

1,6-NAPHTHYRIDINE DERIVATIVES AS POSITIVE ALLOSTERIC MODULATORS OF THE MUSCARINIC ACETYLCHOLINE RECEPTOR M4 USEFUL FOR THE TREATMENT OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/496,811, filed April 18, 2023, and U.S. Provisional Application No. 63/610,209, filed December 14, 2023, each of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to compounds, compositions, and methods for treating neurological and psychiatric disorders associated with muscarinic acetylcholine receptor dysfunction.

BACKGROUND

[0003] Cholinergic neurotransmission involves the activation of nicotinic acetylcholine receptors (nAChRs) or the muscarinic acetylcholine receptors (mAChRs) by the binding of the endogenous orthosteric agonist acetylcholine (ACh). Conditions associated with cognitive impairment, such as Alzheimer's disease, are accompanied by a reduction of acetylcholine content in the brain. This is believed to be the result of degeneration of cholinergic neurons of the basal forebrain, which widely innervate multiple areas of the brain, including the association cortices and hippocampus, which are critically involved in higher processes. Clinical data supports that cholinergic hypofunction contributes to the cognitive deficits of patients suffering from schizophrenia. Efforts to increase acetylcholine levels have focused on increasing levels of choline, the precursor for acetylcholine synthesis, and on blocking acetylcholinesterase (AChE), the enzyme that metabolizes acetylcholine. As a result, acetylcholinesterase (AChE) inhibitors, which inhibit the hydrolysis of ACh, have been approved in the United States for use in the palliative, but not disease-modifying, treatment of the cognitive deficits in AD patients.

[0004] Attempts to augment central cholinergic function through the administration of choline or phosphatidylcholine have not been successful. AChE inhibitors have shown therapeutic efficacy, but have been found to have frequent cholinergic side effects due to peripheral acetylcholine stimulation, including abdominal cramps, nausea, vomiting, and diarrhea. These gastrointestinal side effects have been observed in about a third of the patients treated. In addition, some AChE inhibitors, such as tacrine, have also been found to cause

significant hepatotoxicity with elevated liver transaminases observed in about 30% of patients. The adverse effects of AChE inhibitors have severely limited their clinical utility. An alternative approach to pharmacologically target cholinergic hypofunction is the activation of mAChRs, which are widely expressed throughout the body.

[0005] The mAChRs are members of the family A G protein-coupled receptors (GPCRs) and include five subtypes, designated M₁-M₅. The M₁, M₃ and M₅ subtypes mainly couple to G_q and activate phospholipase C, whereas the M₂ and M₄ subtypes mainly couple to G_{i/o} and associated effector systems. These five distinct mAChR subtypes have been identified in the mammalian central nervous system where they are prevalent and differentially expressed. M₁-M₅ have varying roles in cognitive, sensory, motor and autonomic functions. Thus, without wishing to be bound by a particular theory, it is believed that selective agonists of mAChR subtypes that regulate processes involved in cognitive function could prove to be superior therapeutics for treatment of psychosis, schizophrenia and related disorders. The muscarinic M₄ receptor has been shown to have a major role in cognitive processing and is believed to have a major role in the pathophysiology of psychotic disorders, including schizophrenia.

[0006] Evidence suggests that the most prominent adverse effects of AChE inhibitors and other cholinergic agents are mediated by activation of peripheral M₂ and M₃ mAChRs and include bradycardia, GI distress, excessive salivation, and sweating. In contrast, M₄ has been viewed as the most likely subtype for mediating the effects of muscarinic acetylcholine receptor dysfunction in psychotic disorders, including schizophrenia, cognition disorders, and neuropathic pain. Because of this, considerable effort has been focused on developing selective M₄ agonists for treatment of these disorders. Unfortunately, these efforts have been largely unsuccessful because of an inability to develop compounds that are highly selective for the mAChR M₄. Because of this, mAChR agonists that have been tested in clinical studies induce a range of adverse effects by activation of peripheral mAChRs. To fully understand the physiological roles of individual mAChR subtypes and to further explore the therapeutic utility of mAChR ligands in psychosis, including schizophrenia, cognition disorders and other disorders, it can be important to develop compounds that are highly selective activators of mAChR M₄ and other individual mAChR subtypes.

[0007] Previous attempts to develop agonists that are highly selective for individual mAChR subtypes have failed because of the high conservation of the orthosteric ACh binding site. To

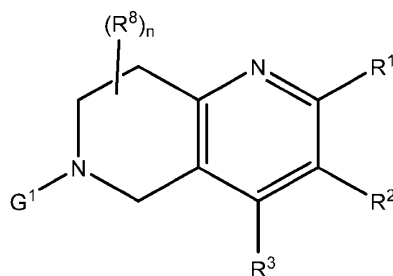
circumvent problems associated with targeting the highly conserved orthosteric ACh binding site, it is believed that developing compounds that act at allosteric sites on mAChRs that are removed from the orthosteric site and are less highly conserved. This approach is proving to be highly successful in developing selective ligands for multiple GPCR subtypes. In the case of mAChRs, a major goal has been to develop allosteric ligands that selectively increase activity of mAChR M₄ or other mAChR subtypes. Allosteric activators can include allosteric agonists, that act at a site removed from the orthosteric site to directly activate the receptor in the absence of ACh as well as positive allosteric modulators (PAMs), which do not activate the receptor directly but potentiate activation of the receptor by the endogenous orthosteric agonist ACh. Also, it is possible for a single molecule to have both allosteric potentiator and allosteric agonist activity.

[0008] More recently, muscarinic agonists including xanomeline have been shown to be active in animal models with similar profiles to known antipsychotic drugs, but without causing catalepsy (Bymaster *et al.*, *Eur. J. Pharmacol.* 1998, 356, 109, Bymaster *et al.*, *Life Sci.* 1999, 64, 527; Shannon *et al.*, *J. Pharmacol. Exp. Ther.* 1999, 290, 901; Shannon *et al.*, *Schizophrenia Res.* 2000, 42, 249). Further, xanomeline was shown to reduce psychotic behavioral symptoms such as delusions, suspiciousness, vocal outbursts, and hallucinations in Alzheimer's disease patients (Bodick *et al.*, *Arch. Neurol.* 1997, 54, 465), however treatment induced side effects, e.g., gastrointestinal effects, have severely limited the clinical utility of this compound.

[0009] Despite advances in muscarinic acetylcholine receptor research, there is still a scarcity of compounds that are potent, efficacious, and selective activators of the M₄ mAChR and also effective in the treatment of neurological and psychiatric disorders associated with cholinergic activity and diseases in which the muscarinic M₄ receptor is involved.

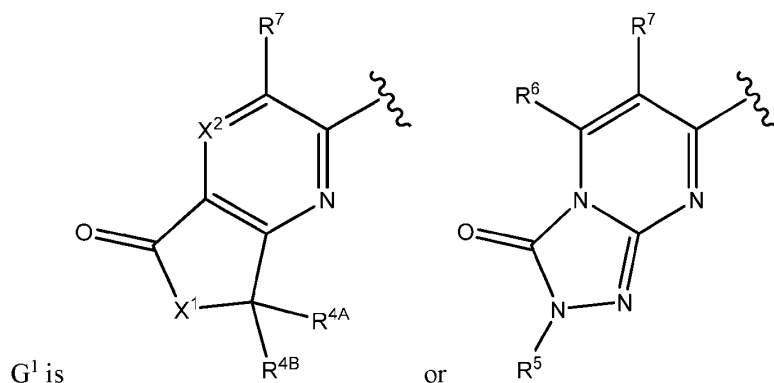
SUMMARY

[0010] In one aspect, disclosed are compounds of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein:

X¹ is NR⁵, O, or CR^{5A}R^{5B};X² is CR⁶ or N;R¹ and R³ are each independently hydrogen, halogen, cyano, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OC₁₋₄alkyl, or -OC₁₋₄fluoroalkyl;R² is G², -NR^bR^c, C₁₋₆haloalkyl, halogen, cyano, NO₂, C₁₋₆alkyl, C₂₋₆alkenyl, -OR^b, -NR^cC(O)R^b, -NR^cSO₂R^a, -N=S(O)(R^a)₂, -P(O)(R^a)₂, -C₁₋₃alkylene-G², -C₂₋₄alkenylene-G², or hydrogen;R^a, at each occurrence, is independently C₁₋₆alkyl, C₁₋₆haloalkyl, G², or -C₁₋₃alkylene-G²;wherein optionally, the two R^a of -N=S(O)(R^a)₂ or -P(O)(R^a)₂ join together as a straight alkylene chain to form a 5- to 7-membered heterocyclic ring;R^b and R^c are independently hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, G², or -C₁₋₃alkylene-G²;

G², at each occurrence, is independently a 5- to 12-membered heteroaryl, a 6- to 12-membered aryl, a 4- to 12-membered heterocyclyl, or a 3- to 12-membered carbocyclyl, wherein the heteroaryl and heterocyclyl each contain 1-4 heteroatoms independently selected from the group consisting of O, N, and S, and G² is optionally substituted with a first substituent selected from the group consisting of halogen, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, oxo, -OR^x, -N(R^x)₂, -SR^x, -SO₂R^x, -C(O)R^x, -C(O)OR^x, -C(O)N(R^x)₂, -C₁₋₆alkylene-OR^x, -C₁₋₆alkylene-N(R^x)₂, G^{2a}, and -C₁₋₃alkylene-G^{2a}, and optionally further substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, and -OR^x;

R^x , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-3}$ alkylene- C_{3-6} cycloalkyl, phenyl, or $-C_{1-3}$ alkylene-phenyl, wherein each cycloalkyl or phenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;

G^{2a} is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a 3- to 8-membered carbocyclyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^{2a} , at each occurrence, is independently optionally substituted with 1-5 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, $-C_{1-6}$ alkylene-OH, oxo, OH, $-OC_{1-4}$ alkyl, $-OC_{1-4}$ haloalkyl, C_{3-4} cycloalkyl, and $-C_{1-3}$ alkylene- C_{3-4} cycloalkyl;

R^{4A} and R^{4B} are independently hydrogen, C_{1-4} alkyl, C_{3-4} cycloalkyl, or $-C_{1-3}$ alkylene-OH;

R^5 is hydrogen, C_{1-6} alkyl, C_{1-6} fluoroalkyl, $-C_{1-6}$ alkylene- R^y , $-C_{1-6}$ fluoroalkylene- R^y , G^5 , or $-C_{1-3}$ alkylene- G^5 ;

R^{5A} and R^{5B} are independently hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkyl, or $-C_{1-4}$ alkylene-OH;

R^y is $-OR^{5a}$, $-N(R^{5a})_2$, $-C(O)R^{5a}$, $-C(O)OR^{5a}$, or $-C(O)N(R^{5a})_2$;

R^{5a} , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, G^5 , or $-C_{1-3}$ alkylene- G^5 ;

G^5 is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a C_{3-8} cycloalkyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^5 is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-2} fluoroalkyl, $-OC_{1-4}$ alkyl, OH, and oxo;

alternatively, R^{4A} and R^{4B} together with the carbon to which they attach form a C_{3-6} cycloalkyl; or R^{4B} and R^5 together with the atoms to which they attach form a 5- to 7-membered heterocycle optionally containing one additional heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur;

R^6 is hydrogen, halogen, cyano, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{2-4} alkenyl, $-OR^{6a}$, $-N(R^{6a})_2$, $-C_{1-3}$ alkylene- OR^{6a} , or C_{3-6} cycloalkyl;

R^{6a} , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-4} cycloalkyl, or $-C_{1-3}$ alkylene- C_{3-4} cycloalkyl;

wherein alternatively, two R^{6a}, together with the nitrogen to which they attach form a 4- to 8-membered heterocyclic ring containing the nitrogen attached to R^{6a} and optionally 1-2 additional heteroatoms that are independently O, N, or S, the heterocyclic ring being optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C₁₋₂alkyl, and C₁₋₂fluoroalkyl;

R⁷ is C₁₋₄alkyl, hydrogen, halogen, cyano, C₁₋₄fluoroalkyl, -OR^{7a}, -C₁₋₃alkylene-OR^{7a}, or G⁷; alternatively, R⁶ and R⁷, together with the atoms to which they are attached, form a 5- to 7-membered heterocycle containing 1 heteroatom or a 5- to 7-membered carbocycle, wherein the heteroatoms are independently selected from the group consisting of N, O, and S, and the heterocycle and carbocycle are optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, halogen, -OC₁₋₄alkyl, C₁₋₄fluoroalkyl, C₃₋₄cycloalkyl, and C₁₋₂alkylene-C₃₋₄cycloalkyl;

R^{7a} is hydrogen, C₁₋₄alkyl, C₁₋₄fluoroalkyl, C₃₋₄cycloalkyl, or -C₁₋₃alkylene-C₃₋₄cycloalkyl;

G⁷ is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a C₃₋₆cycloalkyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G⁵ is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C₁₋₄alkyl, C₁₋₂fluoroalkyl, -OC₁₋₄alkyl, OH, and oxo;

R⁸, at each occurrence, is independently halogen, C₁₋₄alkyl, C₁₋₄fluoroalkyl, or C₃₋₄cycloalkyl; and

n is 0, 1, 2, 3, or 4;

wherein each cycloalkyl at R⁶, R^{6a}, R⁷, R^{7a}, and R⁸ is unsubstituted or substituted with 1-4 substituents independently selected from C₁₋₄alkyl (e.g., methyl) and halogen (e.g., fluoro).

[0011] In another aspect, the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0012] Another aspect provides a method of treating a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal, comprising administering to the mammal a therapeutically effective amount of the compound of formula (I), or pharmaceutically acceptable salt or composition thereof.

[0013] Another aspect provides a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, for use in the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[0014] Another aspect provides use of a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, for the preparation of a medicament for the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[0015] In another aspect, the invention provides kits comprising a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, and instructions for use.

DETAILED DESCRIPTION

[0016] Disclosed herein are positive allosteric modulators (i.e. potentiators) of the muscarinic acetylcholine receptor M₄ (mAChR M₄), methods of making same, pharmaceutical compositions comprising same, and methods of treating neurological and psychiatric disorders associated with muscarinic acetylcholine receptor dysfunction using same. The compounds include naphthyridine-substituted pyridazine compounds.

[0017] The human muscarinic acetylcholine receptor M₄ (mAChR M₄) is a protein of 479 amino acids encoded by the CHRM4 gene. The molecular weight of the unglycosylated protein is about 54 kDa and it is a transmembrane GPCR. As described above, the mAChR M₄ is a member of the GPCR Class A family, or the rhodopsin-like GPCRs, which are characterized by structural features similar to rhodopsin such as seven transmembrane segments. The muscarinic acetylcholine receptors have the N-terminus oriented to the extracellular face of the membrane and the C-terminus located on the cytoplasmic face.

[0018] Previous attempts to develop agonists that are highly selective for individual mAChR subtypes have failed because of the high conservation of the orthosteric ACh binding site. To circumvent problems associated with targeting the highly conserved orthosteric ACh binding site, it is believed that developing compounds that act at allosteric sites on mAChRs that are removed from the orthosteric site and are less highly-conserved. Without wishing to be bound by a particular theory, the disclosed compounds and products of the disclosed methods are believed to bind to an allosteric site distinct from the orthosteric binding site.

1. Definitions

[0019] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

[0020] The terms “comprise(s),” “include(s),” “having,” “has,” “can,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments “comprising,” “consisting of” and “consisting essentially of,” the embodiments or elements presented herein, whether explicitly set forth or not.

[0021] The modifier “about” used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (for example, it includes at least the degree of error associated with the measurement of the particular quantity). The modifier “about” should also be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression “from about 2 to about 4” also discloses the range “from 2 to 4.” The term “about” may refer to plus or minus 10% of the indicated number. For example, “about 10%” may indicate a range of 9% to 11%, and “about 1” may mean from 0.9-1.1. Other meanings of “about” may be apparent from the context, such as rounding off, so, for example “about 1” may also mean from 0.5 to 1.4.

[0022] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books,

Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

[0023] The term “alkoxy,” as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

[0024] The term “alkyl,” as used herein, means a straight or branched, saturated hydrocarbon chain. The term “lower alkyl” or “C₁₋₆alkyl” means a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. The term “C₁₋₄alkyl” means a straight or branched chain saturated hydrocarbon containing from 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-decyl.

[0025] The term “alkenyl,” as used herein, means a straight or branched, hydrocarbon chain containing at least one carbon-carbon double bond.

[0026] The term “alkoxyalkyl,” as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

[0027] The term “alkoxyfluoroalkyl,” as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a fluoroalkyl group, as defined herein.

[0028] The term “alkylene,” as used herein, refers to a divalent group derived from a straight or branched saturated chain hydrocarbon, for example, of 1 to 6 carbon atoms. Representative examples of alkylene include, but are not limited to, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂CH₂-, and -CH₂CH₂CH₂CH₂CH₂-.

[0029] The term “alkylamino,” as used herein, means at least one alkyl group, as defined herein, is appended to the parent molecular moiety through an amino group, as defined herein.

[0030] The term “amide,” as used herein, means -C(O)NR- or -NRC(O)-, wherein R may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0031] The term “aminoalkyl,” as used herein, means at least one amino group, as defined herein, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0032] The term “amino,” as used herein, means $-NR_xR_y$, wherein R_x and R_y may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl. In the case of an aminoalkyl group or any other moiety where amino appends together two other moieties, amino may be $-NR_x-$, wherein R_x may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0033] The term “aryl,” as used herein, refers to a phenyl or a phenyl appended to the parent molecular moiety and fused to a cycloalkane group (e.g., the aryl may be indan-4-yl), fused to a 6-membered arene group (i.e., the aryl is naphthyl), or fused to a non-aromatic heterocycle (e.g., the aryl may be benzo[d][1,3]dioxol-5-yl). The term “phenyl” is used when referring to a substituent and the term 6-membered arene is used when referring to a fused ring. The 6-membered arene is monocyclic (e.g., benzene or benzo). The aryl may be monocyclic (phenyl) or bicyclic (e.g., a 9- to 12-membered fused bicyclic system).

[0034] The term “cyanoalkyl,” as used herein, means at least one $-CN$ group, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0035] The term “cyanofluoroalkyl,” as used herein, means at least one $-CN$ group, is appended to the parent molecular moiety through a fluoroalkyl group, as defined herein.

[0036] The term “cycloalkoxy,” as used herein, refers to a cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

[0037] The term “cycloalkyl” or “cycloalkane,” as used herein, refers to a saturated ring system containing all carbon atoms as ring members and zero double bonds. The term “cycloalkyl” is used herein to refer to a cycloalkane when present as a substituent. A cycloalkyl may be a monocyclic cycloalkyl (e.g., cyclopropyl), a fused bicyclic cycloalkyl (e.g., decahydronaphthalenyl), or a bridged cycloalkyl in which two non-adjacent atoms of a ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms (e.g., bicyclo[2.2.1]heptanyl). Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantyl, and bicyclo[1.1.1]pentanyl.

[0038] The term “cycloalkenyl” or “cycloalkene,” as used herein, means a non-aromatic monocyclic or multicyclic ring system containing all carbon atoms as ring members and at least

one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. The term “cycloalkenyl” is used herein to refer to a cycloalkene when present as a substituent. A cycloalkenyl may be a monocyclic cycloalkenyl (e.g., cyclopentenyl), a fused bicyclic cycloalkenyl (e.g., octahydronaphthalenyl), or a bridged cycloalkenyl in which two non-adjacent atoms of a ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms (e.g., bicyclo[2.2.1]heptenyl). Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl.

[0039] The term “carbocyclyl” means a “cycloalkyl” or a “cycloalkenyl.” The term “carbocycle” means a “cycloalkane” or a “cycloalkene.” The term “carbocyclyl” refers to a “carbocycle” when present as a substituent.

[0040] The term “fluoroalkyl,” as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by fluorine. Representative examples of fluoroalkyl include, but are not limited to, 2-fluoroethyl, 2,2,2-trifluoroethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, and trifluoropropyl such as 3,3,3-trifluoropropyl.

[0041] The term “fluoroalkylene,” as used herein, means an alkylene group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by fluorine. Representative examples of fluoroalkylene include, but are not limited to $-\text{CF}_2-$, $-\text{CH}_2\text{CF}_2-$, 1,2-difluoroethylene, 1,1,2,2-tetrafluoroethylene, 1,3,3,3-tetrafluoropropylene, 1,1,2,3,3-pentafluoropropylene, and perfluoropropylene such as 1,1,2,2,3,3-hexafluoropropylene.

[0042] The term “fluoroalkoxy,” as used herein, means at least one fluoroalkyl group, as defined herein, is appended to the parent molecular moiety through an oxygen atom. Representative examples of fluoroalkoxy include, but are not limited to, difluoromethoxy, trifluoromethoxy and 2,2,2-trifluoroethoxy.

[0043] The term “halogen” or “halo,” as used herein, means Cl, Br, I, or F.

[0044] The term “haloalkyl,” as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five, six, seven or eight hydrogen atoms are replaced by a halogen.

[0045] The term “haloalkoxy,” as used herein, means at least one haloalkyl group, as defined herein, is appended to the parent molecular moiety through an oxygen atom.

[0046] The term “halocycloalkyl,” as used herein, means a cycloalkyl group, as defined herein, in which one or more hydrogen atoms are replaced by a halogen.

[0047] The term “heteroalkyl,” as used herein, means an alkyl group, as defined herein, in which one or more of the carbon atoms has been replaced by a heteroatom selected from S, O, P and N. Representative examples of heteroalkyls include, but are not limited to, alkyl ethers, secondary and tertiary alkyl amines, amides, and alkyl sulfides.

[0048] The term “heteroaryl,” as used herein, refers to an aromatic monocyclic heteroatom-containing ring (monocyclic heteroaryl) or a bicyclic ring system containing at least one monocyclic heteroaromatic ring (bicyclic heteroaryl). The term “heteroaryl” is used herein to refer to a heteroarene when present as a substituent. The monocyclic heteroaryl are five or six membered rings containing at least one heteroatom independently selected from the group consisting of N, O and S (e.g. 1, 2, 3, or 4 heteroatoms independently selected from O, S, and N). The five membered aromatic monocyclic rings have two double bonds and the six membered aromatic monocyclic rings have three double bonds. The bicyclic heteroaryl is an 8- to 12-membered ring system and includes a fused bicyclic heteroaromatic ring system (i.e., 10π electron system) such as a monocyclic heteroaryl ring fused to a 6-membered arene (e.g., quinolin-4-yl, indol-1-yl), a monocyclic heteroaryl ring fused to a monocyclic heteroarene (e.g., naphthyridinyl), and a phenyl fused to a monocyclic heteroarene (e.g., quinolin-5-yl, indol-4-yl). A bicyclic heteroaryl/heteroarene group includes a 9-membered fused bicyclic heteroaromatic ring system having four double bonds and at least one heteroatom contributing a lone electron pair to a fully aromatic 10π electron system, such as ring systems with a nitrogen atom at the ring junction (e.g., imidazopyridine) or a benzoxadiazolyl. A bicyclic heteroaryl also includes a fused bicyclic ring system composed of one heteroaromatic ring and one non-aromatic ring such as a monocyclic heteroaryl ring fused to a monocyclic carbocyclic ring (e.g., 6,7-dihydro-5H-cyclopenta[b]pyridinyl), or a monocyclic heteroaryl ring fused to a monocyclic heterocycle (e.g., 2,3-dihydrofuro[3,2-b]pyridinyl). The bicyclic heteroaryl is attached to the parent molecular moiety at an aromatic ring atom. Other representative examples of heteroaryl include, but are not limited to, indolyl (e.g., indol-1-yl, indol-2-yl, indol-4-yl), pyridinyl (including pyridin-2-yl, pyridin-3-yl, pyridin-4-yl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl (e.g., pyrazol-4-yl), pyrrolyl, benzopyrazolyl, 1,2,3-triazolyl (e.g., triazol-4-yl), 1,3,4-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, imidazolyl, thiazolyl (e.g., thiazol-4-yl), isothiazolyl,

thienyl, benzimidazolyl (e.g., benzimidazol-5-yl), benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, furanyl, oxazolyl, isoxazolyl, purinyl, isoindolyl, quinoxaliny, indazolyl (e.g., indazol-4-yl, indazol-5-yl), quinazolinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, isoquinolinyl, quinolinyl, imidazo[1,2-*a*]pyridinyl (e.g., imidazo[1,2-*a*]pyridin-6-yl), naphthyridinyl, pyridoimidazolyl, thiazolo[5,4-*b*]pyridin-2-yl, and thiazolo[5,4-*d*]pyrimidin-2-yl.

[0049] The term “heterocycle” or “heterocyclic,” as used herein, means a monocyclic heterocycle, a bicyclic heterocycle, or a tricyclic heterocycle. The term “heterocyclyl” is used herein to refer to a heterocycle when present as a substituent. The monocyclic heterocycle is a three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S. The three- or four-membered ring contains zero or one double bond, and one heteroatom selected from the group consisting of O, N, and S. The five-membered ring contains zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The six-membered ring contains zero, one or two double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. The seven- and eight-membered rings contains zero, one, two, or three double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Representative examples of monocyclic heterocyclyls include, but are not limited to, azetidiny, azepany, aziridiny, diazepany, 1,3-dioxany, 1,3-dioxolany, 1,3-dithiolany, 1,3-dithianyl, imidazoliny, imidazolidiny, isothiazoliny, isothiazolidiny, isoxazoliny, isoxazolidiny, morpholiny, 2-oxo-3-piperidiny, 2-oxoazepan-3-yl, oxadiazoliny, oxadiazolidiny, oxazoliny, oxazolidiny, oxetany, oxepany, oxocany, piperaziny, piperidiny, pyranly, pyrazoliny, pyrazolidiny, pyrroliny, pyrrolidiny, tetrahydrofurany, tetrahydropyranly, tetrahydropyridiny, tetrahydrothienyl, thiadiazoliny, thiadiazolidiny, 1,2-thiazinany, 1,3-thiazinany, thiazoliny, thiazolidiny, thiomorpholiny, 1,1-dioxidothiomorpholiny (thiomorpholine sulfone), thiopyranly, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to a 6-membered arene, or a monocyclic heterocycle fused to a monocyclic cycloalkane, or a monocyclic heterocycle fused to a monocyclic cycloalkene, or a monocyclic heterocycle fused to a monocyclic heterocycle, or a monocyclic heterocycle fused to a monocyclic heteroarene, or a spiro heterocycle group, or a bridged monocyclic heterocycle ring system in which two non-adjacent atoms of the ring are

linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. The bicyclic heterocyclyl is attached to the parent molecular moiety at a non-aromatic ring atom (e.g., indolin-1-yl). Representative examples of bicyclic heterocyclyls include, but are not limited to, chroman-4-yl, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzothien-2-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, 2-azaspiro[3.3]heptan-2-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, azabicyclo[2.2.1]heptyl (including 2-azabicyclo[2.2.1]hept-2-yl), azabicyclo[3.1.0]hexanyl (including 3-azabicyclo[3.1.0]hexan-3-yl), 2,3-dihydro-1*H*-indol-1-yl, isoindolin-2-yl, octahydrocyclopenta[*c*]pyrrolyl, octahydropyrrolopyridinyl, tetrahydroisoquinolinyl, 7-oxabicyclo[2.2.1]heptanyl, hexahydro-2*H*-cyclopenta[*b*]furanyl, 2-oxaspiro[3.3]heptanyl, 3-oxaspiro[5.5]undecanyl, 6-oxaspiro[2.5]octan-1-yl, and 3-oxabicyclo[3.1.0]hexan-6-yl. Tricyclic heterocycles are exemplified by a bicyclic heterocycle fused to a 6-membered arene, or a bicyclic heterocycle fused to a monocyclic cycloalkane, or a bicyclic heterocycle fused to a monocyclic cycloalkene, or a bicyclic heterocycle fused to a monocyclic heterocycle, or a bicyclic heterocycle in which two non-adjacent atoms of the bicyclic ring are linked by an alkylene bridge of 1, 2, 3, or 4 carbon atoms, or an alkenylene bridge of two, three, or four carbon atoms. Examples of tricyclic heterocycles include, but are not limited to, octahydro-2,5-epoxypentalene, hexahydro-2*H*-2,5-methanocyclopenta[*b*]furan, hexahydro-1*H*-1,4-methanocyclopenta[*c*]furan, aza-adamantane (1-azatricyclo[3.3.1.1^{3,7}]decane), and oxa-adamantane (2-oxatricyclo[3.3.1.1^{3,7}]decane). The monocyclic, bicyclic, and tricyclic heterocyclyls are connected to the parent molecular moiety at a non-aromatic ring atom.

[0050] The term “hydroxyl” or “hydroxy,” as used herein, means an -OH group.

[0051] The term “hydroxyalkyl,” as used herein, means at least one -OH group, is appended to the parent molecular moiety through an alkylene group, as defined herein.

[0052] The term “hydroxyfluoroalkyl,” as used herein, means at least one -OH group, is appended to the parent molecular moiety through a fluoroalkyl group, as defined herein.

[0053] Terms such as “alkyl,” “cycloalkyl,” “alkylene,” etc. may be preceded by a designation indicating the number of atoms present in the group in a particular instance (e.g., “C₁₋₄alkyl,” “C₃₋₆cycloalkyl,” “C₁₋₄alkylene”). These designations are used as generally understood by those skilled in the art. For example, the representation “C” followed by a subscripted number indicates the number of carbon atoms present in the group that follows.

Thus, "C₃alkyl" is an alkyl group with three carbon atoms (i.e., n-propyl, isopropyl). Where a range is given, as in "C₁₋₄," the members of the group that follows may have any number of carbon atoms falling within the recited range. A "C₁₋₄alkyl," for example, is an alkyl group having from 1 to 4 carbon atoms, however arranged (i.e., straight chain or branched).

[0054] The terms "parent molecule" or "parent molecular moiety" refer to the entire portion of a molecule to which a substituent is attached, i.e., the remainder of the molecule.

[0055] The term "sulfonamide," as used herein, means -S(O)₂NR^z- or -NR^zS(O)-, wherein R^z may be hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkenyl, or heteroalkyl.

[0056] The term "substituents" refers to a group "substituted" on a group such as an alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heteroalkyl, or heterocycle group, at any atom of that group. Any atom can be substituted.

[0057] The term "substituted" refers to a group that may be further substituted with one or more non-hydrogen substituent groups. Substituent groups include, but are not limited to, halogen, =O (oxo), =S (thioxo), cyano, nitro, fluoroalkyl, alkoxyfluoroalkyl, fluoroalkoxy, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, heteroalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocycle, cycloalkylalkyl, heteroarylalkyl, arylalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkylene, aryloxy, phenoxy, benzyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, -COOH, ketone, amide, carbamate, and acyl. In some embodiments, a group is optionally substituted. In some embodiments, a group is optionally substituted with 1, 2, 3, 4, or 5 substituents. In some embodiments, an aryl, heteroaryl, cycloalkyl, or heterocycle is optionally substituted with 1, 2, 3, 4, or 5 substituents. In some embodiments, an aryl, heteroaryl, cycloalkyl, or heterocycle may be independently unsubstituted or substituted with 1, 2, or 3 substituents.

[0058] For compounds described herein, groups and substituents thereof may be selected in accordance with permitted valence of the atoms and the substituents, such that the selections and substitutions result in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[0059] The term "allosteric site" as used herein refers to a ligand binding site that is topographically distinct from the orthosteric binding site.

[0060] The term “modulator” as used herein refers to a molecular entity (e.g., but not limited to, a ligand and a disclosed compound) that modulates the activity of the target receptor protein.

[0061] The term “ligand” as used herein refers to a natural or synthetic molecular entity that is capable of associating or binding to a receptor to form a complex and mediate, prevent or modify a biological effect. Thus, the term “ligand” encompasses allosteric modulators, inhibitors, activators, agonists, antagonists, natural substrates and analogs of natural substrates.

[0062] The terms “natural ligand” and “endogenous ligand” as used herein are used interchangeably, and refer to a naturally occurring ligand, found in nature, which binds to a receptor.

[0063] The term “orthosteric site” as used herein refers to the primary binding site on a receptor that is recognized by the endogenous ligand or agonist for that receptor. For example, the orthosteric site in the mAChR M₄ receptor is the site that acetylcholine binds.

[0064] The term “mAChR M₄ receptor positive allosteric modulator” as used herein refers to any exogenously administered compound or agent that directly or indirectly augments the activity of the mAChR M₄ receptor in the presence or in the absence of acetylcholine, or another agonist, in an animal, in particular a mammal, for example a human. For example, a mAChR M₄ receptor positive allosteric modulator can increase the activity of the mAChR M₄ receptor in a cell in the presence of extracellular acetylcholine. The cell can be Chinese hamster ovary (CHO-K1) cells transfected with human mAChR M₄. The cell can be Chinese hamster ovary (CHO-K1) cells transfected with rat mAChR M₄ receptor. The cell can be Chinese hamster ovary (CHO-K1) cells transfected with a mammalian mAChR M₄. The term “mAChR M₄ receptor positive allosteric modulator” includes a compound that is a “mAChR M₄ receptor allosteric potentiator” or a “mAChR M₄ receptor allosteric agonist,” as well as a compound that has mixed activity comprising pharmacology of both an “mAChR M₄ receptor allosteric potentiator” and an “mAChR M₄ receptor allosteric agonist.” The term “mAChR M₄ receptor positive allosteric modulator” also includes a compound that is a “mAChR M₄ receptor allosteric enhancer.”

[0065] The term “mAChR M₄ receptor allosteric potentiator” as used herein refers to any exogenously administered compound or agent that directly or indirectly augments the response produced by the endogenous ligand (such as acetylcholine) when the endogenous ligand binds to the orthosteric site of the mAChR M₄ receptor in an animal, in particular a mammal, for example a human. The mAChR M₄ receptor allosteric potentiator binds to a site other than the orthosteric

site, that is, an allosteric site, and positively augments the response of the receptor to an agonist or the endogenous ligand. In some embodiments, an allosteric potentiator does not induce desensitization of the receptor, activity of a compound as an mAChR M₄ receptor allosteric potentiator provides advantages over the use of a pure mAChR M₄ receptor orthosteric agonist. Such advantages can include, for example, increased safety margin, higher tolerability, diminished potential for abuse, and reduced toxicity.

[0066] The term “mAChR M₄ receptor allosteric enhancer” as used herein refers to any exogenously administered compound or agent that directly or indirectly augments the response produced by the endogenous ligand (such as acetylcholine) in an animal, in particular a mammal, for example a human. In some embodiments, the allosteric enhancer increases the affinity of the natural ligand or agonist for the orthosteric site. In some embodiments, an allosteric enhancer increases the agonist efficacy. The mAChR M₄ receptor allosteric enhancer binds to a site other than the orthosteric site, that is, an allosteric site, and positively augments the response of the receptor to an agonist or the endogenous ligand. An allosteric enhancer has no effect on the receptor by itself and requires the presence of an agonist or the natural ligand to realize a receptor effect.

[0067] The term “mAChR M₄ receptor allosteric agonist” as used herein refers to any exogenously administered compound or agent that directly activates the activity of the mAChR M₄ receptor in the absence of the endogenous ligand (such as acetylcholine) in an animal, in particular a mammal, for example a human. The mAChR M₄ receptor allosteric agonist binds to a site that is distinct from the orthosteric acetylcholine site of the mAChR M₄ receptor. Because it does not require the presence of the endogenous ligand, activity of a compound as an mAChR M₄ receptor allosteric agonist provides advantages if cholinergic tone at a given synapse is low.

[0068] The term “mAChR M₄ receptor neutral allosteric ligand” as used herein refers to any exogenously administered compound or agent that binds to an allosteric site without affecting the binding or function of agonists or the natural ligand at the orthosteric site in an animal, in particular a mammal, for example a human. However, a neutral allosteric ligand can block the action of other allosteric modulators that act via the same site.

[0069] For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9,

the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the number 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

[0070] Abbreviations:

AcOH is acetic acid;

aq is aqueous;

atm is atmosphere(s);

BINAP is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;

Boc is *tert*-butoxycarbonyl;

Boc₂O is di-*tert*-butyl dicarbonate;

B₂pin₂ is bis(pinacolato)diboron;

BrettPhos is 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl;

BrettPhos Pd G3 is [(2-di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'- triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate;

Bu is butyl;

t-BuOH is *tert*-butanol;

CDI is 1,1'-carbonyldiimidazole;

CD₂O is deuterated formaldehyde;

Celite® is diatomaceous earth;

CSA is (1*S*,4*R*)-10-camphorsulfonic acid;

DCE is 1,2-dichloroethane;

DCM is dichloromethane;

DEA is diethylamine;

DMAP is 4-dimethylaminopyridine;

DMF is *N,N*-dimethylformamide;

DMP or Dess-Martin periodinane is 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one;

DIAD is diisopropyl azodicarboxylate;

DIPEA or DIEA is diisopropylethylamine;

DMSO is dimethyl sulfoxide;

Dowtherm™ A is a eutectic mixture of 26.5% diphenyl + 73.5% diphenyl oxide;

DtBAD is di-*tert*-butyl-azodicarboxylate;

eq or eq. is equivalent(s);

EtOAc is ethyl acetate;

(4,4'-dtbbpy)NiCl₂ is 4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine] nickel (II) dichloride;

Et₂O is diethyl ether;

EtOH is ethanol;

h or hr is hour(s);

Hex is hexane(s);

HMPA is hexamethylphosphoramide;

IPA is isopropyl alcohol;

KOAc is potassium acetate;

LAH is lithium aluminum hydride;

LDA is lithium diisopropylamide;

LiHMDS/LHMDS is lithium bis(trimethylsilyl)amide;

*m*CPBA is meta-chloroperoxy benzoic acid;

MeCN or ACN is acetonitrile;

MeI is iodomethane/methyl iodide;

MeOD is CD₃OD (methanol-d₄);

MeOH is methanol;

min is minute(s);

NaOAc is sodium acetate;

NaOtBu is sodium tert-butoxide;

NaOMe is sodium methoxide;

NBS is *N*-bromosuccinimide;

NCS is *N*-chlorosuccinimide;

NH₄OAc is ammonium acetate;

NMO is 4-methylmorpholine N-oxide;

NMP is *N*-methyl-2-pyrrolidone;

[Pd(allyl)(tBuBrettPhos)]OTf is trifluoromethanesulfonate allyl[(2-Di-tert-butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II);

Pd₂(dba)₃ is tris(dibenzylideneacetone)dipalladium(0);

Pd(dppf)Cl₂ is [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II);

Pd(OAc)₂ is palladium(II)acetate;
Pd(PPh₃)₄ is tetrakis(triphenylphosphine)palladium(0);
PPA is polyphosphoric acid;
PPh₃ is triphenylphosphine;
PPTS is pyridinium *p*-toluenesulfonate;
rt is room temperature;
sat. is saturated;
sec is second(s);
SCX cartridge or HF SCX cartridge is a strong cation exchanger cartridge (i.e. Agilent part# 14256027);
SFC is supercritical fluid chromatography;
TBAC or TBACl is tetrabutylammonium chloride;
t-BuXPhos is 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl;
t-BuXPhos-Pd-G1 is [2-(Di-*tert*-butylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) chloride;
TCICA is trichloroisocyanuric acid;
TEA or Et₃N is triethylamine;
TFA is trifluoroacetic acid;
THF is tetrahydrofuran;
TMB is trimethylboroxine;
TosCl is *para*-toluenesulfonyl chloride;
tosyl is *para*-toluenesulfonyl;
Xantphos is 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

2. Compounds

[0071] In one aspect, the invention provides compounds of formula (I), wherein R¹, R², R³, R⁸, G¹, and n are as defined herein.

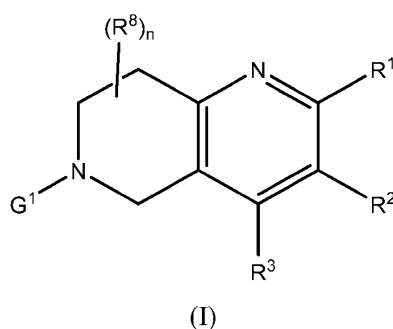
[0072] Unsubstituted or substituted rings (i.e., optionally substituted) such as aryl, heteroaryl, etc. are composed of both a ring system and the ring system's optional substituents. Accordingly, the ring system may be defined independently of its substituents, such that redefining only the ring system leaves any previous optional substituents present. For example, a 5- to 12-membered heteroaryl with optional substituents may be further defined by specifying

the *ring system* of the 5- to 12-membered heteroaryl is a 5- to 6-membered heteroaryl (i.e., 5- to 6-membered heteroaryl ring system), in which case the optional substituents of the 5- to 12-membered heteroaryl are still present on the 5- to 6-membered heteroaryl, unless otherwise expressly indicated.

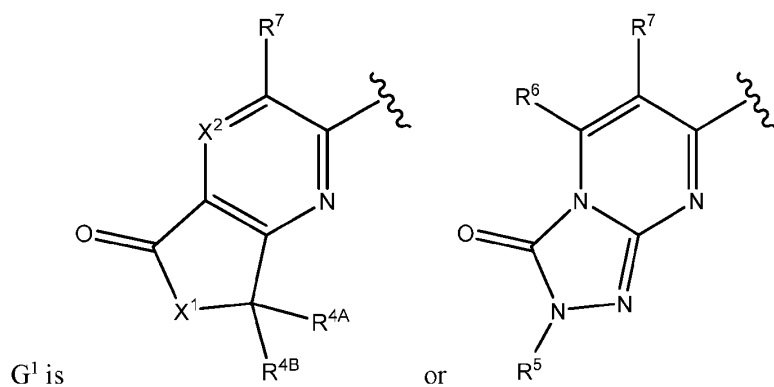
[0073] Where heterocyclic and heteroaromatic ring systems are defined to "contain" or as "containing" specified heteroatoms (e.g., 1-3 heteroatoms independently selected from the group consisting of O, N, and S), any ring atoms of the heterocyclic and heteroaromatic ring systems that are not one of the specified heteroatoms are carbon atoms.

[0074] In the following, numbered embodiments of the invention are disclosed. The first embodiment is denoted E1, subsequent embodiments are denoted E1.1, E1.2, E2, E2.1, E3, E4, E4.1, E4.2, E4.3, E4.4, E4.5, E4.6, E4.7, E5, E5.1, and so forth.

[0075] E1. A compound of formula (I), or a pharmaceutically acceptable salt thereof,



wherein:



X¹ is NR⁵, O, or CR^{5A}R^{5B},

X² is CR⁶ or N;

- R^1 and R^3 are each independently hydrogen, halogen, cyano, C_{1-4} alkyl, C_{1-4} fluoroalkyl, $-OC_{1-4}$ alkyl, or $-OC_{1-4}$ fluoroalkyl;
- R^2 is G^2 , $-NR^bR^c$, C_{1-6} haloalkyl, halogen, cyano, NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, $-OR^b$, $-NR^cC(O)R^b$, $-NR^cSO_2R^a$, $-N=S(O)(R^a)_2$, $-P(O)(R^a)_2$, $-C_{1-3}$ alkylene- G^2 , $-C_{2-4}$ alkenylene- G^2 , or hydrogen;
- R^a , at each occurrence, is independently C_{1-6} alkyl, C_{1-6} haloalkyl, G^2 , or $-C_{1-3}$ alkylene- G^2 ; wherein optionally, the two R^a of $-N=S(O)(R^a)_2$ or $-P(O)(R^a)_2$ join together as a straight alkylene chain to form a 5- to 7-membered heterocyclic ring;
- R^b and R^c are independently hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, G^2 , or $-C_{1-3}$ alkylene- G^2 ;
- G^2 , at each occurrence, is independently a 5- to 12-membered heteroaryl, a 6- to 12-membered aryl, a 4- to 12-membered heterocyclyl, or a 3- to 12-membered carbocyclyl, wherein the heteroaryl and heterocyclyl each contain 1-4 heteroatoms independently selected from the group consisting of O, N, and S, and G^2 is optionally substituted with a first substituent selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, oxo, $-OR^x$, $-N(R^x)_2$, $-SR^x$, $-SO_2R^x$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, $-C_{1-6}$ alkylene- OR^x , $-C_{1-6}$ alkylene- $N(R^x)_2$, G^{2a} , and $-C_{1-3}$ alkylene- G^{2a} , and optionally further substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, and $-OR^x$;
- R^x , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-3}$ alkylene- C_{3-6} cycloalkyl, phenyl, or $-C_{1-3}$ alkylene-phenyl, wherein each cycloalkyl or phenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;
- G^{2a} is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a 3- to 8-membered carbocyclyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^{2a} , at each occurrence, is independently optionally substituted with 1-5 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, $-C_{1-6}$ alkylene-OH, oxo, OH, $-OC_{1-4}$ alkyl, $-OC_{1-4}$ haloalkyl, C_{3-4} cycloalkyl, and $-C_{1-3}$ alkylene- C_{3-4} cycloalkyl;
- R^{4A} and R^{4B} are independently hydrogen, C_{1-4} alkyl, C_{3-4} cycloalkyl, or $-C_{1-3}$ alkylene-OH;

R^5 is hydrogen, C_{1-6} alkyl, C_{1-6} fluoroalkyl, $-C_{1-6}$ alkylene- R^y , $-C_{1-6}$ fluoroalkylene- R^y , G^5 , or $-C_{1-3}$ alkylene- G^5 ;

R^{5A} and R^{5B} are independently hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkyl, or $-C_{1-4}$ alkylene-OH;

R^y is $-OR^{5a}$, $-N(R^{5a})_2$, $-C(O)R^{5a}$, $-C(O)OR^{5a}$, or $-C(O)N(R^{5a})_2$;

R^{5a} , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, G^5 , or $-C_{1-3}$ alkylene- G^5 ;

G^5 is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a C_{3-8} cycloalkyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^5 is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-2} fluoroalkyl, $-OC_{1-4}$ alkyl, OH, and oxo;

alternatively, R^{4A} and R^{4B} together with the carbon to which they attach form a C_{3-6} cycloalkyl; or R^{4B} and R^5 together with the atoms to which they attach form a 5- to 7-membered heterocycle optionally containing one additional heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur;

R^6 is hydrogen, halogen, cyano, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{2-4} alkenyl, $-OR^{6a}$, $-N(R^{6a})_2$, $-C_{1-3}$ alkylene- OR^{6a} , or C_{3-6} cycloalkyl;

R^{6a} , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-4} cycloalkyl, or $-C_{1-3}$ alkylene- C_{3-4} cycloalkyl;

wherein alternatively, two R^{6a} , together with the nitrogen to which they attach form a 4- to 8-membered heterocyclic ring containing the nitrogen attached to R^{6a} and optionally 1-2 additional heteroatoms that are independently O, N, or S, the heterocyclic ring being optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C_{1-2} alkyl, and C_{1-2} fluoroalkyl;

R^7 is C_{1-4} alkyl, hydrogen, halogen, cyano, C_{1-4} fluoroalkyl, $-OR^{7a}$, $-C_{1-3}$ alkylene- OR^{7a} , or G^7 ;

alternatively, R^6 and R^7 , together with the atoms to which they are attached, form a 5- to 7-membered heterocycle containing 1 heteroatom or a 5- to 7-membered carbocycle, wherein the heteroatoms are independently selected from the group consisting of N, O, and S, and the heterocycle and carbocycle are optionally substituted with 1-4 substituents independently selected from the group consisting of C_{1-4} alkyl, halogen, $-OC_{1-4}$ alkyl, C_{1-4} fluoroalkyl, C_{3-4} cycloalkyl, and C_{1-2} alkylene- C_{3-4} cycloalkyl;

R^{7a} is hydrogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-4} cycloalkyl, or $-C_{1-3}$ alkylene- C_{3-4} cycloalkyl;
 G^7 is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a C_{3-6} cycloalkyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^5 is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-2} fluoroalkyl, $-OC_{1-4}$ alkyl, OH, and oxo;
 R^8 , at each occurrence, is independently halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, or C_{3-4} cycloalkyl;
 and
 n is 0, 1, 2, 3, or 4;

wherein each cycloalkyl at R^6 , R^{6a} , R^7 , R^{7a} , and R^8 is unsubstituted or substituted with 1-4 substituents independently selected from C_{1-4} alkyl (e.g., methyl) and halogen (e.g., fluoro).

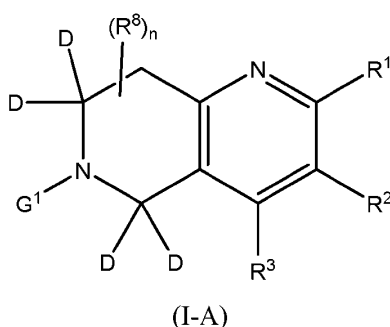
[0076] E1.1. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R^2 is G^2 , $-NR^bR^c$, C_{1-6} haloalkyl, halogen, cyano, NO_2 , C_{1-6} alkyl, $-OR^b$, $-NR^cC(O)R^b$, $-NR^cSO_2R^a$, $-N=S(O)(R^a)_2$, $-P(O)(R^a)_2$, $-C_{1-3}$ alkylene- G^2 , or hydrogen;
 G^2 , at each occurrence, is independently a 5- to 12-membered heteroaryl, a 6- to 12-membered aryl, a 4- to 12-membered heterocyclyl, or a 3- to 12-membered carbocyclyl, wherein the heteroaryl and heterocyclyl each contain 1-4 heteroatoms independently selected from the group consisting of O, N, and S, and G^2 is optionally substituted with a first substituent selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, oxo, $-OR^x$, $-N(R^x)_2$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, $-C_{1-6}$ alkylene- OR^x , $-C_{1-6}$ alkylene- $N(R^x)_2$, G^{2a} , and $-C_{1-3}$ alkylene- G^{2a} , and optionally further substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, and $-OR^x$;
 R^5 is hydrogen, C_{1-6} alkyl, C_{1-6} fluoroalkyl, $-C_{1-6}$ alkylene- R^y , G^5 , or $-C_{1-3}$ alkylene- G^5 ;
 R^{5a} , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{3-4} cycloalkyl, or $-C_{1-3}$ alkylene- C_{3-4} cycloalkyl;
 G^5 is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a C_{3-6} cycloalkyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^5 is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-2} fluoroalkyl, $-OC_{1-4}$ alkyl, OH, and oxo;

R^6 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, $-OR^{6a}$, $-N(R^{6a})_2$, $-C_{1-3}$ alkylene- OR^{6a} , or C_{3-6} cycloalkyl; and

R^7 is C_{1-4} alkyl, hydrogen, halogen, cyano, C_{1-4} fluoroalkyl, $-OR^{7a}$, $-C_{1-3}$ alkylene- OR^{7a} , or C_{3-6} cycloalkyl.

[0077] E1.2. The compound of E1 or E1.1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-A):



and n is 0, 1, or 2.

[0078] E2. The compound of any of E1, E1.1, or E1.2, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen or C_{1-4} alkyl.

[0079] E2.1. The compound of E2, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

[0080] E3. The compound of any of E1-E2.1, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

[0081] E4. The compound of any of E1-E3, or a pharmaceutically acceptable salt thereof, wherein R^2 is G^2 , $-NR^bR^c$, C_{1-6} haloalkyl, C_{2-6} alkenyl, cyano, hydrogen, or $-C_{2-4}$ alkenylene- G^2 .

[0082] E4.1. The compound of E4, or a pharmaceutically acceptable salt thereof, wherein R^2 is G^2 , $-NR^bR^c$, or C_{1-6} haloalkyl.

[0083] E4.2. The compound of E4, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen.

[0084] E4.3. The compound of E4, or a pharmaceutically acceptable salt thereof, wherein R^2 is cyano.

[0085] E4.4. The compound of E4, or a pharmaceutically acceptable salt thereof, wherein R^2 is C_{2-6} alkenyl

[0086] E4.5. The compound of E4.4, or a pharmaceutically acceptable salt thereof,

wherein R^2 is 

[0087] E4.6. The compound of E4, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-C_{2-4}alkenylene-G^2$.

[0088] E4.7. The compound of E4.6, or a pharmaceutically acceptable salt thereof,

wherein R^2 is 

[0089] E5. The compound of E4 or E4.1, or a pharmaceutically acceptable salt thereof, wherein R^2 is $C_{1-6}haloalkyl$.

[0090] E5.1. The compound of E5, or a pharmaceutically acceptable salt thereof, wherein R^2 is CF_3 .

[0091] E6. The compound of E4 or E4.1, or a pharmaceutically acceptable salt thereof, wherein R^2 is G^2 .

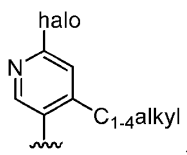
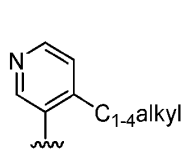
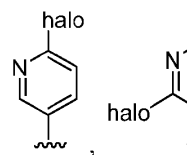
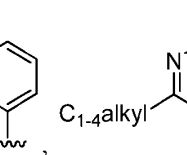
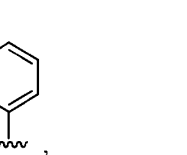
[0092] E7. The compound of any of E1-E4.1, E4.6, E4.7, or E6, or a pharmaceutically acceptable salt thereof, wherein G^2 is the optionally substituted 5- to 12-membered heteroaryl.

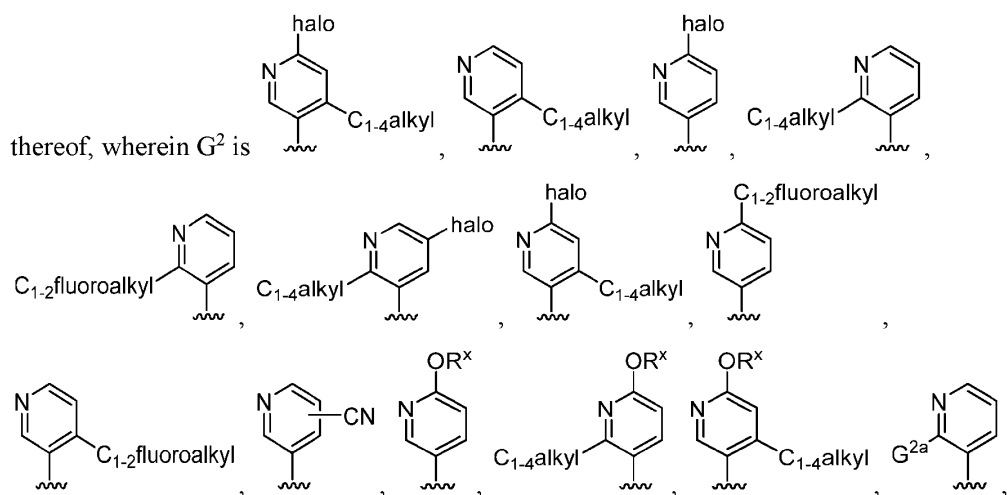
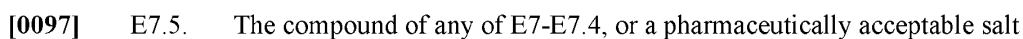
[0093] E7.1. The compound of any of E1-E4.1, E4.6, E4.7, or E6-E7, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 12-membered heteroaryl at G^2 is a 5- to 6- membered heteroaryl containing 1-3 heteroatoms independently selected from the group consisting of O, N, and S.

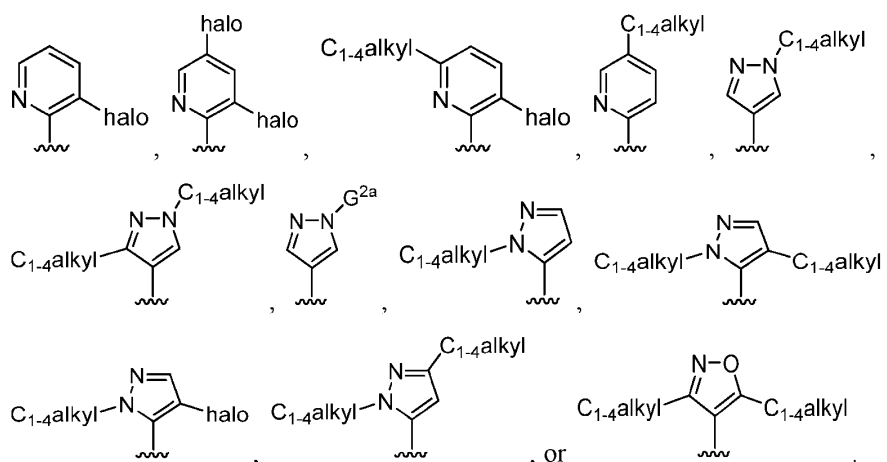
[0094] E7.2. The compound of E7.1, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 6-membered heteroaryl at G^2 is pyridinyl, pyrazolyl, or isoxazolyl.

[0095] E7.3. The compound of E7.2, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 6-membered heteroaryl at G^2 is pyridin-2-yl, pyridin-3-yl, pyrazol-4-yl, pyrazol-5-yl, or isoxazol-4-yl.

