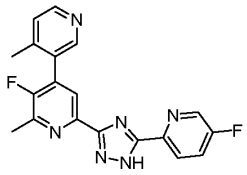
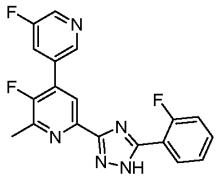
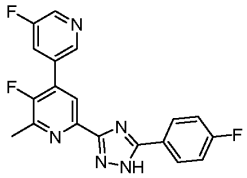
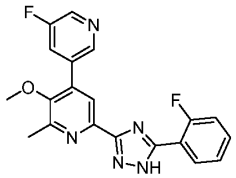
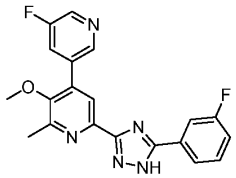
67		3-(4-(3,5-difluorophenyl)-5-fluoro-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	387.0
68		3'-fluoro-6'-(5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl)-2'-methyl-[3,4'-bipyridine]-5-carbonitrile	377.1
69		3-(4-chloro-5'-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	386.0
70		3-chloro-5-(3-fluoro-6-(5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylpyridin-4-yl)benzonitrile	410.0
71		5-(5-fluoropyridin-2-yl)-3-(6-methyl-4-((tetrahydro-2*H*-pyran-4-yl)methyl)pyridin-2-yl)-1,2,4-oxadiazole	355.1
72		3-(5-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-methylthiazol-2-yl)-1,2,4-oxadiazole	354.1

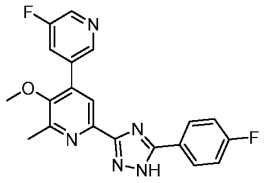
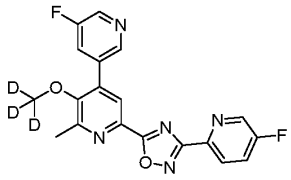
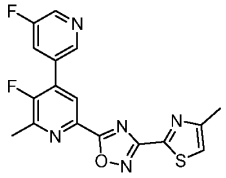
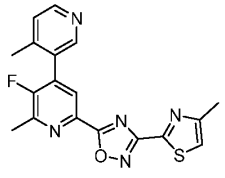
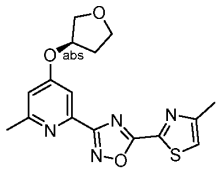
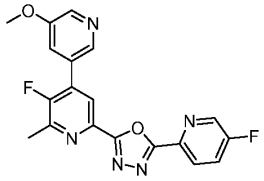
73		2-(5'-fluoro-4-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	382.1
74		2-(4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-5-fluoro-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	391.1
75		2-(4-(1-ethyl-1*H*-pyrazol-4-yl)-5-fluoro-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	369.1
76		2-(5,5'-difluoro-6-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	400.1
77		2-(4-chloro-5'-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	386.0

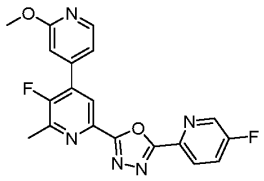
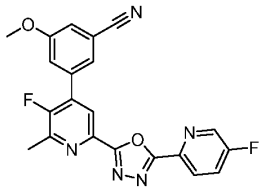
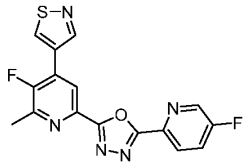
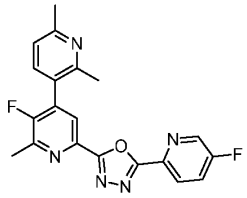
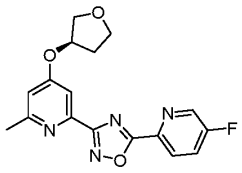
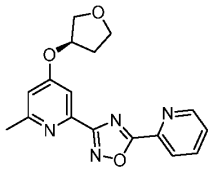
78		5-(6'-(difluoromethyl)-5-fluoro-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	388.1
79		2-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-2-yl)-1,3,4-oxadiazole	352.1
80		2-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole	352.1
81		2-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole	352.1
82		2-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-fluorophenyl)-1,3,4-oxadiazole	369.1
83		2-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(4-methylthiazol-2-yl)-1,3,4-oxadiazole	372.1

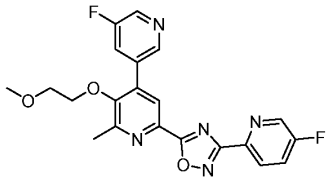
84		2-(6'-(difluoromethyl)-5-fluoro-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	388.0
85		2-(5-fluoro-6'-(methyl-d_3)-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	355.1
86		5-(5-fluoropyridin-2-yl)-3-(6-methyl-4-((tetrahydrofuran-3-yl)methyl)pyridin-2-yl)-1,2,4-oxadiazole	341.2
87		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(5-methylpyridin-3-yl)-1,2,4-oxadiazole	362.1
88		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(4-methylpyridin-2-yl)-1,2,4-oxadiazole	362.1
89		5-(fluoro(phenyl)methyl)-3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	379.2

90		5-(5-fluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	352.1
91		5-(4-chloropyridin-2-yl)-3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-1,2,4-oxadiazole	382.1
92		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(pyridazin-3-yl)-1,2,4-oxadiazole	349.1
93		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(pyridin-4-yl)-1,2,4-oxadiazole	348.1
94		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(pyrazin-2-yl)-1,2,4-oxadiazole	349.1
95		3-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-5-(1-phenylethyl)-1,2,4-oxadiazole	375.1

96		3',5-difluoro-6'-(5-(5-fluoropyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-2'-methyl-3,4'-bipyridine	369.1
97		3'-fluoro-6'-(5-(5-fluoropyridin-2-yl)-1*H*-1,2,4-triazol-3-yl)-2',4-dimethyl-3,4'-bipyridine	365.1
98		3',5-difluoro-6'-(5-(2-fluorophenyl)-1*H*-1,2,4-triazol-3-yl)-2'-methyl-3,4'-bipyridine	368.1
99		3',5-difluoro-6'-(5-(4-fluorophenyl)-1*H*-1,2,4-triazol-3-yl)-2'-methyl-3,4'-bipyridine	368.1
100		5-fluoro-6'-(5-(2-fluorophenyl)-1*H*-1,2,4-triazol-3-yl)-3'-methoxy-2'-methyl-3,4'-bipyridine	380.2
101		5-fluoro-6'-(5-(3-fluorophenyl)-1*H*-1,2,4-triazol-3-yl)-3'-methoxy-2'-methyl-3,4'-bipyridine	380.1

102		5-fluoro-6'-(5-(4-fluorophenyl)-1*H*-1,2,4-triazol-3-yl)-3'-methoxy-2'-methyl-3,4'-bipyridine	380.1
103		5-(5-fluoro-5'-(methoxy-d_3)-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	385.2
104		5-(5,5'-difluoro-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(4-methylthiazol-2-yl)-1,2,4-oxadiazole	372.1
105		5-(5'-fluoro-4,6'-dimethyl-[3,4'-bipyridin]-2'-yl)-3-(4-methylthiazol-2-yl)-1,2,4-oxadiazole	368.1
106		(R)-3-(6-methyl-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)-5-(4-methylthiazol-2-yl)-1,2,4-oxadiazole	345.0
107		2-(5'-fluoro-5-methoxy-6'-methyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	382.2

108		2-(5-fluoro-2'-methoxy-6-methyl-[4,4'-bipyridin]-2-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	382.1
109		3-(3-fluoro-6-(5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazol-2-yl)-2-methylpyridin-4-yl)-5-methoxybenzonitrile	406.1
110		2-(5-fluoro-4-(isothiazol-4-yl)-6-methylpyridin-2-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	358.1
111		2-(5'-fluoro-2,6,6'-trimethyl-[3,4'-bipyridin]-2'-yl)-5-(5-fluoropyridin-2-yl)-1,3,4-oxadiazole	380.2
112		(R)-5-(5-fluoropyridin-2-yl)-3-(6-methyl-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)-1,2,4-oxadiazole	343.1
113		(R)-3-(6-methyl-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)-5-(pyridin-2-yl)-1,2,4-oxadiazole	325.1

114		5-(5-fluoro-5'-(2-methoxyethoxy)-6'-methyl-[3,4'-bipyridin]-2'-yl)-3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazole	426.3

[0001] **Table 2.**

Compound	hmGlu5 NAM	
	IC_{50} (nM)	E_{min} (%)*
1	192	3
2	2630	25
3	744	2
4	166	1
5	98	3
6	59	2
7	159	2
8	124	2
9	328	2
10	641	2
11	452	2
12	1110	2
13	482	2
14	339	2
15	97	2
16	613	9
17	>10,000	25
18	1130	13
19	233	2
20	49	2
21	493	4
22	1090	3
23	117	2
24	85	2
25	3380	12
26	575	2

Compound	hmGlu5 NAM	
	IC_{50} (nM)	E_{min} (%)*
27	308	2
28	69	2
29	1720	37
30	493	3
31	3090	20
32	359	3
33	1020	9
34	577	8
35	207	2
36	>10,000	51
37	>10,000	54
38	2410	14
39	1910	58
40	705	2
41	304	2
42	375	2
43	179	2
44	5800	34
45	946	2
46	677	3
47	5500	34
48	81	3
49	624	3
50	1560	34
51	1070	12
52	>10,000	18

Compound	hmGlu5 NAM	
	IC_{50} (nM)	Emin (%)*
53	481	23
54	562	3
55	190	2
56	>10,000	50
57	1080	4
58	>10,000	31
59	51	4
60	187	4
61	125	6
62	1290	5
63	1090	4
64	>10,000	39
65	>10,000	36
66	1890	9
67	161	3
68	757	3
69	109	3
70	206	3
71	>10,000	45
72	917	11
73	298	2
74	148	2
75	591	2
76	5750	9
77	138	3
78	149	2

