

METHODS OF TREATING MIGRAINE WITH MNK INHIBITORS

BACKGROUND

Technical Field

The present disclosure describes compounds and methods useful as mitogen
5 activated protein kinase-interacting kinase ("MNK") inhibitors, useful for the treatment
of migraines and related conditions.

Description of the Related Art

Migraines are experienced by approximately 35 million people in the U.S. alone
every year. 45% of women and 18% of men will experience migraines at some point in
10 their lives. Not only are migraines painful, they can seriously disrupt the ability of
migraine sufferers to perform even the most basic functions of life. Worse still,
migraines are most typical in people ages 35-45, which are often prime wage-earning
and child-raising years, allowing migraines to often affect much more than just
individual well-being.

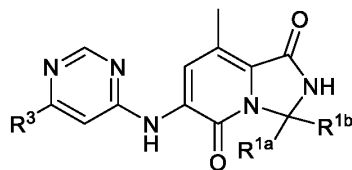
15 The causes of migraines are still not well-understood and, although treatments
have certainly improved in recent years, many common therapies have serious side-
effects or simply don't work for many migraine sufferers.

Accordingly, there is a need to develop compounds that are effective for treating
migraine. Embodiments of the present disclosure fulfill this need and provide further
20 related advantages.

BRIEF SUMMARY

In brief, embodiments of the present disclosure provide compounds useful for
the treatment of migraines, including pharmaceutically acceptable salts, stereoisomers,
tautomers, and prodrugs thereof.

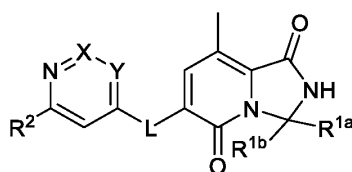
25 In one aspect, the compounds have the following Structure (I):



(I)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
 stereoisomer, tautomer, or prodrug thereof, wherein each of R^{1a}, R^{1b}, and R³ are as
 5 defined herein.

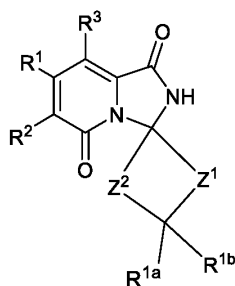
In another aspect, the compounds have the following Structure (II):



(II)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
 10 stereoisomer, tautomer, or prodrug thereof, wherein, R^{1a}, R^{1b}, R², X, Y, and L are as
 defined herein.

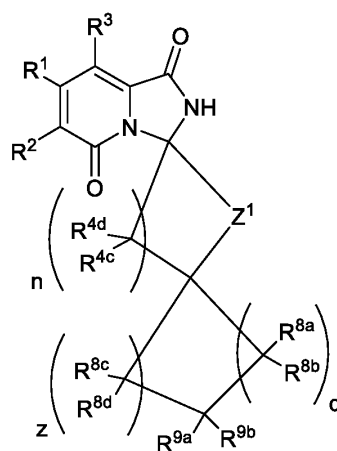
In still another aspect, the compounds have the following Structure (III):



(III)

15 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
 stereoisomer, tautomer, or prodrug thereof, wherein, R^{1a}, R^{1b}, R¹, R², R³, Z¹, and Z² are
 as defined herein.

In still another aspect, the compounds have the following Structure (IX):



(IX)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^2 , R^3 , R^{4c} , R^{4d} , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , Z^1 , n , z , and q are as defined herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the analytical scale chromatogram for the first eluting peak (*i.e.*, "Enantiomer 1 of 4ET-01-027") from the separation of racemic mixture of 4ET-01-027 ("*rac*-4ET-01-027").

FIG. 2 shows the analytical scale chromatogram for the second eluting peak (*i.e.*, "Enantiomer 2 of 4ET-01-027") from the separation of racemic mixture of 4ET-01-027 ("*rac*-4ET-01-027").

FIGs. 3A and 3B show genetic inhibition of MNK partially attenuates facial hypersensitivity and hyperalgesic priming caused by dural interleukin 6 ("IL-6").

FIGs. 4A and 4B illustrate MNK1 knock out ("KO") mice do not prime to low-dose NO donor following repeated stress.

FIGs. 5A and 5B depict how eFT508 reduces dural IL-6-induced facial hypersensitivity and prevents priming to pH 7.0.

FIG. 6 shows *rac*-4ET-01-027, Enantiomer 1 of 4ET-01-027, and 4ET-04-023 reduce dural IL-6-induced facial grimacing.

DETAILED DESCRIPTION

The compounds of the present disclosure are capable of treating and preventing migraines and symptoms associated migraines. It has been discovered that MNK plays a key role in migraines and symptoms associated with migraines. As a result, these
5 MNK inhibitors are useful for treating migraines and symptoms associated with migraines.

Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that
10 compositions of the present teachings also consist essentially of, or consist of, the recited components, and that the processes of the present teachings also consist essentially of, or consist of, the recited processing steps.

In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood
15 that the element or component can be any one of the recited elements or components and can be selected from a group consisting of two or more of the recited elements or components.

The present disclosure is directed to MNK inhibitors and the treatment of migraines and symptoms associated with migraines.

20 In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the disclosure. However, one skilled in the art will understand that the disclosure may be practiced without these details.

Unless the context requires otherwise, throughout the present specification and
25 claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to".

In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the
30 recited range and, when appropriate, fractions thereof (such as one tenth and one

hundredth of an integer), unless otherwise indicated. As used herein, the terms "about" and "approximately" mean $\pm 20\%$, $\pm 10\%$, $\pm 5\%$ or $\pm 1\%$ of the indicated range, value, or structure, unless otherwise indicated. The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives.

5 Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present disclosure. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all
10 referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. As used in the specification and claims, the singular form "a", "an"
15 and "the" include plural references unless the context clearly dictates otherwise.

 As used herein the term "MNK" shall mean mitogen-activated protein (MAP) kinases (MAPK) interacting kinases.

 "Amino" refers to the $-\text{NH}_2$ radical.

 "Carboxy" or "carboxyl" refers to the $-\text{CO}_2\text{H}$ radical.

20 "Cyano" refers to the $-\text{CN}$ radical.

 "Hydroxy" or "hydroxyl" refers to the $-\text{OH}$ radical.

 "Nitro" refers to the $-\text{NO}_2$ radical.

 "Oxo" refers to the $=\text{O}$ substituent.

 "Thiol" refers to the $-\text{SH}$ substituent.

25 "Thioxo" refers to the $=\text{S}$ substituent.

 "Alkyl" refers to a saturated, straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms ($\text{C}_1\text{-C}_{12}$ alkyl), one to eight carbon atoms ($\text{C}_1\text{-C}_8$ alkyl) or one to six carbon atoms ($\text{C}_1\text{-C}_6$ alkyl), or any value within these ranges, such as $\text{C}_4\text{-C}_6$ alkyl and the like,
30 and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl,

n-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl and the like. The number of carbons referred to relates to the carbon backbone and carbon branching, but does not include carbon atoms belonging to any substituents. Unless stated otherwise specifically in the specification,
5 an alkyl group is optionally substituted.

"Alkenyl" refers to an unsaturated, straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which contains one or more carbon-carbon double bonds, having from two to twelve carbon atoms (C₂-C₁₂ alkenyl), two to eight carbon atoms (C₂-C₈ alkenyl) or two to six carbon atoms (C₂-C₆ alkenyl),
10 or any value within these ranges, and which is attached to the rest of the molecule by a single bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. The number of carbons referred to relates to the carbon backbone and carbon branching, but does not include carbon atoms belonging to any substituents. Unless stated otherwise specifically in the specification, an alkenyl group is optionally
15 substituted.

The term "alkynyl" refers to unsaturated straight or branched hydrocarbon radical, having 2 to 12 carbon atoms (C₂-C₁₂ alkynyl), two to nine carbon atoms (C₂-C₉ alkynyl), or two to six carbon atoms (C₂-C₆ alkynyl), or any value within these ranges, and having at least one carbon-carbon triple bond. Examples of alkynyl groups may be
20 selected from the group consisting of ethynyl, propargyl, but-1-ynyl, but-2-ynyl and the like. The number of carbons referred to relates to the carbon backbone and carbon branching, but does not include carbon atoms belonging to any substituents. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted.

25 "Alkoxy" refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined above containing one to twelve carbon atoms (C₁-C₁₂ alkoxy), one to eight carbon atoms (C₁-C₈ alkoxy) or one to six carbon atoms (C₁-C₆ alkoxy), or any value within these ranges. Unless stated otherwise specifically in the specification, an alkoxy group is optionally substituted.

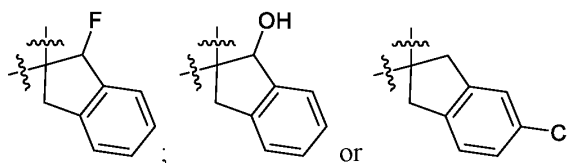
"Aminyl" refers to a radical of the formula $-NR_aR_b$, where R_a is H or C₁-C₆ alkyl and R_b is C₁-C₆ alkyl as defined above. The C₁-C₆ alkyl portion of an aminyl group is optionally substituted unless stated otherwise.

"Aminylalkylcycloalkyl" refers to a radical of the formula $-R_aR_bNR_cR_d$ where
5 R_a is cycloalkyl as defined herein, R_b is C₁-C₆ alkyl, R_c is H or C₁-C₆ alkyl and R_d is C₁-C₆ alkyl as defined above. The cycloalkyl and each C₁-C₆ alkyl portion of an aminylalkylcycloalkyl group are optionally substituted unless stated otherwise.

"Aromatic ring" refers to a cyclic planar molecule or portion of a molecule (*i.e.*, a radical) with a ring of resonance bonds that exhibits increased stability relative to
10 other connective arrangements with the same sets of atoms. Generally, aromatic rings contain a set of covalently bound co-planar atoms and comprises a number of π -electrons (for example, alternating double and single bonds) that is even but not a multiple of 4 (*i.e.*, $4n + 2$ π -electrons, where $n = 0, 1, 2, 3$, etc.). Aromatic rings include, but are not limited to, phenyl, naphthenyl, imidazolyl, pyrrolyl, pyridinyl, pyrimidinyl,
15 pyrazinyl, pyridonyl, pyridazinyl, and pyrimidonyl. Unless stated otherwise specifically in the specification, an "aromatic ring" includes all radicals that are optionally substituted.

"Aryl" refers to a carbocyclic ring system radical comprising 6 to 18 carbon atoms, for example 6 to 10 carbon atoms (C₆-C₁₀ aryl) and at least one carbocyclic
20 aromatic ring. For purposes of embodiments of this disclosure, the aryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene,
25 phenalene, phenanthrene, pleiadene, pyrene, and triphenylene.

"Aryl" as used herein, includes a fused ring system that includes non-aromatic moieties. For example, in some embodiments, aryl may have one of the following structures:



Unless stated otherwise specifically in the specification, an aryl group is optionally substituted.

The term "arylalkyl" or "aralkyl" refers to the group –alkyl-aryl, where the alkyl and aryl groups are as defined herein. Aralkyl groups of the present disclosure are optionally substituted. Examples of arylalkyl groups include, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, fluorenylmethyl and the like.

"Cyanoalkyl" refers to an alkyl group comprising at least one cyano substituent. The –CN substituent may be on a primary, secondary or tertiary carbon. Unless stated otherwise specifically in the specification, a cyanoalkyl group is optionally substituted.

"Carbocyclic" or "carbocycle" refers to a ring system, wherein each of the ring atoms are carbon.

"Cycloalkyl" refers to a non-aromatic monocyclic or polycyclic carbocyclic radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen ring carbon atoms (C_3 - C_{15} cycloalkyl), from three to ten ring carbon atoms (C_3 - C_{10} cycloalkyl), or from three to eight ring carbon atoms (C_3 - C_8 cycloalkyl), or any value within these ranges such as three to four carbon atoms (C_3 - C_4 cycloalkyl), and which is saturated or partially unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group is optionally substituted.

"Alkylcycloalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is a cycloalkyl group and R_b is an alkyl group as defined above. Unless otherwise stated specifically in the specification, an alkylcycloalkyl group is optionally substituted.

"Fused" refers to any ring structure described herein which is fused to another ring structure.

"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by
5 one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group is optionally substituted.

"Halocycloalkyl" refers to a cycloalkyl radical, as defined above, that is
10 substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a halocycloalkyl group is optionally substituted.

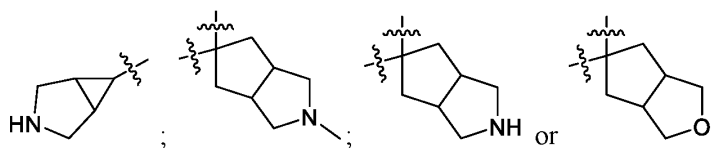
"Haloalkylcycloalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is
15 a cycloalkyl group and R_b is a haloalkyl group as defined above. Unless otherwise stated specifically in the specification, a haloalkylcycloalkyl group is optionally substituted.

"Halocycloalkylalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is
an alkyl group and R_b is a halocycloalkyl group as defined above. Unless otherwise
20 stated specifically in the specification, a halocycloalkylalkyl group is optionally substituted.

"Heterocyclylcycloalkyl" refers to a radical group of the formula $-R_aR_b$ where
 R_a is a cycloalkyl group and R_b is a heterocyclyl group as defined herein. Unless
otherwise stated specifically in the specification, a heterocyclylcycloalkyl group is
25 optionally substituted.

"Hydroxylalkyl" refers to an alkyl radical, as defined above that is substituted by
one or more hydroxyl radical. The hydroxyalkyl radical is joined at the main chain
through the alkyl carbon atom. Unless stated otherwise specifically in the specification,
a hydroxylalkyl group is optionally substituted.

"Heterocyclyl," "heterocyclic," or "heterocycle" refer to a 3- to 18-membered, for example 3- to 10-membered or 3- to 8-membered, non-aromatic ring radical having one to ten ring carbon atoms (*e.g.*, two to ten) and from one to six ring heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated
 5 otherwise specifically in the specification, the heterocyclyl radical is partially or fully saturated and is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused, spirocyclic, and/or bridged ring systems. Nitrogen, carbon, and sulfur atoms in a heterocyclyl radical are optionally oxidized, and nitrogen atoms may be optionally quaternized. Non-limiting examples of heterocyclic units having a single ring
 10 include: diazirinyl, aziridinyl, urazolyl, azetidiny, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolidinyl, isothiazolyl, isothiazolinyl, oxathiazolidinonyl, oxazolidinonyl, hydantoinyl, tetrahydrofuranyl, pyrrolidinyl, morpholinyl, piperazinyl, piperidinyl, dihydropyranyl, tetrahydropyranyl, piperidin-2-onyl (valerolactam), 2,3,4,5-tetrahydro-1*H*-azepinyl, 2,3-dihydro-1*H*-indole, and
 15 1,2,3,4-tetrahydro-quinoline. Non-limiting examples of heterocyclic units having 2 or more rings include: hexahydro-1*H*-pyrroliziny, 3a,4,5,6,7,7a-hexahydro-1*H*-benzo[d]imidazolyl, 3a,4,5,6,7,7a-hexahydro-1*H*-indolyl, 1,2,3,4-tetrahydroquinolinyl, chromanyl, isochromanyl, indolinyl, isoindolinyl, and decahydro-1*H*-cycloocta[b]pyrrolyl. "Heterocyclyl" as used herein, includes a fused ring system that
 20 comprises additional non-heterocyclyl components. For example, in some embodiments, heterocyclyl may have one of the following structures:



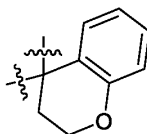
Unless stated otherwise specifically in the specification, a heterocyclyl group is optionally substituted.

25 "Haloheterocyclyl" refers to a heterocyclyl group comprising at least one halo substituent. The halo substituent may be on a primary, secondary or tertiary carbon. Unless stated otherwise specifically in the specification, a haloheterocyclyl group is optionally substituted

"Haloheterocyclalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is an alkyl group and R_b is a haloheterocycl group as defined herein. Unless otherwise stated specifically in the specification, a haloheterocyclalkyl group is optionally substituted.

5 "Heterocyclalkyl" refers to a radical group of the formula $-R_aR_b$ where R_a is an alkyl group and R_b is a heterocycl group as defined herein. Unless otherwise stated specifically in the specification, a heterocyclalkyl group is optionally substituted.

"Heteroaryl" refers to a 5- to 18-membered, for example 5- to 6-membered, ring system radical comprising one to thirteen ring carbon atoms, one to six ring
 10 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. Heteroaryl radicals may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited
 15 to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl,
 20 benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl,
 25 phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolyl, isoquinolyl, tetrahydroquinolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (*i.e.*, thienyl). "Heteroaryl" as used herein, includes a fused ring system where the heteroatom (*e.g.*, oxygen, sulfur, nitrogen, etc.) is not part of the aryl moiety.
 30 For example, in some embodiments, heteroaryl may have the following structure:



Unless stated otherwise specifically in the specification, a heteroaryl group is optionally substituted.

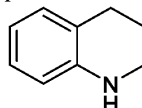
Non-limiting examples of heteroaryl rings containing a single ring include:

- 5 1,2,3,4-tetrazolyl, [1,2,3]triazolyl, [1,2,4]triazolyl, triazinyl, thiazolyl, 1*H*-imidazolyl, oxazolyl, furanyl, thiophenyl, pyrimidinyl, 2-phenylpyrimidinyl, pyridinyl, 3-methylpyridinyl, and 4-dimethylaminopyridinyl. Non-limiting examples of heteroaryl rings containing 2 or more fused rings include: benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, cinnolinyl, naphthyridinyl, phenanthridinyl,
- 10 7*H*-purinyl, 9*H*-purinyl, 6-amino-9*H*-purinyl, 5*H*-pyrrolo[3,2-*d*]pyrimidinyl, 7*H*-pyrrolo[2,3-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, 2-phenylbenzo[*d*]thiazolyl, 1*H*-indolyl, 4,5,6,7-tetrahydro-1-*H*-indolyl, quinoxalinyl, 5-methylquinoxalinyl, quinazolinyl, quinolinyl, 8-hydroxy-quinolinyl, and isoquinolinyl.

- One non-limiting example of a heteroaryl group as described above is C₁-C₅
- 15 heteroaryl, which has 1 to 5 carbon ring atoms and at least one additional ring atom that is a heteroatom (preferably 1 to 4 additional ring atoms that are heteroatoms) independently selected from nitrogen (N), oxygen (O), or sulfur (S). Examples of C₁-C₅ heteroaryl include, but are not limited to, triazinyl, thiazol-2-yl, thiazol-4-yl, imidazol-1-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, isoxazolin-5-yl, furan-2-yl, furan-3-yl,
- 20 thiophen-2-yl, thiophen-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl.

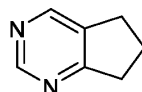
- Unless otherwise noted, when two substituents are taken together to form a ring having a specified number of ring atoms (*e.g.*, R² and R³ taken together with the nitrogen (N) to which they are attached to form a ring having from 3 to 7 ring
- 25 members), the ring can have carbon atoms and optionally one or more (*e.g.*, 1 to 3) additional heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). The ring can be saturated or partially saturated and can be optionally substituted.

For the purposes of the present disclosure fused ring units, as well as spirocyclic rings, bicyclic rings and the like, which comprise a single heteroatom will be considered to belong to the cyclic family corresponding to the heteroatom containing ring. For example, 1,2,3,4-tetrahydroquinoline having the formula:

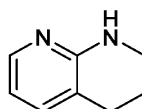


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is, for the purposes of the present disclosure, considered a heterocyclic unit. 6,7-Dihydro-5H-cyclopentapyrimidine having the formula:



is, for the purposes of the present disclosure, considered a heteroaryl unit. When a fused
10 ring unit contains heteroatoms in both a saturated and an aryl ring, the aryl ring will predominate and determine the type of category to which the ring is assigned. For example, 1,2,3,4-tetrahydro-[1,8]naphthyridine having the formula:



is, for the purposes of the present disclosure, considered a heteroaryl unit.

15 Whenever a term or either of their prefix roots appear in a name of a substituent the name is to be interpreted as including those limitations provided herein. For example, whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (*e.g.*, arylalkyl, alkylamino) the name is to be interpreted as including those limitations given above for "alkyl" and "aryl."

20 The term "substituted" is used throughout the specification. The term "substituted" is defined herein as a moiety, whether acyclic or cyclic, which has one or more hydrogen atoms replaced by a substituent or several (*e.g.*, 1 to 10) substituents as defined herein below. The substituents are capable of replacing one or two hydrogen atoms of a single moiety at a time. In addition, these substituents can replace two
25 hydrogen atoms on two adjacent carbons to form said substituent, new moiety or unit. For example, a substituted unit that requires a single hydrogen atom replacement

includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. The term "substituted" is used throughout the present specification to indicate that a moiety can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, difluoromethyl is a substituted C₁ alkyl; trifluoromethyl is a substituted C₁ alkyl; 4-hydroxyphenyl is a substituted aromatic ring; (N,N-dimethyl-5-amino)octanyl is a substituted C₈ alkyl; 3-guanidinopropyl is a substituted C₃ alkyl; and 2-carboxypyridinyl is a substituted heteroaryl.

The variable groups defined herein, *e.g.*, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryloxy, aryl, heterocycle and heteroaryl groups defined herein, whether used alone or as part of another group, can be optionally substituted. Optionally substituted groups are so indicated.

- In some embodiments, the substituents are selected from
- i) $-\text{OR}^{x+2}$; for example, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$;
 - ii) $-\text{C}(\text{O})\text{R}^{x+2}$; for example, $-\text{COCH}_3$, $-\text{COCH}_2\text{CH}_3$, $-\text{COCH}_2\text{CH}_2\text{CH}_3$;
 - iii) $-\text{C}(\text{O})\text{OR}^{x+2}$; for example, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_3$;
 - iv) $-\text{C}(\text{O})\text{N}(\text{R}^{x+2})_2$; for example, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CON}(\text{CH}_3)_2$;
 - v) $-\text{N}(\text{R}^{x+2})_2$; for example, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NH}(\text{CH}_2\text{CH}_3)$;
 - vi) halogen, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, and $-\text{I}$;
 - vii) $-\text{CH}_e\text{X}_g$; wherein X is halogen, m is from 0 to 2, $e+g=3$; for example, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CCl}_3$, or $-\text{CBr}_3$;
 - viii) $-\text{SO}_2\text{R}^{x+2}$; for example, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{C}_6\text{H}_5$;
 - ix) C₁-C₆ linear, branched, or cyclic alkyl;
 - x) Cyano
 - xi) Nitro;
 - xii) $\text{N}(\text{R}^{x+2})\text{C}(\text{O})\text{R}^{x+2}$;
 - xiii) Oxo ($=\text{O}$);
 - xiv) Heterocycle; and
 - xv) Heteroaryl.

wherein each R^{x+2} is independently hydrogen, optionally substituted C_1 - C_6 linear or branched alkyl (*e.g.*, optionally substituted C_1 - C_4 linear or branched alkyl), or optionally substituted C_3 - C_6 cycloalkyl (*e.g.* optionally substituted C_3 - C_4 cycloalkyl); or two R^{x+2} units can be taken together to form a ring comprising 3-7 ring atoms. In certain aspects,
5 each R^{x+2} is independently hydrogen, C_1 - C_6 linear or branched alkyl optionally substituted with halogen or C_3 - C_6 cycloalkyl or C_3 - C_6 cycloalkyl.

At various places in the present specification, substituents of compounds are disclosed in groups or in ranges. It is specifically intended that the description include each and every individual subcombination of the members of such groups and ranges.
10 For example, the term " C_{1-6} alkyl" is specifically intended to individually disclose C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_1 - C_6 , C_1 - C_5 , C_1 - C_4 , C_1 - C_3 , C_1 - C_2 , C_2 - C_6 , C_2 - C_5 , C_2 - C_4 , C_2 - C_3 , C_3 - C_6 , C_3 - C_5 , C_3 - C_4 , C_4 - C_6 , C_4 - C_5 , and C_5 - C_6 , alkyl.

"Patient" or "Subject" refers to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and
15 veterinary applications. In some embodiments, the subject is a mammal, and in some embodiments, the subject is human. Other subjects include mammals that do not tolerate opioids well or that are common pets or domesticated animals, such as dogs, cats, and horses.

"Mammal" includes humans and both domestic animals such as laboratory
20 animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

"Pharmaceutically acceptable" refers to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human.

25 "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

30 "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness of the free bases, which are biologically tolerable, or

otherwise biologically suitable for administration to the subject. See, generally, S.M. Berge, *et al.*, "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002. Preferred pharmaceutically acceptable acid addition salts are those that are pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response.

Pharmaceutically acceptable acid addition salts which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness of the free acids, which are biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, S.M. Berge, *et al.*, "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002. Preferred pharmaceutically acceptable base addition salts are those that are pharmacologically effective and suitable for contact with the

tissues of patients without undue toxicity, irritation, or allergic response.

Pharmaceutically acceptable base addition salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

"Drug" refers to a compound which is biologically active and provides a desired physiological effect following administration of a patient in need.

"Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein (*e.g.*, compounds of Structure (I) through (XLIX)). Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some aspects, a prodrug is inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., *et al.*, "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical

Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, are
5 typically prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or thiol group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or
10 free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of a hydroxy functional group, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like.

Additionally, embodiments of the present disclosure may provide prodrug of an
15 MNK inhibitor. A prodrug is a compound that can be transformed to an active drug. In general, a prodrug is given to a patient and is then converted into a physiologically active form of the compound *in vivo*. In some instance, a prodrug may have a desired physiological effect. The prodrug of the present disclosure may include functional groups including esters, amides, phosphate ester, sulfonamide, or its combination
20 thereof.

"Derivative" refers a compound that can be synthesized from a parent compound by replacement of one atom with another atom or group of atoms.

"Migraine" refers to a headache or aura that results from abnormal brain activity, but is not caused by a tumor, other serious medical problem, or a viral or
25 bacterial infection of the sinus or nasal passageways. There are currently no blood test or scans that can diagnose migraine. As a result, a diagnosis is made by a qualified physician, often after ruling out other causes of headache and taking into account symptoms of migraine and family history of migraine. Migraine symptoms often include: moderate to severe pain; intense pain; inability to conduct activities of daily
30 life while experiencing the headache; aura; throbbing, pounding, or pulsating sensations

in the head; worsening of pain with physical activity; worsening of pain with any movement; nausea and/or vomiting; sensitivity to noise, light, or smells; and duration for more than four hours.

Migraine is often thought of as having four phases, prodrome, aura, headache, and postdrome.

Prodrome is often characterized by extreme tiredness and yawning, irritability or moodiness, difficulty concentrating, and food cravings.

Aura is most typically visual. Visual aura includes flashes of light, blind spots, bright spots, wavy, zig-zag, or C-shaped lines, bright geometrical lines and/or shapes in the visual field, blurred vision, or visual hallucinations. Sensory aura, such as tingling or numbness in a limb or the face or tongue and dysphasic aura are also sometimes observed. Migraines may also be diagnosed, at least in part, by their occurrence in response to triggers, such as caffeine withdrawal, hormonal changes, lack of sleep, alcohol, exercise or physical stress, loud noises, bright lights, missed meals, odors, perfumes, smoking or exposure to smoke, stress, anxiety, and/or eating common trigger foods, such as chocolate, dairy, especially cheeses, MSG, foods with tyramine, especially red wine, aged cheese, smoked fish, chicken liver, figs, and beans, fruits, especially avocado, banana, or citrus, meats containing nitrates, such as bacon, hot dogs, salami, and cured meats, onions, peanuts and other nuts and seeds, fermented foods, and pickled foods.

Postdrome is often characterized by fatigue, body aches, trouble concentrating, dizziness and sensitivity to light.

Not all patients experience prodrome and/or postdrome. In addition, not all patients experience aura, or some experience it along with headache. Some patients experience aura alone, or with prodrome and/or postdrome, but without headache. Any patient experiencing aura and/or headache is typically considered to suffer from migraines.

The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound described herein that is sufficient to effect the intended application including but not limited to disease treatment, as defined below. The

therapeutically effective amount may vary depending upon the intended treatment application (*in vivo*), or the subject and disease condition being treated, *e.g.*, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, *e.g.*, reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

As used herein, "treatment" or "treating" refer to an approach for obtaining beneficial or desired results with respect to a disease, disorder or medical condition including but not limited to a therapeutic effect and/or a prophylactic effect. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof. In certain embodiments, for prophylactic benefit, the compositions are administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass administration of two or more agents to an animal, including humans, so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous

administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

In some embodiments, pharmaceutically acceptable salts include quaternary ammonium salts such as quaternary amine alkyl halide salts (*e.g.*, methyl bromide).

5 The term "*in vivo*" refers to an event that takes place in a subject's body.

Embodiments disclosed herein are also meant to encompass all pharmaceutically acceptable compounds of Structure (I) through (XLIX).

Certain embodiments are also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the
10 oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, embodiments include compounds produced by a process comprising administering a compound of this disclosure to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a
15 radiolabeled compound of the disclosure in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

"Stable compound" and "stable structure" are meant to indicate a compound that
20 is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

Often crystallizations produce a solvate of the compounds disclosed herein. As used herein, the term "solvate" refers to an aggregate that comprises one or more compounds of the disclosure with one or more molecules of solvent. In some
25 embodiments, the solvent is water, in which case the solvate is a hydrate. Alternatively, in other embodiments, the solvent is an organic solvent. Thus, the compounds of the present disclosure may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. In some aspects, the compounds of the disclosure are a

true solvate, while in other cases, the compounds of the disclosure merely retain adventitious water or is a mixture of water plus some adventitious solvent.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where
5 said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

A "pharmaceutical composition" refers to formulations of compounds of the
10 disclosure and a medium generally accepted in the art for the delivery of compounds of the disclosure to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not
15 interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are non-superimposable mirror images of one another.

The compounds of the disclosure (*i.e.*, compounds of Structure (I) through (XLIX)) or their pharmaceutically acceptable salts may contain one or more centers of
20 geometric asymmetry and may thus give rise to stereoisomers such as enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. Embodiments thus include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared
25 using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).
30 When the compounds described herein contain olefinic double bonds or other centers of

geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

Embodiments of the present disclosure include all manner of rotamers and
5 conformationally restricted states of a compound of the disclosure. Atropisomers, which are stereoisomers arising because of hindered rotation about a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual conformers, are also included. As an example, certain compounds of the disclosure may exist as mixtures of atropisomers
10 or purified or enriched for the presence of one atropisomer.

In some embodiments, the compounds of Structure (I) through (XLIX) are a mixture of enantiomers or diastereomers. In other embodiments, the compounds of Structure (I) through (XLIX) are substantially one enantiomer or diastereomer.

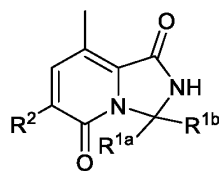
A "tautomer" refers to a proton shift from one atom of a molecule to another
15 atom of the same molecule. Embodiments thus include tautomers of the disclosed compounds.

The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program and/or ChemDraw Professional Version 17.0.0.206 software
20 naming program (CambridgeSoft). For complex chemical names employed herein, a substituent group is typically named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with a cyclopropyl substituent. Except as described below, all bonds are identified in the chemical structure diagrams herein, except for all bonds on some carbon atoms, which are assumed to be bonded to
25 sufficient hydrogen atoms to complete the valency.

Compounds

The present disclosure is directed to MNK inhibitors that are used for treating, preventing, or mitigating the effects of migraines and related symptoms.

In some embodiments, the MNK inhibitor may have the following Structure (Ia):

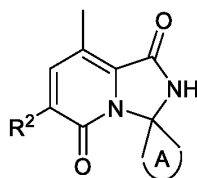


(Ia)

5 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:

R^{1a} and R^{1b} are each independently alkyl. In some embodiments, R^{1a} and R^{1b} are the same. In certain embodiments, R^{1a} and R^{1b} are different. R^{1a} or R^{1b} may be alkyl groups, such as a methyl, ethyl, propyl, isopropyl, or *tert*-butyl group. The R^{1a} or R^{1b} 10 substituent groups may be the same alkyl group, or different alkyl groups. For example, R^{1a} may be a methyl group, while R^{1b} may be an ethyl group. By way of another example, R^{1a} may be an isopropyl group, while R^{1b} may be a *tert*-butyl group. Any alkyl group combinations of substituents R^{1a} or R^{1b} may be used.

In some embodiments, R^{1a} and R^{1b} joint to form a cyclic moiety. In certain 15 embodiments, the compound has the following Structure (Ib):



(Ib)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:

20 R^{1a} and R^{1b} may join together to form ring A.

The Structure (Ib), substituents R^{1a} or R^{1b} may together form a cyclic compound indicated as cyclic moiety A. For example, the cyclic moiety A of the Structure (Ib) may include a five-membered ring. The cyclic moiety A of the Structure (Ib) may be a non-substituted cyclic compound. For instance, the cyclic moiety A may be a non-

substituted five-membered ring such as a cyclopentane. Further, the cyclic moiety A of the Structure (Ib) may have one or more alkyl substitutions. For example, the alkyl substitutions on the cyclic moiety A may include methyl, ethyl, propyl, isopropyl, cyclopropyl, or *tert*-butyl group. Substituted positions may be 2-, 3-, 4-, or 5- position of the cyclopentane. The degree of the substitutions may include mono-, di-, tri-, or tetra-substitutions. For instance, the cyclic moiety A may be 2,2,5,5-tetramethylcyclopentane. Synthetic routes may be used to install different substitution patterns on the cyclopentane ring. For example, the cyclic moiety A may be 3,3,4,4-tetramethylcyclopentane.

10 Additionally, the cyclic moiety A may have a fused ring. A part of the cyclic moiety A may include a fused benzene ring. For example, the cyclic moiety A may include the fused benzene ring with a cyclopentyl or cyclohexyl ring. For instance, the synthetic route to prepare the benzene fused cyclohexyl compound may involve the use of 1-tetralone. Further, the cyclic moiety A may include a fused cyclopentyl or
15 cyclohexyl ring with other cyclic structures.

 The cyclic moiety A may include a six-membered ring. The cyclic moiety A may be non-substituted cyclic moiety. For example, the cyclic moiety A may be a non-substituted six-membered ring such as a cyclohexane. Further, the cyclic moiety A may have one or more alkyl substitutions. For example, the alkyl substitutions on the cyclic
20 moiety A may include methyl, ethyl, propyl, isopropyl, cyclopropyl, or *tert*-butyl group. The cyclic moiety A may have one or more heteroatom-containing substituents, such as alcohols, sulfonamides, or carboxylic acids. Substituted positions may be 2-, 3-, 4-, 5-, or 6- position of the cyclohexane. The degree of the substitutions may include mono-, di-, tri-, or tetra-substitutions. For instance, the cyclic moiety A may be 3,5-
25 dimethylcyclohexane. Synthetic routes may be used to install different substitution patterns on the cyclohexane ring. For example, the cyclic moiety A may be 2,3,4,5,6-pentamethylcyclohexane.

 The cyclic moiety A may include a heterocyclic compound. The heterocyclic compound is a cyclic compound that has atoms of at least two different elements such
30 as a carbon and an oxygen atom. For example, the cyclic moiety A may be

tetrahydropyran. The tetrahydropyran includes one oxygen atom and five carbon atoms in a six-membered ring. The heterocyclic compound may further be substituted with alkyl substituents or functional groups on various positions with various degrees of substitutions. It is noted that, while some of the structures shown in the present
5 disclosure include an oxygen atom in a cyclic compound, such a structure is merely provided for illustrative purposes. Synthetic routes may be used to install different heteroatoms in the cyclic compounds. For example, the cyclic moiety A of the structure (Ib) may include piperidine (a nitrogen atom), phosphinate (a phosphorus atom), silinane (a silicon atom), or thiane (a sulfur atom).

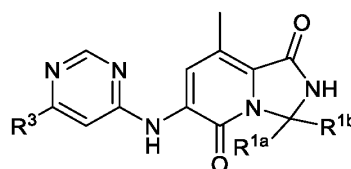
10 The cyclic moiety A may be unsaturated. Unsaturated cyclic compounds may include aromatic cyclic compounds such as a benzene, pyridine, diazine, oxazine, dioxine, or thiazine. Alternatively, the cyclic moiety A may be saturated.

The cyclic moiety A may have one or more functional group substitutions. For example, the functional groups may include a hydroxyl, amine, amide, carboxylic acid,
15 ether, or sulfonamide. Thus, the cyclic moiety A may include 4-hydroxyl cyclohexane, 4-carboxylic acid cyclohexane, 4-methoxyl cyclohexane, or 4-alkylsulfonamide cyclohexane. Substituted positions may be 2-, 3-, 4-, 5-, or 6- position of the cyclohexane. The degree of the substitutions may include mono-, di-, tri-, tetra-, or penta-substitutions. One or more functional groups may be installed on a heterocyclic
20 compound with various substitution positions and degree.

The substituent R^2 of the structures (Ia) and (Ib) may include a nitrogen containing functional group. For example, the nitrogen containing functional group of the substituent R^2 may include amides, amidine, amines, amine oxides, azo, carbamates, carbodiimides, enamines, aromatic heterocycles, non-aromatic heterocycles,
25 hydrazones, hydroxamic acids, imides, imines, nitriles, sulfonamide, or urea. For example, the aromatic heterocycles may include pyrrole, imidazole, pyrazole, thiazole, pyridine, pyridazine, pyrimidine, pyrazine, or triazine. The nitrogen containing functional group of substituent R^2 may be unsubstituted or substituted. For instance, a pyridazine may be substituted with an amine group at 3 position as shown in 4ET-004-
30 006 hereinafter. In another instance, a pyridazine may be substituted with an amide

containing a cyclopropyl ring at 3 position as shown in 4ET-004-003 hereinafter. The degree and location of substitution on the nitrogen containing functional group may differ. The nitrogen containing functional group of the substituent R^2 may be attached via an alkyl chain represented by $-C_nH_{2n}-$ where n is between zero and five. In this regard, the nitrogen containing functional groups of the substituent R^2 and the backbone structures (Ia) and (Ib) are separated by n carbon atoms.

Substituent R^2 of the structures (Ia) and (Ib) may include an aromatic heterocycle. For instance, in some embodiments, substituent R^2 may include 4-aminopyrimidinyl moiety. In some specific embodiments, the compound is a compound of Structure (Ic):



(Ic)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:

R^3 may include an amine.

In some embodiments, the amine is a primary amine. In some embodiments, R^3 is $-NH_2$.

In some embodiments, R^3 may include a secondary amine. When the amine is a secondary amine, R^3 may further include a functional group at one end. For example, the functional group may include a hydroxyl, sulfonamide, carboxylic acid, ester, amine, amide, morpholine, piperazine, or thiomorpholine. The secondary amine and the functional group may be attached via an alkyl chain represented by $-C_nH_{2n}-$ where n is between one and five. Thus, the secondary amine of the substituent R^3 and the functional group may be separated by n carbon atoms. For example, the secondary amine attached to a hydroxyl group separated by carbons atoms forms an aminoalcohol ($HO-C_2H_4NH-$), which is shown as examples 4ET-02-001, 4ET-03-004, 4ET-03-007, and 4ET-03-011 hereinafter. By way of another example, the secondary amine attached

to a sulfonamide group separated by two carbon atoms forms amino sulfonamide ($\text{CH}_3\text{SO}_2\text{NHC}_2\text{H}_4\text{NH}-$), which is shown as examples 4ET-02-004, 4ET-03-012, 4ET-03-013, and 4ET-03-014 hereinafter.

The amine of substituent R^3 may include a tertiary amine. The tertiary amine of the substituent R^3 may be cyclic. The cyclic tertiary amine of the substituent R^3 may be a part of saturated five-membered ring or six-membered ring. For example, the cyclic tertiary amine of the substituent R^3 in a saturated five-membered ring may be pyrrolidine, imidazolidine, or pyrazolidine. The cyclic tertiary amine of the substituent R^3 in a saturated six-membered ring may be piperidine or piperazine.

The tertiary amine may further include a functional group at one end. For example, the functional group may include a hydroxyl, sulfonamide, carboxylic acid, ester, amide, amine, morpholine, piperazine, or thiomorpholine. The tertiary amine and the functional group may be attached via an alkyl chain represented by $-\text{C}_n\text{H}_{2n}-$ where n is between one and five. Thus, the tertiary amine of the substituent R^3 and the functional group may be separated by n carbon atoms.

The tertiary amine of the substituent R^3 may be cyclic. The cyclic tertiary amine of the substituent R^3 may be a part of unsaturated five-membered ring or six-membered ring. For example, the cyclic tertiary amine of the substituent R^3 in an unsaturated five-membered ring may be pyrazole, imidazole, or oxazole. The cyclic tertiary amine of the substituent R^3 in an unsaturated six-membered ring may be pyridine, diazine, triazine, or oxazine.

The amine of substituent R^3 may also include an amide group. The amide group of substituent R^3 may further include a functional group at one end. For example, the functional group may include a hydroxyl, sulfonamide, carboxylic acid, ester, amine, amide, morpholine, piperazine, or thiomorpholine.

The amide of the substituent R^3 and the functional group may be attached via an alkyl chain represented by $-\text{C}_n\text{H}_{2n}-$ where n is between zero and five. Thus, the amide of the substituent R^3 and the functional group may be separated by n carbon atoms. For example, the amide attached to morpholine group by one methylene forms morpholine amide, which is shown as examples 4ET-02-007, 4ET-03-027, and 4ET-03-028

hereinafter. The amide attached to morpholine group by two methylenes forms morpholine amide, which is shown as example 4ET-02-031 hereinafter. The amide of the substituent R^3 may also be directly attached to one of the functional groups.

The amide of the substituent R^3 may be directly attached to a cyclic structure.

5 For example, the amide of the substituent R^3 may be directly attached to cyclopropane. In this case, there is no carbon atom between the amide and cyclopropane. Structures with the amide group directly attached to cyclopropane as a part of the substituent R^3 include 4ET- 02-003, 4ET-02-009, 4ET-02-010, 4ET-02-011, 4ET-02-012, 4ET-02-016, 4ET-03-002, 4ET-03-009, 4ET-03-017, 4ET-03-019, 4ET-03-020, 4ET-03-023,
10 4ET-03-026, 4ET-03-034, and 4ET-04-003 hereinafter. Cyclopropanes may be unsubstituted or substituted with one or more functional groups. For instance, the substituted cyclopropanes may include fluorine, hydroxyl, hydroxylmethylene, alkyl, carboxylic acid, amine, aminomethylene, ester, ether, amide, sulfonamide, morpholine, piperazine, or thiomorpholine group attached to a cyclopropane ring. The substituted
15 position on the cyclopropane where the functional group is attached may be the 1-, 2-, or 3-position. The functional group attached to the cyclopropane may have an additional alkyl chain ($-C_nH_{2n}-$) between the functional group and the cyclopropane where n is between zero and 5. When n is equal to zero, there is no methylene between the functional group and the cyclopropane. Thus, the functional group may be directly
20 attached to the cyclopropane on the 1-, 2-, or 3-position. Similarly, when n is equal to one, there is one methylene between the functional group and the cyclopropane. In this case, the functional group is one carbon away from the cyclopropane, which gives an extra degree of freedom to the structure. Structures with the amide group directly attached to substituted cyclopropane as a part of the substituent R^3 include 4ET- 02-
25 009, 4ET-02-010, 4ET-02-011, 4ET-02-012, 4ET-02-016, 4ET-03-019, 4ET-03-020, 4ET-03-023, 4ET-03-026, and 4ET-03-034 hereinafter.

The amide of the substituent R^3 may be directly attached to cyclobutane. In this case, there is no carbon atom between the amide and cyclobutane. The cyclobutane may further have a functional group. For instance, the functional group may include
30 hydroxyl, alkyl, carboxylic acid, amine, ester, ether, amide, sulfonamide, morpholine,

piperazine, or thiomorpholine. The substituted position on the cyclobutane where the functional group is attached may be the 1-, 2-, 3-, or 4-position. The functional group may have an additional alkyl chain (C_nH_{2n}) between the functional group and the cyclobutane where n is between zero and 5.

5 The cyclic structure that is attached to the amide via an alkyl chain or directly may include at least one heteroatom to form a heterocyclic compound. The heterocyclic compound may include a three-membered ring with one heteroatom or a four-membered ring with one heteroatom. For example, the three-membered ring with one heteroatom may include aziridines or ethylene oxide. By way of another example, the
10 four-membered ring with one heteroatom may include azetidine or oxetane. Azetidine directly attached to the amide is shown for example in 4ET-02-017 hereinafter. As described above, functional groups may be attached to the heterocyclic compound. In the case of ethylene oxide (epoxide), Sharpless epoxidation may be used to generate chiral epoxides.

15 While the examples herein only have a monosubstitution on the cyclic structure, such a configuration is merely provided for illustrative purposes. Embodiments of the present disclosure include disubstituted cyclic structures as well. For example, a total of two amine groups may be attached to the cyclopropane; a first amine group may be attached to 1-position of cyclopropane, while a second amine group is attached to 2-
20 position of cyclopropane.

 The amide of the substituent R^3 may be a reverse amide. Instead of a nitrogen atom of the amide of the substituent R^3 being directly attached to the structure (Ic), a carbon atom of the amide of the substituent R^3 may be attached to the structure (Ic). The reverse amide attached to the structure (Ic) is shown for example in 4ET-03-024
25 hereinafter. Embodiments of the present disclosure described above including the amide in the substituent R^3 may also be replaced with a reverse amide. For instance, the amide group of examples such as 4ET-02-003, 4ET-02-009, 4ET-02-010, 4ET-02-011, 4ET-02-012, 4ET-02-016, 4ET-03-002, 4ET-03-009, 4ET-03-017, 4ET-03-019, 4ET-03-020, 4ET-03-023, 4ET-03-026, 4ET-03-034, 4ET-04-003, 4ET-02-007, 4ET-03-027,
30 4ET-03-028, and 4ET-02-031 may be replaced with a reverse amide.

The structure (Ic) may be equipped with an amide analog of the substituent R^3 . For example, a thioamide group may be used instead of the amide group shown in 4ET-02-013 hereinafter. Similar to the amide substituent, the thioamide group may be replaced with a reverse thioamide. In this regard, instead of a nitrogen atom of the thiamide of the substituent R^3 being directly attached to the structure (Ic), a carbon atom of the thioamide of the substituent R^3 may be attached to the structure (Ic).