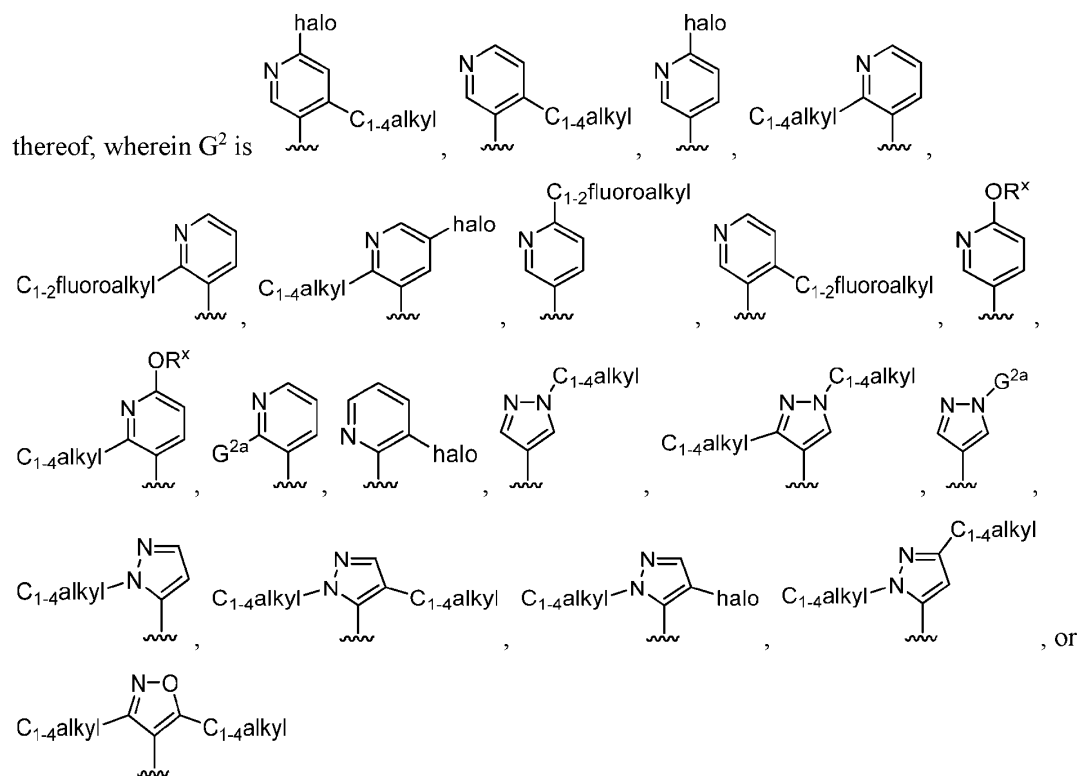
[0096] E7.4. The compound of any of E7-E7.3, or a pharmaceutically acceptable salt

thereof, wherein G^2 is , , , , ,

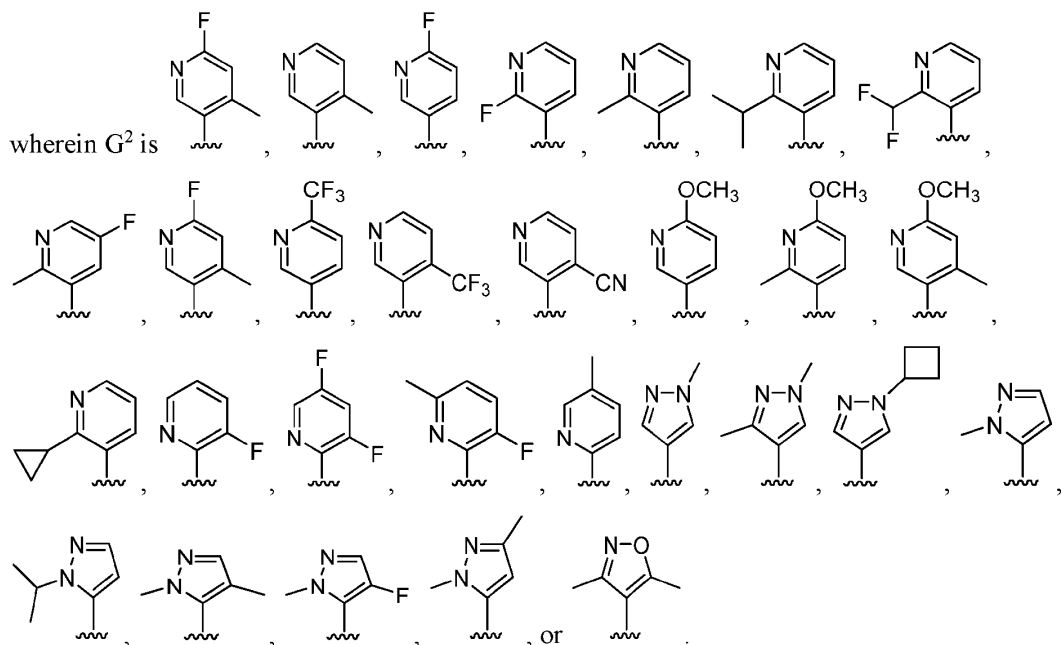




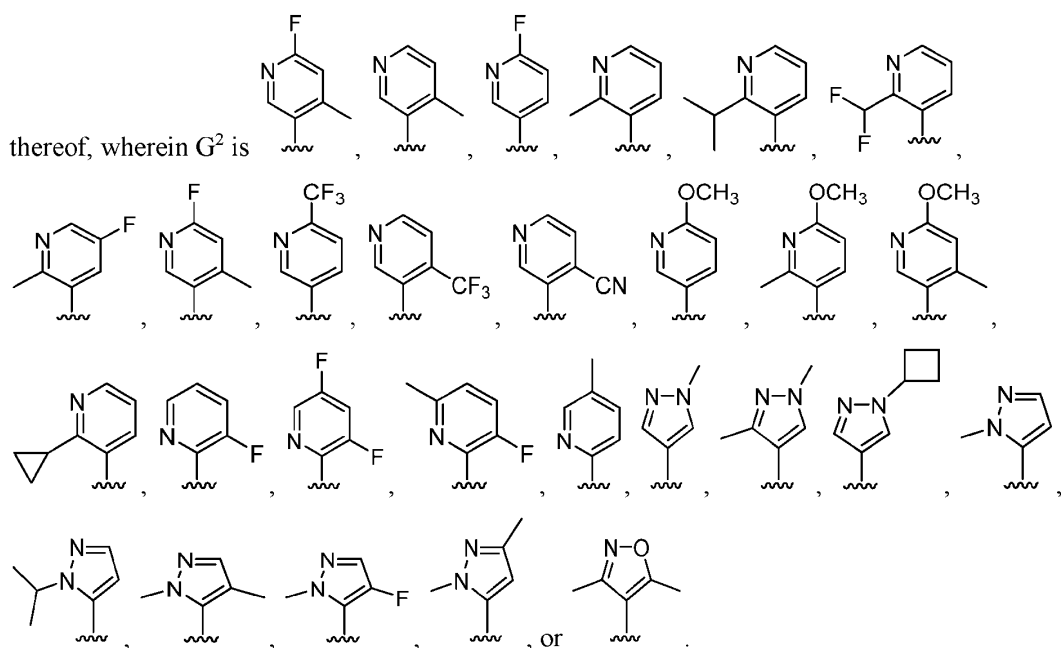
[0098] E7.6. The compound of any of E7-E7.5, or a pharmaceutically acceptable salt



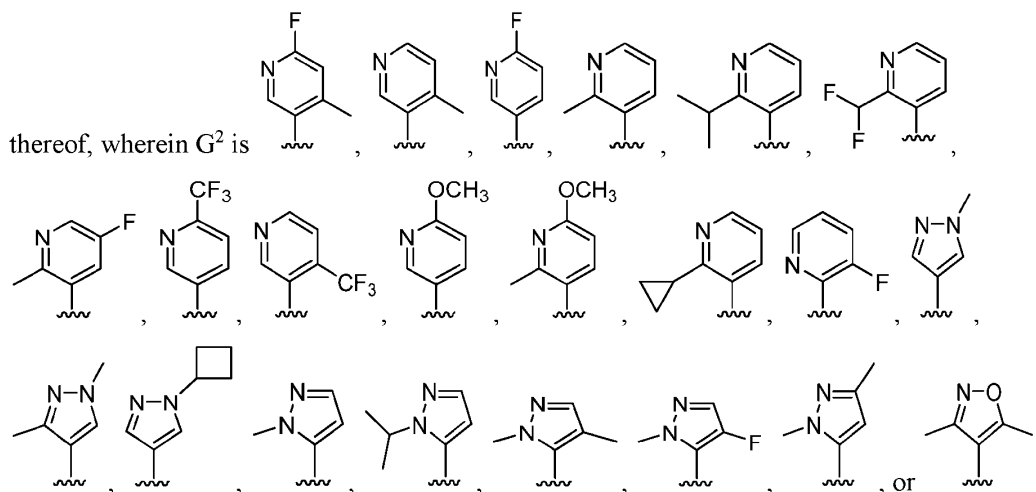
[0099] E7.7. The compound of E7.4, or a pharmaceutically acceptable salt thereof,



[00100] E7.8. The compound of E7.5 or E7.7, or a pharmaceutically acceptable salt thereof, wherein G^2 is



[00101] E7.9. The compound of E7.6 or E7.8, or a pharmaceutically acceptable salt thereof, wherein G^2 is



[00102] E7.10. The compound of any of E1-E4.1, E4.6, E4.7, or E6-E7, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 12-membered heteroaryl at G^2 is a 9- to 10- membered heteroaryl containing 1-3 heteroatoms independently selected from the group consisting of O, N, and S.

[00103] E7.11. The compound of E7.10, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 9- to 10-membered heteroaryl at G^2 is quinolinyl, isoquinolinyl, or imidazopyridinyl.

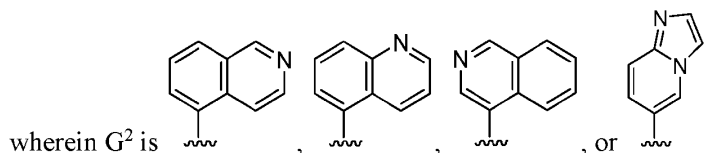
[00104] E7.12. The compound of E7.10 or E7.11, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 9- to 10-membered heteroaryl at G^2 is isoquinolinyl or imidazopyridinyl.

[00105] E7.13. The compound of E7.11, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 9- to 10-membered heteroaryl at G^2 is quinolin-5-yl, isoquinolin-4-yl, isoquinolin-5-yl, or imidazo[1,2-a]pyridin-6-yl.

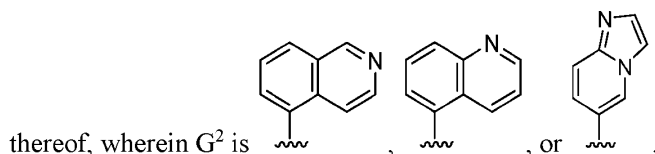
[00106] E7.14. The compound of E7.13, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 9- to 10-membered heteroaryl at G^2 is quinolin-5-yl, isoquinolin-5-yl, or imidazo[1,2-a]pyridin-6-yl.

[00107] E7.15. The compound of E7.12 or E7.14, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 9- to 10-membered heteroaryl at G^2 is isoquinolin-5-yl or imidazo[1,2-a]pyridin-6-yl.

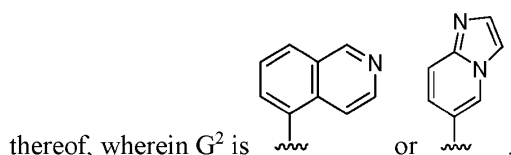
[00108] E7.16. The compound of E7.13, or a pharmaceutically acceptable salt thereof,



[00109] E7.17. The compound of E7.14 or E7.16, or a pharmaceutically acceptable salt thereof,



[00110] E7.18. The compound of E7.15 or E7.17, or a pharmaceutically acceptable salt thereof,



[00111] E7.19. The compound of any of E1-E4.1, E4.6, E4.7, E6-E7.3 or E7.10-E7.15, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with a first substituent selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} fluoroalkyl, $-OR^x$, and G^{2a} , and optionally further substituted with 1-3 substituents independently selected from the group consisting of halogen and C_{1-4} alkyl.

[00112] E7.20. The compound of E7.19, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with a first substituent selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, $-OR^x$, and G^{2a} , and optionally further substituted with 1-3 substituents independently selected from the group consisting of halogen and C_{1-4} alkyl.

[00113] E7.21. The compound of E7.19, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with a first substituent selected from the group consisting of fluoro, cyano, methyl, isopropyl, CF_3 , CHF_2 , $-OR^x$, and G^{2a} , and optionally further substituted with 1-3 substituents independently selected from the group consisting of fluoro and methyl.

[00114] E7.22. The compound of E7.20 or E7.21, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with a first substituent selected from the group consisting of fluoro, methyl, isopropyl, CF_3 , CHF_2 , $-OR^x$, and G^{2a} , and optionally further

substituted with 1-3 substituents independently selected from the group consisting of fluoro and methyl.

[00115] E7.23. The compound of any of E1-E4.1, E4.6, E4.7, E6-E7.5, E7.10-E7.15, or E7.19-E7.22, or a pharmaceutically acceptable salt thereof, wherein R^x , at each occurrence, is independently selected from the group consisting of C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{3-4} cycloalkyl, $-CH_2-C_{3-4}$ cycloalkyl, and $-CH_2$ -phenyl.

[00116] E7.24. The compound of E7.23, or a pharmaceutically acceptable salt thereof, wherein R^x is C_{1-4} alkyl.

[00117] E7.25. The compound of E7.24, or a pharmaceutically acceptable salt thereof, wherein R^x is methyl.

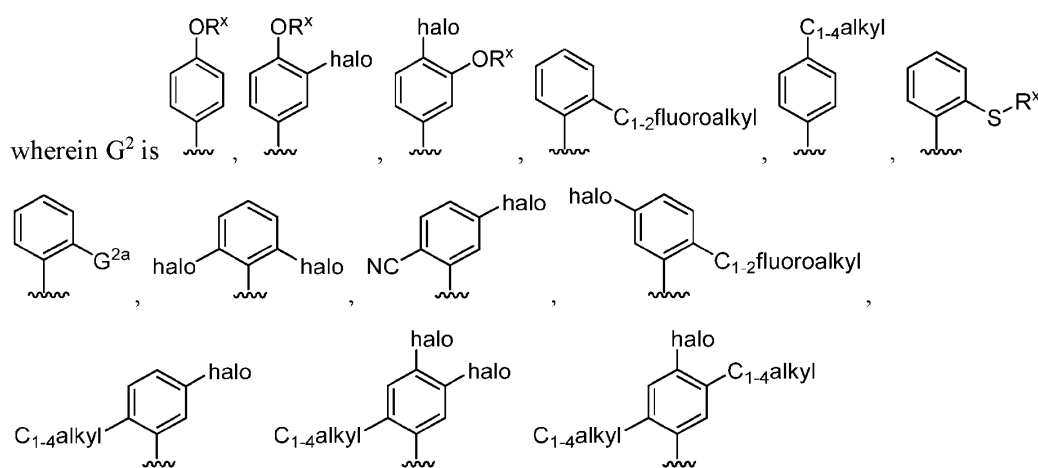
[00118] E7.26. The compound of any of E1-E4.1, E4.6, E4.7, E6-E7.5, E7.10-E7.15, or E7.19-E7.25, or a pharmaceutically acceptable salt thereof, wherein G^{2a} is C_{3-6} cycloalkyl.

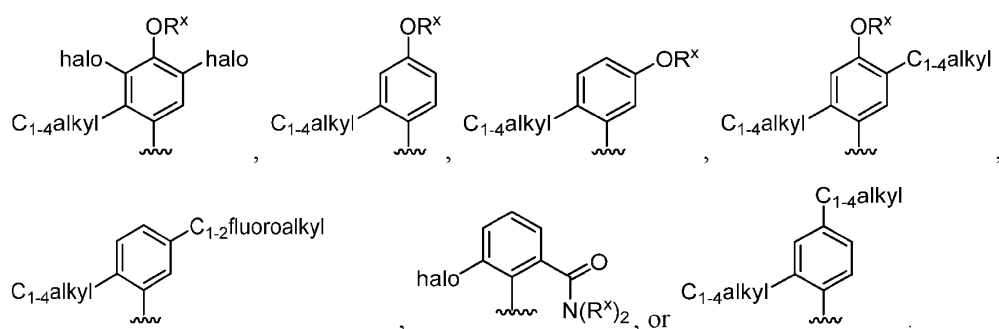
[00119] E7.27. The compound of E7.26, or a pharmaceutically acceptable salt thereof, wherein G^{2a} is cyclopropyl or cyclobutyl.

[00120] E8. The compound of any of E1-E4.1, E4.6, E4.7, or E6, or a pharmaceutically acceptable salt thereof, wherein G^2 is the optionally substituted 6- to 12-membered aryl.

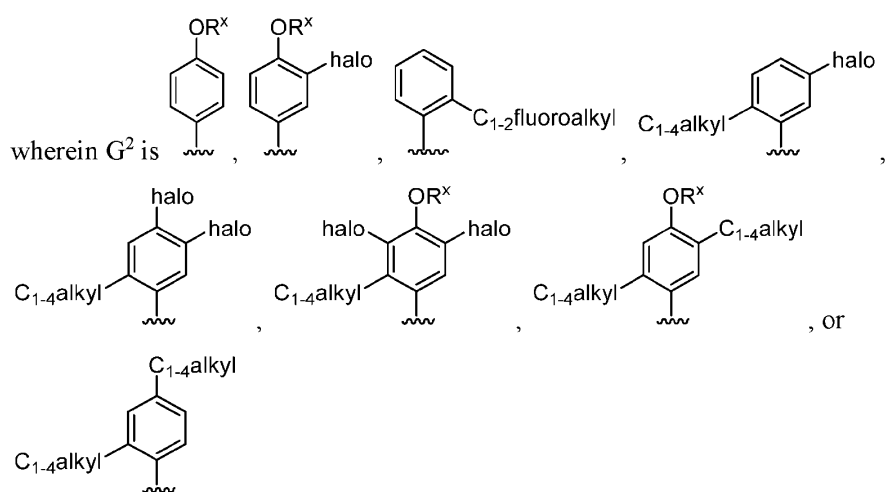
[00121] E8.1. The compound of any of E1-E4.1, E4.6, E4.7, E6, or E8, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 6- to 12-membered aryl at G^2 is phenyl.

[00122] E8.2. The compound of E8.1, or a pharmaceutically acceptable salt thereof,

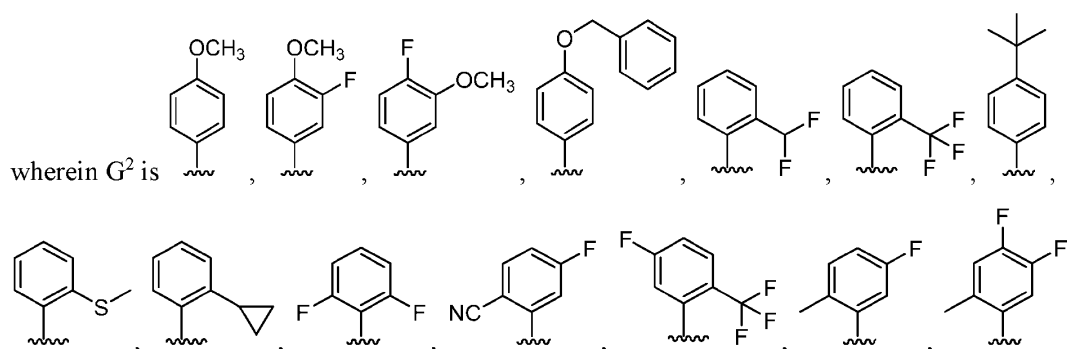


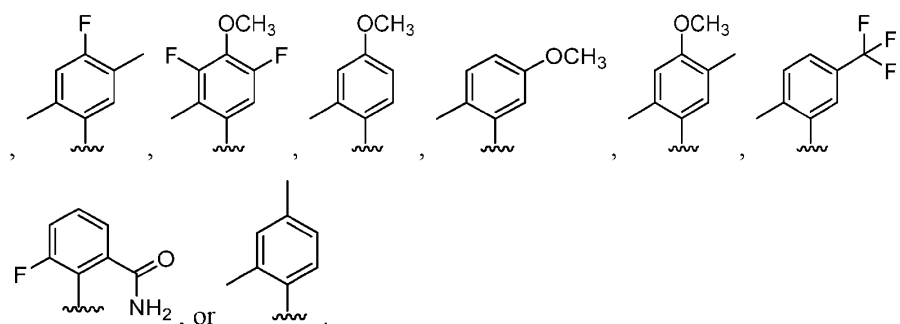


[00123] E8.3. The compound of E8.2, or a pharmaceutically acceptable salt thereof,

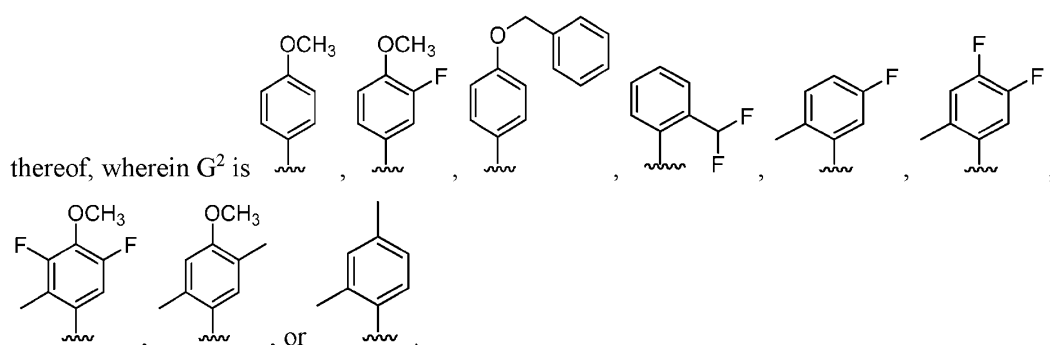


[00124] E8.4. The compound of E8.2, or a pharmaceutically acceptable salt thereof,





[00125] E8.5. The compound of E8.3 or E8.4, or a pharmaceutically acceptable salt



[00126] E8.6. The compound of any of E1-E4.1, E4.6, E4.7, E6, or E8-E8.1, or a pharmaceutically acceptable salt thereof, wherein G² is optionally substituted with a first substituent selected from the group consisting of halogen, cyano, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OR^x, -SR^x, -C(O)N(R^x)₂, and G^{2a}, and optionally further substituted with 1-4 substituents independently selected from the group consisting of halogen and C₁₋₄alkyl.

[00127] E8.7. The compound of E8.6, or a pharmaceutically acceptable salt thereof, wherein G² is optionally substituted with a first substituent selected from the group consisting of halogen, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OR^x, and G^{2a}, and optionally further substituted with 1-4 substituents independently selected from the group consisting of halogen and C₁₋₄alkyl.

[00128] E8.8. The compound of E8.6, or a pharmaceutically acceptable salt thereof, wherein G² is optionally substituted with a first substituent selected from the group consisting of fluoro, cyano, methyl, isopropyl, tert-butyl, CF₃, CHF₂, CF₃, -OR^x, -SR^x, -C(O)N(R^x)₂, and G^{2a}, and optionally further substituted with 1-4 substituents independently selected from the group consisting of fluoro and methyl.

[00129] E8.9. The compound of E8.7 or E8.8, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with a first substituent selected from the group consisting of fluoro, methyl, isopropyl, CF_3 , CHF_2 , $-OR^x$, and G^{2a} , and optionally further substituted with 1-4 substituents independently selected from the group consisting of fluoro and methyl.

[00130] E8.10. The compound of any of E1-E4.1, E4.6, E4.7, E6-E7.6, E7.10-E7.15, E7.19-E7.22, E8-E8.3, or E8.6-E8.9, or a pharmaceutically acceptable salt thereof, wherein R^x , at each occurrence, is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{3-4} cycloalkyl, $-CH_2-C_{3-4}$ cycloalkyl, and $-CH_2$ -phenyl.

[00131] E8.11. The compound of E8.10, or a pharmaceutically acceptable salt thereof, wherein R^x , at each occurrence, is independently selected from the group consisting of C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{3-4} cycloalkyl, $-CH_2-C_{3-4}$ cycloalkyl, and $-CH_2$ -phenyl.

[00132] E8.12. The compound of E8.10, or a pharmaceutically acceptable salt thereof, wherein R^x , at each occurrence, is independently hydrogen or C_{1-4} alkyl.

[00133] E8.13. The compound of E8.12, or a pharmaceutically acceptable salt thereof, wherein R^x is hydrogen.

[00134] E8.14. The compound of E8.11 or E8.12, or a pharmaceutically acceptable salt thereof, wherein R^x is C_{1-4} alkyl.

[00135] E8.15. The compound of E8.14, or a pharmaceutically acceptable salt thereof, wherein R^x is methyl.

[00136] E8.16. The compound of E8.11, or a pharmaceutically acceptable salt thereof, wherein R^x is $-CH_2$ -phenyl.

[00137] E8.17. The compound of any of E1-E4.1, E4.6, E4.7, E6-E7.6, E7.10-E7.15, E7.19-E8.3, or E8.6-E8.16, or a pharmaceutically acceptable salt thereof, wherein G^{2a} is C_{3-4} cycloalkyl.

[00138] E9. The compound of any of E1-E4.1, E4.6, E4.7, or E6, or a pharmaceutically acceptable salt thereof, wherein G^2 is the optionally substituted 4- to 12-membered heterocyclyl.

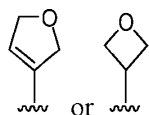
[00139] E9.1. The compound of any of E1-E4.1, E4.6, E4.7, E6, or E9, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 4- to 12-membered heterocyclyl at G^2 is a 4- to 6- membered heterocyclyl containing 1-3 heteroatoms independently selected from the group consisting of O, N and S.

[00140] E9.2. The compound of E9.1, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 4- to 6- membered heterocyclyl at G² contains one oxygen atom.

[00141] E9.3. The compound of E9.2, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 4- to 6- membered heterocyclyl at G² is 2,5-dihydrofuranyl or oxetanyl.

[00142] E9.4. The compound of E9.3, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 4- to 6- membered heterocyclyl at G² is 2,5-dihydrofuran-3-yl or oxetan-3-yl.

[00143] E9.5. The compound of E9.3 or E9.4, or a pharmaceutically acceptable salt



thereof, wherein G² is or .

[00144] E10. The compound of any of E1-E4.1, E4.6, E4.7, or E6, or a pharmaceutically acceptable salt thereof, wherein G² is the optionally substituted 3- to 12-membered carbocyclyl.

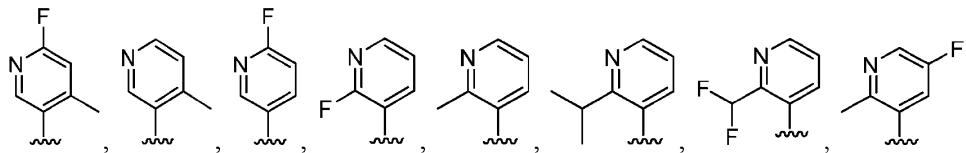
[00145] E10.1. The compound of any of E1-E4.1, E4.6, E4.7, E6, or E10, or a pharmaceutically acceptable salt thereof, wherein the optionally substituted 3- to 12-membered carbocyclyl at G² is C₃₋₆cycloalkyl.

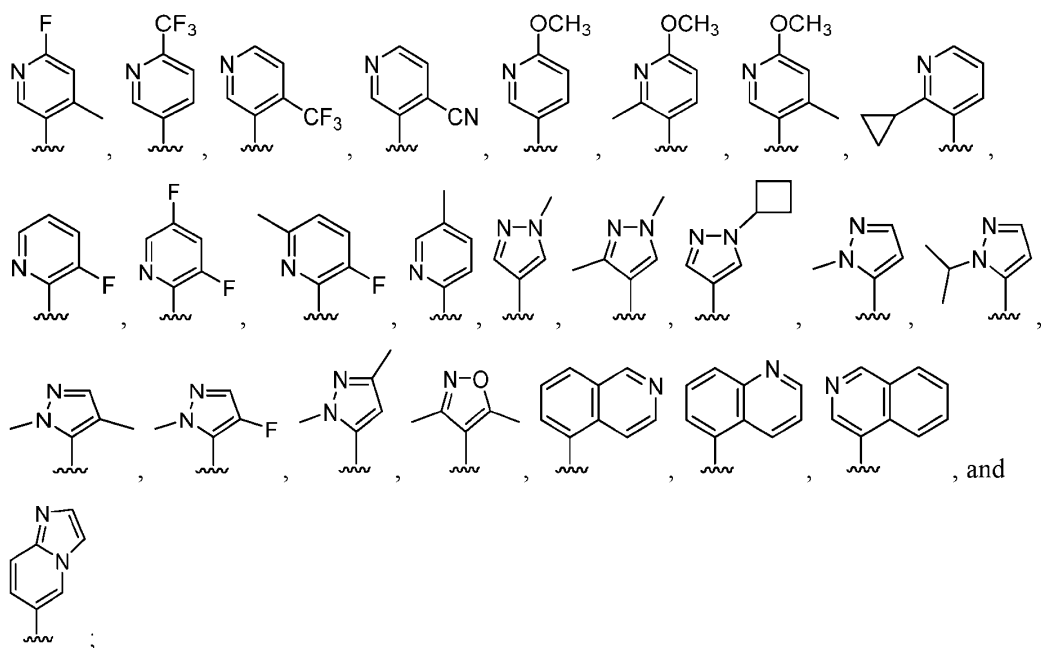
[00146] E10.2. The compound of E10.1, or a pharmaceutically acceptable salt thereof, wherein G² is cyclopropyl.

[00147] E10.3. The compound of E10.1, or a pharmaceutically acceptable salt thereof, wherein G² is cyclobutyl or cyclopentyl.

[00148] E11. The compound of any of E6-E10.3, or a pharmaceutically acceptable salt thereof, wherein G² is:

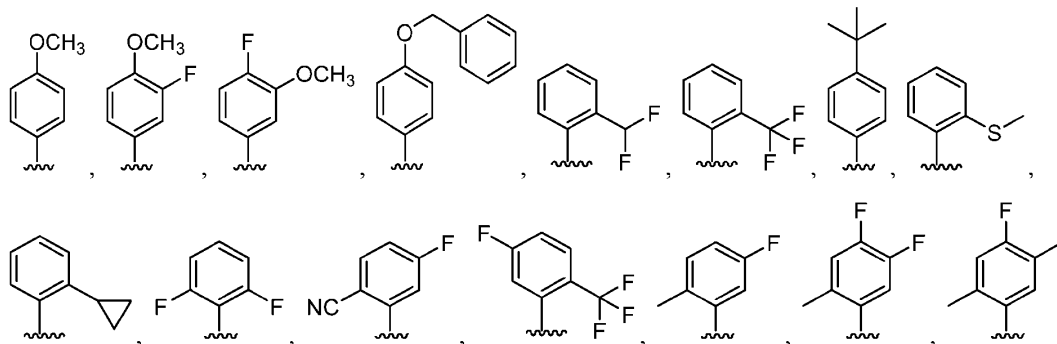
(a) the optionally substituted 5- to 12-membered heteroaryl selected from the group consisting of

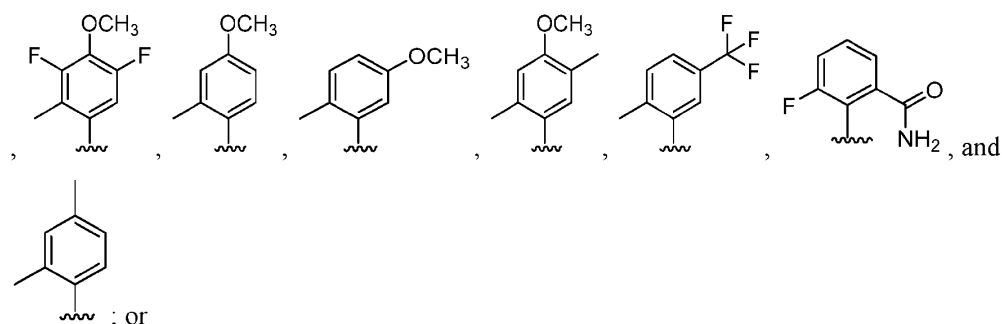




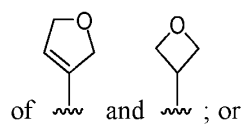
or

(b) the optionally substituted 6- to 12-membered aryl selected from the group consisting of





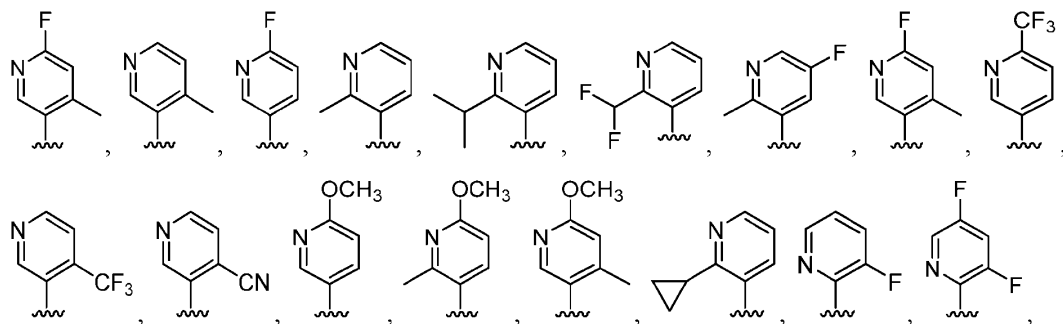
(c) the optionally substituted 4- to 12-membered heterocyclyl selected from the group consisting

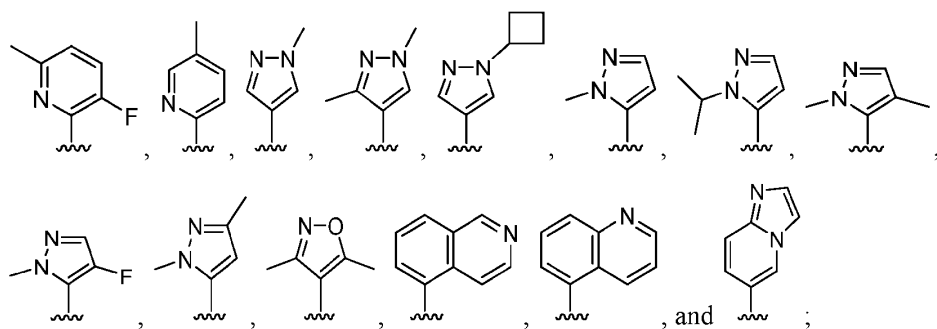


(d) the optionally substituted 3- to 12-membered carbocyclyl that is , , or .

[00149] E11.1. The compound of E11, or a pharmaceutically acceptable salt thereof, wherein G² is:

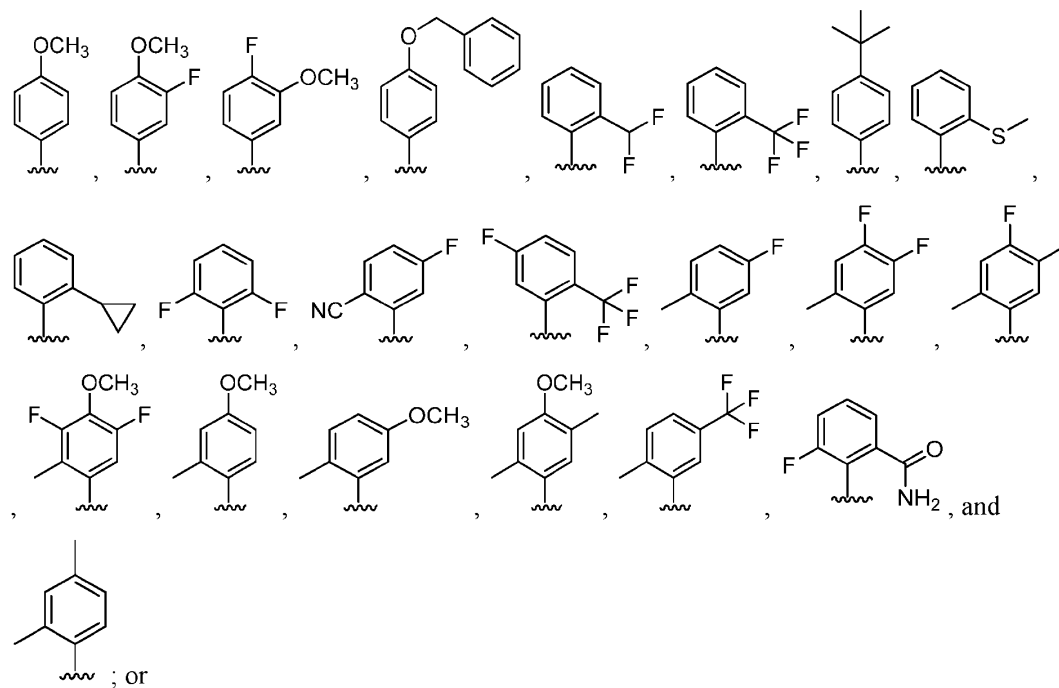
(a) the optionally substituted 5- to 12-membered heteroaryl selected from the group consisting of



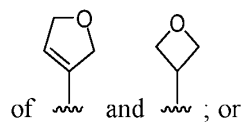


or

(b) the optionally substituted 6- to 12-membered aryl selected from the group consisting of



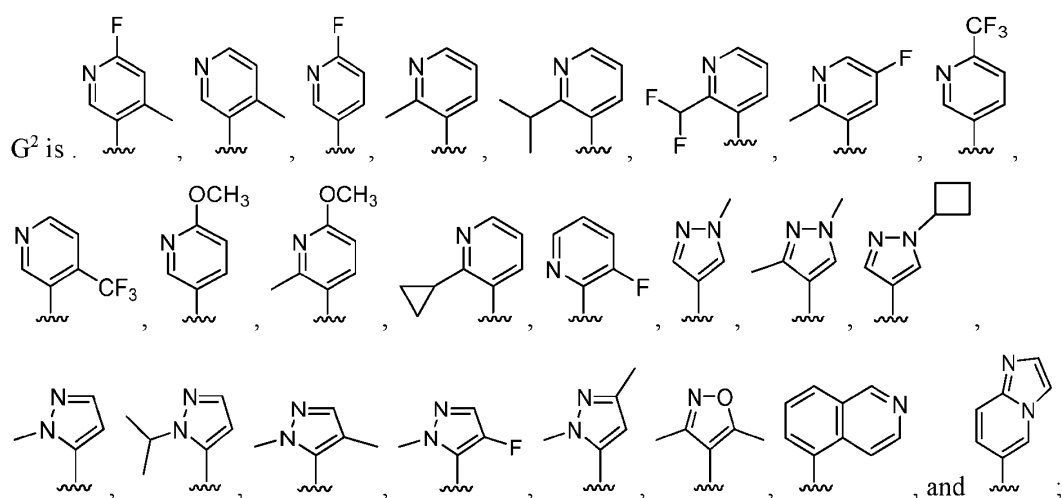
(c) the optionally substituted 4- to 12-membered heterocyclyl selected from the group consisting



(d) the optionally substituted 3- to 12-membered carbocyclyl that is .

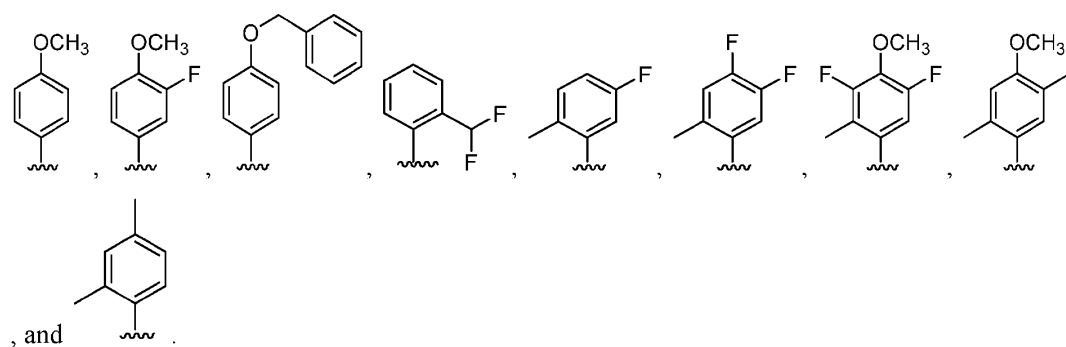
[00150] E11.2. The compound of E11.1, or a pharmaceutically acceptable salt thereof, wherein G^2 is:

(a) the optionally substituted 5- to 12-membered heteroaryl selected from the group consisting of



or

(b) the optionally substituted 6- to 12-membered aryl selected from the group consisting of



[00151] E12. The compound of E4 or E4.1, or a pharmaceutically acceptable salt thereof, wherein

R^2 is $-NR^bR^c$;

R^b is C₁₋₆alkyl, G², or –C₁₋₃alkylene–G²; and

R^c is hydrogen or C₁₋₆alkyl.

[00152] E13. The compound of any of E1-E4.1 or E12, or a pharmaceutically acceptable salt thereof, wherein R^b is G².

[00153] E14. The compound of E12 or E13, or a pharmaceutically acceptable salt thereof, wherein G² is the optionally substituted 5- to 12-membered heteroaryl.

[00154] E14.1. The compound of any of E1-E4.1 or E12-E14, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 12-membered heteroaryl at G² is a 5- to 6- membered heteroaryl containing 1-3 heteroatoms independently selected from the group consisting of O, N, and S.

[00155] E14.2. The compound of E14.1, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 6- membered heteroaryl at G² is pyridinyl.

[00156] E14.3. The compound of E14.2, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 6- membered heteroaryl at G² is pyridin-3-yl.

[00157] E14.4. The compound of E14.2, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 6- membered heteroaryl at G² is pyridin-4-yl.

[00158] E14.5. The compound of any of E1-E4.1 or E12-E14.4, or a pharmaceutically acceptable salt thereof, wherein G² is optionally substituted with a first substituent selected from the group consisting of halogen, C₁₋₄alkyl, C₁₋₂fluoroalkyl, –OR^x, and G^{2a}, and optionally further substituted with 1-3 substituents independently selected from the group consisting of halogen and C₁₋₄alkyl.

[00159] E14.6. The compound of E14.5, or a pharmaceutically acceptable salt thereof, wherein G² is optionally substituted with a first substituent selected from the group consisting of fluoro, methyl, isopropyl, CF₃, CHF₂, –OR^x, and G^{2a}, and optionally further substituted with 1-3 substituents independently selected from the group consisting of fluoro and methyl.

[00160] E14.7. The compound of any of E1-E4.1 or E12-E14.6, or a pharmaceutically acceptable salt thereof, wherein R^x, at each occurrence, is independently selected from the group consisting of C₁₋₄alkyl, C₁₋₂fluoroalkyl, C₃₋₄cycloalkyl, –CH₂–C₃₋₄cycloalkyl, and –CH₂–phenyl.

[00161] E14.8. The compound of E14.7, or a pharmaceutically acceptable salt thereof, wherein R^x is C_{1-4} alkyl.

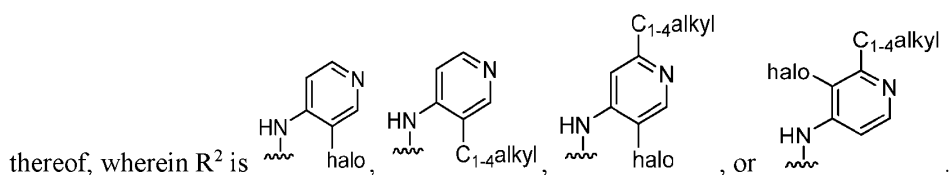
[00162] E14.9. The compound of E14.8, or a pharmaceutically acceptable salt thereof, wherein R^x is methyl.

[00163] E14.10. The compound of any of E1-E4.1 or E12-E14.9, or a pharmaceutically acceptable salt thereof, wherein G^{2a} is C_{3-4} cycloalkyl.

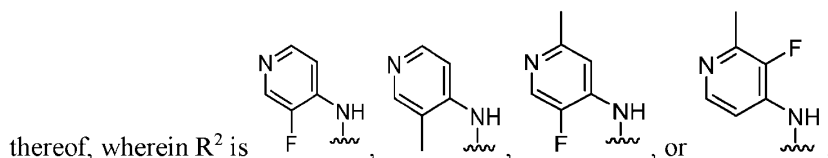
[00164] E14.11. The compound of any of E12-E14.10, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with 1-3 substituents independently selected from the group consisting of halogen and C_{1-4} alkyl.

[00165] E14.12. The compound of E14.11, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with 1-3 substituents independently selected from the group consisting of fluoro and methyl.

[00166] E14.13. The compound of any of E12-E14.11, or a pharmaceutically acceptable salt



[00167] E14.14. The compound of E14.12 or E14.13, or a pharmaceutically acceptable salt



[00168] E15. The compound of E12 or E13, or a pharmaceutically acceptable salt thereof, wherein G^2 is the optionally substituted 6- to 12-membered aryl.

[00169] E15.1. The compound of any of E1-E4.1, E12, E13, or E15, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 6- to 12-membered aryl G^2 is phenyl.

[00170] E15.2. The compound of any of E1-E4.1, E12-E13, or E15-E15.1, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with a first substituent selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-2} fluoroalkyl, $-OR^x$, and G^{2a} , and optionally further substituted with 1-4 substituents independently selected from the group consisting of halogen and C_{1-4} alkyl.

[00171] E15.3. The compound of E15.2, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with a first substituent selected from the group consisting of fluoro, methyl, isopropyl, CF_3 , CHF_2 , $-OR^x$, and G^{2a} , and optionally further substituted with 1-4 substituents independently selected from the group consisting of fluoro and methyl.

[00172] E15.4. The compound of any of E1-E4.1, E12-E13, or E15-E15.3, or a pharmaceutically acceptable salt thereof, wherein R^x , at each occurrence, is independently selected from the group consisting of C_{1-4} alkyl, C_{1-2} fluoroalkyl, C_{3-4} cycloalkyl, $-CH_2-C_{3-4}$ cycloalkyl, and $-CH_2$ -phenyl.

[00173] E15.5. The compound of E15.4, or a pharmaceutically acceptable salt thereof, wherein R^x is C_{1-4} alkyl.

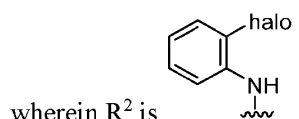
[00174] E15.6. The compound of E15.5, or a pharmaceutically acceptable salt thereof, wherein R^x is methyl.

[00175] E15.7. The compound of any of E1-E4.1, E12-E13, or E15-E15.6, or a pharmaceutically acceptable salt thereof, wherein G^{2a} is C_{3-4} cycloalkyl.

[00176] E15.8. The compound of any of E12-E13 or E15-E15.7, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with 1-3 substituents independently selected from the group consisting of halogen and C_{1-4} alkyl.

[00177] E15.9. The compound of E15.8, or a pharmaceutically acceptable salt thereof, wherein G^2 is optionally substituted with 1-3 substituents independently selected from the group consisting of fluoro and methyl.

[00178] E15.10. The compound of E15.8, or a pharmaceutically acceptable salt thereof,

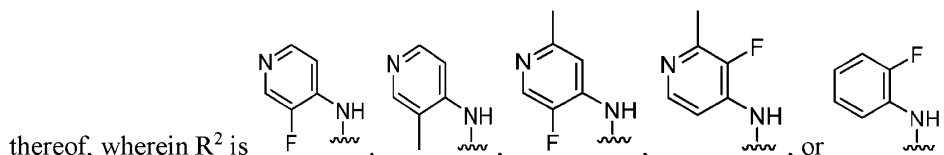


[00179] E15.11. The compound of any of E15.8-E15.10, or a pharmaceutically acceptable



[00180] E16. The compound of any of E1-E4.1 or E12-E15.11, or a pharmaceutically acceptable salt thereof, wherein R^c is hydrogen.

[00181] E17. The compound of any of E12-E16, or a pharmaceutically acceptable salt thereof, wherein R^2 is



[00182] E18. The compound of any of E1-E17, or a pharmaceutically acceptable salt thereof, wherein R^{4A} and R^{4B} are hydrogen.

[00183] E18.1. The compound of E18, or a pharmaceutically acceptable salt thereof, wherein the hydrogen at R^{4A} and R^{4B} are deuterium (2H).

[00184] E19. The compound of any of E1-E18.1, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, C_{1-6} alkyl, C_{1-6} fluoroalkyl, $-C_{1-6}$ alkylene- R^y , G^5 , or $-C_{1-3}$ alkylene- G^5 .

[00185] E19.1. The compound of E19, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, C_{1-6} alkyl, $-C_{1-6}$ alkylene- R^y , or $-C_{1-3}$ alkylene- G^5 .

[00186] E19.2. The compound of E19 or E19.1, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, methyl, CD_3 , $-C_{1-6}$ alkylene- R^y , G^5 , or $-C_{1-3}$ alkylene- G^5 .

[00187] E19.3. The compound of any of E1-E19.2, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

[00188] E19.4. The compound of any of E1-E19.2, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{1-6} alkyl.

[00189] E19.5. The compound of E19.4, or a pharmaceutically acceptable salt thereof, wherein R^5 is methyl, ethyl, isobutyl, neopentyl, or CD_3 .

[00190] E19.6. The compound of any of E1-E18.1, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{1-6} fluoroalkyl.

[00191] E19.7. The compound of E19.6, or a pharmaceutically acceptable salt thereof, wherein R^5 is 2-fluoro-2-methylpropyl.

[00192] E19.8. The compound of any of E1-E19.2, or a pharmaceutically acceptable salt thereof, wherein R^5 is $-C_{1-6}$ alkylene- R^y .

[00193] E19.9. The compound of E19.8, or a pharmaceutically acceptable salt thereof, wherein R^5 is $-CH_2CH_2-R^y$ or $-CH(CH_3)CH_2-R^y$.

[00194] E19.10. The compound of any of E1-E19 or E19.2, or a pharmaceutically acceptable salt thereof, wherein R^5 is G^5 .

[00195] E19.11. The compound of any of E1-E19.2, or a pharmaceutically acceptable salt thereof, wherein R^5 is $-C_{1-3}alkylene-G^5$.

[00196] E19.12. The compound of E19.21, or a pharmaceutically acceptable salt thereof, wherein R^5 is $-CH_2-G^5$.

[00197] E19.13. The compound of any of E1-E19.2 or E19.8-E19.9, or a pharmaceutically acceptable salt thereof, wherein R^y is $-OR^{5a}$ or $-C(O)OR^{5a}$.

[00198] E19.14. The compound of any of E1-E19.2, E19.8-E19.9, or E19.13, or a pharmaceutically acceptable salt thereof, wherein R^{5a} , at each occurrence, is independently $C_{1-4}alkyl$.

[00199] E19.15. The compound of E19.14, or a pharmaceutically acceptable salt thereof, wherein R^{5a} is methyl or isopropyl.

[00200] E19.16. The compound of E19.15, or a pharmaceutically acceptable salt thereof, wherein R^{5a} is methyl.

[00201] E19.17. The compound of any of E1-E19.2, E19.8-E19.9, or E19.13, or a pharmaceutically acceptable salt thereof, wherein R^{5a} is G^5 .

[00202] E19.18. The compound of any of E1-E19.17, or a pharmaceutically acceptable salt thereof, wherein G^5 is the optionally substituted 4- to 8-membered heterocyclyl, $C_{3-8}cycloalkyl$, or phenyl.

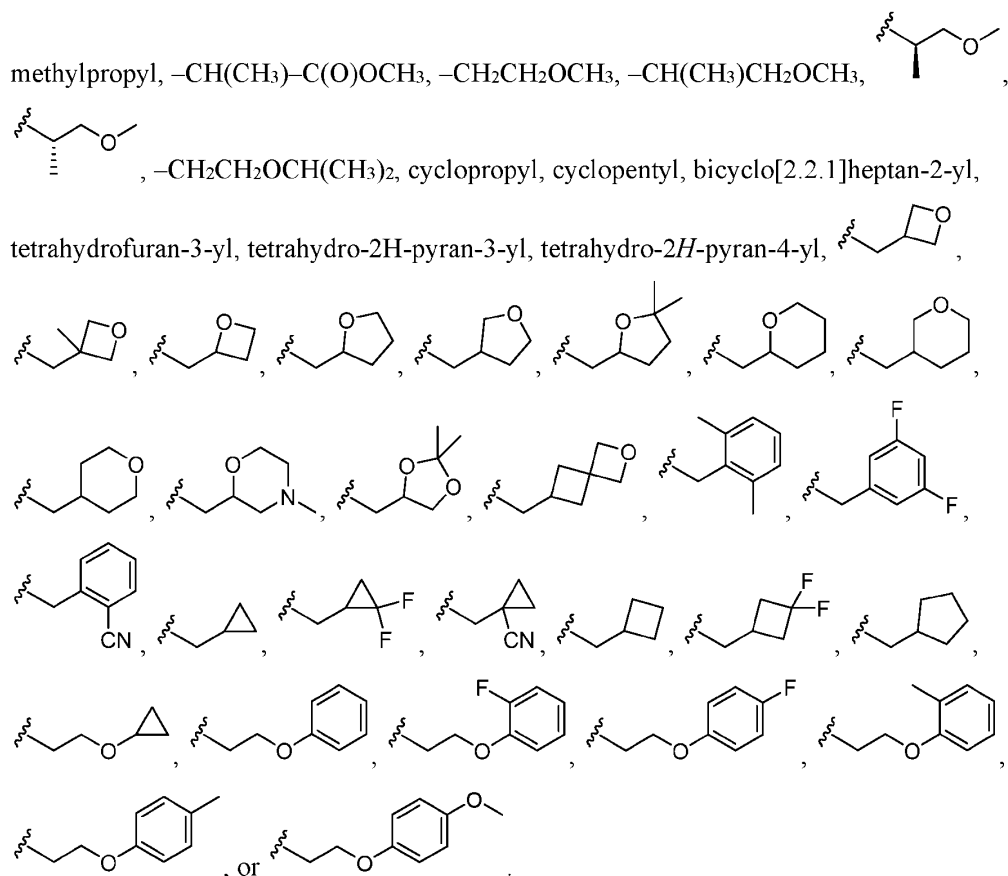
[00203] E19.19. The compound of any of E1-E19.18, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 4- to 8-membered heterocyclyl or $C_{3-8}cycloalkyl$ at G^5 is oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, 1,3-dioxolan-4-yl, 2-oxaspiro[3.3]heptan-6-yl, cyclopropyl, cyclobutyl, cyclopentyl, or bicyclo[2.2.1]heptan-2-yl.

[00204] E19.20. The compound of any of E1-E19.19, or a pharmaceutically acceptable salt thereof, wherein G^5 is optionally substituted with 1-4 substituents independently selected from the group consisting of fluoro, cyano, methyl, and $-OCH_3$.

[00205] E19.21. The compound of any of E1-E19.18 or E19.20, or a pharmaceutically acceptable salt thereof, wherein G^5 is the optionally substituted 4- to 8-membered heterocyclyl or $C_{3-6}cycloalkyl$.

[00206] E19.22. The compound of any of E19.19-E19.21, or a pharmaceutically acceptable salt thereof, wherein G^5 is oxetanyl, tetrahydrofuranyl, cyclopropyl, or cyclopentyl.

[00207] E19.23. The compound of any of E19-E19.22, or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen, methyl, ethyl, isobutyl, neopentyl, CD₃, 2-fluoro-2-



[00208] E19.24. The compound of E19.23, or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen, methyl, CD₃, -CH(CH₃)-C(O)OCH₃, -CH(CH₃)CH₂OCH₃, cyclopropyl, cyclopentyl, tetrahydrofuran-3-yl, or oxetan-3-ylmethyl.

[00209] E20. The compound of any of E1-E17, or a pharmaceutically acceptable salt thereof, wherein R^{4B} and R⁵ together with the atoms to which they attach form the 5- to 7-membered heterocycle.

[00210] E20.1. The compound of any of E1-E17 or E20, or a pharmaceutically acceptable salt thereof, wherein the 5- to 7-membered heterocycle formed by R^{4B} and R⁵ is a piperazine.

[00211] E21. The compound of any of E1-E20.1, or a pharmaceutically acceptable salt thereof, wherein R⁶ is hydrogen, halogen, C₁₋₄alkyl, C₁₋₄fluoroalkyl, -OR^{6a}, or C₃₋₆cycloalkyl.

- [00212] E21.1. The compound of E21, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen.
- [00213] E21.2. The compound of E21, or a pharmaceutically acceptable salt thereof, wherein R^6 is halogen.
- [00214] E21.3. The compound of any of E1-E21 or E21.2, or a pharmaceutically acceptable salt thereof, wherein the halogen at R^6 is chloro.
- [00215] E21.4. The compound of E21, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-4} alkyl.
- [00216] E21.5. The compound of any of E1-E21 or E21.3-E21.4, or a pharmaceutically acceptable salt thereof, wherein the C_{1-4} alkyl at R^6 is methyl.
- [00217] E21.6. The compound of E21, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-4} fluoroalkyl.
- [00218] E21.7. The compound of any of E1-E21, E21.3, or E21.5-E21.6, or a pharmaceutically acceptable salt thereof, wherein the C_{1-4} fluoroalkyl at R^6 is $-CHF_2$.
- [00219] E21.8. The compound of E21, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-OR^{6a}$.
- [00220] E21.9. The compound of any of E1-E21, E21.3, E21.5, or E21.7-E21.8, or a pharmaceutically acceptable salt thereof, wherein R^{6a} is C_{1-4} alkyl.
- [00221] E21.10. The compound of any of E1-E21, E21.3, E21.5, or E21.7-E21.9, or a pharmaceutically acceptable salt thereof, wherein the C_{1-4} alkyl at R^{6a} is methyl.
- [00222] E21.11. The compound of E21, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{3-6} cycloalkyl.
- [00223] E21.12. The compound of any of E1-E21, E21.3, E21.5, E21.7, or E21.9-E21.11, or a pharmaceutically acceptable salt thereof, wherein the C_{3-6} cycloalkyl at R^6 is cyclopropyl.
- [00224] E22. The compound of any of E1-E21.12, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_{1-4} alkyl, halogen, cyano, or G^7 .
- [00225] E22.1. The compound of any of E1-E22, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_{1-4} alkyl, halogen, or cyano.
- [00226] E22.2. The compound of E22.1, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_{1-4} alkyl.

[00227] E22.3. The compound of any of E1-E22.2, or a pharmaceutically acceptable salt thereof, wherein the C₁₋₄alkyl at R⁷ is methyl.

[00228] E22.4. The compound of E22.1, or a pharmaceutically acceptable salt thereof, wherein R⁷ is cyano.

[00229] E22.5. The compound of E22.1, or a pharmaceutically acceptable salt thereof, wherein R⁷ is halogen.

[00230] E22.6. The compound of any of E1-E22.1, E22.3, or E22.5, or a pharmaceutically acceptable salt thereof, wherein the halogen at R⁷ is bromo.

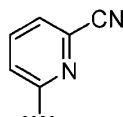
[00231] E22.7. The compound of any of E1-E22.1, E22.3, or E22.5, or a pharmaceutically acceptable salt thereof, wherein the halogen at R⁷ is chloro.

[00232] E22.8. The compound of any of E1-E22, or a pharmaceutically acceptable salt thereof, wherein R⁷ is G⁷.

[00233] E22.9. The compound of any of E1-E22.1, E22.3, or E22.6-E22.8, or a pharmaceutically acceptable salt thereof, wherein G⁷ is the optionally substituted 5- to 6-membered heteroaryl containing 1-3 heteroatoms.

[00234] E22.10. The compound of any of E1-E22.1, E22.3, or E22.6-E22.9, or a pharmaceutically acceptable salt thereof, wherein the ring system of the optionally substituted 5- to 6-membered heteroaryl at G⁷ is pyridinyl.

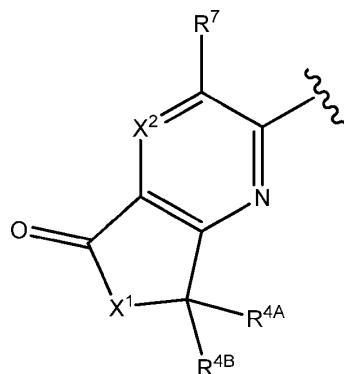
[00235] E22.11. The compound of E22.10, or a pharmaceutically acceptable salt thereof,



wherein G⁷ is .

[00236] E23 The compound of any of E1-E22.11, or a pharmaceutically acceptable salt thereof, wherein n is 0.

[00237] E24. The compound of any of E1-E23, or a pharmaceutically acceptable salt



thereof, wherein G^1 is

[00238] E25. The compound of any of E1-E24, or a pharmaceutically acceptable salt thereof, wherein X^1 is NR^5 .

[00239] E26. The compound of any of E1-E18.1 or E21-E24, or a pharmaceutically acceptable salt thereof, wherein X^1 is O.

[00240] E27. The compound of any of E1-E18.1 or E21-E24, or a pharmaceutically acceptable salt thereof, wherein X^1 is $CR^{5A}R^{5B}$.

[00241] E27.1. The compound of any of E1-E18.1, E21-E24, or E27, or a pharmaceutically acceptable salt thereof, wherein R^{5A} and R^{5B} are independently hydrogen, fluoro, or methyl.

[00242] E27.2. The compound of E27.1, or a pharmaceutically acceptable salt thereof, wherein R^{5A} and R^{5B} are fluoro.

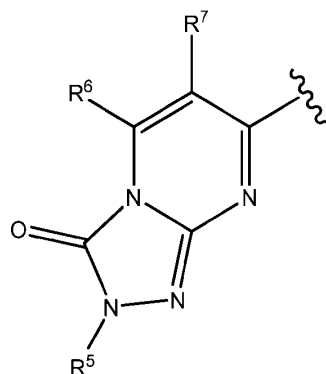
[00243] E27.3. The compound of E27.1, or a pharmaceutically acceptable salt thereof, wherein R^{5A} and R^{5B} are methyl.

[00244] E27.4. The compound of E27.1, or a pharmaceutically acceptable salt thereof, wherein R^{5A} and R^{5B} are hydrogen.

[00245] E28. The compound of any of E1-E27.4, or a pharmaceutically acceptable salt thereof, wherein X^2 is CR^6 .

[00246] E29. The compound of any of E1-E27.4, or a pharmaceutically acceptable salt thereof, wherein X^2 is N.

[00247] E30. The compound of any of E1-E23, or a pharmaceutically acceptable salt



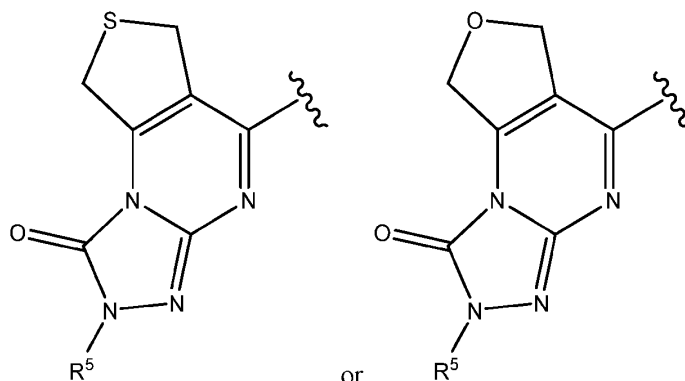
thereof, wherein G^1 is

[00248] E31. The compound of any of E1-E20.1 or E23-E30, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 , together with the atoms to which they are attached, form the optionally substituted 5- to 7-membered heterocycle or a 5- to 7-membered carbocycle.

[00249] E31.1. The compound of E31, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 , together with the atoms to which they are attached, form the optionally substituted 5- to 7-membered heterocycle.

[00250] E31.2. The compound of E31.1, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 , together with the atoms to which they are attached, form a dihydrothiophene or dihydrofuran.