Compound	hmGlu5 NAM	
	IC_{50} (nM)	Emin (%)*
79	673	2
80	3340	58
81	>10,000	55
82	778	2
83	600	2
84	359	1
85	450	1
86	766	1
87	4290	13
88	245	3
89	3600	3
90	123	2
91	155	2
92	>10,000	74
93	221	2
94	>10,000	37
95	>10,000	27
96	64	2
97	183	2
98	82	1
99	47	2
100	300	2
101	114	11
102	663	2
103	624	5
104	122	1

Compound	hmGlu5 NAM	
	IC_{50} (nM)	E_{min} (%)*
105	>10,000	13
106	387	2
107	336	2
108	94	1
109	66	2
110	185	2
111	1530	2
112	>10,000	21
113	46	2

*%Glu max at 30 μM

2. METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY ASSAY

[00260] The utility of the compounds in accordance with the present invention as negative allosteric modulators of metabotropic glutamate receptor activity, in particular mGlu5 activity, can be demonstrated by methodology known in the art. HEK 293A cells stably expressing either rat or human mGlu5 were plated in black-walled, clear-bottomed, poly-D-lysine coated 384-well plates in 20 μL of assay medium (DMEM containing 10% dialyzed FBS, 20 mM HEPES, 100 units/mL penicillin/streptomycin plus 250 ng/mL Fungizone, and 1 mM sodium pyruvate) at a density of 20K cells/well. The cells were grown overnight at 37 °C in the presence of 5% CO_2. The next day, medium was removed and the cells incubated with 20 μL of 2.3 μM Fluo-4, AM prepared as a 2.3 mM stock in DMSO and mixed in a 1:1 ratio with 10% (w/v) pluronic acid F-127 and diluted in assay buffer (Hank's balanced salt solution, 20 mM HEPES, and 2.5 mM probenecid) for 45 minutes at 37 °C. Dye was removed, 20 μL of assay buffer was added, and the plate was incubated for 5 minutes at room temperature.

[00261] Ca^{2+} flux was measured using the Functional Drug Screening System (FDSS7000, Hamamatsu, Japan). After establishment of a fluorescence baseline for about 3 seconds, the compounds of the present invention were added to the cells, and the response in cells was

measured. 2.3 minutes later an EC_{20} concentration of the mGlu5 receptor agonist glutamate was added to the cells, and the response of the cells was measured for 1.9 minutes; an EC_{80} concentration of agonist was added and readings taken for an additional 1.7 minutes. All test compounds were dissolved and diluted to a concentration of 10 mM in 100% DMSO. Compounds were then serially diluted 1:3 in DMSO into 10 point concentration response curves, transferred to daughter plates, and further diluted into assay buffer to a 2x stock. Calcium fluorescence measures were recorded as fold over basal fluorescence; raw data was then normalized to the maximal response to glutamate. Antagonism of the agonist response of the mGlu5 receptor in the present invention was observed as a decrease in response to nearly maximal concentrations of glutamate in the presence of compound compared to the response to glutamate in the absence of compound.

[00262] The raw data file containing all time points was used as the data source in the analysis template. This was saved by the FDSS as a tab-delimited text file. Data were normalized using a static ratio function (F/F_0) for each measurement of the total 360 values per well divided by each well's initial value. Data were then reduced to peak amplitudes (Max – Initial Min) using a time range that starts approximately 3 seconds prior to the glutamate EC_{20}/EC_{80} addition and continues for approximately 90-120 seconds. This is sufficient time to capture the peak amplitude of the cellular calcium response. Individual amplitudes were expressed as % E_{Max} by multiplying each amplitude by 100 and then dividing the product by the mean of the amplitudes derived from the glutamate EC_{Max}-treated wells. IC_{50} values for test compounds were generated by fitting the normalized values versus the log of the test compound concentration (in mol/L) using a 4 parameter logistic equation where none of the parameters were fixed. Each of the three values collected at each concentration of test compound were weighted evenly.

[00263] A compound was designated as a negative allosteric modulator (NAM) if the compound showed a concentration-dependent decrease in the glutamate EC_{80} addition. For NAMs with a CRC that plateaus at a Glu Max (i.e. the amplitude of response in the presence of compound as a percentage of the maximal response to glutamate) below 10%, IC_{50} values are reported. For NAMs with a CRC that plateaus above 10% Glu Max, the IC_{50} values are reported, the compound is designated a "partial NAM" and the % Glu Max is reported. For

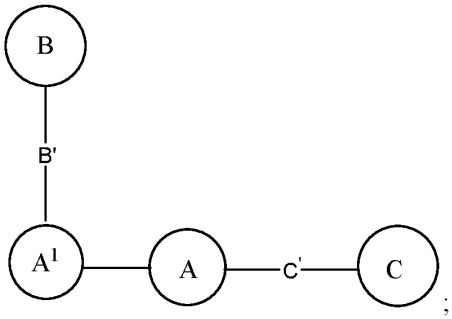
NAMs that show a decrease in the EC_{80} response, but do not hit a plateau, the average of the Glu Max at a single concentration (30 μM) was determined (% Glu Max), reported, and IC_{50} values are reported as ">10,000 nM". Compounds without measurable activity are designated as ">30,000 nM" since the top concentration of compound tested in the assay is 30 μM. Exemplary data are provided in Table 2 above.

[00264] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

EXEMPLARY CLAIMS

What is claimed is:

1. A compound of the following formula:



;

wherein:

A is chosen from oxadiazole, imidazole, or triazole;

A^1 is substituted or unsubstituted pyridine;

B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran;

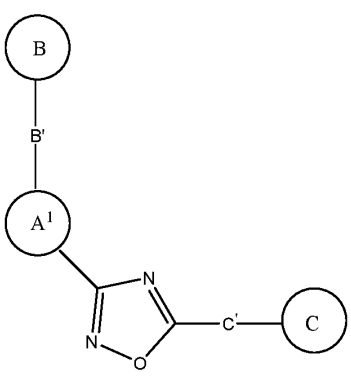
B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;

C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine,

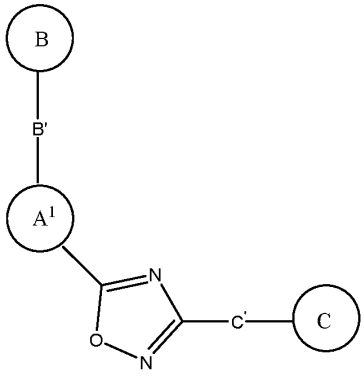
C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

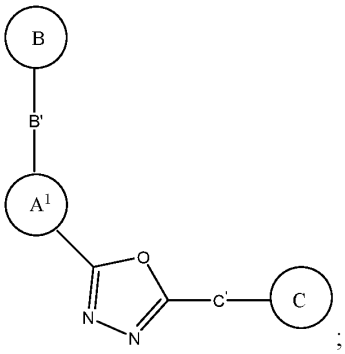
2. A compound of claim 1, of the following formula:



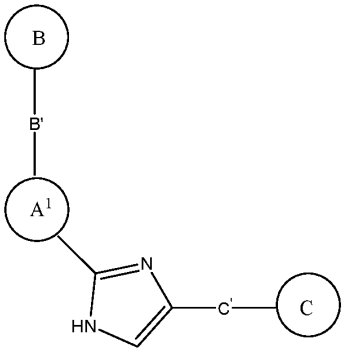
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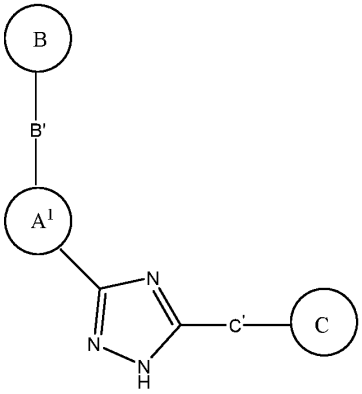
;



;



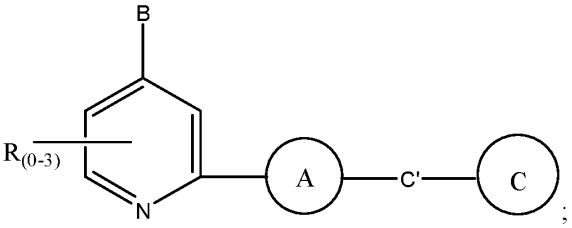
; or



;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, of the following formula:



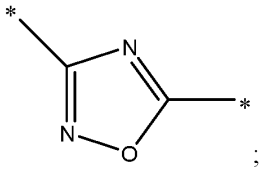
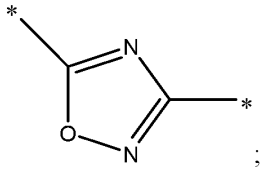
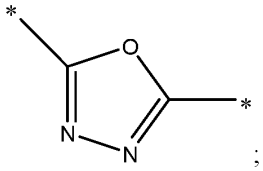
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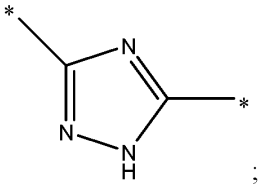
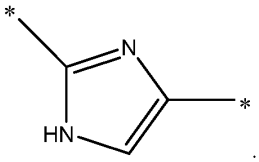
wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy;

R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3

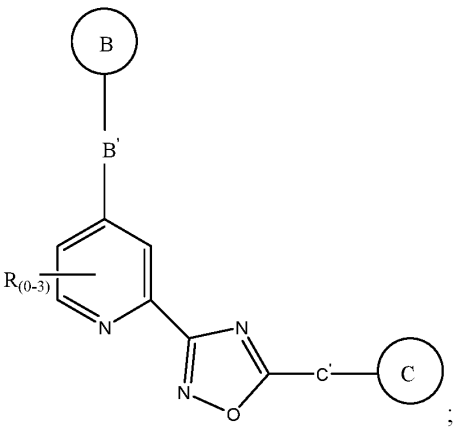
4. The compound of claim 1, wherein A is chosen from 1,2,4-oxadiazole or 1,3,4-oxadiazole.