Additionally, other amide analogs of the substituent R^3 may be used for the structure (Ic). For example, a urea group may be used instead of the amide group shown in 4ET-02-015 hereinafter. By way of another example, a thiourea group may be used instead of the amide group. An amide, a reverse amide, a thioamide, a reverse thioamide, a urea, and a thiourea as a part of the substituent R^3 are interchangeable in the structure (Ic).

In some MNK inhibitors of the present disclosure, the 4-aminopyrimidine moiety in structure (Ic) may be modified. The pyrimidine moiety and the parent structure as shown in the structure (Ia) or (Ib) are connected via the amine linker (-NH-) in the structure (Ic). The amine linker may be extended. For example, the amine linker may include additional alkyl chain ($-C_nH_{2n}-$) between the amine and pyrimidine moiety where n is between one and five. For instance, one extra carbon atom (n=1) may be added, such that the amine linker and pyrimidine are one carbon away from the parent structure, as shown in 4ET-04-004, which gives the structure (Ic) more structural flexibility via an extra degree of freedom. One carbon extension, which is an insertion of a methylene unit, between the amine and the pyrimidine moiety provides a benzylpyrimidine moiety. By way of another example, the amine linker may include additional alkyl chain ($-C_nH_{2n}-$) between the amine and the parent structure shown as the structure (Ia) or (Ib) where n is between one and five. For instance, one extra carbon atom (n=1) may be added, as shown in 4ET-04-015, such that the amine linker and the parent structure shown as the structure (Ia) or (Ib) are one carbon away from the parent structure. One carbon extension, which is an insertion of a methylene unit, between the amine and the structure (Ia) or (Ib) provides a methylaminopyrimidine moiety. In this regard, methylene units may be added both sides of the amine linker of the structure

(Ic). Amine linker extension with extra methylene units may be used in conjunction with any of the other variations of structures (Ia), (Ib), and (Ic) disclosed herein.

Additionally, the pyrimidine moiety in the structure (Ic) may be modified to substitute a different unsaturated six-membered ring with two nitrogen atoms isomer, such as 1,2-diazine (pyridazine) or 1,4-diazine (pyrazine). For example, 1,2-diazine (pyridazine) may be used instead of 1,3-diazine (pyrimidine) in the structure (Ic) shown in example 4ET-04-003 and 4ET-04-006 hereinafter. These modifications may be used in conjunction with any of the other variations of structures (Ia), (Ib), and (Ic) disclosed herein.

Pyrimidine in the structure (Ic) may be replaced with a five-membered heterocyclic compound. Pyrimidine is a six-membered heterocyclic compound with two nitrogen atoms. In general, five-membered heterocyclic compounds have different chemical and physical properties than the six-membered heterocyclic compounds. Some MNK inhibitors of the present disclosure may take advantage of such differences between five- and six-membered heterocyclic compounds. For example, the five-membered heterocyclic compound may include nitrogen and sulfur atoms. For instance, the five-membered heterocyclic compound with N and S may include thiazole as shown in example 4ET-04-001 hereinafter. By way of another example, the five-membered heterocyclic compound with S may include thiophene. The five-membered heterocyclic compound may include nitrogen and oxygen atoms. For instance, the five-membered heterocyclic compound with N and O may include oxazole or isoxazole. Yet in another example, the five-membered heterocyclic compound may include two nitrogen atoms. For instance, the five-membered heterocyclic compound with two nitrogen atoms may include imidazole or pyrazole. These modifications may be used on conjunction with any of the other variations of structures (Ia), (Ib), and (Ic) disclosed herein.

As examples of how various modifications disclosed herein may be used in combination with one another, the amine linker with additional carbon atom may be attached to a pyridazine moiety and the pyridazine moiety may be connected to the pyridone scaffold with an amine or sulfonamide. By way of another example, the amine

linker with additional carbon atom may be attached to a pyridazine moiety and the pyridazine moiety may be directly connected to an amino group.

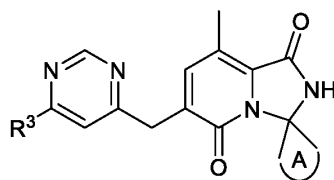
In some MNK inhibitors of the present disclosure, the 4-aminopyrimidine moiety and a parent structure, for example, a pyridone moiety in structure (Ic) may be attached via other nitrogen containing linkers. The pyrimidine moiety and the parent structure as shown in the structure (Ia) or (Ib) are connected via the amine linker (-NH-) in the structure (Ic). Embodiments of the present disclosure may be configured to install an amide group between the 4-aminopyrimidine moiety and the parent structure. This can be synthesized by using an amide containing starting material in Buchwald-Hartwig amination described in Example 1 – MNK inhibitor synthesis. For example, the resulting MNK inhibitor may include an amide as shown in example 4ET-04-013 or a reverse amide as shown in example 4ET-04-014 hereinbelow between the 4-aminopyrimidine moiety and the parent structure.

Further, embodiments of the present disclosure may be configured to install a sulfonamide group between the 4-aminopyrimidine moiety and the parent structure. This can be synthesized by using a sulfonamide containing starting material in Buchwald- Hartwig amination described in Example 1 – MNK inhibitor synthesis. Another approach involves the use of a sulfonyl chloride reagent or intermediate. For example, the resulting MNK inhibitor may include a sulfonamide as shown in examples 4ET-04-010 and 4ET- 04-011 or a reverse sulfonamide as shown in example 4ET-04-012 hereinbelow between the 4-aminopyrimidine moiety and the parent structure.

Additionally, embodiments of the present disclosure may be configured to install an ether group between the 4-aminopyrimidine moiety and the parent structure. This can be synthesized by using an alcohol containing starting material in Buchwald-Hartwig amination described in Example 1 – MNK inhibitor synthesis. Another approach involves using an alcohol containing starting material in an Ullmann-type coupling reaction.

The substituents R^{1a} or R^{1b} of the structure (Ic) may be alkyl groups, as discussed hereinabove in the structure (Ia). Alternatively, the substituents R^{1a} or R^{1b} of the structure (Ic) may together form a cyclic compound indicated as a ring structure A

below. The detailed discussion of the ring structure A of the structure (Ib) may also apply to the structure (Id):

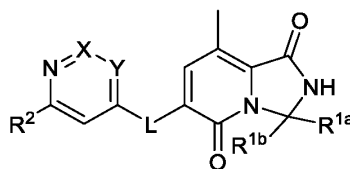


(Id)

- 5 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:

R^3 may include an amine.

One embodiment provides a compound having the following Structure (II):



(II)

10

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein

R^{1a} is C_1 - C_6 alkyl or aryl;

R^{1b} is C_1 - C_6 alkyl or aryl,

- 15 or R^{1a} and R^{1b} , together with the carbon to which they are both attached, join to form cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl;

R^2 is $-NHR^{3a}$, $-NHC(=O)R^{3b}$, $-NHC(=S)R^{3b}$, or $-C(=O)R^{3c}$;

R^{3a} is hydrogen, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl, each of which is optionally substituted with one or more substituents selected from the group consisting of

- 20 hydroxyl, C_3 - C_6 cycloalkyl, $-NHS(O)_2CH_3$, heterocyclyl, $-C(=O)OH$, $-C(=O)N(R^{3d})R^{3d}$, or $-N(R^{3d})R^{3d}$;

R^{3b} is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or heterocyclyl each of which is optionally substituted with one or more substituents selected from the group consisting of

hydroxyl, halo, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -NHS(O)₂CH₃, -N(R^{3d})R^{3d},
heterocyclyl, -C(=O)OH, -C(=O)N(R^{3d})R^{3d}, -NHC(=O)CH₃, -CH₂C(=O)OH,

R^{3c} is -N(R^{3d})R^{3d} or heterocyclyl;

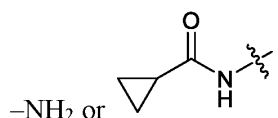
R^{3d} is, at each occurrence, independently hydrogen, C₁-C₆ alkyl, or C₃-C₆
5 cycloalkyl;

L is -NH- or -CH₂NH-; and

X is N and Y is CH or X is CH and Y is N,

provided that:

when R^{1a} and R^{1b} are both -CH₃ or when R^{1a} and R^{1b} join to form a 5- or 6-
10 membered cycloalkyl or heterocyclyl, then R² does not have the following structure:

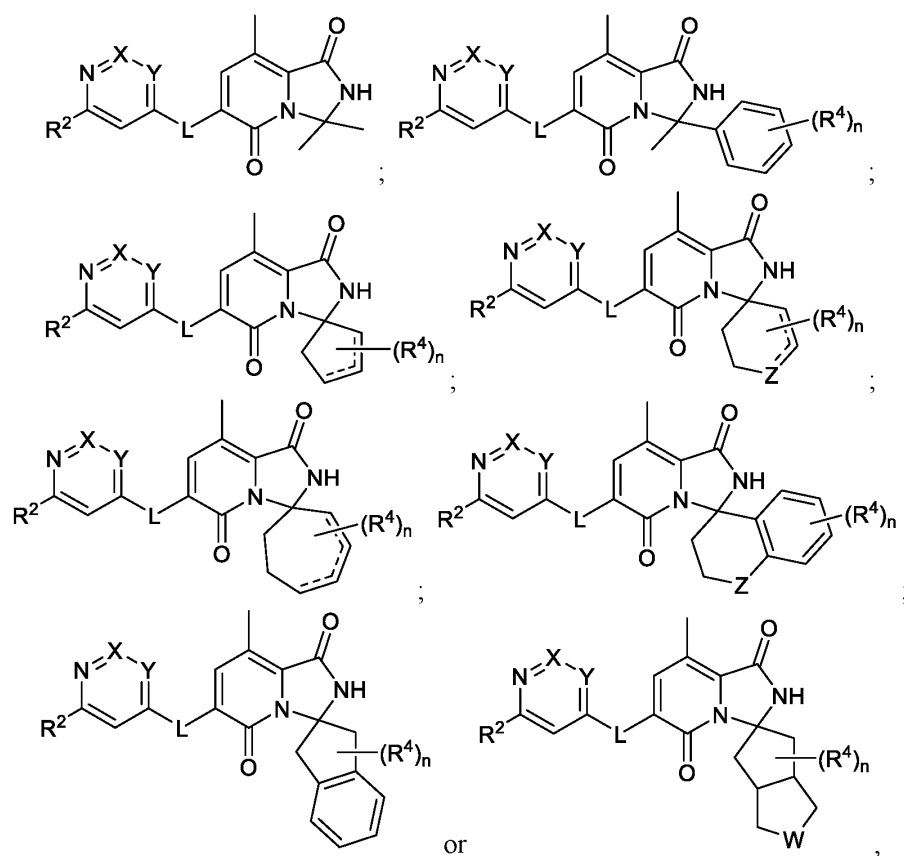


In some embodiments, R^{1a} is C₁-C₆ alkyl. In some embodiments, R^{1a} is methyl.

In certain embodiments, R^{1a} is aryl. In certain embodiments, R^{1a} is phenyl.

In certain specific embodiments, R^{1b} is C₁-C₆ alkyl. In some embodiments, R^{1b}
15 is methyl. In some embodiments, R^{1a} and R^{1b}, together with the carbon to which they
are both attached, join to form cycloalkyl. In more specific embodiments, the cycloalkyl
is cyclopentyl or cyclohexyl. In some embodiments, R^{1a} and R^{1b}, together with the
carbon to which they are both attached, join to form cycloalkenyl. In some
embodiments, the cycloalkenyl is cyclopentenyl, cyclohexenyl, or cycloheptenyl. In
20 certain specific embodiments, R^{1a} and R^{1b}, together with the carbon to which they are
both attached, join to form heterocyclyl. In some specific embodiments, R^{1a} and R^{1b},
together with the carbon to which they are both attached, join to form aryl. In some
embodiments, R^{1a} and R^{1b}, together with the carbon to which they are both attached,
join to form heteroaryl.

25 In more specific embodiments, the compound has one of the following
structures:



- 5 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein

==== indicates a double or single bond;

R^4 is, at each occurrence, independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo, haloalkyl, hydroxyl, $-NHS(O)_2CH_3$, or $-C(O)OH$,

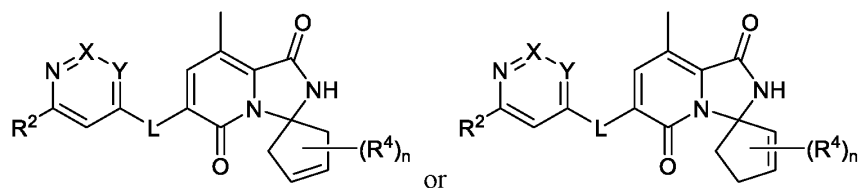
- 10 or two R^4 , together with the carbon to which they are both attached, join to form a cycloalkyl;

W is N or O;

Z is C or O; and

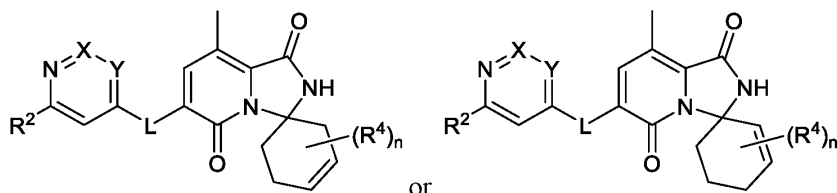
n is 0, 1, 2, 3, or 4.

- 15 In some embodiments, n is 0, 1, or 2. In some more specific embodiments, only one location depicted with ==== is a double bond and the rest are single bonds. In some embodiments, the compound has the following structure:



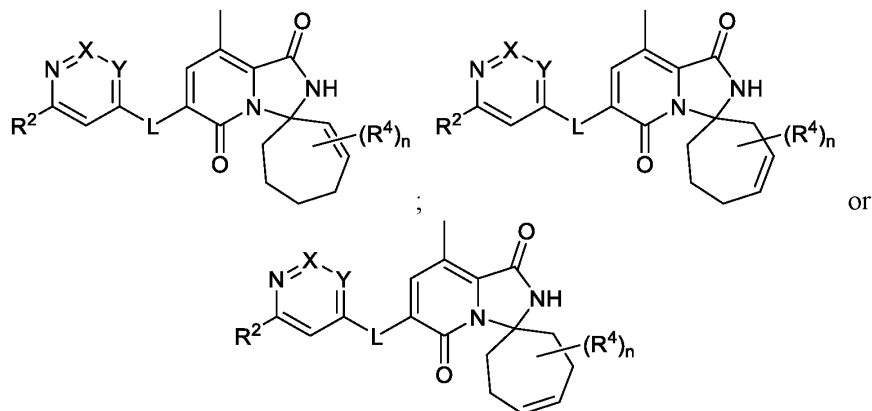
or

In some more specific embodiments, the compound has the following structure:



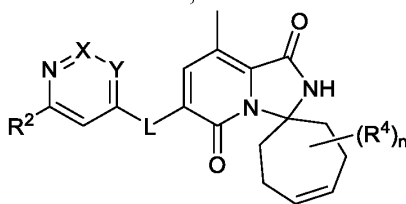
or

In some embodiments, the compound has one of the following structures:

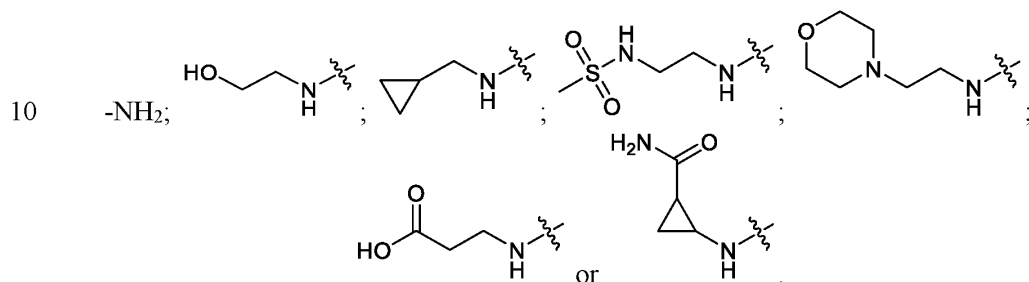


5

or



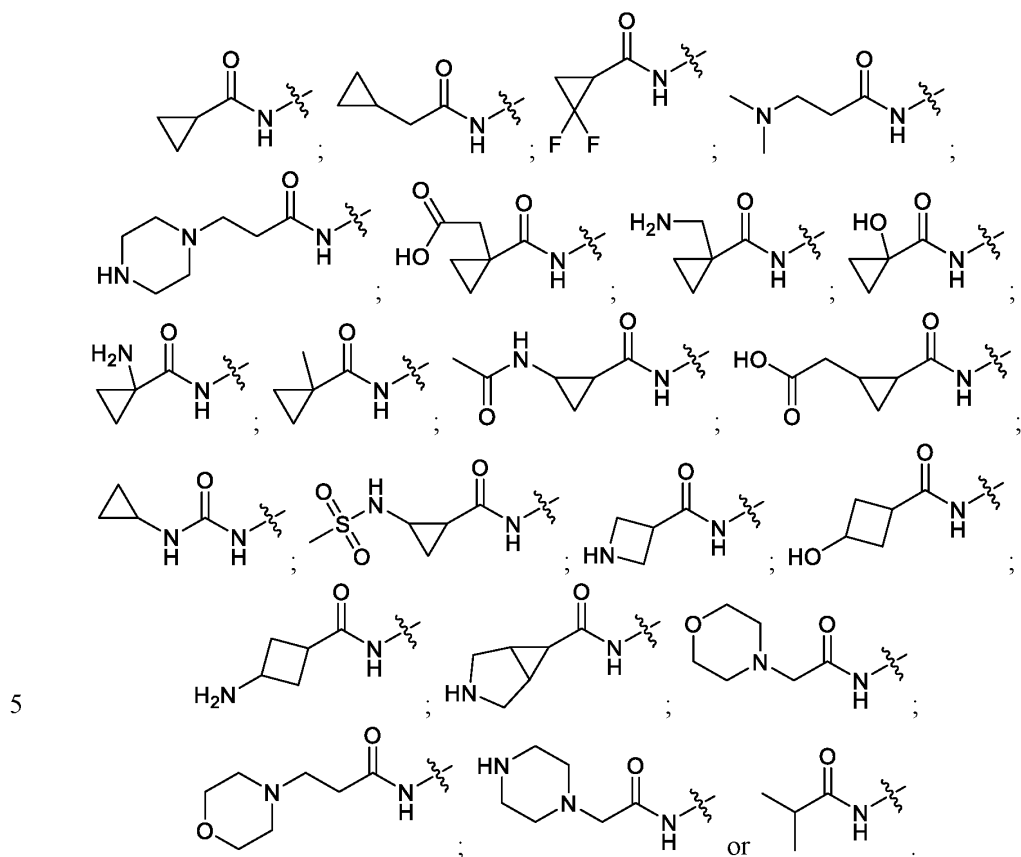
In some embodiments, R² is H. In more specific embodiments, R² is -NHR^{3a}. In more specific embodiments, R² is H or -NHR^{3a}. In more specific embodiments, R² is H or has one of the following structures:



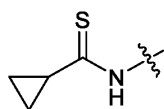
10

or

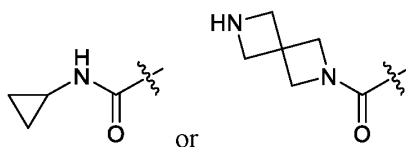
In some embodiments, R² is -NHC(=O)R^{3b}. In some embodiments, R² is H or -NHC(=O)R^{3b}. In more specific embodiments, R² has one of the following structures:



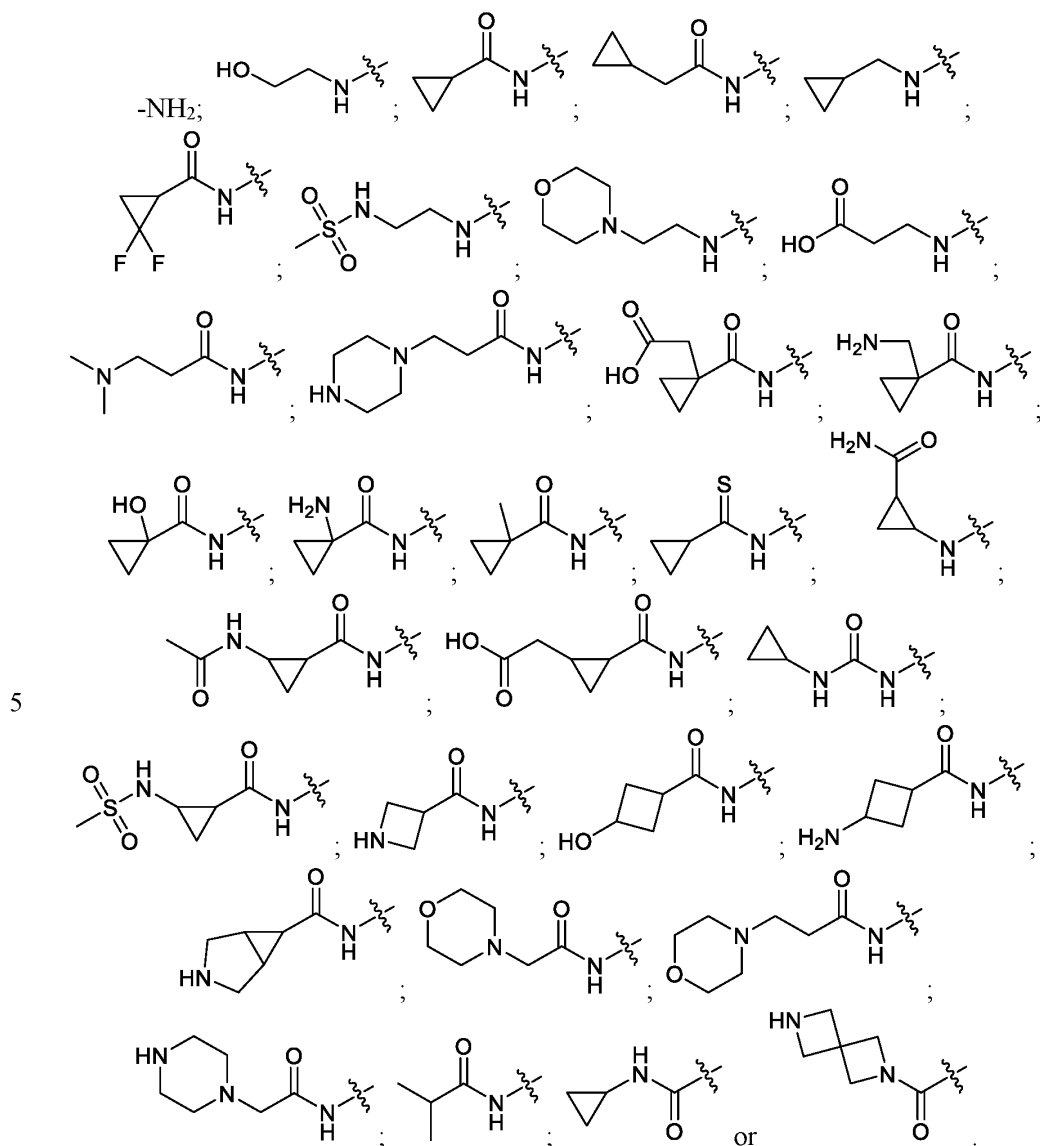
In certain embodiments, R^2 is $-\text{NHC}(=\text{S})R^{3b}$. In certain embodiments, R^2 has the following structure:



10 In certain embodiments, R^2 is $-\text{C}(=\text{O})R^{3c}$. In some embodiments, R^2 has one of the following structures:



In some embodiments, R^2 has one of the following structures:



In certain specific embodiments, R^2 has one of the following structures:

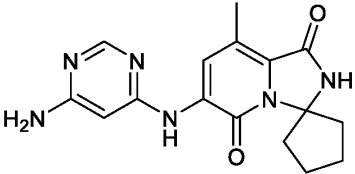
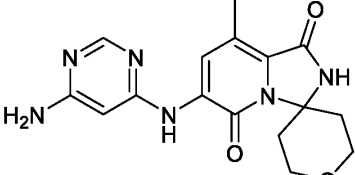
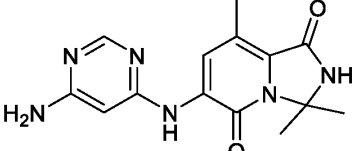
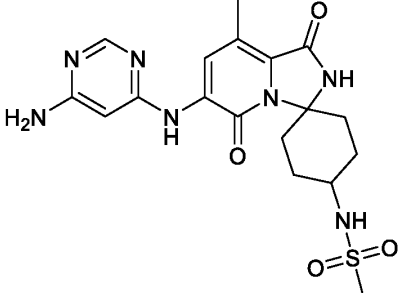
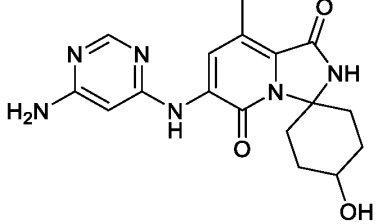
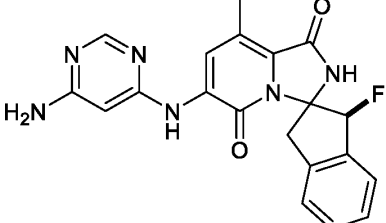


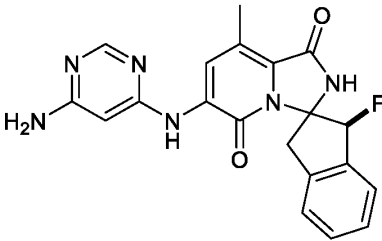
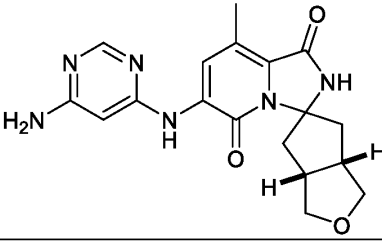
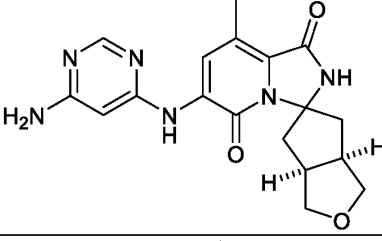
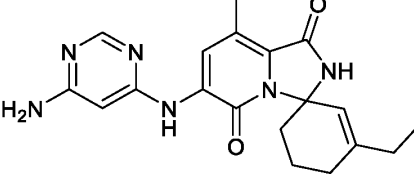
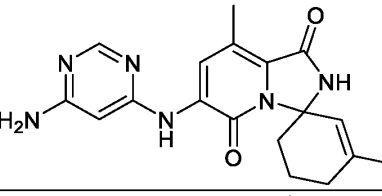
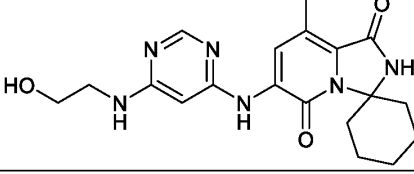
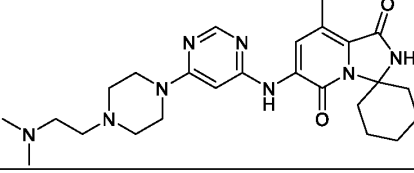
In some embodiments, X is CH and Y is N. In certain embodiments, X is N and Y is CH. In some embodiments, L is -NH- . In more embodiments, L is $\text{-CH}_2\text{NH-}$.

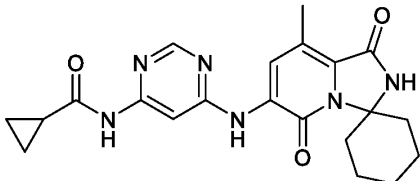
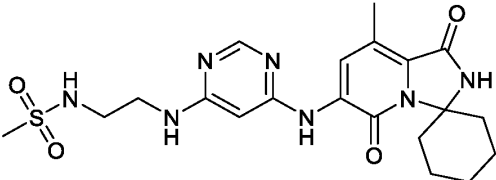
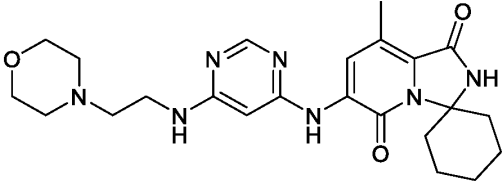
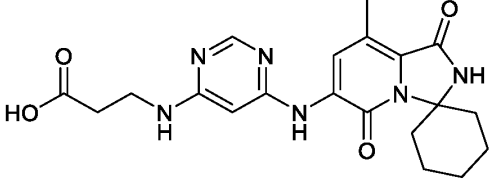
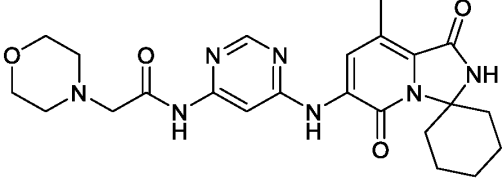
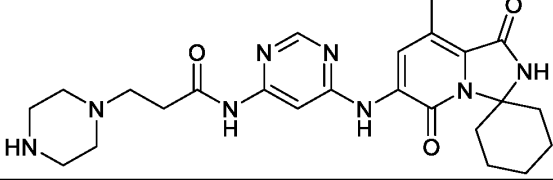
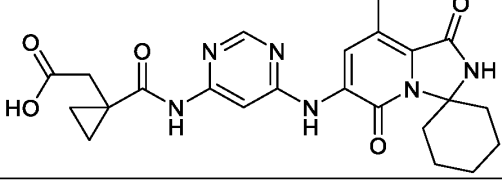
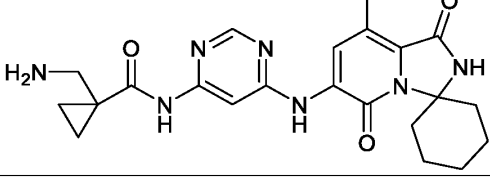
In some embodiments, R^{3a} is a branched C₁-C₆ alkyl. In some embodiments, R^{3a} is iso-propyl.

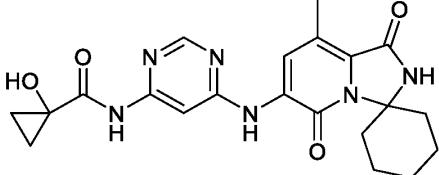
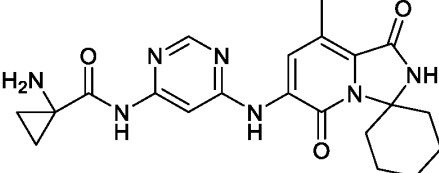
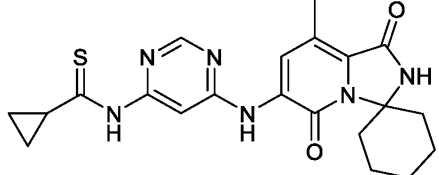
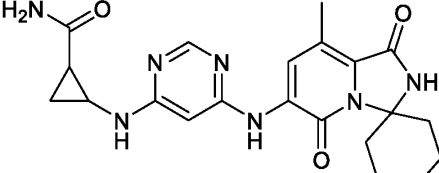
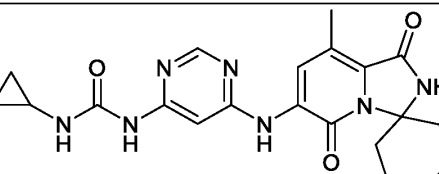
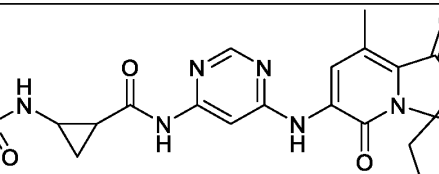
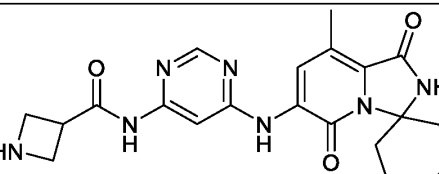
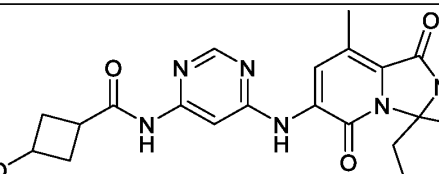
In various different embodiments, the compound has one of the structures set forth in Table 1 below, or a pharmaceutically acceptable salt, hydrate, isotopic isomer, 5 solvate, complex, stereoisomer, tautomer, or prodrug thereof. Compounds in Table 1 were prepared as described in the Examples and/or methods known in the art.

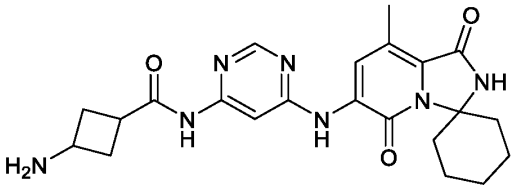
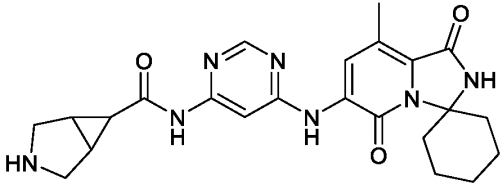
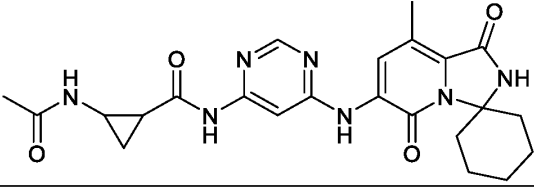
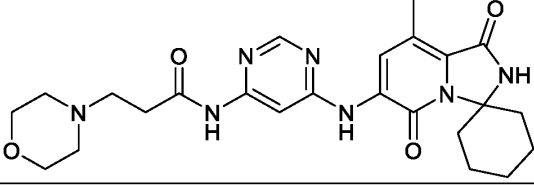
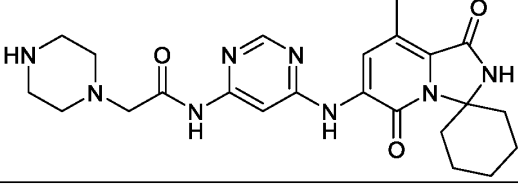
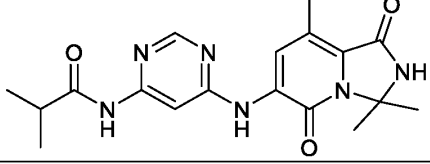
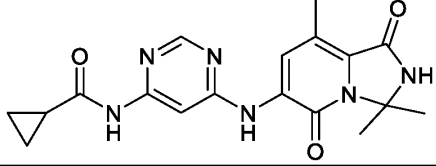
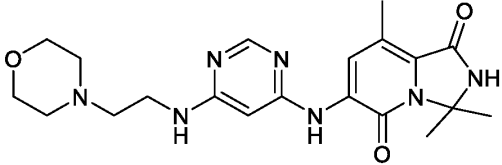
Table 1. Representative Compounds