[00251] E31.3. The compound of E31.2, or a pharmaceutically acceptable salt thereof,



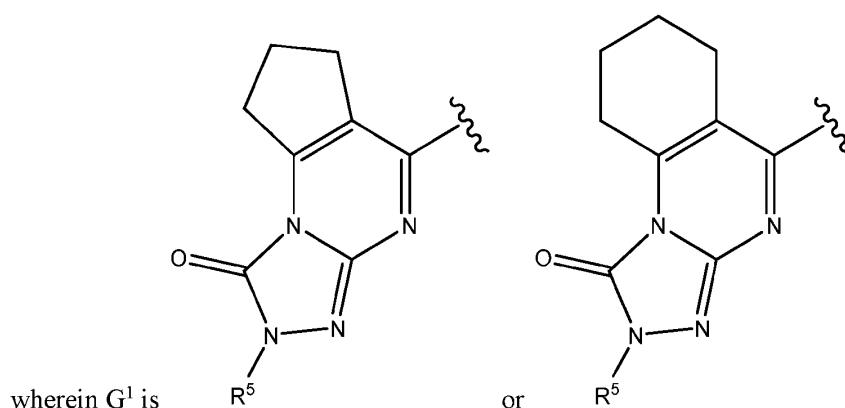
wherein G^1 is

or

[00252] E31.4. The compound of any of E1-E20.1 or E23-30, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 , together with the atoms to which they are attached, form the optionally substituted 5- to 7-membered carbocycle.

[00253] E31.5. The compound of E31.4, or a pharmaceutically acceptable salt thereof, wherein R⁶ and R⁷, together with the atoms to which they are attached, form a cyclopentene or a cyclohexene.

[00254] E31.6. The compound of E31.5, or a pharmaceutically acceptable salt thereof,



[00255] E32. The compound of E1 selected from the group consisting of:

3,6-dimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
methyl 2-(3-methyl-5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,7-dihydro-6 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-6-yl)propanoate
3-methyl-2-(3-(1-methyl-1 <i>H</i> -pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-8,9,10,10 <i>a</i> -tetrahydropyrido[2',3':3,4]pyrrolo[1,2- <i>a</i>]pyrazin-5(7 <i>H</i>)-one
2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one

3-methyl-6-(methyl- <i>d</i> ₃)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-6-(oxetan-3-ylmethyl)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(1-methyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,5,7,7- <i>d</i> ₄ -6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,5,7,7- <i>d</i> ₄ -3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one-7,7- <i>d</i> ₂
2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3,6-dimethyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1,3-dimethyl-1 <i>H</i> -pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1-cyclobutyl-1 <i>H</i> -pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1-isopropyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(6-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1,4-dimethyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-methoxypyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(4-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one

2-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(imidazo[1,2- <i>a</i>]pyridin-6-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1,3-dimethyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(4-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(3-fluoro-4-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(4-(benzyloxy)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-(difluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-cyclopropylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(5-fluoro-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-isopropylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one

2-(3-(6-methoxy-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7H)-one
2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
6-cyclopropyl-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
6-cyclopentyl-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5-oxo-5,7-dihydrofuro[3,4- <i>b</i>]pyridine-3-carbonitrile
2-(3-(6-methoxy-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7H)-one
2-(3-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7H)-one
5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridine-3-carbonitrile
6-(5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-3-yl)picolinonitrile
2-(3-(3,5-difluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(3-fluoro-6-methylpyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(5-methylpyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one

3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-cyclopenta[<i>b</i>]pyridin-5-one
(R)-6-(1-methoxypropan-2-yl)-3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
(S)-6-(1-methoxypropan-2-yl)-3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-chloro-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-chloro-6-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3,4,6-trimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3,4-dimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,4-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,4,6-trimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((5-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((3-fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,5,7,7- <i>d</i> ₄ -3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,5,7,7- <i>d</i> ₄ -6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((3-fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one

2-(3-((5-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl-5,5,7,7- <i>d</i> ₄)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((2-fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl-5,5,7,7- <i>d</i> ₄)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((3-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3,6-dimethyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one

7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-2-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,6-dimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-2-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

2-ethyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6,7,8-tetrahydro-1H-cyclopenta[<i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1-one
5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7,8,9-tetrahydro-[1,2,4]triazolo[4,3- <i>a</i>]quinazolin-1(2H)-one
6-methyl-2-(tetrahydrofuran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(1-methoxypropan-2-yl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-methoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2,6-dimethylbenzyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(3,5-difluorobenzyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-((4-methylmorpholin-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-methoxy-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,8-dihydrothieno[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2H)-one
5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,8-dihydrofuro[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2H)-one

7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-methyl-5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,8-dihydrofuro[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2H)-one
2-(2-cyclopropoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-((5,5-dimethyltetrahydrofuran-2-yl)methyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-(2-phenoxyethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
1-((6-methyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
6-methyl-2-(tetrahydro-2H-pyran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(bicyclo[2.2.1]heptan-2-yl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-isopropoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-(2-fluorophenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-(2-(<i>p</i> -tolylxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

2,5,6-trimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-ethyl-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-chloro-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-chloro-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-(4-fluorophenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-(2-(<i>o</i> -tolylloxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-(4-methoxyphenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-(tetrahydrofuran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2,6-dimethylbenzyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-(2-phenoxyethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-cyclopropoxyethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-methoxypyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-(2,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile

7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(2-(methylthio)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(2-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-(tert-butyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclopropylmethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-fluoro-2-methylpropyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-((3,3-difluorocyclobutyl)methyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-isobutyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-neopentyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclobutylmethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

2-isobutyl-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
2-(cyclobutylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
2-((3,3-difluorocyclobutyl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
5-methoxy-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
7-(3-(2-cyclopropylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(2-methyl-5-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
5,6-dimethyl-2-(2-(<i>o</i> -tolylloxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
7-(3-(4-fluoro-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
2-(2-isopropoxyethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
7-(3-(5-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
5,6-dimethyl-2-((tetrahydrofuran-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
5-cyclopropyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one
5-cyclopropyl-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one

2-((5,6-dimethyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)benzonitrile
1-((5,6-dimethyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
5,6-dimethyl-2-neopentyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-((tetrahydrofuran-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-(cyclopentylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-(tetrahydro-2 <i>H</i> -pyran-4-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-((2-oxaspiro[3.3]heptan-6-yl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-((3-methyloxetan-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-4-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-((2,2-difluorocyclopropyl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-(2-fluoro-2-methylpropyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-(oxetan-2-ylmethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-(2-(2-fluorophenoxy)ethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one

3-fluoro-2-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)benzamide
6-(2-((1-cyanocyclopropyl)methyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile
7-(3-(2,6-difluorophenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
1-((7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((tetrahydrofuran-3-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((3-methyloxetan-3-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-4-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
4-fluoro-2-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)benzonitrile

7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(5-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
1-((7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-((2-fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-((3-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
3-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)isonicotinonitrile
2,5,6-trimethyl-7-(3-(4-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-methoxy-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
1-((7-(3-(1,3-dimethyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(1-cyclopropylvinyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
5-(difluoromethyl)-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

5-cyclopropyl-7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
1-((5,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((5,6-dimethyl-3-oxo-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(5-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((5,6-dimethyl-3-oxo-7-(3-(prop-1-en-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
2,5,6-trimethyl-7-[3-(oxetan-3-yl)-7,8-dihydro-5 <i>H</i> -1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3-one
2,5,6-trimethyl-7-[3-(oxetan-3-yl)-7,8-dihydro-5 <i>H</i> -1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3-one
1-((7-(3-(2,5-dihydrofuran-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((5,6-dimethyl-7-(3-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(2,6-difluorophenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(2-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
3-(6-(2-((1-cyanocyclopropyl)methyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)isonicotinonitrile

1-((7-(3-(isoquinolin-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2-(cyclopropylmethyl)-5,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-(6-(2-(cyclopropylmethyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-4-fluorobenzonitrile
2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-(cyclopropylmethyl)-7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
1-((7-(3-cyclobutyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
7-(3-cyclopentyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one

or a pharmaceutically acceptable salt thereof.

[00256] E33. A pharmaceutical composition comprising the compound of any of E1-E32, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[00257] E34. A method for treating a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal, comprising administering to the mammal a therapeutically effective amount of the compound of any of E1-E32, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition of E33.

[00258] E35. The method of E34, wherein the disorder is associated with a mAChR M₄ dysfunction.

[00259] E36. The method of E34 or E35, wherein the disorder is a neurological and/or psychiatric disorder associated with mAChR M₄ dysfunction.

[00260] E37. The method of any of E34-E36, wherein the disorder is selected from the group consisting of Alzheimer's disease, schizophrenia, a sleep disorder, a pain disorder, and a cognitive disorder.

[00261] E38. The method of E37, wherein the disorder is Alzheimer's disease.

[00262] E39. The method of any of E34-E36, wherein the disorder is selected from the group consisting of psychosis, schizophrenia, conduct disorder, disruptive behavior disorder, bipolar disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, autistic disorder, movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

[00263] E40. A kit comprising the compound of any of E1-E32, or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent known to increase mAChR M₄ activity; (b) at least one agent known to decrease mAChR M₄ activity; (c) at least one agent known to treat a disorder associated with cholinergic activity; (d) instructions for treating a disorder associated with cholinergic activity; (e) instructions for treating a disorder associated with mAChR M₄ receptor activity; and (f) instructions for administering the compound in connection with cognitive or behavioral therapy.

[00264] E38. The compound of any of E1-E32, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of E33, for use in the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[00265] E39. The use of the compound of any of E1-E32, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of E33 for the preparation of a medicament for the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[00266] The compound may exist as a stereoisomer wherein asymmetric or chiral centers are present. The stereoisomer is “*R*” or “*S*” depending on the configuration of substituents around the chiral carbon atom. The terms “*R*” and “*S*” used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, in Pure Appl. Chem., 1976, 45: 13-30. The disclosure contemplates various stereoisomers and mixtures thereof and these are specifically included within the scope of this invention. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of the compounds may be prepared synthetically from commercially available starting materials, which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by methods of resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and optional liberation of the optically pure product from the auxiliary as described in Furniss, Hannaford, Smith, and Tatchell, “Vogel's Textbook of Practical Organic Chemistry,” 5th edition (1989), Longman Scientific & Technical, Essex CM20 2JE, England, or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns, or (3) fractional recrystallization methods.

[00267] It should be understood that the compound may possess tautomeric forms, as well as geometric isomers, and that these also constitute embodiments of the disclosure.

[00268] In the compounds of formula (I), and any subformulas, any “hydrogen” or “H,” whether explicitly recited or implicit in the structure, encompasses hydrogen isotopes ^1H (protium) and ^2H (deuterium).

[00269] The present disclosure also includes an isotopically-labeled compound, which is identical to those recited in formula (I), 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 usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as, but not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Substitution with heavier isotopes such as deuterium, i.e. ^2H , 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. The

compound may incorporate positron-emitting isotopes for medical imaging and positron-emitting tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of formula (I) are ^{11}C , ^{13}N , ^{15}O , and ^{18}F .

[00270] Isotopically-enriched forms of compounds of formula (I), or any subformulas, may generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using an appropriate isotopically-enriched reagent in place of a non-isotopically-enriched reagent. The extent of isotopic enrichment can be characterized as a percent incorporation of a particular isotope at an isotopically-labeled atom (e.g., % deuterium incorporation at a deuterium label).

a. Pharmaceutically Acceptable Salts

[00271] The disclosed compounds may exist as pharmaceutically acceptable salts. The term “pharmaceutically acceptable salt” refers to salts or zwitterions of the compounds which are water or oil-soluble or dispersible, suitable for treatment of disorders without undue toxicity, irritation, and allergic response, commensurate with a reasonable benefit/risk ratio and effective for their intended use. The salts may be prepared during the final isolation and purification of the compounds or separately by reacting an amino group of the compounds with a suitable acid. For example, a compound may be dissolved in a suitable solvent, such as but not limited to methanol and water and treated with at least one equivalent of an acid, like hydrochloric acid. The resulting salt may precipitate out and be isolated by filtration and dried under reduced pressure. Alternatively, the solvent and excess acid may be removed under reduced pressure to provide a salt. Representative salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, isethionate, fumarate, lactate, maleate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, oxalate, maleate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, glutamate, para-toluenesulfonate, undecanoate, hydrochloric, hydrobromic, sulfuric, phosphoric and the like. The amino groups of the compounds may also be quaternized with alkyl chlorides, bromides and iodides such as methyl, ethyl, propyl, isopropyl, butyl, lauryl, myristyl, stearyl and the like.

[00272] Basic addition salts may be prepared during the final isolation and purification of the disclosed compounds by reaction of a carboxyl group with a suitable base such as the hydroxide,

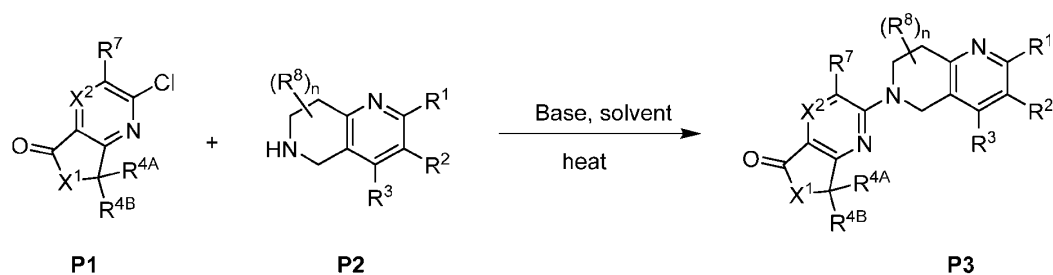
carbonate, or bicarbonate of a metal cation such as lithium, sodium, potassium, calcium, magnesium, or aluminum, or an organic primary, secondary, or tertiary amine. Quaternary amine salts can be prepared, such as those derived from methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-phenamine and *N,N'*-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine, and the like.

b. General Synthesis

[00273] Compounds of formula (I) may be prepared by synthetic processes or by metabolic processes. Preparation of the compounds by metabolic processes includes those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

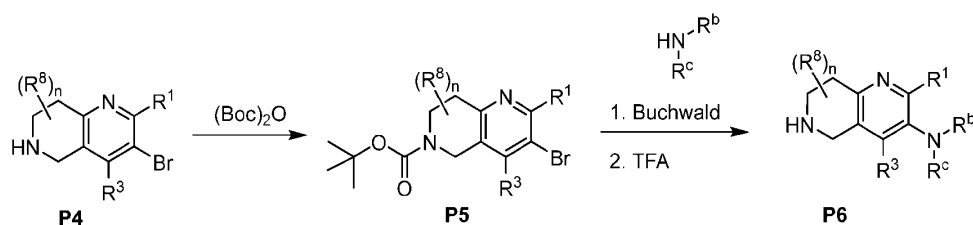
[00274] Compounds of formula (I) may be synthesized as shown in Schemes 1-14.

Scheme 1



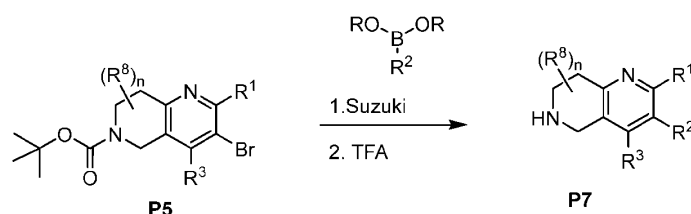
[00275] As illustrated in Scheme 1, intermediate compounds of formula **P2** may be subjected to standard nucleophilic substitution conditions with an intermediate of formula **P1**, base (e.g., DIPEA), solvent (e.g., DMSO) with heating to about 90-160 °C to provide compounds with the formula **P3**.

Scheme 2



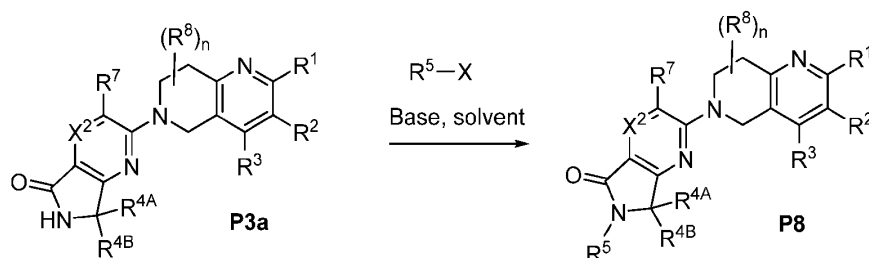
[00276] As shown in Scheme 2, intermediates of type **P4** may be protected with di-*t*-butyl carbonate under Boc-protection conditions, generally known in the art, to provide Boc-protected intermediates of type **P5**. Intermediates of type **P5** may be coupled with an amine under Buchwald coupling conditions, generally known in the art, followed by deprotection to provide products of type **P6**.

Scheme 3



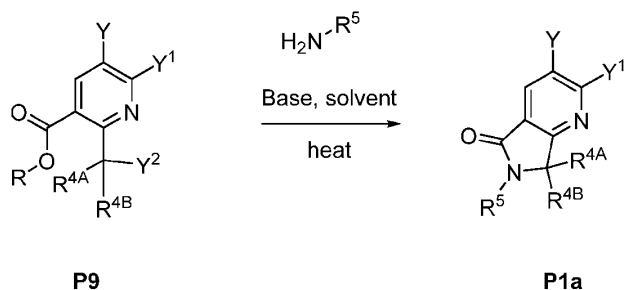
[00277] Scheme 3 illustrates a general route to prepare intermediates of the formula **P7**. Intermediates of the type **P5** may be coupled with a boronic acid or ester under Suzuki coupling conditions, generally known in the art, followed by deprotection to provide compounds of formula **P7**, wherein R^2 is alkyl or G^2 , and G^2 is an optionally substituted aryl or heteroaryl ring system as defined herein. Coupling reactions may be conducted with a palladium catalyst, such as $\text{Pd}(\text{dppf})\text{Cl}_2$, and a base (e.g., K_2CO_3 , Cs_2CO_3) in a solvent mixture of organic solvent, such as DMF or 1,4-dioxane, and water with heating to about 70-90 °C. The reaction may be facilitated with microwave irradiation.

Scheme 4



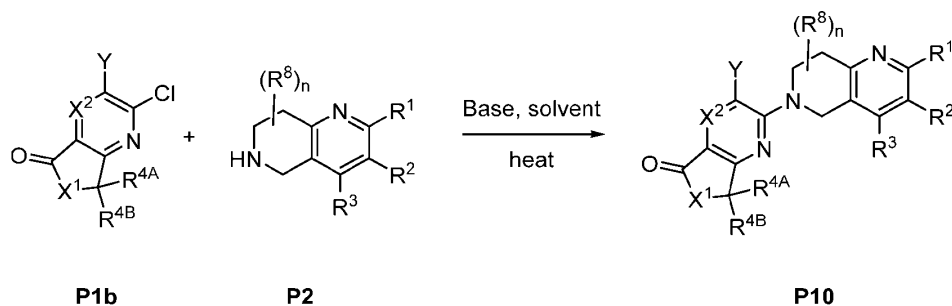
[00278] As illustrated in Scheme 4, intermediate compounds of formula **P3a** may be subjected to base (e.g., NaH, LiHMDS, etc.), solvent (e.g., DMSO) and $\text{R}^5\text{-X}$ (wherein X is halogen, mesylate or other leaving groups) to provide compounds with the formula **P8**.

Scheme 5



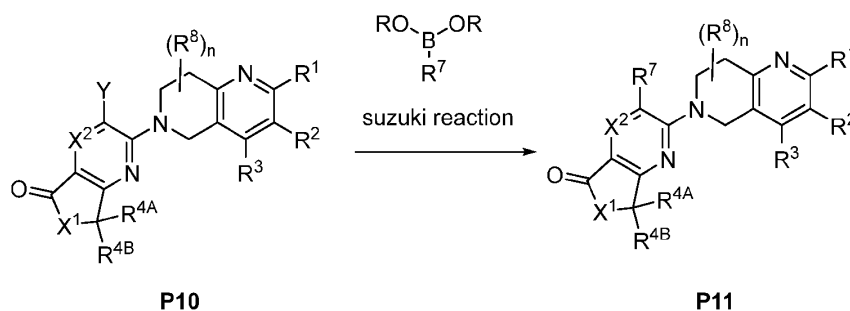
[00279] As shown in Scheme 5, ester intermediate **P9** (wherein Y , Y^1 and Y^2 is a Cl, Br, or I) may be subjected to amines, base (e.g., DIEA) and solvent (e.g., THF) with no heating or heating up to 40-50 °C to provide compounds **P1a**.

Scheme 6



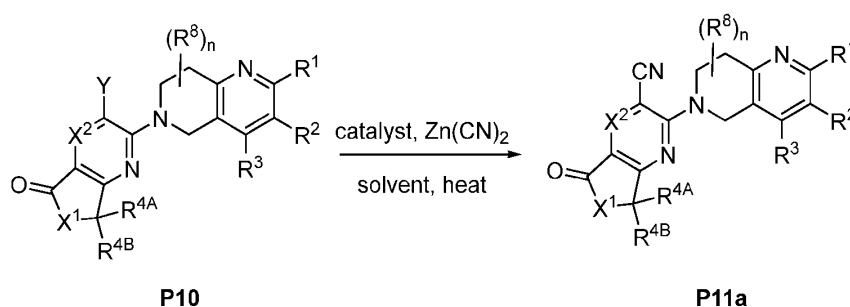
[00280] As illustrated in Scheme 6, intermediate compounds of formula **P2** may be subjected to standard nucleophilic substitution conditions with an intermediate of formula **P1b** (wherein Y is a halogen), base (e.g., DIPEA), solvent (e.g., DMSO) with heating to about 90-120 °C to provide compounds with the formula **P10**.

Scheme 7



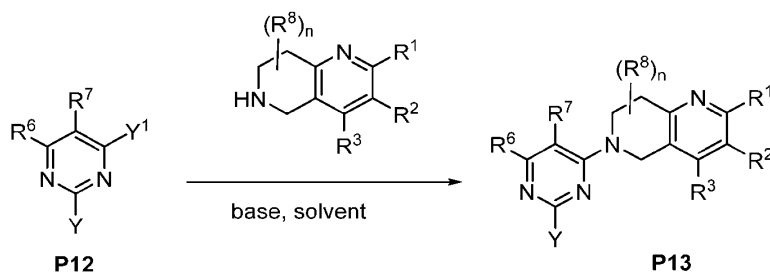
[00281] As shown in Scheme 7, intermediates of formula **P10** (wherein Y is a halogen) may be coupled with a boronic acid or ester under Suzuki coupling conditions, generally known in the art. Coupling reactions may be conducted with a palladium catalyst, such as Pd(dppf)Cl₂, and a base (e.g., K₂CO₃, Cs₂CO₃) in a solvent mixture of organic solvent, such as DMF or 1,4-dioxane, and water with heating to about 70-90 °C. Reactions may be facilitated with microwave irradiation.

Scheme 8



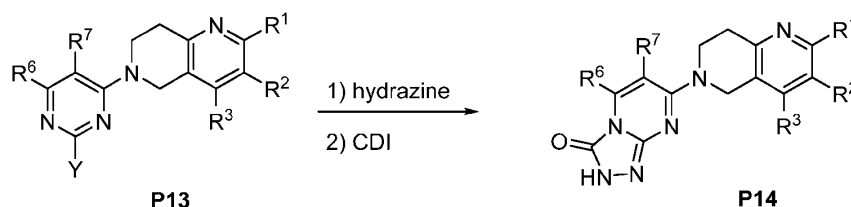
[00282] Shown in Scheme 8, intermediates of formula **P10** (wherein Y is a halogen) may be subjected to catalyst (e.g., Pd(PPh₃)₄), a cyanide source (e.g., Zn(CN)₂) and solvent (e.g., DMF) with heating up to 120-140 °C to afford compounds of formula **P11a**. The reaction may be facilitated with microwave irradiation.

Scheme 9



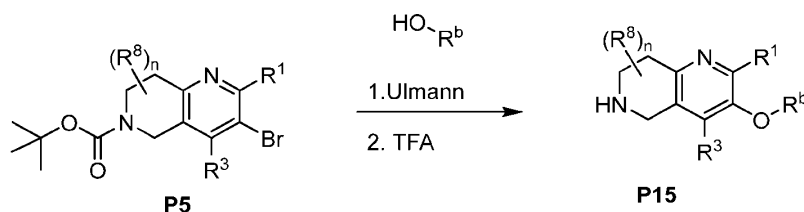
[00283] As illustrated in Scheme 9, intermediate compounds of formula **P12** (wherein Y and Y¹ are fluorine, chlorine, or bromine) may be subjected to standard nucleophilic substitution conditions with amine, base (e.g., DIEA, Et₃N, etc.), solvent (e.g., NMP, DMF) to provide compounds of formula **P13**.

Scheme 10



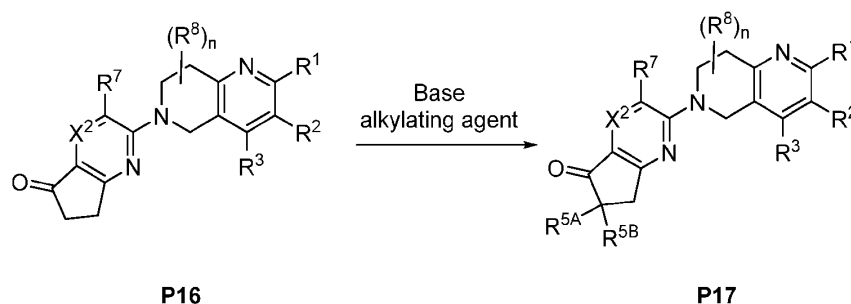
[00284] As shown in Scheme 10, intermediates of formula **P13** (wherein Y is a halogen) may be subjected to hydrazine in solvent (e.g., ethanol) with heating up to 70-80 °C, followed by ring formation (e.g., CDI (CAS# 530-62-1)) and heat up to 70-85 °C to form compounds of formula **P14**.

Scheme 11



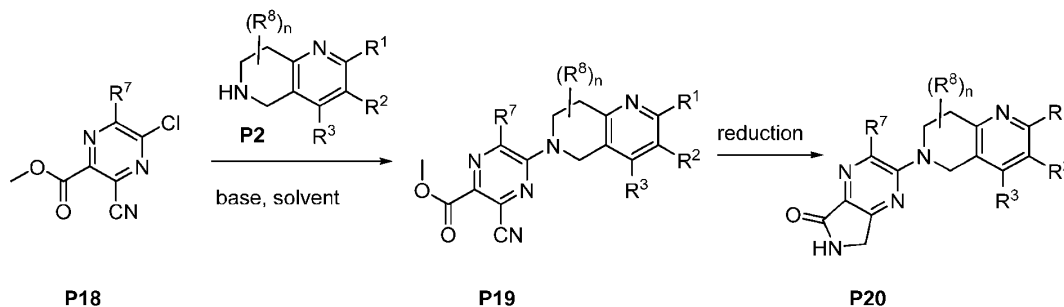
[00285] As shown in Scheme 11, compounds of formula **P5** may be reacted with alcohols under Ullmann conditions, generally known in the art, followed by deprotection with an acid (e.g., TFA) to provide intermediates of type **P15**. Suitable Ullmann conditions for coupling with a phenol include the use of a base (e.g., Cs₂CO₃), 2,2,6,6-tetramethylheptane-3,5-dione, and a copper salt (e.g., copper (I) iodide) with heating in a solvent, such as NMP, up to around 100-120 °C.

Scheme 12



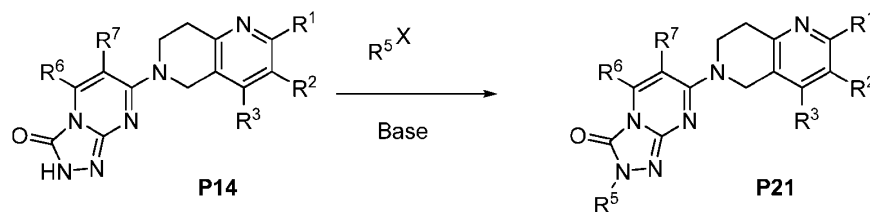
[00286] As shown in Scheme 12, compounds **P17** may be prepared from **P16** by alkylation with base (e.g., NaH) and a suitable alkylating agent (e.g., MeI).

Scheme 13



[00287] As shown in Scheme 13, compounds **P18** may react with compounds **P2** in the presence of base, analogous to Schemes 1 and 6 to provide **P19**. Reduction of the nitrile of **P19** (e.g., Raney nickel, ammonia, and hydrogen (g)) may provide compounds **P20**.

Scheme 14



[00288] As shown in Scheme 14, compounds **P21** may be prepared from **P14** by alkylation with base (e.g., K₂CO₃) and a suitable alkylating agent (e.g., R⁵-X, wherein X is a halogen, tosylate, etc.).

[00289] The following intermediates may be used in the foregoing schemes to prepare compounds of formula (I): 3-bromo-2-chloro-6,7-dihydro-5H-cyclopenta[*b*]pyridin-5-one and 3-bromo-2-chloro-6,6-difluoro-6,7-dihydro-5H-cyclopenta[*b*]pyridin-5-one, described in WO2018/118736.

[00290] Suitable boronic acids/esters, amines, and alcohols for coupling reactions described herein may be readily obtained from commercial sources or prepared by standard methods well known to those skilled in the art.

[00291] The compounds and intermediates may be isolated and purified by methods well-known to those skilled in the art of organic synthesis. Examples of conventional methods for isolating and purifying compounds can include, but are not limited to, chromatography on solid supports such as silica gel, alumina, or silica derivatized with alkylsilane groups, by recrystallization at high or low temperature with an optional pretreatment with activated carbon, thin-layer chromatography, distillation at various pressures, sublimation under vacuum, and trituration, as described for instance in “Vogel's Textbook of Practical Organic Chemistry,” 5th edition (1989), by Furniss, Hannaford, Smith, and Tatchell, pub. Longman Scientific & Technical, Essex CM20 2JE, England.

[00292] A disclosed compound may have at least one basic nitrogen whereby the compound can be treated with an acid to form a desired salt. For example, a compound may be reacted with an acid at or above room temperature to provide the desired salt, which is deposited, and collected by filtration after cooling. Examples of acids suitable for the reaction include, but are not limited to tartaric acid, lactic acid, succinic acid, as well as mandelic, atrolactic, methanesulfonic, ethanesulfonic, toluenesulfonic, naphthalenesulfonic, benzenesulfonic, carbonic, fumaric, maleic, gluconic, acetic, propionic, salicylic, hydrochloric, hydrobromic, phosphoric, sulfuric, citric, hydroxybutyric, camphorsulfonic, malic, phenylacetic, aspartic, or glutamic acid, and the like.

[00293] Reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the reactants used. Specific procedures are provided in the Examples section. Reactions can be worked up in the conventional manner, e.g. by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or can be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature. Starting materials, if not commercially available, can be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above-described schemes or the procedures described in the synthetic examples section.

[00294] Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that cannot be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the invention. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which can be found in PGM Wuts and TW Greene, in Greene's book titled *Protective Groups in Organic Synthesis* (4th ed.), John Wiley & Sons, NY (2006), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the invention can be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

[00295] When an optically active form of a disclosed compound is required, it can be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

[00296] Similarly, when a pure geometric isomer of a compound is required, it can be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

[00297] It can be appreciated that the synthetic schemes and specific examples as described are illustrative and are not to be read as limiting the scope of the invention as it is defined in the appended claims. All alternatives, modifications, and equivalents of the synthetic methods and specific examples are included within the scope of the claims.

c. Muscarinic Acetylcholine Receptor M₄ Activity

[00298] In some embodiments, the disclosed compounds potentiate the agonist response (e.g., acetylcholine) of mAChR M₄. In some embodiments, the disclosed compounds increase mAChR M₄ response to non-maximal concentrations of agonist in the presence of compound compared to the response to agonist in the absence of compound. The potentiation of mAChR M₄ activity can be demonstrated by methodology known in the art. For example, activation of mAChR M₄ activity can be determined by measurement of calcium flux in response to agonist, e.g. acetylcholine, in cells loaded with a Ca²⁺-sensitive fluorescent dye (e.g., Fluo-4) and co-

expression of a chimeric or promiscuous G protein. In some embodiments, the calcium flux was measured as an increase in fluorescent static ratio. In some embodiments, positive allosteric modulator activity was analyzed as a concentration-dependent increase in the EC₂₀ acetylcholine response (i.e. the response of mAChR M₄ at a concentration of acetylcholine that yields 20% of the maximal response).

[00299] In some embodiments, the disclosed compounds activate mAChR M₄ response as an increase in calcium fluorescence in mAChR M₄-transfected CHO-K1 cells in the presence of the compound, compared to the response of equivalent CHO-K1 cells in the absence of the compound. In some embodiments, a disclosed compound activates the mAChR M₄ response with an EC₅₀ of less than about 10 μ M, less than about 5 μ M, less than about 1 μ M, less than about 500 nM, of less than about 100 nM, or less than about 50 nM. In some embodiments, the mAChR M₄-transfected CHO-K1 cells are transfected with human mAChR M₄. In some embodiments, the mAChR M₄-transfected CHO-K1 cells are transfected with rat mAChR M₄.

[00300] The disclosed compounds may exhibit positive allosteric modulation of mAChR M₄ response to acetylcholine as an increase in response to non-maximal concentrations of acetylcholine in CHO-K1 cells transfected with a mAChR M₄ in the presence of the compound, compared to the response to acetylcholine in the absence of the compound. In some embodiments, the disclosed compounds exhibit positive allosteric modulation of the mAChR M₄ response to acetylcholine with an EC₅₀ of less than about 10 μ M, less than about 5 μ M, less than about 1 μ M, less than about 500 nM, or less than about 100 nM. In some embodiments, the EC₅₀ for positive allosteric modulation is determined in CHO-K1 cells are transfected with a mAChR M₄. In some embodiments, the mAChR M₄ transfected human mAChR M₄. In some embodiments, the mAChR M₄ transfected rat mAChR M₄.

[00301] A disclosed compound can have selectivity for the mAChR M₄ receptor vis-à-vis one or more of the mAChR M₁, M₂, M₃ or M₅ receptors. For example, the disclosed compounds may activate mAChR M₄ response in mAChR M₄-transfected CHO-K1 cells with an EC₅₀ less than the EC₅₀ for one or more of mAChR M₁, M₂, M₃ or M₅-transfected CHO-K1 cells. In some embodiments, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₁. In some embodiments, a disclosed compound can activate

mAChR M₄ response with an EC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₂. In some embodiments, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₃. In some embodiments, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₅. In some embodiments, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less than that for the M₂-M₅ receptors, of about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for the mAChR M₁, M₂, M₃, or M₅ receptors.

[00302] The disclosed compounds may activate mAChR M₄ response in M₄-transfected CHO-K1 cells with an EC₅₀ of less than about 10 μ M and exhibits a selectivity for the M₄ receptor vis-à-vis one or more of the mAChR M₁, M₂, M₃, or M₅ receptors. For example, in some embodiments, the compound can have an EC₅₀ of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M₄ response with an EC₅₀ of about 5-fold less, 10-fold less, 20-fold less, 30-fold less, 50-fold less, 100-fold less, 200-fold less, 300-fold less, 400-fold less, or greater than about 500-fold less than that for mAChR M₁. In some embodiments, the compound can have an EC₅₀ of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M₄ response with an EC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₂. In some embodiments, the compound can have an EC₅₀ of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can

also activate mAChR M₄ response with an EC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₃. In some embodiments, the compound can have an EC₅₀ of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M₄ response with an EC₅₀ of about 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less, about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, or greater than about 500-fold less than that for mAChR M₅. In some embodiments, the compound can have an EC₅₀ of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M₄ response with EC₅₀ of 5-fold less, about 10-fold less, about 20-fold less, about 30-fold less than that for the M₂-M₅ receptors, of about 50-fold less, about 100-fold less, about 200-fold less, about 300-fold less, about 400-fold less, M₂, M₃, or M₅ receptors, or greater than about 500-fold less than that for the mAChR M₁, M₂, M₃, or M₅ receptors.

[00303] In vivo efficacy for disclosed compounds can be measured in a number of preclinical rat behavioral models where known, clinically useful antipsychotics display similar positive responses. For example, disclosed compounds may reverse amphetamine-induced hyperlocomotion in male Sprague-Dawley rats at doses ranging from 1 to 100 mg/kg p.o.

3. Pharmaceutical Compositions and Formulations

[00304] The disclosed compounds may be incorporated into pharmaceutical compositions suitable for administration to a subject (such as a patient, which may be a human or non-human). The disclosed compounds may also be provided as formulations, such as spray-dried dispersion formulations.

[00305] The pharmaceutical compositions and formulations may include a “therapeutically effective amount” or a “prophylactically effective amount” of the agent. A “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the composition may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or

detrimental effects of a compound of the invention (e.g., a compound of formula (I)) are outweighed by the therapeutically beneficial effects. A “prophylactically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[00306] For example, a therapeutically effective amount of a compound of formula (I), may be about 1 mg/kg to about 1000 mg/kg, about 5 mg/kg to about 950 mg/kg, about 10 mg/kg to about 900 mg/kg, about 15 mg/kg to about 850 mg/kg, about 20 mg/kg to about 800 mg/kg, about 25 mg/kg to about 750 mg/kg, about 30 mg/kg to about 700 mg/kg, about 35 mg/kg to about 650 mg/kg, about 40 mg/kg to about 600 mg/kg, about 45 mg/kg to about 550 mg/kg, about 50 mg/kg to about 500 mg/kg, about 55 mg/kg to about 450 mg/kg, about 60 mg/kg to about 400 mg/kg, about 65 mg/kg to about 350 mg/kg, about 70 mg/kg to about 300 mg/kg, about 75 mg/kg to about 250 mg/kg, about 80 mg/kg to about 200 mg/kg, about 85 mg/kg to about 150 mg/kg, and about 90 mg/kg to about 100 mg/kg.

[00307] The pharmaceutical compositions and formulations may include pharmaceutically acceptable carriers. The term “pharmaceutically acceptable carrier,” as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such as propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents,

preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00308] Thus, the compounds and their pharmaceutically acceptable salts may be formulated for administration by, for example, solid dosing, eye drop, in a topical oil-based formulation, injection, inhalation (either through the mouth or the nose), implants, or oral, buccal, parenteral, or rectal administration. Techniques and formulations may generally be found in “Remington's Pharmaceutical Sciences,” (Meade Publishing Co., Easton, Pa.). Therapeutic compositions must typically be sterile and stable under the conditions of manufacture and storage.

[00309] The route by which the disclosed compounds are administered and the form of the composition will dictate the type of carrier to be used. The composition may be in a variety of forms, suitable, for example, for systemic administration (e.g., oral, rectal, nasal, sublingual, buccal, implants, or parenteral) or topical administration (e.g., dermal, pulmonary, nasal, aural, ocular, liposome delivery systems, or iontophoresis).

[00310] Carriers for systemic administration typically include at least one of diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, antioxidants, preservatives, glidants, solvents, suspending agents, wetting agents, surfactants, combinations thereof, and others. All carriers are optional in the compositions.

[00311] Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of diluent(s) in a systemic or topical composition is typically about 50 to about 90%.

[00312] Suitable lubricants include silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate, and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of lubricant(s) in a systemic or topical composition is typically about 5 to about 10%.

[00313] Suitable binders include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of binder(s) in a systemic composition is typically about 5 to about 50%.

[00314] Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of disintegrant(s) in a systemic or topical composition is typically about 0.1 to about 10%.

[00315] Suitable colorants include a colorant such as an FD&C dye. When used, the amount of colorant in a systemic or topical composition is typically about 0.005 to about 0.1%.

[00316] Suitable flavors include menthol, peppermint, and fruit flavors. The amount of flavor(s), when used, in a systemic or topical composition is typically about 0.1 to about 1.0%.

[00317] Suitable sweeteners include aspartame and saccharin. The amount of sweetener(s) in a systemic or topical composition is typically about 0.001 to about 1%.

[00318] Suitable antioxidants include butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of antioxidant(s) in a systemic or topical composition is typically about 0.1 to about 5%.

[00319] Suitable preservatives include benzalkonium chloride, methyl paraben and sodium benzoate. The amount of preservative(s) in a systemic or topical composition is typically about 0.01 to about 5%.

[00320] Suitable glidants include silicon dioxide. The amount of glidant(s) in a systemic or topical composition is typically about 1 to about 5%.

[00321] Suitable solvents include water, isotonic saline, ethyl oleate, glycerine, hydroxylated castor oils, alcohols such as ethanol, and phosphate buffer solutions. The amount of solvent(s) in a systemic or topical composition is typically from about 0 to about 100%.

[00322] Suitable suspending agents include AVICEL RC-591 (from FMC Corporation of Philadelphia, PA) and sodium alginate. The amount of suspending agent(s) in a systemic or topical composition is typically about 1 to about 8%.

[00323] Suitable surfactants include lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS from Atlas Powder Company of Wilmington, Delaware. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of surfactant(s) in the systemic or topical composition is typically about 0.1% to about 5%.

[00324] Although the amounts of components in the systemic compositions may vary depending on the type of systemic composition prepared, in general, systemic compositions include 0.01% to 50% of an active compound (e.g., a compound of formula (I)) and 50% to 99.99% of one or more carriers. Compositions for parenteral administration typically include 0.1% to 10% of actives and 90% to 99.9% of a carrier including a diluent and a solvent.

[00325] Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms include a safe and effective amount, usually at least about 5%, and more particularly from about 25% to about 50% of actives. The oral dosage compositions include about 50% to about 95% of carriers, and more particularly, from about 50% to about 75%.

[00326] Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically include an active component, and a carrier comprising ingredients selected from diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, glidants, and combinations thereof. Specific diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmellose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain sweeteners such as aspartame and saccharin, or flavors such as menthol, peppermint, fruit flavors, or a combination thereof.

[00327] Capsules (including implants, time release and sustained release formulations) typically include an active compound (e.g., a compound of formula (I)), and a carrier including one or more diluents disclosed above in a capsule comprising gelatin. Granules typically comprise a disclosed compound, and preferably glidants such as silicon dioxide to improve flow characteristics. Implants can be of the biodegradable or the non-biodegradable type.

[00328] The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention.

[00329] Solid compositions may be coated by conventional methods, typically with pH or time-dependent coatings, such that a disclosed compound is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically include one or more components selected from the group

consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Evonik Industries of Essen, Germany), waxes and shellac.

[00330] Compositions for oral administration can have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically include a disclosed compound and a carrier, namely, a carrier selected from diluents, colorants, flavors, sweeteners, preservatives, solvents, suspending agents, and surfactants. Peroral liquid compositions preferably include one or more ingredients selected from colorants, flavors, and sweeteners.

[00331] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically include one or more of soluble filler substances such as diluents including sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Such compositions may further include lubricants, colorants, flavors, sweeteners, antioxidants, and glidants.

[00332] The disclosed compounds can be topically administered. Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions include: a disclosed compound (e.g., a compound of formula (I)), and a carrier. The carrier of the topical composition preferably aids penetration of the compounds into the skin. The carrier may further include one or more optional components.

[00333] The amount of the carrier employed in conjunction with a disclosed compound is sufficient to provide a practical quantity of composition for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

[00334] A carrier may include a single ingredient or a combination of two or more ingredients. In the topical compositions, the carrier includes a topical carrier. Suitable topical carriers include one or more ingredients selected from phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, and symmetrical alcohols.

[00335] The carrier of a topical composition may further include one or more ingredients selected from emollients, propellants, solvents, humectants, thickeners, powders, fragrances, pigments, and preservatives, all of which are optional.

[00336] Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane. The amount of emollient(s) in a skin-based topical composition is typically about 5% to about 95%.

[00337] Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof. The amount of propellant(s) in a topical composition is typically about 0% to about 95%.

[00338] Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Specific solvents include ethyl alcohol and homotopic alcohols. The amount of solvent(s) in a topical composition is typically about 0% to about 95%.

[00339] Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants include glycerin. The amount of humectant(s) in a topical composition is typically 0% to 95%.

[00340] The amount of thickener(s) in a topical composition is typically about 0% to about 95%.

[00341] Suitable powders include beta-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium aluminum silicate, organically-modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. The amount of powder(s) in a topical composition is typically 0% to 95%.

[00342] The amount of fragrance in a topical composition is typically about 0% to about 0.5%, particularly, about 0.001% to about 0.1%.

[00343] Suitable pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of a topical pharmaceutical composition.

[00344] The pharmaceutical composition or formulation may exhibit positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 10 μ M, less than about 5 μ M, less than about 1 μ M, less than about 500 nM, or less than about 100 nM. The pharmaceutical composition or formulation may exhibit positive allosteric modulation of mAChR M₄ with an EC₅₀ of between about 10 μ M and about 1 nM, about 1 μ M and about 1 nM, about 100 nM and about 1 nM, or between about 10 nM and about 1 nM.

a. Spray-Dried Dispersion Formulations

[00345] The disclosed compounds may be formulated as a spray-dried dispersion (SDD). An SDD is a single-phase, amorphous molecular dispersion of a drug in a polymer matrix. It is a solid solution with the compound molecularly “dissolved” in a solid matrix. SDDs are obtained by dissolving drug and a polymer in an organic solvent and then spray-drying the solution. The use of spray drying for pharmaceutical applications can result in amorphous dispersions with increased solubility of Biopharmaceutics Classification System (BCS) class II (high permeability, low solubility) and class IV (low permeability, low solubility) drugs. Formulation and process conditions are selected so that the solvent quickly evaporates from the droplets, thus

allowing insufficient time for phase separation or crystallization. SDDs have demonstrated long-term stability and manufacturability. For example, shelf lives of more than 2 years have been demonstrated with SDDs. Advantages of SDDs include, but are not limited to, enhanced oral bioavailability of poorly water-soluble compounds, delivery using traditional solid dosage forms (e.g., tablets and capsules), a reproducible, controllable and scalable manufacturing process and broad applicability to structurally diverse insoluble compounds with a wide range of physical properties.

[00346] Thus, in one embodiment, the disclosure may provide a spray-dried dispersion formulation comprising a compound of formula (I).

4. Methods of Use

[00347] The disclosed compounds, pharmaceutical compositions and formulations may be used in methods for treatment of disorders, such as neurological and/or psychiatric disorders, associated with muscarinic acetylcholine receptor dysfunction. The disclosed compounds and pharmaceutical compositions may also be used in methods for the potentiation of muscarinic acetylcholine receptor activity in a mammal, and in methods for enhancing cognition in a mammal. The methods further include cotherapeutic methods for improving treatment outcomes in the context of cognitive or behavioral therapy. In the methods of use described herein, additional therapeutic agent(s) may be administered simultaneously or sequentially with the disclosed compounds and compositions.

a. Treating disorders

[00348] The disclosed compounds, pharmaceutical compositions and formulations may be used for treating disorders, or used in methods for treatment of disorders, such as neurological and/or psychiatric disorders, associated with muscarinic acetylcholine receptor dysfunction. The methods of treatment may comprise administering to a subject in need of such treatment a therapeutically effective amount of the compound of formula (I), or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I).

[00349] In some embodiments, the disclosure provides a method for enhancing cognition in a mammal comprising the step of administering to the mammal a therapeutically effective amount of the compound of formula (I), or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I).

[00350] The compounds and compositions disclosed herein may be useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of disorders associated with selective mAChR M₄ receptor activation. For example, a treatment can include selective mAChR M₄ receptor activation to an extent effective to affect cholinergic activity. A disorder can be associated with cholinergic activity, for example cholinergic hypofunction. 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 or at least one disclosed pharmaceutical composition, in an amount effective to treat the disorder in the subject.

[00351] Also provided is a method for the treatment of one or more disorders associated with mAChR M₄ receptor activity in a subject comprising the step of administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

[00352] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of a disorder associated with the mAChR M₄ receptor. In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of a disorder associated with the mAChR M₄ receptor.

[00353] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment of a disorder associated with the mAChR M₄ receptor.

[00354] In some embodiments, the disclosure provides a method for the treatment of a disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal, comprising the step of administering to the mammal an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising at least one disclosed compound or pharmaceutically acceptable salt thereof.

[00355] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of a disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[00356] In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of a disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[00357] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment of a disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[00358] In some embodiments, the disclosed compounds and compositions have utility in treating a variety of neurological, psychiatric and cognitive disorders associated with the mAChR M₄ receptor, including one or more of the following conditions or diseases: schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In some embodiments, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, Alzheimer's disease, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder.

[00359] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of a neurological, psychiatric, or cognitive disorder associated with the mAChR M₄ receptor, in particular, the disorders described herein. In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of a neurological, psychiatric, or cognitive disorder associated with the mAChR M₄ receptor, in particular, the disorders described herein. In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment of a neurological, psychiatric, or cognitive disorder associated with the mAChR M₄ receptor, in particular, the disorders described herein.

[00360] In some embodiments, the disorder is a neurological disorder selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis.

[00361] In some embodiments, the disorder is a psychotic disorder selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In some embodiments, the schizophrenia is selected from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In some embodiments, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder. In some embodiments, the psychotic disorder is due to a general medical condition and is substance-induced or drug-induced (phencyclidine, ketamine and other dissociative anesthetics, amphetamine and other psychostimulants, and cocaine).

[00362] In some embodiments, the present disclosure provides a method for treating a cognitive disorder, comprising administering to a patient in need thereof an effective amount of a compound or a composition of the present disclosure. In some embodiments, cognitive disorders include dementia (associated with Alzheimer's disease, ischemia, multi-infarct dementia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse), delirium, amnestic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[00363] The text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes cognitive disorders including dementia, delirium, amnestic disorders and age-related cognitive decline. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (2013, American Psychiatric Association, Washington DC) provides a diagnostic tool for neurocognitive disorders (NCDs) that include delirium, followed by the syndromes of major NCD, mild NCD, and their etiological subtypes. The major or mild NCD subtypes include NCD due to Alzheimer's disease, vascular NCD, NCD

with Lewy bodies, NCD due to Parkinson's disease, frontotemporal NCD, NCD due to traumatic brain injury, NCD due to HIV infection, substance/medication-induced NCD, NCD due to Huntington's disease, NCD due to prion disease, NCD due to another medical condition, NCD due to multiple etiologies, and unspecified NCD. The NCD category in DSM-5 encompasses the group of disorders in which the primary clinical deficit is in cognitive function, and that are acquired rather than developmental. As used herein, the term "cognitive disorders" includes treatment of those cognitive disorders and neurocognitive disorders as described in DSM-IV-TR or DSM-5. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term "cognitive disorders" is intended to include like disorders that are described in other diagnostic sources.

[00364] In some embodiments, the present disclosure provides a method for treating schizophrenia or psychosis, comprising administering to a patient in need thereof an effective amount of a compound or composition of the present disclosure. Particular schizophrenia or psychosis pathologies are paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder. DSM-IV-TR provides a diagnostic tool that includes paranoid, disorganized, catatonic, undifferentiated or residual schizophrenia, and substance-induced psychotic disorder. DSM-5 eliminated the subtypes of schizophrenia, and instead includes a dimensional approach to rating severity for the core symptoms of schizophrenia, to capture the heterogeneity in symptom type and severity expressed across individuals with psychotic disorders. As used herein, the term "schizophrenia or psychosis" includes treatment of those mental disorders as described in DSM-IV-TR or DSM-5. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term "schizophrenia or psychosis" is intended to include like disorders that are described in other diagnostic sources.

[00365] In some embodiments, the present disclosure provides a method for treating pain, comprising administering to a patient in need thereof an effective amount of a compound or composition of the present disclosure. Particular pain embodiments are bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular

injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain and neuropathic pain.

[00366] The compounds and compositions may be further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein. The compounds and compositions may be further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions, in combination with other agents.

[00367] In the treatment of conditions which require activation of mAChR M₄, an appropriate dosage level may be about 0.01 to 500 mg per kg patient body weight per day, which can be administered in single or multiple doses. The dosage level may be about 0.1 to about 250 mg/kg per day, or about 0.5 to about 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 or 5 to 50 mg/kg per day. For oral administration, the compositions may be 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, or 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosage regimen can be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[00368] Thus, in some embodiments, the disclosure relates to a method for activating mAChR M₄ receptor activity in at least one cell, comprising the step of contacting the at least one cell with at least one disclosed compound or at least one product of a disclosed method in an amount effective to activate mAChR M₄ in the at least one cell. In some embodiments, the cell is mammalian, for example, human. In some embodiments, the cell has been isolated from a subject prior to the contacting step. In some embodiments, contacting is via administration to a subject.

[00369] In some embodiments, the invention relates to a method for activating mAChR M₄ activity in a subject, comprising the step of administering to the subject at least one disclosed compound or at least one product of a disclosed method in a dosage and amount effective to activating mAChR M₄ activity in the subject. In some embodiments, the subject is mammalian, for example, human. In some embodiments, the mammal has been diagnosed with a need for mAChR M₄ agonism prior to the administering step. In some embodiments, the mammal has been diagnosed with a need for mAChR M₄ activation prior to the administering step. In some embodiments, the method further comprises the step of identifying a subject in need of mAChR M₄ agonism.

[00370] In some embodiments, the invention relates to a method for the treatment of a disorder associated with selective mAChR M₄ activation, for example, a disorder associated with cholinergic activity, in a mammal comprising the step of administering to the mammal at least one disclosed compound or at least one product of a disclosed method in a dosage and amount effective to treat the disorder in the mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal has been diagnosed with a need for treatment for the disorder prior to the administering step. In some embodiments, the method further comprises the step of identifying a subject in need of treatment for the disorder.

[00371] In some embodiments, the disorder can be selected from psychosis, schizophrenia, conduct disorder, disruptive behavior disorder, bipolar disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, autistic disorder, movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

[00372] In some embodiments, the disorder is Alzheimer's disease.

b. Potentiation of Muscarinic Acetylcholine Receptor Activity

[00373] In some embodiments, the disclosure relates to a method for potentiation of muscarinic acetylcholine receptor activity in a mammal comprising the step of administering to the mammal an effective amount of at least one disclosed compound or a pharmaceutically

acceptable salt thereof, or a pharmaceutical composition comprising at least one disclosed compound or pharmaceutically acceptable salt thereof.

[00374] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the potentiation of muscarinic acetylcholine receptor activity in a mammal. In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the potentiation of muscarinic acetylcholine receptor activity in a mammal.

[00375] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the potentiation of muscarinic acetylcholine receptor activity in a mammal.

[00376] In some embodiments, potentiation of muscarinic acetylcholine receptor activity increases muscarinic acetylcholine receptor activity. In some embodiments, potentiation of muscarinic acetylcholine receptor activity is partial agonism of the muscarinic acetylcholine receptor. In some embodiments, potentiation of muscarinic acetylcholine receptor activity is positive allosteric modulation of the muscarinic acetylcholine receptor.

[00377] In some embodiments, the compound administered exhibits potentiation of mAChR M₄ with an EC₅₀ of less than about 10 μ M, less than about 5 μ M, less than about 1 μ M, less than about 500 nM, or less than about 100 nM. In some embodiments, the compound administered exhibits potentiation of mAChR M₄ with an EC₅₀ of between about 10 μ M and about 1 nM, about 1 μ M and about 1 nM, about 100 nM and about 1 nM, or about 10 nM and about 1 nM.

[00378] In some embodiments, the mammal is a human. In some embodiments, the mammal has been diagnosed with a need for potentiation of muscarinic acetylcholine receptor activity prior to the administering step. In some embodiments, the method further comprises the step of identifying a mammal in need of potentiating muscarinic acetylcholine receptor activity. In some embodiments, the potentiation of muscarinic acetylcholine receptor activity treats a disorder associated with muscarinic acetylcholine receptor activity in the mammal. In some embodiments, the muscarinic acetylcholine receptor is mAChR M₄.

[00379] In some embodiments, potentiation of muscarinic acetylcholine receptor activity in a mammal is associated with the treatment of a neurological and/or psychiatric disorder associated

with a muscarinic receptor dysfunction, such as a neurological or psychiatric disorder disclosed herein. In some embodiments, the muscarinic receptor is mAChR M₄.

[00380] In some embodiments, the disclosure provides to a method for potentiation of muscarinic acetylcholine receptor activity in a cell, comprising the step of contacting the cell with an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof. In some embodiments, the cell is mammalian (e.g., human). In some embodiments, the cell has been isolated from a mammal prior to the contacting step. In some embodiments, contacting is via administration to a mammal.

c. Enhancing Cognition

[00381] In some embodiments, the invention relates to a method for enhancing cognition in a mammal comprising the step of administering to the mammal an effective amount of least one disclosed compound; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00382] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the enhancement of cognition in a mammal. In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a method for the enhancement of cognition in a mammal.

[00383] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the enhancement of cognition in a mammal.

[00384] In some embodiments, the mammal is a human. In some embodiments, the mammal has been diagnosed with a need for cognition enhancement prior to the administering step. In some embodiments, the method further comprises the step of identifying a mammal in need of cognition enhancement. In some embodiments, the need for cognition enhancement is associated with a muscarinic receptor dysfunction. In some embodiments, the muscarinic receptor is mAChR M₄.

[00385] In some embodiments, the cognition enhancement is a statistically significant increase in Novel Object Recognition. In some embodiments, the cognition enhancement is a statistically significant increase in performance of the Wisconsin Card Sorting Test.

d. Cotherapeutic methods

[00386] The present invention is further directed to administration of a selective mAChR M₄ activator for improving treatment outcomes in the context of cognitive or behavioral therapy. That is, in some embodiments, the invention relates to a cotherapeutic method comprising a step of administering to a mammal an effective amount and dosage of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[00387] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a cotherapeutic method with cognitive or behavioral therapy in a mammal. In some embodiments, the disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in a cotherapeutic method with cognitive or behavioral therapy in a mammal.

[00388] In some embodiments, the disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for a cotherapeutic method with cognitive or behavioral therapy in a mammal.

[00389] In some embodiments, administration improves treatment outcomes in the context of cognitive or behavioral therapy. Administration in connection with cognitive or behavioral therapy can be continuous or intermittent. Administration need not be simultaneous with therapy and can be before, during, and/or after therapy. For example, cognitive or behavioral therapy can be provided within 1, 2, 3, 4, 5, 6, 7 days before or after administration of the compound. As a further example, cognitive or behavioral therapy can be provided within 1, 2, 3, or 4 weeks before or after administration of the compound. As a still further example, cognitive or behavioral therapy can be provided before or after administration within a period of time of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 half-lives of the administered compound.

[00390] It is understood that the disclosed cotherapeutic methods can be used in connection with the disclosed compounds, compositions, kits, and uses.

e. Combination Therapies

[00391] In the methods of use described herein, additional therapeutic agent(s) may be administered simultaneously or sequentially with the disclosed compounds and compositions. Sequential administration includes administration before or after the disclosed compounds and compositions. In some embodiments, the additional therapeutic agent or agents may be

administered in the same composition as the disclosed compounds. In other embodiments, there may be an interval of time between administration of the additional therapeutic agent and the disclosed compounds. In some embodiments, administration of an additional therapeutic agent with a disclosed compound may allow lower doses of the other therapeutic agents and/or administration at less frequent intervals. When used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula (I). The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds.

[00392] 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 the compound 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 therefor, 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 may be used. 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 can be more efficacious than either as a single agent. Thus, when used in combination with one or more other active ingredients, the disclosed compounds and the other active ingredients can be used in lower doses than when each is used singly.

[00393] 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.

[00394] The above combinations include combinations of a disclosed compound not only with one other active compound, but also with two or more other active compounds. Likewise, disclosed compounds can be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for

which disclosed compounds are useful. Such other drugs can be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to a disclosed compound is preferred. Accordingly, the pharmaceutical compositions include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

[00395] The weight ratio of a disclosed compound to the second active ingredient can be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of a disclosed compound to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[00396] In such combinations a disclosed compound and other active agents can be administered separately or in conjunction. In addition, the administration of one element can be prior to, concurrent to, or subsequent to the administration of other agent(s).

[00397] Accordingly, the disclosed compounds can be used alone or in combination with other agents which are known to be beneficial in the subject indications or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the disclosed compounds. The subject compound and the other agent can be coadministered, either in concomitant therapy or in a fixed combination.

[00398] In some embodiments, the compound can be employed in combination with anti-Alzheimer's agents, beta-secretase inhibitors, cholinergic agents, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, M₁ allosteric agonists, M₁ positive allosteric modulators, NSAIDs including ibuprofen, vitamin E, and anti-amyloid antibodies. In another embodiment, the subject compound can be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics (typical and atypical), antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam,

allobarbitol, alonimid, alprazolam, amisulpride, amitriptyline, amobarbital, amoxapine, aripiprazole, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, clomipramine, clonazepam, cloperidone, clorazepate, chlordiazepoxide, clorethate, chlorpromazine, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flupentixol, fluphenazine, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, haloperidol, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, olanzapine, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, quetiapine, reclazepam, risperidone, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, thiothixene, tracazolate, tranlycypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, ziprasidone, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound can be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

[00399] In some embodiments, the compound can be employed in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist can be in the form of a pharmaceutically acceptable salt, for example, alentemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate. Lisuride and pramipexol are commonly used in a non-salt form.