5. The compound of claim 1, wherein A is chosen from:

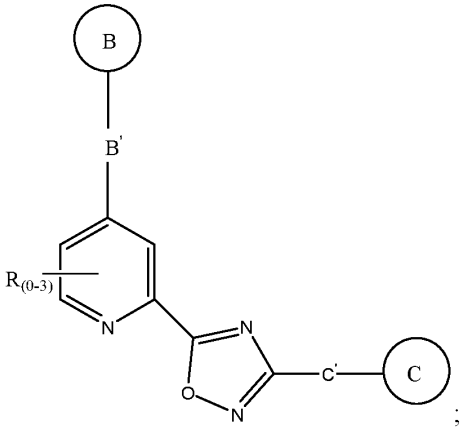
(i)  ; (ii)  ; (iii)  ;

(iv)  ; or (v)  .

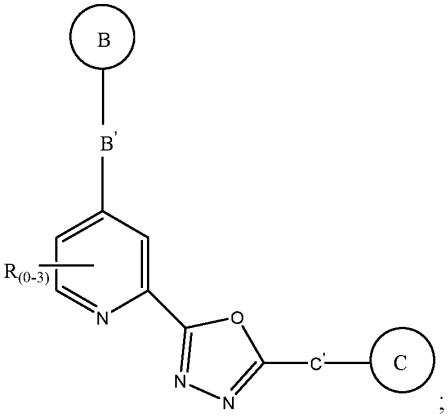
6. The compound of claim 1, of the following formula:



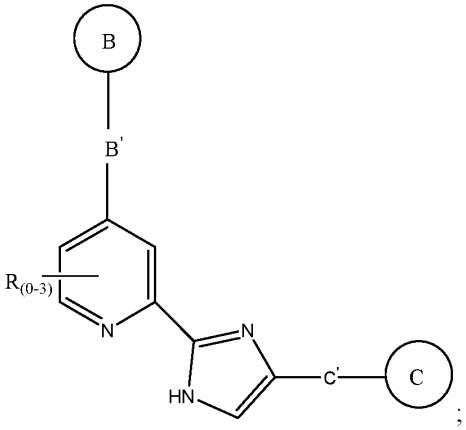
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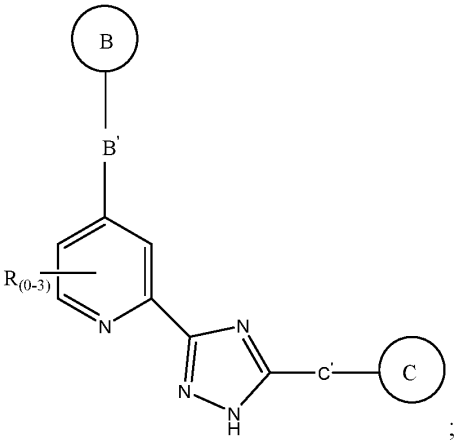
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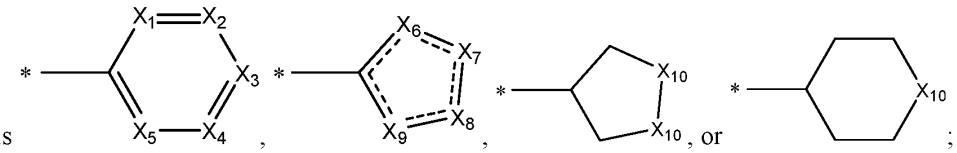
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wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy;

R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3;

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein:

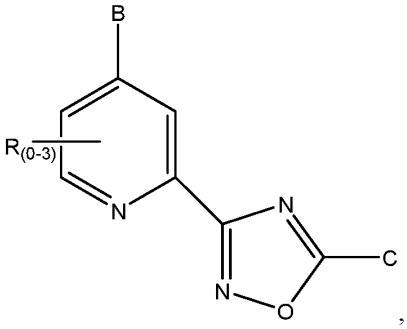
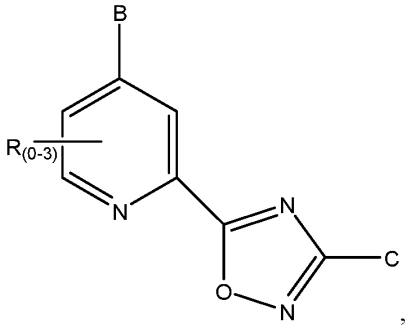
B is  ;

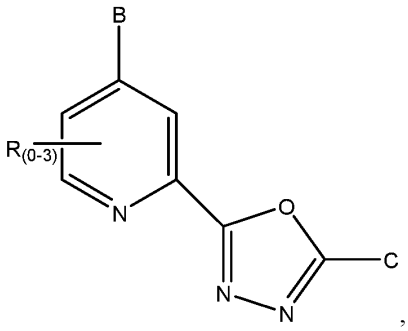
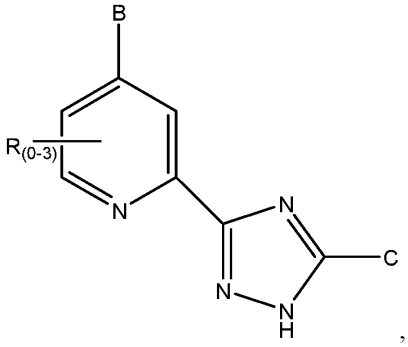
X_1 is CH, C-R_1, or N;
X_2 is CH, C-R_1, or N;
X_3 is CH, C-R_1, or N;
X_4 is CH, C-R_1, or N;
X_5 is CH, C-R_1, or N;
X_6 is CH, CR_1, S, NR_1, or N;
X_7 is CH, CR_1, S, NR_1, or N;
X_8 is CH, CR_1, S, NR_1, or N;
X_9 is CH, CR_1, S, NR_1, or N;
X_{10} is CH_2 or O;

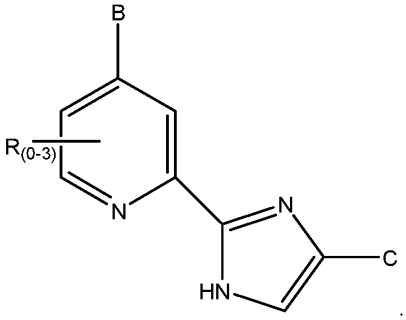
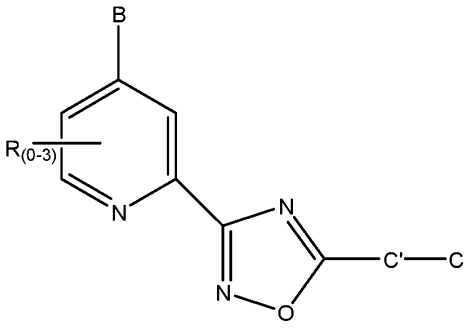
each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, of the following formula:

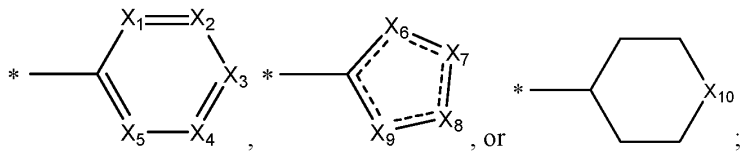
(i)  , (ii)  ,

(iii)  , (iv)  , or

(v)  . (vi)  ; or

a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, wherein:

C is  ;

X_1 is CH, C-R_2, or N;

X_2 is CH, C-R_2, or N;

X_3 is CH, C-R_2, or N;

X_4 is CH, C-R_2, or N;

X_5 is CH, C-R_2, or N;

X_6 is CH, CR_2, S, NR_2, or N;

X_7 is CH, CR_2, S, NR_2, or N;

X_8 is CH, CR_2, S, NR_2, or N;

X_9 is CH, CR_2, S, NR_2, or N;

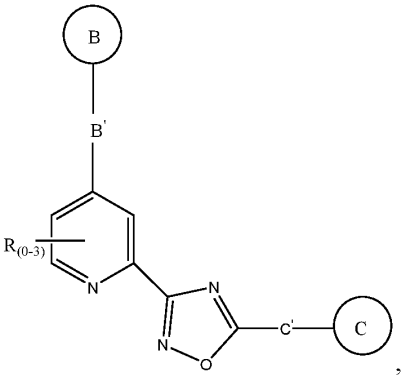
X_{10} is CH_2 or O;

each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

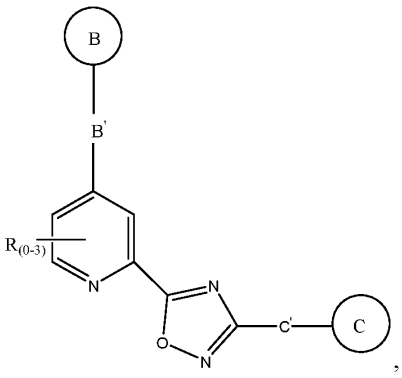
or a pharmaceutically acceptable salt thereof.