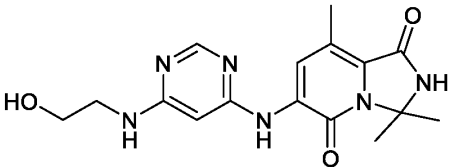
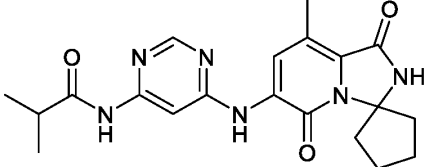
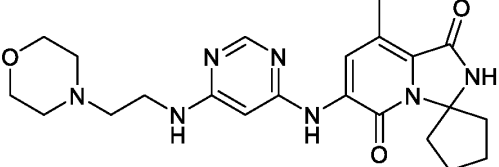
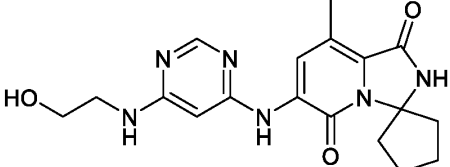
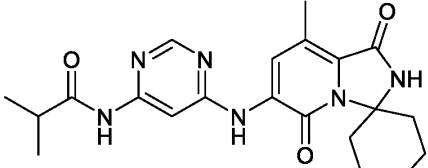
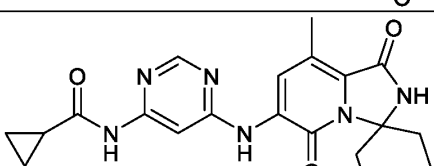
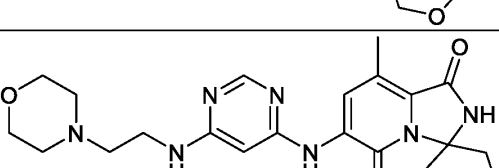
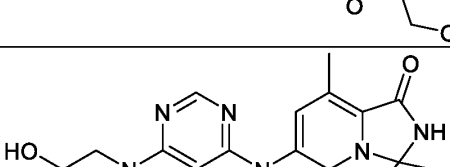
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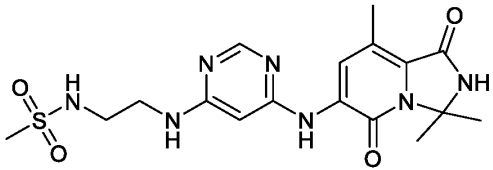
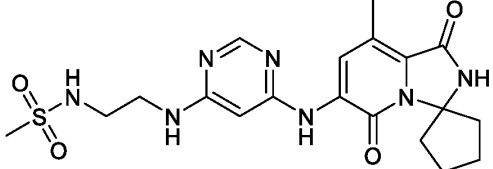
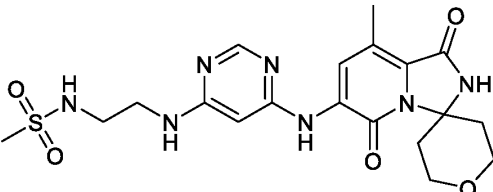
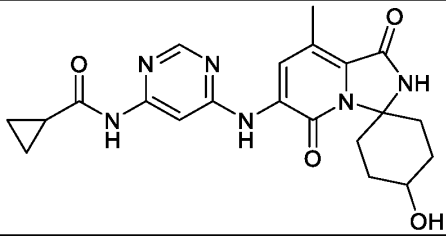
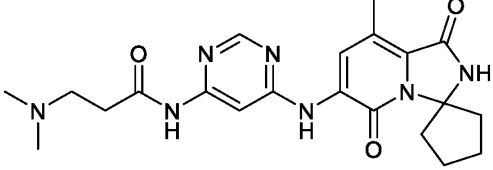
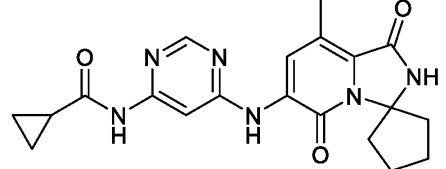
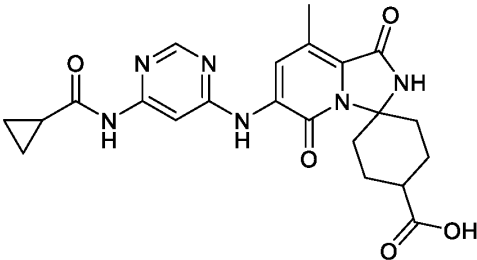
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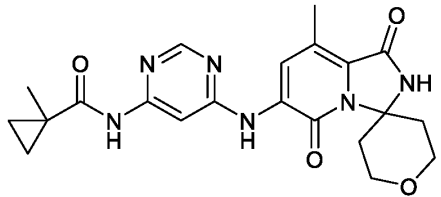
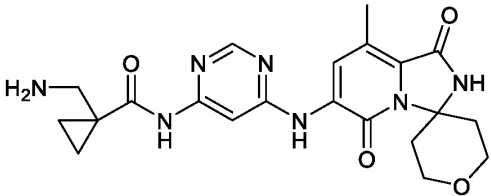
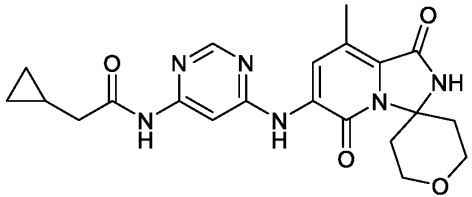
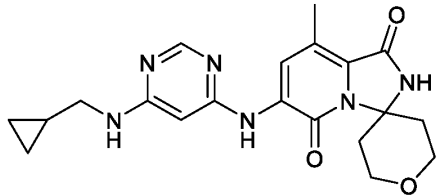
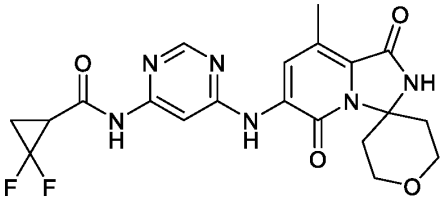
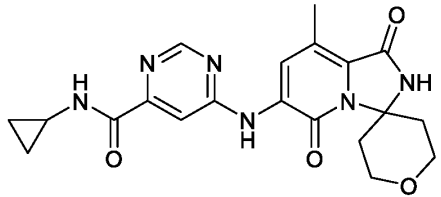
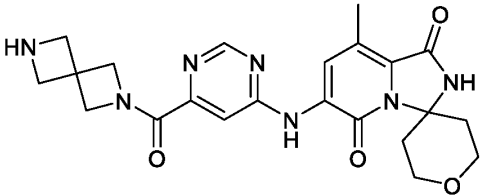
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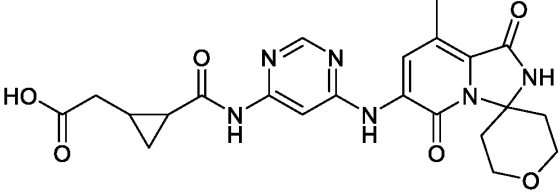
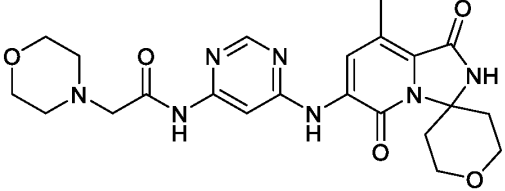
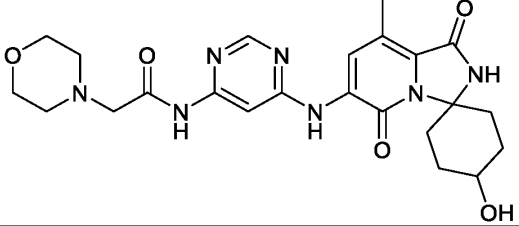
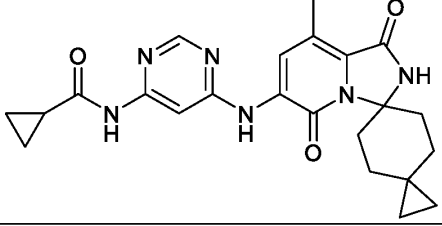
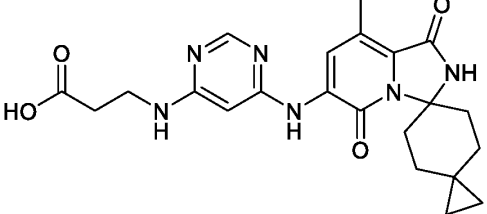
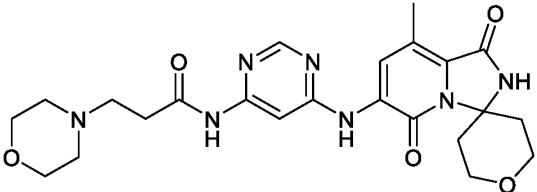
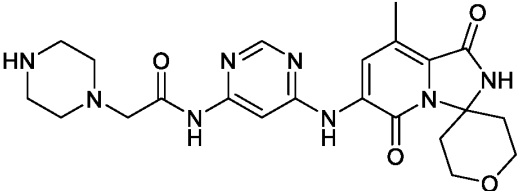
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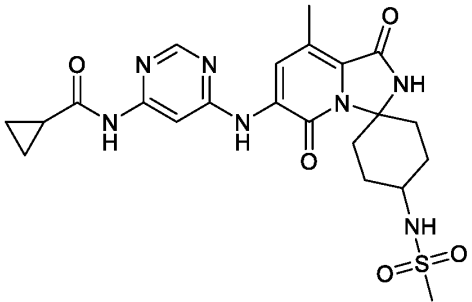
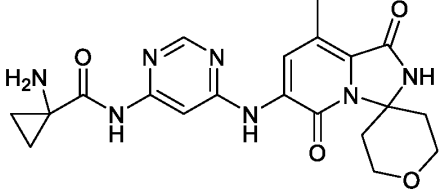
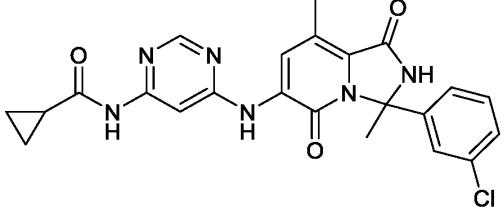
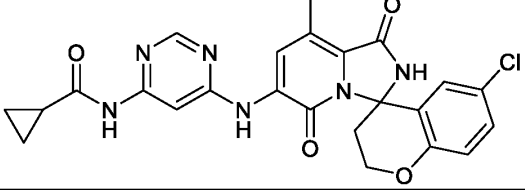
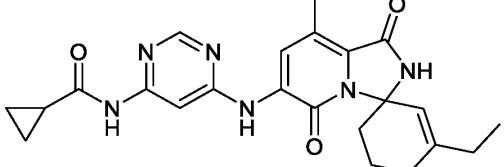
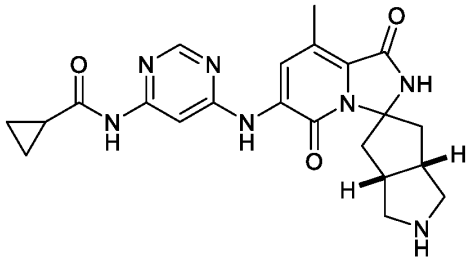
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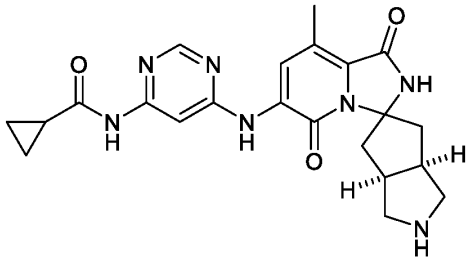
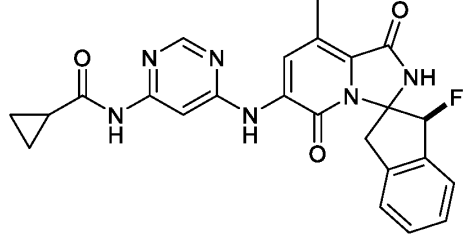
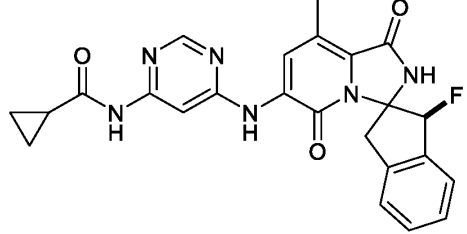
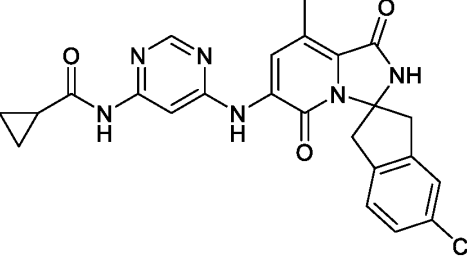
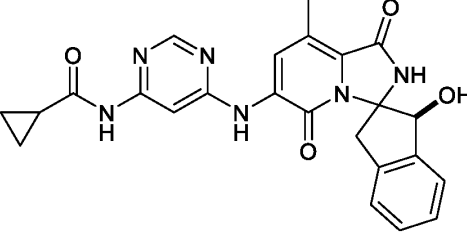
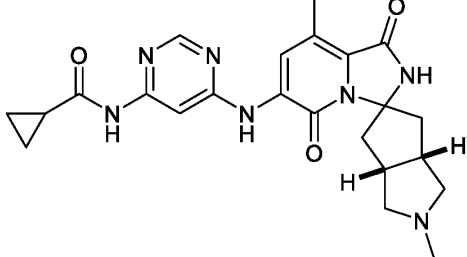
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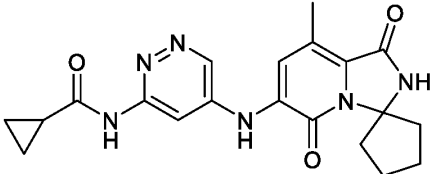
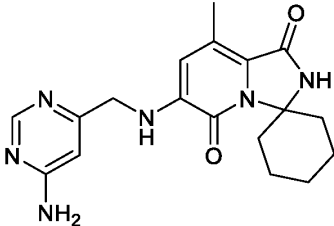
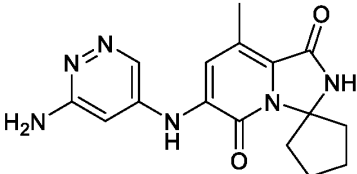
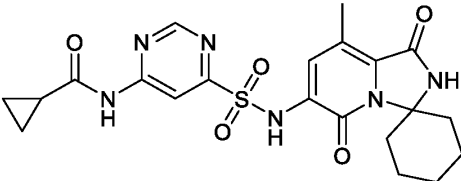
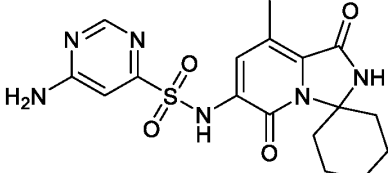
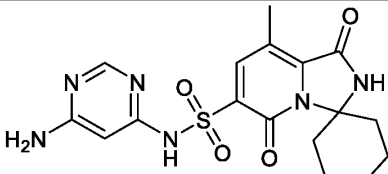
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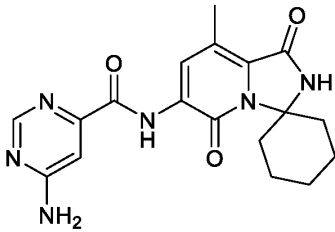
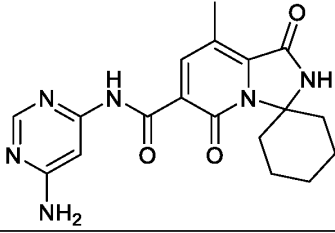
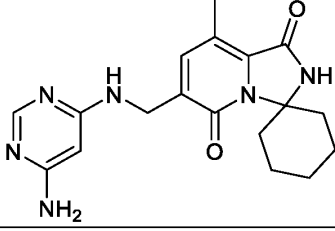
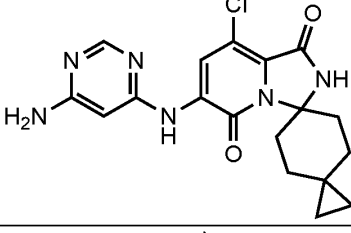
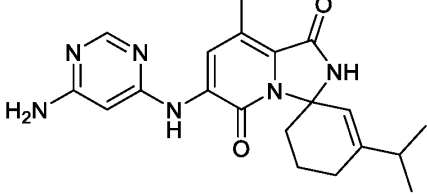
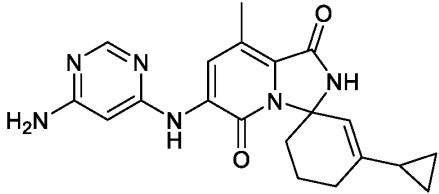
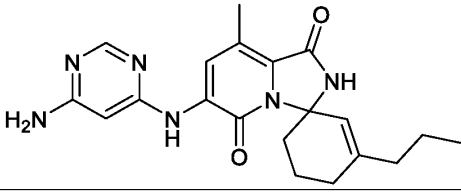
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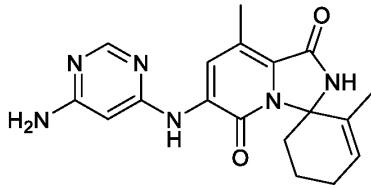
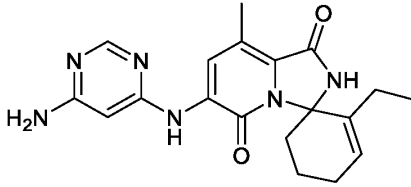
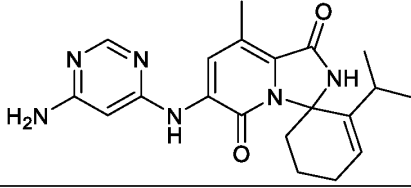
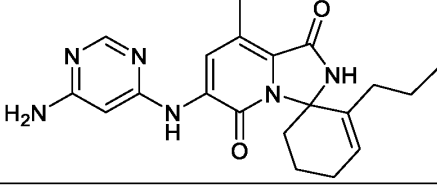
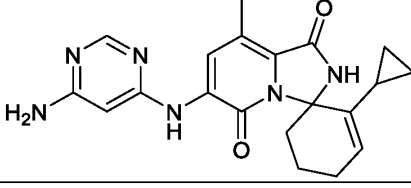
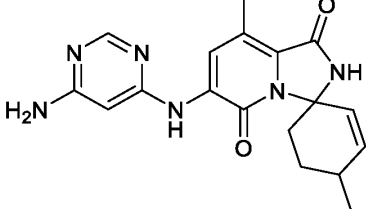
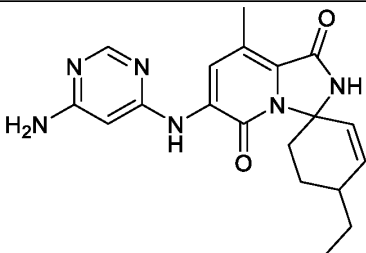
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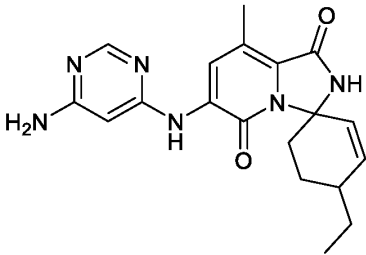
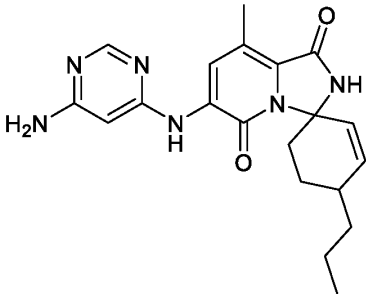
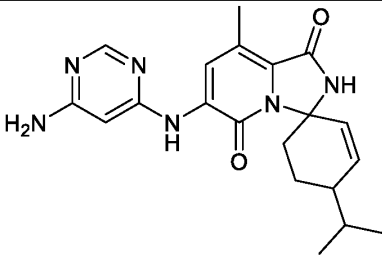
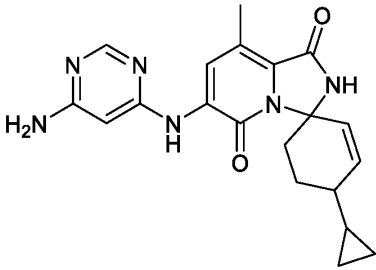
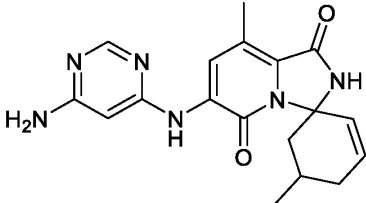
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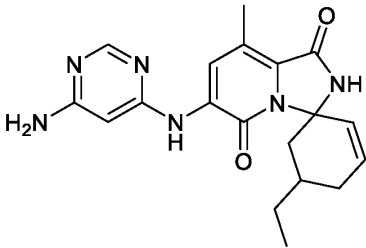
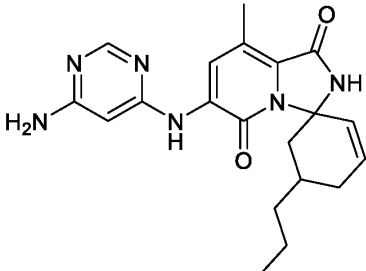
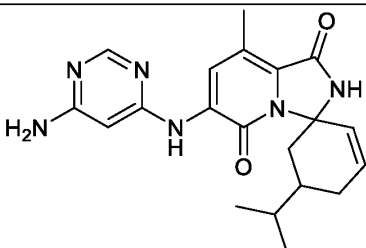
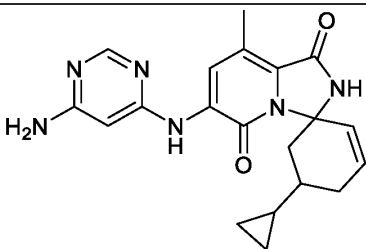
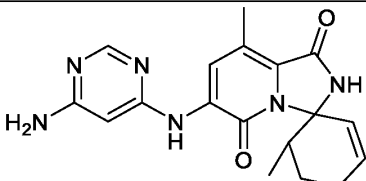
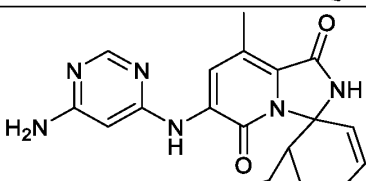
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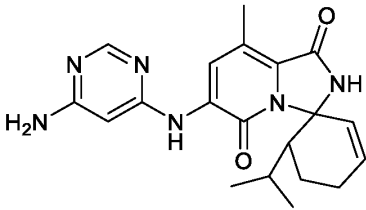
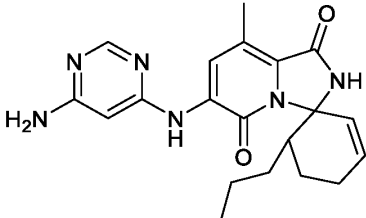
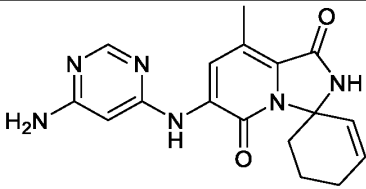
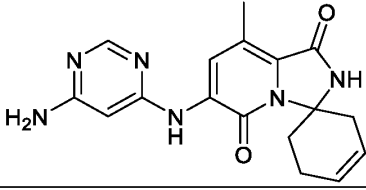
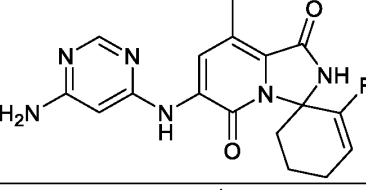
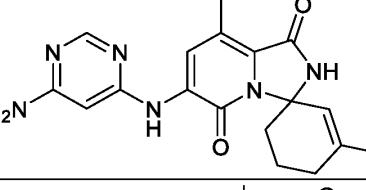
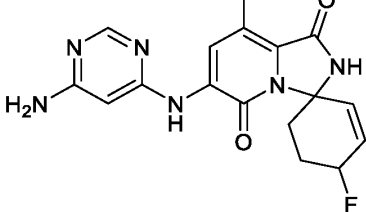
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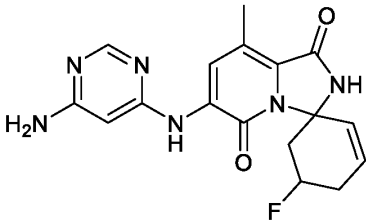
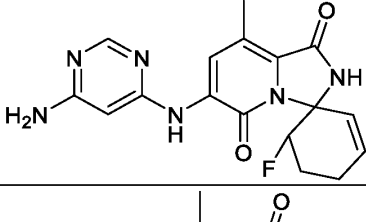
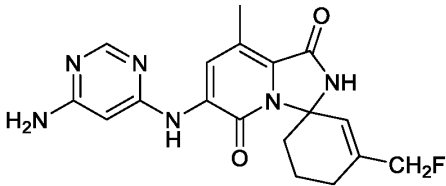
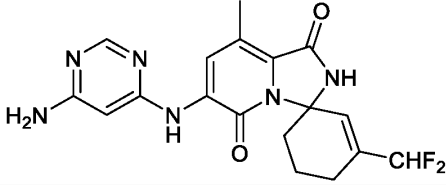
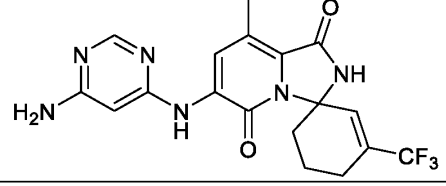
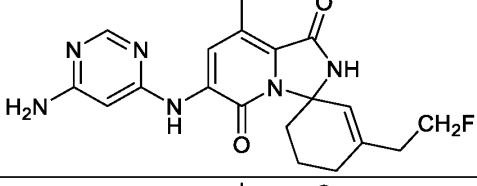
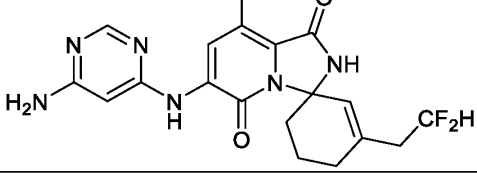
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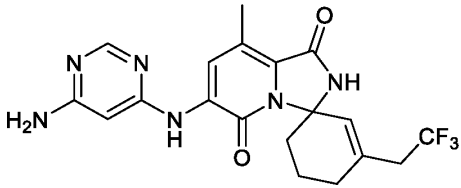
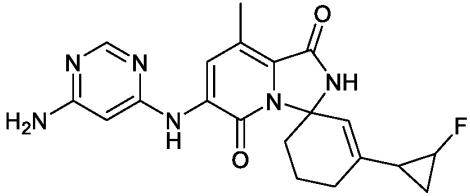
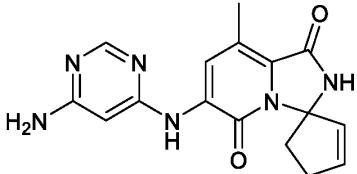
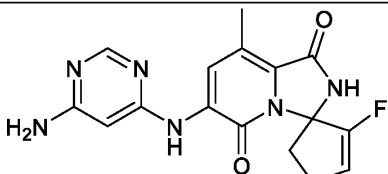
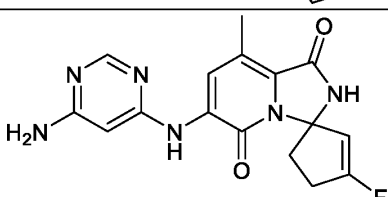
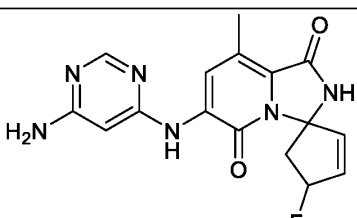
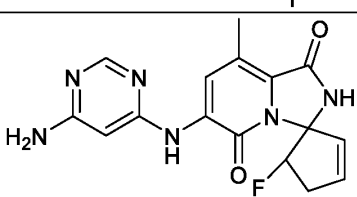
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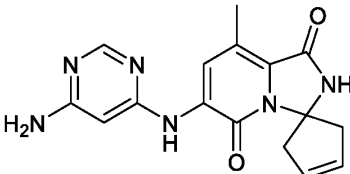
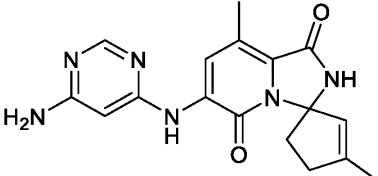
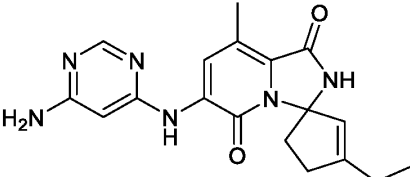
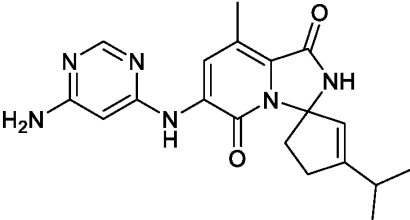
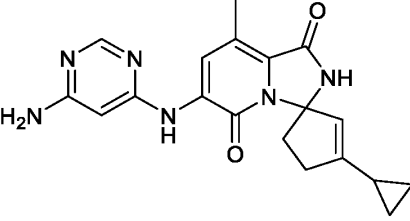
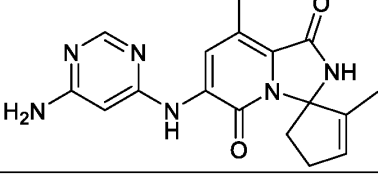
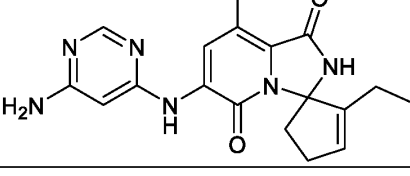
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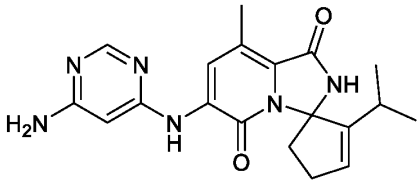
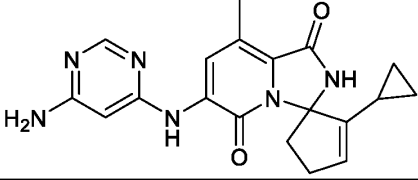
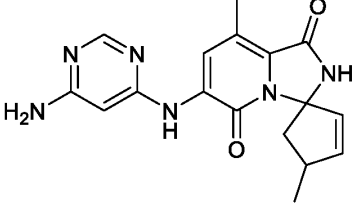
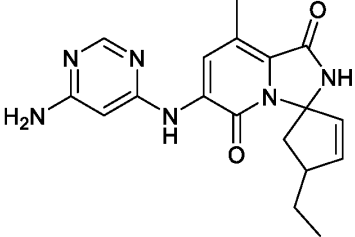
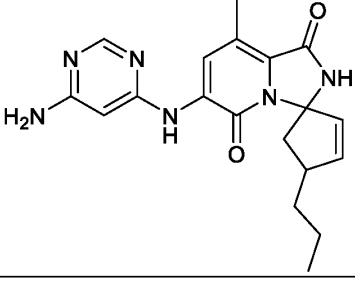
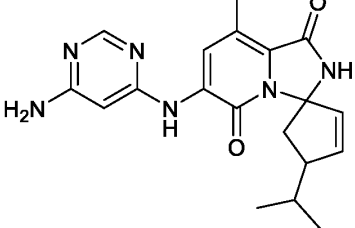
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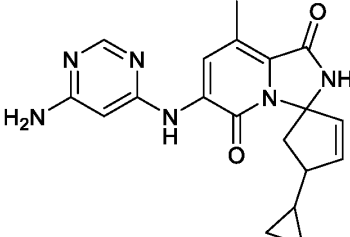
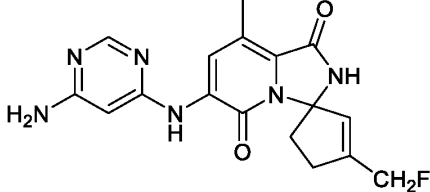
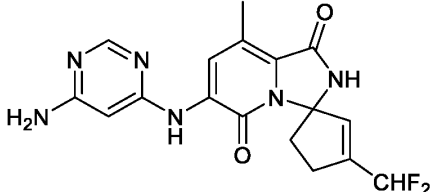
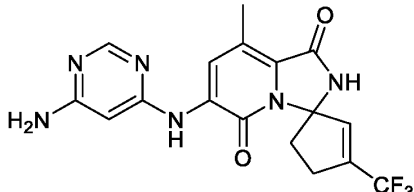
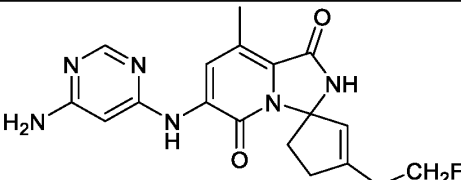
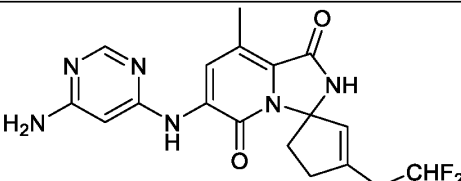
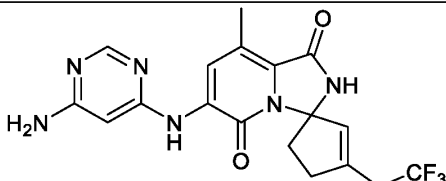
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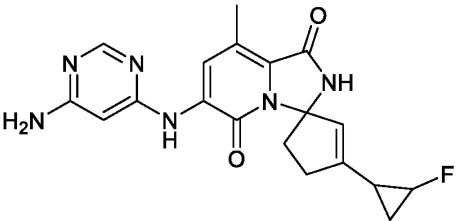
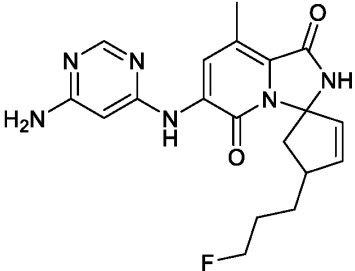
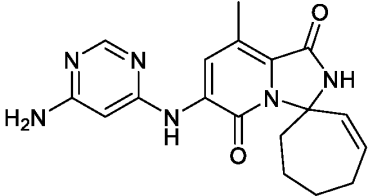
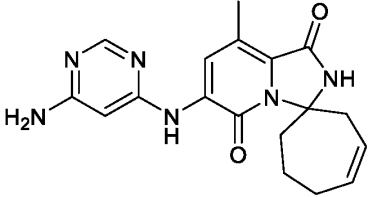
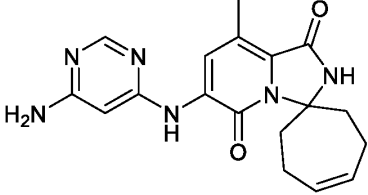
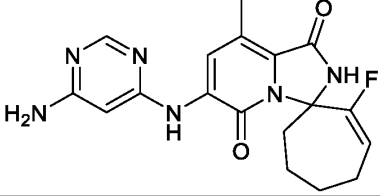
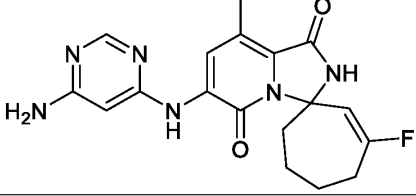
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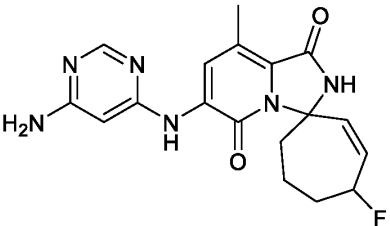
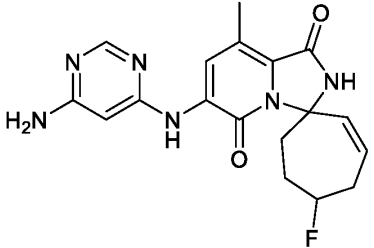
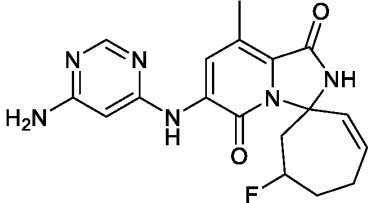
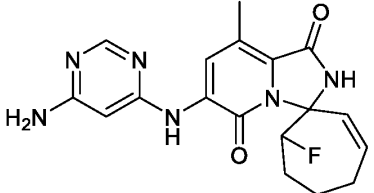
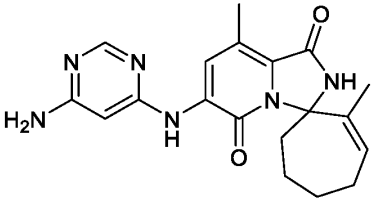
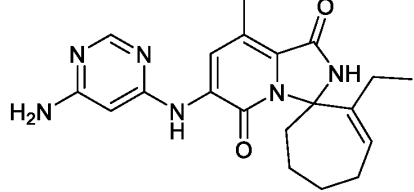
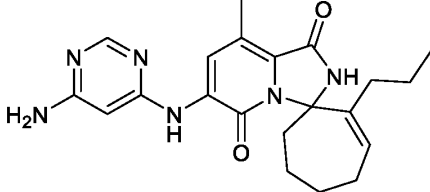
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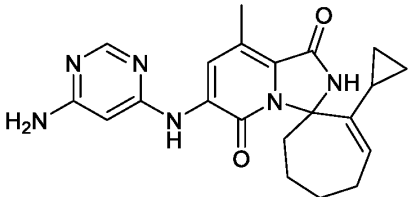
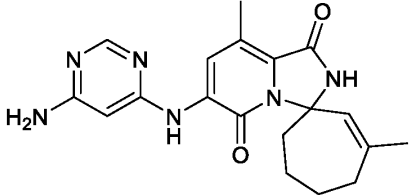
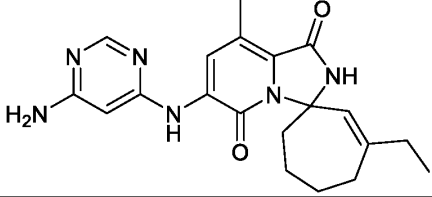
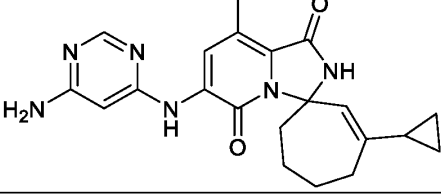
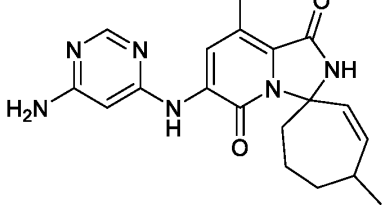
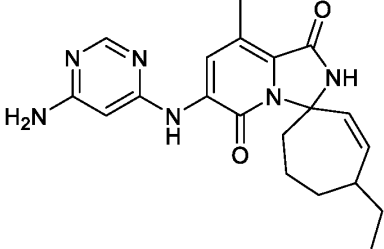
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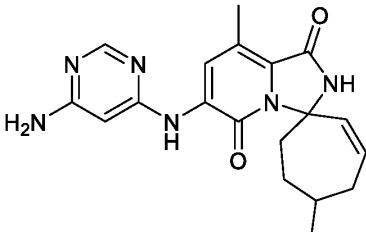
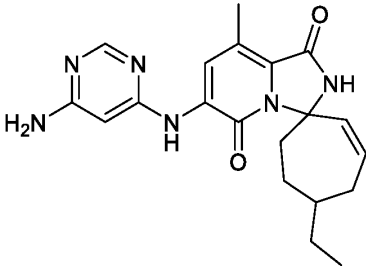
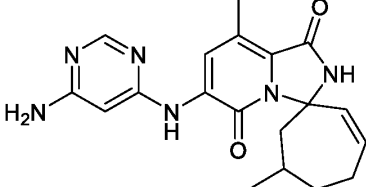
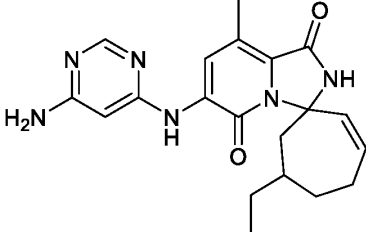
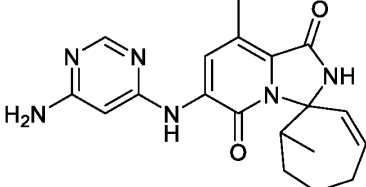
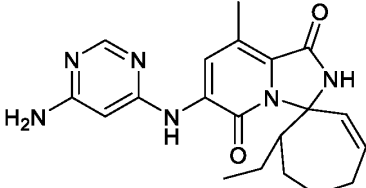
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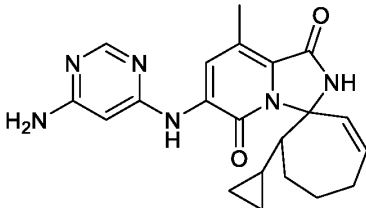
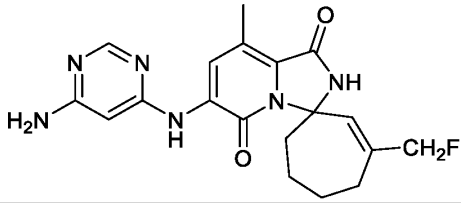
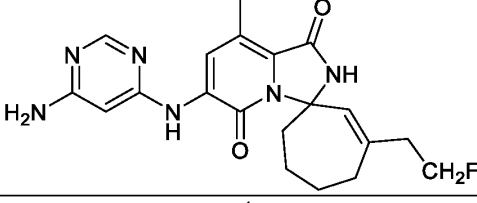
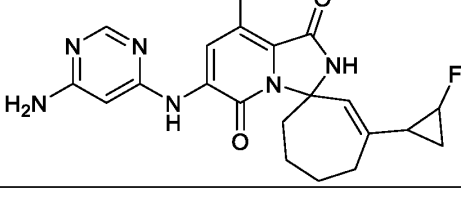
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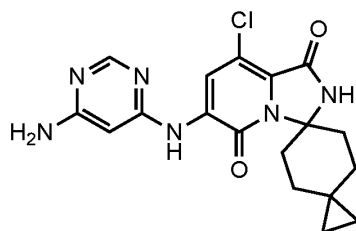
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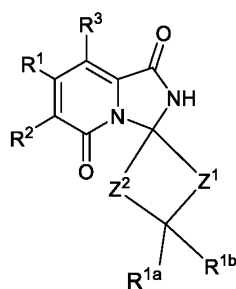
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One embodiment provides a compound having the following structure:



or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
 5 stereoisomer, tautomer, or prodrug thereof.

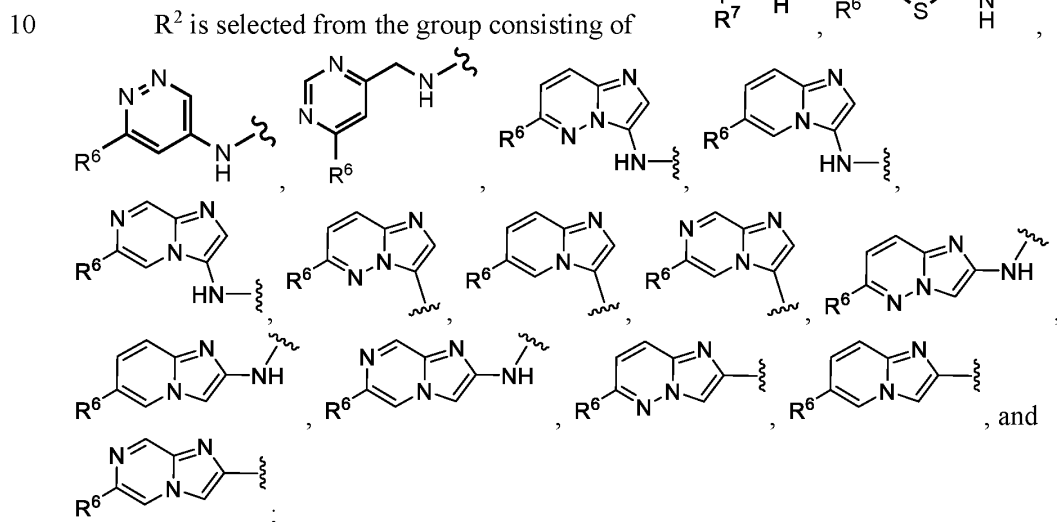
In some embodiments, the MNK inhibitor has the following Structure (III):



(III)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:

- 5 R^1 is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, cyano, C_{1-6} alkoxy, C_{3-7} branched alkoxy, hydroxy, and C_{3-6} cycloalkyl that is optionally substituted with 1 to 3 substituents selected from the groups consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} hydroxyalkyl;



cycloalkyl that is optionally substituted with 1 to 3 substituents selected from the groups consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ hydroxyalkyl;

R^{1a} and R^{1b} are taken together to form a 3- to 7-membered ring having 0-2 heteroatoms selected from the group consisting of N, O and S, wherein the 3- to 7-membered ring may be further optionally substituted with one or more substituents selected from the group consisting of halo, oxo, C₁₋₆ alkyl, R⁸, and -C(=O)OR⁹;

Z¹ and Z² are each independently a direct bond or -{C(R^{4a})(R^{4b})}_p-Y-; wherein p is 0, 1, 2, 3, 4, or 5, Y is a direct bond, -O-, or -N(R⁸)-;

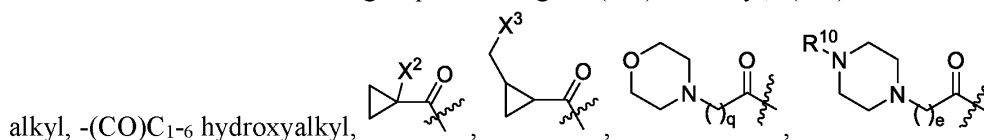
R^{4a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₆ alkoxyl, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl); or two R^{4a} attached to two adjacent carbons to form a direct bond;

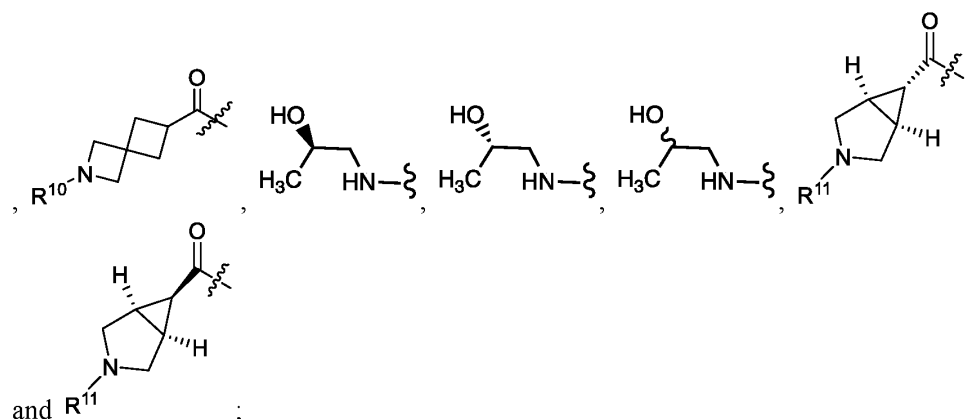
R^{4b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₆ alkoxyl, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl);

R⁵ is selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ alkoxyl, C₃₋₇ branched alkoxy, and hydroxy;

R⁶ is selected from the group consisting of hydrogen, NH₂, NHR^{6a}, NHCH₂CH₂OH, NHCH₂CH₂NHSO₂Me, C₁₋₆ alkoxyl, C₃₋₇ branched alkoxy, and hydroxy;

R^{6a} is selected from the group consisting of -(CO)C₁₋₆ alkyl, -(CO)C₃₋₇ branched

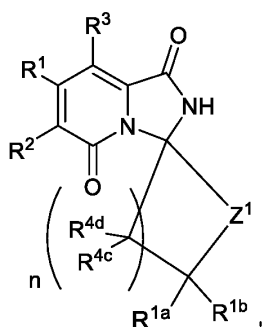




q is 1, 2, 3, 4, 5, or 6;

e is 1, 2, 3, 4, 5, or 6;

- 5 X² is selected from the group consisting of hydrogen, halogen, C₁₋₆alkyl, C₃₋₇ branched alkyl, C₁₋₆haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₆hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, C₁₋₆alkoxy, C₃₋₇ branched alkoxy, C₁₋₆haloalkoxy, C₃₋₇ branched haloalkoxy, NH₂, NH(C₁₋₆alkyl), N(C₁₋₆alkyl)₂, C₁₋₅(COOH), C₁₋₆(NHSO₂Me);
- 10 X³ is selected from the group consisting of hydrogen, halogen, C₁₋₅ alkyl, C₃₋₇ branched alkyl, C₁₋₅ haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₅ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, C₁₋₅ alkoxy, C₃₋₇ branched alkoxy, C₁₋₅ haloalkoxy, C₃₋₇ branched haloalkoxy, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, COOH, C₁₋₅(COOH), NHSO₂Me, C₁₋₅(NHSO₂Me);
- 15 R⁷ is selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, and hydroxyl;
- R⁸ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, CO(C₁₋₆alkyl), CO(C₃₋₇ branched alkyl), SO₂(C₁₋₆alkyl), and SO₂(C₃₋₇ branched alkyl);
- 20 R⁹ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and aralkyl.
- In more specific embodiments, the compound has the following Structure (IV):



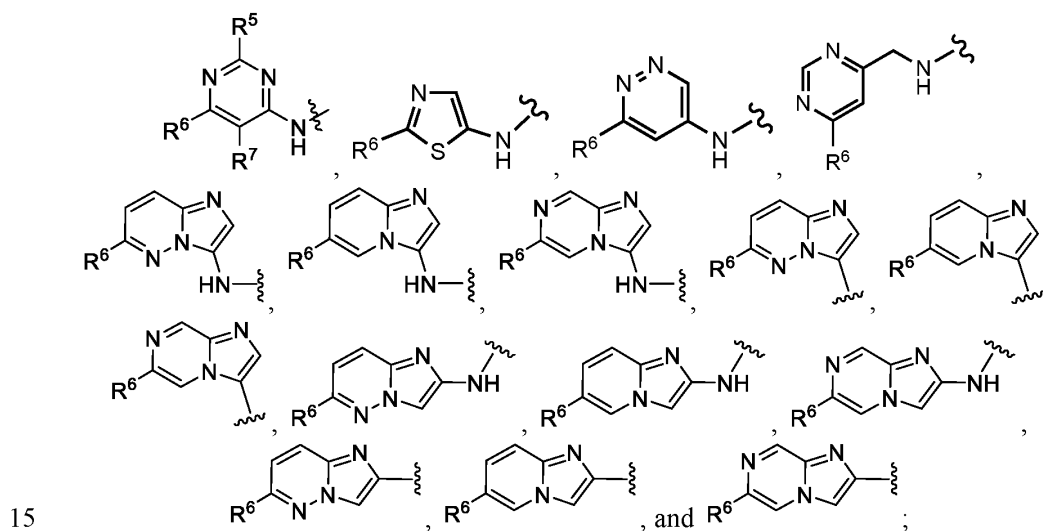
(IV)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:

5 Z^1 is selected from the groups consisting of $\left(\begin{array}{c} R^{4a} \\ R^{4b} \end{array} \right)_m$ and $\begin{array}{c} R^{4e} \\ R^{4f} \end{array}$;

R^1 is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, cyano, C_{1-6} alkoxy, C_{3-7} branched alkoxy, hydroxy, and C_{3-6} cycloalkyl that is optionally substituted with 1 to 3 substituents selected from the
10 groups consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} hydroxyalkyl;

R^2 is selected from the group consisting of:



R³ is selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, cyano, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, hydroxy, and C₃₋₆ cycloalkyl that is optionally substituted with 1 to 3 substituents selected from the groups consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ hydroxyalkyl;

R^{4a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl);

R^{4b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl);

R^{4c} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl);

R^{4d} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl);

R^{4e} is hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, and C₃₋₇ branched haloalkyl;

R^{4f} is hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, and C_{3-7} branched haloalkyl;

R^{1a} and R^{1b} are taken together to form an optionally substituted 3 to 7 membered ring that optionally contains an X^1 group forming a part of the ring;

5 X^1 is selected from the group consisting of $-C(F)_2-$, $-\text{CH}(\text{CO}_2R^{12})-$, $-O-$, $-\text{NH}-$, $-\text{N}(R^8)-$, and $-\text{S}(=\text{O})_2-$;

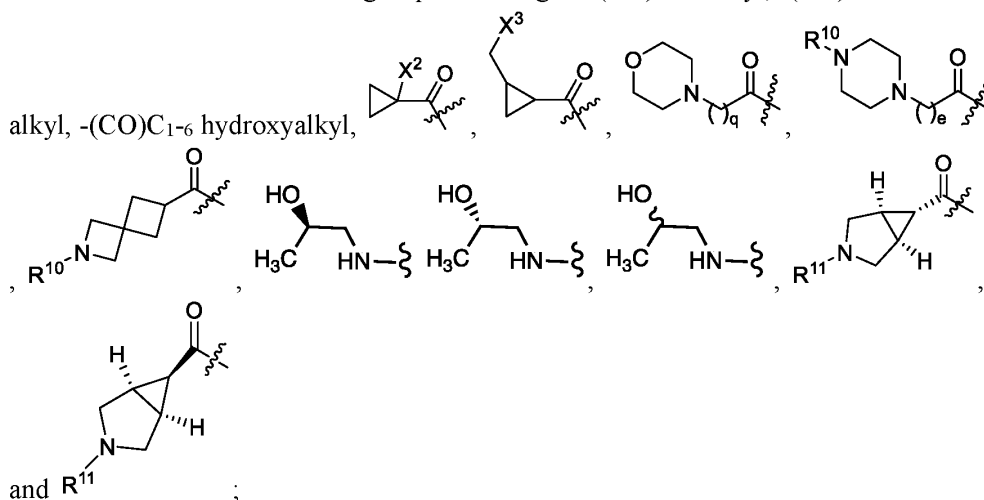
m is 0, 1, or 2;

n is 1, 2, or 3;

10 R^5 is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} alkoxy, C_{3-7} branched alkoxy, and hydroxy;

R^6 is selected from the group consisting of hydrogen, NH_2 , NHR^{6a} , $\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{NHCH}_2\text{CH}_2\text{NHSO}_2\text{Me}$, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} alkoxy, C_{3-7} branched alkoxy, and hydroxy;

15 R^{6a} is selected from the group consisting of $-(\text{CO})C_{1-6}$ alkyl, $-(\text{CO})C_{3-7}$ branched



q is 1, 2, 3, 4, 5, or 6;

20 e is 1, 2, 3, 4, 5, or 6;

X^2 is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, hydroxy, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, C_{1-6} alkoxy, C_{3-7} branched alkoxy, C_{1-6} haloalkoxy, C_{3-7}

branched haloalkoxy, NH_2 , $\text{NH}(\text{C}_{1-6}\text{alkyl})$, $\text{N}(\text{C}_{1-6}\text{alkyl})_2$, $\text{C}_{1-5}(\text{COOH})$, $\text{C}_{1-6}(\text{NHSO}_2\text{Me})$;

X^3 is selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, C_{3-7} branched alkyl, C_{1-5} haloalkyl, C_{3-7} branched haloalkyl, hydroxy, C_{1-5} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, C_{1-5} alkoxy, C_{3-7} branched alkoxy, C_{1-5} haloalkoxy, C_{3-7} branched haloalkoxy, NH_2 , $\text{NH}(\text{C}_{1-6}$ alkyl), $\text{N}(\text{C}_{1-6}$ alkyl) $_2$, COOH , $\text{C}_{1-5}(\text{COOH})$, NHSO_2Me , $\text{C}_{1-5}(\text{NHSO}_2\text{Me})$;

R^7 is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} alkoxy, C_{3-7} branched alkoxy, and hydroxy;

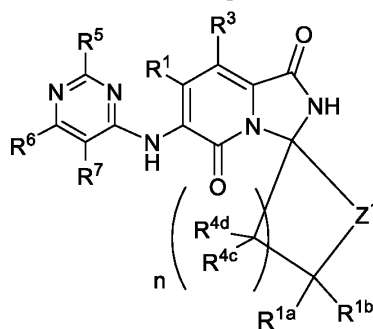
R^8 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $\text{CO}(\text{C}_{1-6}\text{alkyl})$, $\text{CO}(\text{C}_{3-7}$ branched alkyl), $\text{SO}_2(\text{C}_{1-6}\text{alkyl})$, and $\text{SO}_2(\text{C}_{3-7}$ branched alkyl);

R^{10} is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $\text{CO}(\text{C}_{1-6}\text{alkyl})$, $\text{CO}(\text{C}_{3-7}$ branched alkyl), $\text{SO}_2(\text{C}_{1-6}\text{alkyl})$, and $\text{SO}_2(\text{C}_{3-7}$ branched alkyl).

R^{11} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{12} is selected from the group consisting of hydrogen and C_{1-6} alkyl.

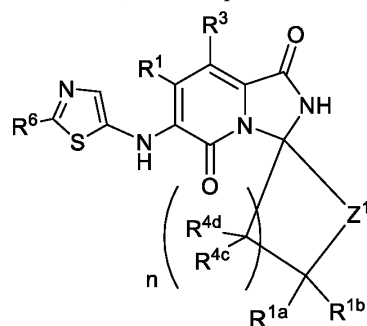
In more specific embodiments, the compound has the following Structure (V):



(V)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein, R^{1a} , R^{1b} , R^1 , R^3 , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^5 , R^6 and R^7 are as defined herein.