[00400] In some embodiments, the compound can be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of

phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. It will be appreciated that the neuroleptic agents when used in combination with the subject compound can be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form. Thus, the subject compound can be employed in combination with acetophenazine, alantemol, aripiprazole, amisulpride, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, quetiapine, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene, trifluoperazine or ziprasidone.

[00401] In some embodiments, the compound can be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranylcypromine and selegiline; moclobemide; venlafaxine; duloxetine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and

prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

[00402] In some embodiments, the compounds can be coadministered with orthosteric muscarinic agonists, muscarinic potentiators, or cholinesterase inhibitors. In some embodiments, the compounds can be coadministered with GlyT1 inhibitors and the like such as, but not limited to: risperidone, clozapine, haloperidol, fluoxetine, prazepam, xanomeline, lithium, phenobarbital, and salts thereof and combinations thereof.

f. Modes of Administration

[00403] Methods of treatment may include any number of modes of administering a disclosed composition. Modes of administration may include tablets, pills, dragees, hard and soft gel capsules, granules, pellets, aqueous, lipid, oily or other solutions, emulsions such as oil-in-water emulsions, liposomes, aqueous or oily suspensions, syrups, elixirs, solid emulsions, solid dispersions or dispersible powders. For the preparation of pharmaceutical compositions for oral administration, the agent may be admixed with commonly known and used adjuvants and excipients such as for example, gum arabic, talcum, starch, sugars (such as, e.g., mannitol, methyl cellulose, lactose), gelatin, surface-active agents, magnesium stearate, aqueous or non-aqueous solvents, paraffin derivatives, cross-linking agents, dispersants, emulsifiers, lubricants, conserving agents, flavoring agents (e.g., ethereal oils), solubility enhancers (e.g., benzyl benzoate or benzyl alcohol) or bioavailability enhancers (e.g. Gelucire.TM.). In the pharmaceutical composition, the agent may also be dispersed in a microparticle, e.g. a nanoparticulate composition.

[00404] For parenteral administration, the agent can be dissolved or suspended in a physiologically acceptable diluent, such as, e.g., water, buffer, oils with or without solubilizers, surface-active agents, dispersants or emulsifiers. As oils for example and without limitation, olive oil, peanut oil, cottonseed oil, soybean oil, castor oil and sesame oil may be used. More generally spoken, for parenteral administration, the agent can be in the form of an aqueous, lipid, oily or other kind of solution or suspension or even administered in the form of liposomes or nano-suspensions.

[00405] The term “parenterally,” as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

5. Kits

[00406] In one aspect, the disclosure provides kits comprising at least one disclosed compound or a pharmaceutically acceptable salt thereof, and one or more of:

- (a) at least one agent known to increase mAChR M₄ activity;
- (b) at least one agent known to decrease mAChR M₄ activity;
- (c) at least one agent known to treat a disorder associated with cholinergic activity;
- (d) instructions for treating a disorder associated with cholinergic activity;
- (e) instructions for treating a disorder associated with M₄ receptor activity; or
- (f) instructions for administering the compound in connection with cognitive or behavioral therapy.

[00407] In some embodiments, the at least one disclosed compound and the at least one agent are co-formulated. In some embodiments, the at least one disclosed compound and the at least one agent are co-packaged. 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.

[00408] The disclosed kits can be employed in connection with disclosed methods of use.

[00409] The kits may further comprise information, instructions, or both that use of the kit may provide treatment for medical conditions in mammals (particularly humans). The information and instructions may be in the form of words, pictures, or both, and the like. In addition or in the alternative, the kit may include the compound, a composition, or both; and information, instructions, or both; regarding methods of application of compound, or of composition, for example with the benefit of treating or preventing medical conditions in mammals (e.g., humans).

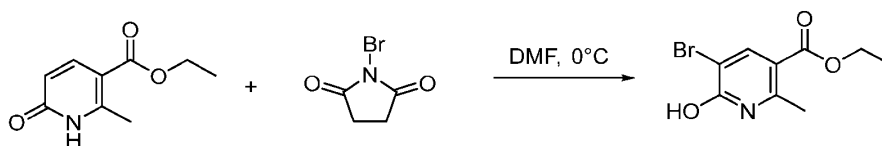
[00410] The compounds and processes of the invention will be better understood by reference to the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

6. Examples

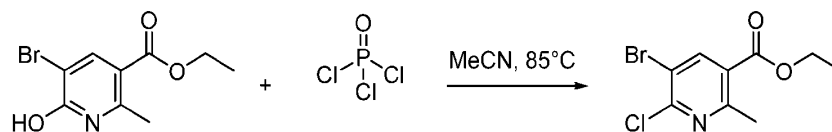
[00411] All NMR spectra were recorded on a 400 MHz AMX Bruker NMR spectrometer. ¹H chemical shifts are reported in δ values in ppm downfield with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, bs =

broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, ABq = AB quartet), coupling constant, integration. Reversed-phase LCMS analysis was performed using an Agilent 1200 system comprised of a binary pump with degasser, high-performance autosampler, thermostatted column compartment, C18 column, diode-array detector (DAD) and an Agilent 6150 MSD with the following parameters. The gradient conditions were 5% to 95% acetonitrile with the aqueous phase 0.1% TFA in water over 1.4 minutes, hold at 95% acetonitrile for 0.1 min, 0.5 mL/min, 55 °C ("90 sec method"). Samples were separated on a Waters Acquity UPLC BEH C18 column (1.7 μ m, 1.0 x 50 mm) at 0.5 mL/min, with column and solvent temperatures maintained at 55 °C. The DAD was set to scan from 190 to 300 nm, and the signals used were 220 nm and 254 nm (both with a band width of 4nm). The MS detector was configured with an electrospray ionization source, and the low-resolution mass spectra were acquired by scanning from 140 to 700 AMU with a step size of 0.2 AMU at 0.13 cycles/second, and peak width of 0.008 minutes. The drying gas flow was set to 13 liters per minute at 300 °C and the nebulizer pressure was set to 30 psi. The capillary needle voltage was set at 3000 V, and the fragmentor voltage was set at 100V. Data acquisition was performed with Agilent Chemstation and Analytical Studio Reviewer software.

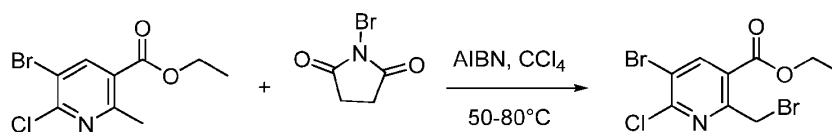
a. Preparation of Intermediates



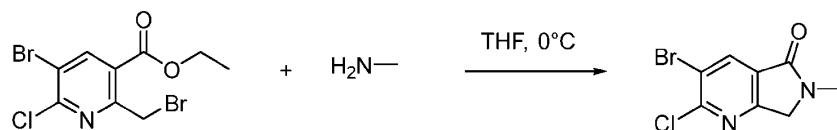
[00412] Ethyl 5-bromo-6-hydroxy-2-methylnicotinate. To a solution of ethyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (10 g, 55.2 mmol) in DMF (185 mL) at 0 °C was slowly added *N*-bromosuccinimide (10.8 g, 60.7 mmol) portionwise. The ice bath was removed. After 18 h, to the reaction was added saturated sodium bisulfite (aq) and stirred for 30 min. The reaction was filtered and the collected solid was dried by vacuum oven to afford the title compound (14.2 g). ¹H NMR (400 MHz, DMSO) δ 8.15 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.32 (s, 3H), 2.55 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ES-MS [*M*+1]⁺: 260.0/262.0.



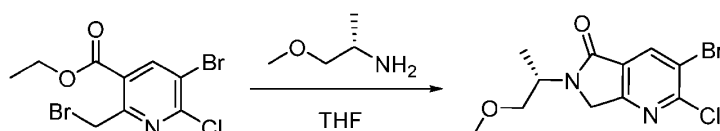
[00413] Ethyl 5-bromo-6-chloro-2-methylnicotinate. To a 500 mL round bottom flask was added ethyl 5-bromo-6-hydroxy-2-methylnicotinate (14.2 g, 54.6 mmol) in MeCN (300 mL) followed by phosphorous (V) oxychloride (29.4 mL, 316 mmol). The reaction was equipped with a condenser and heated at 85 °C. After 18 h, the mixture was cooled to room temperature and concentrated. The residue was dissolved in DCM (10 mL) and slowly added dropwise to a stirred solution of saturated aqueous NaHCO₃ solution, keeping the pH >7. Additional DCM (25 mL) was added and the mixture was allowed to stir for 30 min. The organic layer was separated and the aqueous layer was re-extracted with 3:1 chloroform/IPA (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was purified by normal-phase chromatography (0-25% EtOAc/Hexanes) to afford the title compound (12 g). ¹H NMR (400 MHz, CDCl₃) δ 8.40 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.76 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ES-MS [*M*+1]⁺: 277.9/279.9.



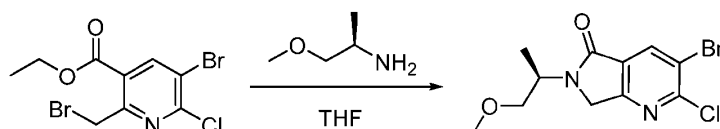
[00414] Ethyl 5-bromo-2-(bromomethyl)-6-chloronicotinate. To a solution of ethyl 5-bromo-6-chloro-2-methylnicotinate (12 g, 43.1 mmol) and 2,2'-azobis(2-methylpropionitrile) (0.71 g, 4.3 mmol) in carbon tetrachloride (287 mL) at 50 °C was added portionwise N-bromosuccinimide (8.43g, 47.4 mmol). After 30 min, the reaction was heated to 80 °C. After 18 h, the reaction was cooled to room temperature, diluted with water, and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was purified by normal-phase chromatography (0-4% EtOAc/Hexanes) to afford the title compound (13.6 g). ¹H NMR (400 MHz, CDCl₃) δ 8.48 (s, 1H), 4.91 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); ES-MS [*M*+1]⁺: 357.9/359.9.



[00415] **3-Bromo-2-chloro-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one.** To a solution of ethyl 5-bromo-2-(bromomethyl)-6-chloronicotinate (2.5 g, 6.99 mmol) in THF (140 mL) at 0 °C was added a 2.0 M solution of methylamine (17.5 mL, 35.0 mmol) and the reaction stirred for 30 min. The reaction was concentrated at rt and purified by normal-phase chromatography (0-30% EtOAc/DCM) to afford the title compound. ¹H NMR (400 MHz, DMSO) δ 8.49 (s, 1H), 4.50 (s, 2H), 3.09 (s, 3H); ES-MS [M+1]⁺: 261.1/263.1.

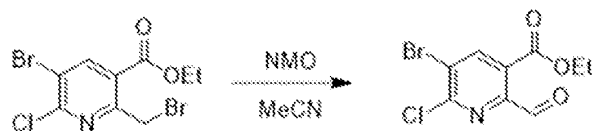


[00416] **(*S*)-3-Bromo-2-chloro-6-(1-methoxypropan-2-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one.** To a solution of ethyl 5-bromo-2-(bromomethyl)-6-chloronicotinate (201 mg, 0.3 mmol) in THF (2.5 mL) was added (*S*)-(+)-1-methoxy-2-propylamine (0.11 mL, 1.0 mmol) and the reaction stirred for 18 hr at room temperature. Additional (*S*)-(+)-1-methoxy-2-propylamine (0.11 mL, 1.0 mmol) was added. After 12h, the mixture was concentrated *in vacuo* and purified by normal phase column chromatography (0-80% EtOAc/Hexanes) to afford the title compound (138 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H), 4.68 (pd, *J* = 6.9, 4.5 Hz, 1H), 4.42 (q, *J* = 18.4 Hz, 3H), 3.60 – 3.48 (m, 3H), 3.33 (s, 4H), 1.32 (d, *J* = 7.0 Hz, 4H). ES-MS [M+1]⁺: 319.0/321.0.

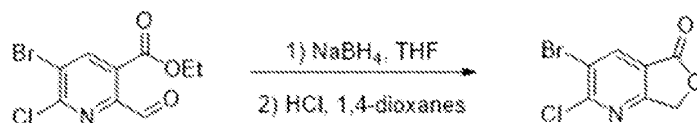


[00417] **(*R*)-3-Bromo-2-chloro-6-(1-methoxypropan-2-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one.** Prepared in the same manner as (*S*)-3-Bromo-2-chloro-6-(1-methoxypropan-2-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one. ¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H),

4.68 (pd, $J = 6.9, 4.5$ Hz, 1H), 4.42 (q, $J = 18.4$ Hz, 3H), 3.60 – 3.48 (m, 3H), 3.33 (s, 4H), 1.32 (d, $J = 7.0$ Hz, 4H). ES-MS $[M+1]^+$: 319.0/320.9.

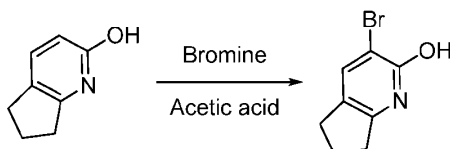


[00418] Ethyl 5-bromo-6-chloro-2-formylnicotinate. To a solution of ethyl 5-bromo-2-(bromomethyl)-6-chloronicotinate (1.36 g, 3.8 mmol) in MeCN (21.5 mL) was added 4-methylmorpholine N-oxide (893 μ L, 8.6 mmol) and the mixture was stirred at ambient temperature for 2 hr. The solution was diluted with EtOAc and washed with water. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified via normal phase column chromatography (0-30% EtOAc/Hexanes) to give the title compound (668 mg). ES-MS $[M+1]^+$: 292/294; 1H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.34 (d, $J = 0.5$ Hz, 1H), 4.45 (q, $J = 7.2$ Hz, 2H), 1.41 (t, $J = 7.1$ Hz, 3H).

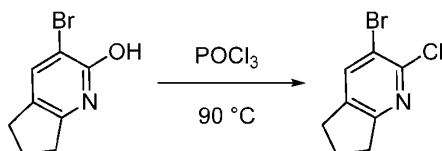


[00419] 3-Bromo-2-chlorofuro[3,4-*b*]pyridin-5(7*H*)-one. To a solution of ethyl 5-bromo-6-chloro-2-formylnicotinate (668 mg, 1.76 mmol) in THF (8.8 mL) at -40 $^{\circ}C$ was added sodium borohydride (27 mg, 0.70 mmol). The reaction was allowed to stir at -40 $^{\circ}C$ for 45 minutes. To the reaction mixture was added water and the reaction was warmed to room temperature. After the reaction was extracted with EtOAc (3x), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was taken up in 1,4-dioxane (4 mL) then hydrochloric acid (879 μ L, 3.52 mmol; 4*M* in 1,4-dioxane) was added and the mixture was heated to 50 $^{\circ}C$ for 18 hr. Additional 4*M* HCl in 1,4-dioxane (400 μ L, 1.6 mmol) was added and the mixture was heated to 50 $^{\circ}C$. After 4 hr, the mixture was concentrated under vacuum and the residue was dissolved in DCM. The solution was washed with an aqueous saturated $NaHCO_3$ solution. The organic layer was separated, dried ($MgSO_4$), and concentrated. The crude residue was purified via normal phase column chromatography (0 - 0.5% MeOH/DCM) to give the title compound.

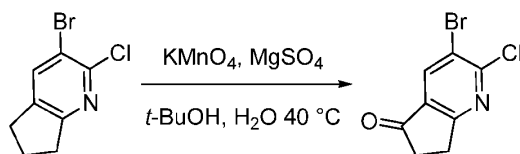
ES-MS $[M+1]^+$: 248/250; ^1H NMR (400 MHz, CDCl_3) δ 8.42 (t, $J = 0.5$ Hz, 1H), 5.28 (d, $J = 0.5$ Hz, 2H).



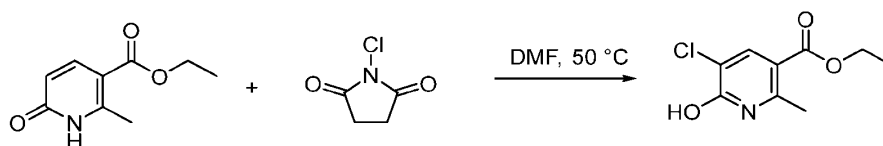
[00420] 3-Bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-2-ol. To a vial, 6,7-dihydro-5H-cyclopenta[b]pyridin-2-ol (500 mg, 3.7 mmol) and acetic acid (5.3 mL) at 15 °C. Bromine (150 μL , 2.9 mmol) was added. The reaction was allowed to come to rt over 3h. The reaction mixture was concentrated *in vacuo*. To the residue was added EtOAc and the mixture was quenched with sat. sodium thiosulfate solution and neutralized with aqueous saturated sodium carbonate solution. The mixture was extracted with EtOAc (3x) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by normal phase column chromatography (0-10% DCM/MeOH with 1% NH_4OH) to give the title compound (493 mg). ^1H NMR (400 MHz, CDCl_3) δ 7.74 (s, 1H), 2.91 (tt, $J = 8.1, 1.2$ Hz, 2H), 2.79 – 2.70 (m, 2H), 2.21 – 2.09 (m, 2H). ES-MS $[M+1]^+$: 214/216.



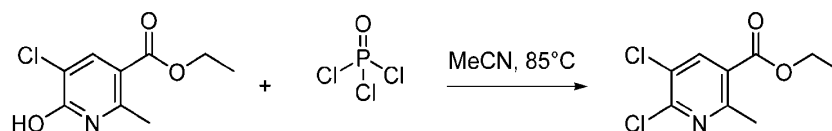
[00421] 3-Bromo-2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine. 3-Bromo-6,7-dihydro-5H-cyclopenta[b]pyridin-2-ol (493 mg, 2.3 mmol) in POCl_3 (1.2 mL, 13.2 mmol). The solution is heated to 90 °C for 18 h. The reaction mixture was concentrated. To the residue was slowly added aqueous saturated sodium carbonate. The mixture was extracted with DCM (3x). The organic layers were combined and washed with water (3x). The organics were dried with sodium sulfate, filtered, and concentrated. The crude material was purified using normal phase column chromatography (0 - 60% EtOAc/Hexanes) to produce the title compound (316 mg). ^1H NMR (400 MHz, CDCl_3) δ 7.72 (t, $J = 1.2$ Hz, 1H), 3.00 – 2.88 (m, 4H), 2.17 (p, $J = 7.7$ Hz, 2H). ES-MS $[M+1]^+$: 232/234.



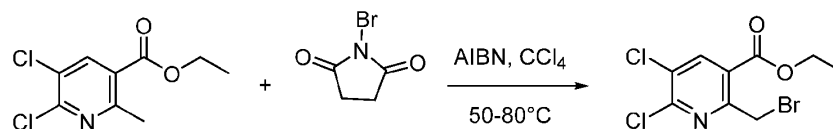
[00422] 3-Bromo-2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridin-5-one. To a solution of magnesium sulfate (833 mg, 6.8 mmol), potassium permanganate (430 mg, 2.7 mmol) in water (1.7 mL) and tert-butanol (5 mL) was added 3-bromo-2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine (316 mg, 1.36 mmol). The mixture was stirred at 40 °C for 3 h. The reaction mixture was filtered over Celite[®], washing with EtOAc and MeOH. The filtrate was concentrated and worked up with water/EtOAc (2x). The combined organic layers were washed with brine (2x), filtered and concentrated under reduced pressure and purified by normal phase column chromatography (0-60% EtOAc/Hexanes) to afford the title compound (40 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 3.26 – 3.18 (m, 2H), 2.87 – 2.80 (m, 2H). ES-MS [M+1]⁺: 246/248.



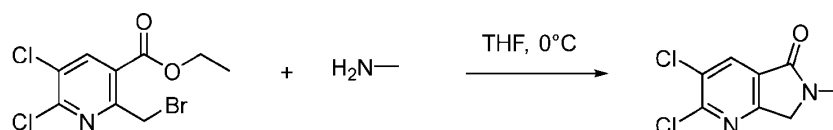
[00423] Ethyl 5-chloro-6-hydroxy-2-methylnicotinate. To a solution of ethyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1 g, 5.5 mmol) in DMF (37 mL) at 0 °C was slowly added *N*-chlorosuccinimide (814 mg, 6.1 mmol) portionwise. The ice bath was removed and after warming to room temperature, the mixture was heated to 50 °C for 22 h. After cooling to ambient temperature, saturated sodium bisulfite (aq) was added to the reaction and the mixture was stirred for 30 min. The mixture was then diluted further with water (50 mL) and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated to afford the title compound. ES-MS [M+1]⁺: 216; ¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.74 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).



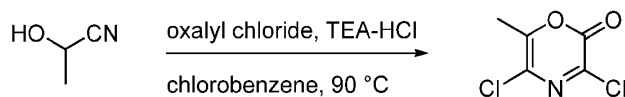
[00424] Ethyl 5,6-dichloro-2-methylnicotinate. Prepared in a similar manner as ethyl 5-bromo-6-chloro-2-methylnicotinate to give the title compound. ES-MS $[M+1]^+$: 234/236; ^1H NMR (400 MHz, CDCl_3) δ 8.27 (s, 1H), 4.39 (q, $J = 7.1$ Hz, 2H), 2.80 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H).



[00425] Ethyl 2-(bromomethyl)-5,6-dichloronicotinate. Prepared in a similar manner as ethyl 5-bromo-2-(bromomethyl)-6-chloronicotinate to give the title compound. ES-MS $[M+1]^+$: 314; ^1H NMR (400 MHz, CDCl_3) δ 8.34 (s, 1H), 4.94 (s, 2H), 4.45 (q, $J = 7.1$ Hz, 2H), 1.44 (t, $J = 7.1$ Hz, 3H).

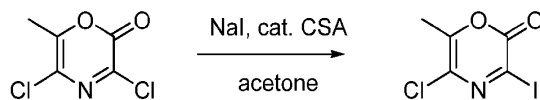


[00426] 2,3-Dichloro-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one. Prepared in a similar manner as 3-bromo-2-chloro-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one to give the title compound. ES-MS $[M+1]^+$: 217/219; ^1H NMR (400 MHz, CDCl_3) δ 8.16 (s, 1H), 4.41 (s, 2H), 3.23 (s, 3H).

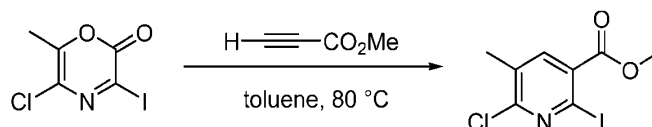


[00427] 3,5-Dichloro-6-methyl-2H-1,4-oxazin-2-one. To a cooled solution of oxalyl chloride (49.1 mL, 563 mmol) in chlorobenzene (75 mL) under inert atmosphere at 0 °C was added dropwise a solution of DL-lactonitrile (10 g, 140.7 mmol) in chlorobenzene (11 mL). The solution was then heated to 90 °C where triethylamine hydrochloride (1.43 g, 10.4 mmol) was added in portions at 90 °C. The resulting mixture was then stirred for 3 hours then cooled to ambient temperature and concentrated *in vacuo*. The resulting solution was then diluted with Et_2O (~300 mL) and solids were filtered out. The filtrate was concentrated and normal phase

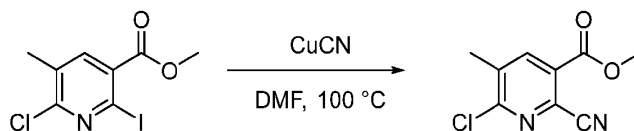
column chromatography on silica gel (0-15% EtOAc/Hex) afforded 16.8 g of title compound. ^1H NMR (400 MHz, CDCl_3) δ 2.38 (s, 1H).



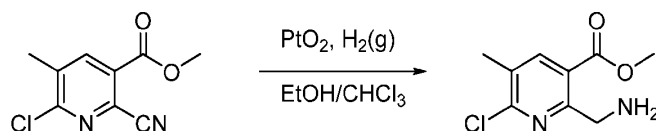
[00428] 5-Chloro-3-iodo-6-methyl-2H-1,4-oxazin-2-one. To a solution of 3,5-dichloro-6-methyl-2H-1,4-oxazin-2-one (16.8 g, 93.4 mmol) in acetone (359 mL) was added sodium iodide (56.4 g, 374 mmol) and (1*S*,4*R*)-10-camphorsulfonic acid (1.52 g, 6.5 mmol) under inert atmosphere. The mixture was stirred at ambient temperature for 18 hours. The reaction mixture was concentrated then diluted with water and extracted with DCM (3x). After washing sequentially with an aqueous saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ and brine, the combined organics were dried (MgSO_4), filtered, and concentrated to afford 22 g of title compound. The material was carried forward without further purification. ^1H NMR (400 MHz, CDCl_3) δ 2.30 (s, 3H); ES-MS $[\text{M}+1]^+$: 272.



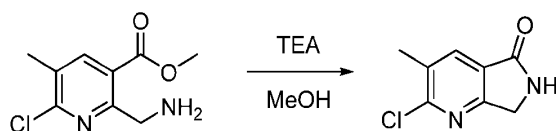
[00429] Methyl 6-chloro-2-iodo-5-methylnicotinate. A solution of 5-chloro-3-iodo-6-methyl-2H-1,4-oxazin-2-one (22g, 81.1 mmol) and methyl propiolate (21.6 mL, 243 mmol) in toluene (80 mL) was heated to 80°C for 42 h. The reaction was cooled to ambient temperature and the volatiles were removed under reduced pressure. Normal phase column chromatography on silica gel (0-10% EtOAc/hexanes, second to elute off column) gave 15.0 g of title compound. ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, $J = 0.8$ Hz, 1H), 3.95 (s, 3H), 2.36 (d, $J = 0.8$ Hz, 3H); ES-MS $[\text{M}+1]^+$: 312.



[00430] Methyl 6-chloro-2-cyano-5-methylnicotinate. A solution of methyl 6-chloro-2-iodo-5-methylnicotinate (15.0 g, 48.2 mmol) and copper(I) cyanide (6.48 g, 72.3 mmol) in DMF (112 mL) was heated at 100 °C for 1 hour. After cooling to ambient temperature, the mixture was filtered over Celite® washing with EtOAc. The filtrate was added to a saturated aqueous NaHCO₃ solution (~150 mL) and extracted with EtOAc (3x). The combined organics were then washed sequentially with an aqueous saturated solution of NH₄Cl (100mL) and brine. The organics were then dried (MgSO₄), filtered, and concentrated. Normal phase column chromatography on silica gel (0-40% EtOAc/hexanes) afforded 8.1 g of title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J* = 0.9 Hz, 1H), 4.04 (s, 3H), 2.52 (d, *J* = 0.8 Hz, 3H); ES-MS [M+1]⁺: 211.

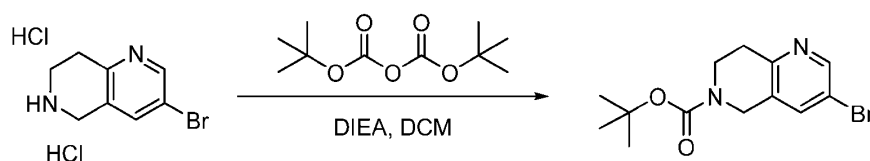


[00431] Methyl 2-(aminomethyl)-6-chloro-5-methylnicotinate. Platinum(IV) oxide (1.48 g, 6.5 mmol) was added to a round bottom flask under nitrogen. Next, a solution of methyl 6-chloro-2-cyano-5-methylnicotinate (8.1 g, 38.5 mmol) in ethanol /chloroform (240 mL; 3:1) was added. The flask was evacuated under vacuum and purged with H₂(g) (3x). The mixture was stirred under an atmosphere of hydrogen (balloon) for 36 hours. The solids were removed by filtration over Celite®, washing with DCM, and the filtrate was concentrated. Material was then dissolved in MeOH and divided equally among 8 Agilent Bond Elut SCX cartridges (10 g cartridges). The cartridges were flushed with MeOH (~80 mL each column) and the eluent was concentrated to afford 5.46 g of methyl 2-(aminomethyl)-6-chloro-5-methylnicotinate. ¹H NMR (400 MHz, MeOD) δ 8.38 (d, *J* = 0.8 Hz, 1H), 4.62 (s, 2H), 3.96 (s, 3H), 2.47 (q, *J* = 0.7 Hz, 3H). ES-MS [M+1]⁺: 215.

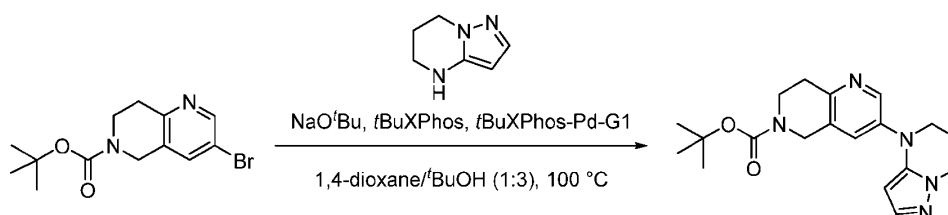


[00432] 2-Chloro-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one. To a vial was added a solution of methyl methyl 2-(aminomethyl)-6-chloro-5-methylnicotinate (5.46 g, 25.4

mmol) and triethylamine (17.7 mL, 127 mmol) in methanol (127 mL). The solution was allowed to stir at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* by half then the solids were removed by vacuum filtration, washing with MeOH to give 1.99 g of desired product. The filtrate was concentrated under reduced pressure onto Celite® and purified via normal phase column chromatography on silica gel (0-3.5% MeOH/DCM with 1% NH₄OH additive) to give 138 mg of desired product. The material was combined to give 2.13 g of the title compound. ¹H NMR (400 MHz, DMSO) δ 8.82 (s, 1H), 8.11 (d, *J* = 0.9 Hz, 1H), 4.39 (s, 2H), 2.42 (d, *J* = 0.8 Hz, 3H); ES-MS [*M*+1]⁺: 183.

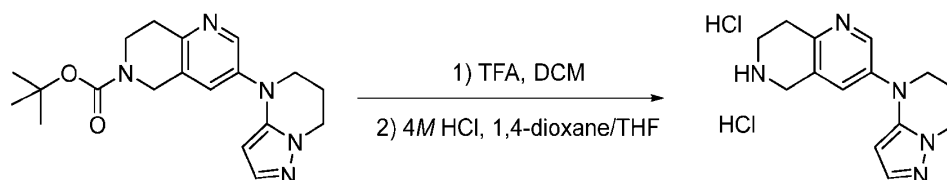


[00433] *tert*-Butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate. To a suspension of 3-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine dihydrochloride (10 g) in DCM (150 mL) at ambient temperature was added di-*tert*-butyl dicarbonate (12 mL) followed by slow addition of DIEA (24.4 mL). After stirring for 18 h at room temperature, the mixture was concentrated under reduced pressure. Purification using normal phase chromatography (0-50% EtOAc/hexanes) provided 10.7 g of the title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, *J* = 2.2 Hz, 1H), 7.60 (s, 1H), 4.59 (s, 2H), 3.74 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 1.49 (s, 9H); ES-MS [*M*+1]⁺: 313.3/315.3.

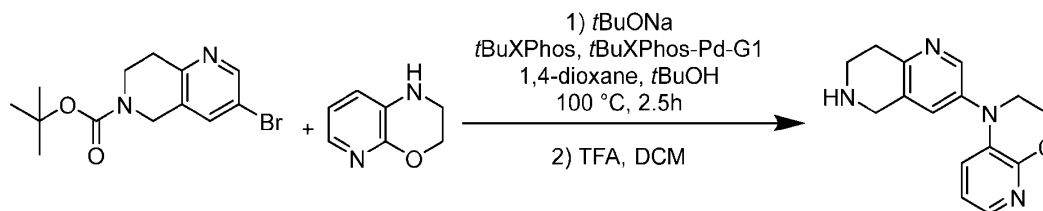


[00434] *tert*-Butyl 3-(6,7-dihydropyrazolo[1,5-*a*]pyrimidin-4(5*H*)-yl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate. Divided equally amongst three microwave vials was added a solution of *tert*-butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (2.82 g), 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine (1.66g), NaOtBu (1.73 g), *t*BuXPhos (382 mg),

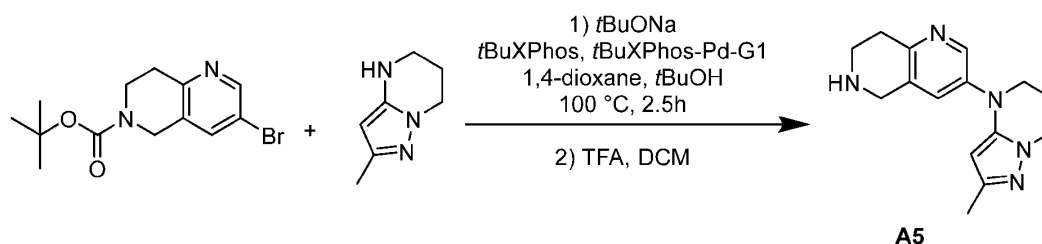
and *t*BuXPhos-Pd-G1 (619 mg) in 1,4-dioxanes (15 mL) and *t*-BuOH (45 mL). The solutions were purged with nitrogen and stirred at 100 °C for 4 h. After cooling to ambient temperature, the mixtures were filtered over a pad of Celite® which was washed thoroughly with EtOAc/DCM. The filtrate was concentrated *in vacuo*, and the resulting residue was dissolved in DMSO/DMF (1:1) (36 mL). After passing through a syringe filter, purification via RP-HPLC (10-50% MeCN/0.1% aqueous TFA) afforded the title compound (3.71 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 (d, *J* = 2.6 Hz, 1H), 7.86 (d, *J* = 2.6 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 5.80 (d, *J* = 2.1 Hz, 1H), 4.61 (s, 2H), 4.13 (t, *J* = 6.2 Hz, 2H), 3.91 – 3.70 (m, 2H), 3.67 (t, *J* = 5.9 Hz, 2H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.21 (p, *J* = 6.1 Hz, 2H), 1.43 (s, 9H); ES-MS [M+1-TFA]⁺: 356.5.



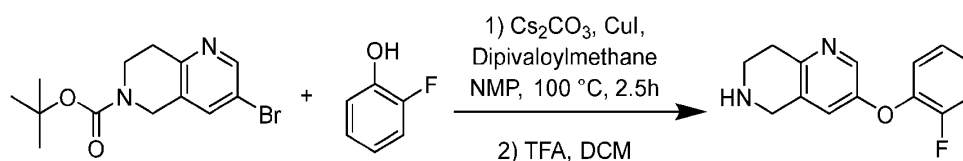
[00435] **3-(6,7-Dihydropyrazolo[1,5-*a*]pyrimidin-4(5*H*)-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine dihydrochloride.** To a solution of *tert*-butyl 3-(6,7-dihydropyrazolo[1,5-*a*]pyrimidin-4(5*H*)-yl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (3.72 g) in DCM (50 mL) was added TFA (10 mL) and the solution was allowed to stir at ambient temperature for 2 h. The reaction mixture was concentrated *in vacuo*, and the crude material was suspended in THF (10 mL). A 4M HCl solution in 1,4-dioxanes (20 mL) was added and the mixture was allowed to stir for 30 minutes and then concentrated *in vacuo*. The residue was then azeotroped with MeOH (3x) to remove excess solvent. The solid was dried in a vacuum oven to provide 1.85 g of the title compound, which was taken forward without further purification. ES-MS [M+1-2·HCl]⁺: 256.2.



[00436] **1-(5,6,7,8-Tetrahydro-1,6-naphthyridin-3-yl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine.** *tert*-Butyl 3-bromo-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (2.82 g, 9.0 mmol), 8-azabenzomorpholine (1.47 g, 10.8 mmol), sodium *tert*-butoxide (1.73 g, 18 mmol), *t*-BuXPhos Palladacycle Gen 1 (928 mg, 1.35 mmol), *t*-BuXPhos (573 mg, 1.35 mmol), 1,4-dioxane (9.0 mL) and *t*-BuOH (27 mL) were combined in a vial and degassed (3x). The reaction was heated at 100 °C for 2.5 h. The reaction was filtered over Celite® rinsed with DCM, and concentrated. The crude oil was purified by reverse-phase chromatography (5-45% MeCN/Water/0.1% aqueous TFA). The desired fractions were concentrated, and the residue was dissolved in DCM (40 mL) and TFA (2.07 mL). After 2 h, the solvents were removed, diluted with MeOH, and loaded onto a SCX-cartridge (HF bond). The cartridge was washed with MeOH and eluted with 7N NH₃ in MeOH to produce the title compound (1.2 g). ES-MS [M + H]⁺ = 269.5.

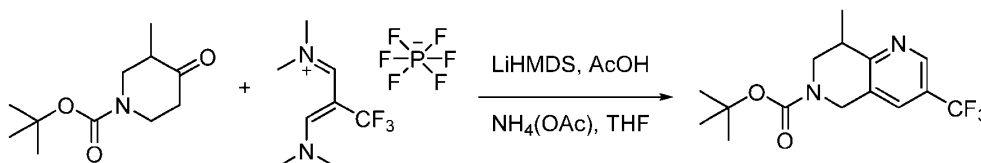


[00437] **3-(2-Methyl-6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine.** Prepared in a similar manner as 1-(5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine. ES-MS [M + H]⁺ = 270.4.



[00438] **3-(2-Fluorophenoxy)-5,6,7,8-tetrahydro-1,6-naphthyridine.** To a microwave vial were added *tert*-butyl 3-bromo-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (3.0 g, 9.58 mmol), 2-fluorophenol (2.15 g, 19.2 mmol), cesium carbonate (6.28 g, 19.2 mmol), Dipivaloylmethane (200 µL, 0.96 mmol), and copper(I) iodide (91.2 mg, 0.48 mmol). The solids were degassed followed by addition of NMP (48 mL). The resulting solution was stirred at 140 °C for 18 h. The reaction was filtered over Celite®, washed with DCM and concentrated.

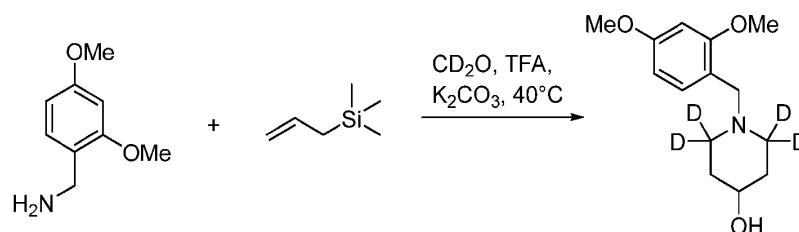
The resulting solution was passed through a syringe filter and purified by reverse-phase HPLC (5-45% MeCN/0.1% aqueous TFA). The desired fractions were concentrated, and the residue was dissolved in DCM (48 mL) and TFA (7.34 mL, 95.8 mmol). After 1 h, the reaction was concentrated, and purified by SCX cartridge (10 G), washed with MeOH, and eluted with 7N NH₃/MeOH to produce the title compound (950 mg). ES-MS [M + H]⁺=245.4.



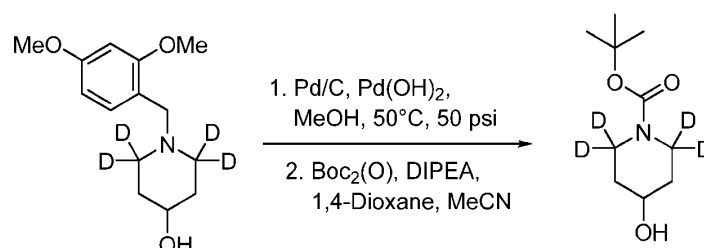
[00439] *tert*-Butyl 8-methyl-3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate. To a -15 °C solution of *N*-Boc-3-methyl-4-piperidone (400 mg) in THF (8 mL) was added dropwise a solution of 1M lithium bis(trimethylsilyl)amide (1.88 mL). The reaction warmed to room temperature for 1.5 h and was then added to a suspension of [(*Z*)-3-(dimethylamino)-2-(trifluoromethyl)prop-2-enylidene]-dimethyl-ammonium hexafluorophosphate (638 mg) in THF (5 mL) at -15 °C. The resulting mixture was stirred at -15 °C for 2 h, then acetic acid (0.161 mL) was added, and the mixture was warmed to room temperature. After 1 h, ammonium acetate (413 mg) was added, and the mixture was heated at 65 °C for 2 h. The mixture was cooled, diluted with water, and extracted with diethyl ether. The organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by normal-phase chromatography on silica gel (0-50% EtOAc/hexanes) to afford the title compound (60 mg). ES-MS [M+1]⁺: 317.2.



[00440] 8-Methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine; 2,2,2-trifluoroacetic acid. To a vial were added *tert*-butyl 8-methyl-3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (60 mg), DCM (0.9 mL), and trifluoroacetic acid (0.15 mL). The reaction stirred 1 hr and was concentrated to afford the title compound (75 mg). ES-MS [M+1]⁺: 217.2.

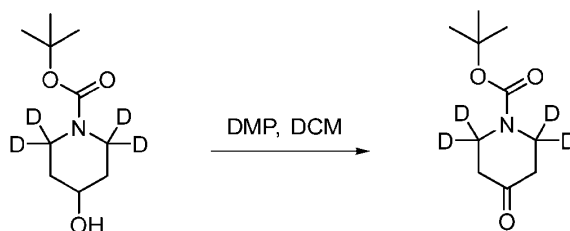


[00441] **1-(2,4-Dimethoxybenzyl)piperidin-2,2,6,6-*d*₄-4-ol**. Deuterated formaldehyde (7.58 mL, 55.0 mmol) was added to 2,4-dimethoxybenzylamine (3.64 mL, 23.9 mmol). Then, trifluoroacetic acid (1.83 mL, 23.9 mmol) was added. The resulting mixture was sonicated for 10 min and then stirred for 1 h at room temperature. To the resulting solution was added allyltrimethylsilane (4.18 mL, 26.3 mmol) and the reaction was heated at 40 °C for 18 h. The reaction was diluted with water (8 mL) and DCM (8 mL), and solid potassium carbonate (1.67 g, 12.0 mmol) was added. The mixture was stirred for 10 min and was then extracted with 3:1 CHCl₃/IPA (5x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude oil was purified by silica gel chromatography (0-20% MeOH/DCM) to afford the title compound. ¹H NMR (400 MHz, MeOD) δ 7.22 (d, *J* = 8.6 Hz, 1H), 6.58 (d, *J* = 2.3, 1H), 6.53 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.84 (s, 3H), 3.83-3.80 (m, 5H), 3.35 (s, 1H), 1.89 (dd, *J* = 13.7, 3.7 Hz, 2H), 1.65 (dd, *J* = 13.6, 8.1 Hz, 2H); ES-MS [*M*+1]⁺: 256.2.

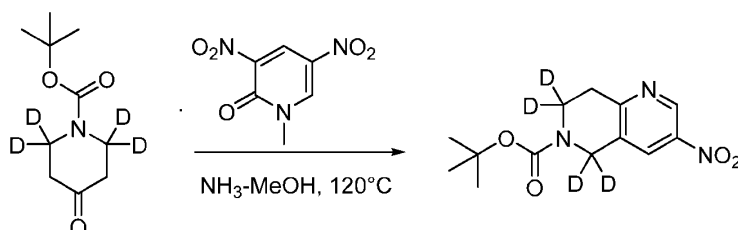


[00442] ***tert*-Butyl 4-hydroxypiperidine-1-carboxylate-2,2,6,6-*d*₄**. To a degassed solution of 1-(2,4-dimethoxybenzyl)piperidin-2,2,6,6-*d*₄-4-ol (3.5 g, 13.7 mmol) in methanol (300 mL) was added palladium hydroxide (0.29 g, 2.1 mmol) and 10% palladium on activated carbon (0.22 g, 2.1 mmol). The reaction was charged with H₂ and stirred at 50 °C under 50 psi for 48 h. The reaction mixture was filtered over Celite®, washed with methanol, and concentrated under reduced pressure. The solid was combined with 1,4-dioxane (45 mL), acetonitrile (45 mL), and *N,N*-diisopropylethylamine (2.9 mL, 16.4 mmol). To the solution was added di-*tert*-butyl

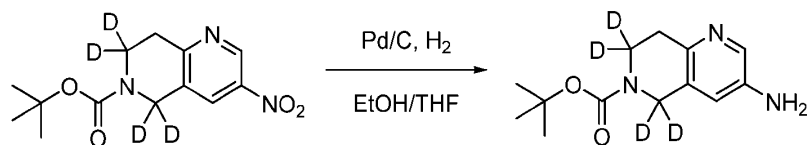
dicarbonate (4.7 mL, 20.5 mmol) and the reaction stirred at room temperature. After 3 h, the reaction was concentrated, and the crude oil was purified by normal-phase chromatography (0-20% MeOH/DCM) to afford the title compound (2.18 g). ^1H NMR (400 MHz, MeOD) δ 3.79-3.71 (m, 1H), 1.79 (dd, J = 13.1, 3.8 Hz, 2H), 1.45 (s, 9H), 1.39-1.34 (m, 2H).



[00443] *tert*-Butyl 4-oxopiperidine-1-carboxylate-2,2,6,6- d_4 . To a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate-2,2,6,6- d_4 (2.18 g, 10.6 mmol) in DCM (30 mL) was added Dess-Martin periodinane (6.75 g, 15.9 mmol). The reaction stirred at room temperature for 18 h. The reaction was concentrated over Celite® and purified by normal-phase chromatography (0-50% EtOAc/Hexanes) to afford the title compound (1.69 g). ^1H NMR (400 MHz, CDCl_3) δ 2.42 (s, 4H), 1.49 (s, 9H).

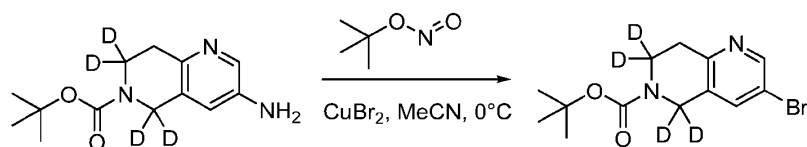


[00444] *tert*-Butyl 3-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-5,5,7,7- d_4 . In four separate microwave vials were combined equal portions of 1-methyl-3,5-dinitro-2-pyridone (1.0 g, 5.1 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate-2,2,6,6- d_4 (1.0 g, 5.1 mmol), and 2M ammonia-methanol solution (20.2 mL). The mixture was heated at 120 °C for 20 min in the microwave reactor. The reaction was concentrated over Celite® and purified by normal-phase chromatography (0-30% EtOAc/Hexanes) to afford the title compound (1.23 g). ^1H NMR (400 MHz, CDCl_3) δ 9.25 (d, J = 2.5 Hz, 1H), 8.23 (d, J = 2.5, 1H), 3.11 (s, 2H), 1.50 (s, 9H); ES-MS $[\text{M}+1]^+$: 284.1.



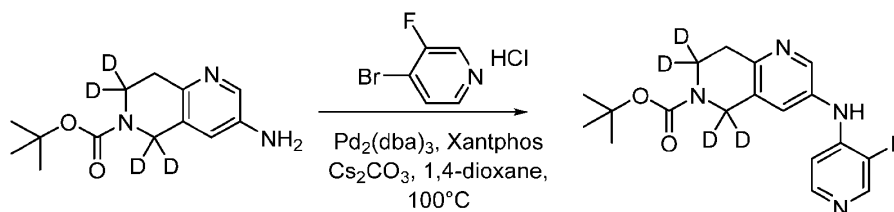
[00445] *tert*-Butyl 3-amino-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄.

To a solution of *tert*-butyl 3-methyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄ (1.23 g, 4.3 mmol) in ethanol (10 mL) and THF (10 mL) was added 10% palladium on activated carbon (527 mg, 4.9 mmol). The mixture was degassed and placed under H₂ balloon at 1 atm for 3 h. The reaction was filtered over Celite®, washed with EtOH, and the filtrate was concentrated to afford the title compound (1.03 g). ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 2.6 Hz, 1H), 6.73 (d, *J* = 2.6, 1H), 3.60 (s, 2H), 2.87 (s, 2H), 1.48 (s, 9H); ES-MS [*M*+1]⁺: 254.1.

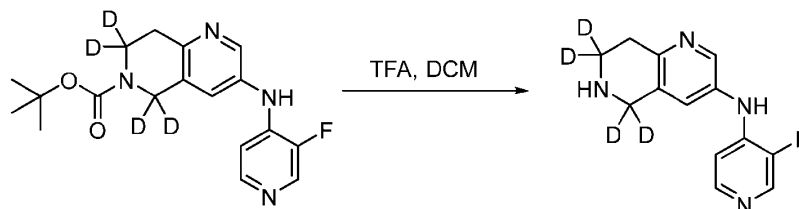


[00446] *tert*-Butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄.

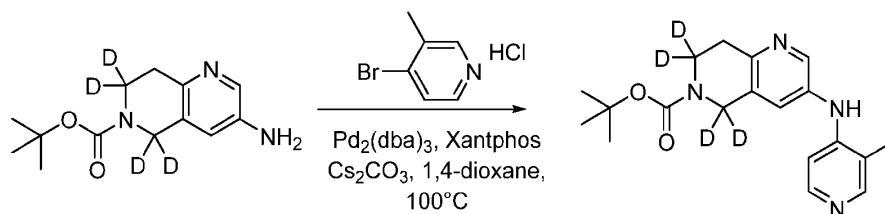
Cupric bromide (767 mg, 3.4 mmol) was added to a solution of *tert*-butyl 3-amino-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄ (580 mg, 2.3 mmol) in MeCN (8 mL). The reaction was cooled to 0 °C followed by dropwise addition of *tert*-butyl nitrite (0.33 mL, 2.8 mmol). The reaction stirred at 0 °C for 1 h and then room temperature for 5 h. The mixture was diluted with water and 3:1 CHCl₃/IPA. The layers were separated and the aqueous layer was re-extracted with 3:1 CHCl₃/IPA (2x). The combined organic phases were washed with brine (2x), dried (MgSO₄), filtered, and concentrated. The crude oil was purified by normal-phase chromatography (0-40% EtOAc/Hexanes) to afford the title compound (520 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.47 (d, *J* = 2.2 Hz, 1H), 7.56 (d, *J* = 2.2, 1H), 2.93 (s, 2H), 1.48 (s, 9H); ES-MS [*M*+1]⁺: 317.1/319.1.



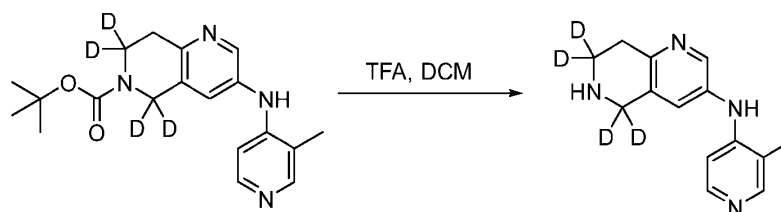
[00447] ***tert*-Butyl 3-((3-fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄**. In a vial were combined 4-bromo-3-fluoropyridine hydrochloride (415 mg, 1.9 mmol), *tert*-butyl 3-amino-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄ (330 mg, 1.3 mmol), tris(dibenzylideneacetone)dipalladium(0) (119 mg, 0.1 mmol), Xantphos (113 mg, 0.2 mmol), and cesium carbonate (1.7 g, 5.2 mmol) in 1,4-dioxane (6.5 mL). The reaction was degassed and heated at 100 °C for 2 h. The mixture was cooled, filtered through a pad of Celite®, and washed with 3:1 CHCl₃/IPA. The solvents were removed, and the crude product was purified by normal-phase chromatography (0-5% MeOH/DCM) to afford the title compound (314 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, *J* = 2.5 Hz, 1H), 8.32 (d, *J* = 2.9 Hz, 1H), 8.13 (d, *J* = 5.5 Hz, 1H), 7.33 (d, *J* = 2.5 Hz, 1H), 6.94 (dd, *J* = 7.0, 5.8, 1H), 6.24 (s, 1H), 3.00 (s, 2H), 1.50 (s, 9H); ES-MS [*M*+1]⁺: 349.3.



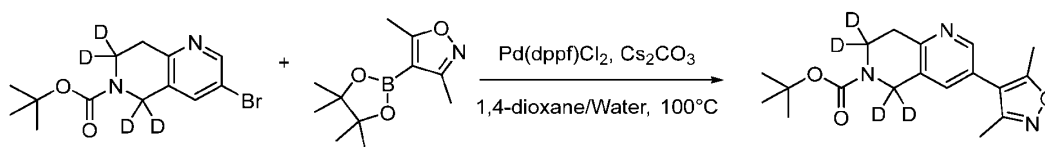
[00448] ***N*-(3-Fluoropyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-5,5,7,7-*d*₄-3-amine**. In a vial were combined *tert*-butyl 3-((3-fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄ (314 mg, 0.9 mmol), trifluoroacetic acid (1.07 mL, 14.0 mmol), and DCM (4 mL). The reaction stirred at room temperature for 2 h. The reaction was concentrated and purified by SCX cartridge, eluting with 2*N* NH₃/MeOH solution. Solvents were removed to afford the title compound (178 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.30 (d, *J* = 2.5 Hz, 1H), 8.23 (s, 1H), 8.17 (d, *J* = 5.7 Hz, 1H), 7.22 (d, *J* = 2.6 Hz, 1H), 6.79 (d, *J* = 5.6, 1H), 5.68 (s, 1H), 2.94 (s, 2H); ES-MS [*M*+1]⁺: 249.3.



[00449] **tert-Butyl 3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-5,5,7,7-*d*₄**. In a vial were combined 4-bromo-3-methylpyridine hydrochloride (407 mg, 1.95 mmol), *tert*-butyl 3-amino-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-5,5,7,7-*d*₄ (330 mg, 1.3 mmol), tris(dibenzylideneacetone)dipalladium(0) (119 mg, 0.13 mmol), xantphos (113 mg, 0.2 mmol), and cesium carbonate (1700 mg, 5.21 mmol) in 1,4-dioxane (6.5 mL). The mixture was heated at 100 °C for 2 h. The mixture was cooled, filtered through a pad of Celite[®], and washed with 3:1 CHCl₃/IPA. The solvents were removed, and the crude product was purified by normal-phase chromatography (0-10% MeOH/DCM) to afford the title compound (366 mg). ES-MS [M+1]⁺: 345.3.



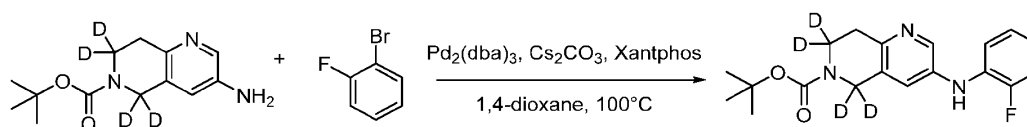
[00450] **N-(3-Methylpyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-5,5,7,7-*d*₄-3-amine**. In a vial were combined *tert*-butyl 3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-5,5,7,7-*d*₄ (366 mg, 1.06 mmol), trifluoroacetic acid (1.30 mL, 17.0 mmol), and DCM (4 mL). The reaction stirred at room temperature for 2 h. The reaction was diluted with 3:1 CHCl₃/IPA and saturated Na₂CO₃ solution. The layers were separated and the aqueous was extracted (2x). The combined organic layers were dried (MgSO₄), filtered, and concentrated to afford the title compound (258 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 2.6 Hz, 1H), 8.26 – 8.21 (m, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 7.22 (d, *J* = 2.6 Hz, 1H), 6.80 (d, *J* = 5.7 Hz, 1H), 5.69 (s, 1H), 2.95 (s, 2H), 2.25 (s, 3H); ES-MS [M+1]⁺: 245.3.



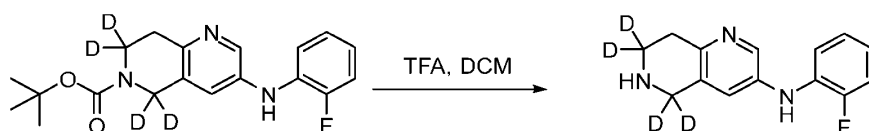
[00451] *tert*-Butyl 3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-5,5,7,7-*d*₄. *tert*-Butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-5,5,7,7-*d*₄ (200 mg, 0.63 mmol), 3,5-dimethylisoxazole-4-boronic acid pinacol ester (169 mg, 0.76 mmol), cesium carbonate (413 mg, 1.26 mmol), and Pd(dppf)Cl₂ (69 mg, 0.09 mmol) were combined in 1,4-dioxane (2.5 mL) and water (0.5 mL) and degassed (3x). The reaction heated at 100 °C for 2.5 h. The mixture was filtered through a pad of Celite®, washed with EtOAc/DCM, and the filtrate was concentrated under reduced pressure. The oil was purified by normal-phase chromatography (0-4% MeOH/DCM) to afford the title compound (202 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.34 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 2.1 Hz, 1H), 3.04 (s, 2H), 2.41 (s, 3H), 2.27 (s, 3H), 1.51 (s, 9H); ES-MS [*M*+1]⁺: 334.1.



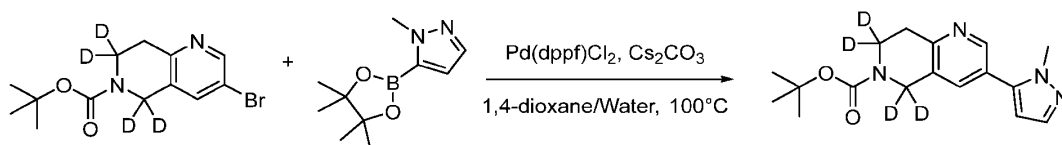
[00452] 3,5-Dimethyl-4-(5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl-5,5,7,7-*d*₄)isoxazole. *tert*-Butyl 3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-5,5,7,7-*d*₄ (200 mg, 0.6 mmol) was combined with DCM (3 mL) and trifluoroacetic acid (0.69 mL, 9.0 mmol). After 2 h, the reaction was complete and was concentrated *in vacuo*. The crude oil was purified by SCX Cartridge, washing with MeOH and eluting compound with 7*N* NH₃/MeOH solution. Solvents were removed to afford the title compound (114 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 2.2 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 2.98 (s, 2H), 2.39 (s, 3H), 2.25 (s, 3H); ES-MS [*M*+1]⁺: 234.3.



[00453] *tert*-Butyl 3-((2-fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄. In a vial were combined xantphos (86 mg, 0.15 mmol), 2-fluorobromobenzene (0.16 mL, 1.48 mmol), *tert*-butyl 3-amino-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄ (250 mg, 0.99 mmol), tris(dibenzylideneacetone)dipalladium(0) (90 mg, 0.1 mmol), and cesium carbonate (1294 mg, 3.95 mmol) in 1,4-dioxane (6.5 mL). The vessel was degassed (3x) and heated at 100 °C for 2 h. The mixture was cooled, filtered through a pad of Celite®, and washed with 3:1 CHCl₃/IPA. The solvents were removed, and the crude product was purified by normal-phase chromatography (0-7% MeOH/DCM) to afford the title compound (407 mg). ES-MS [M+1]⁺: 348.4.



[00454] *N*-(2-Fluorophenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-5,5,7,7-*d*₄-3-amine. In a vial were combined *tert*-butyl 3-((2-fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄ (407 mg, 1.17 mmol), trifluoroacetic acid (1.39 mL, 18.2 mmol), and DCM (4.7 mL). The reaction stirred at room temperature for 2 h. The reaction was diluted with 3:1 CHCl₃:IPA and saturated Na₂CO₃ solution. The layers were separated and the aqueous was extracted (2x). The combined organic layers were dried (MgSO₄), filtered, and concentrated to afford the title compound (241 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J* = 2.7 Hz, 1H), 7.23 – 6.96 (m, 5H), 6.92 – 6.82 (m, 1H), 5.71 (s, 1H), 2.90 (s, 2H); ES-MS [M+1]⁺: 248.2.