10. A compound of claim 1, wherein:

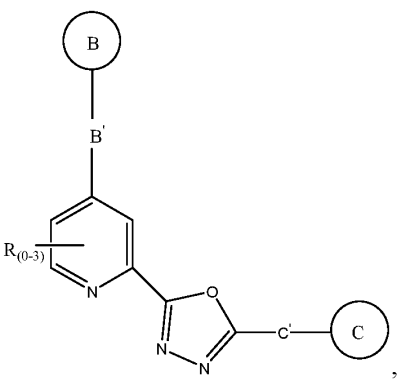
(i) A^1 and A together form:



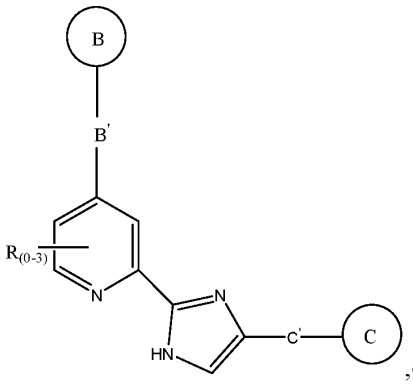
,



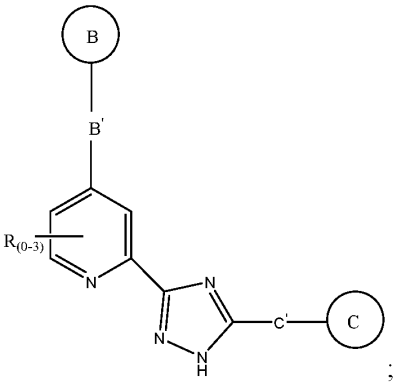
,



,



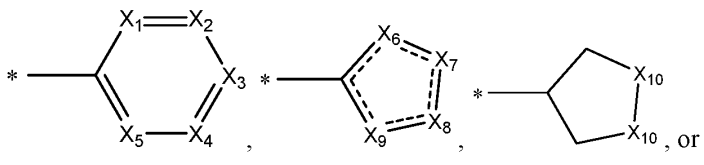
,or



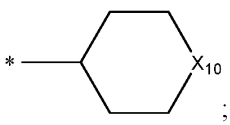
;

wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy;

R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3;

(ii) B is 

, or



;

X_1 is CH, C-R_1, or N;

X_2 is CH, C-R_1, or N;

X_3 is CH, C-R_1, or N;

X_4 is CH, C-R_1, or N;

X_5 is CH, C-R_1, or N;

X_6 is CH, CR_1, S, NR_1, or N;

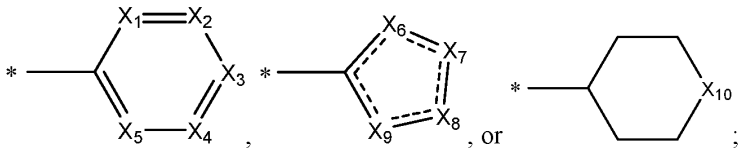
X_7 is CH, CR_1, S, NR_1, or N;

X_8 is CH, CR_1, S, NR_1, or N;

X_9 is CH, CR_1, S, NR_1, or N;

X_{10} is CH_2 or O;

each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; and

(iii) C is  , , or ;

X_1 is CH, C-R_2, or N;

X_2 is CH, C-R_2, or N;

X_3 is CH, C-R_2, or N;

X_4 is CH, C-R_2, or N;

X_5 is CH, C-R_2, or N;

X_6 is CH, CR_2, S, NR_2, or N;

X_7 is CH, CR_2, S, NR_2, or N;

X_8 is CH, CR_2, S, NR_2, or N;

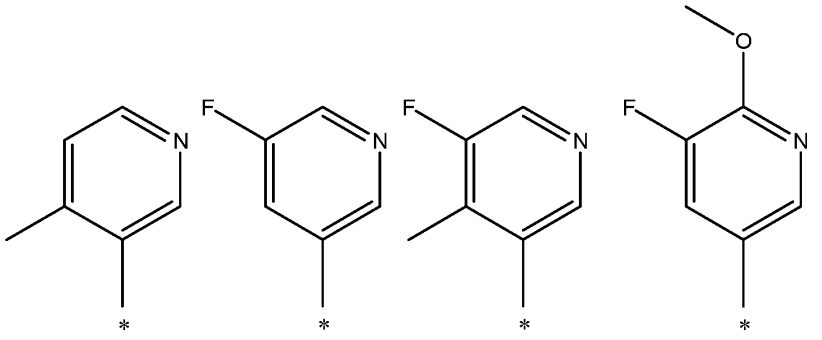
X_9 is CH, CR_2, S, NR_2, or N;

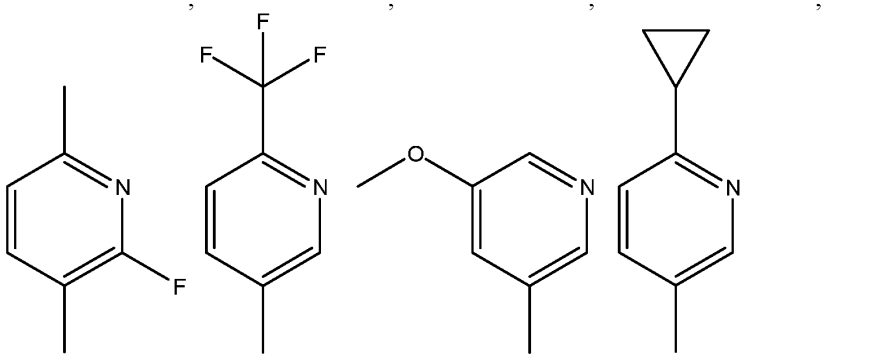
X_{10} is CH_2 or O;

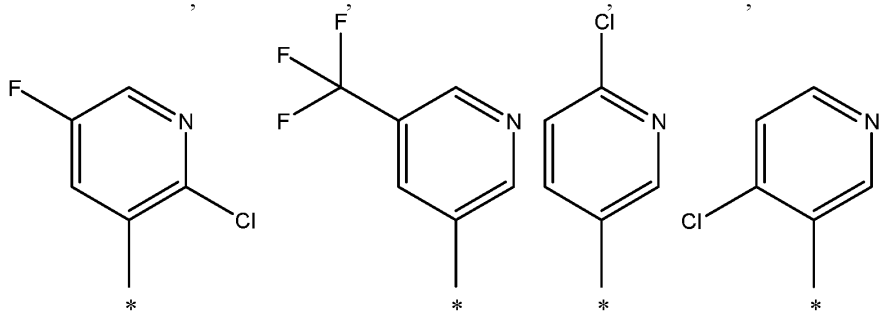
each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

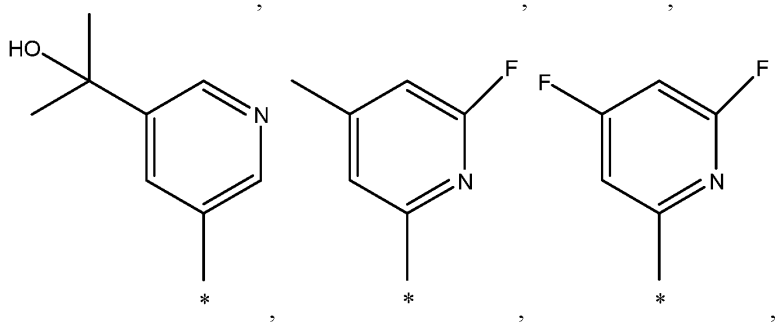
or a pharmaceutically acceptable salt thereof.

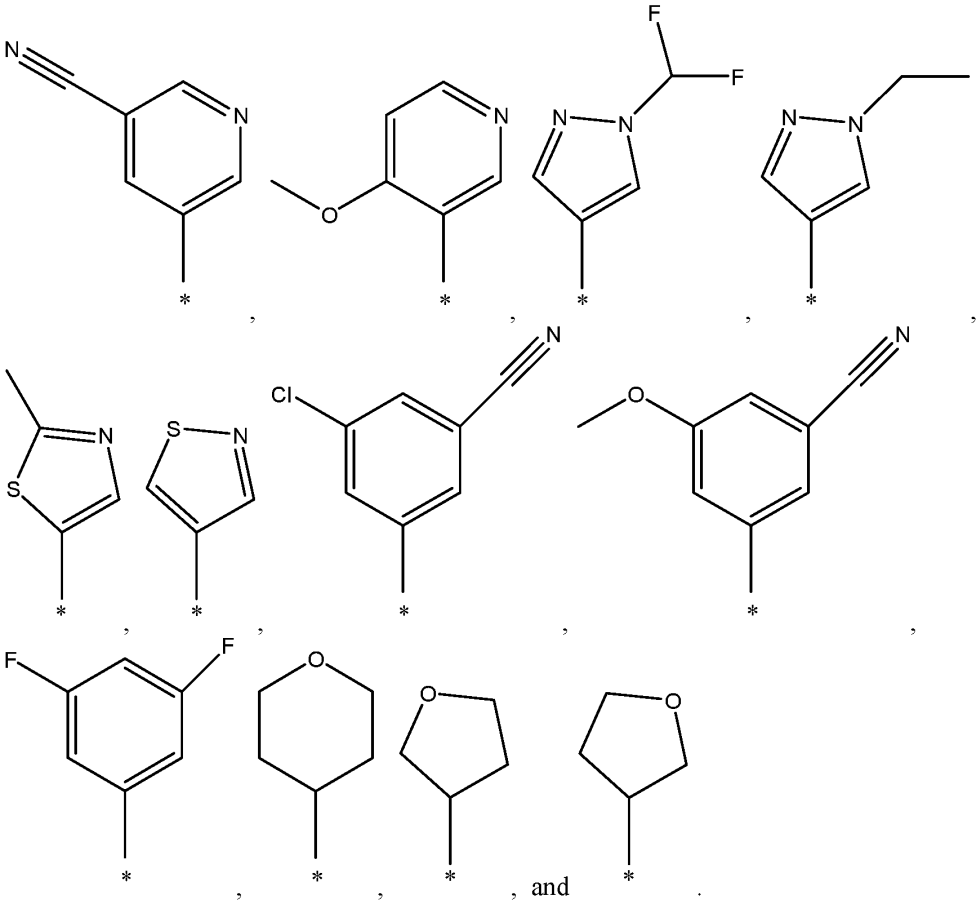
11. The compound of claim 1 or claim 10, wherein B chosen from:



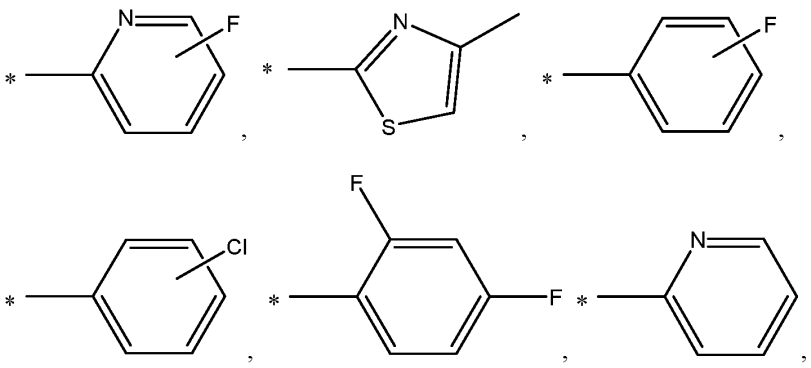


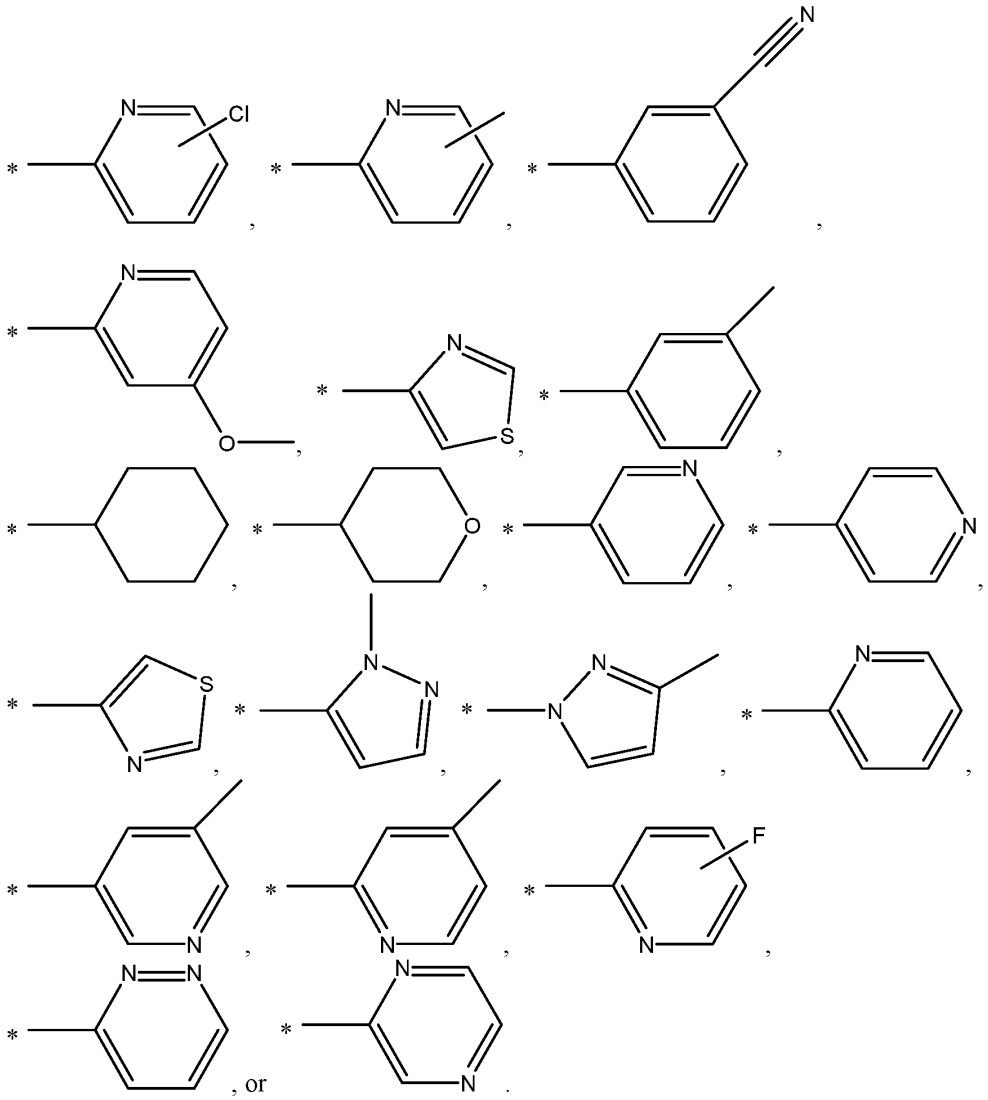




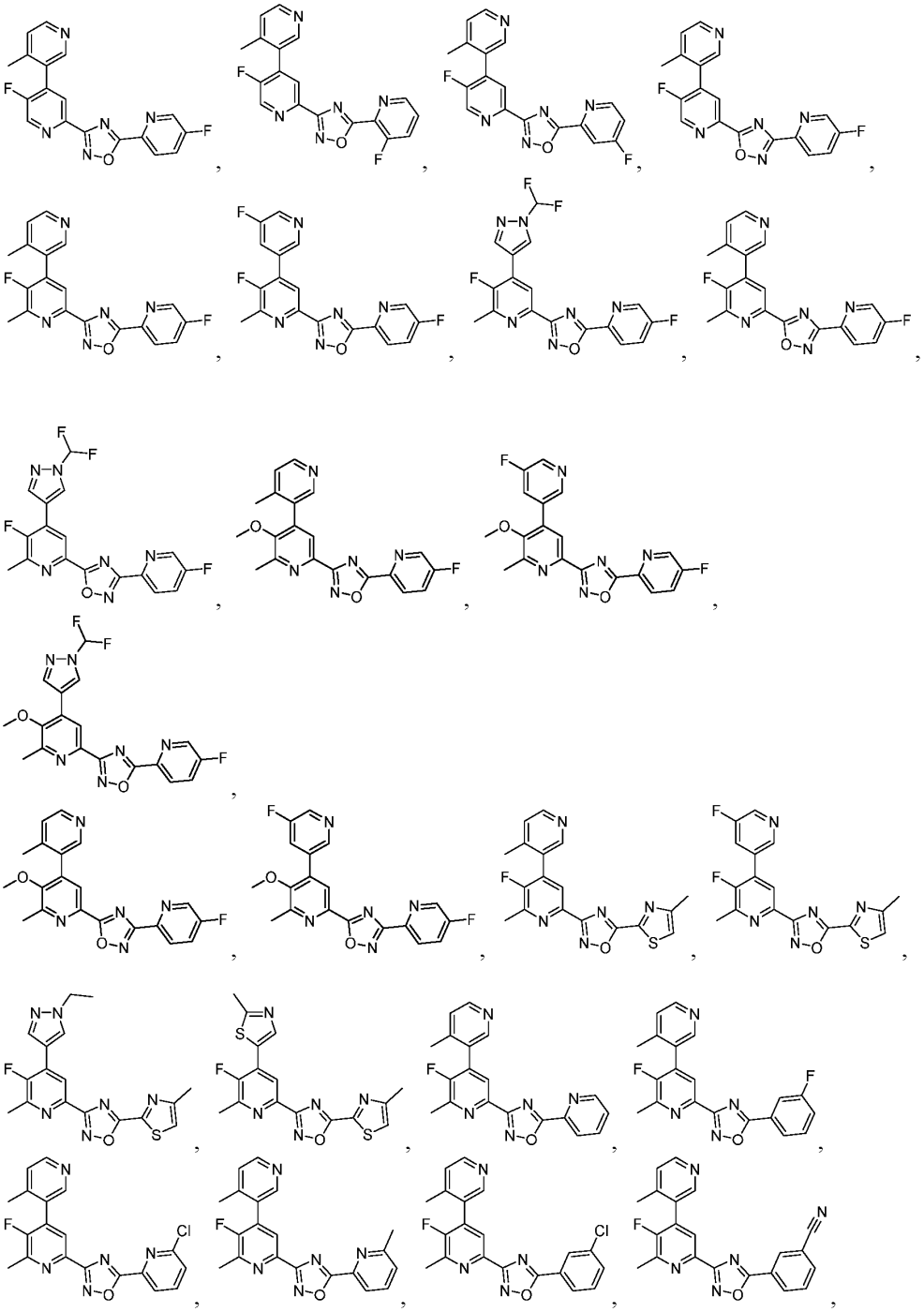


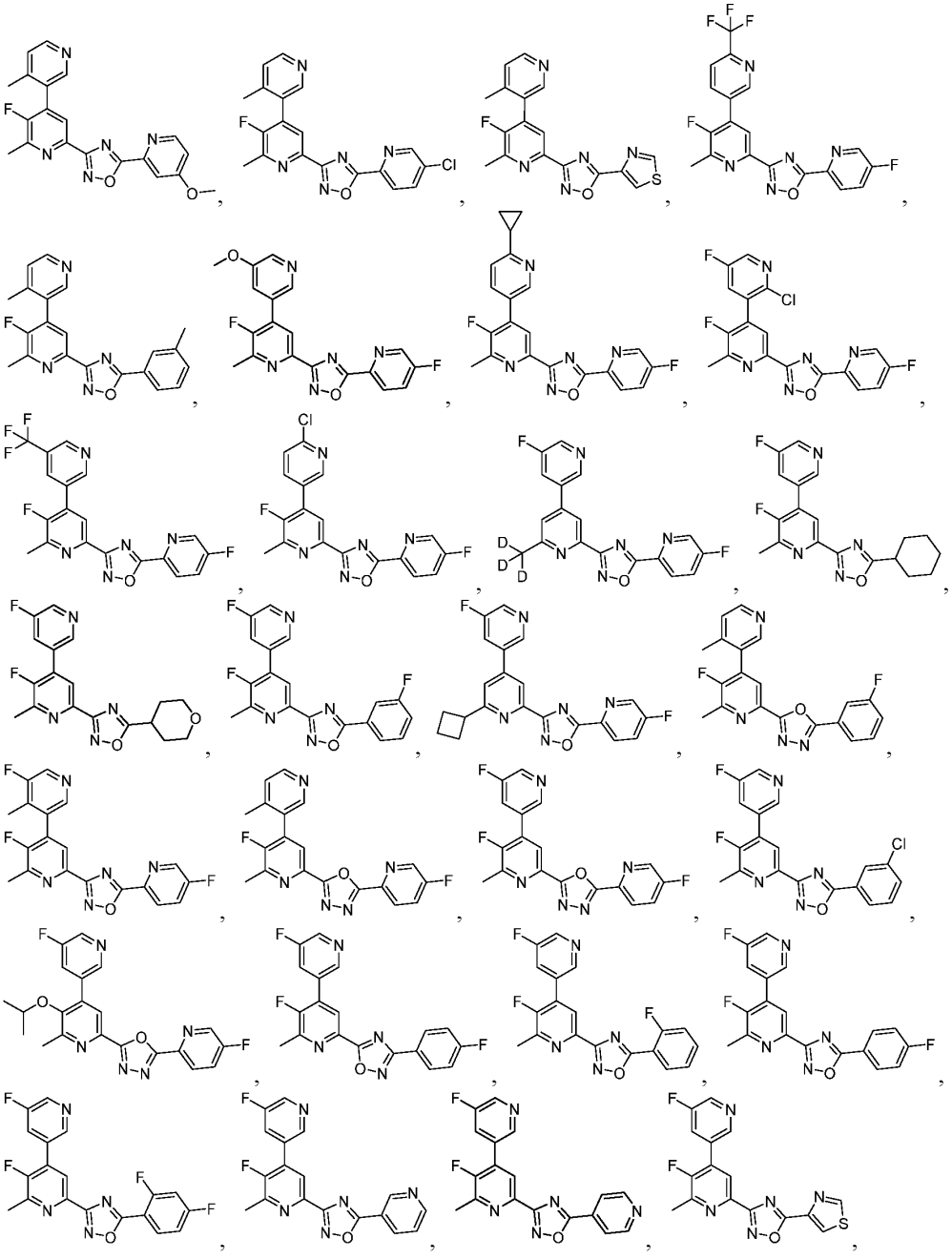
12. The compound of claim 1 or claim 10, wherein C is chosen from:

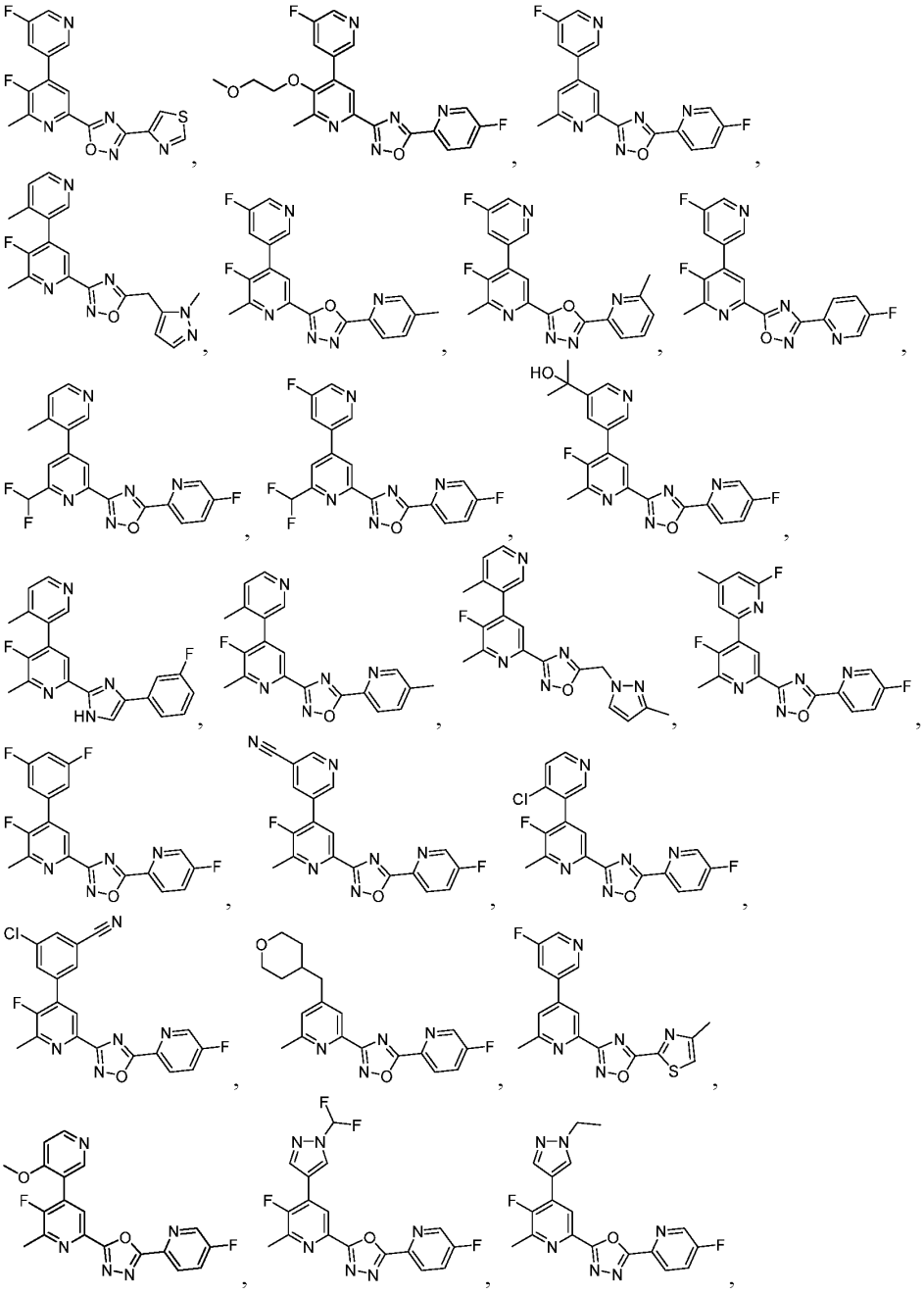


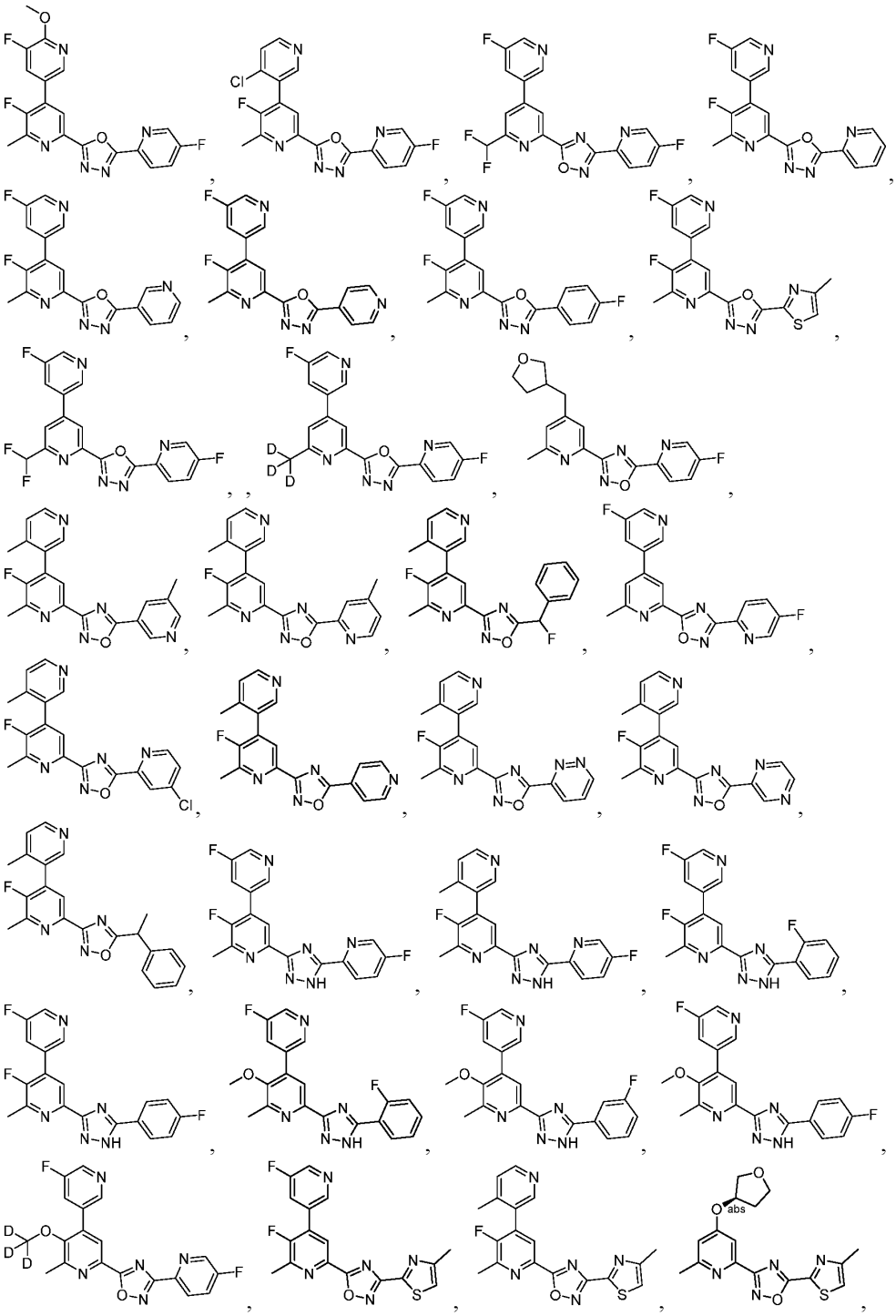


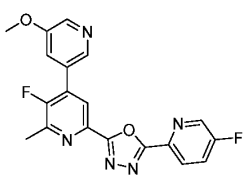
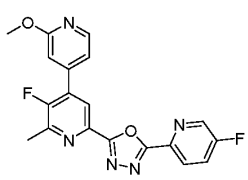
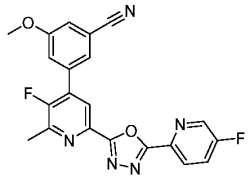
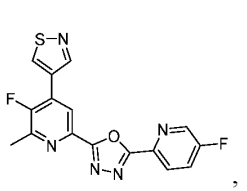
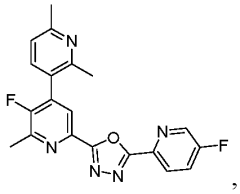
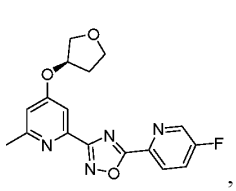
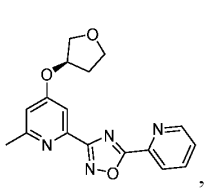
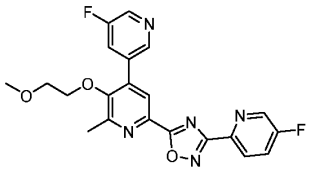
13. The compound of claim 1, of the following formula:









 ,  ,  ,  ,  ,  ,  , and  , or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of one of claims 1 or 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. A pharmaceutical composition comprising a compound of claim 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. A method for the treatment of a disorder associated with metabotropic glutamate receptor activity in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound of one of claims 1-13, or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with metabotropic glutamate receptor activity in the subject.

17. The method of claim 16, wherein the metabotropic glutamate receptor is mGlu5.

18. The method of claim 16, wherein the subject is a human.

19. The method of claim 16, wherein the subject has been diagnosed with a need for treatment of the disorder prior to the administering step.

20. The method of claim 16, further comprising the step of identifying a subject in need of treatment of the disorder.

21. The method of claim 16, wherein the disorder is a neurological and/or psychiatric disorder.

22. The method of claim 21, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman syndrome, Asperger syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN harmartoma syndrome, senile dementia, sleep disorder, substance-related disorder, post-traumatic stress disorder (PTSD) or unipolar depression.

23. The method of claim 21, wherein the neurological and/or psychiatric wherein the disorder is an autism spectrum disorder.

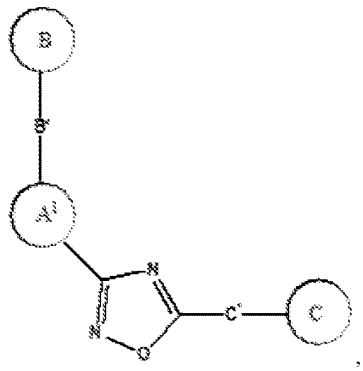
24. The method of claim 23, wherein the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

25. A compound of one of claims 1-12 for use in the treatment of a disorder associated with metabotropic glutamate receptor, such as mGlu5, activity in a subject.