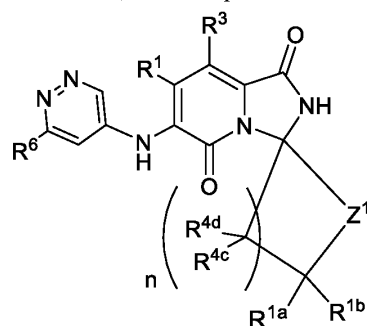
In more specific embodiments, the compound has the following Structure (VI):



(VI)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
 5 stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , n , Z^1 , and R^6 are as defined herein.

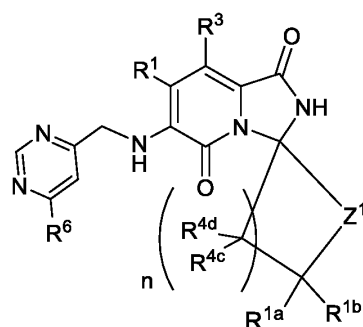
In more specific embodiments, the compound has the following Structure (VII):



(VII)

10 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
 stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , n , Z^1 , and R^6 are as defined herein.

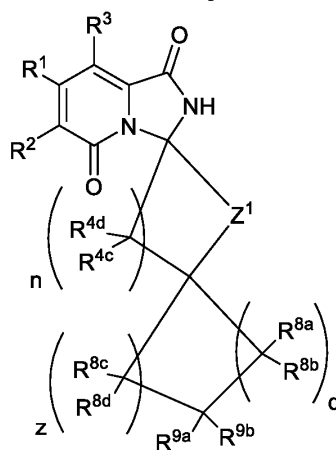
In more specific embodiments, the compound has the following Structure
 (VIII):



(VIII)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , n , Z^1 , and R^6 are as defined herein.

In more specific embodiments, the compound has the following Structure (IX):



(IX)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^2 , R^3 , R^{4d} , R^{4c} , n , and Z^1 are as defined herein;

R^{8a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl),
5 and NHSO₂(C₃₋₇ branched alkyl);

R^{8c} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl),
10 and NHSO₂(C₃₋₇ branched alkyl);

R^{8d} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl),
15 and NHSO₂(C₃₋₇ branched alkyl);

R^{9a} is selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, and C₃₋₇ branched alkoxy;

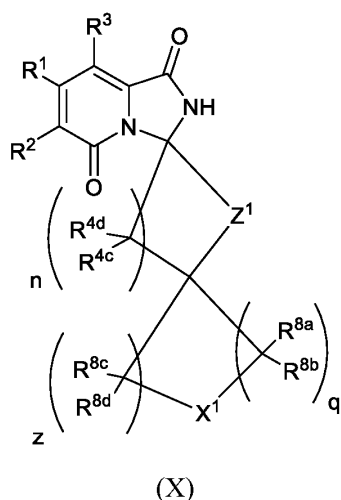
R^{9b} is selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, and C₃₋₇ branched alkoxy;

R^{9a} and R^{9b} are taken together to form an optionally substituted 3 to 7-membered ring;

q is 1, 2, or 3; and

25 z is 0, 1, or 2.

In more specific embodiments, the compound has the following Structure (X):



or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^2 , R^3 , R^{4d} , R^{4c} , Z^1 , X^1 and n are as defined herein;

R^{8a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8c} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

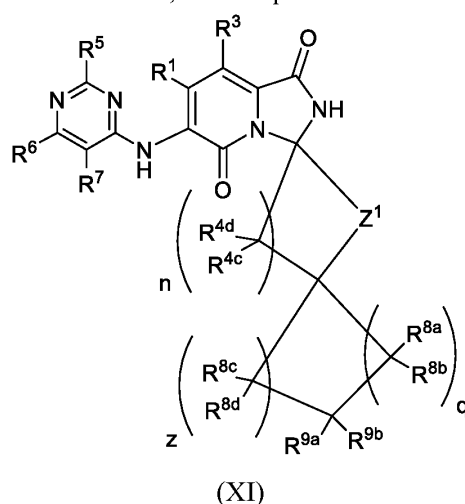
R^{8d} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched

haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl);

q is 1, 2, or 3; and

5 z is 0, 1, or 2.

In more specific embodiments, the compound has the following Structure (XI):



or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R¹, R³, R^{4d}, R^{4c}, Z¹, R⁵, R⁶, R⁷, and n are as defined herein;

R^{8a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl);

R^{8b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl);

R^{8c} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$,
 5 and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8d} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$,
 10 and $NHSO_2(C_{3-7} branched alkyl)$;

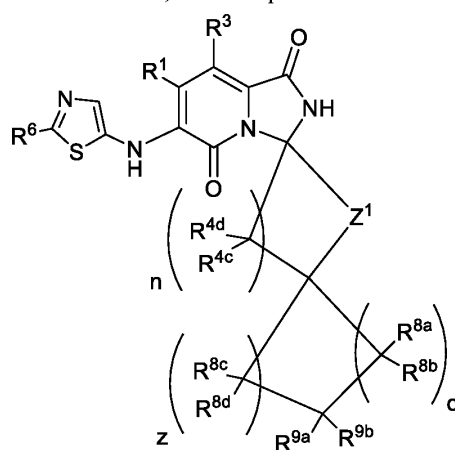
R^{9a} is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

15 R^{9b} is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

q is 1, 2, or 3; and

20 z is 0, 1, or 2.

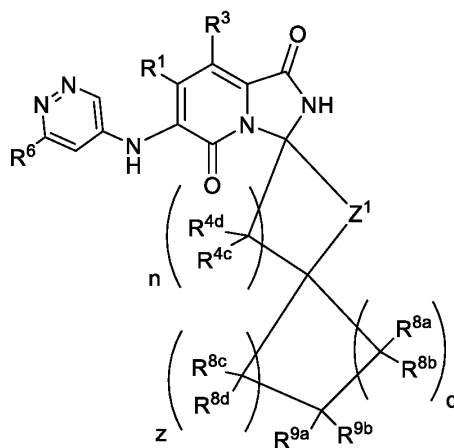
In more specific embodiments, the compound has the following Structure (XII):



(XII)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , Z^1 , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , n and z are as defined herein.

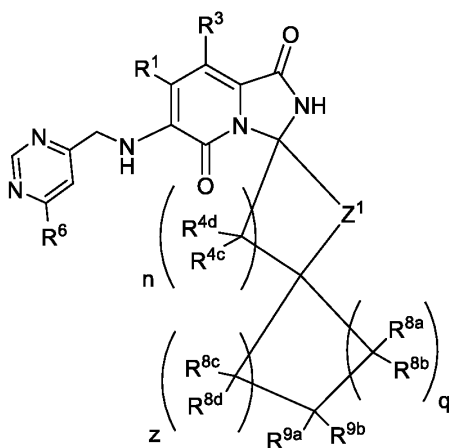
- 5 In more specific embodiments, the compound has the following Structure (XIII):



(XIII)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
 10 stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , Z^1 , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , n and z are as defined herein.

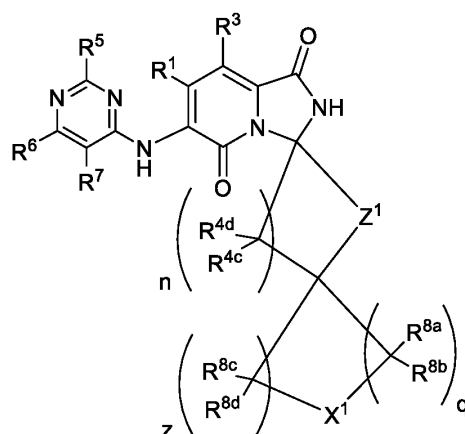
In more specific embodiments, the compound has the following Structure (XIV):



(XIV)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , Z^1 , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , n and z are as defined herein.

5 In more specific embodiments, the compound has the following Structure (XV):



(XV)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , Z^1 , R^5 , R^6 , R^7 , X^1 , and n are as defined herein;

R^{8a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8c} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched

haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl);

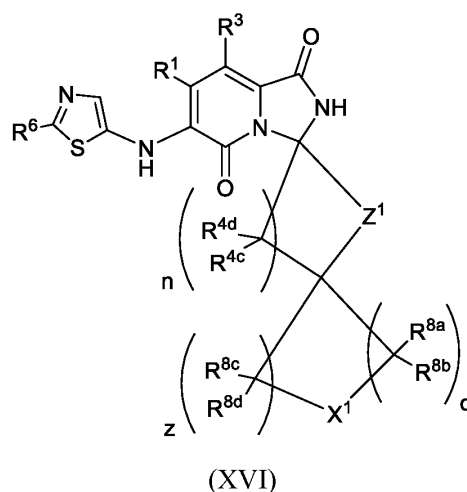
R^{8d} is at each occurrence independently selected from the group consisting of
 5 hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl);

q is 1, 2, or 3; and

10 z is 0, 1, or 2.

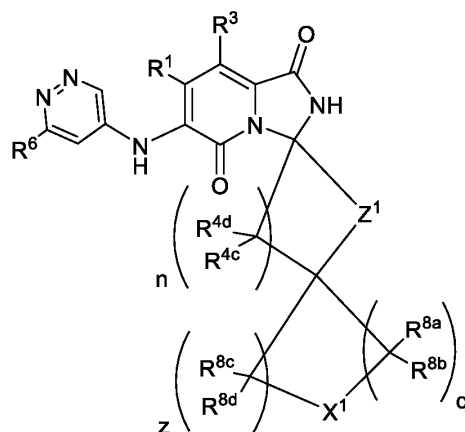
In more specific embodiments, the compound has the following Structure

(XVI):



15 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R¹, R³, R^{4d}, R^{4c}, Z¹, R⁶, R^{8a}, R^{8b}, R^{8c}, R^{8d}, X¹, n and z are as defined herein.

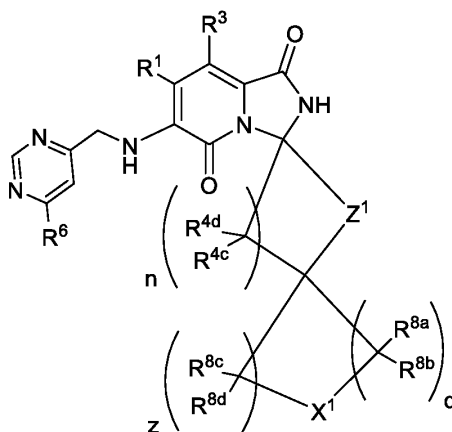
In more specific embodiments, the compound has the following Structure (XVII):



(XVII)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , Z^1 , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , X^1 , n and z are as defined herein.

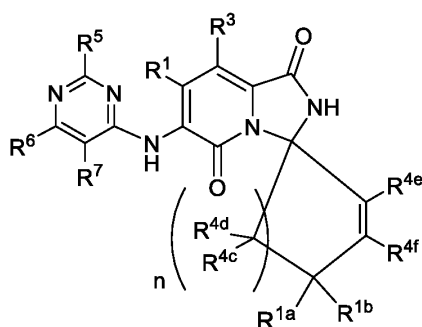
In more specific embodiments, the compound has the following Structure (XVIII):



(XVIII)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , Z^1 , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , X^1 , n and z are as defined herein.

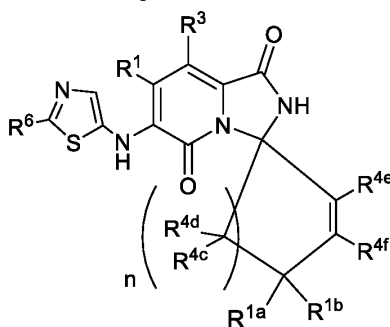
In more specific embodiments, the compound has the following Structure (XIX):



(XIX)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^5 , R^6 , R^7 and n are as defined herein.

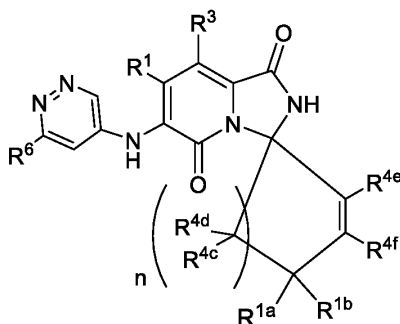
In some embodiments, the compound has the following Structure (XX):



(XX)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^6 , and n are as defined herein.

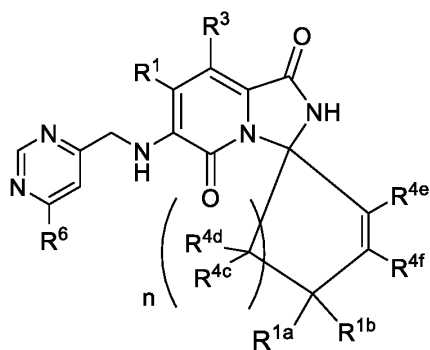
In more specific embodiments, the compound has the following Structure (XXI):



(XXI)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^6 , and n are as defined herein.

5 In more specific embodiments, the compound has the following Structure (XXII):

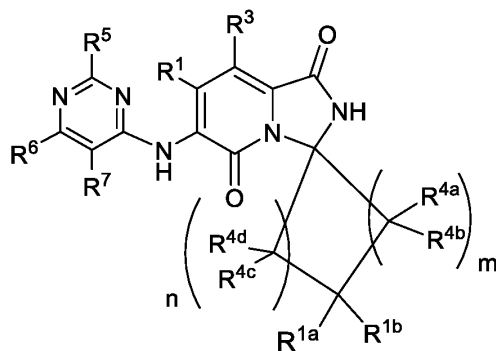


(XXII)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^6 , and n are as defined herein.

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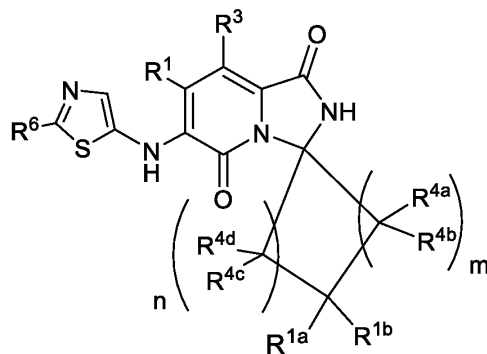
In more specific embodiments, the compound has the following Structure (XXIII):



(XXIII)

15 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4a} , R^{4b} , R^{4d} , R^{4c} , R^5 , R^6 , R^7 , m and n are as defined herein.

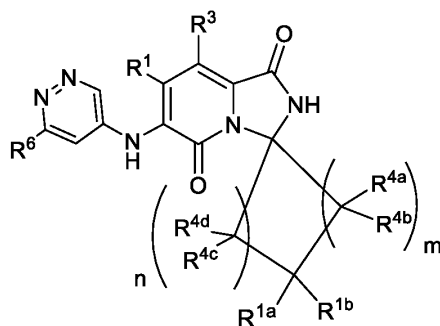
In more specific embodiments, the compound has the following Structure (XXIV):



(XXIV)

- 5 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , R^{4a} , R^{4b} , R^6 , m and n are as defined herein.

In more specific embodiments, the compound has the following Structure (XXV):



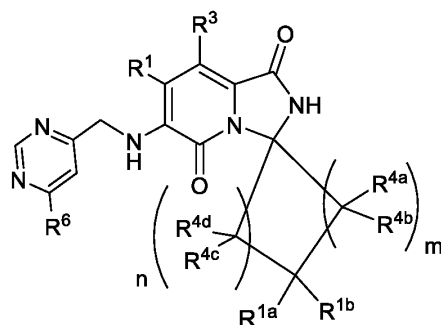
(XXV)

10

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , R^{4a} , R^{4b} , R^6 , m and n are as defined herein.

In more specific embodiments, the compound has the following Structure

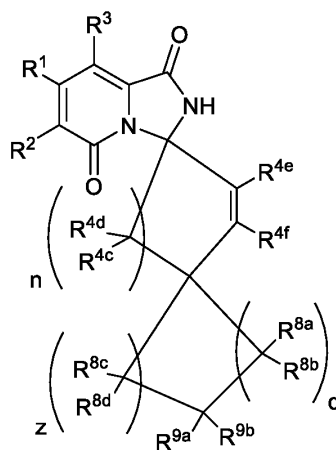
15 (XXVI):



(XXVI)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^{1a} , R^{1b} , R^1 , R^3 , R^{4d} , R^{4c} , R^{4a} , R^{4b} , R^6 , m and n are as defined herein.

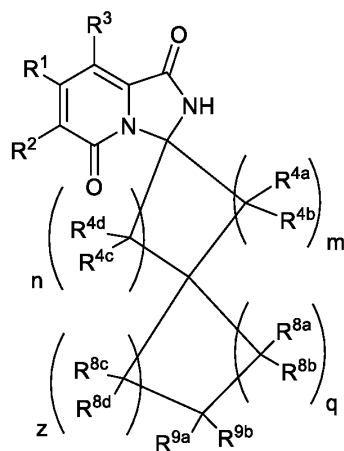
In more specific embodiments, the compound has the following Structure (XXVII):



(XXVII)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^2 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , n , q and z are as defined herein.

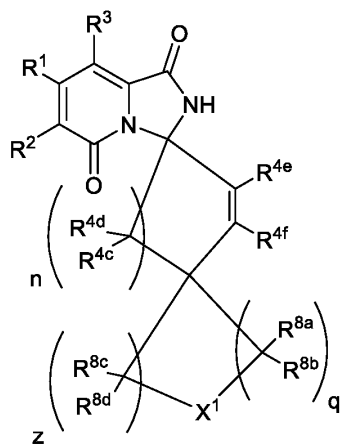
In more specific embodiments, the compound has the following Structure (XXVIII):



(XXVIII)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^2 , R^3 , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , m , n , q and z are as defined herein.

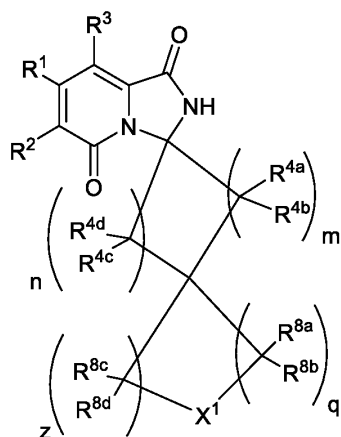
In more specific embodiments, the compound has the following Structure (XXIX):



(XXIX)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^2 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^{8a} , R^{8b} , R^{8c} , R^{8d} , X^1 , n , q and z are as defined herein.

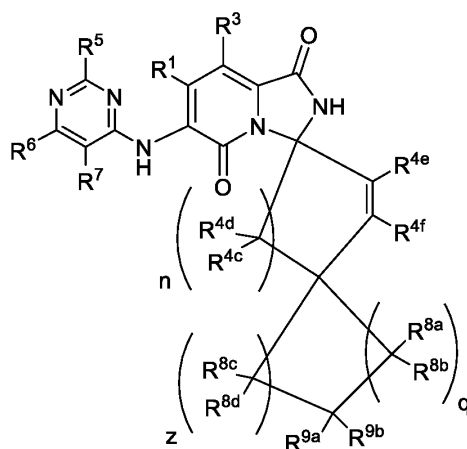
In more specific embodiments, the compound has the following Structure (XXX):



(XXX)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^2 , R^3 , R^{4a} , R^{4b} , R^{4c} , R^{4d} , R^{8a} , R^{8b} , R^{8c} , R^{8d} , X^1 , m , n , q and z are as defined herein.

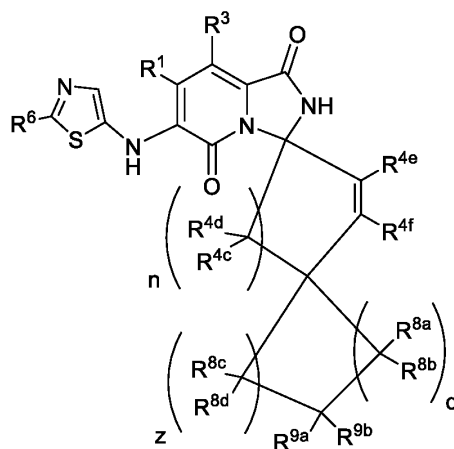
In more specific embodiments, the compound has the following Structure (XXXI):



(XXXI)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^5 , R^6 , R^7 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , n , q and z are as defined herein.

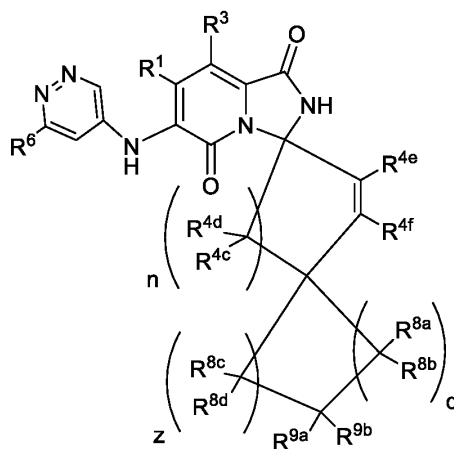
In more specific embodiments, the compound has the following Structure (XXXII):



(XXXII)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , n , q and z are as defined herein.

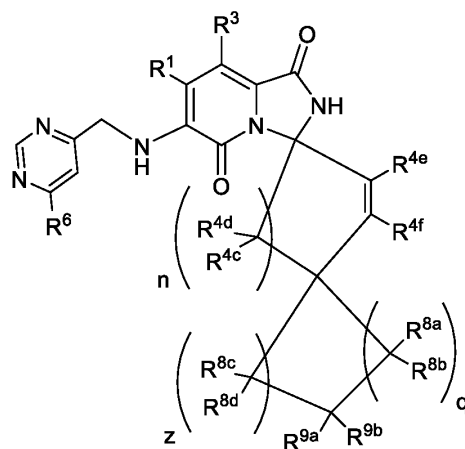
In more specific embodiments, the compound has the following Structure (XXXIII):



(XXXIII)

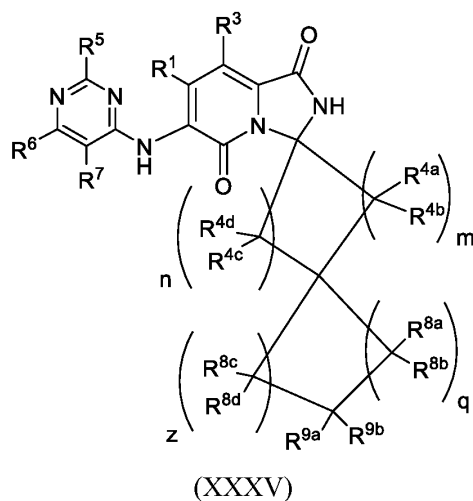
- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , n , q and z are as defined herein.

In more specific embodiments, the compound has the following Structure (XXXIV):



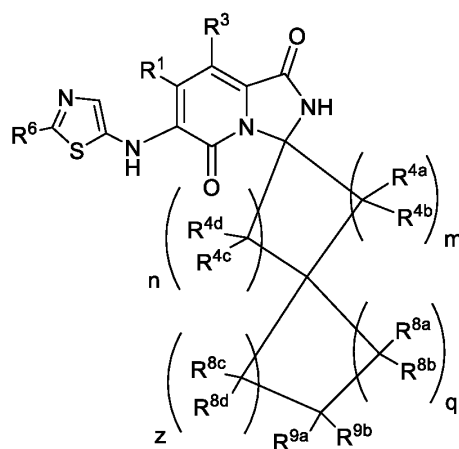
or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , n , q and z are as defined herein.

- 5 In more specific embodiments, the compound has the following Structure (XXXV):



- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
 10 stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4a} , R^{4b} , R^{4d} , R^{4c} , R^5 , R^6 , R^7 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , m , n , q and z are as defined herein.

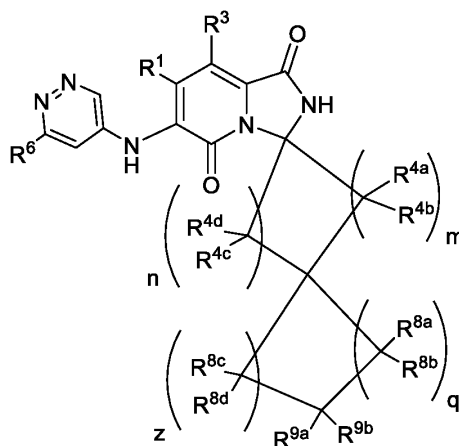
In more specific embodiments, the compound has the following Structure (XXXVI):



(XXXVI)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4a} , R^{4b} , R^{4d} , R^{4c} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , m , n , q and z are as defined herein.

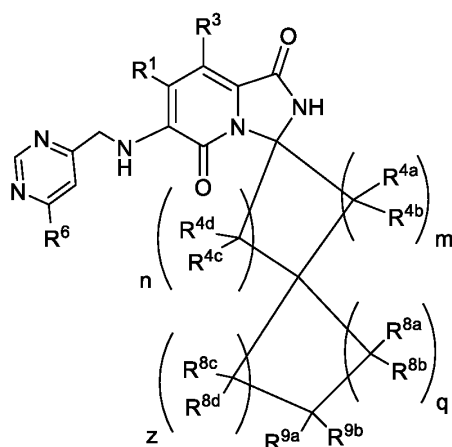
In more specific embodiments, the compound has the following Structure (XXXVII):



(XXXVII)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4a} , R^{4b} , R^{4d} , R^{4c} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , m , n , q and z are as defined herein.

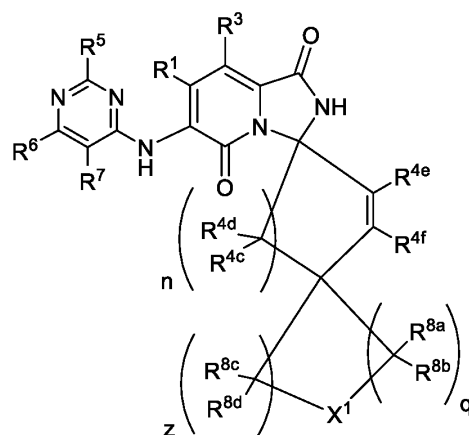
In more specific embodiments, the compound has the following Structure (XXXIX):



(XXXIX)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4a} , R^{4b} , R^{4d} , R^{4c} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , R^{9a} , R^{9b} , m , n , q and z are as defined herein.

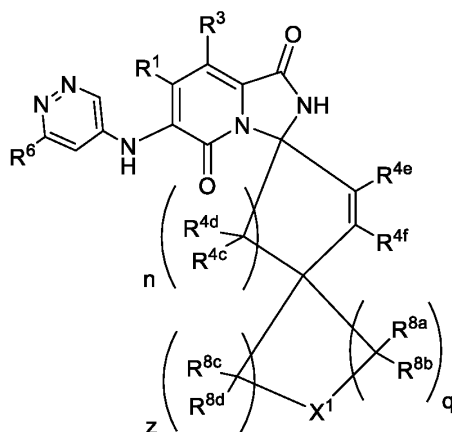
In more specific embodiments, the compound has the following Structure (XL):



(XL)

- or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^5 , R^6 , R^7 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , X^1 , n , q and z are as defined herein.

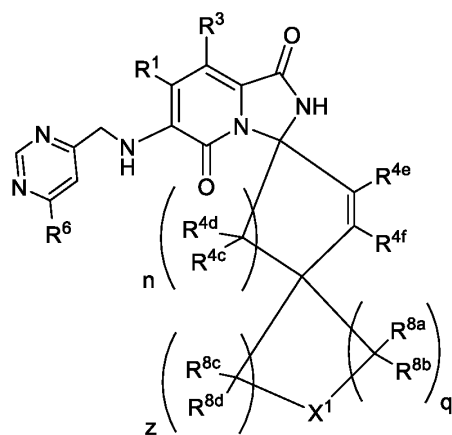
In more specific embodiments, the compound has the following Structure (XLI):



(XLI)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , X^1 , n , q and z are as defined herein.

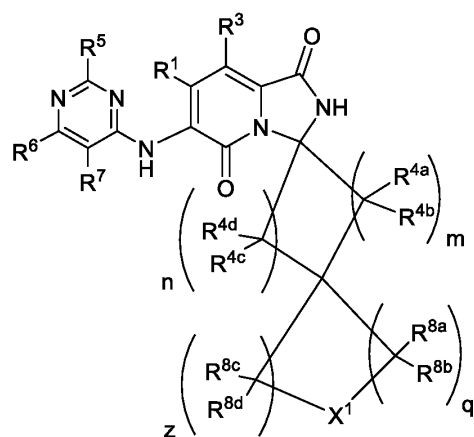
In more specific embodiments, the compound has the following Structure (XLII):



(XLII)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4e} , R^{4f} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , X^1 , n , q and z are as defined herein.

In more specific embodiments, the compound has the following Structure (XLIII):

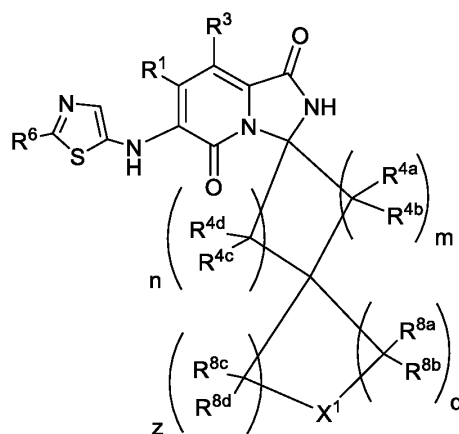


(XLIII)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4a} , R^{4b} , R^5 , R^6 ,

- 5 $R^7, R^{8a}, R^{8b}, R^{8c}, R^{8d}, X^1, m, n, q$ and z are as defined herein.

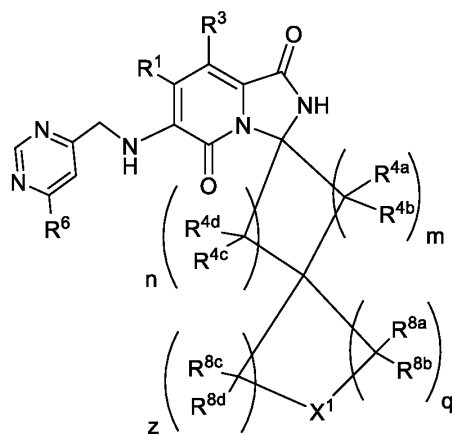
In more specific embodiments, the compound has the following Structure (XLIV):



(XLIV)

- 10 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R¹, R³, R^{4d}, R^{4c}, R^{4a}, R^{4b}, R⁶, R^{8a}, R^{8b}, R^{8c}, R^{8d}, X¹, m, n, q and z are as defined herein.

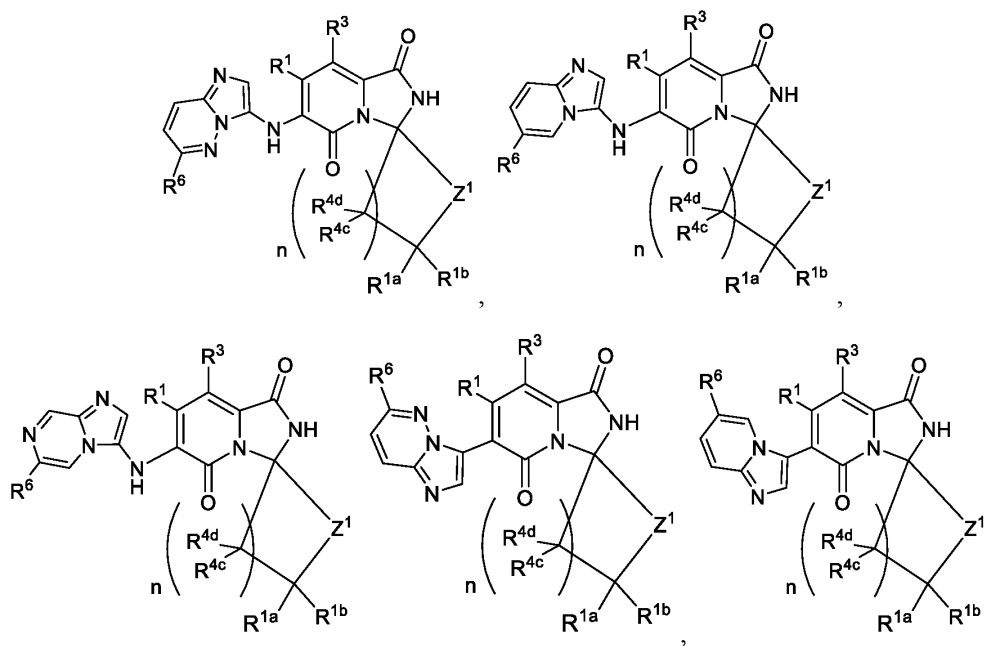
In more specific embodiments, the compound has the following Structure (XLV):

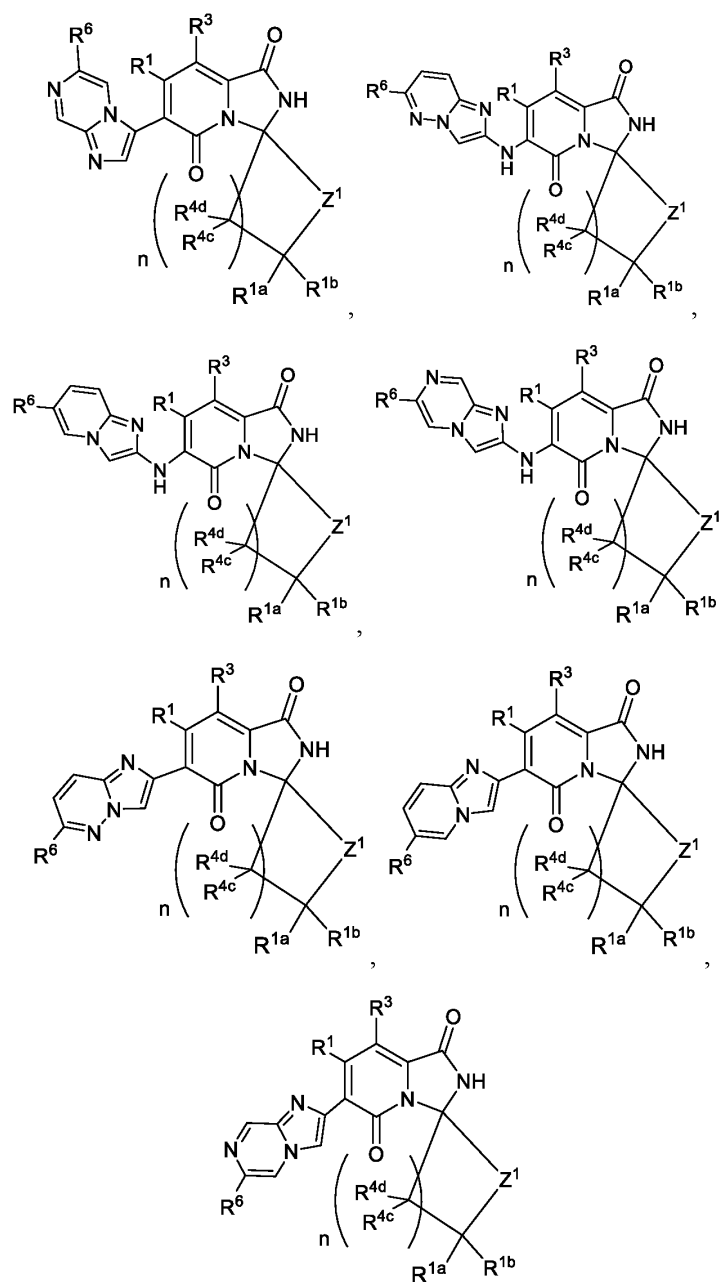


(XLV)

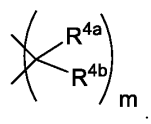
or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^1 , R^3 , R^{4d} , R^{4c} , R^{4a} , R^{4b} , R^6 , R^{8a} , R^{8b} , R^{8c} , R^{8d} , X^1 , m , n , q and z are as defined herein.

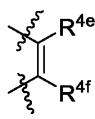
In more specific embodiments, the compound has one of the following Structures:





- 5 or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof.

In some embodiments, Z^1 is .



In some embodiments, Z^1 is

In some embodiments, R^1 is hydrogen.

In some embodiments, R^1 is halogen.

In some embodiments, R^1 is C_{1-6} alkyl.

5 In some embodiments, R^1 is C_{3-7} branched alkyl.

In some embodiments, R^1 is C_{1-6} haloalkyl.

In some embodiments, R^1 is C_{3-7} branched haloalkyl.

In some embodiments, R^1 is C_{1-6} hydroxyalkyl.

In some embodiments, R^1 is C_{3-7} branched hydroxyalkyl.

10 In some embodiments, R^1 is cyano.

In some embodiments, R^1 is C_{1-6} alkoxy.

In some embodiments, R^1 is C_{3-7} branched alkoxy.

In some embodiments, R^1 is hydroxy

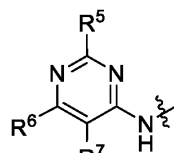
In some embodiments, R^1 is C_{3-6} cycloalkyl.

15 In some embodiments, R^1 is C_{3-6} cycloalkyl that is substituted 1 substituent selected from the groups consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} hydroxyalkyl.

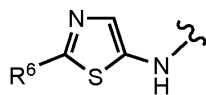
In some embodiments, R^1 is C_{3-6} cycloalkyl that is substituted 2 substituents selected from the groups consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} hydroxyalkyl.

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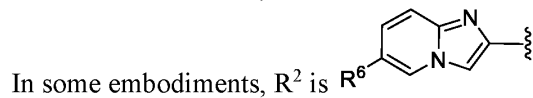
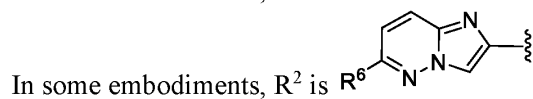
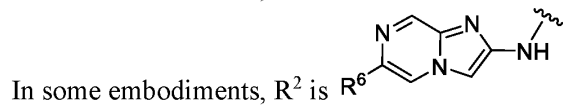
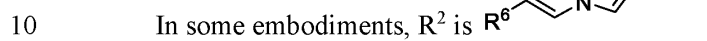
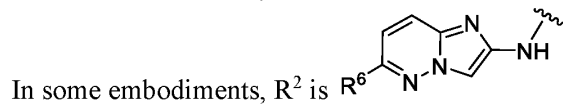
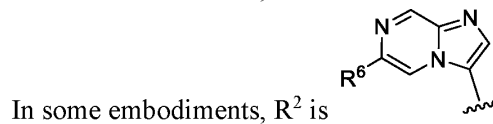
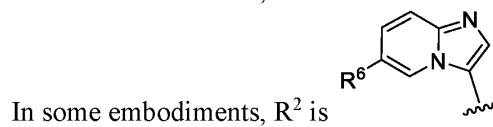
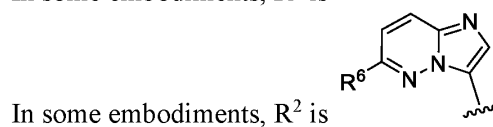
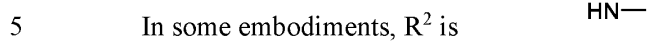
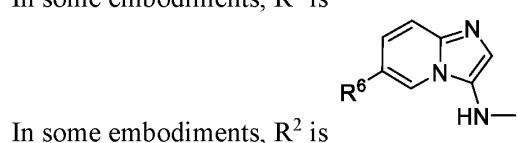
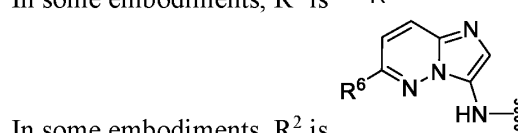
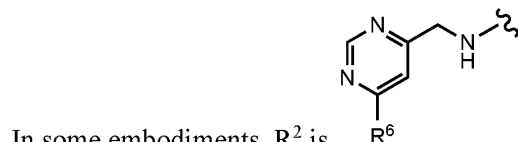
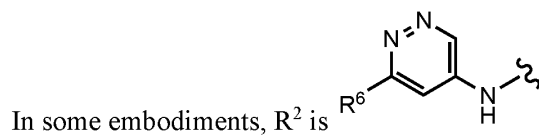
In some embodiments, R^1 is C_{3-6} cycloalkyl that is substituted 3 substituents selected from the groups consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} hydroxyalkyl.

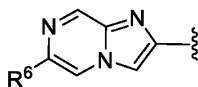


In some embodiments, R^2 is



25 In some embodiments, R^2 is





In some embodiments, R^2 is R^6 .

In some embodiments, R^3 is hydrogen.

In some embodiments, R^3 is halogen.

In some embodiments, R^3 is C_{1-6} alkyl.

5 In some embodiments, R^3 is C_{3-7} branched alkyl.

In some embodiments, R^3 is C_{1-6} haloalkyl.

In some embodiments, R^3 is C_{3-7} branched haloalkyl.

In some embodiments, R^3 is C_{1-6} hydroxyalkyl.

In some embodiments, R^3 is C_{3-7} branched hydroxyalkyl.

10 In some embodiments, R^3 is cyano.

In some embodiments, R^3 is C_{1-6} alkoxy.

In some embodiments, R^3 is C_{3-7} branched alkoxy.

In some embodiments, R^3 is hydroxy.

In some embodiments, R^3 is C_{3-6} cycloalkyl.

15 In some embodiments, R^3 is C_{3-6} cycloalkyl that is substituted with 1 substituent selected from the groups consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} hydroxyalkyl.

In some embodiments, R^3 is C_{3-6} cycloalkyl that is substituted with 2 substituent selected from the groups consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6}

20 hydroxyalkyl.

In some embodiments, R^3 is C_{3-6} cycloalkyl that is substituted with 3 substituent selected from the groups consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} hydroxyalkyl.

In some embodiments, R^{4a} is hydrogen.

25 In some embodiments, R^{4a} is halogen.

In some embodiments, R^{4a} is C_{1-6} alkyl.

In some embodiments, R^{4a} is C_{3-7} branched alkyl.

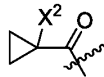
In some embodiments, R^{4a} is C_{1-6} haloalkyl.

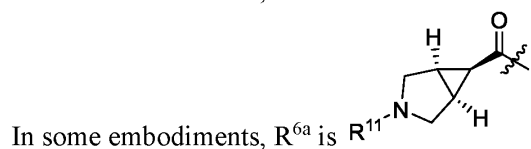
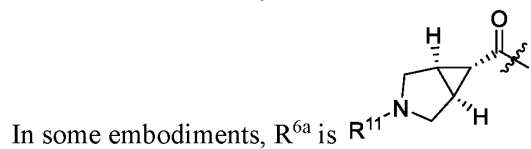
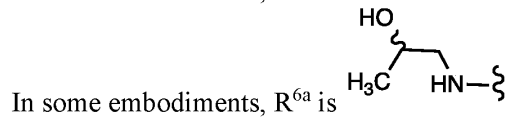
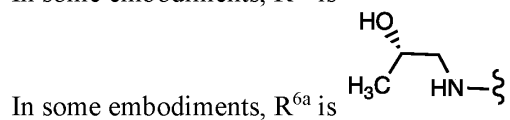
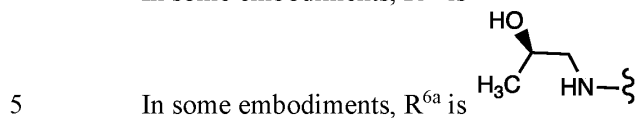
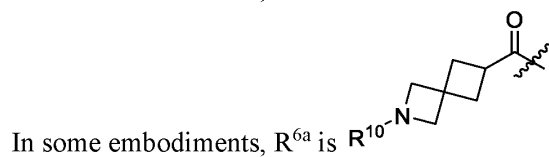
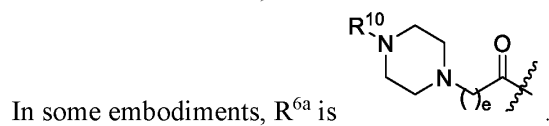
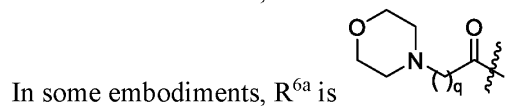
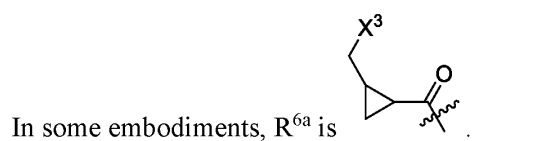
In some embodiments, R^{4a} is C_{3-7} branched haloalkyl.

- In some embodiments, R^{4a} is hydroxy.
- In some embodiments, R^{4a} is C₁₋₆ alkoxy.
- In some embodiments, R^{4a} is C₃₋₇ branched alkoxy.
- In some embodiments, R^{4a} is NHCO(C₁₋₆alkyl).
- 5 In some embodiments, R^{4a} is NHCO(C₃₋₇ branched alkyl).
- In some embodiments, R^{4a} is NHCO(C₃₋₇ cycloalkyl).
- In some embodiments, R^{4a} is NHSO₂(C₁₋₆alkyl).
- In some embodiments, R^{4a} is NHSO₂(C₃₋₇ branched alkyl).
- In some embodiments, R^{4a} is NHSO₂(C₃₋₇ cycloalkyl).
- 10 In some embodiments, R^{4b} is hydrogen.
- In some embodiments, R^{4b} is halogen.
- In some embodiments, R^{4b} is C₁₋₆ alkyl.
- In some embodiments, R^{4b} is C₃₋₇ branched alkyl.
- In some embodiments, R^{4b} is C₁₋₆ haloalkyl.
- 15 In some embodiments, R^{4b} is C₃₋₇ branched haloalkyl.
- In some embodiments, R^{4b} is hydroxy.
- In some embodiments, R^{4b} is C₁₋₆ alkoxy.
- In some embodiments, R^{4b} is C₃₋₇ branched alkoxy.
- In some embodiments, R^{4b} is NHCO(C₁₋₆alkyl).
- 20 In some embodiments, R^{4b} is NHCO(C₃₋₇ branched alkyl).
- In some embodiments, R^{4b} is NHCO(C₃₋₇ cycloalkyl).
- In some embodiments, R^{4b} is NHSO₂(C₁₋₆alkyl).
- In some embodiments, R^{4b} is NHSO₂(C₃₋₇ branched alkyl).
- In some embodiments, R^{4b} is NHSO₂(C₃₋₇ cycloalkyl).
- 25 In some embodiments, R^{4c} is hydrogen.
- In some embodiments, R^{4c} is halogen.
- In some embodiments, R^{4c} is C₁₋₆ alkyl.
- In some embodiments, R^{4c} is C₃₋₇ branched alkyl.
- In some embodiments, R^{4c} is C₁₋₆ haloalkyl.
- 30 In some embodiments, R^{4c} is C₃₋₇ branched haloalkyl.