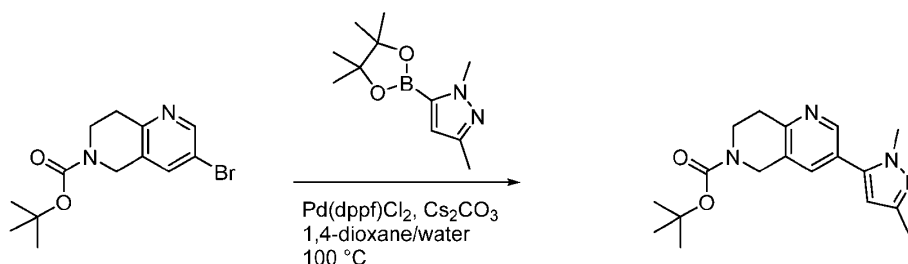
[00455] *tert*-Butyl 3-(1-methyl-1*H*-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄. *tert*-Butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate-5,5,7,7-*d*₄ (170 mg, 0.54 mmol), 1-methylpyrazole-5-boronic acid pinacol ester (133 mg, 0.64 mmol), cesium carbonate (351 mg, 1.07 mmol), and Pd(dppf)Cl₂ (59 mg, 0.08 mmol) were combined in 1,4-dioxane (2.5 mL)/water (0.5 mL). The vessel was degassed, and the reaction heated at 100 °C for 2.5 h. After cooling, the mixture was filtered through a pad of Celite® which

was washed thoroughly with EtOAc/DCM. The filtrate was concentrated under reduced pressure. The residue was purified by normal-phase chromatography (0-5% MeOH/DCM) to afford the title compound (109 mg). ES-MS $[M+1]^+$: 319.3.

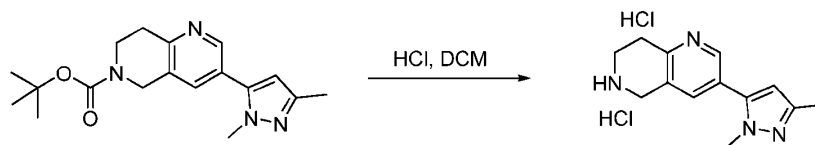


[00456] 3-(1-Methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-5,5,7,7- d_4 .

tert-Butyl 3-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate-5,5,7,7- d_4 (109 mg, 0.34 mmol) was combined with DCM (2.3 mL) and trifluoroacetic acid (0.39 mL, 5.1 mmol). After 2 h, the reaction was concentrated. The crude residue was purified by SCX Cartridge, washing with MeOH and eluting with 7N NH_3 /MeOH solution. Solvents were removed to afford the title compound (71 mg). ES-MS $[M+1]^+$: 219.1.

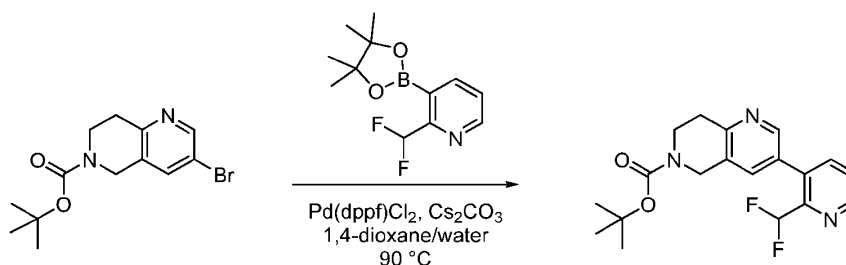


[00457] *tert*-Butyl 3-(1,3-dimethyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. In a vial were mixed cesium carbonate (942 mg, 2.9 mmol), *tert*-butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (300 mg, 0.96 mmol), 1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (532 mg, 2.4 mmol), and Pd(dppf)Cl_2 (70 mg, 0.10 mmol) in 1,4-dioxane /water (11 mL; 5:1). The mixture was stirred at 80 °C for 20 h. After cooling to ambient temperature, the reaction mixture was filtered over Celite®, washed with DCM/MeOH, and concentrated. Purification with normal phase column chromatography on silica gel (0-60% MeOH/DCM) afforded 292 mg of title compound. ES-MS $[M+1]^+$: 329.



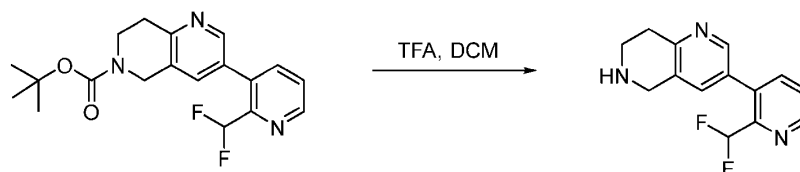
[00458] 3-(1,3-Dimethyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine

hydrochloride. To a solution of *tert*-butyl 3-(1,3-dimethyl-1*H*-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (314 mg, 0.96 mmol) in DCM (4.8 mL) was added hydrochloric acid (4*M* in 1,4-dioxane) (1.2 mL, 4.78 mmol) and the mixture was stirred for 18 h then concentrated *in vacuo*. The material was carried forward without further purification. ES-MS $[M+1]^+$: 229.

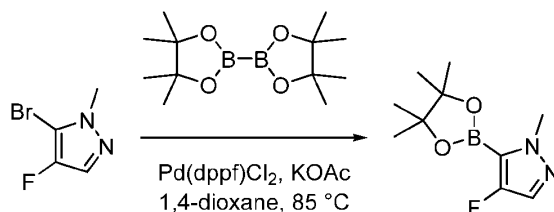


[00459] *tert*-Butyl 3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridine-

6(5*H*)-carboxylate. In a vial were mixed cesium carbonate (942 mg, 2.9 mmol), *tert*-butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (300 mg, 0.96 mmol), 2-(difluoromethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (489 mg, 1.9 mmol), and Pd(dppf)Cl₂ (70 mg, 0.10 mmol) in 1,4-dioxane /water (11 mL; 5:1). The mixture was stirred at 90 °C for 18 h. After cooling to ambient temperature, the reaction mixture was filtered over Celite®, washed with chloroform/IPA (3:1), and concentrated. Purification with normal phase column chromatography on silica gel (0-80% EtOAc/DCM) afforded 318 mg of title compound. ES-MS $[M+1]^+$: 362; ¹H NMR (400 MHz, MeOD) δ 8.72 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.39 (d, *J* = 2.2 Hz, 1H), 7.93 – 7.89 (m, 1H), 7.74 – 7.60 (m, 2H), 6.72 (t, *J* = 53.9 Hz, 1H), 4.70 (s, 2H), 3.82 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 6.0 Hz, 2H), 1.51 (s, 9H).

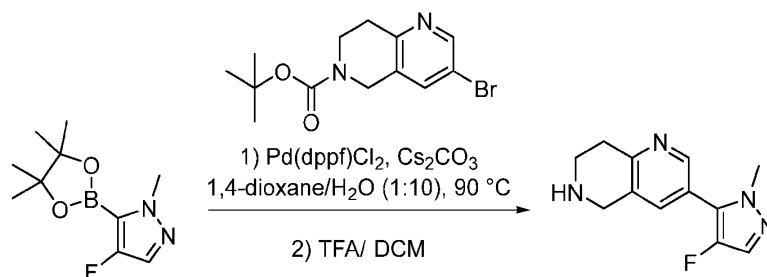


[00460] 3-(2-(Difluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. To a solution of *tert*-butyl 3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (346 mg, 0.96 mmol) in DCM (3.2 mL) was added trifluoroacetic acid (730 μ L) and the mixture was stirred for 18 h then concentrated *in vacuo*. The material was dissolved in MeOH and purified by strong-cation exchange chromatography to afford the title compound. ES-MS $[M+1]^+$: 262; ^1H NMR (400 MHz, MeOD) δ 8.71 (dd, $J = 4.8, 1.6$ Hz, 1H), 8.36 (d, $J = 2.2$ Hz, 1H), 7.90 (ddt, $J = 7.9, 1.6, 0.8$ Hz, 1H), 7.67 (ddt, $J = 7.9, 4.7, 0.9$ Hz, 1H), 7.59 (d, $J = 2.2$ Hz, 1H),

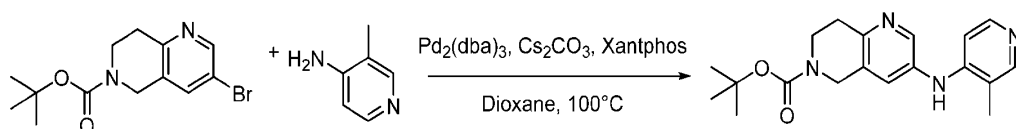


[00461] 4-Fluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole.

To a vial were added 5-bromo-4-fluoro-1-methyl-1*H*-pyrazole (375 mg, 2.1 mmol), potassium acetate (617 mg, 6.29 mmol), bis(pinacolato)diboron (798 mg, 3.14 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (154 mg, 0.21 mmol) in 1,4-dioxane (11 mL). The vial was heated to 85 $^{\circ}\text{C}$ for 18 hr. After cooling to room temperature, the mixture was diluted with EtOAc and subsequently filtered through Celite[®] and concentrated. The material was carried forward without further purification. ES-MS $[M+1]^+$: 145.1.



[00462] 3-(4-Fluoro-1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine. In a vial was added a mixture of *tert*-butyl 3-bromo-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (532 mg, 1.7 mmol), 4-fluoro-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (461 mg, 2.0 mmol), cesium carbonate (1.67 g, 5.1 mmol), and Pd(dppf)Cl₂ (125 mg, 0.17 mmol) in 1,4-dioxane (7 mL) and water (0.7 mL). The mixture was stirred at 90 °C for 18 hr and filtered over Celite[®], washing with EtOAc (50 mL). The organics were then washed with sat. NaHCO₃ and concentrated. The crude residue was purified using silica gel chromatography (0-100% MeOH/DCM). The intermediate was dissolved in DCM (7 mL) and trifluoroacetic acid (1.3 mL) was added. After 18 h at rt, the reaction was concentrated. The crude residue was purified using an SCX cartridge (HF bond), loaded and washed with MeOH, eluting with 2*N* NH₃ in MeOH. Solvents were removed to afford title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.49 (d, *J* = 2.1 Hz, 1H), 7.44 – 7.39 (m, 2H), 4.14 (s, 2H), 3.83 (d, *J* = 0.7 Hz, 3H), 3.33 (t, *J* = 6.1 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H). ES-MS [M+1]⁺: 233.3.

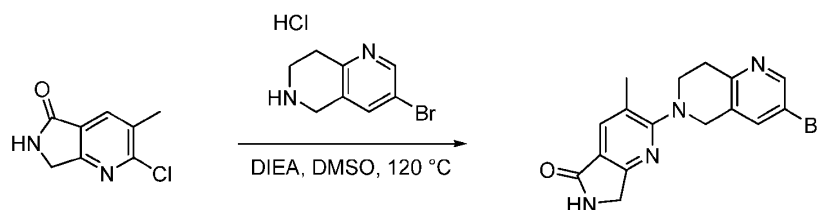


[00463] *tert*-Butyl 3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. To a microwave vial were added *tert*-butyl 3-bromo-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (250 mg, 0.8 mmol), 4-amino-3-methylpyridine (129 mg, 1.2 mmol), cesium carbonate (785 mg, 2.39 mmol), tris(dibenzylideneacetone)dipalladium(0) (73 mg, 0.08 mmol), and xantphos (69 mg, 0.12 mmol) in 1,4-dioxane (4 mL). The reaction was degassed (3x) and heated at 100 °C for 18 h. The reaction was cooled, filtered through a plug of Celite[®], rinsed with 3:1 CHCl₃/IPA and concentrated. The crude residue was purified by

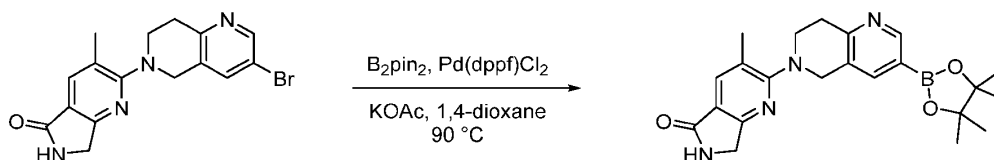
normal-phase chromatography to afford the title compound (265 mg). ^1H NMR (400 MHz, CDCl_3) δ 8.35 (d, $J = 2.5$ Hz, 1H), 8.23 (d, $J = 25.8$ Hz, 2H), 7.32 (d, $J = 2.5$ Hz, 1H), 6.83 (s, 1H), 6.05 (s, 1H), 4.61 (s, 2H), 3.78 (t, $J = 6.0$ Hz, 2H), 3.01 (t, $J = 6.0$ Hz, 2H), 2.28 (s, 3H), 1.50 (s, 9H); ES-MS $[\text{M}+1]^+$: 341.2.



[00464] *N*-(3-Methylpyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-amine. *tert*-Butyl 3-[(3-methylpyridin-4-yl)amino]-7,8-dihydro-5*H*-1,6-naphthyridine-6-carboxylate (204 mg, 0.6 mmol) was combined with DCM (3 mL) and trifluoroacetic acid (0.69 mL). After 2 h, the reaction was concentrated. The crude residue was purified by SCX Cartridge, washing with MeOH and eluting with 7*N* NH_3/MeOH solution. Solvents were removed to afford the title compound (158 mg). ES-MS $[\text{M}+1]^+$: 241.2.

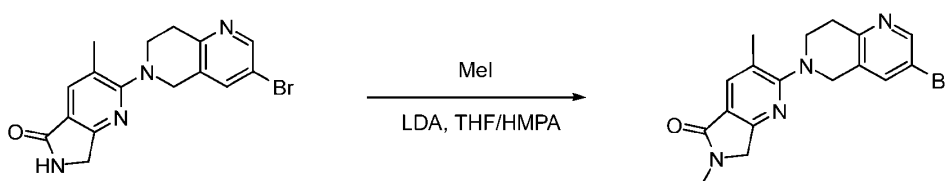


[00465] 2-(3-Bromo-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-3-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one. Prepared in a similar manner as compound **2** to give the desired compound. ES-MS $[\text{M}+1]^+$: 359/361; ^1H NMR (400 MHz, MeOD) δ 8.46 (d, $J = 2.2$ Hz, 1H), 7.88 (d, $J = 2.3$ Hz, 1H), 7.85 (d, $J = 0.9$ Hz, 1H), 4.34 (s, 2H), 3.67 (t, $J = 5.9$ Hz, 2H), 3.35 (s, 2H), 3.10 (t, $J = 5.9$ Hz, 2H), 2.45 (d, $J = 0.8$ Hz, 3H).

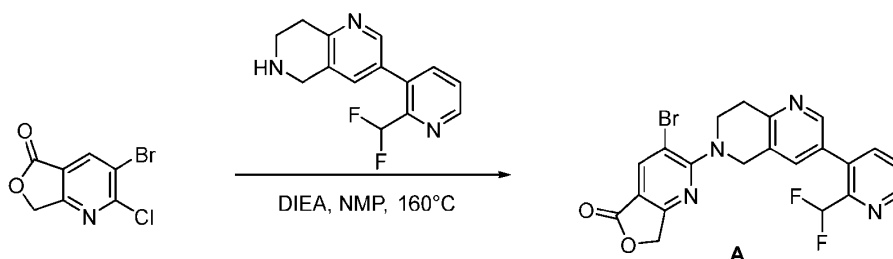


[00466] 3-Methyl-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one. In a vial were

combined 2-(3-bromo-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-3-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (80 mg, 0.22 mmol), bis(pinacolato)diboron (85 mg, 0.33 mmol), Pd(dppf)Cl₂ (16 mg, 0.02 mmol), and potassium acetate (66 mg, 0.67 mmol). After flushing the vial with nitrogen, degassed 1,4-dioxane (1.1 mL) was added and the reaction was heated at 90 °C for 18h. The reaction was filtered over Celite[®], rinsed with 3:1 CHCl₃/IPA, and concentrated. The material was carried forward without further purification. ES-MS [M+1]⁺: 325 (mass of boronic acid).

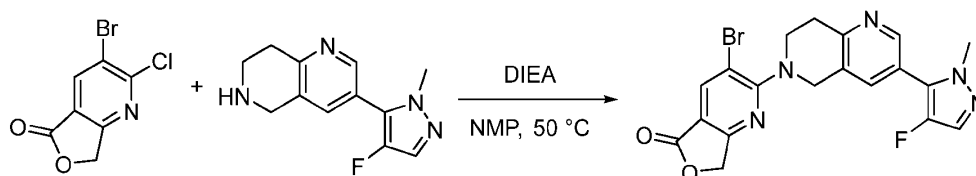


[00467] **2-(3-Bromo-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-3,6-dimethyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one.** Prepared in a similar manner as compound **8** to afford the title compound. ES-MS [M+1]⁺: 373/375; ¹H NMR (400 MHz, CDCl₃) δ 8.55 (s, 1H), 7.84 (s, 1H), 7.80 (s, 1H), 4.56 (s, 2H), 4.29 (s, 2H), 3.59 (t, *J* = 5.9 Hz, 2H), 3.32 – 3.24 (m, 2H), 3.19 (s, 3H), 2.40 (s, 3H).

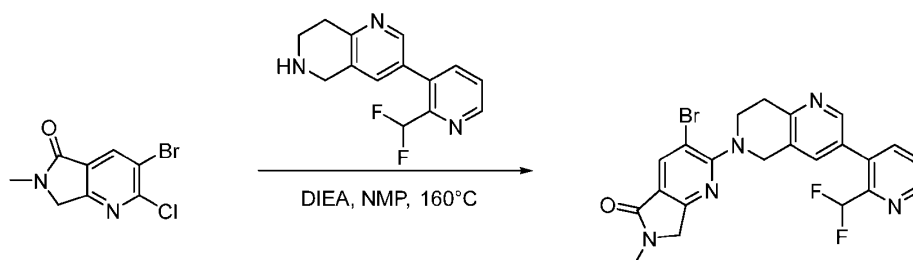


[00468] **3-Bromo-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)furo[3,4-*b*]pyridin-5(7*H*)-one (Intermediate A).** A solution of 3-(2-(difluoromethyl)pyridin-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (49 mg, 0.19 mmol), 3-bromo-2-chlorofuro[3,4-*b*]pyridin-5(7*H*)-one (36 mg, 0.14 mmol), and *N,N*-diisopropylethylamine (252 μL, 1.45 mmol) in NMP (0.5 mL) was heated at 160 °C for 16h. Upon completion, reaction mixture was cooled to ambient temperature then added to water. A precipitate was formed, and the solids were collected by vacuum filtration to afford 61 mg of

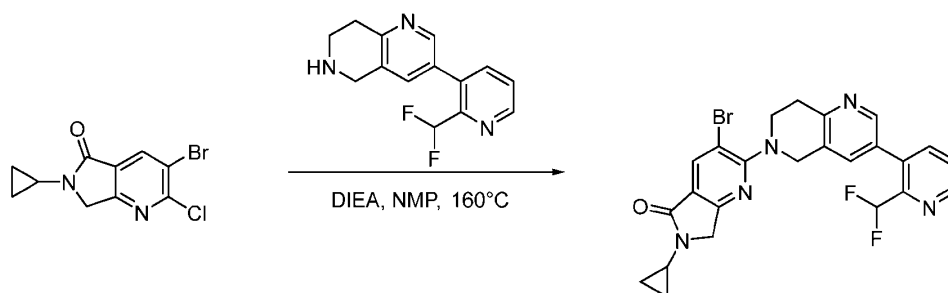
title compound. The material was carried forward without further purification. ES-MS $[M+1]^+$: 473/475. —



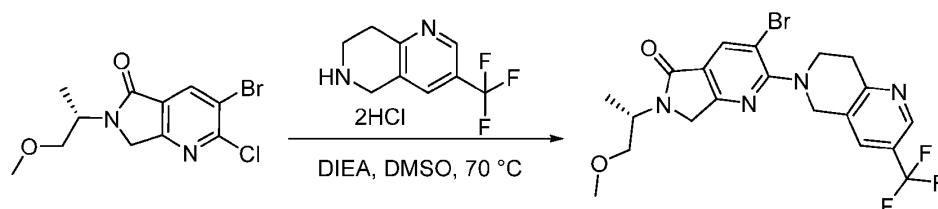
[00469] 3-Bromo-2-(3-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)furo[3,4-b]pyridin-5(7H)-one. To a solution of 3-(4-fluoro-2-methylpyrazol-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (19 mg, 0.08 mmol) in NMP (0.5 mL) was added 3-bromo-2-chloro-7H-furo[3,4-b]pyridin-5-one (20 mg, 0.07 mmol) and *N,N*-diisopropylethylamine (0.04 mL, 0.22 mmol). The mixture was heated at 50 °C for 18 hr. The reaction mixture was added to water and extracted with EtOAc (3x). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The material was carried forward without further purification. ES-MS $[M+1]^+$: 444.1.



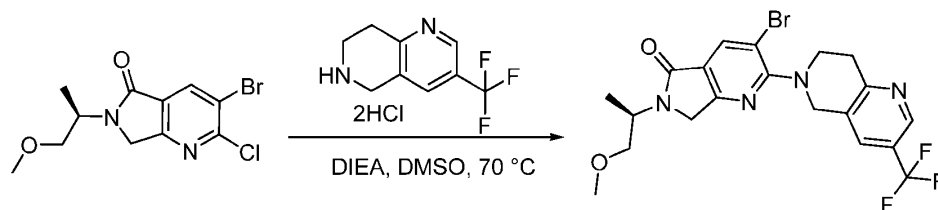
[00470] 3-Bromo-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one. Prepared in a similar manner as Intermediate A to give the title compound. ES-MS $[M+1]^+$: 486/488; ^1H NMR (400 MHz, MeOD) δ 8.73 (dd, $J = 4.8, 1.6$ Hz, 1H), 8.42 (d, $J = 2.2$ Hz, 1H), 8.20 (s, 1H), 8.05 – 7.87 (m, 1H), 7.73 (d, $J = 2.2$ Hz, 1H), 7.68 (dd, $J = 7.9, 4.8$ Hz, 1H), 6.73 (t, $J = 53.9$ Hz, 1H), 4.76 (s, 2H), 4.41 (s, 2H), 3.93 (t, $J = 5.8$ Hz, 2H), 3.18 (s, 3H) (CH_2 group under solvent).



[00471] **3-Bromo-6-cyclopropyl-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one**. Prepared in a similar manner as Intermediate A to give the title compound. ES-MS $[M+1]^+$: 512/514.



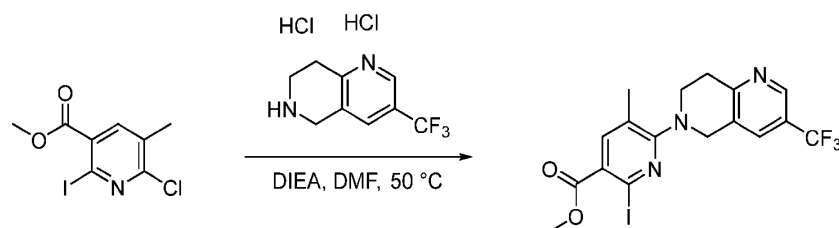
[00472] **(S)-3-Bromo-6-(1-methoxypropan-2-yl)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one**. To a solution of (S)-3-bromo-2-chloro-6-(1-methoxypropan-2-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (30 mg, 0.09 mmol) in DMSO (0.5 mL) was added 7-(trifluoromethyl)-2,5-diazatetralin dihydrochloride (28.4 mg, 0.1 mmol) and *N,N*-diisopropylethylamine (98 μ L, 0.56 mmol). The mixture was heated to 70 °C for 48 hr. After cooling to RT, the mixture was poured into water and extracted with EtOAc (3x). The organics were pooled, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified using reverse phase HPLC (20–60% MeCN/0.05% aqueous NH_4OH). The fractions containing the desired product were concentrated to afford the title compound (26 mg). ^1H NMR (400 MHz, CDCl_3) δ 8.72 (d, $J = 2.0$ Hz, 1H), 8.21 (s, 1H), 7.70 (d, $J = 2.2$ Hz, 1H), 4.73 – 4.63 (m, 1H), 4.68 (s, 2H), 4.34 (q, 2H), 3.85 (t, $J = 5.8$ Hz, 2H), 3.60 – 3.46 (m, 2H), 3.34 (s, 3H), 3.34 – 3.30 (m, 2H), 1.31 (d, $J = 7.0$ Hz, 3H). ES-MS $[M+1]^+$: 485.2/487.2.



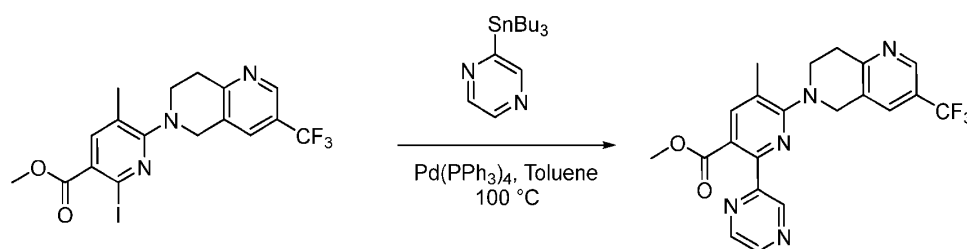
[00473] **(R)-3-Bromo-6-(1-methoxypropan-2-yl)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one.** Prepared in the same manner as (*S*)-3-bromo-6-(1-methoxypropan-2-yl)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one. ES-MS $[M+1]^+$: 485.2/487.2.



[00474] **3-Bromo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-cyclopenta[b]pyridin-5-one.** To a solution of 3-bromo-2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridin-5-one (13 mg, 0.05 mmol) in DMSO (0.5 mL) was added 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (10 mg, 0.06 mmol) and *N,N*-diisopropylethylamine (55 μ L, 0.32 mmol). The mixture heated to 50 °C for 18 h. The mixture was poured into water and extracted with EtOAc (3x). The organics were pooled, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified using normal phase column chromatography (0-5% MeOH/DCM with 1% NH_4OH) to afford the title compound (19 mg). 1H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, $J = 2.2$ Hz, 1H), 8.11 (s, 1H), 7.73 (d, $J = 2.3$ Hz, 1H), 4.80 (s, 2H), 3.97 (t, $J = 5.9$ Hz, 2H), 3.35 (t, $J = 5.9$ Hz, 2H), 3.11 – 3.04 (m, 2H), 2.79 – 2.72 (m, 2H). $[M+1]^+$: 412/414.

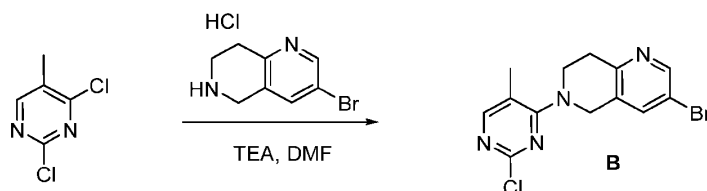


[00475] **Methyl 2-iodo-5-methyl-6-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)nicotinate.** To a solution of methyl 6-chloro-2-iodo-5-methylnicotinate (500 mg, 1.6 mmol) in DMF (7 mL) was added 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine dihydrochloride (662 mg, 2.4 mmol) and *N,N*-diisopropylethylamine (1.7 mL, 9.6 mmol). The mixture heated to 50 °C for 48 h. The reaction was diluted with water (~100 mL) and extracted with EtOAc (3x). The combined organics were dried (MgSO₄), filtered, and concentrated. Purification with normal-phase column chromatography on silica gel (0-30% EtOAc/Hex) afforded 239 mg of title compound. ES-MS [M+1]⁺: 478.

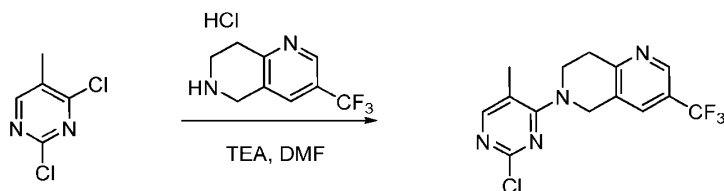


[00476] **Methyl 5-methyl-2-(pyrazin-2-yl)-6-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)nicotinate.** To a solution of methyl methyl 2-iodo-5-methyl-6-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)nicotinate (239 mg, 0.5 mmol) and 2-(tributylstannyl)pyrazine (277 mg, 0.75 mmol) in toluene (7.7 mL) was added tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol). The reaction mixture was stirred at 100 °C for 18 h under inert atmosphere. The mixture was cooled to room temperature and additional 2-(tributylstannyl)pyrazine (277 mg, 0.75 mmol) was added and reaction was heated to 100 °C for 16 h. After cooling to room temperature, the mixture was diluted with water (10 mL) and extracted with EtOAc (3x). The combined organics were washed with water (20 mL x 3), dried (MgSO₄), filtered, and concentrated. Purification with normal-phase column chromatography on silica gel (0-60% EtOAc/Hex) afforded 140 mg of title compound. ES-MS [M+1]⁺: 430; ¹H NMR (400 MHz, CDCl₃) δ 9.13 (d, *J* = 1.5 Hz, 1H), 8.81 (s, 1H), 8.60 (d, *J* =

2.6 Hz, 1H), 8.60 – 8.54 (m, 1H), 8.17 (s, 1H), 7.90 (s, 1H), 4.78 (s, 2H), 3.76 (s, 3H), 3.69 (t, $J = 5.8$ Hz, 2H), 3.66 – 3.51 (m, 2H), 2.44 (s, 3H).



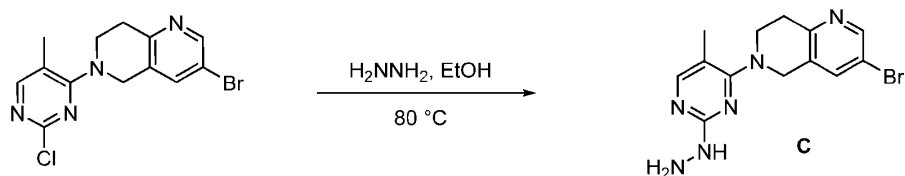
[00477] 3-Bromo-6-(2-chloro-5-methylpyrimidin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (Intermediate B). To a solution of 3-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (800 mg, 3.2 mmol) in DMF (9.7 mL) was added triethylamine (2.2 mL, 16.0 mmol) and 2,4-dichloro-5-methylpyrimidine (575 mg, 3.5 mmol). The mixture was stirred at ambient temperature for 18 hours. The mixture was then diluted with water and the precipitate was collected by vacuum filtration to afford 857 mg of title compound. ES-MS $[M+1]^+$: 339/341; ^1H NMR (400 MHz, MeOD) δ 8.47 (d, $J = 2.2$ Hz, 1H), 8.01 (d, $J = 0.9$ Hz, 1H), 7.92 (d, $J = 2.2$ Hz, 1H), 4.81 (s, 2H), 3.94 (t, $J = 5.9$ Hz, 2H), 3.09 (t, $J = 5.9$ Hz, 2H), 2.35 (d, $J = 0.9$ Hz, 3H).



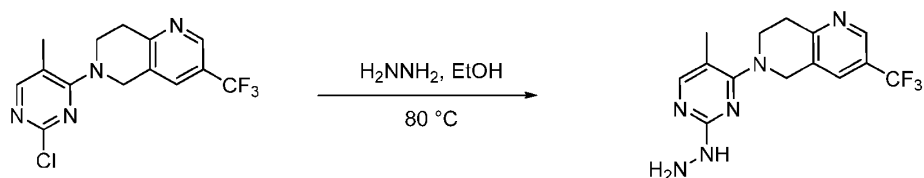
[00478] 6-(2-Chloro-5-methylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. Prepared in a similar manner as intermediate **B** to give the title compound. ES-MS $[M+1]^+$: 329; ^1H NMR (400 MHz, CDCl_3) δ 8.73 (d, $J = 1.2$ Hz, 1H), 8.05 (q, $J = 0.8$ Hz, 1H), 7.74 (d, $J = 1.5$ Hz, 1H), 4.78 (s, 2H), 3.87 (t, $J = 5.9$ Hz, 2H), 3.26 (t, $J = 5.9$ Hz, 2H), 2.32 (d, $J = 0.9$ Hz, 3H).



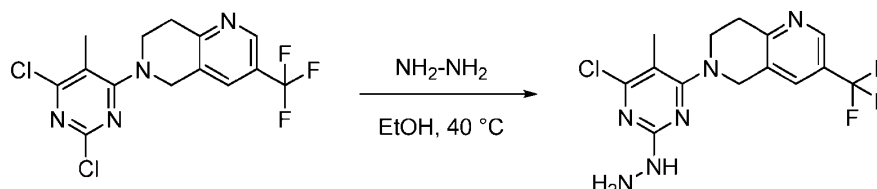
[00479] 6-(2,6-Dichloro-5-methylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. To a solution of 2,4,6-trichloro-5-methylpyrimidine (110 mg, 0.55 mmol) in DMSO (1.5 mL) was added 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (139 mg, 0.54 mmol) and *N,N*-diisopropylethylamine (352 μ L, 2.52 mmol). The mixture was heated to 70 °C for 18 h. The mixture was poured into water and extracted with EtOAc (3x). The organics were pooled, dried over MgSO_4 , filtered, and concentrated. The crude residue was purified using normal phase column chromatography (0-80% EtOAc/Hexanes) to afford the title compound (140 mg).



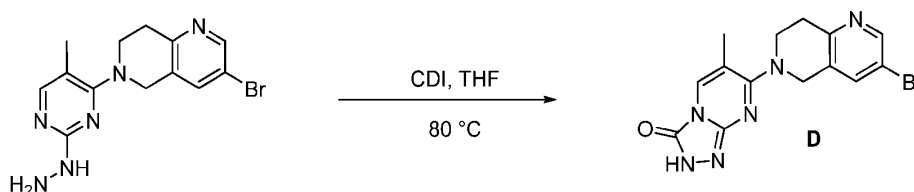
[00480] 3-Bromo-6-(2-hydrazineyl-5-methylpyrimidin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (Intermediate C). To a solution of 3-bromo-6-(2-chloro-5-methylpyrimidin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (200 mg, 0.59 mmol) in ethanol (4.0 mL) was added hydrazine (370 μ L, 11.8 mmol) and the mixture was stirred at 80 °C for 4 hours. After cooling to ambient temperature, the mixture was concentrated *in vacuo* and carried forward without further purification. ES-MS $[\text{M}+1]^+$: 335/337.



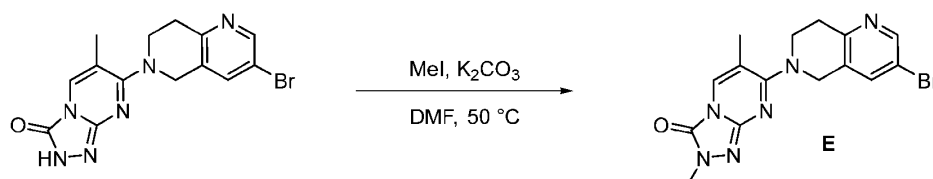
[00481] **6-(2-Hydrazineyl-5-methylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine**: Prepared in a similar manner as intermediate C to give the title compound. ES-MS $[M+1]^+$: 325.



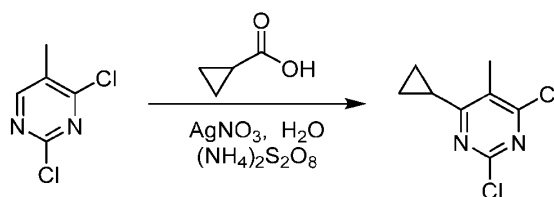
[00482] **6-(6-Chloro-2-hydrazineyl-5-methylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine**. To vial of 6-(2,6-dichloro-5-methylpyrimidin-4-yl)-3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridine (100 mg, 0.28 mmol) in ethanol (10 mL) was added hydrazine (0.17 mL, 5.51 mmol) and the mixture was stirred at 40 °C for 6 h. After cooling to ambient temperature, the mixture was concentrated *in vacuo* and carried forward without further purification. ES-MS $[M+1]^+$: 335/337.



[00483] **7-(3-Bromo-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-3(2H)-one (Intermediate D)**. To a solution of 3-bromo-6-(2-hydrazineyl-5-methylpyrimidin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (557 mg, 1.7 mmol) in 1,4-dioxane (2.9 mL) was added 1,1'-carbonyldiimidazole (431 mg, 2.7 mmol). The reaction was heated to 80 °C for 18 hours, after which the mixture was cooled to ambient temperature. The mixture was then diluted with water and the precipitate was collected by vacuum filtration to afford 425 mg of title compound. ES-MS $[M+1]^+$: 361/363; ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 2.2$ Hz, 1H), 8.50 (s, 1H), 7.69 (d, $J = 1.4$ Hz, 1H), 7.63 (d, $J = 2.2$ Hz, 1H), 4.71 (s, 2H), 3.81 (t, $J = 5.9$ Hz, 2H), 3.16 (t, $J = 5.9$ Hz, 2H), 2.31 (d, $J = 1.3$ Hz, 3H).

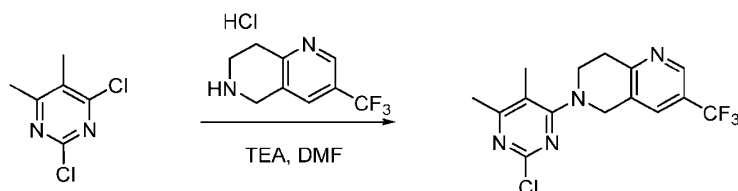


[00484] 7-(3-Bromo-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (Intermediate E). To a solution of 7-(3-bromo-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (200 mg, 0.55 mmol) in DMF (5.5 mL) was added potassium carbonate (155 mg, 1.11 mmol) followed by iodomethane (52 µL, 0.83 mmol). The mixture was heated to 50 °C for 18 hours. After cooling to ambient temperature, the reaction was diluted with water and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated to give 170 mg of title compound. The material was carried forward without further purification. ES-MS [M+1]⁺: 375/377; ¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, *J* = 2.3 Hz, 1H), 7.68 (q, *J* = 1.3 Hz, 1H), 7.61 (d, *J* = 2.2 Hz, 1H), 4.69 (s, 2H), 3.79 (t, *J* = 5.9 Hz, 2H), 3.58 (s, 3H), 3.15 (t, *J* = 5.8 Hz, 2H), 2.30 (d, *J* = 1.2 Hz, 3H).

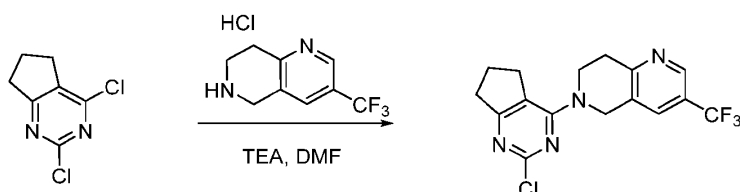


[00485] 2,4-Dichloro-6-cyclopropyl-5-methylpyrimidine. A solution of 2,4-dichloro-5-methylpyrimidine (1.0 g, 6.1 mmol), silver nitrate (521 mg, 3.1 mmol) and cyclopropanecarboxylic acid (1.47 mL, 18.4 mmol) in water (31 mL) was heated to 72 °C. Ammonium persulfate (2.1 g, 9.2 mmol) was added portion wise over 15 minutes. After heating an additional 20 minutes at 72 °C, sulfuric acid (491 µL, 9.2 mmol) was added and the mixture was heated to 90 °C for 1 h. After cooling to ambient temperature, the reaction mixture was slowly poured into a solution of saturated aqueous bicarbonate and DCM and stirred for an additional 20 minutes. The organic layer was isolated and the aqueous layer was further extracted with DCM (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification via normal phase column chromatography (0-25% EtOAc/Hexanes)

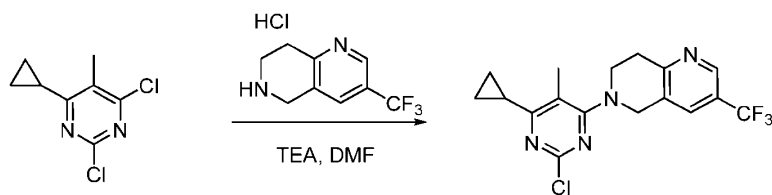
afforded title compound (872 mg). ES-MS $[M+1]^+$: 203/205; ^1H NMR (400 MHz, CDCl_3) δ 2.45 (s, 3H), 2.11 (tt, $J = 7.9, 4.6$ Hz, 1H), 1.29 – 1.23 (m, 2H), 1.18 – 1.12 (m, 2H).



[00486] 6-(2-Chloro-5,6-dimethylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. Prepared in a similar manner as intermediate **B** to give the title compound. ES-MS $[M+1]^+$: 343; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.72 (s, 1H), 4.65 (s, 2H), 3.69 (t, $J = 5.9$ Hz, 2H), 3.27 (t, $J = 5.9$ Hz, 2H), 2.44 (s, 3H), 2.22 (s, 3H).

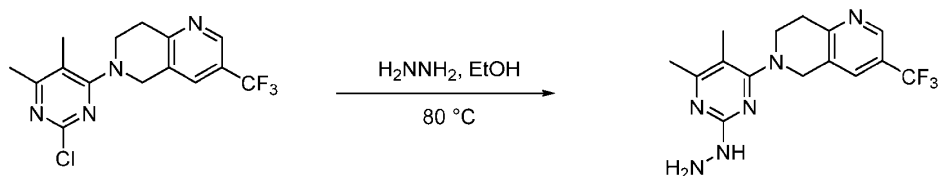


[00487] 6-(2-Chloro-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. Prepared in a similar manner as intermediate **B** to give the title compound. ES-MS $[M+1]^+$: 355; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.74 (s, 1H), 4.98 (s, 2H), 4.07 (t, $J = 6.0$ Hz, 2H), 3.20 (t, $J = 6.0$ Hz, 2H), 3.11 (t, $J = 7.3$ Hz, 2H), 2.89 (t, $J = 7.9$ Hz, 2H), 2.13 (p, $J = 7.7$ Hz, 2H).

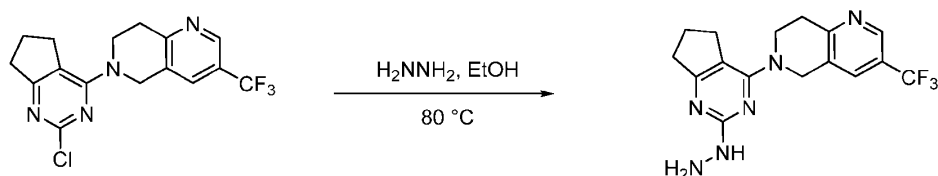


[00488] 6-(2-Chloro-6-cyclopropyl-5-methylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. Prepared in a similar manner as intermediate **B** to give the title compound. ES-MS $[M+1]^+$: 369; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (dd, $J = 2.2, 0.8$ Hz, 1H),

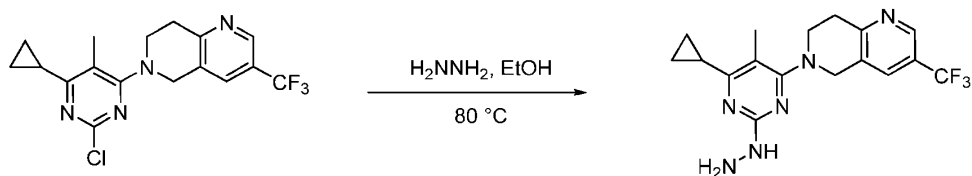
7.71 (dd, $J = 2.0, 0.9$ Hz, 1H), 4.62 (s, 2H), 3.66 (t, $J = 5.9$ Hz, 2H), 3.27 (t, $J = 5.9$ Hz, 2H), 2.33 (s, 3H), 2.07 – 1.96 (m, 1H), 1.24 – 1.14 (m, 2H), 1.08 – 0.99 (m, 2H).



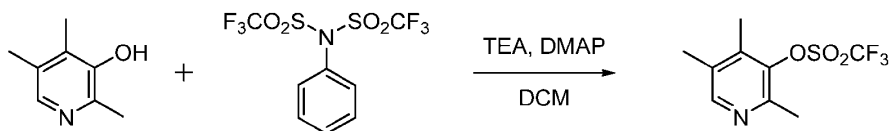
[00489] 6-(2-Hydrazineyl-5,6-dimethylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. Prepared in a similar manner as intermediate **C** to give the title compound. ES-MS $[M+1]^+$: 339.



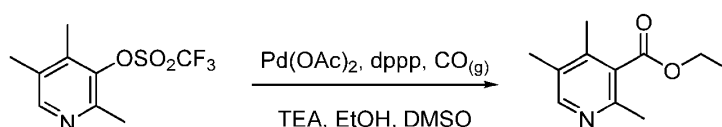
[00490] 6-(2-Hydrazineyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. Prepared in a similar manner as intermediate **C** to give the title compound. ES-MS $[M+1]^+$: 351.



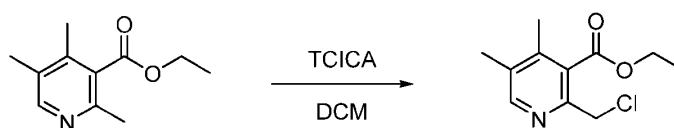
[00491] 6-(6-Cyclopropyl-2-hydrazineyl-5-methylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. Prepared in a similar manner as intermediate **C** to give the title compound. ES-MS $[M+1]^+$: 365.



[00492] **2,4,5-Trimethylpyridin-3-yl trifluoromethanesulfonate.** A solution of 2,4,5-trimethylpyridin-3-ol (1.0 g, 7.29 mmol), triethylamine (2.03 mL, 14.6 mmol), and 4-dimethylaminopyridine (178 mg, 1.46 mmol) in DCM (21 mL) was cooled to 0 °C and *N*-phenylbis(trifluoromethanesulfonimide) (2.76 g, 7.73 mmol) was added. The solution was warmed to ambient temperature and stirred for 18 hours. The reaction mixture was concentrated onto Celite® and purified by normal-phase chromatography (0-15% EtOAc/Hex) to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, 1H), 2.57 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H). ES-MS [M+1]⁺: 270.

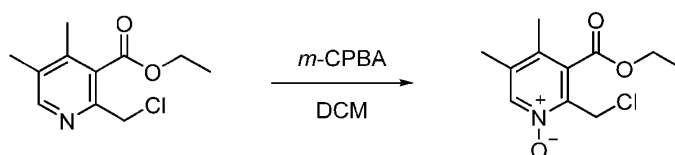


[00493] **Ethyl 2,4,5-trimethylnicotinate.** To a solution of 2,4,5-trimethylpyridin-3-yl trifluoromethanesulfonate (1.9 g, 7.06 mmol) in ethanol (12 mL) and DMSO (6 mL) were added triethylamine (9.8 mL, 70.6 mmol), 1,3-bis(diphenylphosphino)propane (437 mg, 1.06 mmol) and palladium(II) acetate (240 mg, 1.06 mmol). The mixture was placed under an atmosphere of CO_(g) (50 psi) and heated to 80 °C for 18 hours. The reaction mixture was filtered over a pad of Celite® then washed with DCM/MeOH and concentrated. The residue was then diluted with water (~150 mL) and extracted with EtOAc (4x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was purified by normal-phase chromatography (0-60% EtOAc/Hex) to afford title compound. ¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). ES-MS [M+1]⁺: 194.

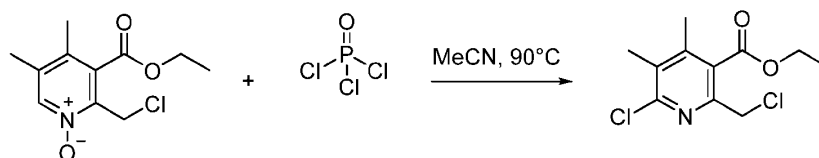


[00494] **Ethyl 2-(chloromethyl)-4,5-dimethylnicotinate.** To a stirred solution of ethyl 2,4,5-trimethylnicotinate (752 mg, 3.89 mmol) in DCM (19.5 mL) was added trichloroisocyanuric acid (1085 mg, 4.67 mmol) and the mixture was allowed to stir at ambient temperature for 12h.

Additional TCICA (226 mg, 0.97 mmol) was added and stirred for an additional 18 hours. Additional TCICA (300 mg, 1.29 mmol) was added and the mixture was allowed to stir for 3 hours. The pH was adjusted to 8 with a saturated aqueous Na_2CO_3 solution. The organic layer was isolated and the aqueous layer was further extracted with DCM (3x). The combined organics were dried (MgSO_4), filtered, and concentrated. The crude residue was purified by normal-phase chromatography (0-5% MeOH/DCM) to afford title compound. ^1H NMR (400 MHz, CDCl_3) δ 8.35 (s, 1H), 4.71 (s, 2H), 4.46 (q, $J = 7.2$ Hz, 2H), 2.29 (s, 3H), 2.28 (s, 3H), 1.43 (t, $J = 7.1$ Hz, 3H). ES-MS $[\text{M}+1]^+$: 228.

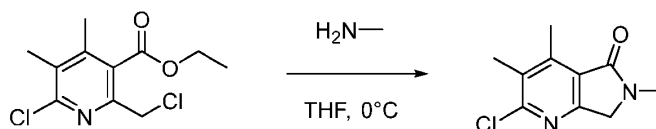


[00495] 2-(Chloromethyl)-3-(ethoxycarbonyl)-4,5-dimethylpyridine 1-oxide. To a solution of ethyl 2-(chloromethyl)-4,5-dimethylnicotinate (216 μL , 1.38 mmol) in DCM (6.9 mL) at 0 °C was added 3-chloroperoxybenzoic acid (285 mg, 1.65 mmol) portionwise. The ice bath was removed and after 18 hours at rt, the mixture was concentrated directly onto Celite[®] and purified by normal-phase chromatography (0-80% EtOAc/DCM then 0-10% MeOH/DCM) to afford title compound. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 4.84 (s, 2H), 4.48 (q, $J = 7.2$ Hz, 2H), 2.25 (s, 3H), 2.22 (s, 3H), 1.44 (t, $J = 7.2$ Hz, 3H). ES-MS $[\text{M}+1]^+$: 244.

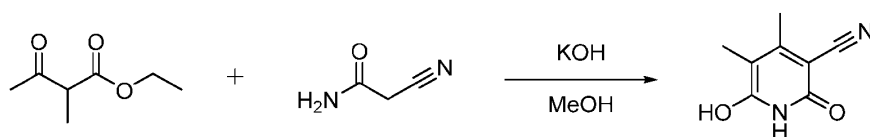


[00496] Ethyl 6-chloro-2-(chloromethyl)-4,5-dimethylnicotinate. To a solution of 2-(chloromethyl)-3-(ethoxycarbonyl)-4,5-dimethylpyridine 1-oxide (182 mg, 0.75 mmol) in MeCN (1.6 mL) was added phosphorus(V) oxychloride (348 μL , 3.73 mmol). The vial was sealed and the mixture was heated to 90 °C for 20 hours. After cooling to ambient temperature, the reaction mixture was slowly added to a stirred solution of saturated aqueous NaHCO_3 , keeping the pH alkaline. DCM was added and the mixture was allowed to stir for 30 minutes. The organic layer

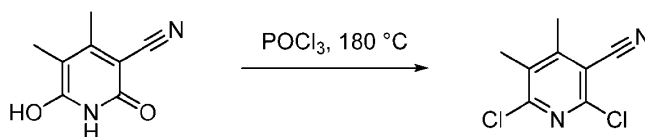
was isolated and the aqueous layer was back extracted with chloroform/IPA (3:1) (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was purified by normal-phase chromatography (0-15% EtOAc/hexanes) to afford the title compound. ¹H NMR (400 MHz, CDCl₃) δ 4.66 (s, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 2.33 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H). ES-MS [*M*+1]⁺: 262/264.



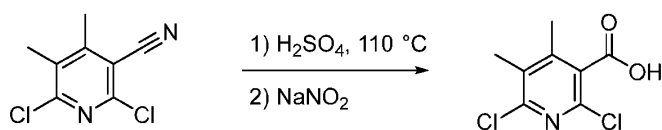
[00497] 2-Chloro-3,4,6-trimethyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one. To a solution of ethyl 6-chloro-2-(chloromethyl)-4,5-dimethylnicotinate (68 mg, 0.26 mmol) in THF (1.3 mL) was added methylamine (2.0*M* solution in THF) (650 μL, 1.3 mmol) and the reaction was heated to 30 °C for 18 hours. The reaction was concentrated *in vacuo* to afford title compound. ¹H NMR (400 MHz, CDCl₃) δ 4.29 (s, 3H), 3.18 (s, 2H), 2.73 (s, 3H), 2.39 (s, 3H). ES-MS [*M*+1]⁺: 211.



[00498] 6-Hydroxy-4,5-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile. To a solution of 2-cyanoacetamide (2.0 g, 23.8 mmol) dissolved in methanol (30 mL) were added ethyl 2-methyl-3-oxobutanoate (3.37 mL, 23.89 mmol) and potassium hydroxide (2.04 g, 35.7 mmol). The mixture was then stirred at 65 °C for 4 hours before cooling to 4 °C. The solids were collected by vacuum filtration rinsing with MeOH. The solid was dissolved in ~175 mL of hot water (70 °C). The solution was adjusted to pH~1 with aqueous HCl (5*M*) and a precipitate was observed. The solids were collected by vacuum filtration rinsing with water to give title compound. ¹H NMR (400 MHz, DMSO) δ 2.23 (s, 1H), 1.90 (s, 1H). ES-MS [*M*+1]⁺: 165.



[00499] **2,6-Dichloro-4,5-dimethylnicotinonitrile.** A solution of 6-hydroxy-4,5-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (2.28 g, 13.88 mmol) in phosphorus(v) oxychloride (10 mL) was heated to 180 °C. After 6 hours, the heat source was removed and the reaction mixture was poured into ice water (100 mL) at rt. The precipitate was collected by vacuum filtration to afford title compound. ¹H NMR (400 MHz, CDCl₃) δ 2.58 (s, 3H), 2.39 (s, 3H). ES-MS [M+1]⁺: 201/203.

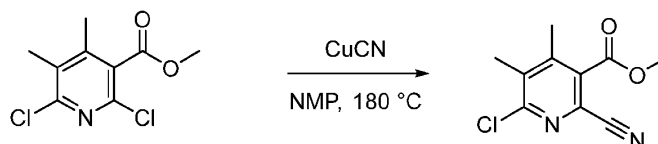


[00500] **2,6-Dichloro-4,5-dimethylnicotinic acid.** A stirred solution of 2,6-dichloro-4,5-dimethylnicotinonitrile (1.48 g, 7.36 mmol) in sulfuric acid (2.0 mL) was heated to 110 °C for 1 hour. After cooling to ambient temperature, the reaction mixture was cooled to 0 °C where an aqueous solution of sodium nitrite (671 mg, 9.58 mmol) (2.6M in water) was added dropwise over a period of 15 minutes resulting in evolution of heat and a brown gas. The mixture was then warmed to ambient temperature for 15 minutes, then heated to 60 °C for 18 hours. After cooling to ambient temperature, the reaction mixture was again cooled to 0 °C and an aqueous solution of sodium nitrite (186 mg, 2.66 mmol) (2.6M in water) was added dropwise over a period of 15 minutes. The mixture was then warmed to ambient temperature for 15 minutes, then heated to 60 °C for an additional 18 hours. After cooling to room temperature, the reaction mixture was added to ice water and the precipitate was collected by vacuum filtration to give title compound. ¹H NMR (400 MHz, DMSO) δ 2.32 (s, 3H), 2.31 (s, 3H). ES-MS [M+1]⁺: 220/222.

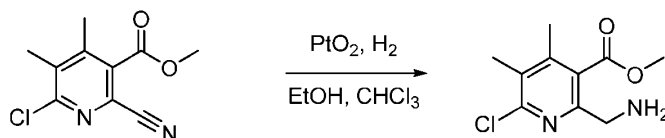


[00501] **Methyl 2,6-dichloro-4,5-dimethylnicotinate.** To a solution of 2,6-dichloro-4,5-dimethylnicotinic acid (960 mg, 4.36 mmol) in DMF (14.5 mL) was added potassium carbonate (918 mg, 6.54 mmol) and iodomethane (543 μL, 8.73 mmol). The mixture was stirred for 1 hour at ambient temperature before diluting with water and extracting with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. The crude residue was

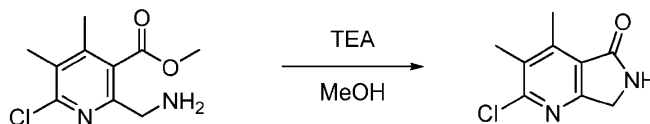
purified by normal-phase chromatography (0-10% EtOAc/Hex) to afford the title compound. ^1H NMR (400 MHz, CDCl_3) δ 3.97 (s, 3H), 2.35 (s, 3H), 2.29 (s, 3H). ES-MS $[\text{M}+1]^+$: 234/236.



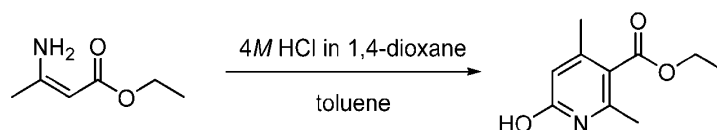
[00502] Methyl 6-chloro-2-cyano-4,5-dimethylnicotinate. A solution of methyl 2,6-dichloro-4,5-dimethylnicotinate (868 mg, 3.71 mmol) in NMP (4.4 mL) and copper(I) cyanide (498 mg, 5.56 mmol) was stirred for 3 hours at $180\text{ }^\circ\text{C}$ under inert atmosphere. After cooling to ambient temperature, the reaction was poured into ice water and the solids were removed by filtration and washed with EtOAc. The filtrate was then extracted with EtOAc (3x) and the combined organics were dried (MgSO_4), filtered, and concentrated. The crude residue was purified by normal-phase chromatography (0-40% EtOAc/Hex) to afford the title compound. ES-MS $[\text{M}+1]^+$: 225.



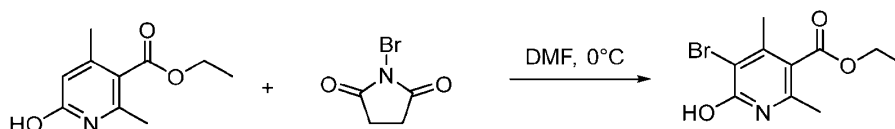
[00503] Methyl 2-(aminomethyl)-6-chloro-4,5-dimethylnicotinate. A solution of methyl 6-chloro-2-cyano-4,5-dimethylnicotinate (219 mg, 0.98 mmol) in ethanol (4.6 mL)/chloroform (1.5 mL) (3:1) was added platinum(IV) oxide (38 mg, 0.17 mmol). The flask was evacuated under vacuum and purged with hydrogen gas (process repeated 3x). The mixture was stirred under an atmosphere of hydrogen (balloon) for 25 hours. The reaction mixture was filtered over Celite[®], washed with DCM/MeOH, and the filtrate was concentrated and carried forward without further purification. ES-MS $[\text{M}+1]^+$: 229.



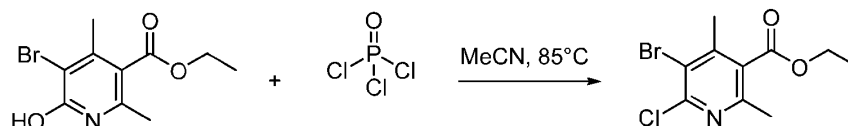
[00504] **2-Chloro-3,4-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one.** To a vial was added a solution of methyl 2-(aminomethyl)-6-chloro-4,5-dimethylnicotinate (236 mg, 0.97 mmol) and triethylamine (680 μ L, 4.88 mmol) in methanol (4.9 mL). The solution was allowed to stir at ambient temperature for 18 hours then concentrated onto Celite[®] and purified by normal-phase chromatography (0-3% MeOH/DCM) to afford the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.06 (s, 1H), 4.38 (s, 2H), 2.74 (s, 3H), 2.41 (s, 3H). ES-MS [M+1]⁺: 197.



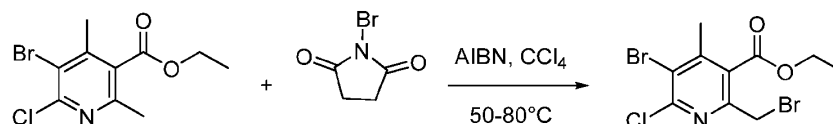
[00505] **Ethyl 6-hydroxy-2,4-dimethylnicotinate.** To a solution of ethyl (Z)-3-aminobut-2-enoate (1.96 mL, 15.5 mmol) in toluene (11.6 mL) was added a solution of hydrochloric acid (4M in dioxanes) (7.74 mL, 30.9 mmol) and the reaction was heated to 115 °C for 18 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was concentrated *in vacuo* and the crude residue was purified by normal-phase chromatography (0-90% EtOAc/DCM) to afford the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.25 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.46 (s, 3H), 2.29 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). ES-MS [M+1]⁺: 196.