26. A compound of claim 25, wherein the disorder is a neurological and/or psychiatric disorder, such as affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman syndrome, Asperger syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN harmartoma syndrome, senile dementia, sleep disorder, substance-related disorder, post-traumatic stress disorder (PTSD), or unipolar depression.

26. A compound of claim 25, wherein the neurological and/or psychiatric is an autism spectrum disorder, such as autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

27. A compound of claim 1, of the following formula:



wherein:

A^1 is substituted or unsubstituted pyridine;

B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran;

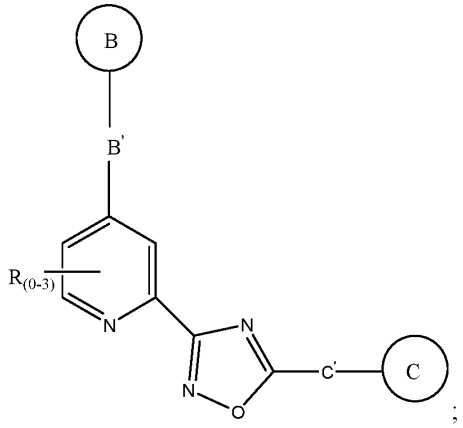
B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;

C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine,

C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

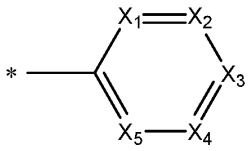
28. A compound of the following formula:



;

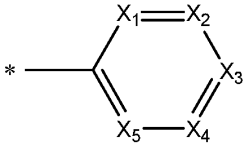
wherein B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy; R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3;

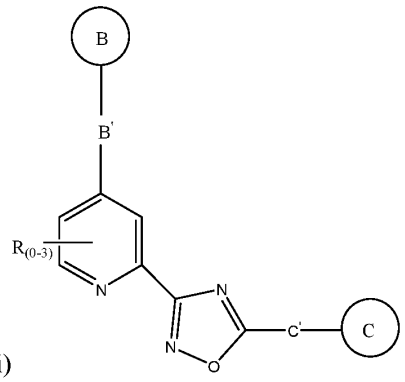
B is 

; wherein X_1 is CH, C-R_1, or N; X_2 is CH, C-R_1, or N; X_3 is CH, C-R_1, or N; X_4 is CH, C-R_1, or N; X_5 is CH, C-R_1, or N;

each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

C is  ; wherein X_1 is CH, C-R_2, or N; X_2 is CH, C-R_2, or N; X_3 is CH, C-R_2, or N; X_4 is CH, C-R_2, or N; X_5 is CH, C-R_2, or N; each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

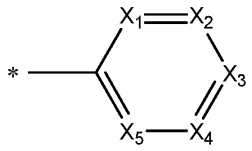
29. The compound of claim 28, of the following formula:



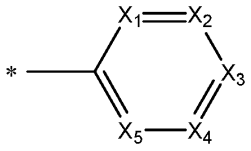
(i)

B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;

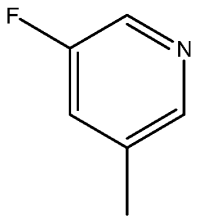
C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

(ii) B is  ; X_1 is N; X_2 is CH, C-R_1, or N; X_3 is CH, C-R_1, or N; X_4 is CH, C-R_1, or N; X_5 is CH, C-R_1, or N; each R_1, when present, is independent and chosen

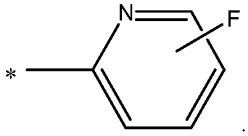
from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; and

(iii) C is 

; X_1 is N; X_2 is CH, C-R_2, or N; X_3 is CH, C-R_2, or N; X_4 is CH, C-R_2, or N; X_5 is CH, C-R_2, or N; each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

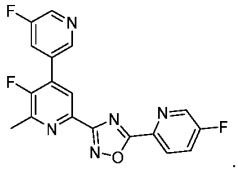
30. The compound of claim 28, wherein B is 

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31. The compound of claim 28, wherein C is 