- In some embodiments, R^{4c} is hydroxy.
- In some embodiments, R^{4c} is C₁₋₆ alkoxy.
- In some embodiments, R^{4c} is C₃₋₇ branched alkoxy.
- In some embodiments, R^{4c} is NHCO(C₁₋₆alkyl).
- 5 In some embodiments, R^{4c} is NHCO(C₃₋₇ branched alkyl).
- In some embodiments, R^{4c} is NHCO(C₃₋₇ cycloalkyl).
- In some embodiments, R^{4c} is NHSO₂(C₁₋₆alkyl).
- In some embodiments, R^{4c} is NHSO₂(C₃₋₇ branched alkyl).
- In some embodiments, R^{4c} is NHSO₂(C₃₋₇ cycloalkyl).
- 10 In some embodiments, R^{4d} is hydrogen.
- In some embodiments, R^{4d} is halogen.
- In some embodiments, R^{4d} is C₁₋₆ alkyl.
- In some embodiments, R^{4d} is C₃₋₇ branched alkyl.
- In some embodiments, R^{4d} is C₁₋₆ haloalkyl.
- 15 In some embodiments, R^{4d} is C₃₋₇ branched haloalkyl.
- In some embodiments, R^{4d} is hydroxy.
- In some embodiments, R^{4d} is C₁₋₆ alkoxy.
- In some embodiments, R^{4d} is C₃₋₇ branched alkoxy.
- In some embodiments, R^{4d} is NHCO(C₁₋₆alkyl).
- 20 In some embodiments, R^{4d} is NHCO(C₃₋₇ branched alkyl).
- In some embodiments, R^{4d} is NHCO(C₃₋₇ cycloalkyl).
- In some embodiments, R^{4d} is NHSO₂(C₁₋₆alkyl).
- In some embodiments, R^{4d} is NHSO₂(C₃₋₇ branched alkyl).
- In some embodiments, R^{4d} is NHSO₂(C₃₋₇ cycloalkyl).
- 25 In some embodiments, R^{4e} is hydrogen.
- In some embodiments, R^{4e} is halogen.
- In some embodiments, R^{4e} is C₁₋₆ alkyl.
- In some embodiments, R^{4e} is C₃₋₇ branched alkyl.
- In some embodiments, R^{4e} is C₁₋₆ haloalkyl.
- 30 In some embodiments, R^{4e} is C₃₋₇ branched haloalkyl.

- In some embodiments, R^{4f} is hydrogen.
- In some embodiments, R^{4f} is halogen.
- In some embodiments, R^{4f} is C_{1-6} alkyl.
- In some embodiments, R^{4f} is C_{3-7} branched alkyl.
- 5 In some embodiments, R^{4f} is C_{1-6} haloalkyl.
- In some embodiments, R^{4f} is C_{3-7} branched haloalkyl.
- In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 3 membered ring.
- In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 4 membered ring.
- 10 In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 5 membered ring.
- In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 6 membered ring.
- 15 In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 7 membered ring.
- In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 3 membered ring that contains an X^1 group.
- In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 4 membered ring that contains an X^1 group.
- 20 In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 5 membered ring that contains an X^1 group.
- In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 6 membered ring that contains an X^1 group.
- 25 In some embodiments, R^{1a} and R^{1b} are taken together to form an optionally substituted 7 membered ring that contains an X^1 group.
- In some embodiments, X^1 is CF_2 .
- In some embodiments, X^1 is $CHCO_2R^{12}$.
- In some embodiments, X^1 is O.
- 30 In some embodiments, X^1 is NH.

- In some embodiments, X^1 is NR^8 .
- In some embodiments, X^1 is SO_2 .
- In some embodiments, m is 0.
- In some embodiments, m is 1.
- 5 In some embodiments, m is 2.
- In some embodiments, n is 1.
- In some embodiments, n is 2.
- In some embodiments, n is 3.
- In some embodiments, R^5 is hydrogen.
- 10 In some embodiments, R^5 is halogen.
- In some embodiments, R^5 is C_{1-6} alkyl.
- In some embodiments, R^5 is C_{3-7} branched alkyl.
- In some embodiments, R^5 is C_{1-6} haloalkyl.
- In some embodiments, R^5 is C_{3-7} branched haloalkyl.
- 15 In some embodiments, R^5 is C_{1-6} alkoxy.
- In some embodiments, R^5 is C_{3-7} branched alkoxy.
- In some embodiments, R^5 is hydroxy.
- In some embodiments, R^6 is hydrogen.
- In some embodiments, R^6 is NH_2 .
- 20 In some embodiments, R^6 is NHR^{6a} .
- In some embodiments, R^6 is $NHCH_2CH_2OH$.
- In some embodiments, R^6 is $NHCH_2CH_2NHSO_2Me$.
- In some embodiments, R^6 is C_{1-6} alkoxy.
- In some embodiments, R^6 is C_{3-7} branched alkoxy.
- 25 In some embodiments, R^6 is hydroxy.
- In some embodiments, R^{6a} is $-(CO)C_{1-6}$ alkyl.
- In some embodiments, R^{6a} is $-(CO)C_{3-7}$ branched alkyl.
- In some embodiments, R^{6a} is $-(CO)C_{1-6}$ hydroxyalkyl.
- In some embodiments, R^{6a} is .



10 In some embodiments, q is 1.

In some embodiments, q is 2.

In some embodiments, q is 3.

In some embodiments, q is 4.

In some embodiments, q is 5.

15 In some embodiments, q is 6.

In some embodiments, e is 1.

- In some embodiments, e is 2.
- In some embodiments, e is 3.
- In some embodiments, e is 4.
- In some embodiments, e is 5.
- 5 In some embodiments, e is 6.
- In some embodiments, X² is hydrogen.
- In some embodiments, X² is halogen.
- In some embodiments, X² is C₁₋₆alkyl.
- In some embodiments, X² is C₃₋₇ branched alkyl.
- 10 In some embodiments, X² is C₁₋₆haloalkyl.
- In some embodiments, X² is C₃₋₇ branched haloalkyl.
- In some embodiments, X² is hydroxy.
- In some embodiments, X² is C₁₋₆hydroxyalkyl.
- In some embodiments, X² is C₃₋₇ branched hydroxyalkyl.
- 15 In some embodiments, X² is C₁₋₆alkoxy.
- In some embodiments, X² is C₃₋₇ branched alkoxy.
- In some embodiments, X² is C₁₋₆haloalkoxy.
- In some embodiments, X² is C₃₋₇ branched haloalkoxy.
- In some embodiments, X² is NH₂.
- 20 In some embodiments, X² is NH(C₁₋₆alkyl).
- In some embodiments, X² is N(C₁₋₆alkyl)₂.
- In some embodiments, X² is C₁₋₅(COOH).
- In some embodiments, X² is C₁₋₆(NHSO₂Me).
- In some embodiments, X³ is hydrogen.
- 25 In some embodiments, X³ is halogen.
- In some embodiments, X³ is C₁₋₅ alkyl.
- In some embodiments, X³ is C₃₋₇ branched alkyl.
- In some embodiments, X³ is C₁₋₅ haloalkyl.
- In some embodiments, X³ is C₃₋₇ branched haloalkyl.
- 30 In some embodiments, X³ is hydroxy.

- In some embodiments, X^3 is C_{1-5} hydroxyalkyl.
- In some embodiments, X^3 is C_{3-7} branched hydroxyalkyl.
- In some embodiments, X^3 is C_{1-5} alkoxy.
- In some embodiments, X^3 is C_{3-7} branched alkoxy.
- 5 In some embodiments, X^3 is C_{1-5} haloalkoxy.
- In some embodiments, X^3 is C_{3-7} branched haloalkoxy.
- In some embodiments, X^3 is NH_2 .
- In some embodiments, X^3 is $NH(C_{1-6} \text{ alkyl})$.
- In some embodiments, X^3 is $N(C_{1-6} \text{ alkyl})_2$.
- 10 In some embodiments, X^3 is $COOH$.
- In some embodiments, X^3 is $C_{1-5}(COOH)$.
- In some embodiments, X^3 is $NHSO_2Me$.
- In some embodiments, X^3 is $C_{1-5}(NHSO_2Me)$.
- In some embodiments, R^7 is hydrogen.
- 15 In some embodiments, R^7 is halogen.
- In some embodiments, R^7 is C_{1-6} alkyl.
- In some embodiments, R^7 is C_{3-7} branched alkyl.
- In some embodiments, R^7 is C_{1-6} haloalkyl.
- In some embodiments, R^7 is C_{3-7} branched haloalkyl.
- 20 In some embodiments, R^7 is C_{1-6} alkoxy.
- In some embodiments, R^7 is C_{3-7} branched alkoxy.
- In some embodiments, R^7 is hydroxy.
- In some embodiments, R^8 is C_{1-6} alkyl.
- In some embodiments, R^8 is C_{1-6} haloalkyl.
- 25 In some embodiments, R^8 is C_{3-7} branched haloalkyl.
- In some embodiments, R^8 is C_{1-6} hydroxyalkyl.
- In some embodiments, R^8 is C_{3-7} branched hydroxyalkyl.
- In some embodiments, R^8 is C_{1-6} alkoxy.
- In some embodiments, R^8 is C_{3-7} branched alkoxy.
- 30 In some embodiments, R^8 is $CO(C_{1-6} \text{ alkyl})$.

- In some embodiments, R^8 is $\text{CO}(\text{C}_{3-7}$ branched alkyl).
- In some embodiments, R^8 is $\text{SO}_2(\text{C}_{1-6}\text{alkyl})$.
- In some embodiments, R^8 is $\text{SO}_2(\text{C}_{3-7}$ branched alkyl).
- In some embodiments, R^{8a} is hydrogen.
- 5 In some embodiments, R^{8a} is halogen.
- In some embodiments, R^{8a} is C_{1-6} alkyl.
- In some embodiments, R^{8a} is C_{3-7} branched alkyl.
- In some embodiments, R^{8a} is C_{1-6} haloalkyl.
- In some embodiments, R^{8a} is C_{3-7} branched haloalkyl.
- 10 In some embodiments, R^{8a} is C_{1-6} hydroxyalkyl.
- In some embodiments, R^{8a} is C_{3-7} branched hydroxyalkyl.
- In some embodiments, R^{8a} is hydroxy.
- In some embodiments, R^{8a} is C_{1-6} alkoxy.
- In some embodiments, R^{8a} is C_{3-7} branched alkoxy.
- 15 In some embodiments, R^{8a} is $\text{NHCO}(\text{C}_{1-6}\text{alkyl})$.
- In some embodiments, R^{8a} is $\text{NHCO}(\text{C}_{3-7}$ branched alkyl).
- In some embodiments, R^{8a} is $\text{NHSO}_2(\text{C}_{1-6}\text{alkyl})$.
- In some embodiments, R^{8a} is $\text{NHSO}_2(\text{C}_{3-7}$ branched alkyl).
- In some embodiments, R^{8b} is hydrogen.
- 20 In some embodiments, R^{8b} is halogen.
- In some embodiments, R^{8b} is C_{1-6} alkyl.
- In some embodiments, R^{8b} is C_{3-7} branched alkyl.
- In some embodiments, R^{8b} is C_{1-6} haloalkyl.
- In some embodiments, R^{8b} is C_{3-7} branched haloalkyl.
- 25 In some embodiments, R^{8b} is C_{1-6} hydroxyalkyl.
- In some embodiments, R^{8b} is C_{3-7} branched hydroxyalkyl.
- In some embodiments, R^{8b} is hydroxy.
- In some embodiments, R^{8b} is C_{1-6} alkoxy.
- In some embodiments, R^{8b} is C_{3-7} branched alkoxy.
- 30 In some embodiments, R^{8b} is $\text{NHCO}(\text{C}_{1-6}\text{alkyl})$.

- In some embodiments, R^{8b} is NHCO(C₃₋₇ branched alkyl).
- In some embodiments, R^{8b} is NHSO₂(C₁₋₆alkyl).
- In some embodiments, R^{8b} is NHSO₂(C₃₋₇ branched alkyl).
- In some embodiments, R^{8c} is hydrogen.
- 5 In some embodiments, R^{8c} is halogen.
- In some embodiments, R^{8c} is C₁₋₆ alkyl.
- In some embodiments, R^{8c} is C₃₋₇ branched alkyl.
- In some embodiments, R^{8c} is C₁₋₆ haloalkyl.
- In some embodiments, R^{8c} is C₃₋₇ branched haloalkyl.
- 10 In some embodiments, R^{8c} is C₁₋₆ hydroxyalkyl.
- In some embodiments, R^{8c} is C₃₋₇ branched hydroxyalkyl.
- In some embodiments, R^{8c} is hydroxy.
- In some embodiments, R^{8c} is C₁₋₆ alkoxyl.
- In some embodiments, R^{8c} is C₃₋₇ branched alkoxy.
- 15 In some embodiments, R^{8c} is NHCO(C₁₋₆alkyl).
- In some embodiments, R^{8c} is NHCO(C₃₋₇ branched alkyl).
- In some embodiments, R^{8c} is NHSO₂(C₁₋₆alkyl).
- In some embodiments, R^{8c} is NHSO₂(C₃₋₇ branched alkyl).
- In some embodiments, R^{8d} is hydrogen.
- 20 In some embodiments, R^{8d} is halogen.
- In some embodiments, R^{8d} is C₁₋₆ alkyl.
- In some embodiments, R^{8d} is C₃₋₇ branched alkyl,
- In some embodiments, R^{8d} is C₁₋₆ haloalkyl.
- In some embodiments, R^{8d} is C₃₋₇ branched haloalkyl.
- 25 In some embodiments, R^{8d} is C₁₋₆ hydroxyalkyl.
- In some embodiments, R^{8d} is C₃₋₇ branched hydroxyalkyl.
- In some embodiments, R^{8d} is hydroxy.
- In some embodiments, R^{8d} is C₁₋₆ alkoxyl.
- In some embodiments, R^{8d} is C₃₋₇ branched alkoxy
- 30 In some embodiments, R^{8d} is NHCO(C₁₋₆alkyl).

- In some embodiments, R^{8d} is $\text{NHCO}(\text{C}_{3-7}$ branched alkyl).
- In some embodiments, R^{8d} is $\text{NHSO}_2(\text{C}_{1-6}$ alkyl).
- In some embodiments, R^{8d} is $\text{NHSO}_2(\text{C}_{3-7}$ branched alkyl).
- In some embodiments, R^{9a} is hydrogen.
- 5 In some embodiments, R^{9a} is halogen.
- In some embodiments, R^{9a} is C_{1-6} alkyl.
- In some embodiments, R^{9a} is C_{3-7} branched alkyl.
- In some embodiments, R^{9a} is C_{1-6} haloalkyl.
- In some embodiments, R^{9a} is C_{3-7} branched haloalkyl.
- 10 In some embodiments, R^{9a} is C_{1-6} hydroxyalkyl.
- In some embodiments, R^{9a} is C_{3-7} branched hydroxyalkyl.
- In some embodiments, R^{9a} is hydroxy.
- In some embodiments, R^{9a} is C_{1-6} alkoxyl.
- In some embodiments, R^{9a} is C_{3-7} branched alkoxy.
- 15 In some embodiments, R^{9b} is hydrogen.
- In some embodiments, R^{9b} is halogen.
- In some embodiments, R^{9b} is C_{1-6} alkyl.
- In some embodiments, R^{9b} is C_{3-7} branched alkyl.
- In some embodiments, R^{9b} is C_{1-6} haloalkyl.
- 20 In some embodiments, R^{9b} is C_{3-7} branched haloalkyl.
- In some embodiments, R^{9b} is C_{1-6} hydroxyalkyl.
- In some embodiments, R^{9b} is C_{3-7} branched hydroxyalkyl.
- In some embodiments, R^{9b} is hydroxy.
- In some embodiments, R^{9b} is C_{1-6} alkoxyl.
- 25 In some embodiments, R^{9b} is C_{3-7} branched alkoxy.
- In some embodiments, R^{9a} and R^{9b} are taken together to form a 3 membered ring.
- In some embodiments, R^{9a} and R^{9b} are taken together to form a 4 membered ring.

In some embodiments, R^{9a} and R^{9b} are taken together to form a 5 membered ring.

In some embodiments, R^{9a} and R^{9b} are taken together to form a 6 membered ring.

5 In some embodiments, R^{9a} and R^{9b} are taken together to form a 7 membered ring.

In some embodiments, R^{9a} and R^{9b} are taken together to form an optionally substituted 3 membered ring.

10 In some embodiments, R^{9a} and R^{9b} are taken together to form an optionally substituted 4 membered ring.

In some embodiments, R^{9a} and R^{9b} are taken together to form an optionally substituted 5 membered ring.

In some embodiments, R^{9a} and R^{9b} are taken together to form an optionally substituted 6 membered ring.

15 In some embodiments, R^{9a} and R^{9b} are taken together to form an optionally substituted 7 membered ring.

In some embodiments, q is 1.

In some embodiments, q is 2.

In some embodiments, q is 3.

20 In some embodiments, z is 0.

In some embodiments, z is 1.

In some embodiments, z is 2.

In some embodiments, R¹⁰ is hydrogen

In some embodiments, R¹⁰ is C₁₋₆ alkyl.

25 In some embodiments, R¹⁰ is C₁₋₆ haloalkyl.

In some embodiments, R¹⁰ is C₃₋₇ branched haloalkyl.

In some embodiments, R¹⁰ is C₁₋₆ hydroxyalkyl.

In some embodiments, R¹⁰ is C₁₋₆ alkoxy.

In some embodiments, R¹⁰ is C₃₋₇ branched alkoxy.

30 In some embodiments, R¹⁰ is CO(C₁₋₆alkyl).

In some embodiments, R¹⁰ is CO(C₃₋₇ branched alkyl).

In some embodiments, R¹⁰ is SO₂(C₁₋₆alkyl).

In some embodiments, R¹⁰ is SO₂(C₃₋₇ branched alkyl).

In some embodiments, R¹¹ is hydrogen.

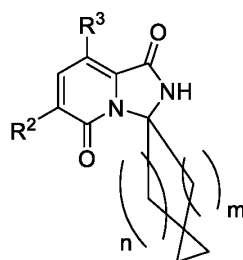
5 In some embodiments, R¹¹ is C₁₋₆ alkyl.

In some embodiments, R¹² is hydrogen.

In some embodiments, R¹² is C₁₋₆ alkyl.

In some embodiments the compounds of Formula (I), (I') or substructures
exclude *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-
10 cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-
yl)cyclopropanecarboxamide; and/or 3-((6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-
dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-
yl)amino)pyrimidin-4-yl)amino)propanoic acid.

In some embodiments, the compound has the following Structure (XLVII):



15

(XLVII)

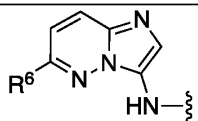
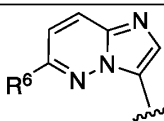
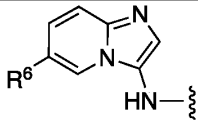
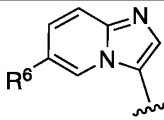
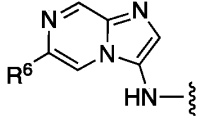
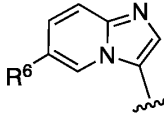
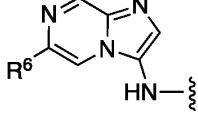
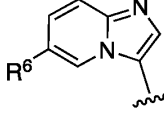
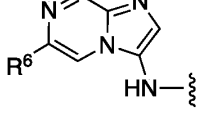
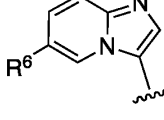
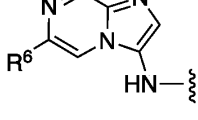
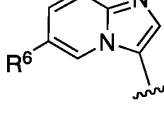
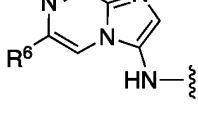
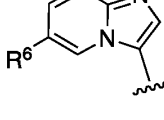
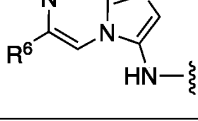
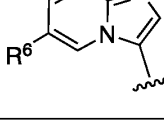
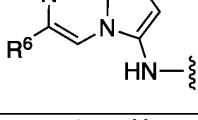
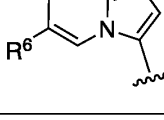
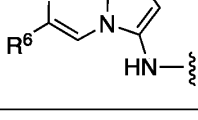
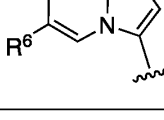
or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex,
stereoisomer, tautomer, or prodrug thereof, wherein m, n, R³ and R² are as defined
herein.

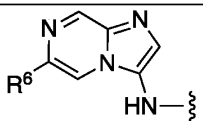
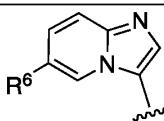
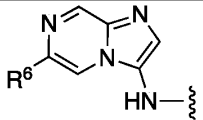
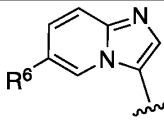
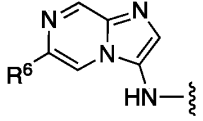
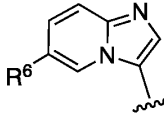
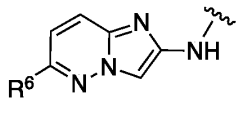
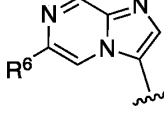
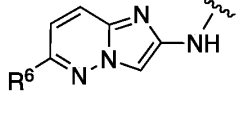
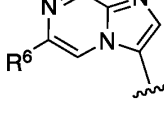
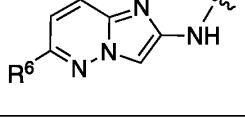
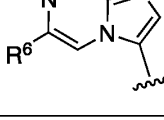
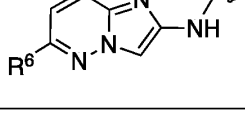
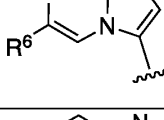
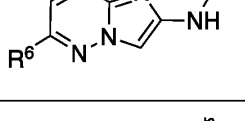
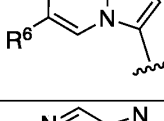
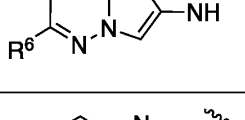
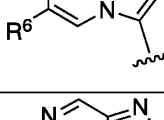
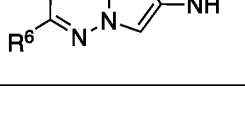
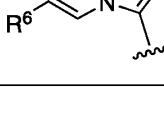
20 Examples of R², R³, m and n, without limitation, are set forth in Table 2, below.

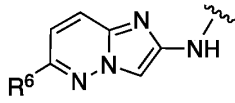
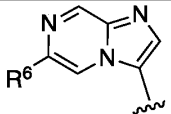
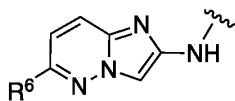
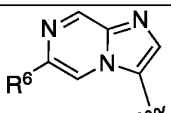
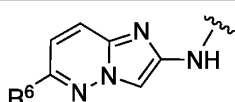
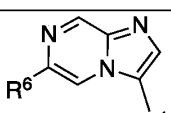
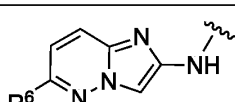
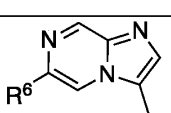
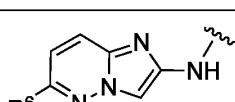
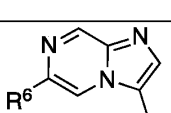
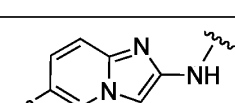
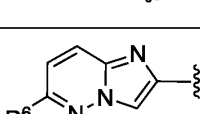
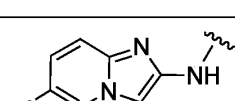
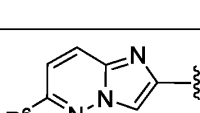
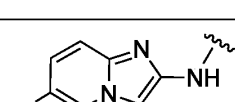
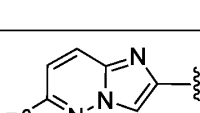
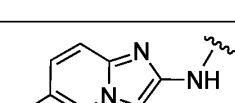
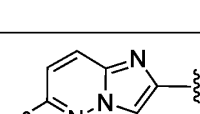
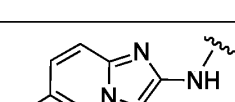
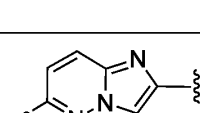
Table 2. Exemplary moieties for R², R³, m, and n

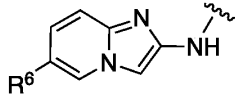
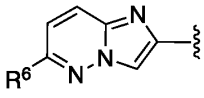
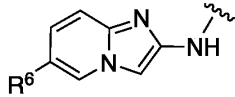
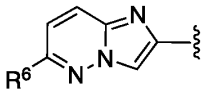
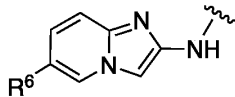
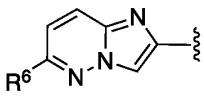
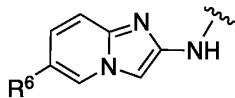
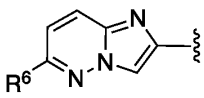
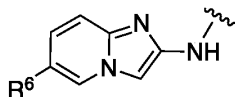
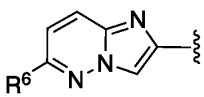
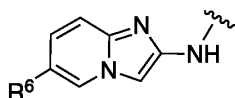
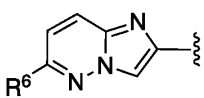
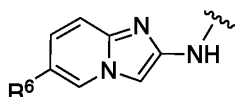
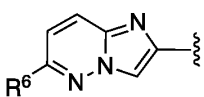
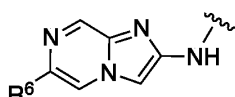
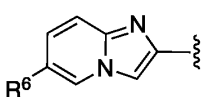
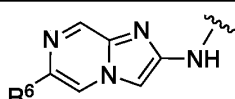
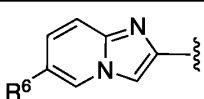
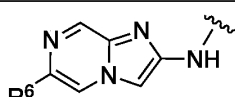
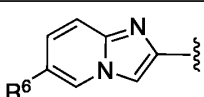
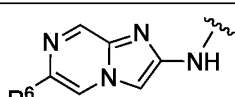
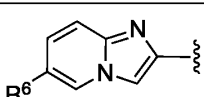
Entry	R ²	R ³	n	m	Entry	R ²	R ³	m	n
1		CH ₃	1	1	73		CH ₃	1	1

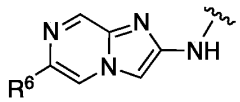
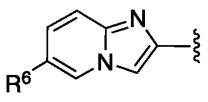
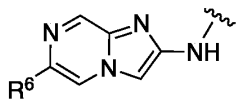
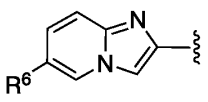
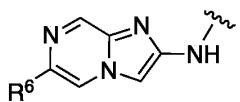
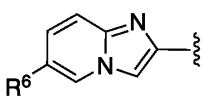
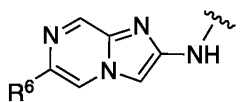
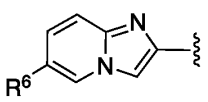
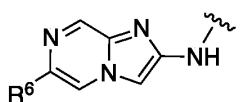
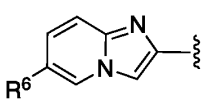
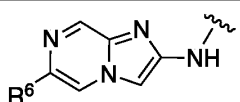
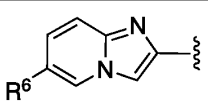
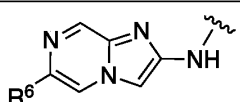
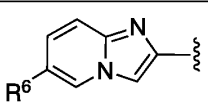
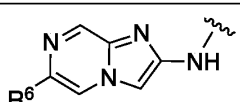
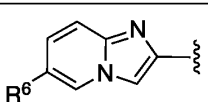
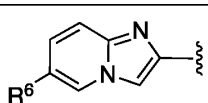
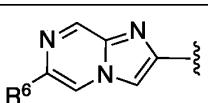
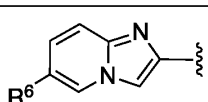
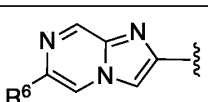
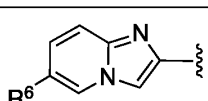
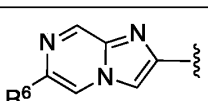
Entry	R ²	R ³	n	m	Entry	R ²	R ³	m	n
2		CH ₃	2	1	74		CH ₃	2	1
3		CH ₃	3	1	75		CH ₃	3	1
4		CH ₃	2	2	76		CH ₃	2	2
5		CH ₃	3	2	77		CH ₃	3	2
6		CH ₃	4	1	78		CH ₃	4	1
7		Cl	1	1	79		Cl	1	1
8		Cl	2	1	80		Cl	2	1
9		Cl	3	1	81		Cl	3	1
10		Cl	2	2	82		Cl	2	2
11		Cl	3	2	83		Cl	3	2

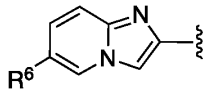
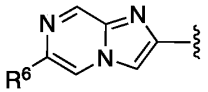
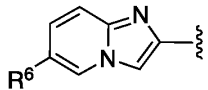
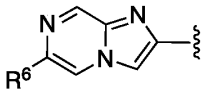
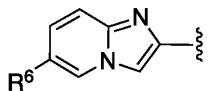
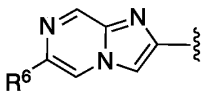
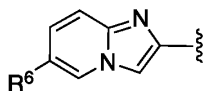
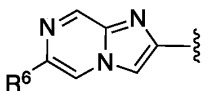
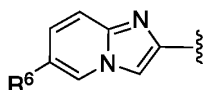
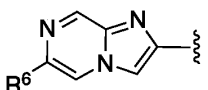
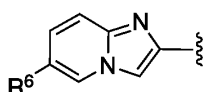
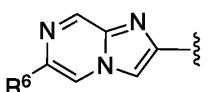
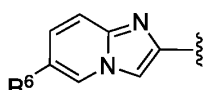
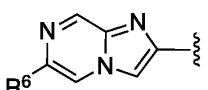
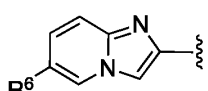
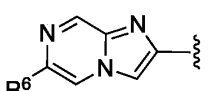
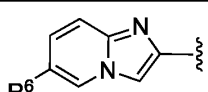
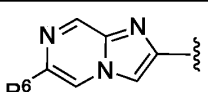
Entry	R ²	R ³	n	m	Entry	R ²	R ³	m	n
12		Cl	4	1	84		Cl	4	1
13		CH ₃	1	1	85		CH ₃	1	1
14		CH ₃	2	1	86		CH ₃	2	1
15		CH ₃	3	1	87		CH ₃	3	1
16		CH ₃	2	2	88		CH ₃	2	2
17		CH ₃	3	2	89		CH ₃	3	2
18		CH ₃	4	1	90		CH ₃	4	1
19		Cl	1	1	91		Cl	1	1
20		Cl	2	1	92		Cl	2	1
21		Cl	3	1	93		Cl	3	1

Entry	R ²	R ³	n	m	Entry	R ²	R ³	m	n
22		Cl	2	2	94		Cl	2	2
23		Cl	3	2	95		Cl	3	2
24		Cl	4	1	96		Cl	4	1
25		CH ₃	1	1	97		CH ₃	1	1
26		CH ₃	2	1	98		CH ₃	2	1
27		CH ₃	3	1	99		CH ₃	3	1
28		CH ₃	2	2	100		CH ₃	2	2
29		CH ₃	3	2	101		CH ₃	3	2
30		CH ₃	4	1	102		CH ₃	4	1
31		Cl	1	1	103		Cl	1	1

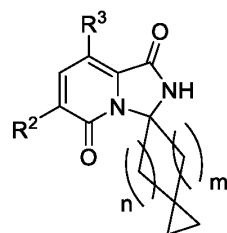
Entry	R ²	R ³	n	m	Entry	R ²	R ³	m	n
32		Cl	2	1	104		Cl	2	1
33		Cl	3	1	105		Cl	3	1
34		Cl	2	2	106		Cl	2	2
35		Cl	3	2	107		Cl	3	2
36		Cl	4	1	108		Cl	4	1
37		CH ₃	1	1	109		CH ₃	1	1
38		CH ₃	2	1	110		CH ₃	2	1
39		CH ₃	3	1	111		CH ₃	3	1
40		CH ₃	2	2	112		CH ₃	2	2
41		CH ₃	3	2	113		CH ₃	3	2

Entry	R ²	R ³	n	m	Entry	R ²	R ³	m	n
42		CH ₃	4	1	114		CH ₃	4	1
43		Cl	1	1	115		Cl	1	1
44		Cl	2	1	116		Cl	2	1
45		Cl	3	1	117		Cl	3	1
46		Cl	2	2	118		Cl	2	2
47		Cl	3	2	119		Cl	3	2
48		Cl	4	1	120		Cl	4	1
49		CH ₃	1	1	121		CH ₃	1	1
50		CH ₃	2	1	122		CH ₃	2	1
51		CH ₃	3	1	123		CH ₃	3	1
52		CH ₃	2	2	124		CH ₃	2	2

Entry	R ²	R ³	n	m	Entry	R ²	R ³	m	n
53		CH ₃	3	2	125		CH ₃	3	2
54		CH ₃	4	1	126		CH ₃	4	1
55		Cl	1	1	127		Cl	1	1
56		Cl	2	1	128		Cl	2	1
57		Cl	3	1	129		Cl	3	1
58		Cl	2	2	130		Cl	2	2
59		Cl	3	2	131		Cl	3	2
60		Cl	4	1	132		Cl	4	1
61		CH ₃	1	1	133		CH ₃	1	1
62		CH ₃	2	1	132		CH ₃	2	1
63		CH ₃	3	1	135		CH ₃	3	1

Entry	R ²	R ³	n	m	Entry	R ²	R ³	m	n
64		CH ₃	2	2	136		CH ₃	2	2
65		CH ₃	3	2	137		CH ₃	3	2
66		CH ₃	4	1	138		CH ₃	4	1
67		Cl	1	1	139		Cl	1	1
68		Cl	2	1	140		Cl	2	1
69		Cl	3	1	141		Cl	3	1
70		Cl	2	2	142		Cl	2	2
71		Cl	3	2	143		Cl	3	2
72		Cl	4	1	144		Cl	4	1

In some embodiments, the compound has the following Structure (XLVIII):

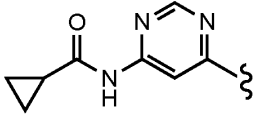
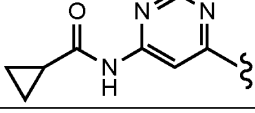
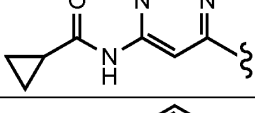
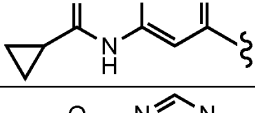
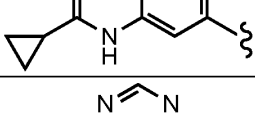
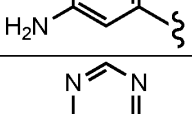
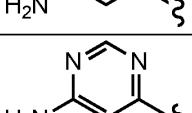
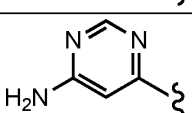
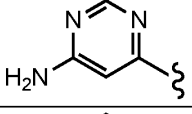
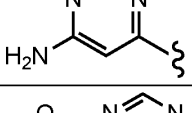
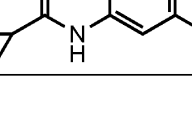


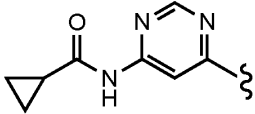
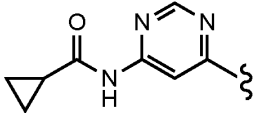
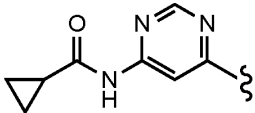
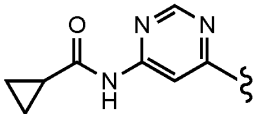
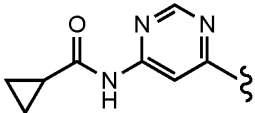
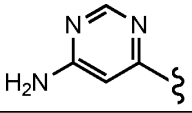
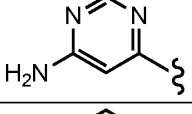
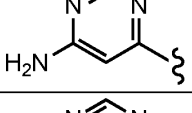
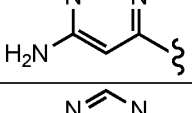
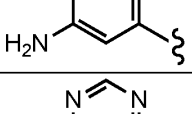
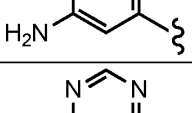
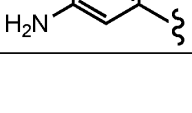
(XLVIII)

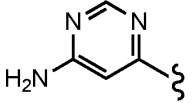
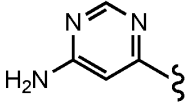
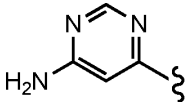
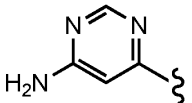
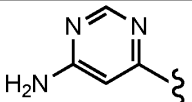
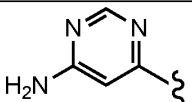
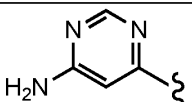
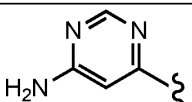
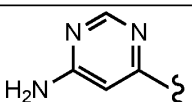
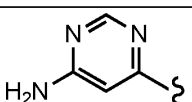
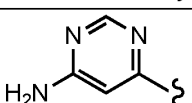
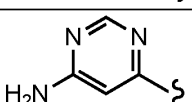
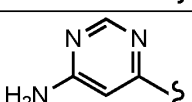
or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein R^2 , R^3 , n , and m are as defined herein. Non-limiting examples of R^2 , R^3 , n , and m are defined herein below in Table 3, below.

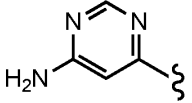
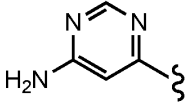
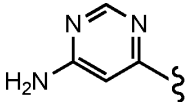
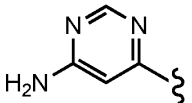
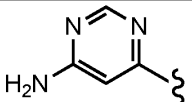
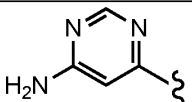
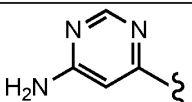
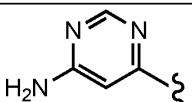
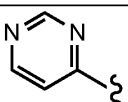
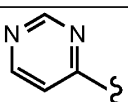
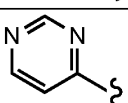
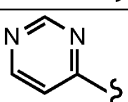
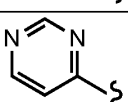
Table 3. Exemplary moieties for R^2 , R^3 , n , and m

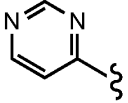
	R^3	R^2	m	n
1	CH ₃		1	1
2	CH ₃		2	1
3	CH ₃		3	1
4	CH ₃		2	2
5	CH ₃		3	2
6	CH ₃		4	1
7	CH ₃		1	1

	R ³	R ²	m	n
8	CH ₃		2	1
9	CH ₃		3	1
10	CH ₃		2	2
11	CH ₃		3	2
12	CH ₃		4	1
13	Cl		1	1
14	Cl		2	1
15	Cl		3	1
16	Cl		2	2
17	Cl		3	2
18	Cl		4	1
19	CH ₃		1	1

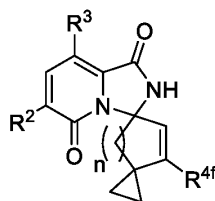
	R ³	R ²	m	n
20	CH ₃		2	1
21	CH ₃		3	1
22	CH ₃		2	2
23	CH ₃		3	2
24	CH ₃		4	1
25	Br		1	1
26	Br		2	1
27	CH ₂ F		1	1
28	CH ₂ F		2	1
29	CH ₂ F		3	1
30	CH ₂ F		2	2
31	CH ₂ F		3	2

	R ³	R ²	m	n
32	CH ₂ F		4	1
33	CH ₂ CH ₃		1	1
34	CH ₂ CH ₃		2	1
35	CH ₂ CH ₃		3	1
36	CH ₂ CH ₃		2	2
37	CH ₂ CH ₃		3	2
38	CH ₂ CH ₃		4	1
39	CH ₂ CH ₂ F		1	1
40	CH ₂ CH ₂ F		2	1
41	CH ₂ CH ₂ F		3	1
42	CH ₂ CH ₂ F		2	2
43	CH ₂ CH ₂ F		3	2
44	CH ₂ CH ₂ F		4	1

	R ³	R ²	m	n
45	CF ₂ CH ₃		1	1
46	CF ₂ CH ₃		2	1
47	CF ₂ CH ₃		3	1
48	CF ₂ CH ₃		2	2
49	CF ₂ CH ₃		3	2
50	CF ₂ CH ₃		4	1
51	Br		3	2
52	Br		4	2
53	CH ₃		1	1
54	CH ₃		2	1
55	CH ₃		3	1
56	CH ₃		2	2
57	CH ₃		3	2

	R ³	R ²	m	n
58	CH ₃		4	1

Compounds of the present disclosure include compounds having the formula (XLIX) or a pharmaceutically acceptable salt form thereof:



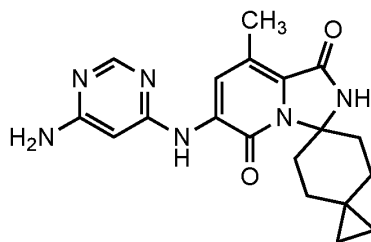
(XLIX)

wherein non-limiting examples of R³, R^{4f}, and n are defined herein below in Table 4.

Table 4. Exemplary moieties for R³, R^{4f}, and n

Entry	R ³	R ^{4f}	n	Entry	R ³	R ^{4f}	n
1	CH ₃	H	1	19	Cl	H	1
2	CH ₃	CH ₃	1	20	Cl	CH ₃	1
3	CH ₃	CH ₂ CH ₃	1	21	Cl	CH ₂ CH ₃	1
4	CH ₃	CH(CH ₃) ₂	1	22	Cl	CH(CH ₃) ₂	1
5	CH ₃	CH ₂ F	1	23	Cl	CH ₂ F	1
6	CH ₃	CH ₂ CH ₂ F	1	24	Cl	CH ₂ CH ₂ F	1
7	CH ₃	H	2	25	Cl	H	2
8	CH ₃	CH ₃	2	29	Cl	CH ₃	2
9	CH ₃	CH ₂ CH ₃	2	27	Cl	CH ₂ CH ₃	2
10	CH ₃	CH(CH ₃) ₂	2	28	Cl	CH(CH ₃) ₂	2
11	CH ₃	CH ₂ F	2	29	Cl	CH ₂ F	2
12	CH ₃	CH ₂ CH ₂ F	2	30	Cl	CH ₂ CH ₂ F	2
13	CH ₃	H	3	31	Cl	H	3
14	CH ₃	CH ₃	3	32	Cl	CH ₃	3
15	CH ₃	CH ₂ CH ₃	3	33	Cl	CH ₂ CH ₃	3
16	CH ₃	CH(CH ₃) ₂	3	34	Cl	CH(CH ₃) ₂	3
17	CH ₃	CH ₂ F	3	35	Cl	CH ₂ F	3
18	CH ₃	CH ₂ CH ₂ F	3	36	Cl	CH ₂ CH ₂ F	3

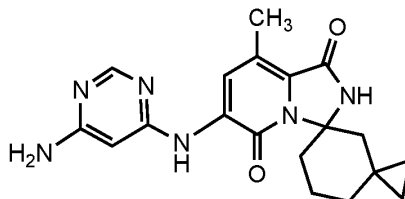
For the purposes of demonstrating the manner in which the compounds of the present disclosure are named and referred to herein, the compound having the formula:



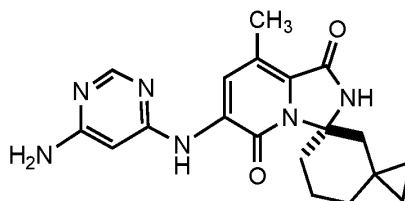
5

has the chemical name 6'-(((6-aminopyrimidin-4-yl)amino)-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-1'',5''-dione.

For the purposes of the present disclosure, a compound depicted by the racemic formula, for example:

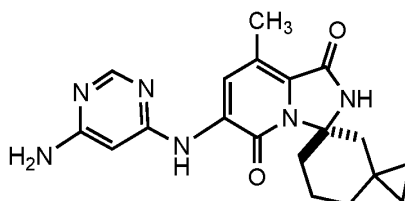


will stand equally well for either of the two enantiomers having the formula:



5

or the formula:



or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof.

10 For the purposes of the present disclosure, a compound depicted by the racemic formula will stand equally well for either of the two enantiomers or mixtures thereof, or in the case where a second chiral center is present, all diastereomers.

In all of the embodiments provided herein, examples of suitable optional substituents are not intended to limit the scope of the claimed disclosure. The compounds of the disclosure may contain any of the substituents, or combinations of substituents, provided herein. It is understood that in the present description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

15 In an additional embodiment, various compounds of the disclosure which exist in free base or acid form can be converted to their pharmaceutically acceptable salts by

20

treatment with the appropriate inorganic or organic base or acid by methods known to one skilled in the art. Salts of the compounds of the disclosure can be converted to their free base or acid form by standard techniques.

Pharmaceutical Compositions

5 To facilitate delivery to a cell, tissue, or patient, an MNK inhibitor of the present disclosure may, in various compositions, be formulated with a pharmaceutically-acceptable carrier, excipient, or diluent. Suitable pharmaceutical carriers, excipients, and/or diluents for use in the present disclosure include, but are not limited to, lactose, sucrose, starch powder, talc powder, cellulose esters of alkoanoic acids, magnesium
10 stearate, magnesium oxide, crystalline cellulose, methyl cellulose, carboxymethyl cellulose, gelatin, glycerin, sodium alginate, gum arabic, acacia gum, sodium and calcium salts of phosphoric and sulfuric acids, polyvinylpyrrolidone and/or polyvinyl alcohol, saline, and water. Specific formulations of compounds for therapeutic treatment are discussed in Hoover, J. E., Remington's Pharmaceutical Sciences (Easton,
15 Pa.: Mack Publishing Co., 1975) and Liberman and Lachman, eds. Pharmaceutical Dosage Forms (New York, N.Y.: Marcel Decker Publishers, 1980), incorporated by reference herein.