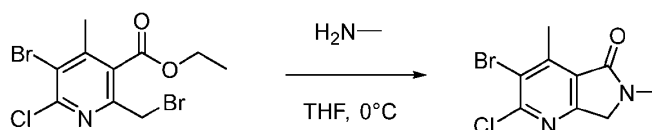
[00506] **Ethyl 5-bromo-6-hydroxy-2,4-dimethylnicotinate.** Prepared in a similar manner as ethyl 5-bromo-6-hydroxy-2-methylnicotinate. ¹H NMR (400 MHz, CDCl₃) δ 4.36 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ES-MS [M+1]⁺: 274/276.



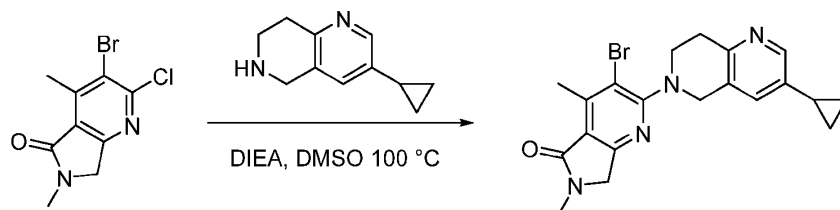
[00507] Ethyl 5-bromo-6-chloro-2,4-dimethylnicotinate: Prepared in a similar manner as ethyl 5-bromo-6-chloro-2-methylnicotinate. ^1H NMR (400 MHz, CDCl_3) δ 4.43 (q, $J = 7.1$ Hz, 2H), 2.47 (s, 3H), 2.43 (s, 3H), 1.40 (t, $J = 7.1$ Hz, 3H). ES-MS $[\text{M}+1]^+$: 292/294.



[00508] Ethyl 5-bromo-2-(bromomethyl)-6-chloro-4-methylnicotinate: Prepared in a similar manner as ethyl 5-bromo-2-(bromomethyl)-6-chloronicotinate. ^1H NMR (400 MHz, CDCl_3) δ 4.53 (s, 2H), 4.48 (q, $J = 7.2$ Hz, 2H), 2.48 (s, 3H), 1.43 (t, $J = 7.2$ Hz, 3H). ES-MS $[\text{M}+1]^+$: 370/372/374.



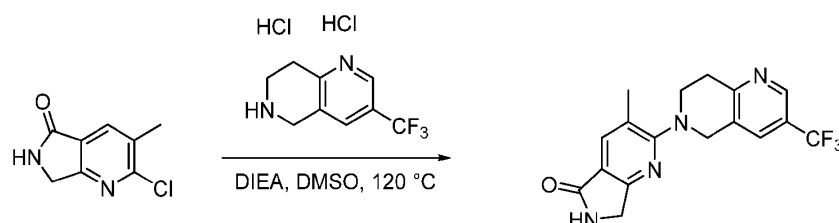
[00509] 3-Bromo-2-chloro-4,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one: Prepared in a similar manner as 3-bromo-2-chloro-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one. ^1H NMR (400 MHz, DMSO) δ 4.43 (s, 2H), 3.07 (s, 3H), 2.75 (s, 3H). ES-MS $[\text{M}+1]^+$: 275/277.



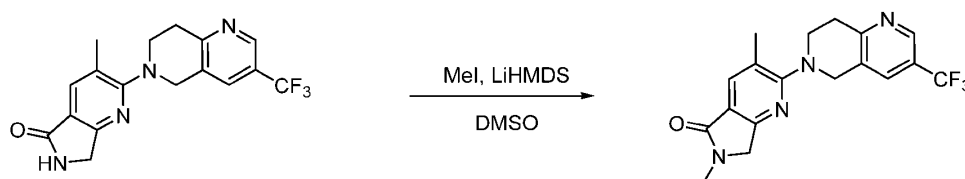
[00510] 3-Bromo-2-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-4,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one. To a solution of 3-cyclopropyl-5,6,7,8-tetrahydro-1,6-naphthyridine (51 mg, 0.29 mmol) and 3-bromo-2-chloro-4,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (40 mg, 0.15 mmol) in DMSO (0.5 mL) was added N,N-diisopropylethylamine (126 μL , 0.73 mmol). The reaction heated to 100 $^{\circ}\text{C}$ for 18 hours. After cooling, the reaction mixture was added to water (~ 10 mL) and the solid was

collected by vacuum filtration to give title compound. ^1H NMR (400 MHz, CDCl_3) δ 8.27 (d, J = 2.2 Hz, 1H), 7.07 (d, J = 2.2 Hz, 1H), 4.53 (s, 2H), 4.22 (s, 2H), 3.74 (t, J = 5.8 Hz, 2H), 3.23 (t, J = 5.8 Hz, 2H), 3.17 (s, 3H), 2.79 (s, 3H), 1.88 (tt, J = 8.5, 5.1 Hz, 1H), 1.06 – 0.91 (m, 2H), 0.69 (dt, J = 6.6, 4.8 Hz, 2H). ES-MS $[\text{M}+1]^+$: 414.

b. Synthesis of representative compounds of the invention

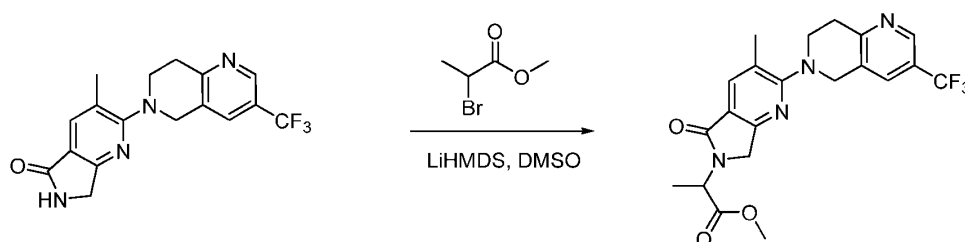


[00511] **3-Methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound 2)**. To a solution of 2-chloro-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (100 mg, 0.55 mmol) in DMSO (1.8 mL) was added 7-(trifluoromethyl)-2,5-diazatetralin dihydrochloride (226 mg, 0.82 mmol) and *N,N*-diisopropylethylamine (572 μL , 3.3 mmol). The mixture heated to 120 $^{\circ}\text{C}$ for 18 h. Additional *N,N*-diisopropylethylamine (572 μL , 3.3 mmol) was added and the mixture was heated to 120 $^{\circ}\text{C}$ for 18 h. After cooling to ambient temperature, the mixture was poured into water (~30 mL) and a precipitate formed. The solid was collected by vacuum filtration and dried under a stream of nitrogen to give the title compound. ES-MS $[\text{M}+1]^+$: 349; ^1H NMR (400 MHz, CDCl_3) δ 8.76 (s, 1H), 7.89 (d, J = 0.9 Hz, 1H), 7.86 (s, 1H), 5.99 (s, 1H), 4.66 (s, 2H), 4.39 (s, 2H), 3.66 (t, J = 5.8 Hz, 2H), 3.39 (t, J = 5.8 Hz, 2H), 2.43 (d, J = 0.8 Hz, 3H).

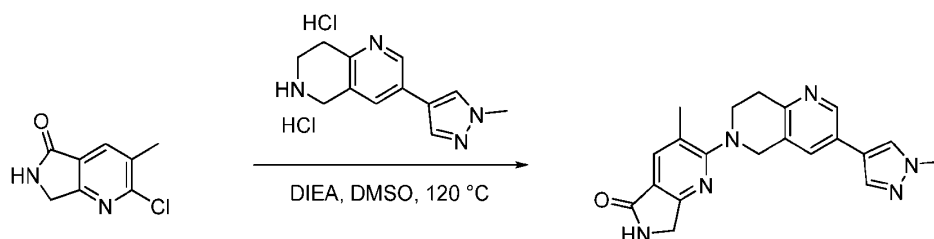


[00512] **3,6-Dimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound 1)**. To a solution of 3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (15 mg, 0.04 mmol) in DMSO (0.62 mL) was added lithium bis(trimethylsilyl)amide (43

μL , 0.04 mmol) (1M in THF) at ambient temperature. The reaction was stirred for 20 minutes before iodomethane (2.7 μL , 0.04 mmol) was added. The reaction was stirred for 4 h and the mixture was directly purified by RP-HPLC (5-60% ACN/ 0.05% aqueous NH_4OH) to afford the title compound. ES-MS $[\text{M}+1]^+$: 363; ^1H NMR (400 MHz, CDCl_3) δ 8.87 (s, 1H), 8.29 (s, 1H), 8.00 (s, 1H), 4.91 (s, 2H), 4.46 (s, 2H), 3.87 – 3.72 (m, 2H), 3.76 – 3.66 (m, 2H), 3.23 (s, 3H), 2.48 (s, 3H).

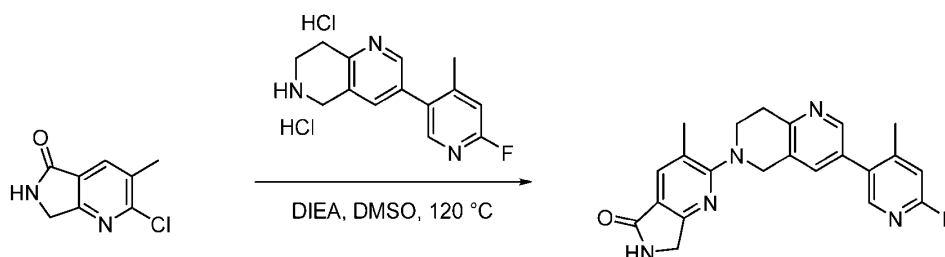


[00513] Methyl 2-(3-methyl-5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)propanoate (compound 3). Prepared in a similar manner as compound 1 to give the title compound. ES-MS $[\text{M}+1]^+$: 435; ^1H NMR (400 MHz, CDCl_3) δ 8.76 (s, 1H), 7.88 (s, 2H), 5.20 (q, $J = 7.5$ Hz, 1H), 4.67 (s, 2H), 4.51 (d, $J = 17.0$ Hz, 1H), 4.35 (d, $J = 17.1$ Hz, 1H), 3.73 (s, 3H), 3.66 (t, $J = 5.8$ Hz, 2H), 3.45 – 3.30 (m, 0H), 2.43 (d, $J = 0.9$ Hz, 3H), 1.58 (d, $J = 7.5$ Hz, 3H).

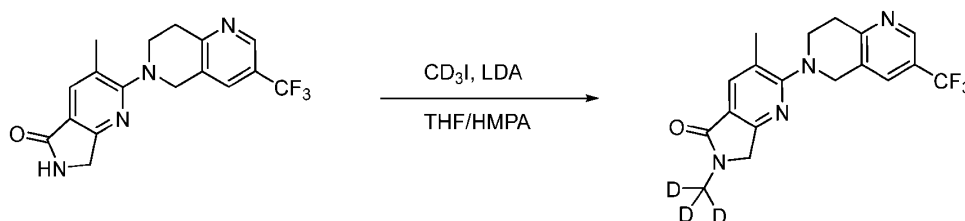


[00514] 3-Methyl-2-(3-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (compound 4). To a solution of 2-chloro-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (15 mg, 0.08 mmol) in DMSO (0.5 mL) was added 3-(1-methyl-1H-pyrazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (39 mg, 0.12 mmol) and *N,N*-diisopropylethylamine (86 μL , 0.49 mmol). The mixture was heated to 120 °C for 18 h. After cooling to ambient temperature, the crude mixture was purified using RP-HPLC (5-45% ACN/0.1% aqueous TFA). Fractions containing desired product were basified

with saturated aqueous NaHCO₃ then extracted with 3:1 chloroform/IPA (3x). The combined organics were passed through a phase separator and the solvents were concentrated to afford 11.4 mg of title compound. ES-MS [M+1]⁺: 361; ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 2.2 Hz, 1H), 7.85 (d, *J* = 0.9 Hz, 1H), 7.76 (d, *J* = 0.8 Hz, 1H), 7.65 (s, 1H), 7.53 (d, *J* = 2.2 Hz, 1H), 5.96 (s, 1H), 4.58 (s, 2H), 4.38 (s, 2H), 3.97 (s, 3H), 3.63 (t, *J* = 5.9 Hz, 2H), 3.22 (t, *J* = 5.8 Hz, 2H), 2.44 (s, 3H).

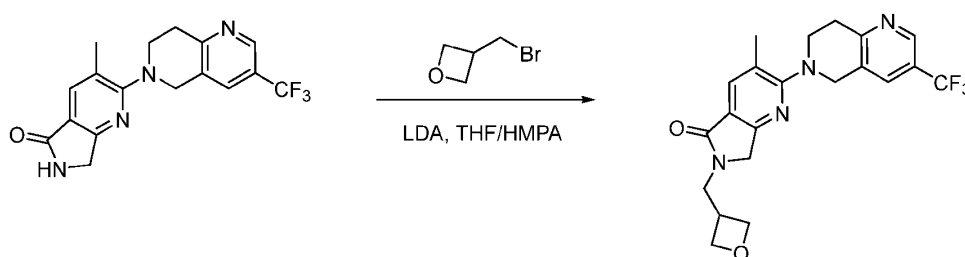


[00515] 2-(3-(6-Fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound 5). Prepared in a similar manner as compound 4 to afford the title compound. ES-MS [M+1]⁺: 390; ¹H NMR (400 MHz, CDCl₃) δ 8.42 (d, *J* = 2.2 Hz, 1H), 8.05 (s, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 5.98 (s, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 3.66 (t, *J* = 5.9 Hz, 2H), 3.29 (t, *J* = 5.9 Hz, 2H), 2.50 (s, 3H), 2.34 (s, 3H).



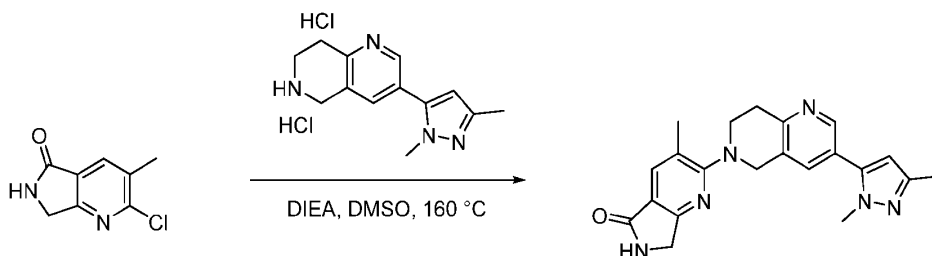
[00516] 3-Methyl-6-(methyl-*d*₃)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound 8). To a solution of 3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (10 mg, 0.03 mmol) in THF (400 μL) and HMPA (100 μL) at 0 °C was added lithium diisopropylamide (35 μL, 0.03 mmol) (1M in THF). The reaction warmed to ambient temperature and stirred for 30 minutes after which time iodomethane-*d*₃ (4.3 μL, 0.04 mmol) was added. The reaction was stirred for 50 minutes then water was added and the mixture

was extracted with EtOAc (3x). The organics were dried (MgSO₄), filtered, and concentrated. The crude product was dissolved in DMSO (2 mL) and purified using RP-HPLC (5-60% ACN/ 0.1% aqueous TFA). Fractions containing desired product were basified with saturated aqueous NaHCO₃ then extracted with 3:1 chloroform/IPA (3x). The combined organics were passed through a phase separator and the solvents were concentrated to give the title compound. ES-MS [M+1]⁺: 366; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 7.83 (s, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 4.58 (s, 2H), 4.29 (s, 2H), 3.61 (t, *J* = 5.9 Hz, 2H), 3.27 (t, *J* = 5.9 Hz, 2H), 2.41 (s, 3H).

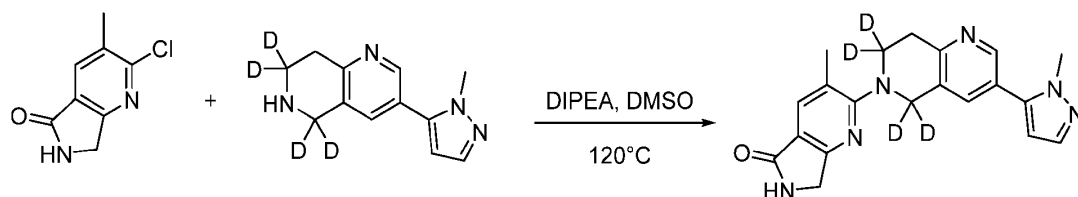


[00517] 3-Methyl-6-(oxetan-3-ylmethyl)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound 9).

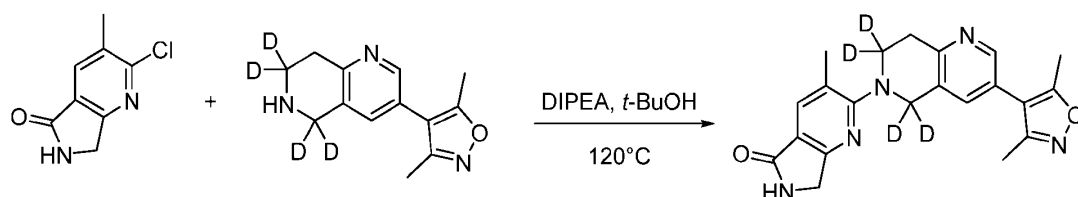
Prepared in a similar manner as compound 8 to afford the title compound. ES-MS [M+1]⁺: 419.



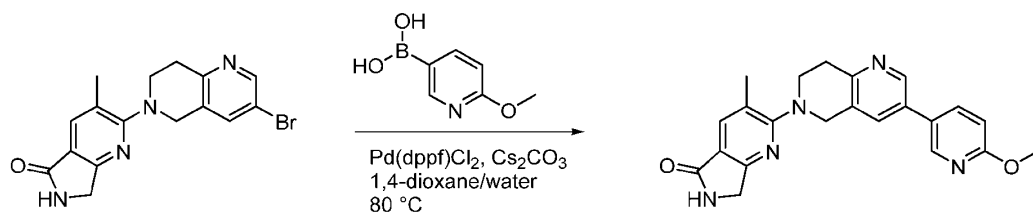
[00518] 2-(3-(1,3-Dimethyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound 24). Prepared in a similar manner as compound 4 to give the title compound. ES-MS [M+1]⁺: 375; ¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, *J* = 2.1 Hz, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 6.14 (s, 1H), 5.99 (s, 1H), 4.61 (s, 2H), 4.39 (s, 2H), 3.84 (s, 3H), 3.64 (t, *J* = 5.9 Hz, 2H), 3.26 (s, 2H), 2.44 (s, 3H), 2.31 (s, 3H).



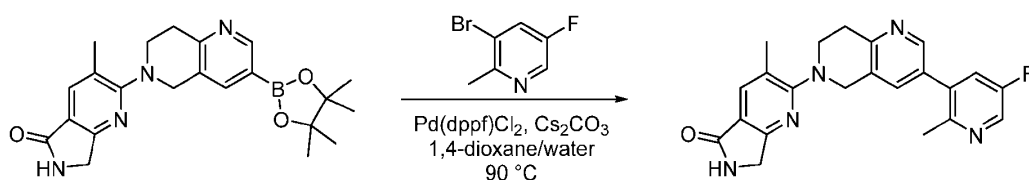
[00519] **3-Methyl-2-(3-(1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl-5,5,7,7-*d*₄)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (Compound 10).** To a solution of 2-chloro-3-methyl-6,7-dihydropyrrolo[3,4-*b*]pyridin-5-one (15 mg, 0.08 mmol) and *N,N*-diisopropylethylamine (0.07 mL, 0.41 mmol) in DMSO (0.8 mL) was added 3-(1-methyl-1H-pyrazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-5,5,7,7-*d*₄ (18 mg, 0.08 mmol). The reaction heated at 120 °C for 18 h. The reaction was purified by reverse-phase HPLC (5-45% MeCN/Water/0.05% NH₄OH) to afford the title compound (3.2 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, *J* = 2.2 Hz, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.54 (dd, *J* = 9.6, 2.1 Hz, 2H), 6.36 (d, *J* = 1.9 Hz, 1H), 6.06 (s, 1H), 4.38 (s, 2H), 3.92 (s, 3H), 3.27 (s, 2H), 2.44 (d, *J* = 0.8 Hz, 3H); ES-MS [M+1]⁺: 365.5.



[00520] **2-(3-(3,5-Dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl-5,5,7,7-*d*₄)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (compound 11).** To a solution of 2-chloro-3-methyl-6,7-dihydropyrrolo[3,4-*b*]pyridin-5-one (15 mg, 0.08 mmol) and *N,N*-diisopropylethylamine (0.07 mL, 0.41 mmol) in DMSO (0.8 mL) was added 3,5-dimethyl-4-(5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl-5,5,7,7-*d*₄)isoxazole (19 mg, 0.08 mmol). The reaction heated at 120 °C for 18 h. The reaction was purified by reverse-phase HPLC (5-45% MeCN/Water/0.05% NH₄OH) to afford the title compound (5.7 mg). ES-MS [M+1]⁺: 380.5; ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 2.1 Hz, 1H), 7.87 (s, 1H), 7.52 (s, 1H), 6.33 (s, 1H), 4.38 (s, 2H), 3.37 (s, 2H), 2.61 (s, 3H), 2.44 (s, 3H), 2.29 (s, 3H).

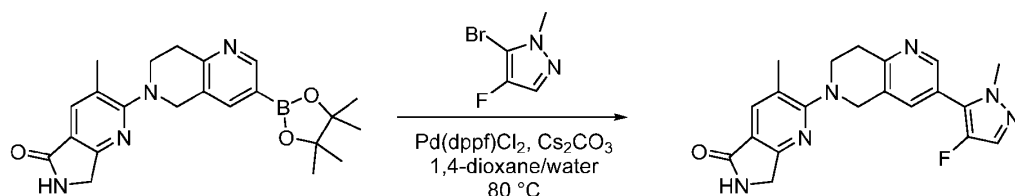


[00521] 2-(3-(6-Methoxypyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound 20). In a vial were mixed cesium carbonate (41 mg, 0.13 mmol), 2-(3-bromo-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (15 mg, 0.04 mmol), (6-methoxypyridin-3-yl)boronic acid (13 mg, 0.08 mmol), and Pd(dppf)Cl₂ (3.1 mg, 0.004 mmol) in 1,4-dioxane (350 μ L)/water (70 μ L) (5:1). The mixture was stirred at 80 °C for 16 h. After cooling to ambient temperature, the reaction mixture was filtered over Celite[®], washed with DCM/MeOH, and concentrated. The crude product was dissolved in DMSO (2 mL) and purified via RP-HPLC (5-50% ACN/0.1% aqueous TFA). Fractions containing desired product were basified with saturated aqueous NaHCO₃ then extracted with 3:1 chloroform/IPA (3x). The combined organics were passed through a phase separator and the solvents were concentrated to afford the title compound. ES-MS [M+1]⁺: 388; ¹H NMR (400 MHz, CDCl₃) δ 8.69 (d, *J* = 2.1 Hz, 1H), 8.42 (dd, *J* = 2.8, 0.6 Hz, 1H), 7.91 (s, 1H), 7.78 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 5.96 (s, 1H), 4.74 (s, 2H), 4.37 (s, 2H), 4.08 – 3.91 (m, 4H), 3.68 (s, 3H), 2.43 (d, *J* = 0.8 Hz, 3H).

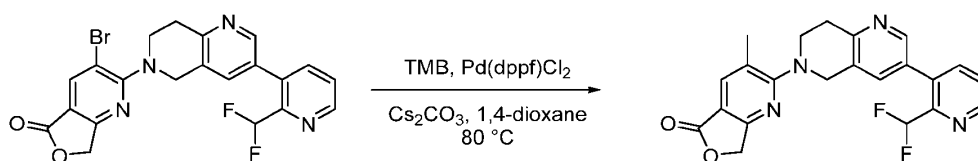


[00522] 2-(3-(5-Fluoro-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound 33). In a vial were combined cesium carbonate (55 mg, 0.17 mmol), 3-methyl-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (23 mg, 0.06 mmol), 3-bromo-5-fluoro-2-methylpyridine (21 mg, 0.11 mmol), and Pd(dppf)Cl₂ (4.1 mg, 0.01 mmol) in 1,4-dioxane (350 μ L)/water (70 μ L) (5:1). The mixture was stirred at 90 °C for 18 h then cooled to ambient temperature. The reaction mixture was

filtered over Celite® and rinsed with 3:1 CHCl₃/IPA. The organics were then washed with saturated aqueous NaHCO₃, passed through a phase separator, and concentrated. The crude residue was dissolved in DMSO (1.5 mL) and purified via RP-HPLC (5-45% ACN/0.1% aqueous TFA). Fractions containing desired product were basified with saturated aqueous NaHCO₃ then extracted with 3:1 chloroform/IPA (3x). The combined organics were passed through a phase separator and the solvents were concentrated to give the title compound. ES-MS [M+1]⁺: 390; ¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, *J* = 2.2 Hz, 1H), 8.42 (d, *J* = 2.9 Hz, 1H), 7.87 (d, *J* = 0.9 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.28 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.00 (s, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 3.66 (t, *J* = 5.9 Hz, 2H), 3.30 (t, *J* = 5.9 Hz, 2H), 2.50 (d, *J* = 1.2 Hz, 3H), 2.45 (s, 3H).

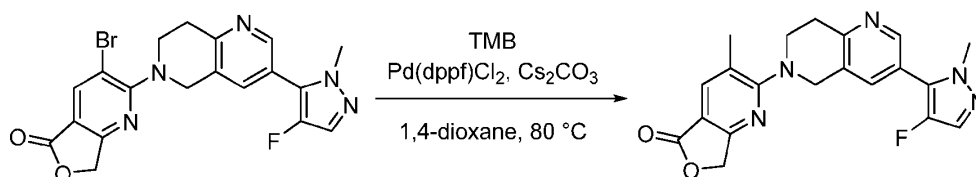


[00523] 2-(3-(4-Fluoro-1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (compound 37). Prepared in a similar manner as compound 33 to give the title compound. ES-MS [M+1]⁺: 379; ¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, *J* = 2.1 Hz, 1H), 7.87 (s, 1H), 7.58 – 7.53 (m, 1H), 7.44 (d, *J* = 4.5 Hz, 1H), 6.01 (s, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.87 (s, 3H), 3.65 (t, *J* = 5.9 Hz, 2H), 3.29 (t, *J* = 5.9 Hz, 2H), 2.45 (s, 3H).

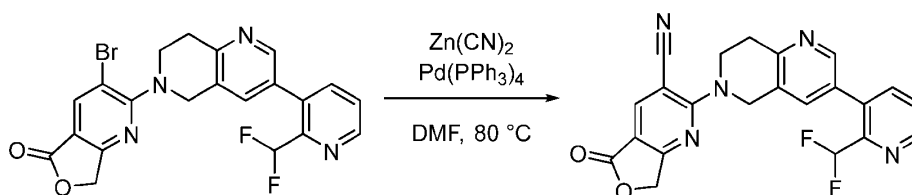


[00524] 2-(3-(2-(Difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methylfuro[3,4-*b*]pyridin-5(7H)-one (compound 38). 3-Bromo-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)furo[3,4-*b*]pyridin-5(7H)-one (30 mg, 0.05 mmol), cesium carbonate (46 mg, 0.14 mmol), trimethylboroxine (50% wt in THF) (40 μL, 0.14 mmol), Pd(dppf)Cl₂ (7.0 mg, 0.01 mmol), and 1,4-dioxane (0.5 mL) were charged into a vial. The mixture was evacuated and purged with nitrogen then stirred at 80 °C

for 18 h. After cooling to ambient temperature, the reaction was filtered through a pad of Celite® which was rinsed thoroughly with DCM/MeOH. Solvents were removed and the crude sample was dissolved in DMSO (1.5 mL) and purified by RP-HPLC (30-50% ACN/ 0.05% aqueous NH₄OH). Fractions containing the desired product were concentrated to give 6.5 mg of title compound. ES-MS [M+1]⁺: 409.

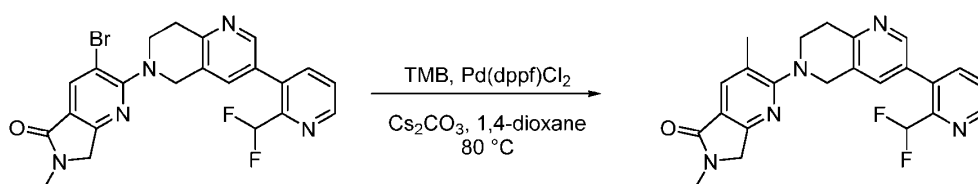


[00525] 2-(3-(4-Fluoro-1-methyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methylfuro[3,4-b]pyridine-5(7H)-one (compound 44). 3-Bromo-2-[3-(4-fluoro-2-methylpyrazol-3-yl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-7H-furo[3,4-b]pyridine-5-one (15 mg, 0.03 mmol), cesium carbonate (33 mg, 0.1 mmol), trimethylboroxine (50% wt in THF) (0.03 mL, 0.1 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5.0 mg, 0.01 mmol), and 1,4-dioxane (0.5 mL) were charged into a vial. The vial was evacuated and purged with nitrogen (3x) and heated to 80 °C for 18 hr. The reaction was filtered through a pad of Celite®, which was rinsed thoroughly with EtOAc. The solvents were removed under vacuo and the crude residue was purified by RP- HPLC (15-55% MeCN/Water/0.1% TFA). The desired fractions were subjected to a basic workup with saturated NaHCO₃, extracted with CHCl₃/iPA (3:1), and the organic layers were concentrated to afford the title compound. ES-MS [M+1]⁺: 423.

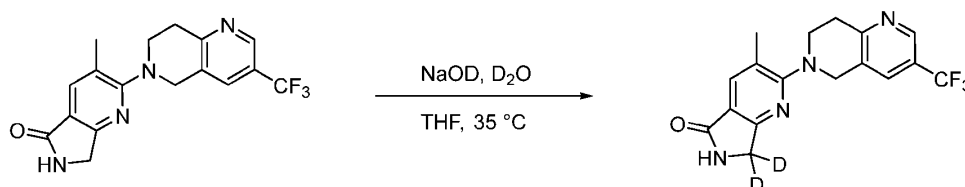


[00526] 2-(3-(2-(Difluoromethyl)pyridine-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5-oxo-5,7-dihydrofuro[3,4-b]pyridine-3-carbonitrile (compound 42). 3-Bromo-2-[3-[2-(difluoromethyl)pyridin-3-yl]-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-7H-furo[3,4-b]pyridin-5-

one (25 mg, 0.05 mmol) and zinc cyanide (9.3 mg, 0.08 mmol) were suspended in DMF (0.5 mL). The mixture was degassed with nitrogen and then tetrakis(triphenylphosphine)palladium(0) (9.0 mg, 0.01 mmol) was added. The reaction was heated to 80 °C for 5 hr. The reaction was diluted with EtOAc. The organic phase was washed with sat. NaHCO₃ (aq) (2x) and brine, dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica gel column chromatography (0-10% NH₄OH/MeOH/DCM) to give the title compound. ES-MS [M+1]⁺: 420.3.

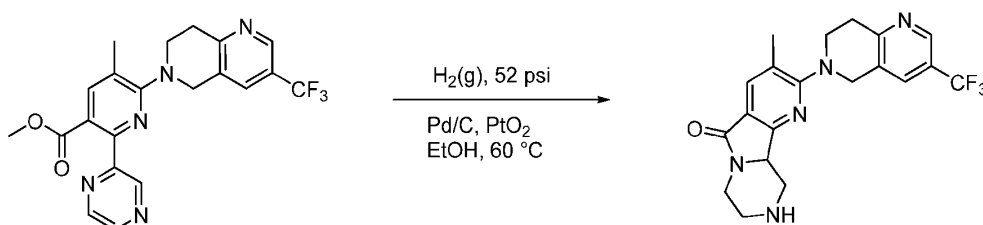


[00527] 2-(3-(2-(Difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (compound 39). Prepared in a similar manner as compound 38 to give the title compound. ES-MS [M+1]⁺: 422; ¹H NMR (400 MHz, CDCl₃) δ 8.76 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.48 (d, *J* = 2.2 Hz, 1H), 7.83 (d, *J* = 0.9 Hz, 1H), 7.76 – 7.69 (m, 1H), 7.53 (m, 2H), 6.64 (t, *J* = 54.2 Hz, 1H), 4.60 (s, 2H), 4.30 (s, 2H), 3.64 (t, *J* = 5.9 Hz, 2H), 3.29 (t, *J* = 5.9 Hz, 2H), 3.20 (s, 3H), 2.44 (s, 1H).

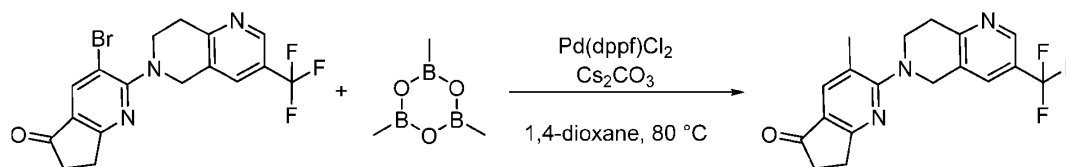


[00528] 3-Methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one-7,7-*d*₂ (compound 12). 3-Methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (41 mg, 0.12 mmol) was dissolved in THF (780 μL) and deuterium oxide (410 μL). Next, sodium deuteroxide (40 wt% in D₂O) was added and the resulting mixture was stirred at 35 °C for 16 h. The mixture was extracted with DCM (3x) and the combined extracts were passed through a phase separator and concentrated. The crude material was subjected a second time to the same reaction conditions as described above. After 16 h. The reaction mixture was

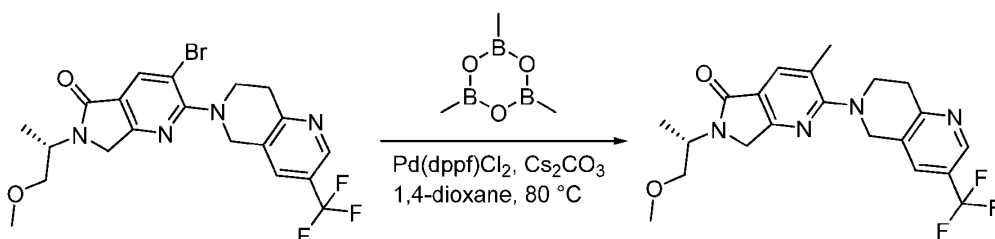
extracted with DCM (3x) and the combined extracts were passed through a phase separator and concentrated. Purification using normal phase chromatography on silica gel (0-80% EtOAc/DCM then 0-1% MeOH/DCM) afforded the title compound. The material underwent a second purification using RP-HPLC (5-55% ACN/0.1% aqueous TFA). Fractions containing desired product were basified with saturated aqueous NaHCO₃ then extracted with 3:1 chloroform/IPA (3:1) (3x). The combined organics were passed through a phase separator and the solvents were concentrated to afford the title compound. ES-MS [M+1]⁺: 351 (~98% deuterium incorporation by HRMS); ¹H NMR (400 MHz, CDCl₃) δ 8.78 (s, 1H), 7.98 (s, 1H), 7.91 (s, 1H), 5.96 (s, 1H), 4.71 (s, 2H), 3.68 (t, *J* = 5.8 Hz, 2H), 3.49 (t, *J* = 5.6 Hz, 2H), 2.44 (d, *J* = 0.8 Hz, 3H).



[00529] 3-Methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-8,9,10,10a-tetrahydropyrido[2',3':3,4]pyrrolo[1,2-a]pyrazin-5(7H)-one (compound 6). To an autoclave reactor was added methyl 5-methyl-2-(pyrazin-2-yl)-6-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)nicotinate (40 mg, 0.09 mmol), palladium on activated carbon (19.8 mg, 0.02 mmol), and platinum(IV) oxide (2.1 mg, 0.01 mmol) in ethanol (5 mL). The reaction was stirred under hydrogen gas at 52 psi while heating to 60 °C for 20 h. The mixture was cooled to ambient temperature and filtered over Celite® washing with EtOAc. The organics were concentrated and the crude residue was dissolved in DMSO (2 mL) and purified using RP-HPLC (5-50% ACN/ 0.05% aqueous NH₄OH). Fraction containing the desired product were concentrated to give the title compound. ES-MS [M+1]⁺: 404.

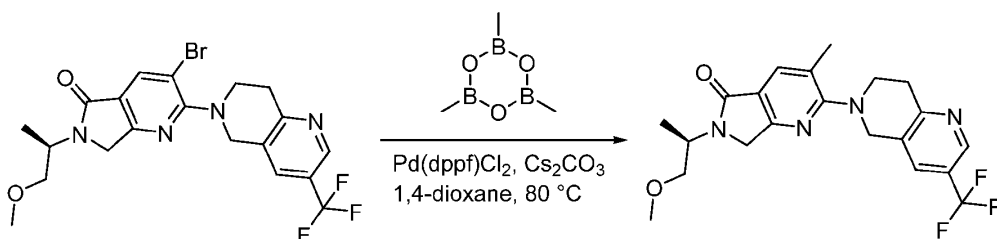


[00530] 3-Methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-cyclopenta[*b*]pyridin-5-one (Compound 50). 3-Bromo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-cyclopenta[*b*]pyridin-5-one (19 mg, 0.05 mmol), cesium carbonate (45 mg, 0.14 mmol), trimethylboroxine (50% wt in THF) (35 μ L, 0.04 mmol), Pd(dppf)Cl₂ (7.0 mg, 0.009 mmol), and 1,4-dioxane (0.5 mL) were charged into a vial. The mixture was evacuated and purged with nitrogen and stirred at 80 °C for 18 h. The reaction mixture was diluted with EtOAc, filtered over Celite® and concentrated. The crude residue was dissolved in DMSO (1.5 mL) and purified using the reverse-phase chromatography (10-50% MeCN/0.1% aqueous TFA). The fractions containing desired product were basified with sat. NaHCO₃ (aq) then extracted with 3:1 chloroform/IPA (3x). The combined organics were passed through a hydrophobic phase separator and the solvents were concentrated to afford the title compound (4.3 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 7.73 (s, 2H), 4.70 (s, 2H), 3.72 (t, *J* = 5.9 Hz, 2H), 3.29 (t, *J* = 6.0 Hz, 2H), 3.12 – 3.05 (m, 2H), 2.75 – 2.68 (m, 2H), 2.39 (d, *J* = 0.9 Hz, 3H). [M+1]⁺: 348.2.



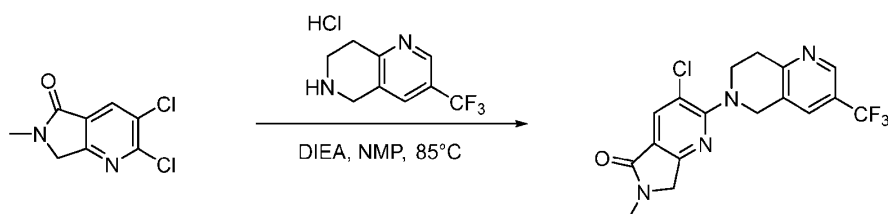
[00531] (S)-6-(1-Methoxypropan-2-yl)-3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (Compound 51). (S)-3-Bromo-6-(1-methoxypropan-2-yl)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (26 mg, 0.05 mmol), cesium carbonate (52 mg, 0.16 mmol), trimethylboroxine (50% wt in THF) (0.04 mL, 0.16 mmol), Pd(dppf)Cl₂ (8.0 mg, 0.01 mmol), and 1,4-dioxane (0.5 mL) were charged into a vial. The mixture was evacuated and purged with nitrogen and stirred at 80 °C for 18 h. The reaction mixture was diluted with EtOAc, filtered over Celite® and concentrated. The crude residue was purified using reverse phase HPLC (20-60% MeCN/0.1% aqueous TFA). The fractions containing desired product were basified with sat. NaHCO₃ then extracted with chloroform/IPA (3:1) (3x). The combined organics were

passed through a hydrophobic phase separator and the solvents were concentrated to afford the title compound (8.5 mg). ES-MS $[M+1]^-$: 421.4.

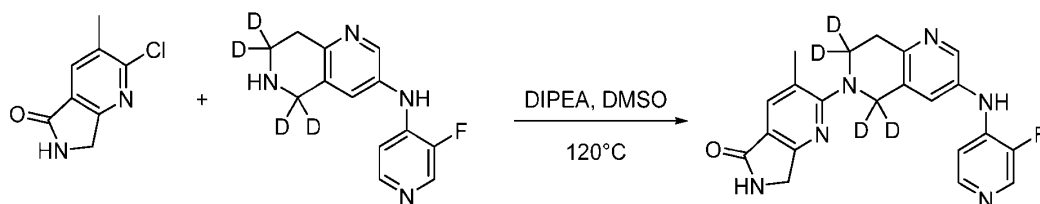


[00532] **(R)-6-(1-Methoxypropan-2-yl)-3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound 52).**

Prepared in the same manner as Compound 51. ES-MS $[M+1]^+$: 421.4.

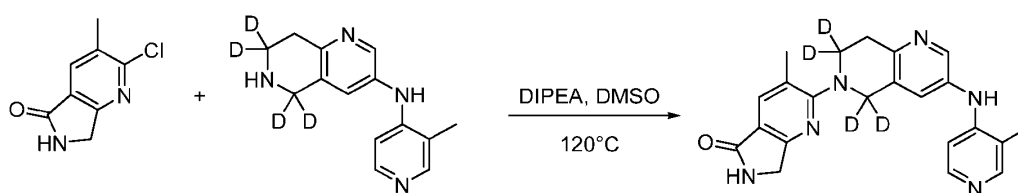


[00533] **3-Chloro-6-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound 55).** Prepared in a similar manner as Intermediate A to give the title compound. ES-MS $[M+1]^+$: 383; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 8.00 (s, 1H), 7.71 (s, 1H), 4.72 (s, 2H), 4.30 (s, 2H), 3.89 (t, $J = 5.8$ Hz, 2H), 3.31 (t, $J = 5.9$ Hz, 2H), 3.19 (s, 3H).

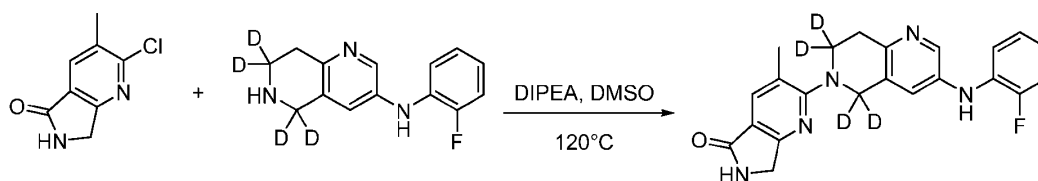


[00534] **2-(3-((3-Fluoropyridin-4-yl)amino))-7,8-dihydro-1,6-naphthyridin-6(5H)-yl-5,5,7,7-d4-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-5-one (compound A2).** To a solution of 2-chloro-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (15 mg, 0.08 mmol) and

N,N-diisopropylethylamine (0.07 mL, 0.41 mmol) in DMSO (0.8 mL) was added *N*-(3-fluoropyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-5,5,7,7-*d*₄-3-amine (25 mg, 0.1 mmol). The reaction heated at 120 °C for 18 h. The reaction was purified by reverse-phase HPLC (5-45% MeCN/Water/0.05% NH₄OH) to afford the title compound (3.5 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 2.6 Hz, 1H), 8.32 (d, *J* = 3.0 Hz, 1H), 8.13 (d, *J* = 5.6 Hz, 1H), 7.86 (s, 1H), 7.40 (d, *J* = 2.6 Hz, 1H), 6.96 (dd, *J* = 7.4, 5.5 Hz, 1H), 6.21 (d, *J* = 5.1 Hz, 2H), 4.38 (s, 2H), 3.21 (s, 2H), 2.44 (s, 3H); ES-MS [*M*+1]⁺: 395.5.



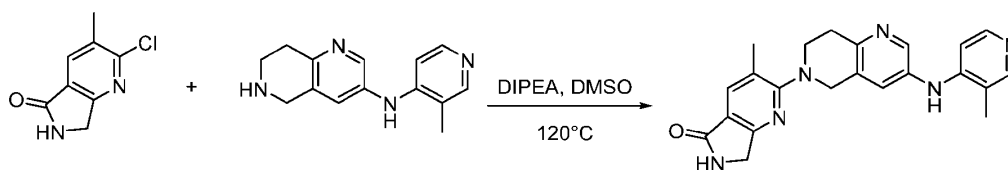
[00535] 3-Methyl-2-(3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl-5,5,7,7-*d*₄)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (compound A3). To a solution of 2-chloro-3-methyl-6,7-dihydropyrrolo[3,4-*b*]pyridin-5-one (15 mg, 0.08 mmol) and *N,N*-diisopropylethylamine (0.07 mL, 0.41 mmol) in DMSO (0.8 mL) was added *N*-(3-methylpyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-5,5,7,7-*d*₄-3-amine (24 mg, 0.1 mmol). The reaction heated at 120 °C for 18 h. The reaction was purified by reverse-phase HPLC (5-45% MeCN/Water/0.05% NH₄OH) to afford the title compound (3.7 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.36 (d, *J* = 2.6 Hz, 1H), 8.25 (s, 1H), 8.18 (d, *J* = 5.7 Hz, 1H), 7.85 (s, 1H), 7.38 (d, *J* = 2.6 Hz, 1H), 6.85 (d, *J* = 5.6 Hz, 1H), 6.40 (s, 1H), 5.77 (s, 1H), 4.38 (s, 2H), 3.20 (s, 2H), 2.43 (s, 3H), 2.26 (s, 3H); ES-MS [*M*+1]⁺: 391.5.



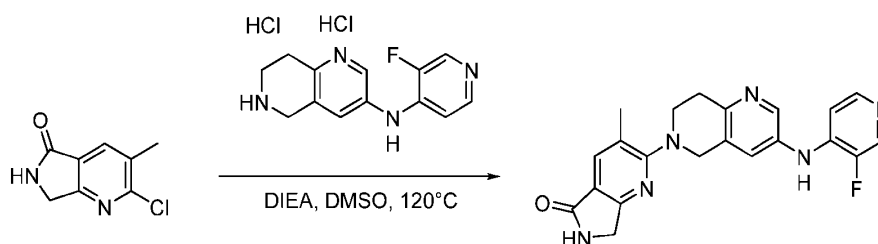
[00536] 2-(3-((2-Fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl-5,5,7,7-*d*₄)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one (compound A6). To a solution of 2-chloro-3-methyl-6,7-dihydropyrrolo[3,4-*b*]pyridin-5-one (15 mg, 0.08 mmol) and *N,N*-

diisopropylethylamine (0.07 mL, 0.41 mmol) in DMSO (0.8 mL) was added *N*-(2-fluorophenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-5,5,7,7-*d*₄-3-amine (20 mg, 0.08 mmol). The reaction heated at 120 °C for 18 h. The reaction was purified by reverse-phase HPLC (5-45%

MeCN/Water/0.05% NH₄OH) to afford the title compound (8.3 mg). ES-MS [M+1]⁺: 394.1; ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, *J* = 2.6 Hz, 1H), 7.83 (d, *J* = 1.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.16 – 7.00 (m, 2H), 6.97 – 6.88 (m, 1H), 6.56 (s, 1H), 6.06 (s, 1H), 4.36 (s, 2H), 3.18 (s, 2H), 2.41 (s, 3H).

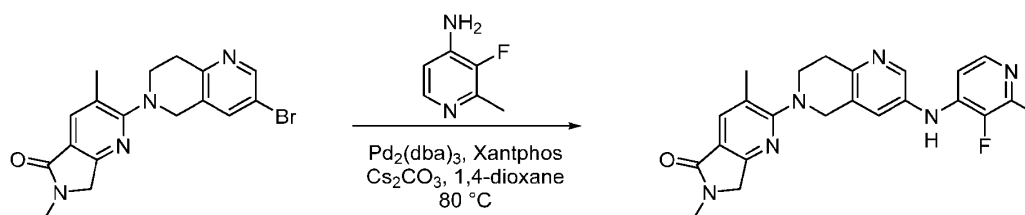


[00537] 3-Methyl-2-(3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound A7). To a solution of 2-chloro-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (15 mg, 0.08 mmol) and *N,N*-diisopropylethylamine (0.07 mL, 0.41 mmol) in DMSO (0.8 mL) was added *N*-(3-methylpyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-amine (20 mg, 0.08 mmol). The reaction heated at 120 °C for 18 h. The reaction was purified by reverse-phase HPLC (5-35% MeCN/Water/0.05% NH₄OH) to afford the title compound (3.3 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.36 (d, *J* = 2.5 Hz, 1H), 8.25 (s, 1H), 8.19 (d, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 0.9 Hz, 1H), 7.38 (d, *J* = 2.5 Hz, 1H), 6.85 (d, *J* = 5.7 Hz, 1H), 6.09 (s, 1H), 5.75 (s, 1H), 4.56 (s, 2H), 4.38 (s, 2H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.22 (t, *J* = 5.9 Hz, 2H), 2.46 – 2.42 (m, 3H), 2.27 (s, 3H); ES-MS [M+1]⁺: 387.4.

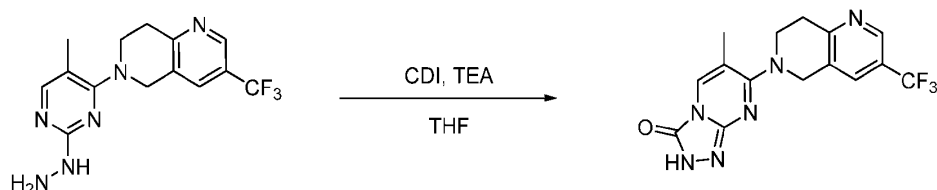


[00538] 2-(3-((3-Fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound A4). To a solution of 2-chloro-3-methyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (15 mg, 0.08 mmol) in DMSO (0.5

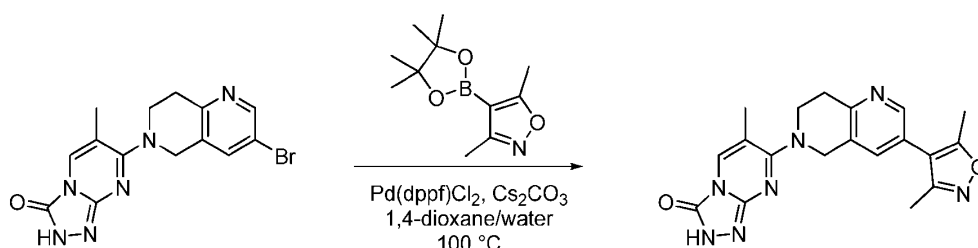
mL) was added *N*-(3-fluoropyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-amine dihydrochloride (39 mg, 0.12 mmol) and *N,N*-diisopropylethylamine (86 μ L, 0.49 mmol). The mixture heated to 120 °C for 40 h then cooled to ambient temperature. Purification by RP-HPLC (5-45% ACN/ 0.05% aqueous NH_4OH) gave the title compound which still contained impurities as determined by LCMS. The material underwent a second RP-HPLC purification (5-35% ACN/ 0.1% aqueous TFA). Fractions containing desired product were basified with saturated aqueous NaHCO_3 then extracted with 3:1 chloroform/IPA (3:1) (3x). The combined organics were passed through a phase separator and the solvents were concentrated to afford the title compound. ES-MS $[\text{M}+1]^+$: 391; ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 2.5$ Hz, 1H), 8.32 (d, $J = 3.1$ Hz, 1H), 8.13 (d, $J = 5.5$ Hz, 1H), 7.87 (d, $J = 0.9$ Hz, 1H), 7.40 (d, $J = 2.5$ Hz, 1H), 6.96 (dd, $J = 7.4, 5.5$ Hz, 1H), 6.16 (d, $J = 3.2$ Hz, 1H), 5.98 (s, 1H), 4.58 (s, 2H), 4.38 (s, 2H), 3.63 (t, $J = 5.9$ Hz, 2H), 3.23 (t, $J = 5.9$ Hz, 2H), 2.44 (d, $J = 0.9$ Hz, 3H).



[00539] 2-((3-Fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (compound A8). To a vial was added 2-(3-bromo-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (15 mg, 0.04 mmol), 3-fluoro-2-methylpyridin-4-amine (7.6 mg, 0.06 mmol), cesium carbonate (40 mg, 0.12 mmol), Xantphos (3.5 mg, 0.01 mmol), and tris(dibenzylideneacetone)dipalladium(0) (3.7 mg, 0.004 mmol) in 1,4-dioxane (0.5 mL) (degassed). The mixture was heated to 80 °C for 16 h under a nitrogen atmosphere. The mixture was cooled to ambient temperature and filtered through a pad of Celite[®] which was washed thoroughly with MeOH/DCM and concentrated. The residue was dissolved in DMSO (2 mL) and purified via RP-HPLC (5-40% ACN/0.1% aqueous TFA). Fractions containing desired product were basified with saturated aqueous NaHCO_3 then extracted with 3:1 chloroform/IPA (3x). The combined organics were passed through a phase separator and the solvents were concentrated to give the title compound. ES-MS $[\text{M}+1]^+$: 419.

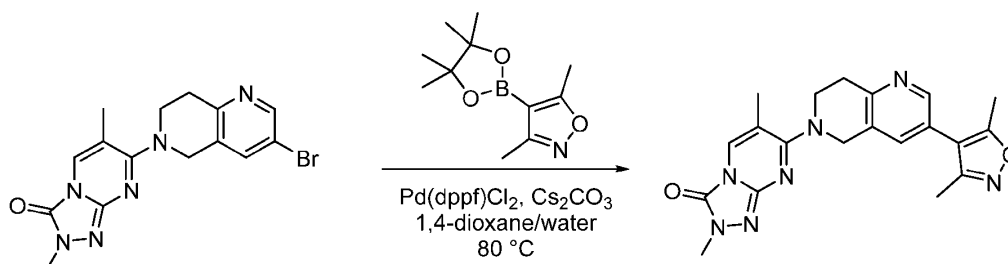


[00540] **6-Methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (compound B1).** Prepared in a similar manner as intermediate D to give the title compound. ES-MS $[M+1]^+$: 351.

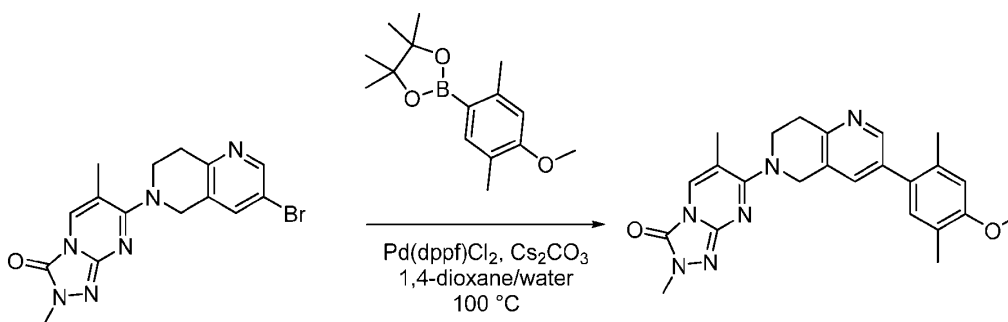


[00541] **7-(3-(3,5-Dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (compound B2).** In a vial was added a mixture of cesium carbonate (82 mg, 0.25 mmol), 7-(3-bromo-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (30 mg, 0.08 mmol), 3,5-dimethylisoxazole-4-boronic acid pinacol ester (37 mg, 0.17 mmol), and Pd(dppf)Cl₂ (6 mg, 0.01 mmol) in 1,4-dioxane (460 μ L)/water (93 μ L) (5:1). The mixture was stirred at 80 °C for 18 hours. Additional 3,5-dimethylisoxazole-4-boronic acid pinacol ester (37 mg, 0.17 mmol) was added and the mixture was heated to 80 °C for another 2.5 hours. After cooling to room temperature, the mixture was filtered over Celite[®] and washed with chloroform/IPA (3:1). The organics were then washed with saturated NaHCO₃ and passed through a phase separator before concentrating. The residue was purified using the RP-HPLC (5-40% ACN/0.1% aqueous TFA). Fractions containing desired product were basified with saturated aqueous NaHCO₃, then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a phase separator and the solvents were concentrated to afford the title compound. ES-MS $[M+1]^+$: 378; ¹H NMR (400 MHz, CDCl₃) δ 8.69 (s, 1H), 8.39 (d, J = 2.2 Hz, 1H), 7.71 (q, J = 1.2 Hz, 1H),

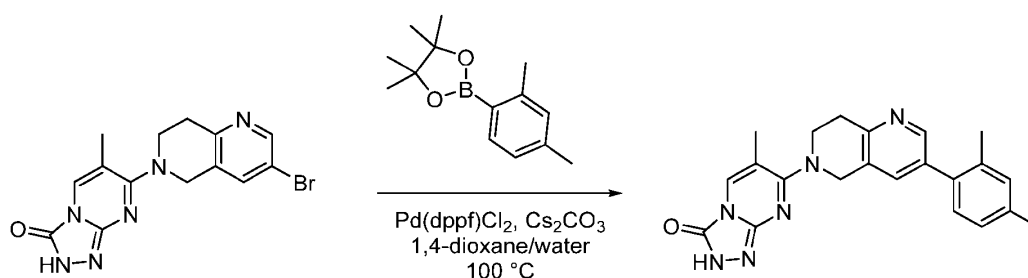
7.38 (d, $J = 2.1$ Hz, 1H), 4.79 (s, 2H), 3.86 (t, $J = 5.9$ Hz, 2H), 3.26 (t, $J = 5.9$ Hz, 2H), 2.43 (s, 3H), 2.34 (d, $J = 1.3$ Hz, 3H), 2.28 (s, 3H).



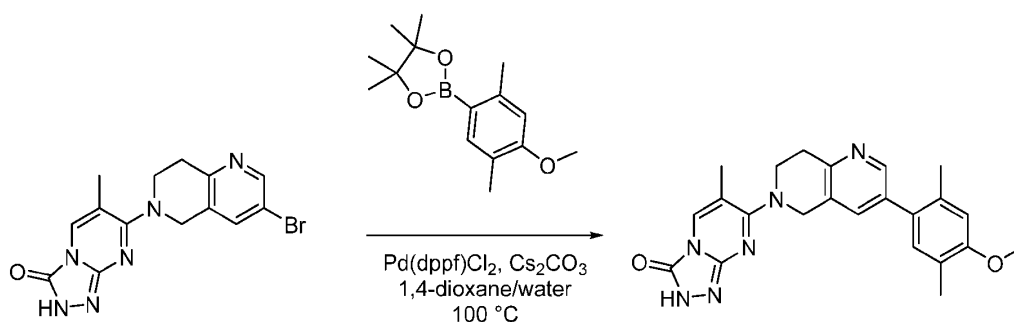
[00542] 7-(3-(3,5-Dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (compound B10). In a vial was added a mixture of cesium carbonate (40 mg, 0.12 mmol), 7-(3-bromo-7,8-dihydro-5H-1,6-naphthyridin-6-yl)-2,6-dimethyl-1,2,4-triazolo[4,3-a]pyrimidin-3-one (15 mg, 0.04 mmol), 3,5-dimethylisoxazole-4-boronic acid (14 mg, 0.1 mmol), and Pd(dppf)Cl₂ (3.0 mg, 0.004 mmol) in 1,4-dioxane (0.5 mL)/water (0.1 mL) (5:1). The mixture was stirred at 80 °C for 16 hr, filtered over Celite®, washed with EtOAc, and concentrated. The crude residue was purified using the RP-HPLC (5-50% ACN/0.1% aqueous TFA). Fractions containing desired product were basified with sat. NaHCO₃ then extracted with 3:1 chloroform/IPA (3x). The combined organics were passed through a phase separator and the solvents were concentrated to provide the title compound. ES-MS $[M+1]^+$: 392.3. ¹H NMR (400 MHz, DMSO) δ 8.43 (d, $J = 2.2$ Hz, 1H), 7.99 (d, $J = 1.4$ Hz, 1H), 7.78 (d, $J = 2.2$ Hz, 1H), 4.72 (s, 2H), 3.83 (t, $J = 5.8$ Hz, 2H), 3.41 (s, 3H), 3.12 (t, $J = 5.8$ Hz, 2H), 2.43 (s, 3H), 2.29 (d, $J = 1.2$ Hz, 3H), 2.25 (s, 3H).