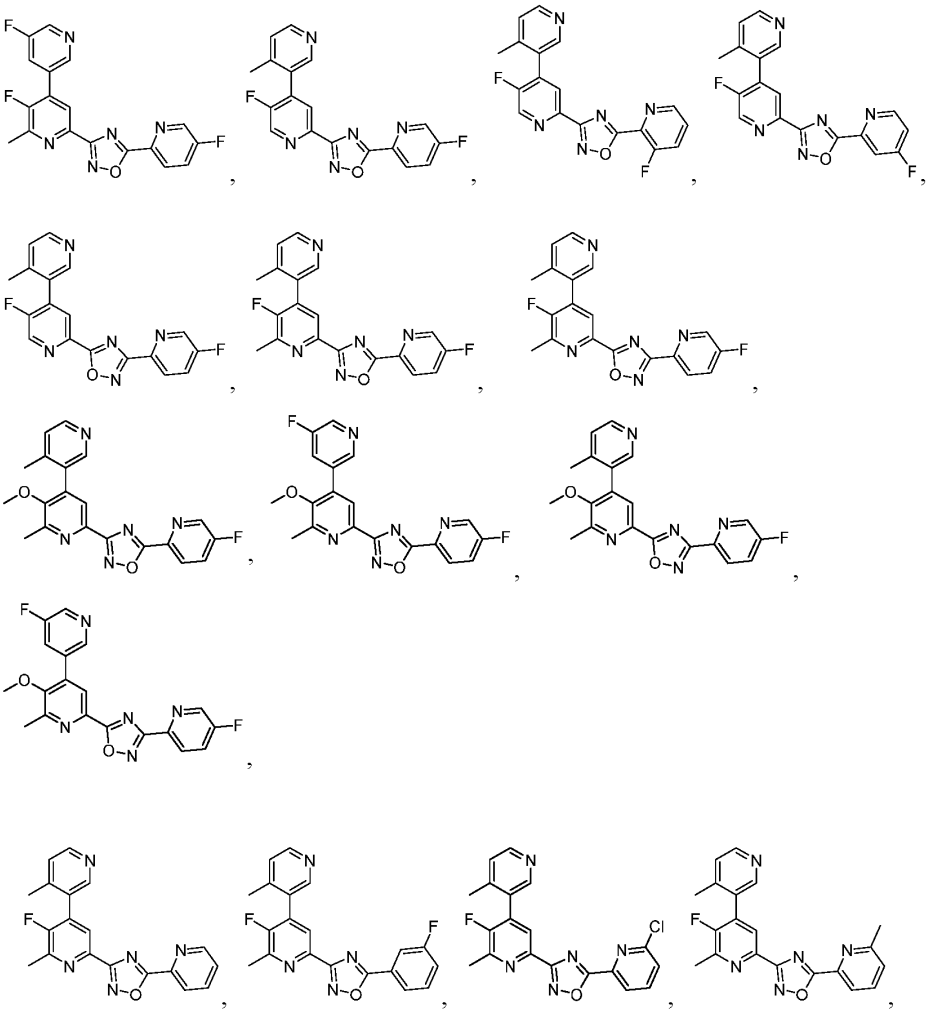
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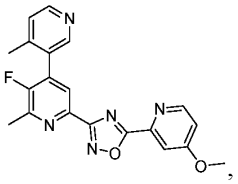
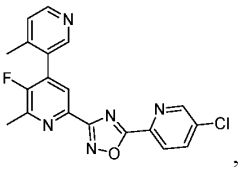
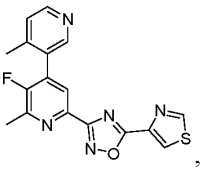
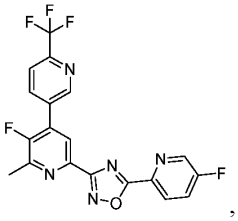
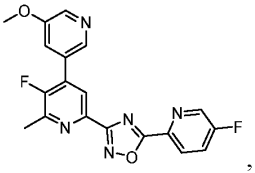
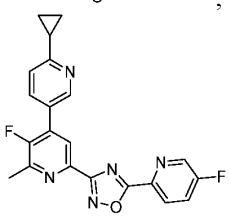
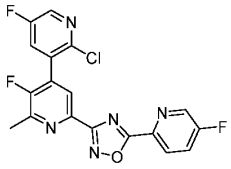
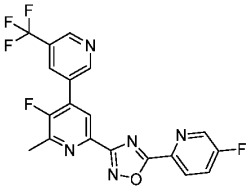
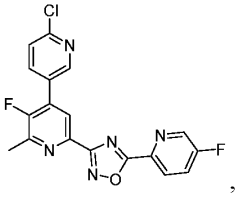
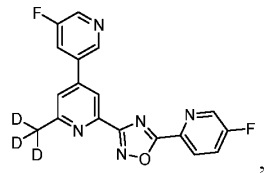
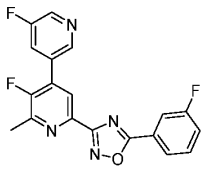
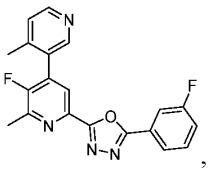
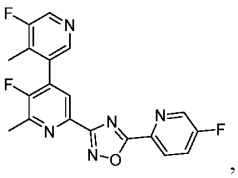
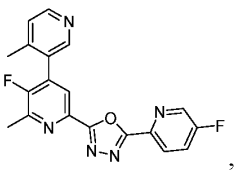
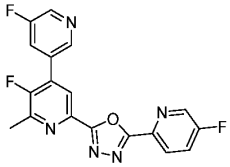
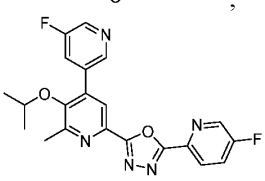
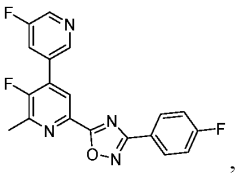
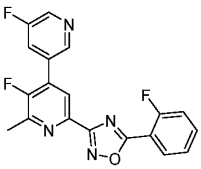
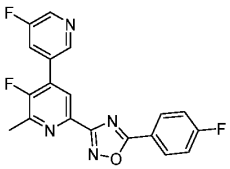
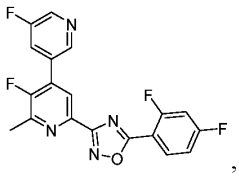
32. The compound of claim 28, wherein the compound is:

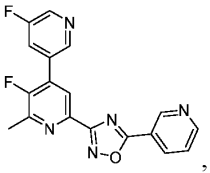
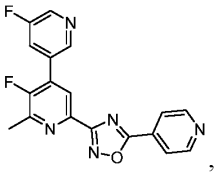
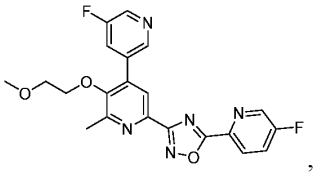
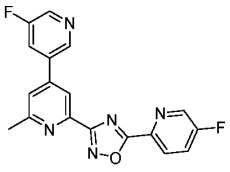
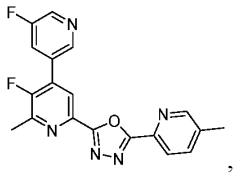
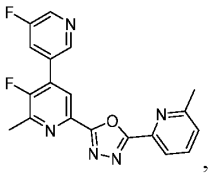
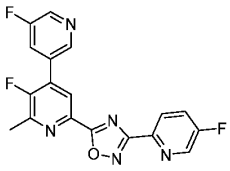
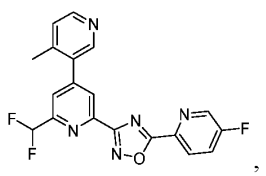
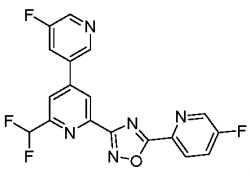
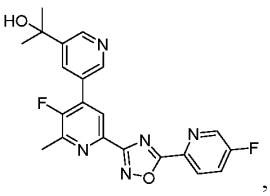
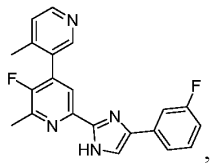
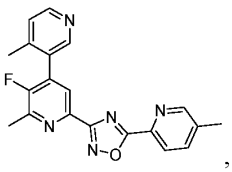
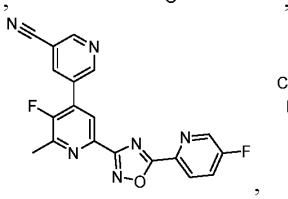
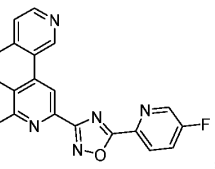
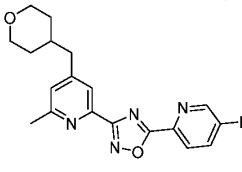


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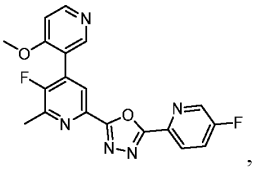
33. The compound of claim 28, wherein the compound is chosen from:




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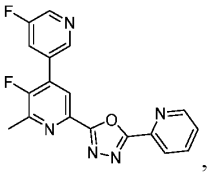
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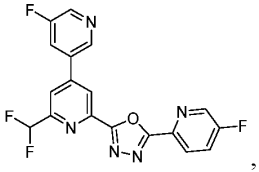
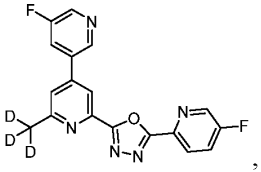
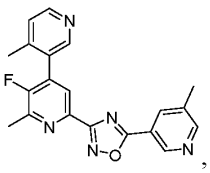
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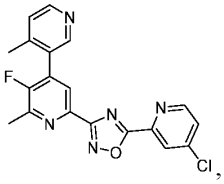
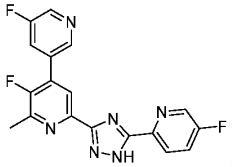
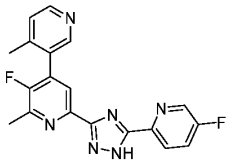
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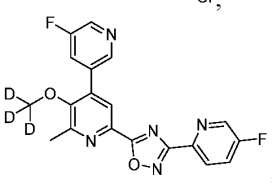
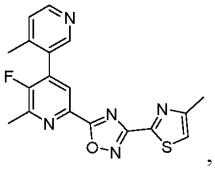
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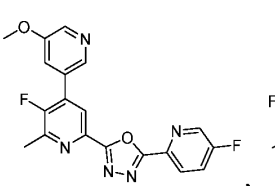
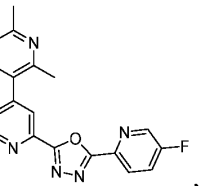
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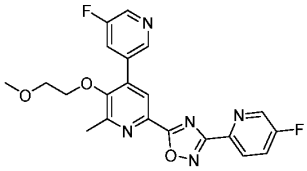
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