Other embodiments are directed to pharmaceutical compositions. The pharmaceutical composition comprises any one (or more) of the foregoing compounds
20 and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection. In still more embodiments, the pharmaceutical compositions comprise a compound as disclosed herein and an additional therapeutic agent. Non-limiting examples of such therapeutic agents are
25 described herein below.

Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous,

intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly
5 into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the compound is delivered in a targeted drug delivery system, for example, in a liposome coated with and organ-specific antibody. In such embodiments,
10 the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

15 In treatment methods according to embodiments of the disclosure, an effective amount of at least one compound of Structure (I) through (XLIX) is administered to a subject suffering from or diagnosed as having such a disease, disorder, or medical condition. Effective amounts or doses may be ascertained by methods such as modeling, dose escalation studies or clinical trials, *e.g.*, the mode or route of
20 administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician.

The compounds according to the disclosure are effective over a wide dosage
25 range. For example, in the treatment of adult humans, dosages from 10 to 5000 mg, from 100 to 5000 mg, from 1000 mg to 4000 mg per day, and from 1000 to 3000 mg per day are examples of dosages that are used in some embodiments. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and
30 the preference and experience of the attending physician.

In some embodiments, compounds of the disclosure are administered in a single dose. Typically, such administration will be by injection, *e.g.*, intravenous injection, in order to introduce the agent quickly. However, other routes are used as appropriate. A single dose of a compound of the disclosure may also be used for treatment of an acute condition.

In some embodiments, compounds of the disclosure are administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments, dosing is about once a month, once every two weeks, once a week, or once every other day. In another embodiment compounds of the disclosure and another agent are administered together about once per day to about 6 times per day. In another embodiment the administration of compounds of the disclosure and an agent continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

Administration of compounds of the disclosure may continue as long as necessary. In some embodiments, compounds of the disclosure are administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, compounds of the disclosure are administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, compounds of the disclosure are administered chronically on an ongoing basis, *e.g.*, for the treatment of chronic migraine or for prevention of migraine. In some embodiments, compounds of the disclosure may be administered only when migraine symptoms are manifest, such as during prodrome or aura, or even during headache.

In some embodiments, the compounds of the disclosure are administered in individual dosage forms. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy.

In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable

carriers comprising excipients and auxiliaries which facilitate processing of the disclosed compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to

5 formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage

10 Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

Provided herein are pharmaceutical compositions comprising one or more compounds of Structure (I) through (XLIX), and a pharmaceutically acceptable carrier.

Provided herein are pharmaceutical compositions comprising one or more compounds selected from compounds of Structure (I) through (XLIX) and

15 pharmaceutically acceptable diluent(s), excipient(s), and carrier(s). In certain embodiments, the compounds described are administered as pharmaceutical compositions in which one or more compounds selected from compounds of Structure (I) through (XLIX) are mixed with other active ingredients, as in combination therapy. Encompassed herein are all combinations of actives set forth in the combination

20 therapies section below and throughout this disclosure. In specific embodiments, the pharmaceutical compositions include one or more compounds of Structure (I) through (XLIX).

A pharmaceutical composition, as used herein, refers to a mixture of one or more compounds selected from compounds of Structure (I) through (XLIX) with other

25 chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, therapeutically effective amounts of one or more compounds selected from compounds of Structure (I) through (XLIX) provided herein are

30 administered in a pharmaceutical composition to a mammal having a disease, disorder

or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds described herein are used singly or in
5 combination with one or more therapeutic agents as components of mixtures.

In addition, an MNK inhibitor as described herein may be formulated with another MNK inhibitor as described herein, another MNK inhibitor, another pain therapeutic, a neuroregeneration therapeutic, or another small molecule or biologic therapeutic, or any combinations thereof. Example pain therapeutics and
10 neuroregeneration therapeutics are described herein with respect to therapeutic methods using MNK inhibitors.

In one embodiment, one or more compounds selected from compounds of Structure (I) through (XLIX) are formulated in aqueous solutions. In specific embodiments, the aqueous solution is selected from, by way of example only, a
15 physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, one or more compounds selected from compounds of Structure (I) through (XLIX) are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein
20 the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or non-aqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

In another embodiment, compounds described herein are formulated for oral
25 administration. Compounds described herein are formulated by combining the active compounds with, *e.g.*, pharmaceutically acceptable carriers or excipients. In various embodiments, the compounds described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

5 Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium

10 carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

In one embodiment, dosage forms, such as dragee cores and tablets, are

15 provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or

20 pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

In certain embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated into other oral dosage forms. Oral dosage

25 forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments,

30 soft capsules, contain one or more active compound that is dissolved or suspended in a

suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

In still other embodiments, the compounds described herein are formulated for
5 parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (*e.g.*, in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection
10 as sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, suspensions of one or
15 more compounds selected from compounds of Structure (I) or (II) are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection
20 suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable
25 vehicle, *e.g.*, sterile pyrogen-free water, before use.

Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient, and one or more compounds selected from compounds of Structure (I) through (XLIX), described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt
30 form. In addition, the methods and pharmaceutical compositions described herein

include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated
5 as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for
10 regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid.
15 Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and
20 creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

25 In some embodiments, pharmaceutical compositions comprising one or more compounds selected from compounds of Structure (I) through (XLIX) illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a suspension, a first portion of the agent is present in solution and a second portion of the agent is present in particulate

form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

In certain embodiments, aqueous suspensions contain one or more polymers as suspending agents. Polymers include water-soluble polymers such as cellulosic
5 polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate
10 and dextran.

Pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of one or more compounds selected from compounds of Structure (I) through (XLIX). The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable
15 nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

Furthermore, pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic,
20 phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

25 Compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and
30 ammonium sulfate.

Other pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

Compositions may include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40.

Compositions may include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

In certain embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as *N*-methylpyrrolidone are also employed. In additional embodiments, the compounds described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v

methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and
 5 other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

In some embodiments, the concentration of one or more compounds selected from compounds of Structure (I) through (XLIX) provided in the pharmaceutical compositions of the present disclosure is greater than 90%, 80%, 70%, 60%, 50%, 40%,
 10 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%,
 15 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 1.25%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or
 20 0.0001% w/w, w/v, or v/v.

In some embodiments, the concentration of one or more compounds selected from compounds of Structure (I) through (XLIX) provided in the pharmaceutical compositions of the present disclosure is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately
 25 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately
 30 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately

0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v.

5 In some embodiments, the amount the one or more compounds selected from compounds of Structure (I) through (XLIX) provided in the pharmaceutical compositions of the present disclosure is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g,
10 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

 In some embodiments, the amount of the one or more compounds selected from
15 compounds of Structure (I) through (XLIX) provided in the pharmaceutical compositions of the present disclosure is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

 Packaging materials for use in packaging pharmaceutical compositions described herein include those found in, *e.g.*, U.S. Pat. Nos. 5,323,907, 5,052,558 and
20 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes one or more compounds described herein, optionally in a composition or in combination with
25 another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

For example, a kit typically includes one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not
5 limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded or
10 etched into the container itself, a label is associated with a container when it is present within a receptacle or carrier that also holds the container, *e.g.*, as a package insert. In addition, a label is used to indicate that the contents are to be used for a specific therapeutic application. In addition, the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical
15 compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack for example contains metal or plastic foil, such as a blister pack. Or, the pack or dispenser device is accompanied by instructions for administration. Or, the pack or dispenser is accompanied with a notice associated with the container in form prescribed by a
20 governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound provided herein
25 formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Methods of Treatment

One embodiment of the present disclosure provides a method of treating a disease or disorder, comprising administering a therapeutically effective amount of a

compound of Structure (I) through (XLIX), or the pharmaceutical composition as described herein, to a subject in need thereof. In more specific embodiments, the disease or disorder is migraines or symptoms associated with migraines.

Certain compounds of the present disclosure may be able to pass through the
5 blood brain barrier. These brain penetrant compounds may be used for administration to neurons or brain tissues.

Embodiments of the present disclosure are useful for treating migraines and symptoms associated with migraines in a host species. The host species or patient can belong to any mammalian species, for example a primate species, particularly humans;
10 rodents, including mice, rats and hamsters; rabbits; horses, cows, dogs, cats, *etc.* Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

Embodiments of the disclosure also relate to the use of compounds according to Structure (I) through (XLIX) and/or physiologically acceptable salts thereof for the
15 prophylactic or therapeutic treatment and/or monitoring of diseases that are caused, mediated and/or modulated by the mitogen-activated protein kinase-interacting kinases (MNK) activity. Furthermore, embodiments of the disclosure relate to the use of compounds according to Structure (I) through (XLIX) and/or physiologically acceptable salts thereof for the production of a medicament for the prophylactic or
20 therapeutic treatment and/or monitoring of diseases. In certain embodiments, the use of a compound according to Structure (I) through (XLIX) or physiologically acceptable salts thereof, for the production of a medicament for the prophylactic or therapeutic treatment.

Compounds as disclosed herein may be administered as a single dose or
25 multiple doses. For example, where multiple doses are administered, they may be administered at intervals of 3 times per 24 hours, 2 times per 24 hours, 1 time per 24 hours, 1 time every other day, 1 time every 3 days, 1 time every 4 days, 1 time per week, 2 times per week, or 3 times per week. The compound may also be delivered continuously, for example via a continuous pump. The administration schedule may

depend on dose administered, severity of disease, response to treatment, and other factors, or any combinations thereof.

The dose may be any effective amount. However, in specific examples the dose may be 25 mg, 50 mg, 100 mg, 200 mg, or 500 mg.

5 The initial dose may be greater than subsequent doses or all doses may be the same. The dose may depend on the administration schedule, severity of disease, response to treatment, and other factors, or any combinations thereof. The compound may be administered over a period of one week, two weeks, three weeks, four weeks, one month, two months, three months, four months, five months, six months, seven
10 months, eight months, nine months, ten months, eleven months, one year, two years or three years. The duration of administration may depend on the severity of diseases, response to treatment, and other factors, or any combinations thereof.

For example, a less frequent administration schedule for the same dose may be adopted as the patient responds to treatment. Alternatively, the administration schedule
15 may remain unchanged, but the dose may be decreased as the patient responds to treatment.

In specific embodiments, the pharmaceutical compositions may be administered daily or periodically even in the absence of migraine symptoms in order to prevent migraines. Such administration may be particularly useful in patients who suffer from
20 chronic migraine, patients who are severely incapacitated by migraine, or patients whose lifestyle or occupation is severely interrupted by migraine (e.g. parents of young children, those employed to operate automotive or heavy equipment, those who perform lengthy and visually-intensive processes, such as surgeons, etc.)

In other specific embodiments, the pharmaceutical compositions may be
25 administered when migraines are more likely (such as during certain times of the menstrual cycle in women), or when migraine symptoms are present. Typically, the pharmaceutical compositions may be administered prior to headache, such as at the onset of or during prodrome or aura symptoms.

A compound according to the present disclosure may be administered in
30 conjunction with an additional therapeutic, including another MNK inhibitor or a

therapeutic that is not an MNK inhibitor, particularly another migraine therapeutic. Suitable additional therapeutics include both small molecules and biologics. A compound according to the present disclosure may be administered with any combination or combinations of additional therapeutics.

5 For example, a compound of the present disclosure may be administered with one or more other pain and/or migraine therapeutics. Suitable therapeutics include mild pain relievers, such as non-steroidal anti-inflammatory drugs, including ibuprofen, ketoprofen, aspirin, other salicates, and naproxen, acetaminophen; triptans, such as sumatriptan and rizatriptan; dihydroergotamine; lasmiditan; ubrogepant; rimegepant, or
10 other CGRP antagonists; opioids; anti-nausea medications such as metoclopramide, prochlorperazine; beta blockers, such as propranolol or metoprolol tartarate; calcium channel blockers, such as verapamil; tricyclic antidepressants such as amitriptyline; anti-seizure drugs, such as valproate or topiramate; botox injections; and anti-CGRP monoclonal antibodies.

15 When administered with another pain therapeutic, a compound according to the present disclosure may allow a reduction in the dose or administration frequency of the other pain therapeutic, or a decrease in the total duration of time the other therapeutic is administered. Such an administration schedule may be particularly beneficial when the additional pain therapeutic is addictive, such as an opioid.

20 The agents disclosed herein or other suitable agents are administered depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other agents. When used in combination therapy, the compounds described herein are administered with the second agent simultaneously or separately. This administration in combination can include
25 simultaneous administration of the two or more agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any additional agent (*e.g.*, an anti-inflammatory agent, a pain management agent, *etc.*) can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the disclosure and
30 additional agent can be simultaneously administered, wherein both the agents are

present in separate formulations. In another alternative, a compound of the present disclosure can be administered just followed by an additional agent, or vice versa. In some embodiments of the separate administration protocol, a compound of the disclosure and additional agent are administered a few minutes apart, or a few hours
5 apart, or a few days apart. In some embodiments, the compounds of Structure (I) through (XLIX) are administered as a mono-therapy.

The methods of embodiments of the disclosure can be performed either *in vitro* or *in vivo*. The susceptibility of a particular patient, subject, or cell to treatment with the compounds of Structure (I) through (XLIX) can be
10 particularly determined by *in vitro* tests, whether in the course of research or clinical application.

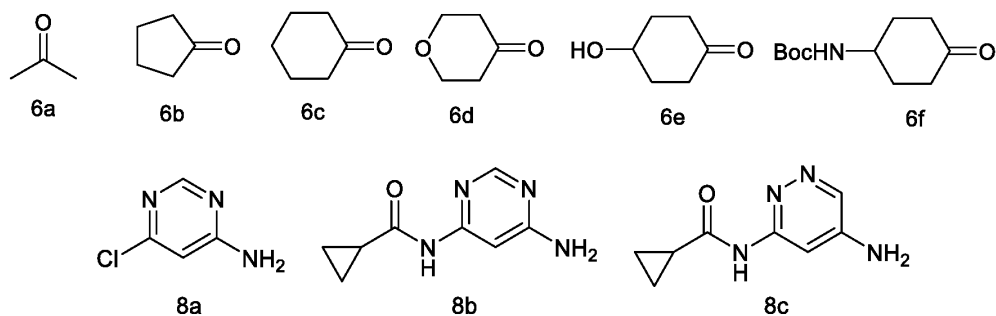
EXAMPLES

The examples and preparations provided below further illustrate and exemplify the compounds of the present disclosure and methods of preparing and testing such
15 compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations. In the following examples, and throughout the specification and claims, molecules with a single stereocenter, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more stereocenters, unless otherwise noted, exist as a racemic mixture of
20 diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art. Methods for producing the compounds described herein is provided below. In general, starting components may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according to sources known to those skilled in the
25 art (see, for example, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th edition (Wiley, December 2000)) or prepared as described herein.

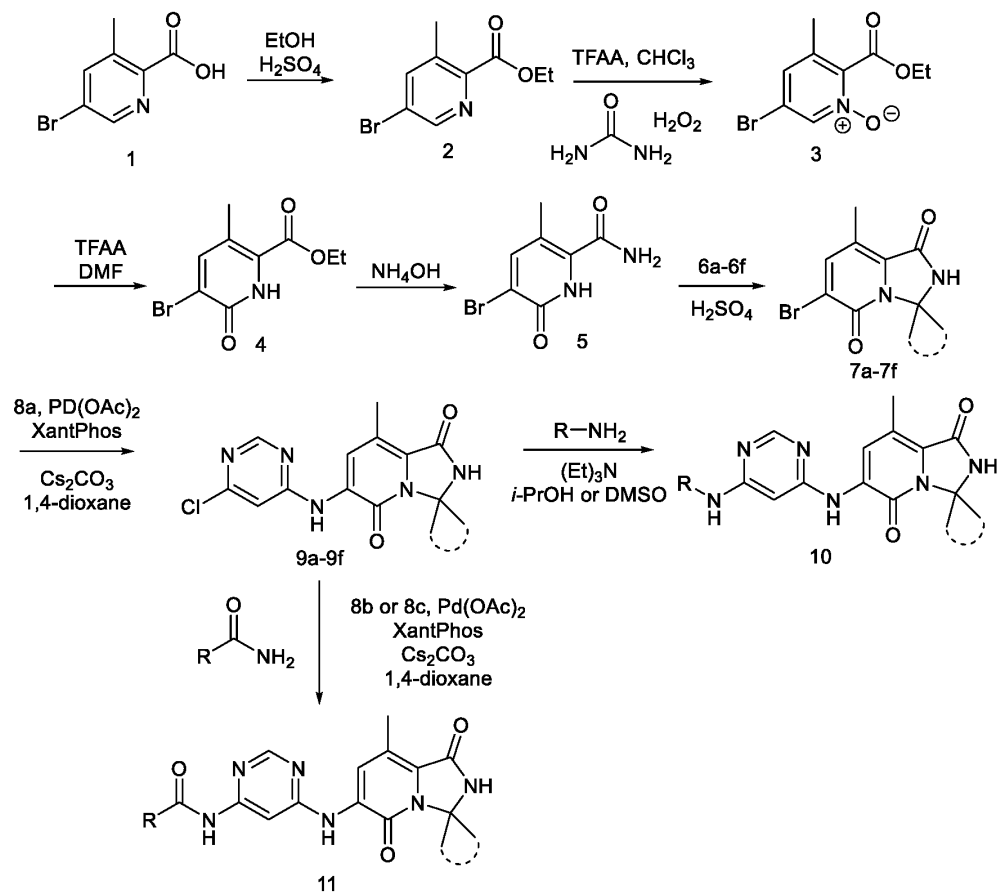
General Reaction Scheme 1

The following General Reaction Scheme includes variation of various ingredients in order to achieve different synthetic targets. For example, as referenced below, compounds 6a-6f and compounds 8a-8c have the following structures,

5 respectively:



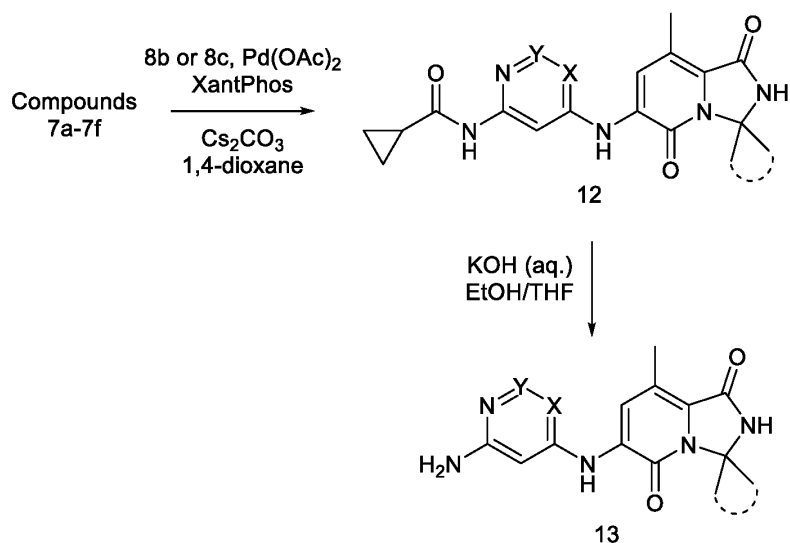
General Reaction Scheme 1 is depicted below:



Any of the above reaction schemes can be modified at any step to add and/or modify a substituent or change the order of the steps as appropriate during any stage of the overall synthesis of desired compounds. For example, General Reaction Scheme 1

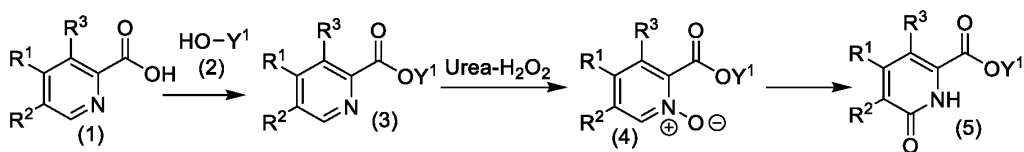
5 may be modified after the step yielding compounds 7a-7f according to the following General Reaction Scheme 2, wherein X and Y are either N or C depending on the identity of the reactants used.

General Reaction Scheme 2



General Reaction Scheme 3

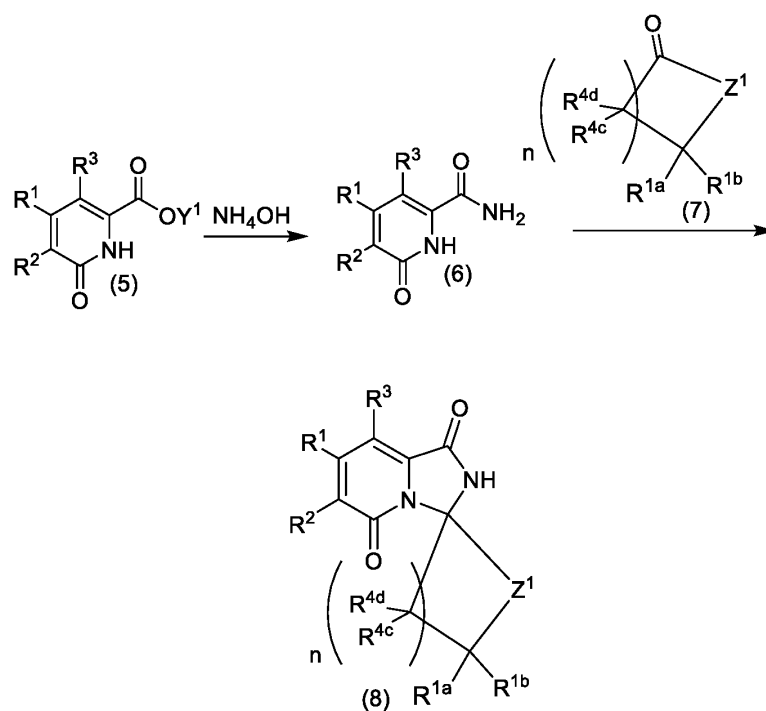
Compounds of the present disclosure may be prepared according to the process outlined in General Reaction Schemes 3-20. Compound numbering corresponds to structures shown in the schemes herein.



A compound (1), a known compound or a compound prepared by known methods, is reacted with a compound of the formula (2), a known compound or a compound prepared by known methods wherein Y¹ is C₁₋₆ alkyl, in the presence of an acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, and the like, in a solvent such as ethanol, methanol, tetrahydrofuran, 1,4-dioxane, methylene chloride, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (3). A compound of the formula (3) is reacted with urea hydrogen peroxide in the presence of an acid anhydride such as trifluoroacetic anhydride, acetic anhydride, and the like, in a solvent such as methylene chloride,

chloroform, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (4). A compound of the formula (4) is reacted with an acid anhydride such as trifluoroacetic anhydride, acetic anhydride, and the like, in a solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, methylene chloride, chloroform, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (5).

General Reaction Scheme 4

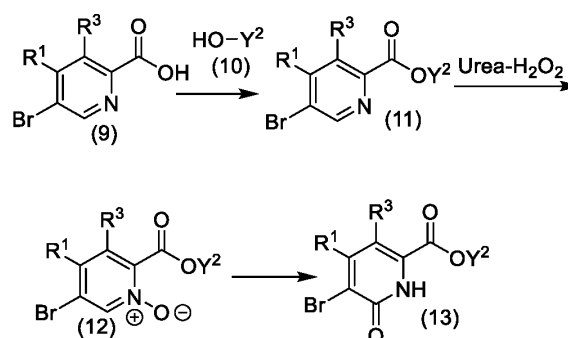


10

A compound of the formula (5) is reacted with ammonium hydroxide, optionally in the presence of a solvent such as methanol, ethanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, methylene chloride, chloroform, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (6). A compound of the formula (6) is reacted with a compound of the formula (7), a known

compound or compound prepared by known methods, in the presence of an acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, and the like, in a solvent such as ethanol, methanol, tetrahydrofuran, 1,4-dioxane, methylene chloride, and the like, optionally with heating, optionally with microwave irradiation to provide a
 5 compound of the formula (8).

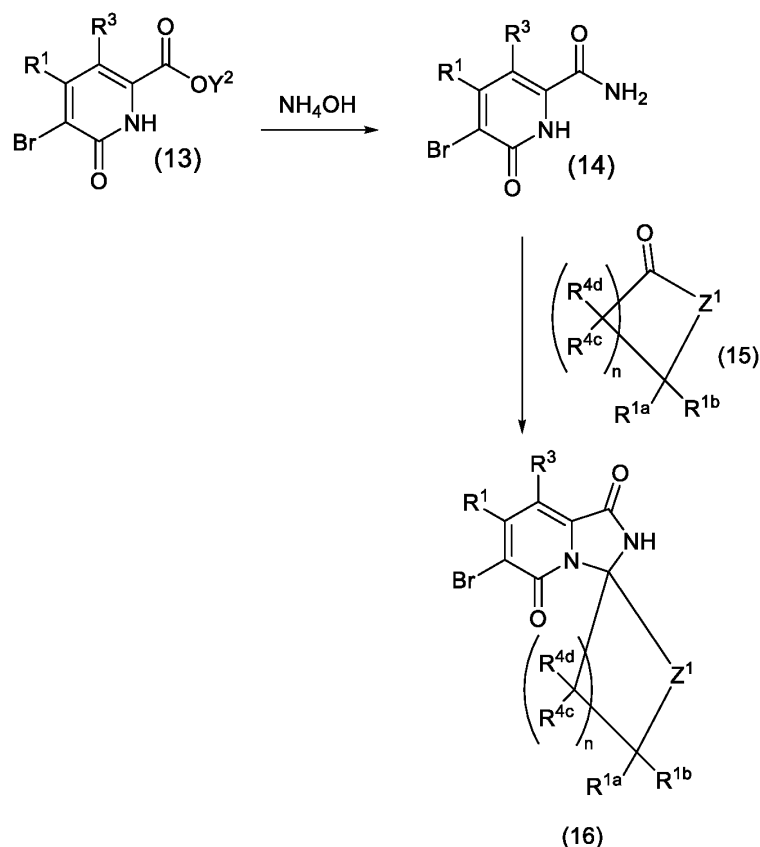
General Reaction Scheme 5



A compound of the formula (9), a known compound or a compound prepared by known methods, is reacted with a compound of the formula (10), a known compound or
 10 a compound prepared by known methods wherein Y² is C₁₋₆ alkyl, in the presence of an acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, and the like, in a solvent such as ethanol, methanol, tetrahydrofuran, 1,4-dioxane, methylene chloride, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (11). A compound of the formula (11) is reacted
 15 with urea hydrogen peroxide in the presence of an acid anhydride such as trifluoroacetic anhydride, acetic anhydride, and the like, in a solvent such as methylene chloride, chloroform, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (12). A compound of the formula (12) is reacted with an acid anhydride such as
 20 trifluoroacetic anhydride, acetic anhydride, and the like, in a solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, methylene chloride, chloroform, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with

heating, optionally with microwave irradiation to provide a compound of the formula (13).

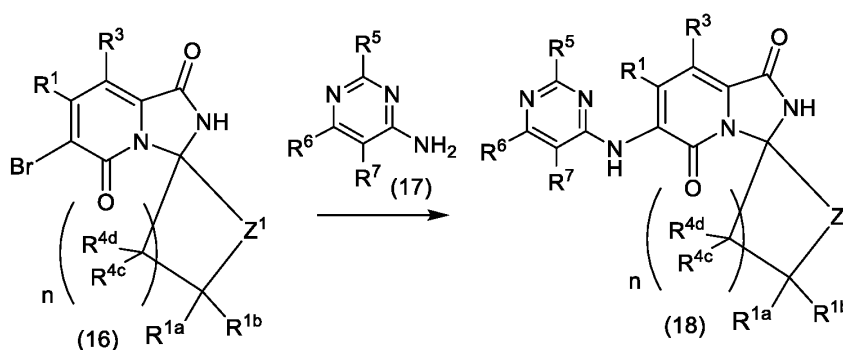
General Reaction Scheme 6



- 5 A compound of the formula (13) is reacted with ammonium hydroxide, optionally in the presence of a solvent such as methanol, ethanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, methylene chloride, chloroform, dichloroethane, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (14). A compound of the
- 10 formula (14) is reacted with a compound of the formula (15), a known compound or compound prepared by known methods, in the presence of an acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, and the like, in a solvent such as ethanol, methanol, tetrahydrofuran, 1,4-dioxane, methylene chloride, and the like,

optionally with heating, optionally with microwave irradiation to provide a compound of the formula (16).

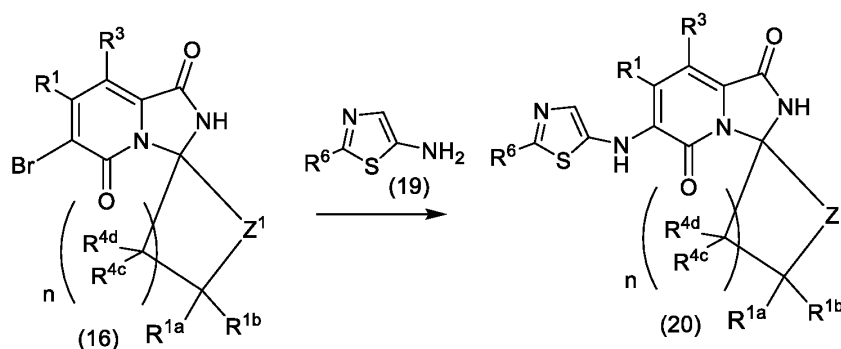
General Reaction Scheme 7



- 5 A compound of the formula (16) is reacted with a compound of the formula (17), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon,
- 10 bis(acetonitrile)dichloro palladium(II), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bispalladium-tri(1,3-dibenzylidene)acetone, and the like, optionally in the presence of an organophosphine such as 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine, 2-dicyclohexylphosphino-2',6'-
- 15 dimethoxybiphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl, (2-biphenyl)dicyclohexylphosphine, (2-biphenyl)di-tert-butylphosphine, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, Sodium 2'-
- 20 dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate, 2-di-tert-butylphosphino-2'-methylbiphenyl, 2-dicyclohexylphosphino-2'-methylbiphenyl, 2'-(di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N'-dimethyl-(1,1'-biphenyl)-2-amine, and the like, in the presence of a base such as sodium

carbonate, lithium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, lithium hydroxide, potassium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, methylene chloride, chloroform, 1,2-dichloroethane, 1,2-dimethoxyethane, and the like, optionally in the presence of water, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (18).

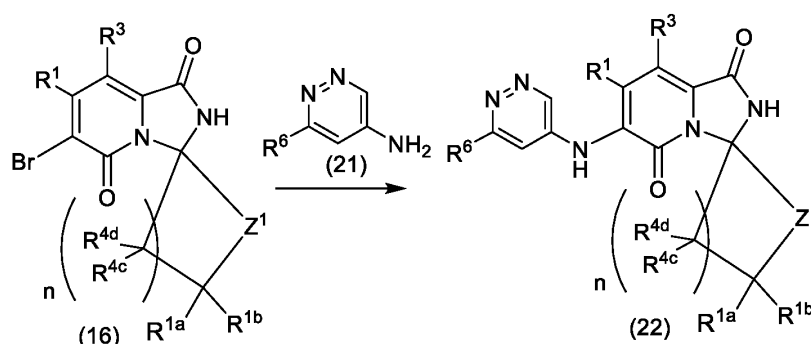
General Reaction Scheme 8



10 A compound of the formula (16) is reacted with a compound of the formula (19), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, 15 bis(acetonitrile)dichloro palladium(II), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bispalladium-tri(1,3-dibenzylidene)acetone, and the like, optionally in the presence of an organophosphine such as 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine, 2-dicyclohexylphosphino-2',6'-20 dimethoxybiphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl, (2-biphenyl)dicyclohexylphosphine, (2-biphenyl)di-tert-butylphosphine, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, 2-di-tert-

butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, Sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate, 2-di-tert-butylphosphino-2'-methylbiphenyl, 2-dicyclohexylphosphino-2'-methylbiphenyl, 2'-(di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N'-dimethyl-(1,1'-biphenyl)-2-amine, and the like, in the presence of a base such as sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, lithium hydroxide, potassium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, methylene chloride, chloroform, 1,2-dichloroethane, 1,2-dimethoxyethane, and the like, optionally in the presence of water, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (20).

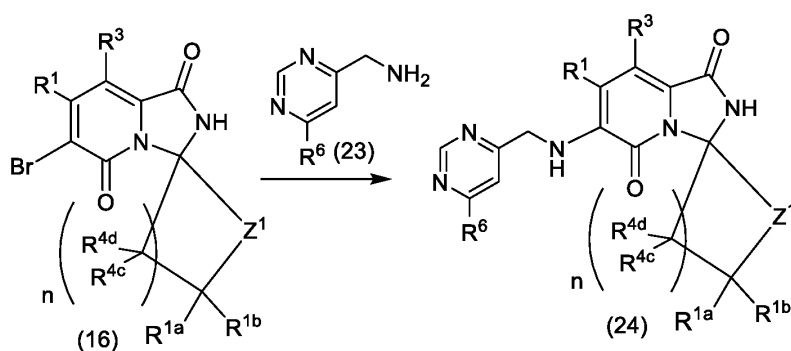
General Reaction Scheme 9



A compound of the formula (16) is reacted with a compound of the formula (21), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloro palladium(II), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bispalladium-tri(1,3-dibenzylidene)acetone, and the like, optionally in the presence of an organophosphine such as 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dicyclohexyl(2',6'-

dimethoxybiphenyl-2-yl)phosphine, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl, (2-biphenyl)dicyclohexylphosphine, (2-biphenyl)di-tert-butylphosphine, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, Sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate, 2-di-tert-butylphosphino-2'-methylbiphenyl, 2-dicyclohexylphosphino-2'-methylbiphenyl, 2'-(di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N'-dimethyl-(1,1'-biphenyl)-2-amine, and the like, in the presence of a base such as sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, lithium hydroxide, potassium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, methylene chloride, chloroform, 1,2-dichloroethane, 1,2-dimethoxyethane, and the like, optionally in the presence of water, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (22).

General Reaction Scheme 10



A compound of the formula (16) is reacted with a compound of the formula (23), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0),

dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloro palladium(II), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bispalladium-tri(1,3-dibenzylidene)acetone, and the like, optionally in the presence of an organophosphine

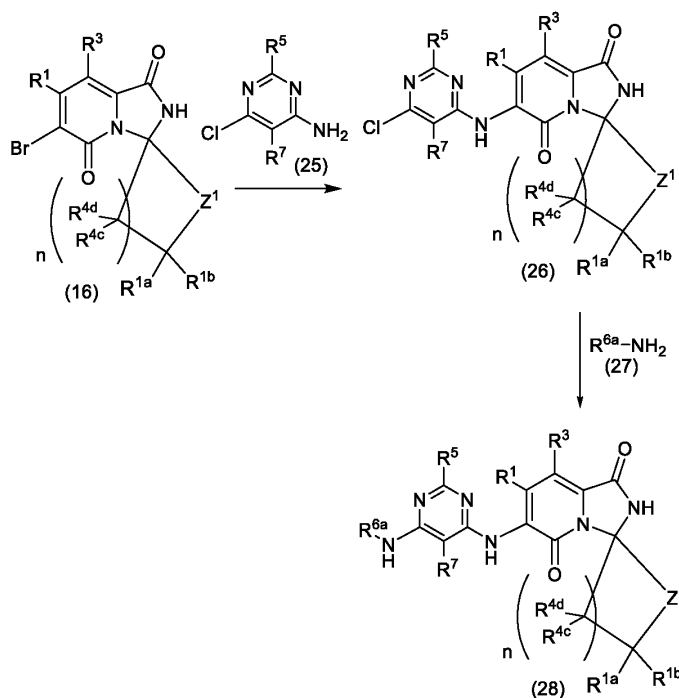
5 such as 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl, (2-biphenyl)dicyclohexylphosphine, (2-biphenyl)di-tert-

10 butylphosphine, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, Sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate, 2-di-tert-butylphosphino-2'-methylbiphenyl, 2-dicyclohexylphosphino-2'-methylbiphenyl, 2'-(di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N'-

15 dimethyl-(1,1'-biphenyl)-2-amine, and the like, in the presence of a base such as sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, lithium hydroxide, potassium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, methylene chloride, chloroform, 1,2-

20 dichloroethane, 1,2-dimethoxyethane, and the like, optionally in the presence of water, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (24).

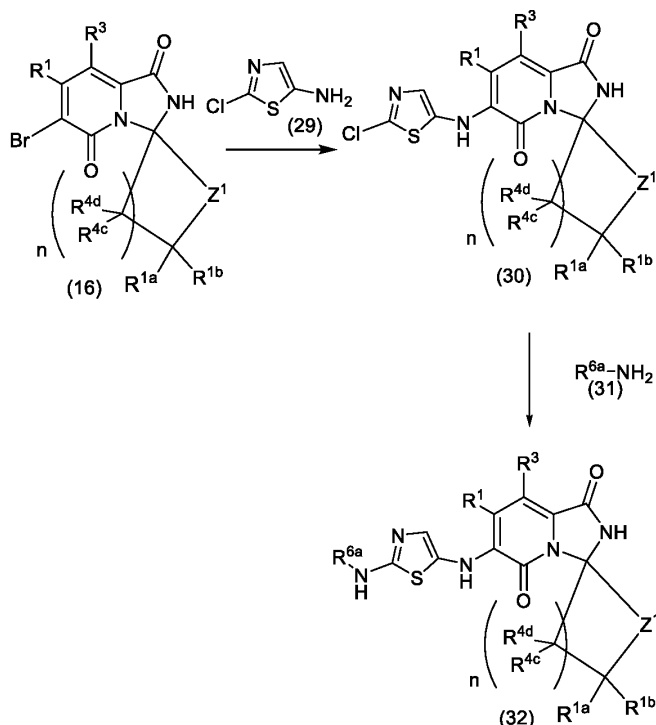
General Reaction Scheme 11



A compound of the formula (16) is reacted with a compound of the formula (25), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloro palladium(II), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bispalladium-tri(1,3-dibenzylidene)acetone, and the like, optionally in the presence of an organophosphine such as 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl, (2-biphenyl)dicyclohexylphosphine, (2-biphenyl)di-tert-butylphosphine, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, Sodium 2'-

dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate, 2-di-tert-butylphosphino-2'-methylbiphenyl, 2-dicyclohexylphosphino-2'-methylbiphenyl, 2'-(di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N'-dimethyl-(1,1'-biphenyl)-2-amine, and the like, in the presence of a base such as sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, lithium hydroxide, potassium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, methylene chloride, chloroform, 1,2-dichloroethane, 1,2-dimethoxyethane, and the like, optionally in the presence of water, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (26). A compound of the formula (26) is reacted with a compound of the formula (27), a known compound or a compound prepared by known methods, in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as methanol, ethanol, isopropanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (28).

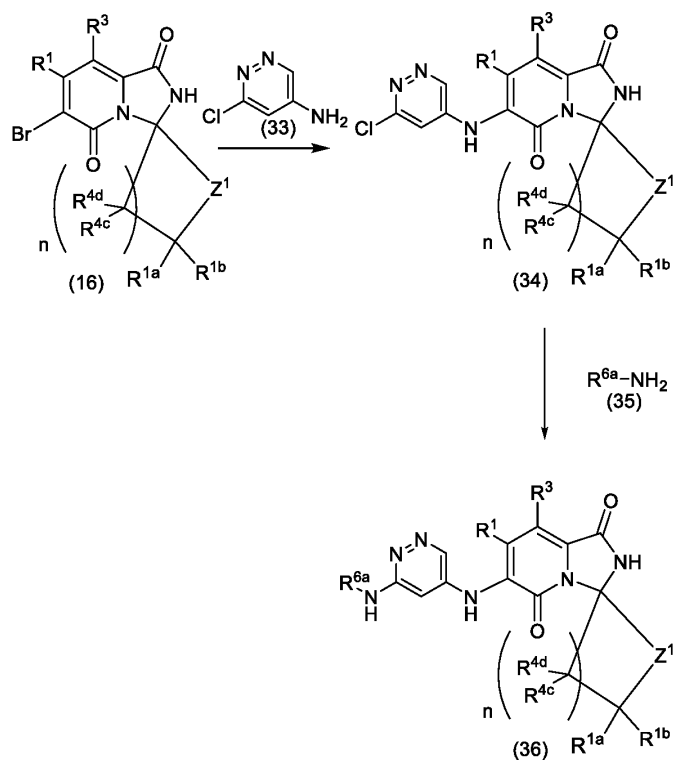
General Reaction Scheme 12



A compound of the formula (16) is reacted with a compound of the formula (29), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloro palladium(II), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bispalladium-tri(1,3-dibenzylidene)acetone, and the like, optionally in the presence of an organophosphine such as 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl, (2-biphenyl)dicyclohexylphosphine, (2-biphenyl)di-tert-butylphosphine, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, 2-di-tert-

butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, Sodium 2'-
dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate, 2-di-tert-
butylphosphino-2'-methylbiphenyl, 2-dicyclohexylphosphino-2'-methylbiphenyl, 2'-(di-
tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N'-
5 dimethyl-(1,1'-biphenyl)-2-amine, and the like, in the presence of a base such as sodium
carbonate, lithium carbonate, potassium carbonate, cesium carbonate, sodium
hydroxide, lithium hydroxide, potassium hydroxide, triethylamine, N,N-
diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as
tetrahydrofuran, 1,4-dioxane, acetonitrile, methylene chloride, chloroform, 1,2-
10 dichloroethane, 1,2-dimethoxyethane, and the like, optionally in the presence of water,
optionally with heating, optionally with microwave irradiation to provide a compound
of the formula (30). A compound of the formula (30) is reacted with a compound of the
formula (31), a known compound or a compound prepared by known methods, in the
presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-
15 dimethylpyridine, and the like, in a solvent such as methanol, ethanol, isopropanol,
N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran,
1,4-dioxane, and the like, optionally with heating, optionally with microwave
irradiation to provide a compound of the formula (32).

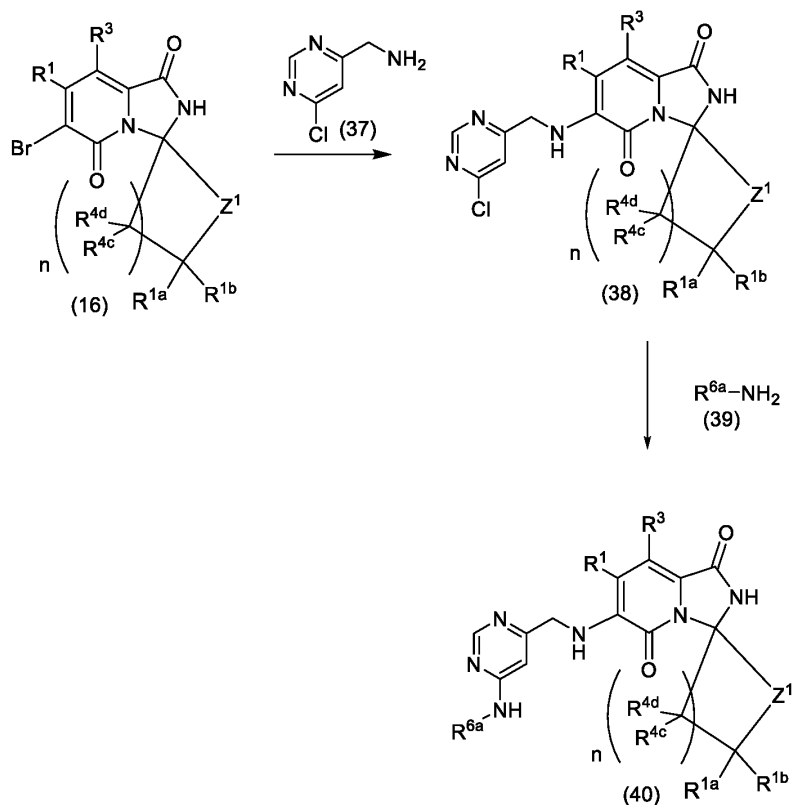
General Reaction Scheme 13



A compound of the formula (16) is reacted with a compound of the formula (33), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloro palladium(II), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bispalladium-tri(1,3-dibenzylidene)acetone, and the like, optionally in the presence of an organophosphine such as 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl, (2-biphenyl)dicyclohexylphosphine, (2-biphenyl)di-tert-butylphosphine, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, 2-di-tert-

butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, Sodium 2'-
dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate, 2-di-tert-
butylphosphino-2'-methylbiphenyl, 2-dicyclohexylphosphino-2'-methylbiphenyl, 2'-(di-
tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N'-
5 dimethyl-(1,1'-biphenyl)-2-amine, and the like, in the presence of a base such as sodium
carbonate, lithium carbonate, potassium carbonate, cesium carbonate, sodium
hydroxide, lithium hydroxide, potassium hydroxide, triethylamine, N,N-
diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as
tetrahydrofuran, 1,4-dioxane, acetonitrile, methylene chloride, chloroform, 1,2-
10 dichloroethane, 1,2-dimethoxyethane, and the like, optionally in the presence of water,
optionally with heating, optionally with microwave irradiation to provide a compound
of the formula (34). A compound of the formula (34) is reacted with a compound of the
formula (35), a known compound or a compound prepared by known methods, in the
presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-
15 dimethylpyridine, and the like, in a solvent such as methanol, ethanol, isopropanol,
N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran,
1,4-dioxane, and the like, optionally with heating, optionally with microwave
irradiation to provide a compound of the formula (36).