[00543] 7-(3-(4-Methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-3(2H)-one (compound B11). Prepared in a similar manner as compound B10 to afford the title compound. ES-MS $[M+1]^+$:430.5; ^1H NMR (400 MHz, DMSO) δ 8.34 (d, J = 2.2 Hz, 1H), 7.98 (d, J = 1.3 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H), 7.01 (s, 1H), 6.89 (s, 1H), 4.71 (s, 2H), 3.88 – 3.82 (m, 2H), 3.82 (s, 3H), 3.40 (s, 3H), 3.11 (t, J = 5.8 Hz, 2H), 2.29 (d, J = 1.3 Hz, 3H), 2.24 (s, 3H), 2.14 (s, 3H).

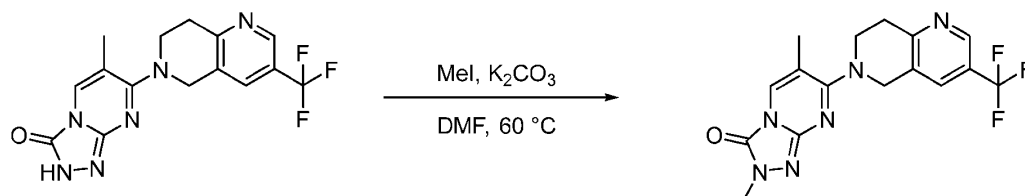


[00544] 7-(3-(2,4-Dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-3(2H)-one (Compound B12). Prepared in a similar manner as compound B2 to afford the title compound. ES-MS $[M+1]^+$:387.2; ^1H NMR (400 MHz, DMSO) δ 8.35 (d, J = 2.2 Hz, 1H), 7.94 (d, J = 1.3 Hz, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.13 (dd, J = 12.3, 4.7 Hz, 3H), 4.70 (s, 2H), 3.82 (t, J = 5.8 Hz, 3H), 3.12 (t, J = 6.2 Hz, 3H), 2.32 (s, 3H), 2.28 (d, J = 1.2 Hz, 3H), 2.23 (s, 3H).

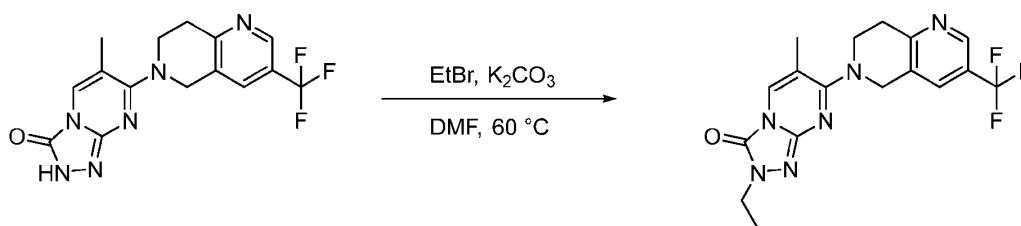


[00545] 7-(3-(4-Methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-3(2H)-one (compound B13). Prepared in a similar manner as compound B2 to afford the title compound. ES-MS $[M+1]^+$:417.3; ^1H NMR (400 MHz, DMSO) δ 8.33 (d, J = 2.2 Hz, 1H), 7.94 (d, J = 1.5 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H), 7.01

(s, 1H), 6.89 (s, 1H), 4.69 (s, 2H), 3.86 – 3.79 (m, 5H), 3.11 (t, $J = 5.9$ Hz, 2H), 2.28 (d, $J = 1.3$ Hz, 3H), 2.24 (s, 3H), 2.14 (s, 3H).

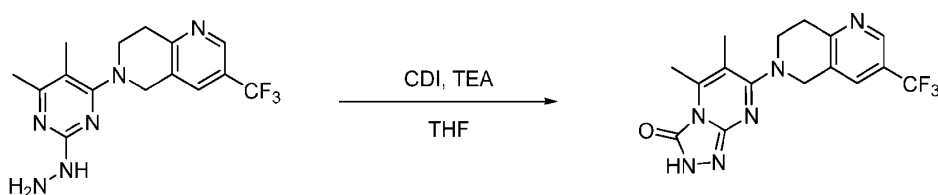


[00546] 2,6-Dimethyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (Compound B24). To a solution of 6-methyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-2H-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (15 mg, 0.043 mmol) in DMF (0.7 mL) was added potassium carbonate (12 mg, 0.086 mmol) followed by iodomethane (3.9 μ L, 0.064 mmol). The mixture was heated to 60 °C for 2.5 hours. After cooling to ambient temperature, the reaction was further dissolved in DMF (1 mL), filtered, and purified using the RP-HPLC (10-60% ACN/0.1% aqueous TFA). The fractions containing desired product were basified with saturated aqueous NaHCO₃ then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a hydrophobic phase separator and the solvents were concentrated to give the title compound. ES-MS $[M+1]^+$: 365; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 7.70 (d, $J = 1.3$ Hz, 2H), 4.76 (s, 2H), 3.83 (t, $J = 5.9$ Hz, 2H), 3.58 (s, 3H), 3.27 (t, $J = 5.9$ Hz, 2H), 2.31 (d, $J = 1.2$ Hz, 3H).

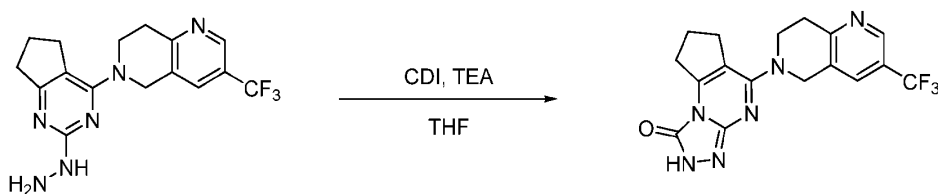


[00547] 2-Ethyl-6-methyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (Compound B25). To a solution of 6-methyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-2H-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (15 mg, 0.043 mmol) in DMF (0.7 mL) was added potassium carbonate (12 mg, 0.086 mmol) followed by bromoethane (4.8 μ L, 0.064 mmol). The mixture was heated to 60 °C for 2.5

hours. After cooling to ambient temperature, the reaction was further dissolved in DMF (1 mL), filtered, and purified using the RP-HPLC (10-65% ACN/0.1% aqueous TFA). The fractions containing desired product were basified with saturated aqueous NaHCO₃ then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a hydrophobic phase separator and the solvents were concentrated to give the title compound. ES-MS [M+1]⁺: 379; ¹H NMR (400 MHz, CDCl₃) δ 8.76 (s, 1H), 8.00 (d, *J* = 1.3 Hz, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 4.87 (s, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.99 (t, *J* = 5.9 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 2.40 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H).

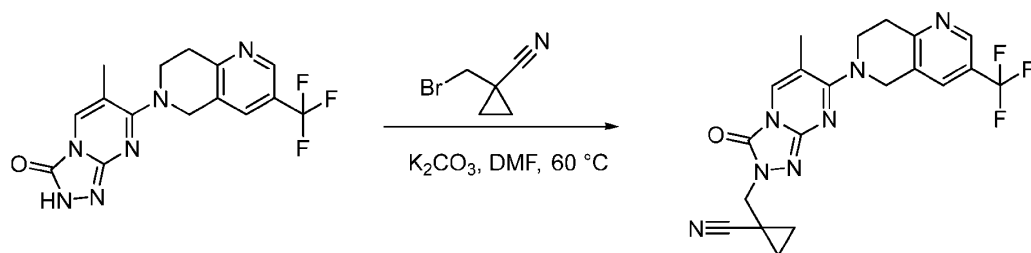


[00548] **5,6-Dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (Compound B26).** Prepared in a similar manner as intermediate **D** to give the title compound. ES-MS [M+1]⁺: 365; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 8.51 (s, 1H), 7.70 (s, 1H), 4.66 (s, 2H), 3.67 (t, *J* = 5.9 Hz, 2H), 3.28 (t, *J* = 6.0 Hz, 2H), 2.81 (d, *J* = 1.0 Hz, 3H), 2.17 (d, *J* = 1.0 Hz, 3H).

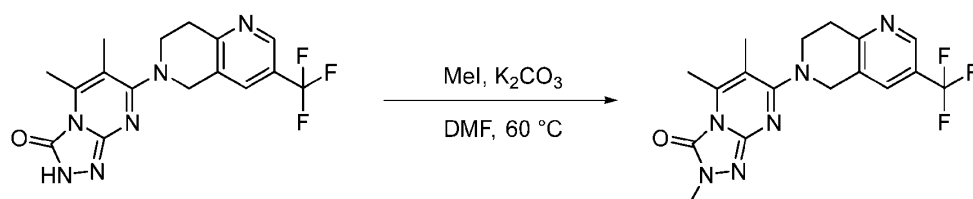


[00549] **5-(3-(Trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6,7,8-tetrahydro-1H-cyclopenta[e][1,2,4]triazolo[4,3-a]pyrimidin-1-one (Compound B27).**

Prepared in a similar manner as intermediate **D** to give the title compound. ES-MS [M+1]⁺: 377; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 8.37 (s, 1H), 7.71 (s, 1H), 4.99 (s, 2H), 4.06 (t, *J* = 5.9 Hz, 2H), 3.38 (t, *J* = 7.8 Hz, 2H), 3.22 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.25 (p, *J* = 7.7 Hz, 2H).

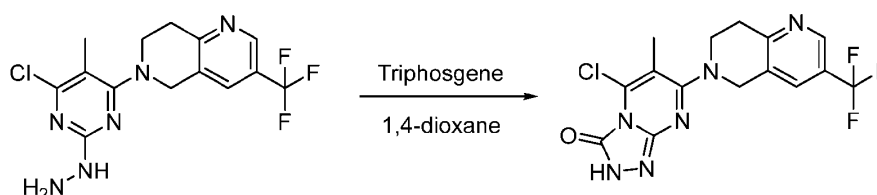


[00550] 1-[[6-Methyl-3-oxo-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3-a]pyrimidin-2-yl]methyl]cyclopropane-1-carbonitrile (Compound B47). To a solution of 6-methyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-2H-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (13 mg, 0.037 mmol) in DMF (0.5 mL) was added potassium carbonate (10.4 mg, 0.074 mmol) followed by 1-(Bromomethyl)cyclopropane-1-carbonitrile (5.6 μ L, 0.056 mmol). The mixture was heated to 60 °C for 2.5 hours. After cooling to ambient temperature, the reaction was further dissolved in DMF (1 mL), filtered, and purified using the RP-HPLC (20-70% ACN/0.1% aqueous TFA). The fractions containing desired product were basified with saturated aqueous NaHCO_3 then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a hydrophobic phase separator and the solvents were concentrated to give the title compound. ES-MS $[\text{M}+1]^+$: 430; ^1H NMR (400 MHz, MeOD) δ 8.70 (d, $J = 1.2$ Hz, 1H), 8.06 (d, $J = 1.0$ Hz, 1H), 7.85 (q, $J = 1.2$ Hz, 1H), 4.86 (s, 2H), 4.00 (s, 2H), 3.97 (t, $J = 5.9$ Hz, 2H), 3.27 (t, $J = 6.0$ Hz, 2H), 2.38 (d, $J = 1.3$ Hz, 3H), 1.34 – 1.32 (m, 2H), 1.31 – 1.28 (m, 2H).

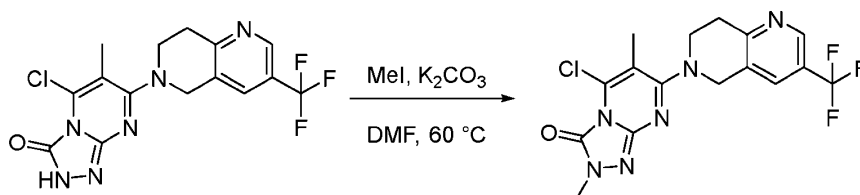


[00551] 2,5,6-Trimethyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (Compound B53). To a solution of 5,6-dimethyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-2H-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (13 mg, 0.036 mmol) in DMF (0.7 mL) was added potassium carbonate (10 mg, 0.071 mmol) followed by iodomethane (3.5 μ L, 0.054 mmol). The mixture was heated to 60 °C for 18

hours. After cooling to ambient temperature, the reaction was further dissolved in DMF (1 mL), filtered, and purified using the RP-HPLC (15-65% ACN/0.1% aqueous TFA). The fractions containing desired product were basified with saturated aqueous NaHCO₃ then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a hydrophobic phase separator and the solvents were concentrated to give the title compound. ES-MS [M+1]⁺: 379; ¹H NMR (400 MHz, CDCl₃) δ 8.71 (s, 1H), 7.68 (s, 1H), 4.64 (s, 2H), 3.66 (t, *J* = 5.9 Hz, 2H), 3.55 (s, 3H), 3.26 (t, *J* = 5.9 Hz, 2H), 2.82 (d, *J* = 0.9 Hz, 3H), 2.16 (d, *J* = 1.0 Hz, 3H).

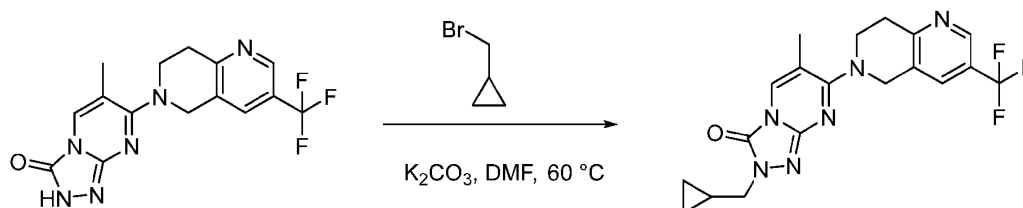


[00552] 5-Chloro-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (Compound B55). To a solution of 6-(6-chloro-2-hydrazineyl-5-methylpyrimidin-4-yl)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (10 mg, 0.03 mmol) in 1,4-dioxane (0.2 mL) was added triphosgene (8.3 mg, 0.03 mmol) at 25 °C. After 2 h, the reaction mixture was concentrated and the crude residue was purified using reverse-phase chromatography (20-50% MeCN/0.1% aqueous TFA). The fractions containing desired product were basified with sat. NaHCO₃ then extracted with 3:1 chloroform/IPA (3x). The combined organics were passed through a hydrophobic phase separator and the solvents were concentrated to afford the title compound (4 mg). ES-MS [M+1]⁺: 385.1/387.1.

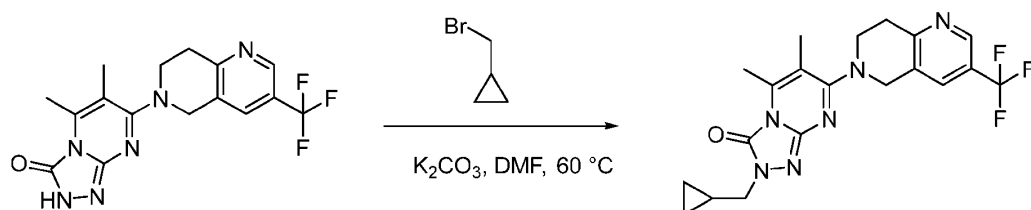


[00553] 5-Chloro-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (Compound B56). To a solution of 5-chloro-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-

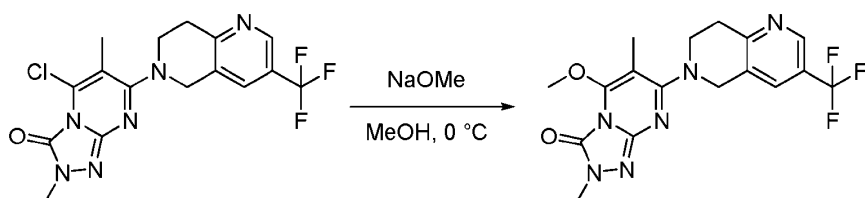
[1,2,4]triazolo[4,3-*a*]pyrimidin-3(2*H*)-one (15 mg, 0.04 mmol) and potassium carbonate (11 mg, 0.08 mmol) in DMF (0.5 mL) at room temperature was added iodomethane (4 μ L, 0.06 mmol), and the mixture was stirred at 60 °C for 18h. The mixture was further dissolved in DMF (1 mL), filtered, and purified using reverse phase chromatography (30-60% MeCN/0.1% aqueous TFA). The fractions containing desired product were basified with sat. NaHCO₃ then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a hydrophobic phase separator and concentrated to afford the title compound (9 mg). ¹H NMR (400 MHz, DMSO) δ 8.78 (s, 1H), 8.17 (dd, *J* = 2.4, 1.0 Hz, 1H), 4.68 (s, 2H), 3.75 (t, *J* = 5.9 Hz, 2H), 3.38 (s, 3H), 3.17 (t, *J* = 5.8 Hz, 2H), 2.23 (s, 3H). ES-MS [M+1]⁺: 399.3/401.2.



[00554] 2-(Cyclopropylmethyl)-6-methyl-7-[3-(trifluoromethyl)-7,8-dihydro-5*H*-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3-*a*]pyrimidin-3-one (Compound B74). To a solution of 6-methyl-7-[3-(trifluoromethyl)-7,8-dihydro-5*H*-1,6-naphthyridin-6-yl]-2*H*-[1,2,4]triazolo[4,3-*a*]pyrimidin-3-one (13 mg, 0.037 mmol) in DMF (0.5 mL) was added potassium carbonate (10.4 mg, 0.074 mmol) followed by (bromomethyl)cyclopropane (5.4 μ L, 0.056 mmol). The mixture was heated to 60 °C for 18 hours. After cooling to ambient temperature, the reaction was further dissolved in DMF (1 mL), filtered, and purified using the RP-HPLC (20-75% ACN/0.1% aqueous TFA). The fractions containing desired product were basified with saturated aqueous NaHCO₃ then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a hydrophobic phase separator and were concentrated to give the title compound. ES-MS [M+1]⁺: 405; ¹H NMR (400 MHz, CDCl₃) δ 8.73 (d, *J* = 2.2 Hz, 1H), 7.71 (q, *J* = 1.2 Hz, 1H), 7.69 (s, 1H), 4.77 (s, 2H), 3.82 (t, *J* = 5.9 Hz, 2H), 3.78 (d, *J* = 7.1 Hz, 2H), 3.27 (t, *J* = 5.9 Hz, 2H), 2.31 (d, *J* = 1.3 Hz, 3H), 1.37 – 1.26 (m, 1H), 0.61 – 0.50 (m, 2H), 0.42 (dt, *J* = 6.2, 4.6 Hz, 2H).

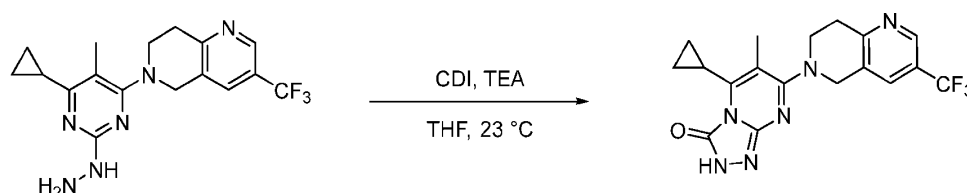


[00555] **2-(Cyclopropylmethyl)-5,6-dimethyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (Compound B80).** To a solution of 5,6-dimethyl-7-[3-(trifluoromethyl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-2H-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (13 mg, 0.036 mmol) in DMF (0.5 mL) was added potassium carbonate (10 mg, 0.071 mmol) followed by (bromomethyl)cyclopropane (5.2 μ L, 0.054 mmol). The mixture was heated to 60 °C for 5 hours. After cooling to ambient temperature, the reaction was further dissolved in DMF (1.0 mL), filtered, and purified using the RP-HPLC (20-80% ACN/0.1% aqueous TFA). The fractions containing desired product were basified with saturated aqueous NaHCO_3 then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a hydrophobic phase separator and the solvents were concentrated to give the title compound. ES-MS $[\text{M}+1]^+$: 419; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.67 (s, 1H), 4.65 (s, 2H), 3.74 (d, $J = 7.1$ Hz, 2H), 3.65 (t, $J = 5.9$ Hz, 2H), 3.27 (t, $J = 5.9$ Hz, 2H), 2.82 (d, $J = 0.9$ Hz, 3H), 2.16 (d, $J = 1.0$ Hz, 3H), 1.37 – 1.23 (m, 1H), 0.61 – 0.50 (m, 2H), 0.46 – 0.38 (m, 2H).

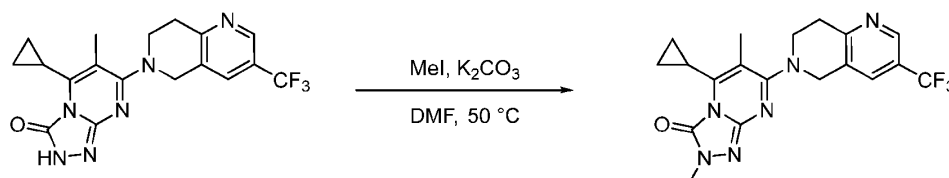


[00556] **5-Methoxy-2,6-dimethyl-7-[3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (Compound B85).** At 0 °C, to a solution of sodium methoxide (60 μ L, 0.03 mmol) in methanol (0.20 mL) was added 5-chloro-2,6-dimethyl-7-[3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (6 mg, 0.02 mmol). The ice bath was removed and after 30 min at room temperature, the reaction mixture was concentrated. The residue was purified using reverse-

phase chromatography (5-40% MeCN/ 0.05% aqueous NH_4OH). The fractions containing the desired product were concentrated to give impure product. The impure product was re-purified using reverse phase chromatography (10-40% MeCN/ 0.1% aqueous TFA). The fractions containing desired product were basified with sat. NaHCO_3 then extracted with chloroform/IPA (3:1) (3x). The combined organics were passed through a hydrophobic phase separator and the solvents were concentrated to afford the title compound (5 mg). ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 7.69 (s, 1H), 4.70 (s, 2H), 4.14 (s, 3H), 3.75 (t, $J = 5.9$ Hz, 2H), 3.54 (s, 3H), 3.26 (t, $J = 5.9$ Hz, 2H), 2.17 (s, 3H). ES-MS $[\text{M}+1]^+$: 395.3.

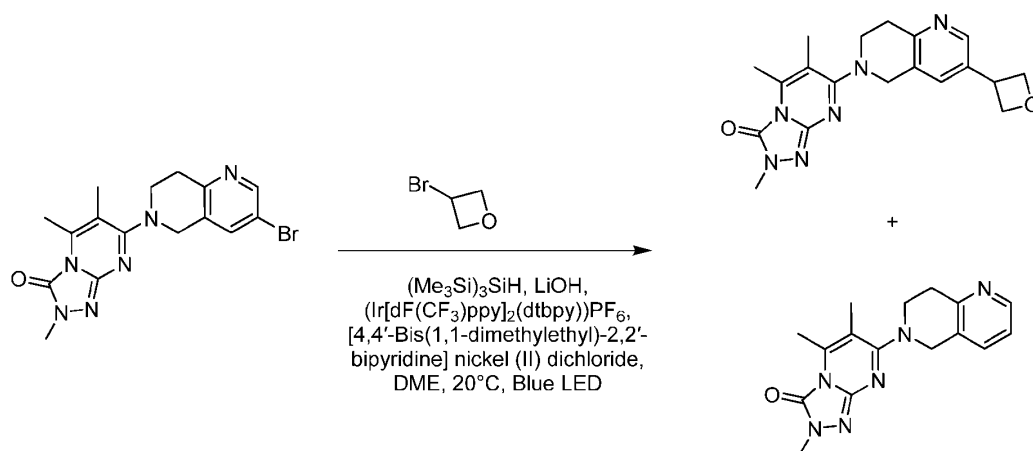


[00557] **5-Cyclopropyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (Compound B93).** Prepared in a similar manner as intermediate **D** to give the title compound. ES-MS $[\text{M}+1]^+$: 391; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H), 8.38 (s, 1H), 7.69 (s, 1H), 4.67 (s, 2H), 3.68 (t, $J = 5.9$ Hz, 2H), 3.26 (t, $J = 5.9$ Hz, 2H), 2.29 (d, $J = 1.3$ Hz, 3H), 2.27 – 2.15 (m, 1H), 1.39 – 1.28 (m, 2H), 0.89 (q, $J = 5.8$ Hz, 2H).



[00558] **5-Cyclopropyl-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3-a]pyrimidin-3(2H)-one (Compound B94).**

Prepared in a similar manner as intermediate **E** to give the title compound. ES-MS $[\text{M}+1]^+$: 405; ^1H NMR (400 MHz, CDCl_3) δ 8.71 (dd, $J = 2.1, 0.8$ Hz, 1H), 7.68 (dd, $J = 2.4, 1.0$ Hz, 1H), 4.65 (s, 2H), 3.67 (t, $J = 5.9$ Hz, 2H), 3.55 (s, 3H), 3.25 (t, $J = 5.9$ Hz, 2H), 2.28 (d, $J = 1.3$ Hz, 3H), 2.24 – 2.15 (m, 1H), 1.40 – 1.28 (m, 2H), 0.95 – 0.83 (m, 2H).



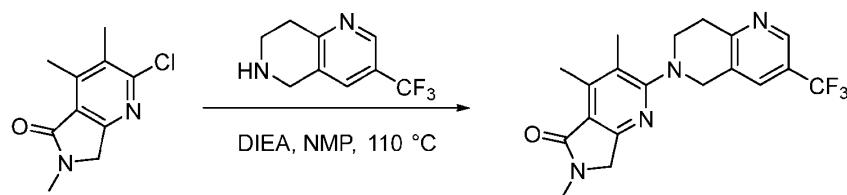
[00559] 2,5,6-Trimethyl-7-[3-(oxetan-3-yl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (Compound B140) and 7-(7,8-dihydro-5H-1,6-naphthyridin-6-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (Compound B141).

To a solution of 7-(3-bromo-7,8-dihydro-5H-1,6-naphthyridin-6-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3-a]pyrimidin-3-one (30 mg, 0.077 mmol) in DME (1.0 mL) was added 3-bromooxetane (19.2 μL , 0.231 mmol), tris(trimethylsilyl)silane (35.7 μL , 0.116 mmol), lithium Hydroxide (5.5 mg, 0.231 mmol), and $(\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy}))\text{PF}_6$ (4.3 mg, 0.0039 mmol). Nitrogen was bubbled through the reaction mixture 10 minutes before the addition of $[4,4'\text{-bis}(1,1\text{-dimethylethyl})\text{-}2,2'\text{-bipyridine}]$ nickel (II) dichloride (1.5 mg, 0.0039 mmol). Nitrogen was bubbled through the reaction mixture for an additional 5 minutes, sonicated under an inert atmosphere, sealed with parafilm, and stirred under blue LED at room temperature. After 18 hours, Compound B140 and Compound B141 were observed in a 1:1 ratio via LCMS. The reaction mixture was concentrated and purified using the RP-HPLC (0-50% ACN/0.1% aqueous TFA). The fractions containing each desired products were basified with saturated aqueous NaHCO_3 then extracted with chloroform/IPA (3:1) (3x). The combined organic layers were passed through a hydrophobic phase separator and the solvents were concentrated to give the title compounds, respectively. [Reference: Zhang et al. *J. Am. Chem. Soc.* **2016**, *138*, 8084-8087].

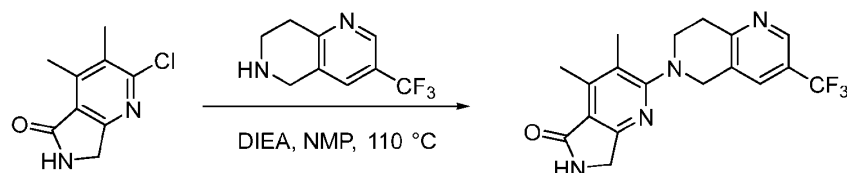
[00560] **Compound B140:** ES-MS $[\text{M}+1]^+$: 367; ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 5.11 (dd, J = 8.3, 6.1 Hz, 2H), 4.73 (t, J = 6.3 Hz, 2H),

4.61 (s, 2H), 4.22 (tt, $J = 8.3, 6.5$ Hz, 1H), 3.65 (t, $J = 5.9$ Hz, 2H), 3.54 (s, 3H), 3.19 (t, $J = 5.9$ Hz, 2H), 2.81 (d, $J = 1.0$ Hz, 3H), 2.16 (d, $J = 1.0$ Hz, 3H);

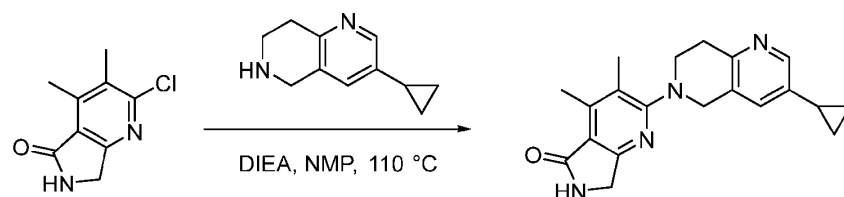
[00561] **Compound B141**: ES-MS $[M+1]^+$: 311; ^1H NMR (400 MHz, CDCl_3) δ 8.46 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.46 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.15 (dd, $J = 7.8, 4.8$ Hz, 1H), 4.59 (s, 2H), 3.63 (t, $J = 5.9$ Hz, 2H), 3.54 (s, 3H), 3.21 (t, $J = 5.9$ Hz, 2H), 2.80 (d, $J = 0.9$ Hz, 3H), 2.16 (d, $J = 1.0$ Hz, 3H).



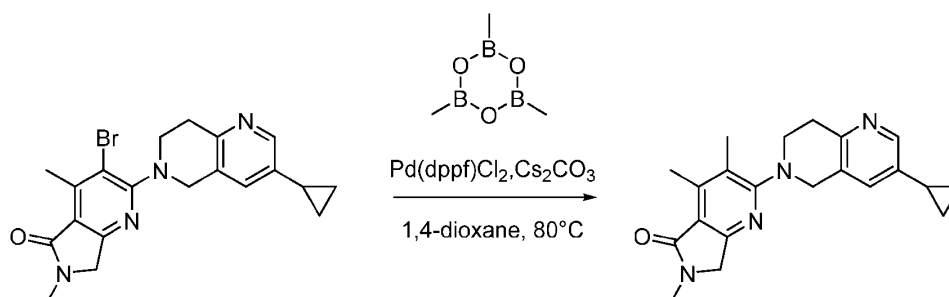
[00562] **3,4,6-Trimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one**. Prepared in a similar manner as Intermediate A. ^1H NMR (400 MHz, CDCl_3) δ 8.71 (dd, $J = 2.2, 0.9$ Hz, 1H), 7.70 (dd, $J = 2.1, 1.0$ Hz, 1H), 4.52 (s, 2H), 4.23 (s, 2H), 3.52 (t, $J = 5.9$ Hz, 2H), 3.27 (t, $J = 5.9$ Hz, 2H), 3.17 (s, 3H), 2.67 (s, 3H), 2.29 (s, 3H). ES-MS $[M+1]^+$: 377.



[00563] **3,4-Dimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one**. Prepared in a similar manner as Intermediate A. ^1H NMR (400 MHz, CDCl_3) δ 8.72 (dd, $J = 2.3, 1.1$ Hz, 1H), 7.70 (dd, $J = 2.1, 1.0$ Hz, 1H), 5.98 (s, 1H), 4.54 (s, 2H), 4.31 (s, 2H), 3.54 (t, $J = 5.9$ Hz, 2H), 3.28 (t, $J = 5.9$ Hz, 2H), 2.67 (s, 3H), 2.30 (s, 3H). ES-MS $[M+1]^+$: 362.



[00564] 2-(3-Cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,4-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one. Prepared in a similar manner as Intermediate A. ^1H NMR (400 MHz, CDCl_3) δ 8.27 (d, $J = 2.2$ Hz, 1H), 7.08 (d, $J = 2.2$ Hz, 1H), 5.86 (s, 1H), 4.43 (s, 2H), 4.31 (s, 2H), 3.50 (t, $J = 5.9$ Hz, 2H), 3.18 (t, $J = 5.9$ Hz, 2H), 2.66 (s, 3H), 2.29 (s, 3H), 1.89 (tt, $J = 8.5, 5.1$ Hz, 1H), 1.05 – 0.93 (m, 2H), 0.83 – 0.65 (m, 2H). ES-MS $[\text{M}+1]^+$: 335.



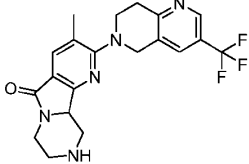
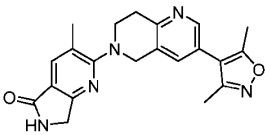
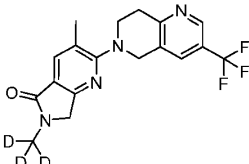
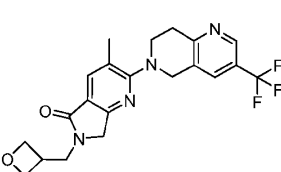
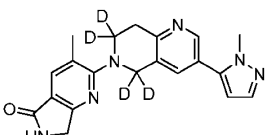
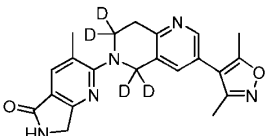
[00565] 2-(3-Cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,4,6-trimethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one. A solution of 3-bromo-2-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-4,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (33 mg, 0.06 mmol), cesium carbonate (59 mg, 0.18 mmol), trimethylboroxine (50 wt% in THF) (50 μL , 0.18 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (8.8 mg, 0.01 mmol) in 1,4-dioxane (0.5457 mL) was stirred at 80 °C for 18 hours. After cooling, the reaction was filtered through a pad of Celite[®] rinsing thoroughly with chloroform/IPA/MeOH. Solvents were removed and the crude sample was purified by RP-HPLC to afford title compound. ^1H NMR (400 MHz, CDCl_3) δ 8.27 (d, $J = 2.2$ Hz, 1H), 7.08 (d, $J = 2.2$ Hz, 1H), 4.41 (s, 2H), 4.23 (s, 2H), 3.47 (t, $J = 5.9$ Hz, 2H), 3.19 – 3.14 (m, 5H), 2.66 (s, 3H), 2.27 (s, 3H), 1.89 (tt, $J = 8.5, 5.1$ Hz, 1H), 1.05 – 0.96 (m, 2H), 0.76 – 0.63 (m, 2H). ES-MS $[\text{M}+1]^+$: 349.

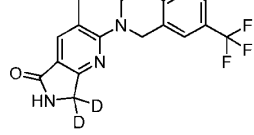
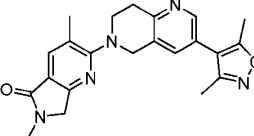
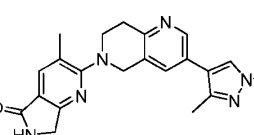
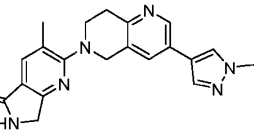
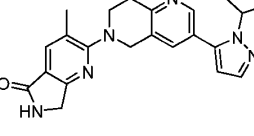
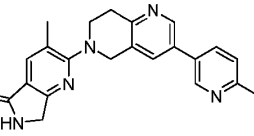
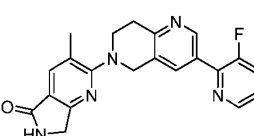
[00566] The compounds shown in Table 1 may be prepared using the methods shown in the

preceding Schemes and Examples with the appropriate starting materials.

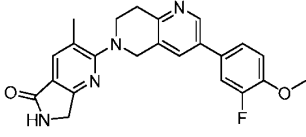
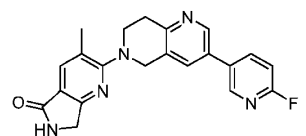
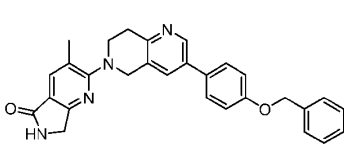
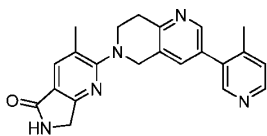
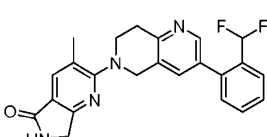
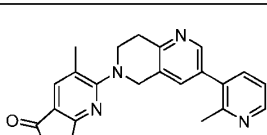
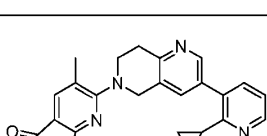
Table 1

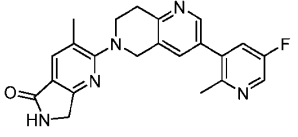
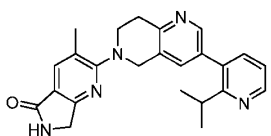
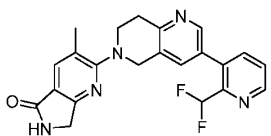
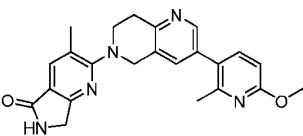
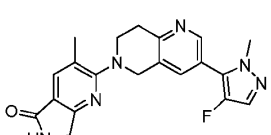
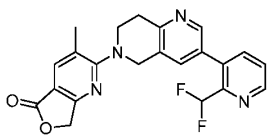
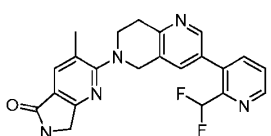
Cpd. No.	Name	Structure	ES-MS [M+1] ⁺
1	3,6-dimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		363.3
2	3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		349.2
3	methyl 2-(3-methyl-5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,7-dihydro-6H-pyrrolo[3,4- <i>b</i>]pyridin-6-yl)propanoate		435.3
4	3-methyl-2-(3-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		361.3
5	2-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		390.3

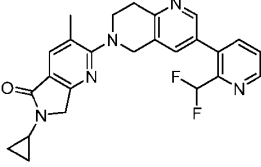
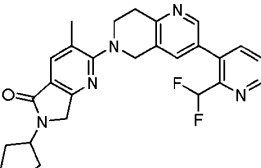
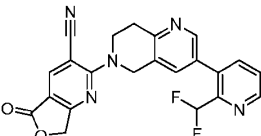
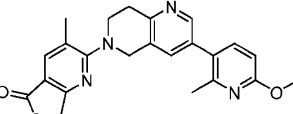
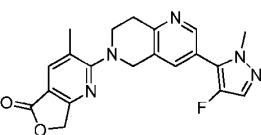
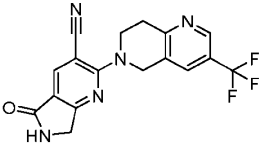
6	3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-8,9,10,10 <i>a</i> -tetrahydropyrido[2',3':3,4]pyrrolo[1,2- <i>a</i>]pyrazin-5(7 <i>H</i>)-one		404.3
7	2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		376.2
8	3-methyl-6-(methyl- <i>d</i> ₃)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		366.3
9	3-methyl-6-(oxetan-3-ylmethyl)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		419.3
10	3-methyl-2-(3-(1-methyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,5,7,7- <i>d</i> ₄ -6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		365
11	2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,5,7,7- <i>d</i> ₄ -3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		380

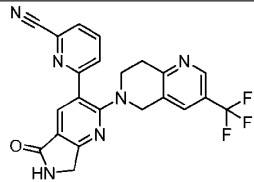
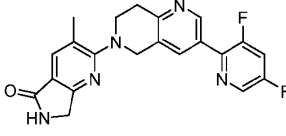
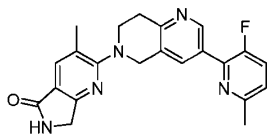
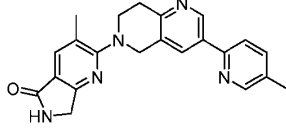
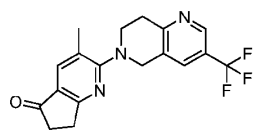
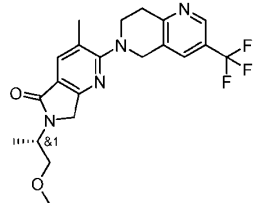
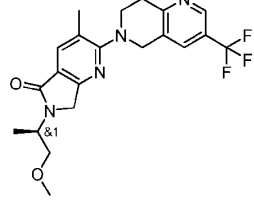
12	3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one-7,7- <i>d</i> ₂		351.3
13	2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3,6-dimethyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		390.3
14	2-(3-(1,3-dimethyl-1 <i>H</i> -pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		375.3
15	2-(3-(1-cyclobutyl-1 <i>H</i> -pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		401.4
16	2-(3-(1-isopropyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		389.3
17	3-methyl-2-(3-(6-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		426.3
18	2-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		376.3

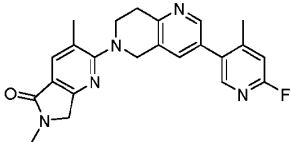
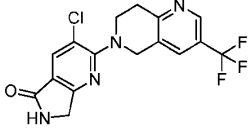
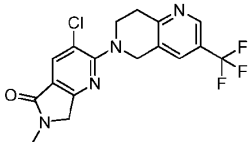
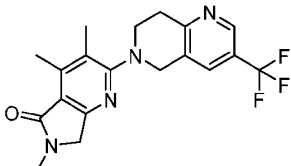
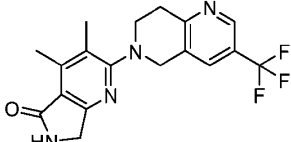
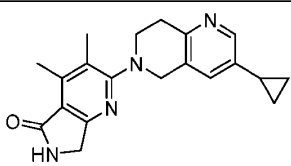
19	2-(3-(1,4-dimethyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		375.3
20	2-(3-(6-methoxypyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		388.3
21	3-methyl-2-(3-(4-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		426.3
22	2-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		408.3
23	2-(3-(imidazo[1,2- <i>a</i>]pyridin-6-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		397.4
24	2-(3-(1,3-dimethyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		375.4
25	2-(3-(4-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		387.4

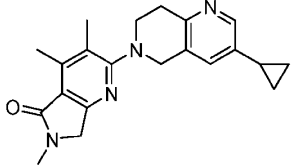
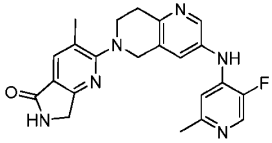
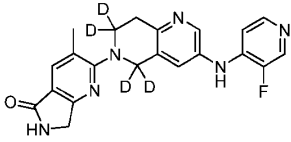
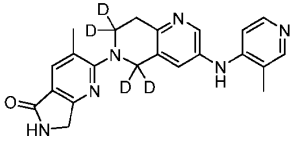
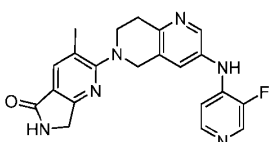
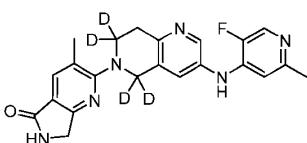
26	2-(3-(3-fluoro-4-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		405.4
27	2-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		376.3
28	2-(3-(4-(benzyloxy)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		463.4
29	3-methyl-2-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		372.4
30	2-(3-(2-(difluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		407.3
31	3-methyl-2-(3-(2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		372.4
32	2-(3-(2-cyclopropylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		398.4

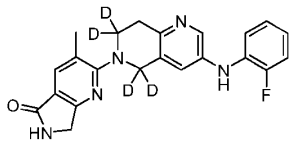
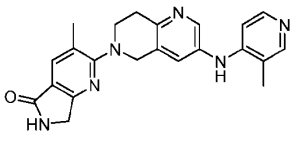
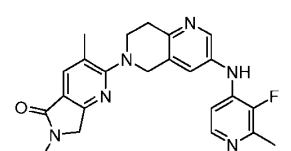
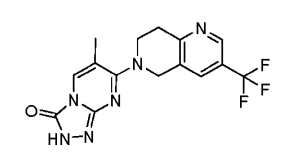
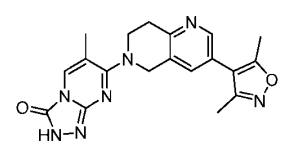
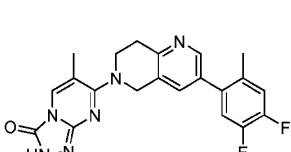
33	2-(3-(5-fluoro-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		390.4
34	2-(3-(2-isopropylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		400.5
35	2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		408.3
36	2-(3-(6-methoxy-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		401.5
37	2-(3-(4-fluoro-1-methyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		379.1
38	2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7 <i>H</i>)-one		409.3
39	2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3,6-dimethyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		422.3

40	6-cyclopropyl-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		448.3
41	6-cyclopentyl-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		476.4
42	2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5-oxo-5,7-dihydrofuro[3,4- <i>b</i>]pyridine-3-carbonitrile		420.3
43	2-(3-(6-methoxy-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7 <i>H</i>)-one		403.3
44	2-(3-(4-fluoro-1-methyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7 <i>H</i>)-one		380.2
45	5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridine-3-carbonitrile		360.1

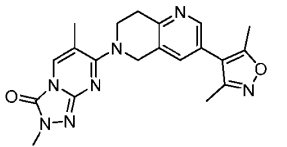
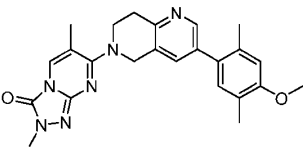
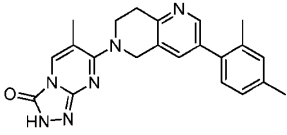
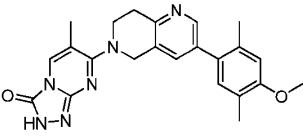
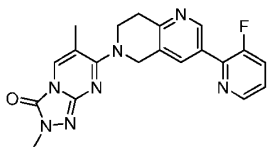
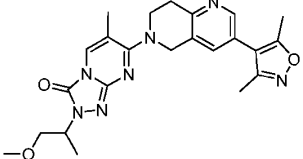
46	6-(5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-3-yl)picolinonitrile		437.3
47	2-(3-(3,5-difluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		394.3
48	2-(3-(3-fluoro-6-methylpyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		390.3
49	3-methyl-2-(3-(5-methylpyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		372.3
50	3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -cyclopenta[<i>b</i>]pyridin-5-one		348.2
51	(<i>S</i>)-6-(1-methoxypropan-2-yl)-3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		421.4
52	(<i>R</i>)-6-(1-methoxypropan-2-yl)-3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		421.4

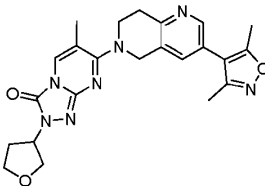
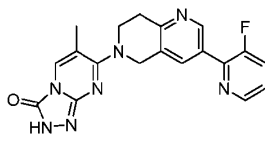
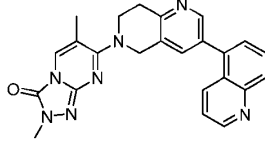
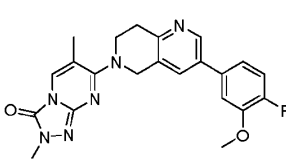
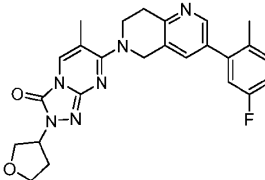
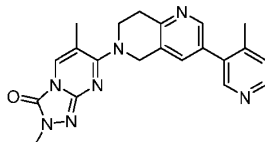
53	2-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		404.3
54	3-chloro-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		369.1
55	3-chloro-6-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		383.2
56	3,4,6-trimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		377.2
57	3,4-dimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		363.2
58	2-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,4-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one		335.2

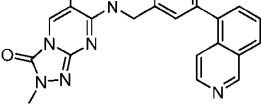
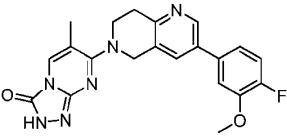
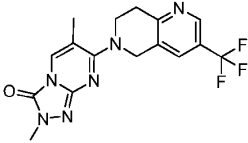
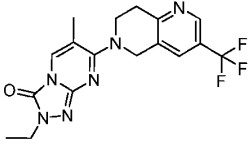
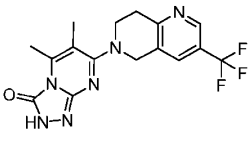
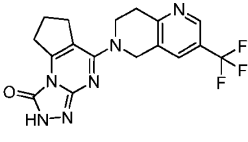
59	2-(3-(cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3,4,6-trimethyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		349.2
A1	2-(3-((5-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		405
A2	2-(3-((3-fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl-5,5,7,7- <i>d</i> ₄)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		394
A3	3-methyl-2-(3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl-5,5,7,7- <i>d</i> ₄)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		391
A4	2-(3-((3-fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		391.3
A5	2-(3-((5-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl-5,5,7,7- <i>d</i> ₄)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		409.3

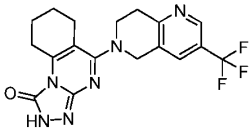
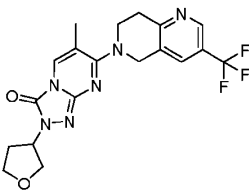
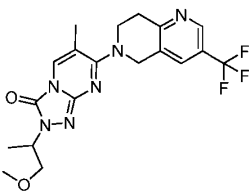
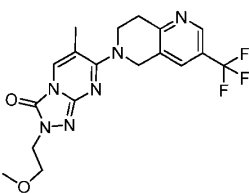
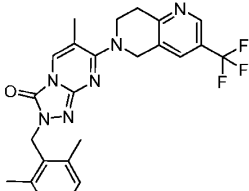
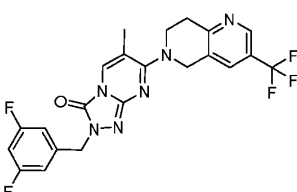
A6	2-(3-((2-fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl-5,5,7,7- <i>d</i> 4)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		394
A7	3-methyl-2-(3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		387
A8	2-(3-((3-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3,6-dimethyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one		419.3
B1	6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		351.2
B2	7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		378.3
B3	7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		409.3

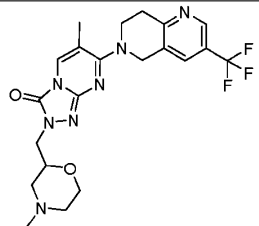
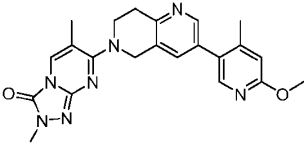
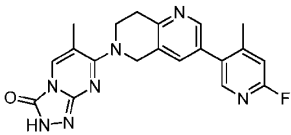
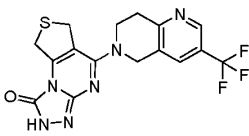
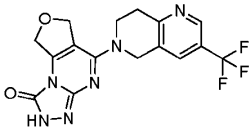
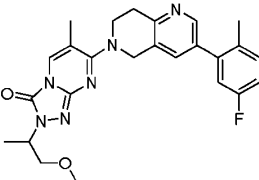
B4	7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		423.4
B5	7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		405.3
B6	7-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		406.3
B7	7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		453.4
B8	7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		391.3
B9	7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		439.4

B10	7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		392.3
B11	7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		431.4
B12	7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		387.2
B13	7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		417.3
B14	7-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		392.3
B15	7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		450.3

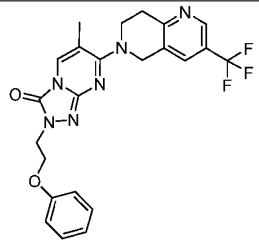
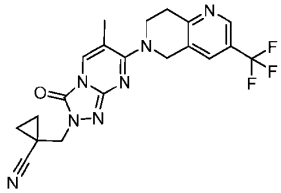
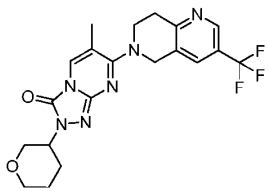
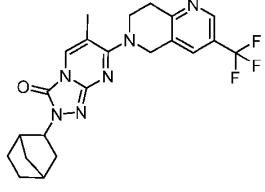
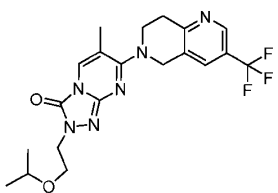
B16	7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-2-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		448.3
B17	7-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		378
B18	2,6-dimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		424.4
B19	7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		421.4
B20	7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-2-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		461.3
B21	2,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		388.4

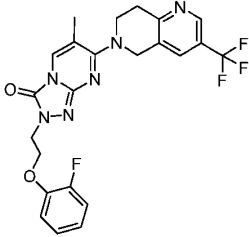
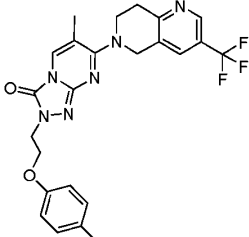
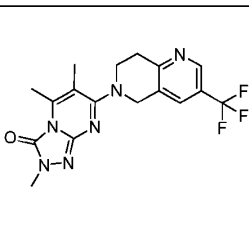
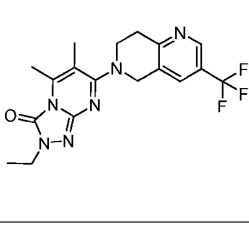
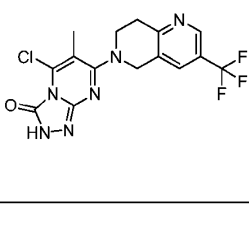
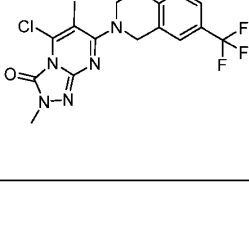
B22	7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		424.2
B23	7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		407.3
B24	2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		365.2
B25	2-ethyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		379.3
B26	5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		365.2
B27	5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6,7,8-tetrahydro-1 <i>H</i> -cyclopenta[<i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1-one		377.2

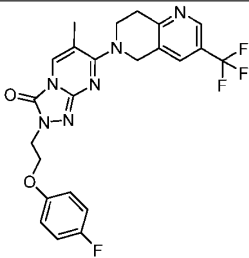
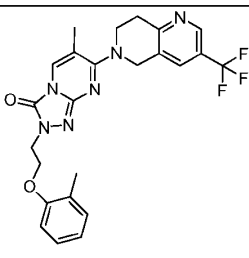
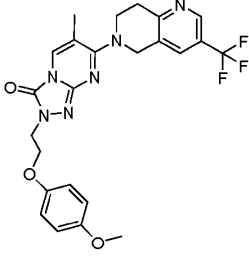
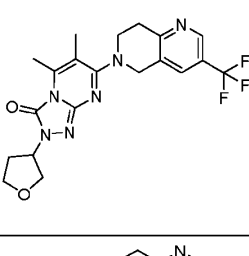
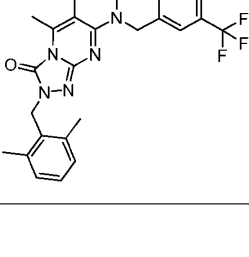
B28	5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7,8,9-tetrahydro-[1,2,4]triazolo[4,3- <i>a</i>]quinazolin-1(2 <i>H</i>)-one		391.2
B29	6-methyl-2-(tetrahydrofuran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		421.3
B30	2-(1-methoxypropan-2-yl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		423.2
B31	2-(2-methoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		409.3
B32	2-(2,6-dimethylbenzyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		469.2
B33	2-(3,5-difluorobenzyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		477.1

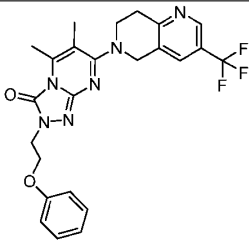
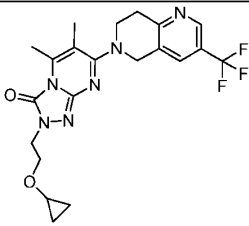
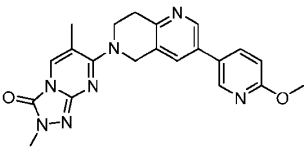
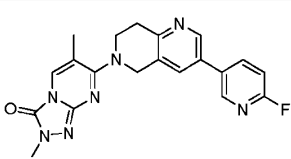
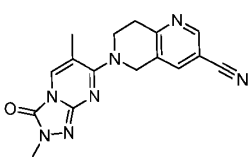
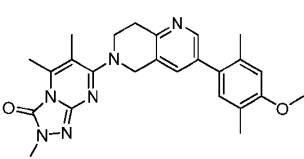
B34	6-methyl-2-((4-methylmorpholin-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		464.2
B35	7-(3-(6-methoxy-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		418.3
B36	7-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		392.3
B37	5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,8-dihydrothieno[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2 <i>H</i>)-one		395.2
B38	5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,8-dihydrofuro[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2 <i>H</i>)-one		379.2
B39	7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		463.2

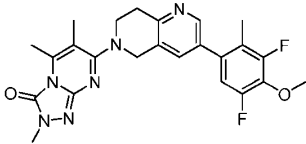
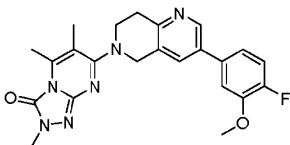
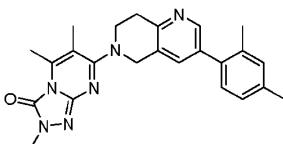
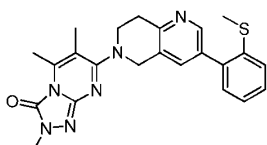
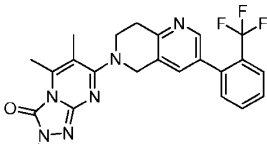
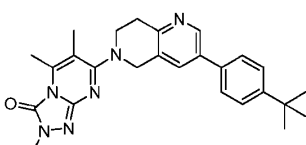
B40	7-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		450.2
B41	2-methyl-5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,8-dihydrofuro[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2 <i>H</i>)-one		393.2
B42	2-(2-cyclopropoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		435.3
B43	7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		479.2
B44	7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		459.4
B45	2-((5,5-dimethyltetrahydrofuran-2-yl)methyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		463.2

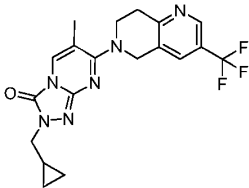
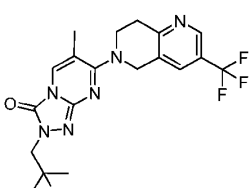
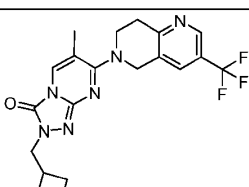
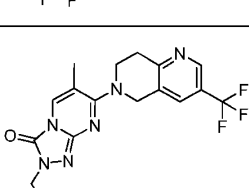
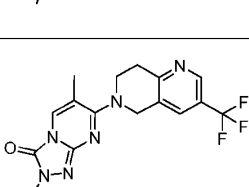
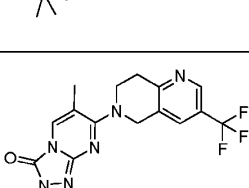
B46	6-methyl-2-(2-phenoxyethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		471.2
B47	1-((6-methyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		430.2
B48	6-methyl-2-(tetrahydro-2 <i>H</i> -pyran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		435.3
B49	2-(bicyclo[2.2.1]heptan-2-yl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		445.3
B50	2-(2-isopropoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		437.2

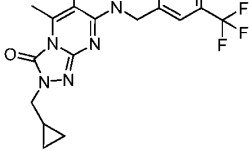
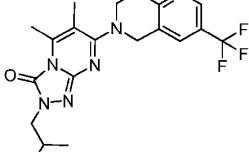
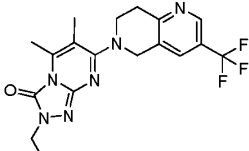
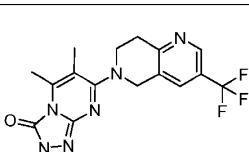
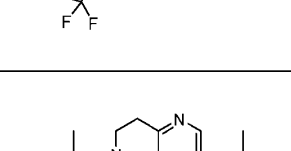
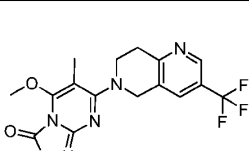
B51	2-(2-(2-fluorophenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		489.3
B52	6-methyl-2-(2-(p-tolyloxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		485.3
B53	2,5,6-trimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		379.3
B54	2-ethyl-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		393.3
B55	5-chloro-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		385.1
B56	5-chloro-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		399.3

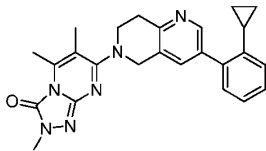
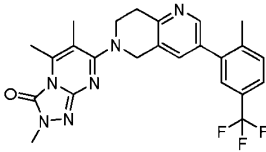
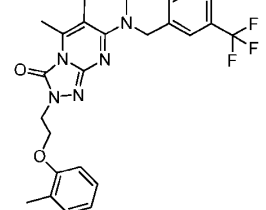
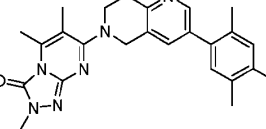
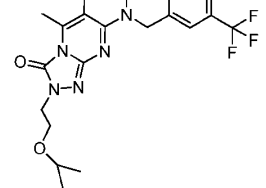
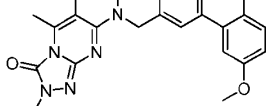
B57	2-(2-(4-fluorophenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		489.2
B58	6-methyl-2-(2-(o-tolylloxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		485.2
B59	2-(2-(4-methoxyphenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		501.3
B60	5,6-dimethyl-2-(tetrahydrofuran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		435.3
B61	2-(2,6-dimethylbenzyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		483.3

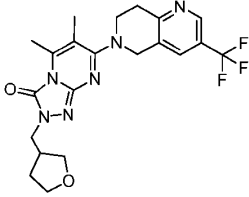
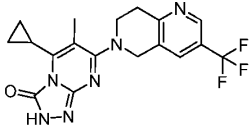
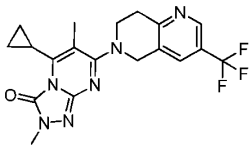
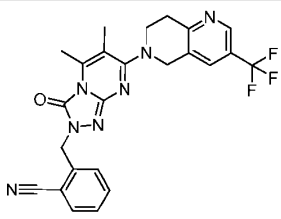
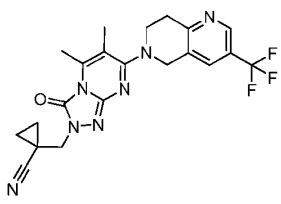
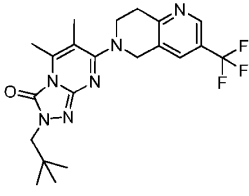
B62	5,6-dimethyl-2-(2-phenoxyethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		485.3
B63	2-(2-(2-cyclopropoxyethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		449.3
B64	7-(3-(6-methoxypyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		404.3
B65	7-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		392.3
B66	6-(2,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile		322.2
B67	7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		445.4

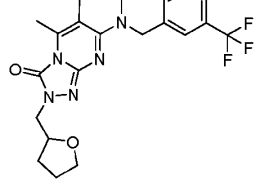
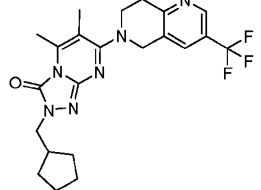
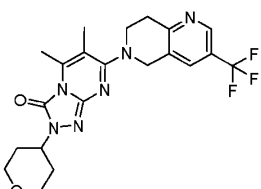
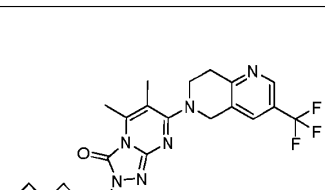
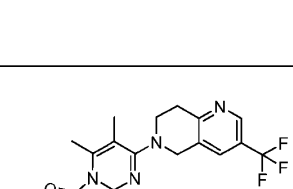
B68	7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		467.4
B69	7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		435.4
B70	7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		415.4
B71	2,5,6-trimethyl-7-(3-(2-(methylthio)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		433.4
B72	2,5,6-trimethyl-7-(3-(2-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		455.3
B73	7-(3-(4-(tert-butyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		443.4

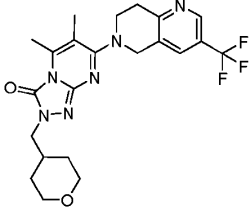
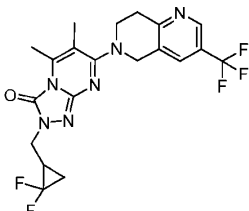
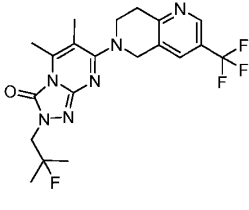
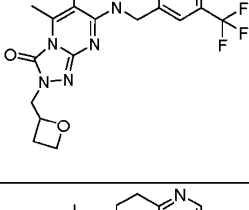
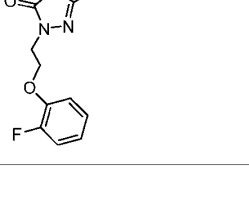
B74	2-(cyclopropylmethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		405.3
B75	2-(2-fluoro-2-methylpropyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		425.3
B76	2-((3,3-difluorocyclobutyl)methyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		455.3
B77	2-isobutyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		407.3
B78	6-methyl-2-neopentyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		421.4
B79	2-(cyclobutylmethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		419.3

B80	2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		419.3
B81	2-isobutyl-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		421.4
B82	2-(cyclobutylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		433.3
B83	2-((3,3-difluorocyclobutyl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		469.3
B84	7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		437.4
B85	5-methoxy-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		395.3

B86	7-(3-(2-cyclopropylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		427.4
B87	2,5,6-trimethyl-7-(3-(2-methyl-5-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		469.3
B88	5,6-dimethyl-2-(2-(o-tolyloxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		499.2
B89	7-(3-(4-fluoro-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		433.4
B90	2-(2-isopropoxyethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		451.3
B91	7-(3-(5-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		431.4

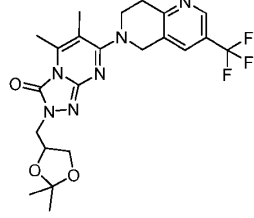
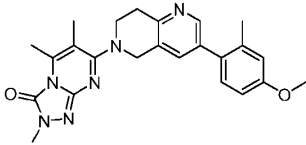
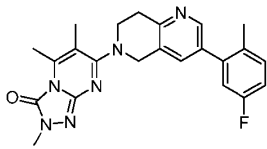
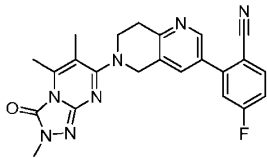
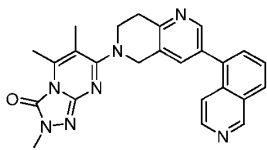
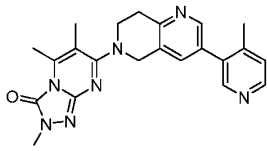
B92	5,6-dimethyl-2-((tetrahydrofuran-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		449.3
B93	5-cyclopropyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		391.3
B94	5-cyclopropyl-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		405.3
B95	2-((5,6-dimethyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)benzonitrile		480.4
B96	1-((5,6-dimethyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		444.3
B97	5,6-dimethyl-2-neopentyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		435.4

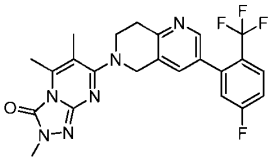
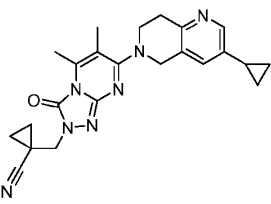
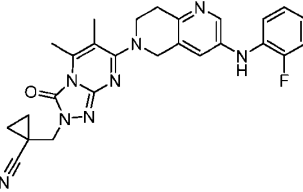
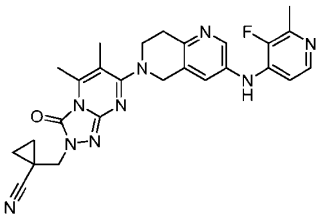
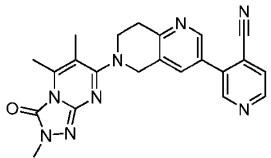
B98	5,6-dimethyl-2-((tetrahydrofuran-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		449.4
B99	2-(cyclopentylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		447.3
B100	5,6-dimethyl-2-(tetrahydro-2 <i>H</i> -pyran-4-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		449.3
B101	2-((2-oxaspiro[3.3]heptan-6-yl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		475.3
B102	5,6-dimethyl-2-((3-methyloxetan-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		449.3

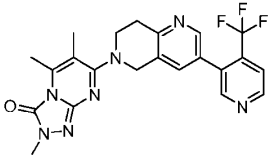
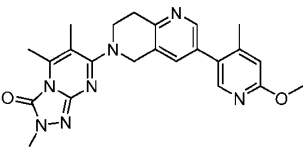
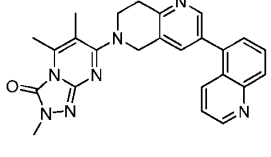
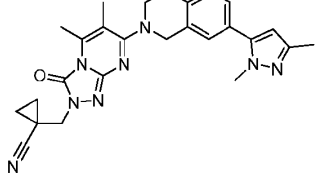
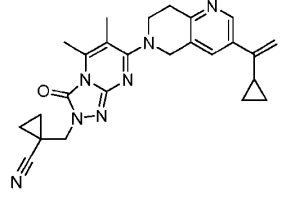
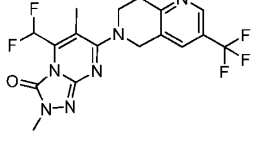
B103	5,6-dimethyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one		463.2
B104	2-((2,2-difluorocyclopropyl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one		455.2
B105	2-(2-fluoro-2-methylpropyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one		439.4
B106	5,6-dimethyl-2-(oxetan-2-ylmethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one		435.4
B107	2-(2-(2-fluorophenoxy)ethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one		503.1

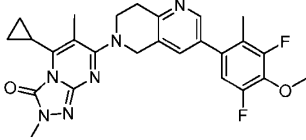
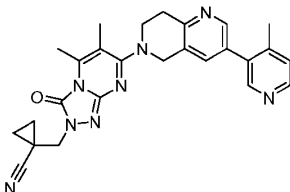
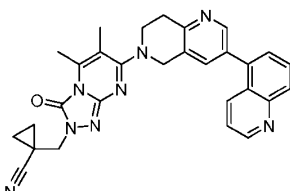
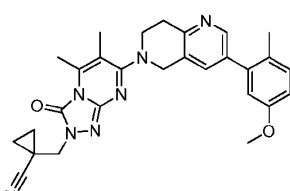
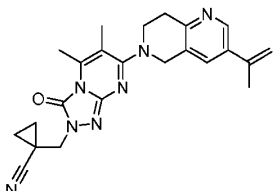
B108	7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		351.3
B109	3-fluoro-2-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)benzamide		448.4
B110	6-(2-((1-cyanocyclopropyl)methyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile		401.3
B111	7-(3-(2,6-difluorophenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		423.3
B112	1-((7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		532.2

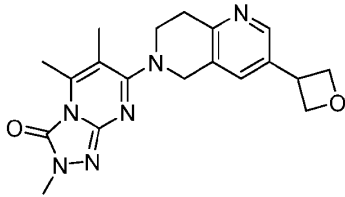
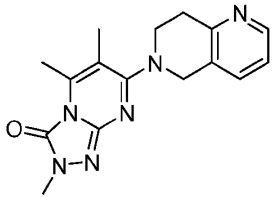
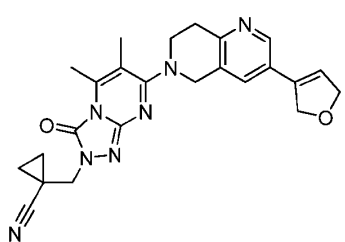
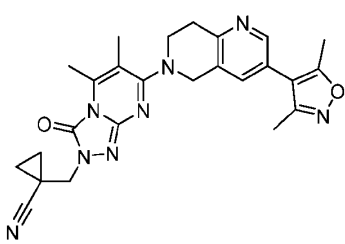
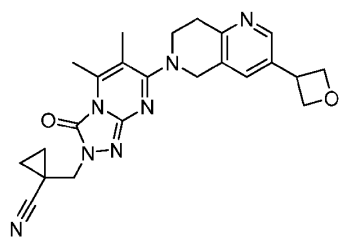
B113	7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((tetrahydrofuran-3-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		537.3
B114	7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((3-methyloxetan-3-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		537.3
B115	7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-4-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		551.4
B116	5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		463.2
B117	5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		463.2

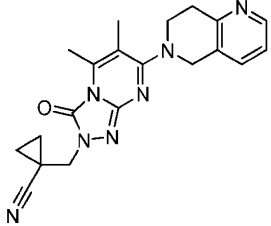
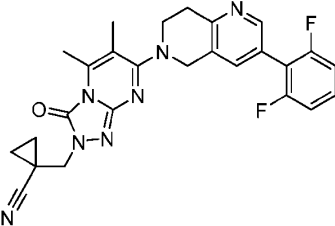
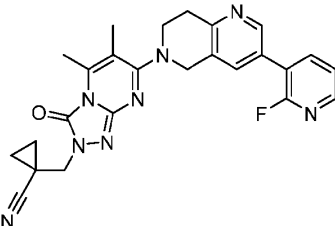
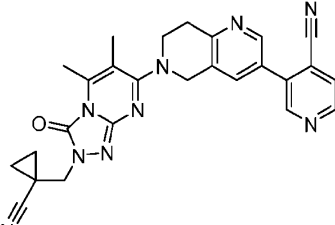
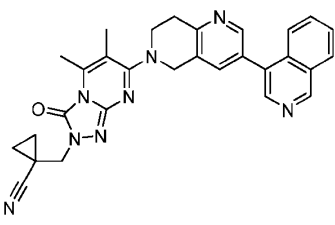
B118	2-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		479.2
B119	7-(3-(4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		431.4
B120	7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		419.4
B121	4-fluoro-2-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)benzonitrile		430.3
B122	7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		438.2
B123	2,5,6-trimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		402.3

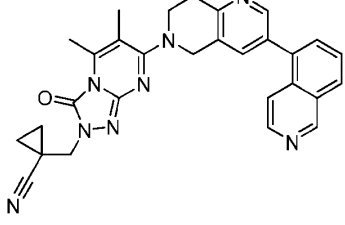
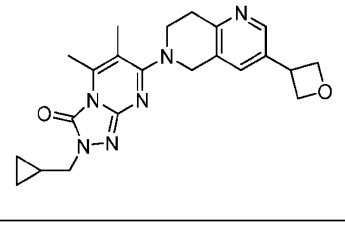
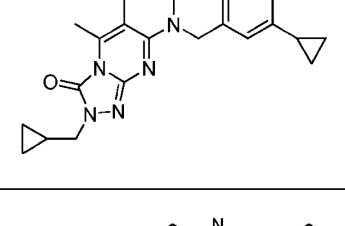
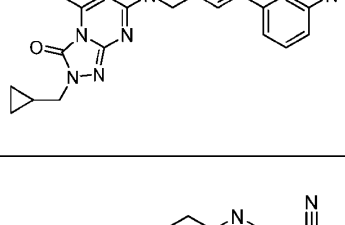
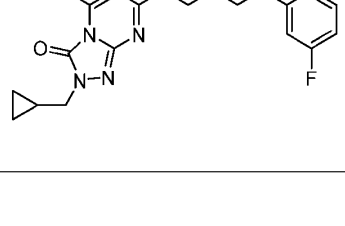
B124	7-(3-(5-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		473.2
B125	1-((7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		416.3
B126	1-((7-(3-((2-fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		485.3
B127	1-((7-(3-((3-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		500.3
B128	3-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)isonicotinonitrile		413.2

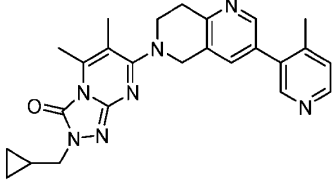
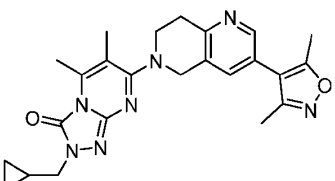
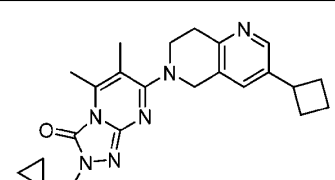
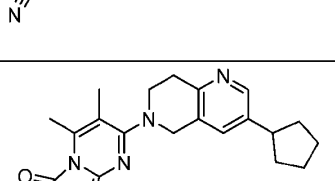
B129	2,5,6-trimethyl-7-(3-(4-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		456.2
B130	7-(3-(6-methoxy-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		432.3
B131	2,5,6-trimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		438.3
B132	1-((7-(3-(1,3-dimethyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		470.3
B133	1-((7-(3-(1-cyclopropylvinyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		442.3
B134	5-(difluoromethyl)-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		415.2

B135	5-cyclopropyl-7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		493.3
B136	1-((5,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		467.3
B137	1-((5,6-dimethyl-3-oxo-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		503.2
B138	1-((7-(3-(5-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		496.3
B139	1-((5,6-dimethyl-3-oxo-7-(3-(prop-1-en-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		416.3

B140	2,5,6-trimethyl-7-[3-(oxetan-3-yl)-7,8-dihydro-5 <i>H</i> -1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3- <i>α</i>]pyrimidin-3-one		367.3
B141	2,5,6-trimethyl-7-[3-(oxetan-3-yl)-7,8-dihydro-5 <i>H</i> -1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3- <i>α</i>]pyrimidin-3-one		311.3
B142	1-((7-(3-(2,5-dihydrofuran-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>α</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		444.3
B143	1-((7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>α</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		471.3
B144	1-((5,6-dimethyl-7-(3-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-oxo-[1,2,4]triazolo[4,3- <i>α</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		432.3

B145	1-((7-(7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		376.3
B146	1-((7-(3-(2,6-difluorophenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		488.2
B147	1-((7-(3-(2-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		471.2
B148	3-(6-(2-((1-cyanocyclopropyl)methyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)isonicotinonitrile		478.4
B149	1-((7-(3-(isoquinolin-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		503.2

B150	1-((7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		503.3
B151	2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		407.4
B152	7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2-(cyclopropylmethyl)-5,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		391.3
B153	2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		478.2
B154	2-(6-(2-(cyclopropylmethyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-4-fluorobenzonitrile		470.3

B155	2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		442.3
B156	2-(cyclopropylmethyl)-7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		446.3
B157	1-((7-(3-cyclobutyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile		430.3
B158	7-(3-cyclopentyl-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one		379.3

Biological Activity

A. Cell Lines Expressing Muscarinic Acetylcholine Receptors

[00567] Human and rat M₄ cDNAs, along with the chimeric G protein G_{q15}, were transfected into Chinese hamster ovary (CHO-K1) cells purchased from the American Type Culture Collection using Lipofectamine2000. The transfected cells were subjected to selection antibiotic treatment to generate stable cell lines; G418 sulfate (1 mg/ml) for selecting M₄ expressing cells and Hygromycin B (500 µg/mL) for selecting G_{q15} expressing cells. The resulting polyclones were further screened to obtain monoclones of hM₄-G_{q15} and rM₄-G_{q15} for compound screening assay. Stable monoclonal cells were maintained in Ham's F-12 medium containing 10% heat-inactivated fetal bovine serum (FBS), 1X Antibiotic/Antimycotic, 20 mM HEPES, 500 µg/mL

G418 sulfate, and 200 µg/mL Hygromycin B in 37 °C humidified incubators in the presence of 5% CO₂.

B. Cell-Based Functional Assay of Muscarinic Acetylcholine Receptor Activity

[00568] The high throughput assay was employed to measure receptor-induced mobilization of intracellular calcium to determine compound activity. Test compound was added to cells expressing the muscarinic receptors that were loaded with calcium sensitive fluorescent dye. After a ~2.5 minute incubation period, a submaximal (EC₂₀) concentration of acetylcholine was added, and the response measured. This kinetic assay allows for simultaneous screening and potency determination of multiple pharmacological modes of action including agonist and potentiator activity. CHO-K1 cells stably expressing muscarinic receptors were plated in growth medium lacking G418 and hygromycin at 15,000 cells/20 µL/well in Greiner 384-well black-walled, tissue culture (TC)-treated, clear-bottom plates (Greiner Bio-One). Cells were incubated overnight at 37 °C and 5% CO₂. The next day, calcium assay buffer (Hank's balanced salt solution (HBSS), 20 mM HEPES, 2.5 mM Probenecid, 4.16 mM sodium bicarbonate (Sigma-Aldrich, St. Louis, MO)) was prepared to dilute compounds, agonists, and Fluo-4-acetomethoxyester (Fluo-4-AM), fluorescent calcium indicator dye. Compounds were serially diluted 1:3 into 10 point concentration response curves in DMSO using the Bravo Liquid Handler (Agilent, Santa Clara, CA), transferred to a 384 well daughter plates using an Echo acoustic liquid handler (Beckman Coulter, Indianapolis, Indiana), and diluted in assay Buffer to a 2X final concentration. The agonist plates were prepared using acetylcholine (ACh, Sigma-Aldrich, St. Louis, MO) concentrations for the EC₂₀ and EC_{MAX} responses by diluting in assay buffer to a 5X final concentration. The 2X dye solution (2.3 µM) was prepared by mixing a 2.3 mM Fluo-4-AM stock in DMSO with 10% (w/v) pluronic acid F-127 in a 1:1 ratio in assay buffer. Using a microplate washer (BioTek, Winooski, VT), cells were washed with assay buffer for 3 times to remove medium. After the final wash, 20 µL of assay buffer remained in the cell plates. Immediately, 20 µL of the 2X dye solution (final 1.15 µM) was added to each well of the cell plate using a Multidrop Combi dispenser (Thermo Fisher, Waltham, MA). After cells were incubated with the dye solutions for 45 min at 37 °C in the presence of 5% CO₂, the dye solutions were removed and replaced with assay buffer using a microplate washer, leaving 20 µL of assay buffer in the cell plate.

[00569] The prepared compound, agonist, and cell plates were placed inside the Functional

Drug Screening System uCell (FDSS uCell, Hamamatsu, Japan) to measure the calcium flux. The triple add protocol was used to measure Ca kinetics; Compound, ACh for EC₂₀, and ACh for EC₈₀ adds in an order. Briefly, after establishment of a fluorescence baseline for 2 seconds (excitation, 480 nm; emission, 530 nm), first add occurred by adding 20 μ L of test compound to the cells, and the response was measured for 140 seconds. This is followed by second add; 10 μ L (5X) of an EC₂₀ concentration of ACh agonist was added to the cells, and the response of the cells was measured for 125 seconds. Immediately, the third add occurred by adding 12 μ L (5X) of an EC₈₀ concentration of ACh and the response of the cells was measured for 90 seconds. Acetylcholine-mediated maximum response (EC_{max}) was measured by adding 1 mM ACh as third add in the control wells. DMSO vehicle was added to the control wells in the first add for assessing ACh EC₂₀, EC₈₀, and EC_{max} responses. Calcium fluorescence was recorded as fold over basal fluorescence and raw data were normalized to the maximal response to ACh agonist. Agonist activity was analyzed as a concentration-dependent increase in calcium mobilization upon compound addition. Positive allosteric modulator activity was analyzed as a concentration-dependent increase in the EC₂₀ acetylcholine response. Antagonist activity was analyzed as a concentration-dependent decrease in the EC₈₀ acetylcholine response. Concentration-response curves were generated using a four-parameter logistical equation using GraphPad Prism (La Jolla, CA) or the Dotmatics software platform (Woburn, MA).

[00570] The above-described assay was also operated in a second mode where an appropriate fixed concentration of the present compounds was added to the cells after establishment of a fluorescence baseline for about 3 seconds, and the response in cells was measured. 140 s later, the appropriate concentration of agonist was added and the calcium response (maximum-local minima response) was measured. The EC₅₀ values for the agonist in the presence of test compound were determined by nonlinear curve fitting. A decrease in the EC₅₀ value of the agonist with increasing concentrations of the present compounds (a leftward shift of the agonist concentration-response curve) is an indication of the degree of muscarinic positive allosteric modulation at a given concentration of the present compound. An increase in the EC₅₀ value of the agonist with increasing concentrations of the present compounds (a rightward shift of the agonist concentration response curve) is an indication of the degree of muscarinic antagonism at a given concentration of the present compound. The second mode also indicates whether the present compounds also affect the maximum response of the muscarinic receptor to agonists.

C. Activity of Compounds in a mAChR M₄ Cell-Based Assay

[00571] Compounds were synthesized as described above. Activity (EC₅₀ and E_{max}) was determined in the M₄ cell-based functional assay as described above and the data are shown in Table 2. The compound number corresponds to the compound numbers used in Table 1.

Table 2.

No.	Human M₄ EC₅₀ (nM)	E_{max} (%)*
1	409	91
2	23	88
3	51	73
4	1264	59
5	707	97
6	70	95
7	727	71
8	4700	74
9	86	75
10	39	79
11	406	73
12	ND	ND
13	20	91
14	44	85
15	51	91
16	57	104
17	43	83
18	31	87
19	62	105
20	8	102
21	219	80
22	4	99
23	71	90
24	29	80

25	49	81
26	85	76
27	19	85
28	17	78
29	17	78
30	73	76
31	106	76
32	75	78
33	134	80
34	341	84
35	58	93
36	38	93
37	22	89
38	23	79
39	77	82
40	73	76
41	145	75
42	314	63
43	14	74
44	6	82
45	196	99
46	>10,000	59
47	122	95
48	93	83
49	91	80
50	5	101
51	345	103
52	374	89
53	40	82
54	59	91

55	89	88
56	6	103
57	3	102
58	1	101
59	4	102
A1	8	87
A2	3	94
A3	79	94
A4	3	104
A5	3	102
A6	2	89
A7	39	98
A8	11	102
B1	25	97
B2	38	101
B3	28	78
B4	28	79
B5	12	75
B6	27	76
B7	25	70
B8	9	78
B9	15	86
B10	24	112
B11	8	101
B12	16	96
B13	9	93
B14	173	89
B15	201	80
B16	16	84
B17	1867	82

B18	21	82
B19	13	91
B20	6	89
B21	27	110
B22	4	87
B23	46	96
B24	9	96
B25	16	86
B26	9	85
B27	14	90
B28	325	84
B29	13	88
B30	139	82
B31	46	82
B32	208	90
B33	11	83
B34	113	88
B35	8	85
B36	24	95
B37	193	83
B38	882	80
B39	206	94
B40	904	84
B41	945	82
B42	103	92
B43	281	74
B44	563	97
B45	147	100
B46	22	105
B47	22	104

B48	22	94
B49	130	89
B50	77	90
B51	21	99
B52	98	102
B53	14	95
B54	7	95
B55	14	89
B56	3	100
B57	35	88
B58	44	96
B59	43	92
B60	10	95
B61	90	85
B62	34	102
B63	21	104
B64	8	112
B65	12	108
B66	25	87
B67	8	105
B68	7	78
B69	15	100
B70	7	95
B71	67	92
B72	101	85
B73	998	79
B74	10	88
B75	90	107
B76	7	85
B77	15	84

B78	34	81
B79	10	86
B80	2	90
B81	11	92
B82	8	98
B83	12	105
B84	49	88
B85	114	85
B86	43	94
B87	15	98
B88	70	97
B89	17	96
B90	13	91
B91	39	87
B92	5	88
B93	30	79
B94	32	73
B95	36	89
B96	49	94
B97	297	96
B98	32	98
B99	25	111
B100	11	102
B101	13	97
B102	16	95
B103	20	94
B104	8	95
B105	72	94
B106	7	92
B107	330	87

B108	2	83
B109	480	81
B110	26	82
B111	14	76
B112	144	75
B113	44	102
B114	93	93
B115	111	85
B116	12	88
B117	16	84
B118	19	85
B119	6	87
B120	4	86
B121	20	77
B122	4	81
B123	2	83
B124	87	79
B125	1	82
B126	6	84
B127	5	97
B128	59	96
B129	101	74
B130	10	89
B131	23	88
B132	33	82
B133	12	79
B134	121	75
B135	109	64
B136	18	83
B137	56	91

B138	21	108
B139	3	92
B140	9	103
B141	56	104
B142	18	106
B143	27	109
B144	5	118
B145	26	115
B146	101	93
B147	44	89
B148	180	83
B149	126	85
B150	16	87
B151	11	95
B152	1	102
B153	37	102
B154	80	96
B155	3	108
B156	7	122
B157	9	112
B158	5	100

* %ACh maximum at 30 μ M.

D. Functional assessment of M₄ activator compounds in cellular cAMP assay

Cellular cAMP G_i HTRF Assay

[00572] Activation of the M₄ receptor leads to the inhibition of cAMP production by coupling to G_{i/o} proteins. To measure the level of cAMP inhibition by M₄ allosteric modulators, a Homogeneous Time-Resolved Fluorescence (HTRF[®]) cAMP assay was employed using CHO cells stably expressing human or rat M₄ receptors. The HTRF cAMP assay is a Time-Resolved Resonance Energy Transfer (TR-FRET) competitive immunoassay. Endogenous intracellular

cAMP generated by cells competes with Europium cryptate-labeled cAMP (Europium donor, emission 665 nm) for the binding to a cAMP antibody labeled with d2 (d2-acceptor, emission 620 nm). Thus, the fluorescence emission ratio (665 nm/620 nm) is inversely proportional to the cAMP amount in the cells. Compound-mediated M₄ activation results in an increase in HTRF ratio (665 nm/620 nm), indicative of a decrease in intracellular cAMP level. To monitor agonist activity, compounds were added to the M₄ cells in the presence of an EC₈₀ concentration of forskolin (adenylyl cyclase activator) which induces a submaximal intracellular cAMP level. To assess potentiator activity, compounds were added to the M₄ cells with an EC₈₀ concentration of forskolin in the presence of an EC₂₀ concentration of acetylcholine. This functional assay allows determination of the potency and efficacy of compounds directly activating or potentiating the G_{i/o}-coupled M₄ receptor.

[00573] Functional agonist and potentiator activities of compounds were determined by measuring cAMP levels in Chinese Hamster Ovary (CHO) cells stably expressing human or rat M₄ muscarinic receptors using an HTRF cAMP G_{i/o} kit. Cells were maintained in F12 medium containing 10% FBS, 20 mM HEPES, 1X Antibiotic/Antimycotic, and G418 (500 µg/ml) in 37 °C humidified incubators in the presence of 5% CO₂. The day before assay, the cells were trypsinized and resuspended in plating medium (growth medium without G418). The cells were plated to white, solid, flat-bottomed, 384 well plates at densities of 4,000 and 6,000 cells/10 µL/well, of human M₄ and rat M₄ cells, respectively. The cell plates were spun at 100xg for 1 min, then immediately placed in a 37 °C incubator in the presence of 5% CO₂ overnight.

[00574] The next day, reagents were freshly diluted at a 2X concentration in assay buffer using F12 basal medium or stimulation buffer. All assay buffers contained 500 µM IBMX to block cAMP degradation. Activation of M₄ by compounds was examined in cells stimulated with an EC₈₀ concentration of forskolin to induce submaximal intracellular cAMP levels. Forskolin EC₈₀ concentrations were determined from forskolin concentration response curves (CRCs) and ranged from 1.5 to 2.5 µM. Compounds (10 mM) were prepared in 100% DMSO and further serially diluted either 1:3 or 1:5 into a 13-point CRC in DMSO using a Bravo Liquid Handler in a 384 well microplate.

[00575] Agonist assay mode was used to assess the abilities of M₄ compounds to directly activate M₄ receptors in the absence of the agonist, acetylcholine. The 10-point serially diluted compounds, starting 30 µM as a final concentration, were transferred to a compound plate using

an Echo plate reformat protocol. 2X assay buffer containing an EC₈₀ concentration of forskolin concentration was added to the compound plate. Vehicle (1% DMSO) was added to the following control wells; baseline cAMP (no forskolin), forskolin max, and forskolin EC₈₀. 10 µL/well of the prepared 2X assay buffer was immediately added to the cell plates using a Bravo 384 well tip liquid handler. The cell plates were immediately spun for 30 seconds at 100 x g and incubated at 37 °C for 10 min with gentle shaking at 50 rpm. An acetylcholine CRC was also performed in the presence of an EC₈₀ concentration of forskolin to determine the concentrations of acetylcholine inducing maximal (EC_{max}) and submaximal (EC₂₀) cAMP inhibition in order to prepare for the subsequent potentiator mode assay.

[00576] In potentiator assay mode, the 10-point serially diluted compounds, starting 1.1 µM as a final concentration, were transferred to a compound plate using an Echo plate reformat protocol. 2X assay buffer containing an EC₈₀ concentration of forskolin and an EC₂₀ concentration of acetylcholine was added to the compound plate. Vehicle (1% DMSO) was added to the following: (1) for forskolin controls wells - baseline cAMP (no forskolin), forskolin max, and forskolin EC₈₀, (2) for agonist control wells containing forskolin EC₈₀ – basal (no agonist), and acetylcholine EC₂₀ and EC_{max}. 10 µL/well of the prepared 2X assay buffer was immediately added to the cell plates using a Bravo 384 well tip liquid handler. The cell plates were immediately spun for 30 seconds at 100x g and incubated at 37 °C for 10 min with gentle shaking at 50 rpm. During the 10-minute incubation period, cAMP Eu-cryptate donor (20X) and anti-cAMP d2 antibody acceptor (20X) were diluted in lysis/detection buffer in separate tubes. Immediately after the incubation, cells were lysed by sequentially adding 10 µL/well of cAMP Eu-cryptate solution and 10 µL/well of anti-cAMP d2 antibody solution. The cell plates were immediately spun for 30 seconds at 100x g and incubated for 60 minutes at 25 °C with gentle shaking at 50 rpm. Immediately after the detection incubation, TR-FRET signals were measured at two channels, 665 and 620 nm, using an EnVision Plate reader (Perkin Elmer). All emission ratios (665/620) were normalized to % acetylcholine max. Individual CRCs were generated using a four-parameter logistical equation using GraphPad Prism (La Jolla, CA), and EC₅₀ was extracted from the fitting, and maximal response (% ACh Max) was determined;

$$y = bottom + \frac{top - bottom}{1 + 10^{(LogEC_{50} - A)Hillslope}}$$

where *A* is the molar concentration of the compound; *bottom* and *top* denote the lower and upper plateaus of the concentration-response curve; HillSlope is the Hill coefficient that describes the steepness of the curve; and EC₅₀ is the molar concentration of compound required to generate a response halfway between the *top* and *bottom*.

Table 3. Materials and Equipment

	Item	Manufacturer	Cat #
Cell culture	F12 medium	Thermo Fisher	11765054
	Fetal bovine serum	Thermo Fisher	16140089
	Antibiotic/Antimycotic	Thermo Fisher	15240062
	1 M HEPES (2-[4-(2-hydroxyethyl) piperazin-1-yl] ethanesulfonic acid)	Thermo Fisher	15630080
	G418 Sulfate	Thermo Fisher	10131027
	TrypLE Express	Thermo Fisher	12605036
cAMP Assay	HTRF cAMP-Gi kit	Cisbio	62AM9PEC
	CELLSTAR, 384 well plate, TC-treated, White, Solid-flat bottom	Greiner	781080
	IBMX (3-isobutyl-1-methylxanthine)	Sigma	I5879
	Forskolin	Sigma	F6886
	Acetylcholine chloride	Sigma	A6625
	DMSO (Dimethyl sulfoxide)	Sigma	D8418
	Echo 650 liquid handler	Beckman	001-16079
	Bravo liquid handler	Agilent	G5563AA
	EnVision plate reader	Perkin Elmer	2105-0011

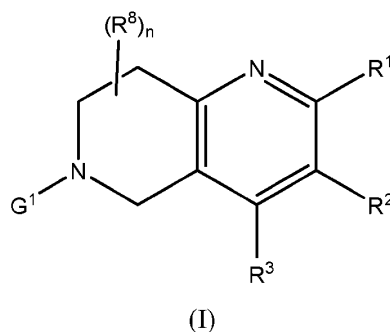
[00577] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents.

[00578] Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, compositions, formulations, or methods of use of the invention, may be made without departing from the spirit and scope thereof.

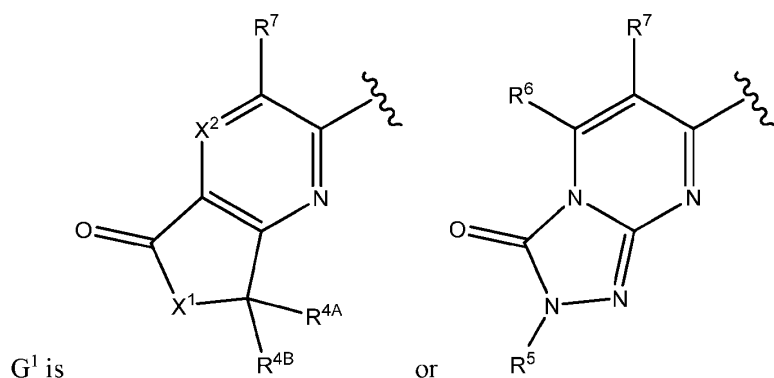
CLAIMS

What is claimed is:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof,



wherein:



G^1 is

X^1 is NR^5 , O, or $CR^{5A}R^{5B}$;

X^2 is CR^6 or N;

R^1 and R^3 are each independently hydrogen, halogen, cyano, C_{1-4} alkyl, C_{1-4} fluoroalkyl, $-OC_{1-4}$ alkyl, or $-OC_{1-4}$ fluoroalkyl;

R^2 is G^2 , $-NR^bR^c$, C_{1-6} haloalkyl, halogen, cyano, NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, $-OR^b$, $-NR^cC(O)R^b$, $-NR^cSO_2R^a$, $-N=S(O)(R^a)_2$, $-P(O)(R^a)_2$, $-C_{1-3}$ alkylene- G^2 , $-C_{2-4}$ alkenylene- G^2 , or hydrogen;

R^a , at each occurrence, is independently C_{1-6} alkyl, C_{1-6} haloalkyl, G^2 , or $-C_{1-3}$ alkylene- G^2 ;

wherein optionally, the two R^a of $-N=S(O)(R^a)_2$ or $-P(O)(R^a)_2$ join together as a straight alkylene chain to form a 5- to 7-membered heterocyclic ring;

R^b and R^c are independently hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, G^2 , or $-C_{1-3}$ alkylene- G^2 ;
 G^2 , at each occurrence, is independently a 5- to 12-membered heteroaryl, a 6- to 12-membered aryl, a 4- to 12-membered heterocyclyl, or a 3- to 12-membered carbocyclyl, wherein the heteroaryl and heterocyclyl each contain 1-4 heteroatoms independently selected from the group consisting of O, N, and S, and G^2 is optionally substituted with a first substituent selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, oxo, $-OR^x$, $-N(R^x)_2$, $-SR^x$, $-SO_2R^x$, $-C(O)R^x$, $-C(O)OR^x$, $-C(O)N(R^x)_2$, $-C_{1-6}$ alkylene- OR^x , $-C_{1-6}$ alkylene- $N(R^x)_2$, G^{2a} , and $-C_{1-3}$ alkylene- G^{2a} , and optionally further substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, and $-OR^x$;
 R^x , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, $-C_{1-3}$ alkylene- C_{3-6} cycloalkyl, phenyl, or $-C_{1-3}$ alkylene-phenyl, wherein each cycloalkyl or phenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C_{1-4} alkyl, and C_{1-4} haloalkyl;
 G^{2a} is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a 3- to 8-membered carbocyclyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^{2a} , at each occurrence, is independently optionally substituted with 1-5 substituents independently selected from the group consisting of halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, $-C_{1-6}$ alkylene-OH, oxo, OH, $-OC_{1-4}$ alkyl, $-OC_{1-4}$ haloalkyl, C_{3-4} cycloalkyl, and $-C_{1-3}$ alkylene- C_{3-4} cycloalkyl;
 R^{4A} and R^{4B} are independently hydrogen, C_{1-4} alkyl, C_{3-4} cycloalkyl, or $-C_{1-3}$ alkylene-OH;
 R^5 is hydrogen, C_{1-6} alkyl, C_{1-6} fluoroalkyl, $-C_{1-6}$ alkylene- R^y , $-C_{1-6}$ fluoroalkylene- R^y , G^5 , or $-C_{1-3}$ alkylene- G^5 ;
 R^{5A} and R^{5B} are independently hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkyl, or $-C_{1-4}$ alkylene-OH;
 R^y is $-OR^{5a}$, $-N(R^{5a})_2$, $-C(O)R^{5a}$, $-C(O)OR^{5a}$, or $-C(O)N(R^{5a})_2$;
 R^{5a} , at each occurrence, is independently hydrogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, G^5 , or $-C_{1-3}$ alkylene- G^5 ;
 G^5 is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a C_{3-8} cycloalkyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G^5 is optionally

substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C₁₋₄alkyl, C₁₋₂fluoroalkyl, -OC₁₋₄alkyl, OH, and oxo;

alternatively, R^{4A} and R^{4B} together with the carbon to which they attach form a C₃₋₆cycloalkyl; or R^{4B} and R⁵ together with the atoms to which they attach form a 5- to 7-membered heterocycle optionally containing one additional heteroatom selected from the group consisting of oxygen, nitrogen, and sulfur;

R⁶ is hydrogen, halogen, cyano, C₁₋₄alkyl, C₁₋₄fluoroalkyl, C₂₋₄alkenyl, -OR^{6a}, -N(R^{6a})₂, -C₁₋₃alkylene-OR^{6a}, or C₃₋₆cycloalkyl;

R^{6a}, at each occurrence, is independently hydrogen, C₁₋₄alkyl, C₁₋₄fluoroalkyl, C₃₋₄cycloalkyl, or -C₁₋₃alkylene-C₃₋₄cycloalkyl;

wherein alternatively, two R^{6a}, together with the nitrogen to which they attach form a 4- to 8-membered heterocyclic ring containing the nitrogen attached to R^{6a} and optionally 1-2 additional heteroatoms that are independently O, N, or S, the heterocyclic ring being optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, C₁₋₂alkyl, and C₁₋₂fluoroalkyl;

R⁷ is C₁₋₄alkyl, hydrogen, halogen, cyano, C₁₋₄fluoroalkyl, -OR^{7a}, -C₁₋₃alkylene-OR^{7a}, or G⁷;

alternatively, R⁶ and R⁷, together with the atoms to which they are attached, form a 5- to 7-membered heterocycle containing 1 heteroatom or a 5- to 7-membered carbocycle, wherein the heteroatoms are independently selected from the group consisting of N, O, and S, and the heterocycle and carbocycle are optionally substituted with 1-4 substituents independently selected from the group consisting of C₁₋₄alkyl, halogen, -OC₁₋₄alkyl, C₁₋₄fluoroalkyl, C₃₋₄cycloalkyl, and C₁₋₂alkylene-C₃₋₄cycloalkyl;

R^{7a} is hydrogen, C₁₋₄alkyl, C₁₋₄fluoroalkyl, C₃₋₄cycloalkyl, or -C₁₋₃alkylene-C₃₋₄cycloalkyl;

G⁷ is a phenyl, a 5- to 6-membered heteroaryl containing 1-3 heteroatoms, a 4- to 8-membered heterocyclyl containing 1-2 heteroatoms, or a C₃₋₆cycloalkyl, wherein the heteroatoms are independently selected from the group consisting of O, N, and S, and G⁵ is optionally substituted with 1-4 substituents independently selected from the group consisting of halogen, cyano, C₁₋₄alkyl, C₁₋₂fluoroalkyl, -OC₁₋₄alkyl, OH, and oxo;

R⁸, at each occurrence, is independently halogen, C₁₋₄alkyl, C₁₋₄fluoroalkyl, or C₃₋₄cycloalkyl;

and

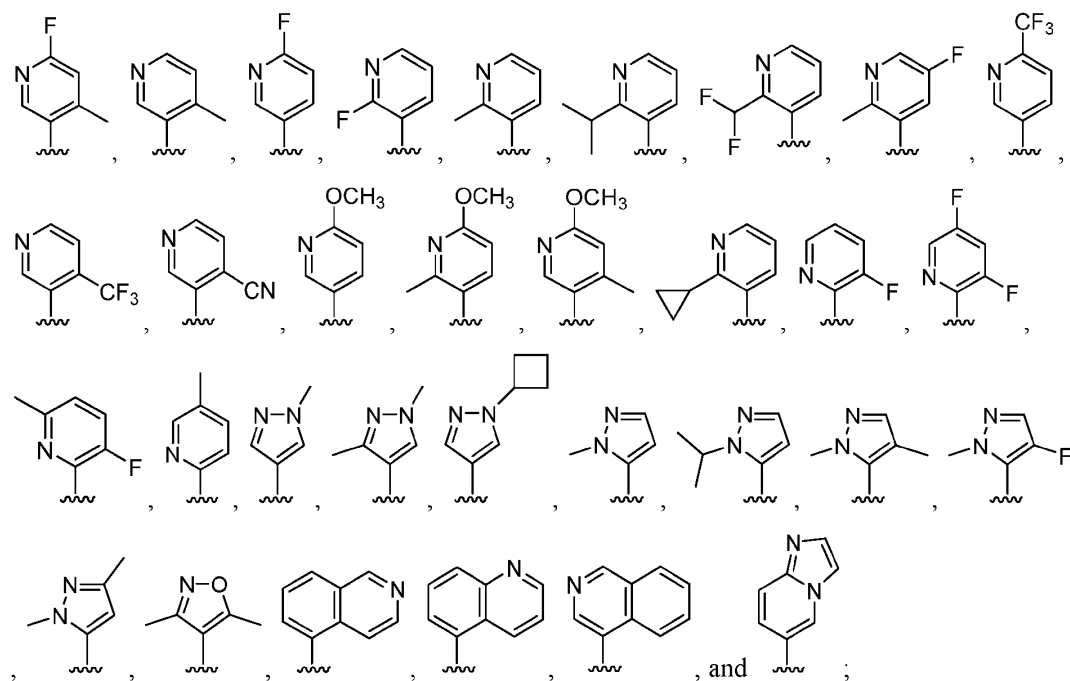
n is 0, 1, 2, 3, or 4;

wherein each cycloalkyl at R⁶, R^{6a}, R⁷, R^{7a}, and R⁸ is unsubstituted or substituted with 1-4 substituents independently selected from C₁₋₄alkyl and halogen.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen or C₁₋₄alkyl.
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen.
4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, R² is G², -NR^bR^c, C₁₋₆haloalkyl, C₂₋₆alkenyl, cyano, hydrogen, or -C₂₋₄alkenylene-G².
5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein R² is C₁₋₆haloalkyl.
6. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein R² is G².
7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein G² is the optionally substituted 5- to 12-membered heteroaryl.
8. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein G² is the optionally substituted 6- to 12-membered aryl.
9. The compound of any of claims 1-4, or 6, or a pharmaceutically acceptable salt thereof, wherein G² is the optionally substituted 4- to 12-membered heterocyclyl.
10. The compound of any of claims 1-4, or 6, or a pharmaceutically acceptable salt thereof, wherein G² is the optionally substituted 3- to 12-membered carbocyclyl.
11. The compound of any of claims 6-10, or a pharmaceutically acceptable salt thereof,

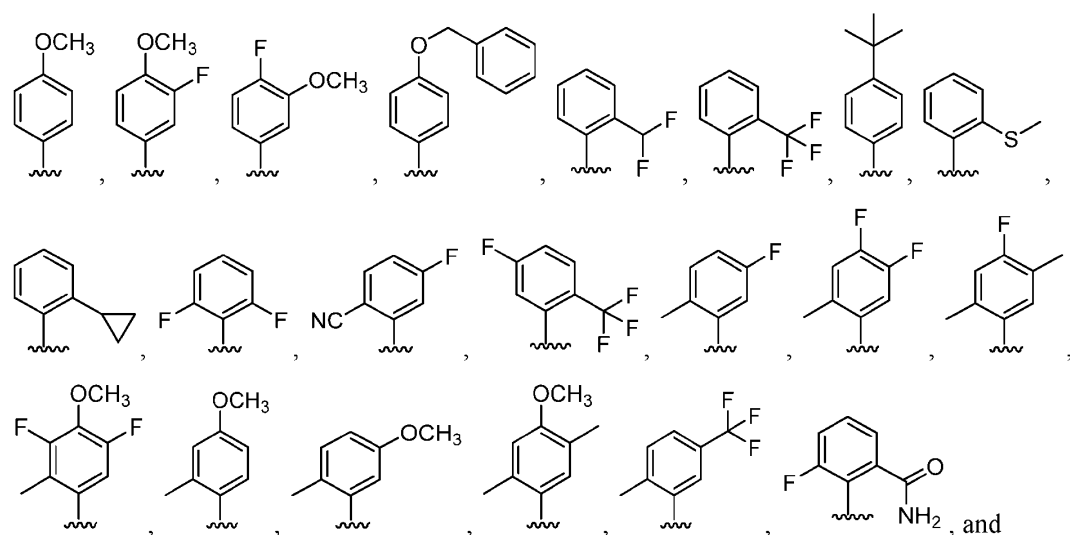
wherein G^2 is:

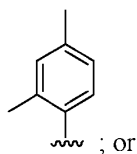
(a) the optionally substituted 5- to 12-membered heteroaryl selected from the group consisting of



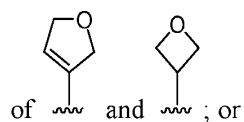
or

(b) the optionally substituted 6- to 12-membered aryl selected from the group consisting of





(c) the optionally substituted 4- to 12-membered heterocyclyl selected from the group consisting



(d) the optionally substituted 3- to 12-membered carbocyclyl that is , , or .

12. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein

R^2 is $-NR^bR^c$;

R^b is C_{1-6} alkyl, G^2 , or $-C_{1-3}$ alkylene- G^2 ; and

R^c is hydrogen or C_{1-6} alkyl.

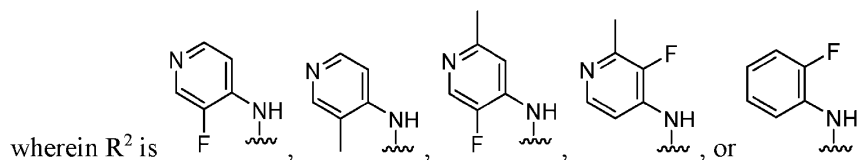
13. The compound of any of claims 1-4 or 12, or a pharmaceutically acceptable salt thereof, wherein R^b is G^2 .

14. The compound of claim 12 or 13, or a pharmaceutically acceptable salt thereof, wherein G^2 is the optionally substituted 5- to 12-membered heteroaryl.

15. The compound of claim 12 or 13, or a pharmaceutically acceptable salt thereof, wherein G^2 is the optionally substituted 6- to 12-membered aryl.

16. The compound of any of claims 1-4 or 12-15, or a pharmaceutically acceptable salt thereof, wherein R^c is hydrogen.

17. The compound of any of claims 12-16, or a pharmaceutically acceptable salt thereof,



18. The compound of any of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^{4A} and R^{4B} are hydrogen.

19. The compound of any of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, C_{1-6} alkyl, C_{1-6} fluoroalkyl, $-C_{1-6}$ alkylene- R^y , G^5 , or $-C_{1-3}$ alkylene- G^5 .

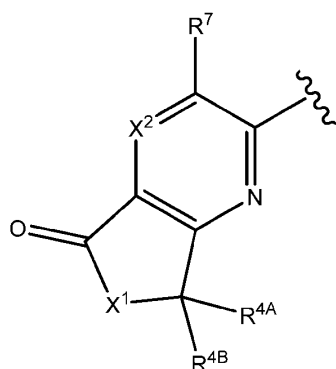
20. The compound of any of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^{4B} and R^5 together with the atoms to which they attach form the 5- to 7-membered heterocycle.

21. The compound of any of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, $-OR^{6a}$, or C_{3-6} cycloalkyl.

22. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_{1-4} alkyl, halogen, cyano, or G^7 .

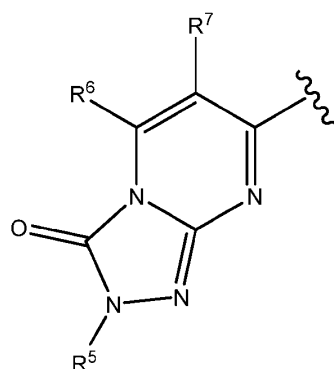
23. The compound of any of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein n is 0.

24. The compound of any of claims 1-23, or a pharmaceutically acceptable salt thereof,



wherein G^1 is

25. The compound of any of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein X^1 is NR^5 .
26. The compound of any of claims 1-18 or 21-24, or a pharmaceutically acceptable salt thereof, wherein X^1 is O.
27. The compound of any of claims 1-18 or 21-24, or a pharmaceutically acceptable salt thereof, wherein X^1 is $CR^{5A}R^{5B}$.
28. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein X^2 is CR^6 .
29. The compound of any of claims 1-27, or a pharmaceutically acceptable salt thereof, wherein X^2 is N.
30. The compound of any of claims 1-23, or a pharmaceutically acceptable salt thereof,



wherein G^1 is

31. The compound of any of claims 1-20 or 23-30, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 , together with the atoms to which they are attached, form the optionally substituted 5- to 7-membered heterocycle or a 5- to 7-membered carbocycle.

32. The compound of claim 1 selected from the group consisting of:

3,6-dimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
methyl 2-(3-methyl-5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,7-dihydro-6H-pyrrolo[3,4- <i>b</i>]pyridin-6-yl)propanoate
3-methyl-2-(3-(1-methyl-1H-pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-8,9,10,10a-tetrahydropyrido[2',3':3,4]pyrrolo[1,2- <i>a</i>]pyrazin-5(7H)-one
2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-6-(methyl- <i>d</i> ₃)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one

3-methyl-6-(oxetan-3-ylmethyl)-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(1-methyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,5,7,7- <i>d</i> ₄)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,5,7,7- <i>d</i> ₄)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one-7,7- <i>d</i> ₂
2-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1,3-dimethyl-1 <i>H</i> -pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1-cyclobutyl-1 <i>H</i> -pyrazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1-isopropyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(6-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1,4-dimethyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-methoxypyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(4-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one

2-(3-(imidazo[1,2- <i>a</i>]pyridin-6-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(1,3-dimethyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(4-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(3-fluoro-4-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(4-(benzyloxy)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-(difluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-cyclopropylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(5-fluoro-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-isopropylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-methoxy-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one

2-(3-(4-fluoro-1-methyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7 <i>H</i>)-one
2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3,6-dimethyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
6-cyclopropyl-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
6-cyclopentyl-2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(2-(difluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5-oxo-5,7-dihydrofuro[3,4- <i>b</i>]pyridine-3-carbonitrile
2-(3-(6-methoxy-2-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7 <i>H</i>)-one
2-(3-(4-fluoro-1-methyl-1 <i>H</i> -pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methylfuro[3,4- <i>b</i>]pyridin-5(7 <i>H</i>)-one
5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridine-3-carbonitrile
6-(5-oxo-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-3-yl)picolinonitrile
2-(3-(3,5-difluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(3-fluoro-6-methylpyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-3-methyl-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(5-methylpyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-6,7-dihydro-5 <i>H</i> -cyclopenta[<i>b</i>]pyridin-5-one

(R)-6-(1-methoxypropan-2-yl)-3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
(S)-6-(1-methoxypropan-2-yl)-3-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-chloro-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-chloro-6-methyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3,4,6-trimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3,4-dimethyl-2-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,4-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,4,6-trimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((5-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((3-fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,5,7,7- <i>d</i> ₄ -3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,5,7,7- <i>d</i> ₄ -6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((3-fluoropyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((5-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,5,7,7- <i>d</i> ₄ -3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one

2-(3-((2-fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl-5,5,7,7- <i>d</i> ₄)-3-methyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
3-methyl-2-(3-((3-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
2-(3-((3-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3,6-dimethyl-6,7-dihydro-5H-pyrrolo[3,4- <i>b</i>]pyridin-5-one
6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-2-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(3-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,6-dimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-2-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-ethyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6,7,8-tetrahydro-1H-cyclopenta[<i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1-one
5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,7,8,9-tetrahydro-[1,2,4]triazolo[4,3- <i>a</i>]quinazolin-1(2H)-one
6-methyl-2-(tetrahydrofuran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(1-methoxypropan-2-yl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-methoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2,6-dimethylbenzyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(3,5-difluorobenzyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-((4-methylmorpholin-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-methoxy-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-fluoro-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,8-dihydrothieno[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2H)-one
5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,8-dihydrofuro[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2H)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

7-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-methyl-5-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-6,8-dihydrofuro[3,4- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-1(2H)-one
2-(2-cyclopropoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(1-methoxypropan-2-yl)-6-methyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-((5,5-dimethyltetrahydrofuran-2-yl)methyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-(2-phenoxyethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
1-((6-methyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
6-methyl-2-(tetrahydro-2H-pyran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(bicyclo[2.2.1]heptan-2-yl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-isopropoxyethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-(2-fluorophenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-(2-(<i>p</i> -tolylloxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

2-ethyl-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-chloro-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-chloro-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-(4-fluorophenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-(2-(<i>o</i> -tolylloxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-(4-methoxyphenoxy)ethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-(tetrahydrofuran-3-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2,6-dimethylbenzyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-(2-phenoxyethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-cyclopropoxyethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-methoxypyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-(2,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile
7-(3-(4-methoxy-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-3-methoxyphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(2,4-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(2-(methylthio)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(2-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-(tert-butyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclopropylmethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-fluoro-2-methylpropyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-((3,3-difluorocyclobutyl)methyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-isobutyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
6-methyl-2-neopentyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclobutylmethyl)-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-isobutyl-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

2-(cyclobutylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-((3,3-difluorocyclobutyl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4,5-difluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-methoxy-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(2-cyclopropylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(2-methyl-5-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-(2-(<i>o</i> -tolylloxy)ethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(4-fluoro-2,5-dimethylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-isopropoxyethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(5-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-((tetrahydrofuran-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-cyclopropyl-6-methyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-cyclopropyl-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-((5,6-dimethyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)benzonitrile

1-((5,6-dimethyl-3-oxo-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
5,6-dimethyl-2-neopentyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-((tetrahydrofuran-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclopentylmethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-(tetrahydro-2H-pyran-4-yl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-((2-oxaspiro[3.3]heptan-6-yl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-((3-methyloxetan-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-((tetrahydro-2H-pyran-4-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-((2,2-difluorocyclopropyl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-fluoro-2-methylpropyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5,6-dimethyl-2-(oxetan-2-ylmethyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(2-(2-fluorophenoxy)ethyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
3-fluoro-2-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)benzamide

6-(2-((1-cyanocyclopropyl)methyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile
7-(3-(2,6-difluorophenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
1-((7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3 <i>H</i>)-yl)methyl)cyclopropane-1-carbonitrile
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((tetrahydrofuran-3-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((3-methyloxetan-3-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-4-yl)methyl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-3-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
5,6-dimethyl-2-((tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
2-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
7-(3-(5-fluoro-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one
4-fluoro-2-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)benzonitrile
7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5 <i>H</i>)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2 <i>H</i>)-one

2,5,6-trimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(5-fluoro-2-(trifluoromethyl)phenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
1-((7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-((2-fluorophenyl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-((3-fluoro-2-methylpyridin-4-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
3-(6-(2,5,6-trimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)isonicotinonitrile
2,5,6-trimethyl-7-(3-(4-(trifluoromethyl)pyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-(6-methoxy-4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2,5,6-trimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
1-((7-(3-(1,3-dimethyl-1H-pyrazol-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(1-cyclopropylvinyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
5-(difluoromethyl)-2,6-dimethyl-7-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
5-cyclopropyl-7-(3-(3,5-difluoro-4-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

1-((5,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((5,6-dimethyl-3-oxo-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(5-methoxy-2-methylphenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((5,6-dimethyl-3-oxo-7-(3-(prop-1-en-2-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
2,5,6-trimethyl-7-[3-(oxetan-3-yl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3-one
2,5,6-trimethyl-7-[3-(oxetan-3-yl)-7,8-dihydro-5H-1,6-naphthyridin-6-yl]-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3-one
1-((7-(3-(2,5-dihydrofuran-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((5,6-dimethyl-7-(3-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(2,6-difluorophenyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
1-((7-(3-(2-fluoropyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
3-(6-(2-((1-cyanocyclopropyl)methyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)isonicotinonitrile
1-((7-(3-(isoquinolin-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile

1-((7-(3-(isoquinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
7-(3-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2-(cyclopropylmethyl)-5,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(quinolin-5-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(6-(2-(cyclopropylmethyl)-5,6-dimethyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-7-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-4-fluorobenzonitrile
2-(cyclopropylmethyl)-5,6-dimethyl-7-(3-(4-methylpyridin-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
2-(cyclopropylmethyl)-7-(3-(3,5-dimethylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one
1-((7-(3-cyclobutyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-5,6-dimethyl-3-oxo-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-2(3H)-yl)methyl)cyclopropane-1-carbonitrile
7-(3-cyclopentyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)-2,5,6-trimethyl-[1,2,4]triazolo[4,3- <i>a</i>]pyrimidin-3(2H)-one

or a pharmaceutically acceptable salt thereof.

33. A pharmaceutical composition comprising the compound of any of claims 1-32, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

34. A compound of any of claims 1-32, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 33, for use in the treatment of a neurological and/or psychiatric disorder, wherein the disorder is selected from Alzheimer's disease, schizophrenia, a sleep disorder, a pain disorder, and a cognitive disorder.