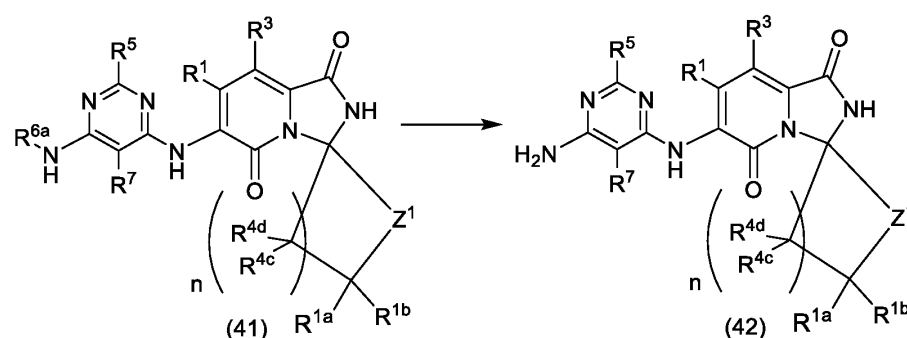
General Reaction Scheme 14



A compound of the formula (16) is reacted with a compound of the formula (37), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, bis(acetonitrile)dichloro palladium(II), 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), bispalladium-tri(1,3-dibenzylidene)acetone, and the like, optionally in the presence of an organophosphine such as 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino) biphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl, (2-biphenyl)dicyclohexylphosphine, (2-biphenyl)di-tert-

butylphosphine, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, Sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate, 2-di-tert-butylphosphino-2'-methylbiphenyl, 2-dicyclohexylphosphino-2'-methylbiphenyl, 2'-(di-tert-butylphosphino)-N,N-dimethylbiphenyl-2-amine, 2'-(diphenylphosphino)-N,N'-dimethyl-(1,1'-biphenyl)-2-amine, and the like, in the presence of a base such as sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, lithium hydroxide, potassium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, methylene chloride, chloroform, 1,2-dichloroethane, 1,2-dimethoxyethane, and the like, optionally in the presence of water, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (38). A compound of the formula (38) is reacted with a compound of the formula (39), a known compound or a compound prepared by known methods, in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and the like, in a solvent such as methanol, ethanol, isopropanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (40).

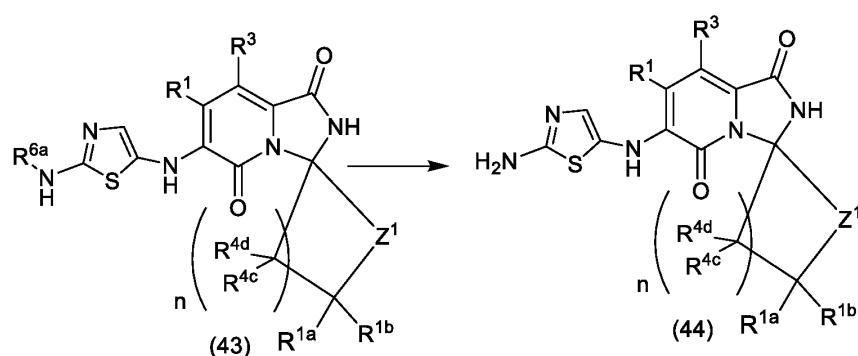
General Reaction Scheme 15



A compound of the formula (41) is reacted with a base such as sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, lithium

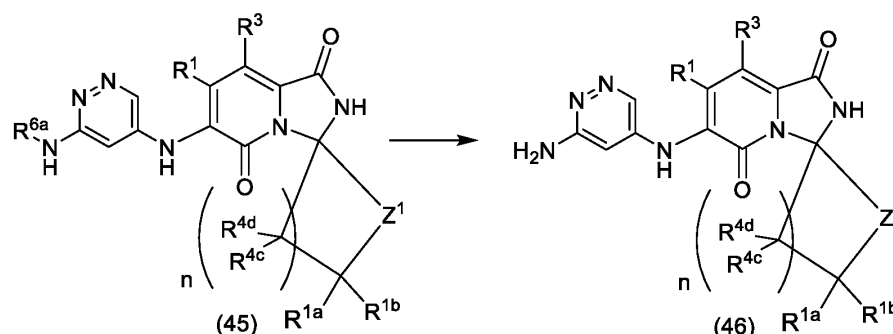
carbonate, potassium carbonate, cesium carbonate, and the like, optionally in the presence of ethylenediamine, optionally in the presence of water, in the presence of a solvent such methanol, ethanol, isopropanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (42).

General Reaction Scheme 16



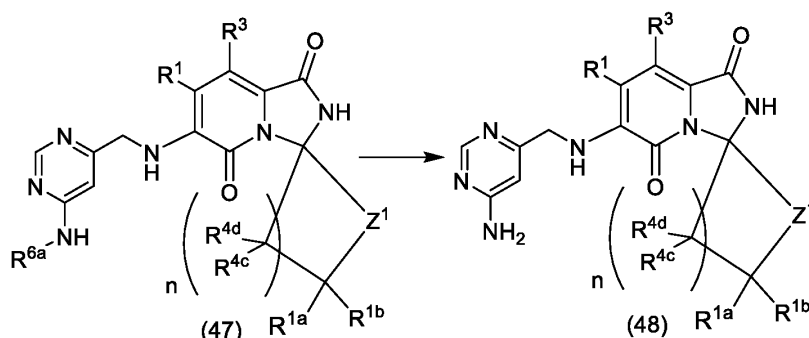
A compound of the formula (43) is reacted with a base such as sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, and the like, optionally in the presence of ethylenediamine, optionally in the presence of water, in the presence of a solvent such methanol, ethanol, isopropanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (44).

General Reaction Scheme 17



A compound of the formula (45) is reacted with a base such as sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, and the like, optionally in the presence of ethylenediamine, optionally in the presence of water, in the presence of a solvent such as methanol, ethanol, isopropanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (46).

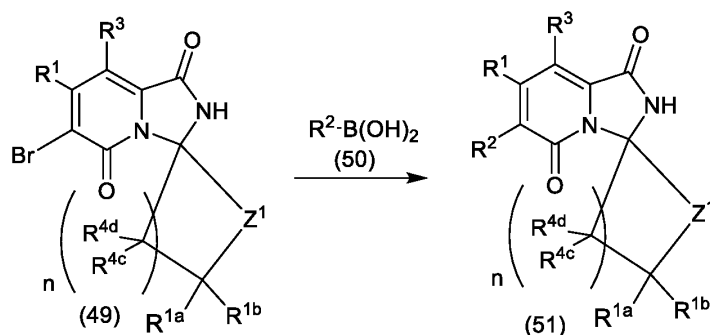
General Reaction Scheme 18



A compound of the formula (47) is reacted with a base such as sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, lithium carbonate, potassium carbonate, cesium carbonate, and the like, optionally in the presence of ethylenediamine, optionally in the presence of water, in the presence of a solvent such as methanol, ethanol, isopropanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide,

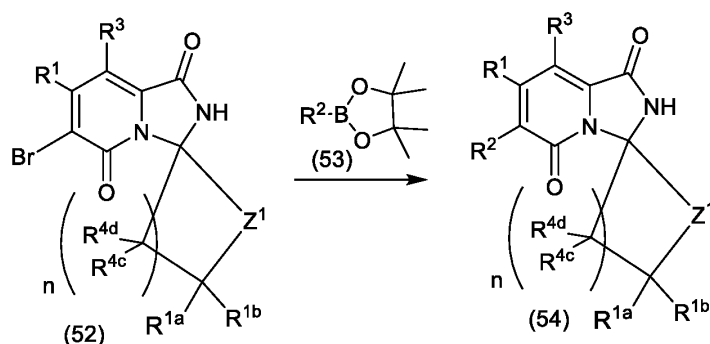
tetrahydrofuran, 1,4-dioxane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (48).

General Reaction Scheme 19



A compound of the formula (49) is reacted with a compound of the formula (50), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenyl phosphine)palladium(II), bis(acetonitrile)dichloropalladium(II), tris(dibenzylideneacetone) dipalladium(0), and the like, in the presence of a base such as sodium carbonate, potassium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, cesium carbonate, lithium bicarbonate, triethylamine, diisopropylethylamine, pyridine, and the like, optionally in the presence of water, in a solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, N,N-dimethyl formamide, N,N-dimethylacetamide, methylene chloride, 1,2-dichloroethane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (51).

General Reaction Scheme 20



A compound of the formula (52) is reacted with a compound of the formula (53), a known compound or a compound prepared by known methods, in the presence of a palladium catalyst such as palladium (II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis (triphenyl phosphine)palladium(II), bis(acetonitrile)dichloropalladium(II), tris(dibenzylideneacetone) dipalladium(0), and the like, in the presence of a base such as sodium carbonate, potassium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, cesium carbonate, lithium bicarbonate, triethylamine, diisopropylethylamine, pyridine, and the like, optionally in the presence of water, in a solvent such as tetrahydrofuran, 1,4-dioxane, acetonitrile, N,N-dimethyl formamide, N,N-dimethylacetamide, methylene chloride, 1,2-dichloroethane, and the like, optionally with heating, optionally with microwave irradiation to provide a compound of the formula (54). The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*, ^1H or ^{13}C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatography such as high pressure liquid chromatography (HPLC), gas chromatography (GC), gel-permeation chromatography (GPC), or thin layer chromatography (TLC).

Preparation of the compounds can involve protection and deprotection of various chemical groups. The need for protection and deprotection and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene *et al.*, *Protective Groups in Organic Synthesis*, 2d. Ed. (Wiley & Sons, 1991), the entire disclosure of which is incorporated by reference herein for all purposes.

The reactions or the processes described herein can be carried out in suitable solvents which can be readily selected by one skilled in the art of organic synthesis. Suitable solvents typically are substantially nonreactive with the reactants, intermediates, and/or products at the temperatures at which the reactions are carried out, *i.e.*, temperatures that can range from the solvent's freezing temperature to the solvent's

boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

The Examples provided below provide representative methods for preparing
5 exemplary compounds of the present disclosure. The skilled practitioner will know how to substitute the appropriate reagents, starting materials and purification methods known to those skilled in the art, in order to prepare the compounds of the present disclosure.

It will also be appreciated by those skilled in the art that in the processes for
10 preparing the compounds described herein the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include, but are not limited to, hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl,
15 benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R" (where R" is alkyl, aryl or arylalkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. Protecting groups are optionally added or removed in accordance with
20 standard techniques, which are known to one skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, *Protective Groups in Organic Synthesis* (1999), 3rd Ed., Wiley. As one of skill in the art would appreciate, the protecting group may also be a polymer resin such as a Wang resin, Rink resin or a 2-chlorotrityl-chloride resin.

25 It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of this disclosure may not possess pharmacological activity as such, they may be administered to a mammal and thereafter metabolized in the body to form compounds of the disclosure which are pharmacologically active. Such derivatives may therefore be described as "prodrugs." Prodrugs of compounds of this
30 disclosure are included within the scope of embodiments of the disclosure.

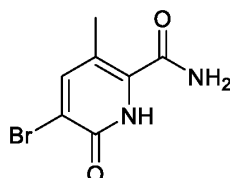
Features of these examples may be combined with elements of the foregoing detailed description unless clearly mutually exclusive. More specific reagent conditions and results from the General Reaction Schemes above are detailed in the Examples below.

5 The following abbreviations are used in the reaction schemes and synthetic examples herein. This list is not meant to be an all-inclusive list of abbreviations used in the present disclosure as additional standard abbreviations, which are readily understood by those skilled in the art can also be used in the synthetic schemes and examples.

10 DMA: Dimethylacetamide
DMF: Dimethylformamide
DMSO: Dimethylsulfoxide
TFAA: Trifluoroacetic anhydride
XantPhos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

15 EXAMPLE 1

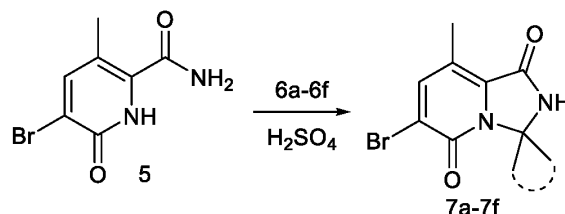
SYNTHESIS OF 5-BROMO-3-METHYL-6-OXO-1,6-DIHYDROPYRIDINE-2-CARBOXAMIDE



To a solution of compound 1 (10 g, 42.3 mmol) in ethanol (37 mL) was added H₂SO₄ (2.3 mL, 18.4 M, 42.3 mmol) at room temperature. The reaction mixture was heated at 80 °C for 16 h. Solvent was removed under reduced pressure and EtOAc (250 mL) was added. After washing with NaHCO₃ (200 mL × 2) and water (200 mL × 2), the organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford ethyl 5-bromo-3-methylpicolinate (2, 9.6 g, 39 mmol, 93%) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H), 7.76 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.56 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H).

- To a solution of compound 2 (9.6 g, 39 mmol) in CH₂Cl₂ (111 mL) was added urea hydrogen peroxide (6.4 g, 68.3 mmol), followed by the addition of trifluoroacetic anhydride (9.6 mL, 68.3 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h and was poured into ice/water mixture (100 mL). After extraction with CH₂Cl₂ (50 mL × 3), the combined organic phase was washed with NaHCO₃ (50 mL × 3) and water (50 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford 5-bromo-2-(ethoxycarbonyl)-3-methylpyridine 1-oxide (3, 10.1 g, 39 mmol, 99%) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 7.26 (s, 1H), 4.47 (q, J = 7.1 Hz, 2H), 2.27 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H).
- To a solution of compound 3 (10.1 g, 39 mmol) in DMF (30.5 mL) was added trifluoroacetic anhydride (9.6 mL, 68.3 mmol) at 0 °C. The reaction mixture was stirred at 40 °C for 8 h and diluted with water (100 mL). After extraction with EtOAc (100 mL × 3), the combined organic phase was washed with brine (100 mL × 5), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by Biotage flash chromatography (silica gel, 0% to 30% EtOAc in hexanes) to afford ethyl 5-bromo- 3-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate (4, 6.8 g, 26.1 mmol, 67%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.83 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H).
- Ammonium hydroxide (130.5 mL, 28% v/v) was added to compound 4 (6.8 g, 26.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h and concentrated under reduced pressure to afford 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (compound 5 of General Reaction Scheme 1, 6.0 g, 26 mmol, 99%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.87 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 2.12 (s, 3H).

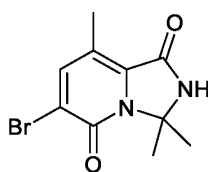
GENERAL PROCEDURE A

SYNTHESIS OF 2,3-DIHYDROIMIDAZO[1,5-*A*]PYRIDINE-1,5-DIONES

To a solution of compound 5 (1 equiv) in 1,4-dioxane (0.2M) was added ketone 5 6a-f (4 equiv), followed by the addition of H₂SO₄ (0.5 equiv). Compounds 6a-6f are as depicted in General Reaction Scheme 1.

The reaction mixture was sealed in a pressure vessel and heated in at 100 °C for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The resulting crude material was purified by Biotage flash 10 chromatography (gradient elution, 30 → 85% EtOAc in hexanes or 0 → 10% MeOH in CH₂Cl₂) to afford compounds 7a-f.

EXAMPLE 2

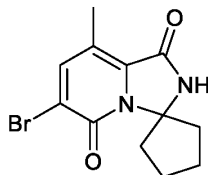
SYNTHESIS OF 6-BROMO-3,3,8-TRIMETHYL-2,3-DIHYDROIMIDAZO[1,5-*A*]PYRIDINE-1,5-DIONE (7A)

15

Compound 7d was synthesized according to General Procedure A. Compound 5 (150 mg, 0.65 mmol, 1.0 equiv), acetone (0.48 mL, 6.5 mmol, 10.0 equiv) and H₂SO₄ (3 mg, 0.03 mmol, 0.05 equiv) in 1,4-dioxane (2 mL) generated compound 7a (150 mg, 0.55 mmol, 85% yield) as white solid.

EXAMPLE 3

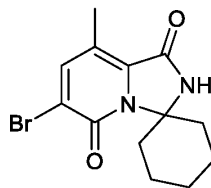
SYNTHESIS OF 6'-BROMO-8'-METHYL-2'H-SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (7B)



5 Compound 7d was synthesized according to General Procedure A. Compound 5 (600 mg, 2.6 mmol), cyclopentanone (6b, 0.92 mL, 10.4 mmol), and H₂SO₄ (0.07 mL, 1.3 mmol) in 1,4-dioxane (5.2 mL) generated compound 7b (585 mg, 1.97 mmol, 76%).

EXAMPLE 4

10 SYNTHESIS OF 6-BROMO-8-METHYL-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (7C)

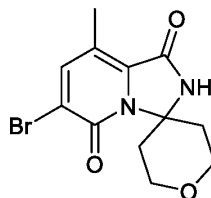


Compound 7d was synthesized according to General Procedure A. Compound 5 (1 g, 4.33 mmol), cyclohexanone (6c, 1.8 mL, 17.31 mmol), and H₂SO₄ (0.12 mL, 2.16 mmol) in 1,4-dioxane (16 mL) generated compound 7c (954 mg, 3.06 mmol, 71%).

15

EXAMPLE 5

SYNTHESIS OF 6-BROMO-8-METHYL-2',3',5',6'-TETRAHYDRO-2H-SPIRO[IMIDAZO[1,5-A]PYRIDINE-3,4'-PYRAN]-1,5-DIONE (7D)

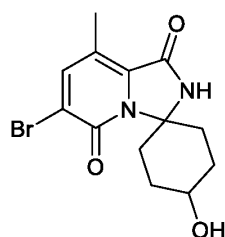


Compound 7d was synthesized according to General Procedure A. Compound 5 (500 mg, 2.16 mmol), tetrahydro-4H-pyran-4-one (6d, 0.8 mL, 8.65 mmol), and H₂SO₄ (0.058 mL, 1.08 mmol) in 1,4-dioxane (12 mL) generated compound 7d (486 mg, 1.55 mmol, 72%).

5

EXAMPLE 6

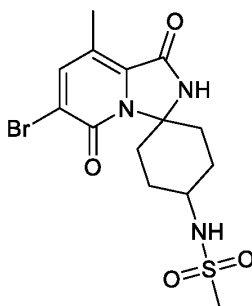
SYNTHESIS OF 6-BROMO-4-HYDROXY-8'-METHYL-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (7E)



Compound 7e was synthesized according to General Procedure A. Compound 5 (300 mg, 1.29 mmol), 4-hydroxycyclohexan-1-one (6e, 592mg, 5.19 mmol) and H₂SO₄ (0.035 mL, 0.645 mmol) in 1,4-dioxane (13 mL) generated compound 7e (196 mg, 0.60 mmol, 46%).

EXAMPLE 7

SYNTHESIS OF N-(6'-BROMO-8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-4-YL)METHANESULFONAMIDE (7F)

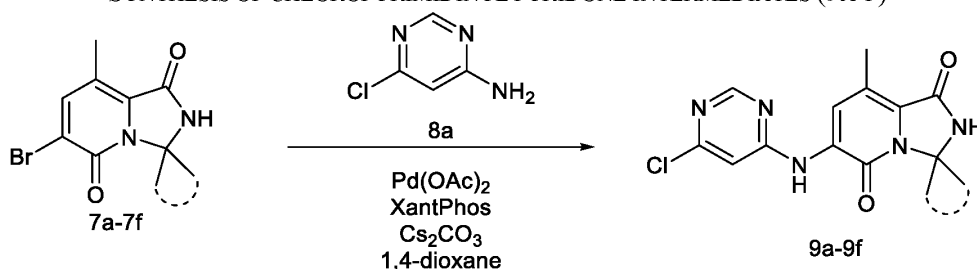


Compound 7e was synthesized according to General Procedure A. Compound 5, *tert*-butyl (4-oxocyclohexyl)carbamate (6f), and H₂SO₄ in 1,4-dioxane (13 mL)

generated intermediate 4-amino-6'-bromo-8'-methyl-2'H- spiro[cyclohexane-1,3'-imidazo[1,5-a]pyridine]-1',5'-dione. The primary amino intermediate was treated with sulfonyl chloride in CH₂Cl₂ to afford the methylsulfonamide 7f (36% over two steps).

GENERAL PROCEDURE B

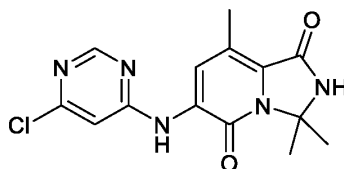
5 SYNTHESIS OF CHLOROPYRIMIDINYL PYRIDONE INTERMEDIATES (9A-F)



One of Compound 7a-7f (1 equiv), 4-amino-6-chloropyrimidine 8a (1.2 equiv), Cs₂CO₃ (3 equiv), Xantphos (20 mol%), and Pd(OAc)₂ (10 mol%) was combined in 1,4-dioxane (0.1M) and the mixture was purged with inert gas (nitrogen or argon) for 20 minutes. The reaction vessel was sealed and heated at 90 °C for 16 hours. The reaction mixture was cooled to ambient temperature and washed with water and extracted with 2-propanol/chloroform (v:v/1:4) until full recovery of the product was confirmed (TLC: 80% EtOAc/hexanes). The extracts were combined and concentrated under reduced pressure, and the crude material was purified by either recrystallization (CH₂Cl₂ in hexanes) or Biotage flash chromatography (gradient elution; 0% → 10% MeOH in CH₂Cl₂) to afford compounds 9a-f.

EXAMPLE 8

SYNTHESIS OF 6-((6-CHLOROPYRIMIDIN-4-YL)AMINO)-3,3,8-TRIMETHYL-2,3-DIHYDROIMIDAZO[1,5-A]PYRIDINE-1,5-DIONE (9A)

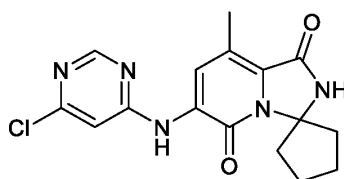


20

Compound 9a was synthesized according to General Procedure B; the compound was purified and analyzed according to the following parameters: UHPLC-MS (HESI/APCI): R_t 1.36 min, m/z 320.3 [M+H].

EXAMPLE 9

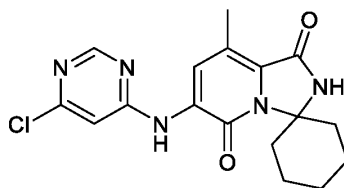
- 5 SYNTHESIS OF 6'-((6-CHLOROPYRIMIDIN-4-YL)AMINO)-8'-METHYL-2'H-SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (9B)



- Compound 9b was synthesized according to General Procedure B. Compound 7b (270 mg, 1.33 mmol), 4-amino-6-chloropyrimidine 8a (150 mg, 1.6 mmol), Cs₂CO₃ (950 mg, 4.0 mmol), Xantphos (110 mg, 0.27 mmol), and Pd(OAc)₂ (20 mg, 0.13 mmol) in 1,4-dioxane (4.7 mL) generated compound 9b (209 mg, 0.60 mmol, 45%). ¹H NMR (400 MHz, DMSO-d₆) δ 9.88 (s, 1H), 9.62 (s, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 7.45 (s, 1H), 2.76 (m, 2H), 2.40 (s, 3H), 1.94 (m, 2H), 1.80 (m, 2H), 1.67 (m, 2H). UHPLC-MS (HESI/APCI): R_t 1.42 min, m/z 346.2 [M+H].

- 15 EXAMPLE 10

SYNTHESIS OF 6'-((6-CHLOROPYRIMIDIN-4-YL)AMINO)-8'-METHYL-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (9C)

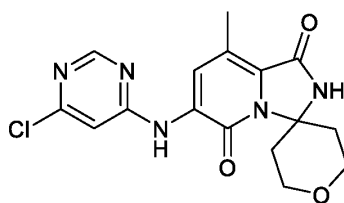


- Compound 9c was synthesized according to General Procedure B. Compound 7c (400 mg, 1.29 mmol), 4-amino-6-chloropyrimidine 8a (200 mg, 1.54 mmol), Cs₂CO₃ (1.25 g, 3.9 mmol), Xantphos (149 mg, 0.26 mmol), and Pd(OAc)₂ (29 mg, 0.13 mmol) in 1,4-dioxane (16 mL) generated compound 9c (400 mg, 1.11 mmol, 86%). ¹H NMR

(500 MHz, DMSO) δ 8.70 (s, 1H), 8.43 (s, 1H), 8.25 (s, 1H), 6.28 (s, 1H), 5.03 (s, 1H), 3.10 (m, 2H), 2.84 – 2.76 (m, 2H), 2.42 (s, 3H), 2.04 – 1.94 (m, 2H), 1.88 – 1.80 (m, 2H), 1.74 – 1.66 (m, 2H). UHPLC-MS (HESI/APCI): Rt 1.48 min, m/z 360.2 [M+H].

EXAMPLE 11

5 SYNTHESIS OF 6-((6-CHLOROPYRIMIDIN-4-YL)AMINO)-8-METHYL-2',3',5',6'-TETRAHYDRO-2H- SPIRO[IMIDAZO[1,5-A]PYRIDINE-3,4'-PYRAN]-1,5-DIONE (9D)

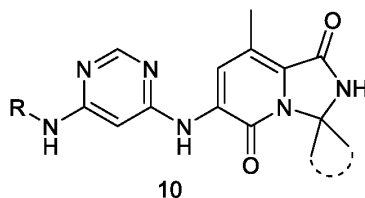


Compound 9d was synthesized according to General Procedure B. The title compound was purified and analyzed according to the following parameters:

10 UHPLC-MS (HESI/APCI): Rt 1.37 min, m/z 362.2 [M+H].

GENERAL PROCEDURE C

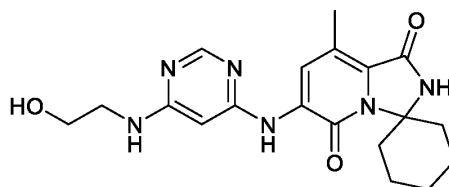
SYNTHESIS OF AMINOPYRIMIDINYL PYRIDONES (10)



To a mixture of chloropyrimidine 9a-9f (1 equiv) in 2-propanol or DMSO
 15 (0.1M) was added triethylamine (5 equiv) and the corresponding amine (5 equiv). The reaction mixture was stirred at temperatures ranging from 100 to 120°C for 16 hours. The reaction was cooled to ambient temperature and concentrated under reduced pressure. The crude material was purified by Biotage flash chromatography (silica gel, 0% → 10% MeOH in CH₂Cl₂; C₁₈, 0% to 10% MeOH in water) and then Prep-TLC if
 20 necessary to afford aminopyrimidines of the general structure 10.

EXAMPLE 12

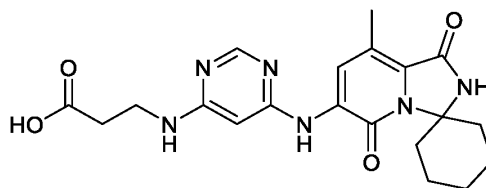
SYNTHESIS OF 6'-((6-((2-HYDROXYETHYL)AMINO)PYRIMIDIN-4-YL)AMINO)-8'-METHYL-2'H- SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (4ET-02-001)



5 Compound 4ET-02-001 was synthesized according to General Procedure C. Compound 9c (48 mg, 0.13 mmol), ethanolamine (48 mg, 0.78 mmol), and triethylamine (0.13 mL, 0.93 mmol) in 2-propanol (2 mL) generated compound 4ET-02-001 (10 mg, 0.026 mmol, 20%) as a beige solid. ¹H NMR (400 MHz, DMSO) δ 9.98 (br s, 1H), 8.54 (s, 1H), 8.37 (s, 1H), 8.21 (s, 1H), 6.97 (br s, 1H), 6.26 (s, 1H), 4.70 (t, J = 5.4 Hz, 1H), 3.57-3.46 (m, 2H), 3.29-3.23 (m, 2H), 3.00 (dt, J = 3.9, 13.0 Hz, 2H), 2.43 (s, 3H), 1.80-1.61 (m, 5H), 1.44 (br d, J = 11.5 Hz, 2H), 1.23 (s, 1H). LCMS (ES-API): Rt 3.57 min, m/z 385.2 [M+H].

EXAMPLE 13

SYNTHESIS OF 3-((6-((8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-4-YL)AMINO)PROPANOIC ACID (4ET-02-006)

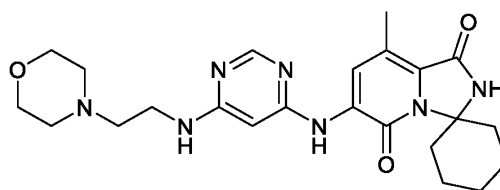


Compound 4ET-02-006 was synthesized according to General Procedure C. Compound 9c (70 mg, 0.19 mmol), beta-alanine (87 mg, 0.97 mmol), and triethylamine (0.16 mL, 1.16 mmol) in DMSO (2.5 mL) generated compound 4ET-02-006 (4 mg, 0.009 mmol, 5%). ¹H NMR (500 MHz, DMSO) δ 10.01 (s, 1H), 8.56 (s, 1H), 8.40 (s, 1H), 8.19 (s, 1H), 7.70 (d, J = 13.8 Hz, 1H), 7.07 (s, 1H), 6.24 (s, 1H), 5.03 (s, 2H), 3.21 (d, J = 36.3 Hz, 3H), 3.08 – 2.91 (m, 1H), 2.40 (d, J = 32.2 Hz, 1H), 2.18 (s, 1H),

2.04 (s, 1H), 1.70 (dd, J = 55.2, 16.1 Hz, 4H), 1.44 (d, J = 11.4 Hz, 2H). UHPLC-MS (HESI/APCI): Rt 1.08 min, m/z 413.3 [M+H].

EXAMPLE 14

SYNTHESIS OF 8'-METHYL-6'-((6-((2-MORPHOLINOETHYL)AMINO)PYRIMIDIN-4-
5 YL)AMINO)-2'H- SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (4ET-
03-006)

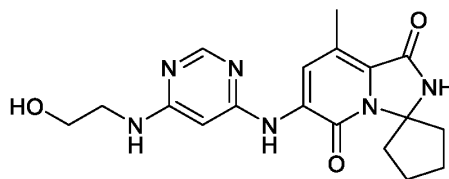


Compound 4ET-03-006 was synthesized according to General Procedure C. Compound 9b (40 mg, 0.11 mmol), 2-morpholinoethylamine (72 mg, 0.55 mmol), and triethylamine (56 mg, 0.55 mmol) in 2-propanol (1.1 mL) generated the title compound
10 4ET-03-006 (5.2 mg, 0.01 mmol, 11%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.82 (s, 1H), 8.68 (s, 1H), 8.44 (s, 1H), 8.22 (s, 1H), 6.93 (s, 1H), 6.28 (s, 1H), 3.58 (s, 4H), 3.32 (s, 2H), 2.80 (m, 2H), 2.48-2.37 (m, 6H), 2.44 (s, 3H), 1.98 (s, 2H), 1.84 (s, 2H), 1.69 (s, 2H); UHPLC-MS (HESI/APCI): Rt 0.90 min, m/z 440.3 [M+H].

15

EXAMPLE 15

SYNTHESIS OF 6'-((6-((2-HYDROXYETHYL)AMINO)PYRIMIDIN-4-YL)AMINO)-8'-METHYL-
2'H- SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (4ET-03-007)

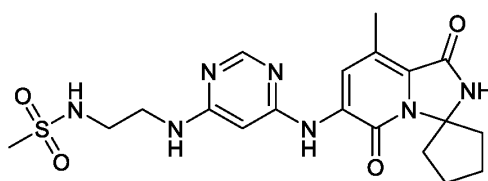


Compound 4ET-03-007 was synthesized according to General Procedure C.
20 Compound 9b (41 mg, 0.12 mmol), ethanolamine (37 mg, 0.6 mmol), and triethylamine (61 mg, 0.6 mmol) in 2-propanol (1.2 mL) generated the title compound 4ET-03-007 (1.1 mg, 0.003 mmol, 2%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.82 (s, 1H), 8.64 (s,

1H), 8.42 (s, 1H), 8.22 (s, 1H), 7.02 (s, 1H), 6.28 (s, 1H), 4.74 (s, OH), 3.51 (s, 2H), 3.32 (s, 2H), 2.80 (m, 2H), 2.42 (s, 3H), 1.98 (s, 2H), 1.84 (s, 2H), 1.69 (s, 2H); UHPLC-MS (HESI/APCI): Rt 0.46 min, m/z 371.2 [M+H].

EXAMPLE 16

5 SYNTHESIS OF N-(2-(((6-((8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-4-YL)AMINO)ETHYL)METHANESULFONAMIDE (4ET-03-013)



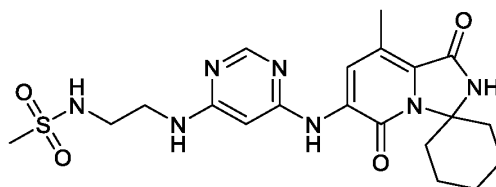
Compound 4ET-03-013 was synthesized according to General Procedure C.

10 Compound 9b (40 mg, 0.12 mmol), N-(2-aminoethyl)-methanesulfonamide (0.1 mL, 0.6 mmol), and triethylamine (0.1 mL, 0.7 mmol) in 2-propanol (2 mL) generated compound 10e (4ET-03-013) (4 mg, 0.009 mmol, 8%). ¹H NMR (500 MHz, CD₃OD) δ 8.37 (s, 1H), 8.26 (s, 1H), 6.14 (s, 1H), 4.63 (s, 3H), 3.66 (s, 1H), 3.54 – 3.43 (m, 2H), 3.31 – 3.26 (m, 2H), 3.03 (s, 3H), 2.97 (s, 1H), 2.53 (s, 2H), 2.17 – 2.08 (m, 2H), 1.95 – 1.86 (m, 2H), 1.83 – 1.74 (m, 2H). UHPLC-MS (HESI/APCI): Rt 1.13 min, m/z 448.3 [M+H].

15

EXAMPLE 17

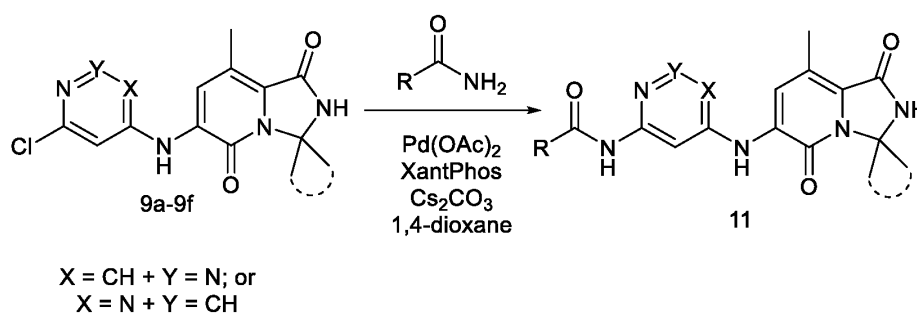
20 SYNTHESIS OF N-(2-(((6-((8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-4-YL)AMINO)ETHYL)METHANESULFONAMIDE (4ET-02-004)



Compound 4ET-02-004 was synthesized according to General Procedure C. Compound 9c (70 mg, 0.19 mmol), ethylenediamine (0.07 mL, 0.97 mmol), triethylamine (0.16 mL, 1.17 mmol) in 2-propanol (4 mL) to generate the 1,2-diamine intermediate (20 mg, 0.052 mmol, 27%). Methanesulfonyl chloride (0.004 mL, 0.05 mmol) was added to a mixture of the diamine intermediate (20 mg, 0.05 mmol) and pyridine (5 mg, 0.057 mmol) in CH₂Cl₂ (0.2 mL) at 0°C. The reaction mixture was allowed to warm to room temp (~23 °C), stirred for 16 hours, and then quenched with 3N NaOH. The aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL), and then a few drops of 12N HCl were added to the aqueous mixture until acidic to pH paper (pH 2-4). The aqueous layer was extracted with 3:1 (CHCl₃/IPA) × 3 and combined with the CH₂Cl₂ extracts, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to generate compound 4ET-02-004 (15mg, 0.032 mmol, 63%). ¹H NMR (500 MHz, CD₃OD) δ 8.42 (s, 1H), 8.03 (s, 1H), 6.35 (s, 1H), 3.56 (s, 1H), 3.31 – 3.26 (m, 2H), 3.21 – 3.10 (m, 2H), 2.98 (s, 3H), 2.67 – 2.58 (m, 3H), 2.54 (s, 3H), 2.0 – 1.75 (m, 4H), 1.73 – 1.35 (m, 6H). UHPLC- MS (HESI/APCI): Rt 1.19 min, m/z 462.3 [M+H].

GENERAL PROCEDURE D

SYNTHESIS OF SYNTHESIS OF AMIDOPYRIMIDINYL PYRIDONES FROM CHLOROPYRIMIDINYL PYRIDONES AND AMIDES

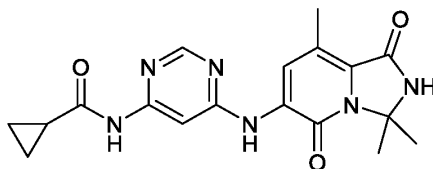


A mixture of the corresponding chloropyrimidine (X=N; Y=CH) pyridone or chloropyridazine (X=CH; Y=N) pyridone (1 equiv), amide (1.2 equiv), Cs₂CO₃ (3 equiv), XantPhos (20 mol%), Pd(OAc)₂ (10 mol%) and 1,4-dioxane (0.1 M) was purged with inert gas (nitrogen or argon) for 20 minutes. The reaction vessel was sealed and

heated at 90°C for 16 hours. The reaction was cooled to ambient temperature and the solvent was removed under reduced pressure. The resulting crude material was purified by Biotage flash chromatography (gradient elution, 0% → 10% MeOH in CH₂Cl₂) and then Prep-TLC, if necessary, to afford the amidopyrimidinyl or amidopyridazinyl pyridone amins (compound 11).

EXAMPLE 18

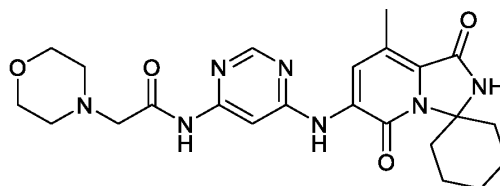
SYNTHESIS OF *N*-(6-((3,3,8-TRIMETHYL-1,5-DIOXO-1,2,3,5-TETRAHYDROIMIDAZO[1,5-*A*]PYRIDIN-6-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-002)



Compound 4ET-03-002 was synthesized according to General Procedure D. Compound 9a (50 mg, 0.16 mmol), cyclopropane carboxamide (16 mg, 0.19 mmol), Cs₂CO₃ (153 mg, 0.47 mmol), Xantphos (18 mg, 0.03 mmol), and Pd(OAc)₂ (4 mg, 0.016 mmol), and 1,4-dioxane (2 mL) generated compound 4ET-03-002 (5.5 mg, 0.015 mmol, 10%).

EXAMPLE 19

SYNTHESIS OF *N*-(6-((8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-4-YL)-2-MORPHOLINOACETAMIDE (4ET-02-007)



Compound 4ET-02-007 was synthesized according to General Procedure D. Compound 9c (100 mg, 0.28 mmol), 2-morpholinoacetamide (48 mg, 0.33 mmol), Cs₂CO₃ (272 mg, 0.83 mmol), Xantphos (32 mg, 0.06 mmol), and Pd(OAc)₂ (6 mg,

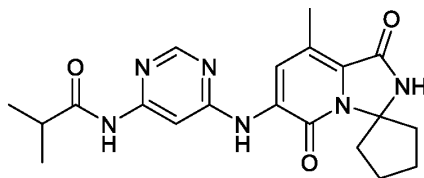
0.03 mmol) in 1,4-dioxane (3 mL) generated compound 4ET-02-007 (13 mg, 0.03 mmol, 10%). ¹H NMR (500 MHz, DMSO) δ 10.07 (d, J = 27.4 Hz, 1H), 9.29 (s, 1H), 8.52 (d, J = 25.5 Hz, 2H), 7.92 (s, 1H), 3.72 – 3.57 (m, 3H), 3.27 – 3.13 (m, 3H), 3.01 (t, J = 11.3 Hz, 2H), 2.59 – 2.52 (m, 2H), 2.44 (d, J = 11.5 Hz, 2H), 1.83 – 1.58 (m, 4H), 1.46 (d, J = 11.8 Hz, 2H), 1.24 (s, 2H). UHPLC-MS (HESI/APCI): Rt 1.2 min, m/z 468.3 [M+H].

EXAMPLE 20

SYNTHESIS OF *N*-(6-((8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-4-YL)ISOBUTYRAMIDE (4ET-03-

10

005)

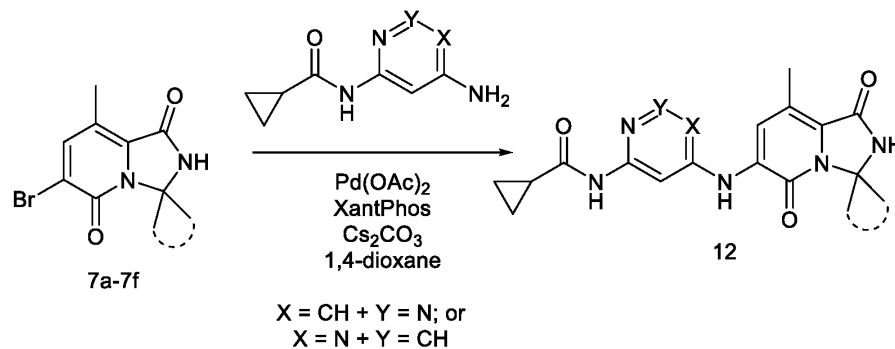


Compound 4ET-03-005 was synthesized according to General Procedure D.

Compound 9b (40 mg, 0.12 mmol), isobutyramide (11 mg, 0.13 mmol), Cs₂CO₃ (117 mg, 0.36 mmol), Xantphos (14 mg, 0.024 mmol), and Pd(OAc)₂ (2.7 mg, 0.012 mmol) in 1,4-dioxane (0.6 mL) generated compound 4ET-03-005 (3.8 mg, 0.01 mmol, 8%). ¹H NMR (500 MHz, DMSO-d₆) δ 10.51 (s, 1H), 9.89 (s, 1H), 9.23 (s, 1H), 8.53 (s, 1H), 8.51 (s, 1H), 7.91 (s, 1H), 2.80 (m, 3H), 2.44 (s, 3H), 1.98 (s, 2H), 1.84 (s, 2H), 1.69 (s, 2H), 1.09 (d, J = 6.8 Hz, 6H); UHPLC-MS (HESI/APCI): Rt 1.40 min, m/z 397.3 [M+H].

GENERAL PROCEDURE E

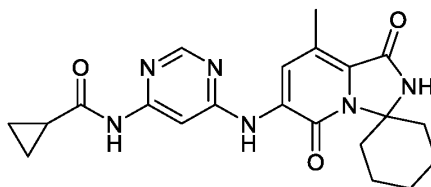
SYNTHESIS OF AMIDOPYRIMIDINYL- AND AMIDOPYRIDAZINYL PYRIDONES FROM BROMOPYRIDONES AND AMINOPYRIMIDINES/AMINOPYRIDAZINES



- 5 To a mixture of compound 7a-7f (1 equiv), N-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide (8b) or N-(5-aminopyridazin-3-yl)cyclopropanecarboxamide (8c) (1.2 equiv), Cs_2CO_3 (3 equiv), Xantphos (20 mol%), and $\text{Pd}(\text{OAc})_2$ (10 mol%) was added 1,4-dioxane (0.1M), and purged the suspension with inert gas (nitrogen or argon) for 20 minutes. The reaction vessel was sealed and
- 10 heated at 90°C for 16 hours and then cooled to ambient temperature. The crude material was purified using Biotage flash chromatography (gradient elution, 0% $\rightarrow$ 10% MeOH in CH_2Cl_2) to afford the amidopyrimidinyl or amidopyridazinyl pyridone ainals (compound 12).

EXAMPLE 21

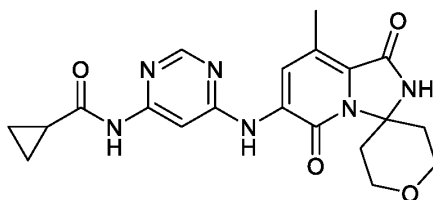
- 15 SYNTHESIS OF *N*-(6-((8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'*H*-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-*A*]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-02-003)



Compound 4ET-02-003 was synthesized according to General Procedure E. Compound 7c (149 mg, 0.48 mmol), N-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide (102 mg, 0.575 mmol), Cs₂CO₃ (468 mg, 1.44 mmol), Xantphos (56 mg, 0.096 mmol), and Pd(OAc)₂ (11 mg, 0.048 mmol) in 1,4-dioxane (5 mL) generated the title compound 4ET-02-003 (50 mg, 0.122 mmol, 26%).

EXAMPLE 22

SYNTHESIS OF N-(6-((8-METHYL-1,5-DIOXO-1,2',3',5,5',6'-HEXAHYDRO-2H-SPIRO[IMIDAZO[1,5-A]PYRIDINE-3,4'-PYRAN]-6-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-009)

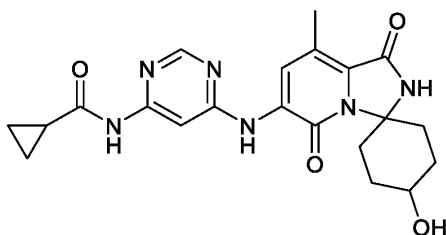


10

Compound 4ET-03-009 was synthesized according to General Procedure E. Compound 7d (100 mg, 0.32 mmol), cyclopropylamido pyrimidinylamide 8b (85 mg, 0.48 mmol), Cs₂CO₃ (312 mg, 0.96 mmol), XantPhos (37 mg, 0.06 mmol), and Pd(OAc)₂ (7.1 mg, 0.03 mmol) in 1,4-dioxane (3.2 mL) generated compound 4ET-03-009 (96 mg, 0.23 mmol, 74%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.86 (s, 1H), 10.32 (s, 1H), 9.18 (s, 1H), 8.53 (s, 1H), 8.50 (s, 1H), 7.89 (s, 1H), 3.93 (m, 2H), 3.69 (m, 2H), 3.25 (m, 2H), 2.45 (s, 3H), 2.02 (pent, J = 6.0 Hz, 1H), 1.43 (m, 2H), 0.85 (d, J = 6.0 Hz, 4H); UHPLC-MS (HESI/APCI): Rt 0.71 min, m/z 411.3 [M+H].

EXAMPLE 23

SYNTHESIS OF N-(6-((4-HYDROXY-8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-015)



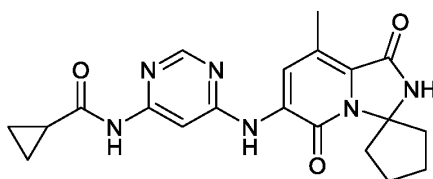
5

Compound 4ET-03-015 was synthesized according to General Procedure E. Compound 7e (100 mg, 0.30 mmol), cyclopropylamido pyrimidinyl amide 8b (82 mg, 0.45 mmol), Cs₂CO₃ (300 mg, 0.92 mmol), Xantphos (35 mg, 0.06 mmol), and Pd(OAc)₂ (6.8 mg, 0.03 mmol), and 1,4-dioxane (3.2 mL) generated compound 4ET-03-015 (99 mg, 0.23 mmol, 78%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.87 (s, 1H), 10.01 (s, 1H), 9.12 (s, 1H), 8.53 (s, 1H), 8.47 (s, 1H), 7.85 (s, 1H), 4.62 (br, 1H), 3.48 (m, 1H), 2.44 (s, 3H), 2.02 (pent, J = 6.0 Hz, 1H), 1.87-1.57 (m, 4H), 1.42 (m, 2H), 1.17 (m, 2H), 0.84 (d, J = 6.0 Hz, 4H); UHPLC-MS (HESI/APCI): Rt 0.81 min, m/z 425.3 [M+H].

15

EXAMPLE 24

SYNTHESIS OF N-(6-((8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-017)



20

Compound 4ET-03-017 was synthesized according to General Procedure E. Compound 7b (100 mg, 0.34 mmol), N-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide (8b) (72 mg, 0.4 mmol), Cs₂CO₃ (329 mg, 1.0 mmol),

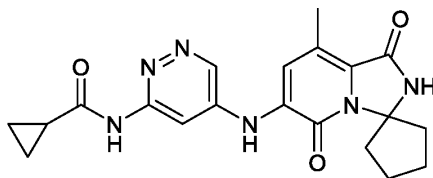
XantPhos (39 mg, 0.07 mmol), and Pd(OAc)₂ (8 mg, 0.034 mmol) in 1,4-dioxane (3.5 mL) generated compound 4ET-03-017 (33 mg, 0.084 mmol, 25%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.83 (s, 1H), 9.84 (s, 1H), 9.16 (s, 1H), 8.50 (s, 1H), 8.46 (s, 1H), 7.83 (s, 1H), 2.80-2.74 (comp, 3H), 2.40 (s, 3H), 2.01-1.94 (m, 2H), 1.82-1.79 (m, 2H), 1.67-1.63 (m, 2H), 0.81 (d, J = 4.0 Hz, 4 H); UHPLC-MS (HESI/APCI): Rt 1.3 min, m/z 395.3 [M+H].

EXAMPLE 25

SYNTHESIS OF N-(5-((8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-6'-YL)AMINO)PYRIDAZIN-3-YL)

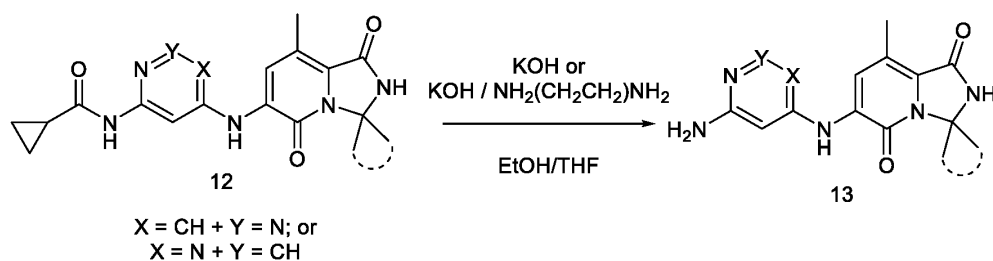
10

CYCLOPROPANECARBOXAMIDE (4ET-04-003)



Compound 4ET-04-003 was synthesized according to General Procedure E. In General Procedure E, Compound 7b (100 mg, 0.33 mmol), N-(5-aminopyridazin-3-yl)cyclopropanecarboxamide (8c) (90 mg, 0.50 mmol), Cs₂CO₃ (328 mg, 1.01 mmol), XantPhos (39 mg, 0.06 mmol), and Pd(OAc)₂ (7.5 mg, 0.03 mmol) in 1,4-dioxane (3.2 mL) generated compound 4ET-04-003 (114 mg, 0.29 mmol, 88%). ¹H NMR (500 MHz, DMSO-d₆) δ 11.15 (s, 1H), 9.93 (s, 1H), 9.04 (s, 1H), 8.88 (s, 1H), 8.12 (s, 1H), 7.33 (s, 1H), 2.79 (m, 2H), 2.40 (s, 3H), 2.04 (pent, J = 6.0 Hz, 1H), 1.96 (m, 2H), 1.83 (m, 2H), 1.69 (m, 2H), 0.83 (d, J = 6.0 Hz, 4H); UHPLC-MS (HESI/APCI): Rt 1.17 min, m/z 395.3 [M+H].

GENERAL PROCEDURES F1 AND F2

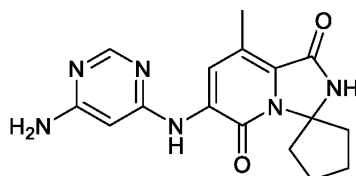
SYNTHESIS OF AMINOPYRIMIDINYL- AND AMINOPYRIDAZINYL PYRIDONES
FROM CYCLOPROPYLAMIDES

- 5 General Procedure F1: Aqueous potassium hydroxide (12 equiv) and ethylenediamine (12 equiv) were sequentially added to a solution of cyclopropylamide 12 (1 equiv) in tetrahydrofuran and ethanol (1:1, v/v). After stirring at room temperature for 24 hours, the mixture was concentrated under reduced pressure, and the residue was diluted with dichloromethane and then washed with water. The organic
- 10 layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified on an InterChim automated chromatography system (silica gel column), eluting with a gradient of 0 to 10% methanol in dichloromethane to give the aminopyrimidine or aminopyridazine.

- General Procedure F2: To a mixture of cyclopropylamide (1 equiv) in
- 15 EtOH/THF/water (v:v:v/2:1:1) was added KOH (6M in H_2O ; 4.8 equiv). The resulting mixture was stirred at ambient temperature for 16 hours, after which the mixture was concentrated under reduced pressure and azeotropically washed with toluene. The crude material was purified by Biotage flash chromatography (gradient elution; 0% $\rightarrow$ 25% MeOH in CH_2Cl_2) to afford the aminopyrimidine or aminopyridazine.

EXAMPLE 26

SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8'-METHYL-2'H-SPIRO[CYCLOPENTANE-1,3'-IMIDAZO[1,5-A]PYRIDINE]-1',5'-DIONE (4ET-01-001)

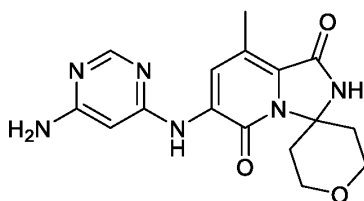


- 5 Compound 4ET-01-001 was synthesized according to General Procedure F1. Potassium hydroxide (214 mg, 3.82 mmol, 12.0 equiv) in water (1 mL), ethylenediamine (230 mg, 3.82 mmol, 12.0 equiv), and compound 4ET-03-017 (125 mg, 0.318 mmol, 1.0 equiv) in tetrahydrofuran (2 mL) and ethanol (2 mL), to give compound 4ET-01-001 (12 mg, 12% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.78 (s, 1H), 8.62 (s, 1H), 8.40 (s, 1H), 8.17 (s, 1H), 6.49 (s, 2H), 6.16 (d, J = 0.9 Hz, 1H), 2.84-2.75 (m, 2H), 2.41 (s, 3H), 2.02-1.93 (m, 2H), 1.88-1.78 (m, 2H), 1.68 (td, J = 5.8, 11.9 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆) δ 164.4, 161.6, 159.9, 158.1, 153.8, 134.0, 122.3, 121.3, 117.0, 88.2, 36.0, 25.3, 14.2; LCMS (ES-API): Rt 3.0 min, m/z 327.1 [M+H].
- 10

15

EXAMPLE 27

SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8-METHYL-2',3',5',6'-TETRAHYDRO-2H-SPIRO[IMIDAZO[1,5-A]PYRIDINE-3,4'-PYRAN]-1,5-DIONE (4ET-01-002)

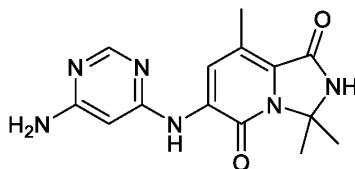


- Compound 4ET-01-002 was synthesized according to General Procedure F1.
- 20 Potassium hydroxide (51 mg, 0.91 mmol, 12.0 equiv) in water (0.5 mL), ethylenediamine (54 mg, 0.91 mmol, 12.0 equiv), and compound 4ET-03-009 (31 mg, 0.076 mmol, 1.0 equiv) in tetrahydrofuran (0.7 mL) and ethanol (0.7 mL), to give compound 4ET-01-002 (23 mg, 89% yield) as a white solid. ¹H NMR (400 MHz,

DMSO-d₆) δ 10.2 (br s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 6.50 (s, 2H), 6.19 (d, J = 0.7 Hz, 1H), 3.95-3.90 (m, 2H), 3.73-3.66 (m, 2H), 3.26 (dt, J = 5.5, 13.0 Hz, 2H), 2.43 (s, 3H), 1.42 (br d, J = 12.5 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆) δ 164.4, 162.3, 159.8, 158.1, 154.1, 134.3, 121.9, 121.8, 117.5, 88.3, 77.0, 63.8, 33.3, 14.3; LCMS (ES-API): Rt 2.6 min, m/z 343.1 [M+H].

EXAMPLE 28

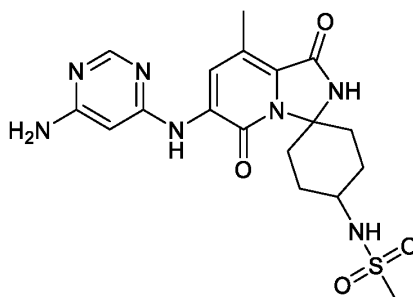
SYNTHESIS OF 6-((6-AMINOPYRIMIDIN-4-YL)AMINO)-3,3,8-TRIMETHYL-2,3-DIHYDROIMIDAZO[1,5-A]PYRIDINE-1,5-DIONE (4ET-01-003)



Compound 4ET-01-003 was synthesized according to General Procedure F1. Potassium hydroxide (84 mg, 1.5 mmol, 12.0 equiv) in water (0.5mL), ethylenediamine (90 mg, 1.5 mmol, 12.0 equiv), and compound 4ET-03-002 (46 mg, 0.12 mmol, 1.0 equiv) in tetrahydrofuran (1.0 mL) and ethanol (1.0 mL), to give compound 4ET-01-003 (33 mg, 88% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 9.44 (s, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 8.17 (s, 1H), 6.49 (s, 2H), 6.17 (d, J = 0.9 Hz, 1H), 2.41 (s, 3H), 1.78 (s, 6H); ¹³C NMR (100 MHz, DMSO-d₆) δ 164.4, 161.5, 159.9, 158.1, 153.9, 134.0, 122.0, 121.9, 117.1, 88.2, 76.3, 25.3, 14.3; LCMS (ES-API): Rt 2.6 min, m/z 301.1 [M+H].

EXAMPLE 29

SYNTHESIS OF *N*-(6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'*H*-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-*A*]PYRIDIN]-4-YL)METHANESULFONAMIDE (4ET-01-004)



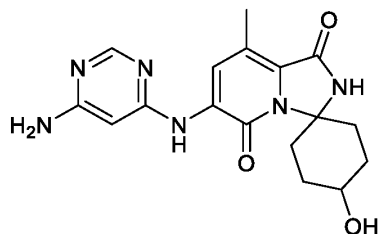
5

Compound 4ET-01-004 was synthesized according to General Procedure F1. Potassium hydroxide (48 mg, 0.86 mmol, 12.0 equiv) in water (0.35 mL), ethylenediamine (52 mg, 0.86 mmol, 12.0 equiv) and compound 4ET-03-033 (vide infra) (36 mg, 0.07 mmol, 1.0 equiv) in tetrahydrofuran (0.7 mL) and ethanol (0.7 mL) to give 20 mg, which was repurified to give 6 mg compound 4ET-01-004 as an off-white solid (19%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 8.33 (s, 1H), 8.13 (s, 1H), 7.30 (br s, 2H), 6.49 (s, 2H), 6.13 (s, 1H), 3.14-3.10 (m, 1H), 2.93 (s, 3H), 2.39 (s, 3H), 1.96-1.91 (m, 2H), 1.73-1.64 (m, 2H), 1.45 (br d, *J* = 16.0 Hz, 2H), 1.26-1.14 (m, 2H); UHPLC-MS (HESI/APCI): *R*_t 0.78 min, *m/z* 434.2 [*M*+*H*].

15

EXAMPLE 30

SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-4-HYDROXY-8'-METHYL-2'*H*-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-*A*]PYRIDINE]-1',5'-DIONE (4ET-01-005)



Compound 4ET-01-005 was synthesized according to General Procedure F2. cyclopropylamide **11f** (4ET-03-015) (50 mg, 0.12 mmol) and KOH (6M in H₂O; 0.1

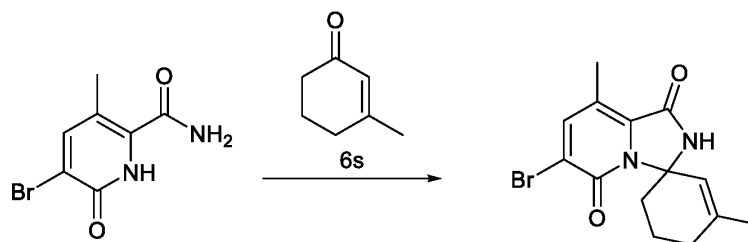
mL, 0.58 mmol) in EtOH/THF/water (v:v:v/2:1:1, 2.0 mL) to give compound 4ET-01-005 (25 mg, 0.07 mmol, 63%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.00 (s, 1H), 8.56 (s, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 6.51 (br, 2H), 6.15 (s, 1H), 4.62 (br, 1H), 3.57-3.40 (m, 2H), 3.10 (m, 1H), 2.42 (s, 3H), 1.87-1.56 (m, 4H), 1.30 (m, 2H); UHPLC-MS (HESI/APCI): Rt 0.47 min, m/z 357.3 [M+H].

Others of compounds 4ET-01-001-005, 4ET-02-001-023, 4ET-03-001-034, 4ET-04-003 for which the synthesis is not specifically set forth in these examples may be readily synthesized by applying general principles known to one of ordinary skill in the art to the synthesis methods described herein.

10

EXAMPLE 31

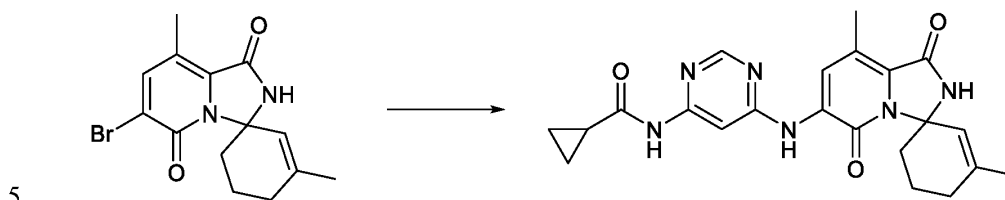
SYNTHESIS OF 6'-BROMO-3,8'-DIMETHYL-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-2-ENE-1',5'-DIONE



In General Procedure A, compound 5 (100 mg, 0.433 mmol), 3-methylcyclohex-2-en-1-one (6s, 477 mg, 4.328 mmol), H₂SO₄ (0.012 mL, 0.216 mmol), and 1,4-dioxane (4.0 mL) generated the title compound (60 mg, 0.186 mmol, 43%). ¹H NMR (400 MHz, CDCl₃) δ 7.75 (s, 1 H), 6.70 (s, 1 H), 5.51 (s, 1 H), 3.89 (d, *J* = 16.9 Hz, 1 H), 3.21 (td, *J* = 12.5, 6.9 Hz, 1 H), 2.48 (s, 3 H), 2.24 (m, 2 H), 1.78 (d, *J* = 16.6 Hz, 1 H), 1.70 (s, 3 H), 1.59 (d, *J* = 6.6 Hz, 1 H). UHPLC-MS (ESI): Rt 1.05 min, m/z 323.2 [M]⁺.

EXAMPLE 32

SYNTHESIS OF *N*-(6-((3,8'-DIMETHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'*H*-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-*a*]PYRIDIN]-2-EN-6'-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE

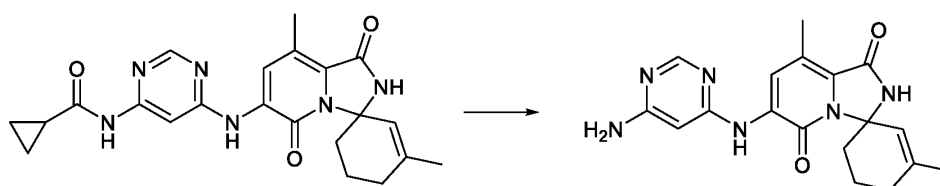


According to general procedure E, 6'-Bromo-3,8'-dimethyl-2'*H*-spiro[cyclohexane-1,3'-imidazo[1,5-*a*]pyridin]-2-ene-1',5'-dione (60 mg, 0.186 mmol), *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide (40 mg, 0.223 mmol), Cs₂CO₃ (181 mg, 0.557 mmol), Xantphos (21 mg, 0.037 mmol), Pd(OAc)₂ (4.0 mg, 0.019 mmol), and 1,4-dioxane (4.0 mL) generated the title compound (15 mg, 0.035 mmol, 19%). ¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, *J* = 3.2 Hz, 2 H), 8.30 (s, 1 H), 7.67 (s, 1 H), 6.89 (s, 1 H), 5.60-5.55 (m, 1 H), 3.84 (d, *J* = 16.9 Hz, 1 H), 3.18 (td, *J* = 12.4, 6.8 Hz, 1 H), 2.57 (s, 3 H), 2.42 (d, *J* = 18.2 Hz, 1 H), 1.90 – 1.76 (comp, 3 H), 1.72 (s, 3 H), 1.66 – 1.60 (m, 1 H), 1.12 (q, *J* = 3.8 Hz, 2 H), 0.95 (dq, *J* = 7.4, 4.0 Hz, 2 H).

15 UHPLC-MS (ESI): Rt 1.15 min, *m/z* 421.4 [M]⁺.

EXAMPLE 33

SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-3,8'-DIMETHYL-2'*H*-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-*a*]PYRIDIN]-2-ENE-1',5'-DIONE (4ET-01-058)

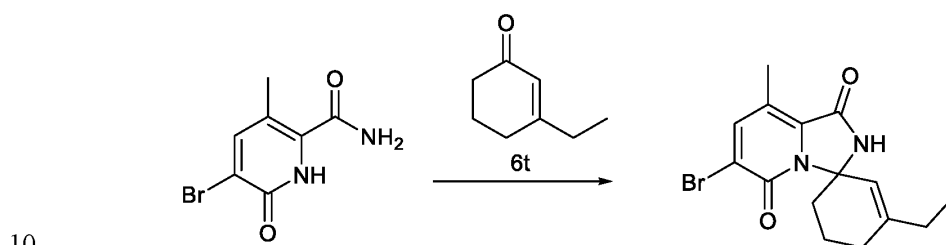


20 According to general procedure F2, *N*-(6-((3,8'-Dimethyl-1',5'-dioxo-1',5'-dihydro-2'*H*-spiro[cyclohexane-1,3'-imidazo[1,5-*a*]pyridin]-2-en-6'-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide (10 mg, 0.024 mmol), 6N KOH

aqueous solution (0.079 mL, 0.476 mmol) in EtOH/THF/H₂O (2 mL, v:v:v/2:1:1) generated the title compound (4ET-01-058) (7 mg, 0.020 mmol, 88%). ¹H NMR (400 MHz, DMSO-d₆) δ 9.65 (s, 1 H), 8.54 (s, 1 H), 8.38 (s, 1 H), 8.15 (s, 1 H), 6.48 (s, 2 H), 6.14 (d, J = 1.0 Hz, 1 H), 5.46 (s, 1 H), 3.65 (d, J = 17.0 Hz, 1 H), 2.98 (td, J = 12.2, 6.8 Hz, 1 H), 2.41 (s, 3 H), 2.27-2.17 (m, 2 H), 1.77 (d, J = 16.3 Hz, 1 H), 1.64 (s, 3 H), 1.47 (d, J = 13.7 Hz, 1 H); UHPLC-MS (ESI): Rt 0.95 min, m/z 353.3 [M+H]⁺.

EXAMPLE 34

SYNTHESIS OF 6'-BROMO-3-ETHYL-8'-METHYL-2'*H*-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-*A*]PYRIDIN]-2-ENE-1',5'-DIONE

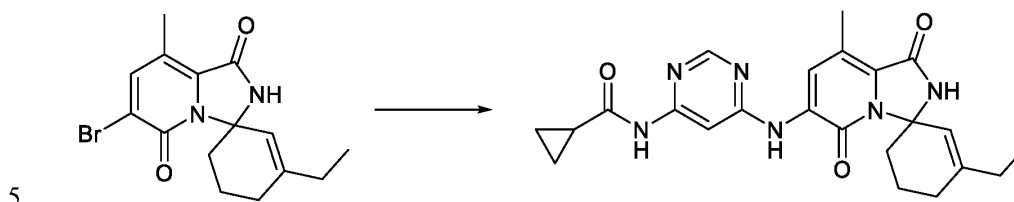


In General Procedure A, compound 5 (200 mg, 0.86 mmol), 3-ethylcyclohex-2-en-1-one (6t, 322 mg, 2.60 mmol), H₂SO₄ (0.023 mL, 0.43 mmol), and 1,4-dioxane (8.0 mL) generated the title compound (65 mg, 0.19 mmol, 22%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.04 (s, 1 H), 8.04 (s, 1 H), 5.46 (s, 1 H), 3.61 (m, 1 H), 2.95 (m, 1 H), 2.39 (s, 3 H), 2.25 (m, 2 H), 1.97 (m, 2 H), 1.81 (m, 1 H), 1.55 (m, 1 H), 0.96 (t, J = 7.4 Hz, 3 H). UHPLC-MS (ESI): Rt 0.78 min, m/z 337.1 [M]⁺.

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EXAMPLE 35

SYNTHESIS OF *N*-(6-((3-ETHYL-8'-METHYL-1',5'-DIOXO-1',5'-DIHYDRO-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-2-EN-6'-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-039)

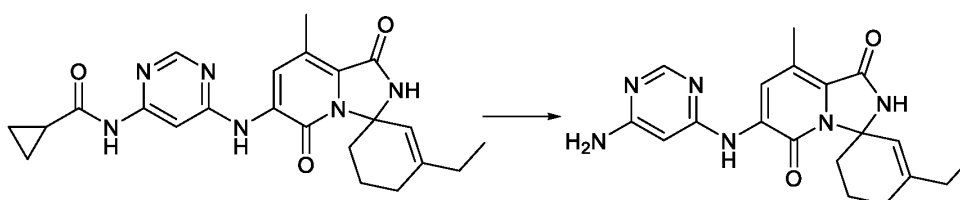


In general procedure E, compound 7h (63 mg, 0.18 mmol), *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide (50 mg, 0.28 mmol), Cs₂CO₃ (183 mg, 0.56 mmol), Xantphos (21.6 mg, 0.037 mmol), Pd(OAc)₂ (4.2 mg, 0.019 mmol), and 1,4-dioxane (2.0 mL) generated the title compound (4ET-03-039) (42 mg, 0.096 mmol, 53%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.85 (s, 1 H), 9.72 (br s, 1 H), 9.12 (s, 1 H), 8.53 (s, 1 H), 8.49 (s, 1 H), 7.85 (s, 1 H), 5.48 (br s, 1 H), 3.67 (m, 1 H), 3.03 (m, 1 H), 2.45 (s, 3 H), 2.27 (m, 2 H), 2.00 (m, 3 H), 1.82 (m, 1 H), 1.52 (m, 1 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 0.84 (d, *J* = 6.2 Hz, 4 H). UHPLC-MS (ESI): Rt 0.78 min, *m/z* 435.3 [M+H]⁺.

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EXAMPLE 36

15 SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-3-ETHYL-8'-METHYL-2'H-SPIRO[CYCLOHEXANE-1,3'-IMIDAZO[1,5-A]PYRIDIN]-2-ENE-1',5'-DIONE (4ET-01-021)



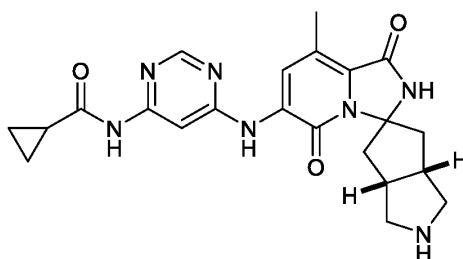
In General Procedure F2, compound 4ET-03-039 (30mg, 0.069 mmol), 6N KOH aqueous solution (0.060 mL, 0.35 mmol) in EtOH/THF/H₂O (2 mL, v:v:v/2:1:1) generated the title compound 12g (4ET-01-021) (18 mg, 0.049 mmol, 72%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.66 (br, 1H), 8.57 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 6.50 (br, 2H), 6.16 (s, 1H), 5.48 (s, 1H), 3.70 (m, 1H), 3.03 (m, 1H), 2.43 (s, 3H), 2.27 (m, 2H),

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1.97 (m, 2H), 1.82 (m, 1H), 1.50 (m, 1H), 0.97 (m, 3H). UHPLC-MS (ESI): Rt 0.65 min, m/z 367.3 [M+H]⁺.

EXAMPLE 37

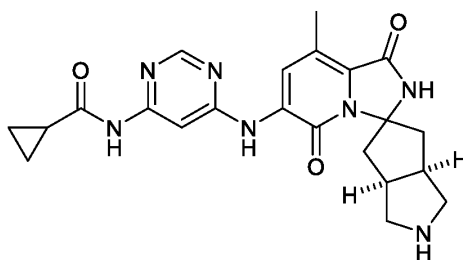
SYNTHESIS OF *N*-(6-((8'-METHYL-1',5'-DIOXO-1',2,3,3A,4,5',6,6A-OCTAHYDRO-1*H*,2'*H*-
5 SPIRO[CYCLOPENTA[C]PYRROLE-5,3'-IMIDAZO[1,5-*A*]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-
4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-050A)



Second eluting isomer on reverse phase HPLC: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.85 (s, 1 H), 9.18 (s, 1 H), 8.55 (s, 1 H), 8.50 (s, 1 H), 7.85 (s, 1 H), 3.15-2.98 (m, 8
10 H), 2.42 (s, 3 H), 2.05-1.99 (m, 1 H), 1.95-1.80 (m, 2 H), 0.82 (d, *J* = 6.2 Hz, 4 H);
UHPLC-MS (ESI): Rt 0.61 min, m/z 436.3 [M+H]⁺.

EXAMPLE 38

SYNTHESIS OF *N*-(6-((8'-METHYL-1',5'-DIOXO-1',2,3,3A,4,5',6,6A-OCTAHYDRO-1*H*,2'*H*-
15 SPIRO[CYCLOPENTA[C]PYRROLE-5,3'-IMIDAZO[1,5-*A*]PYRIDIN]-6'-YL)AMINO)PYRIMIDIN-
4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-050B)

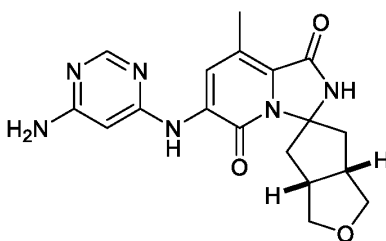


First eluting isomer on reverse phase HPLC: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.85 (s, 1 H), 9.18 (s, 1 H), 8.55 (s, 1 H), 8.51 (s, 1 H), 7.86 (s, 1 H), 3.55-3.40 (m, 4

H), 3.10-3.04 (m, 2 H), 3.10-2.95 (m, 2 H), 2.42 (s, 3 H), 2.04-1.98 (m, 1 H), 1.95-1.81 (m, 2 H), 0.84-0.78 (m, 4 H). UHPLC-MS (ESI): Rt 0.60 min, m/z 436.3 [M+H]⁺.

EXAMPLE 39

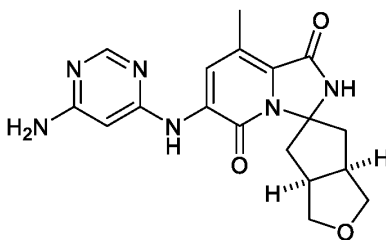
SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8'-METHYL-3A,4,6,6A-
5 TETRAHYDRO-1*H*,2'*H*,3*H*-SPIRO[CYCLOPENTA[C]FURAN-5,3'-IMIDAZO[1,5-*A*]PYRIDINE]-
1',5'-DIONE (4ET-01-014A)



Second eluting isomer on reverse phase HPLC): ¹H NMR (400 MHz, CDCl₃) δ
8.48 (s, 1 H), 8.38 (s, 1 H), 7.98 (s, 1 H), 7.83 (s, 1 H), 5.80 (s, 1 H), 4.69 (br s, 2 H),
10 3.93 (d, *J* = 10.0 Hz, 2 H), 3.75-3.65 (m, 4 H), 3.48 (s, 2 H), 3.15-3.02 (m, 2 H), 2.55 (s,
3 H); UHPLC-MS (ESI): Rt 0.61 min, m/z 369.3 [M+H]⁺.

EXAMPLE 40

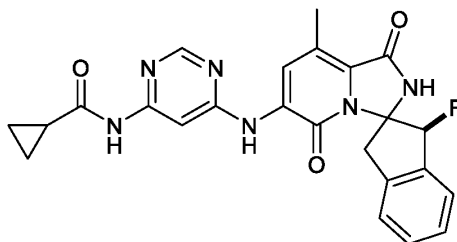
SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8'-METHYL-3A,4,6,6A-
TETRAHYDRO-1*H*,2'*H*,3*H*-SPIRO[CYCLOPENTA[C]FURAN-5,3'-IMIDAZO[1,5-*A*]PYRIDINE]-
15 1',5'-DIONE (4ET-01-014B)



First eluting isomer on reverse phase HPLC): ¹H NMR (400 MHz, CDCl₃) δ
8.48 (s, 1 H), 8.38 (s, 1 H), 7.98 (br s, 1 H), 7.83 (br s, 1 H), 5.80 (s, 1 H), 4.69 (br s, 2
H), 3.93 (d, *J* = 10.0 Hz, 2 H), 3.75-3.66 (m, 4 H), 3.48 (s, 2 H), 3.12-3.05 (m, 2 H),
20 2.55 (s, 3 H); UHPLC-MS (ESI): Rt 0.58 min, m/z 369.3 [M+H]⁺.

EXAMPLE 41

SYNTHESIS OF *N*-(6-((1'-FLUORO-8-METHYL-1,5-DIOXO-1,1',3',5-TETRAHYDRO-2*H*-SPIRO[IMIDAZO[1,5-*A*]PYRIDINE-3,2'-INDEN]-6-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-052A)



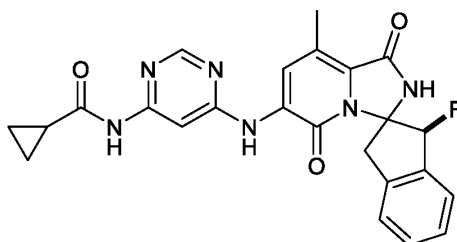
5

First eluting atropisomer on reverse phase HPLC: ^1H NMR (400 MHz, DMSO- d_6) δ 10.76 (s, 1 H), 9.78 (br s, 1 H), 9.22 (s, 1 H), 8.49 (s, 1 H), 7.79 (s, 1 H), 7.42-7.38 (m, 2 H), 7.30-7.26 (m, 2 H), 6.00 (d, $J = 55.2$ Hz, 1 H), 4.02 (d, $J = 17.6$ Hz, 1 H), 3.36-3.30 (m, 1 H), 2.65 (s, 0.5 H), 2.48 (s, 3 H), 2.30 (s, 0.5 H), 1.99-1.94 (m, 1 H), 0.80-0.77 (d, $J = 5.6$ Hz, 4 H); UHPLC-MS (ESI): R_t 0.73 min, m/z 461.3 $[\text{M}+\text{H}]^+$.

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EXAMPLE 42

SYNTHESIS OF *N*-(6-((1'-FLUORO-8-METHYL-1,5-DIOXO-1,1',3',5-TETRAHYDRO-2*H*-SPIRO[IMIDAZO[1,5-*A*]PYRIDINE-3,2'-INDEN]-6-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-052B)



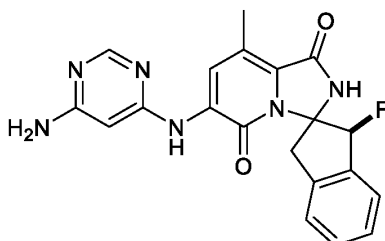
15

Second eluting atropisomer on reverse phase HPLC: ^1H NMR (400 MHz, DMSO- d_6) δ 10.82 (s, 1 H), 9.98 (br s, 1 H), 9.16 (s, 1 H), 8.52 (s, 1 H), 7.81 (s, 1 H), 7.47-7.33 (m, 4 H), 6.58 (d, $J = 20.8$ Hz, 1 H), 4.19 (d, $J = 16.4$ Hz, 1 H), 3.30-3.12 (m, 1 H), 2.56-2.45 (m, 1 H), 2.47 (s, 3 H), 2.01-1.96 (m, 1 H), 0.80 (d, $J = 6.0$ Hz, 4 H); UHPLC-MS (ESI): R_t 3.3 min, m/z 461.3. $[\text{M}+\text{H}]^+$.

20

EXAMPLE 43

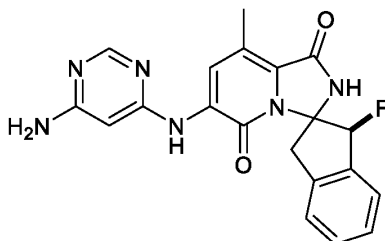
SYNTHESIS OF 6-((6-AMINOPYRIMIDIN-4-YL)AMINO)-1'-FLUORO-8-METHYL-1',3'-DIHYDRO-2H-SPIRO[IMIDAZO[1,5-*A*]PYRIDINE-3,2'-INDENE]-1,5-DIONE (4ET-01-010A)



5 *Second eluting atropisomer on reverse phase HPLC*: ^1H NMR (400 MHz, DMSO- d_6) δ 9.90 (br s, 1 H), 8.61 (s, 1 H), 8.48 (s, 1 H), 8.17 (s, 1 H), 7.50-7.17 (m, 4 H), 6.49 (s, 2 H), 6.12 (s, 1 H), 4.20-4.12 (m, 1 H), 3.24-3.19 (m, 2 H), 2.42 (s, 3 H); UHPLC-MS (ESI): Rt 0.64 min, m/z 393.2 $[\text{M}+\text{H}]^+$.

EXAMPLE 44

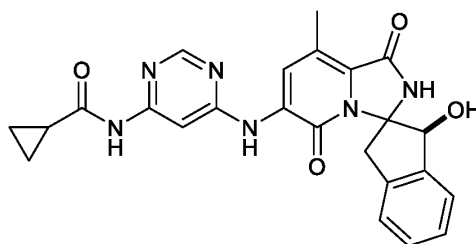
10 SYNTHESIS OF 6-((6-AMINOPYRIMIDIN-4-YL)AMINO)-1'-FLUORO-8-METHYL-1',3'-DIHYDRO-2H-SPIRO[IMIDAZO[1,5-*A*]PYRIDINE-3,2'-INDENE]-1,5-DIONE (4ET-01-010B)



15 *First eluting atropisomer on reverse phase HPLC*: ^1H NMR (400 MHz, DMSO- d_6) δ 8.60 (br s, 1 H), 8.40 (s, 1 H), 8.12 (s, 1 H), 7.42-7.37 (m, 2 H), 7.35-7.23 (m, 2 H), 6.41 (s, 2 H), 6.08 (s, 1 H), 6.02 (br s, 0.5 H), 5.88 (br s, 0.5 H), 4.00 (d, J = 16.0 Hz, 1 H), 3.18-3.16 (m, 1 H), 2.64-2.62 (m, 1 H), 2.41 (s, 3 H); UHPLC-MS (ESI): Rt 0.62 min, m/z 393.3 $[\text{M}+\text{H}]^+$.

EXAMPLE 45

SYNTHESIS OF *N*-(6-((1'-HYDROXY-8-METHYL-1,5-DIOXO-1,1',3',5-TETRAHYDRO-2*H*-SPIRO[IMIDAZO[1,5-*a*]PYRIDINE-3,2'-INDEN]-6-*YL*)AMINO)PYRIMIDIN-4-*YL*)CYCLOPROPANECARBOXAMIDE (4ET-03-063)

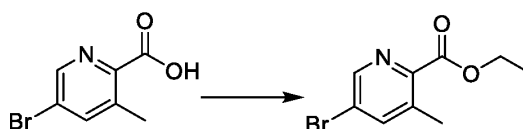


5

¹H NMR (400 MHz, DMSO-*d*₆, *one NH proton not detected*) δ 10.81 (s, 1 H), 8.18 (s, 1 H), 8.56-8.50 (m, 2 H), 7.88-7.72 (m, 2 H), 7.72 (s, 1 H), 7.68-7.62 (m, 1 H), 7. 7.56-7.49 (m, 1 H), 4.08 (d, *J* = 12.0 Hz, 1 H), 3.41 (d, *J* = 12.0 Hz, 1 H), 2.42 (s, 3 H), 2.01-1.91 (m, 2 H), 1.80-1.78 (m, 1 H), 0.85-0.72 (m, 4 H); UHPLC-MS (ESI): Rt 10 0.76 min, *m/z* 457.3 [M+H]⁺.

EXAMPLE 46

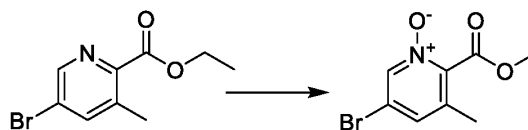
SYNTHESIS OF 5-BROMO-3-METHYL-6-OXO-1,6-DIHYDROPYRIDINE-2-CARBOXAMIDE



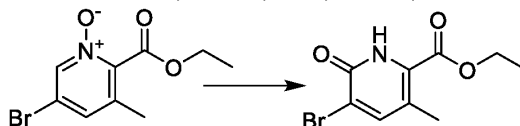
Step 1: Synthesis of ethyl 5-bromo-3-methylpicolinate. To a solution of 5-bromo-3-methylpicolinic acid (10 g, 42.3 mmol) in ethanol (37 mL) was added H₂SO₄ (2.3 mL, 18.4 M, 42.3 mmol) at 23 °C. The reaction mixture was heated at 80 °C for 16 hours. The solvent was removed under reduced pressure and ethyl acetate (250 mL) was added. After washing with NaHCO₃ (200 mL × 2) and water (200 mL × 2), the organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford ethyl 5-bromo-3-methylpicolinate (9.6 g, 39 mmol, 93%) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H), 7.76 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.56 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

15

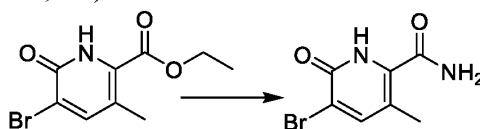
20



Step 2: Synthesis of 5-bromo-2-(ethoxycarbonyl)-3-methylpyridine 1-oxide. To a solution of ethyl 5-bromo-3-methylpicolinate (9.6 g, 39 mmol) in CH₂Cl₂ (111 mL) was added urea hydrogen peroxide (6.4 g, 68.3 mmol), followed by the addition of trifluoroacetic anhydride (9.6 mL, 68.3 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 4 hours and was poured into ice/water mixture (100 mL). After extraction with CH₂Cl₂ (50 mL × 3), the combined organic phase was washed with NaHCO₃ (50 mL × 3) and water (50 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford 5-bromo-2-(ethoxycarbonyl)-3-methylpyridine 1-oxide (10.1 g, 39 mmol, 99%) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (s, 1H), 7.26 (s, 1H), 4.47 (q, J = 7.1 Hz, 2H), 2.27 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H).



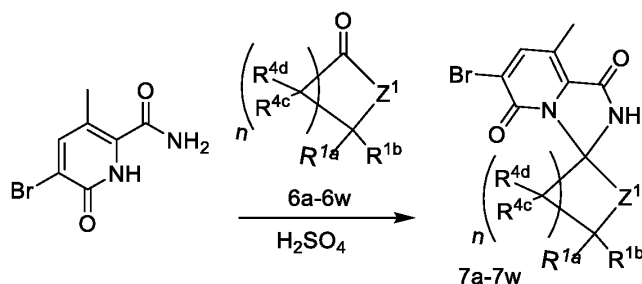
Step 3: Synthesis of ethyl 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate. To a solution of compound 3 (10.1 g, 39 mmol) in N,N-dimethylformamide (30.5 mL) was added trifluoroacetic anhydride (9.6 mL, 68.3 mmol) at 0 °C. The reaction mixture was stirred at 40 °C for 8 hours and diluted with water (100 mL). After extraction with ethyl acetate (100 mL × 3), the combined organic phase was washed with brine (100 mL × 5), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by Biotage flash chromatography (silica gel, 0% to 30% ethyl acetate in hexanes) to afford ethyl 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate (6.8 g, 26.1 mmol, 67%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.83 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H).



Step 4: Synthesis of 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide. Ammonium hydroxide (130.5 mL, 28% in water) was added to ethyl 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate (6.8 g, 26.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 6 hours and concentrated under reduced pressure to afford 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (5, 6.0 g, 26 mmol, 99%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.87 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 2.12 (s, 3H).

GENERAL PROCEDURE G

SYNTHESIS OF SPIROCYCLOALKYL PYRIDONES (7A-7W)



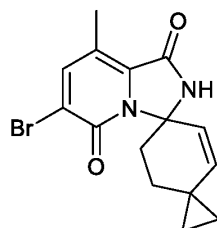
10

To a solution of compound 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (1 equiv) in 1,4-dioxane (0.2M) was added ketone 6a-6w (4 equiv), followed by the addition of H₂SO₄ (0.5 equiv). The reaction mixture was sealed in a pressure vessel and heated in at 100 °C for 16 hours. The reaction mixture was cooled to 23 °C and concentrated under reduced pressure. The resulting crude material was purified by Biotage flash chromatography (gradient elution, 30 to 85% ethyl acetate in hexanes or 0 to 10% MeOH in CH₂Cl₂) to afford compounds 7a-7w.

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EXAMPLE 47

SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDIN]-2'-ENE-1'',5''-DIONE (7f3)



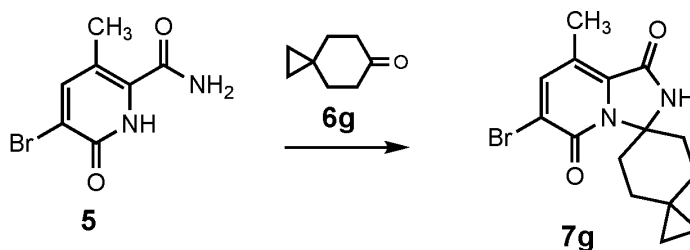
5

(7f3)

The title compound (7f3) was prepared according to General Procedure G except that 4 angstrom molecular sieves were added to the reaction using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide and spiro[2.5]oct-4-en-6-one (6u) to afford 6''-Bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-*α*]pyridin]-2'-ene-1'',5''-dione (7f3) in 43% yield: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.15 (s, 1H), 8.01 (s, 1H), 5.43 (d, *J* = 9.6 Hz, 1H), 5.36 (d, *J* = 9.3 Hz, 1H), 3.16 – 3.10 (m, 1H), 2.38 (s, 3H), 2.28 (t, *J* = 14.2 Hz, 1H), 1.58 (d, *J* = 12.5 Hz, 1H), 1.23 (d, *J* = 12.9 Hz, 1H), 0.78 – 0.53 (m, 4H).

EXAMPLE 48

15 SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7G)



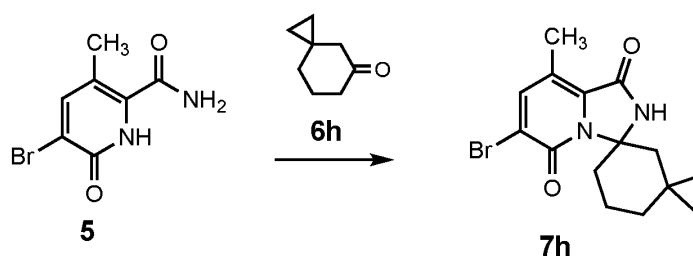
The title compound (7g) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (144 mg, 0.63 mmol), spiro[2.5]octan-6-one (6g, 232 mg, 1.87 mmol), H₂SO₄ (0.017 mL, 0.31 mmol), and

20

1,4-dioxane (6.3 mL). 6''-Bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione (7g) yield: (105 mg, 0.31 mmol, 50%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.42 (s, 1H), 8.02 (s, 1H), 3.11 (dt, *J* = 13.3, 4.5 Hz, 2H), 2.39 (s, 3H), 2.12 (dt, *J* = 14.6, 3.8 Hz, 2H), 1.41 (d, *J* = 12.4 Hz, 2H), 0.88 (d, *J* = 12.8 Hz, 2H), 0.38 (m, 2H), 0.29 (m, 2H). UHPLC-MS (ESI): Rt 0.79 min, *m/z* 337.1 [M]⁺.

EXAMPLE 49

SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7h)

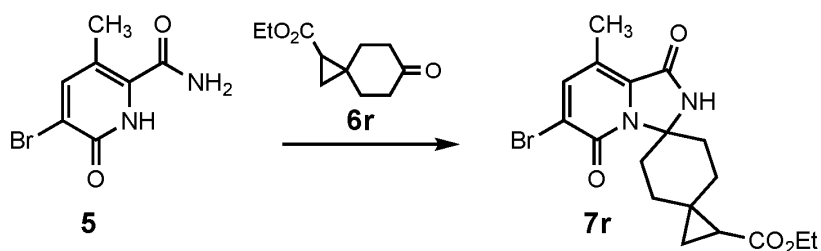


10

The title compound (7h) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (150 mg, 0.65 mmol), spiro[2.5]octan-5-one (6h, 121 mg, 0.97 mmol), H₂SO₄ (0.018 mL, 0.33 mmol), and 1,4-dioxane (6.0 mL). 6''-Bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-a]pyridine]-1'',5''-dione (7h) yield: (114 mg, 0.34 mmol, 52%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.00 (br, 1H), 7.73 (s, 1H), 3.73 (m, 1H), 3.20 (dt, *J* = 4.0, 13.6 Hz, 1H), 2.48 (s, 3H), 2.00–1.90 (m, 2H), 1.65 (m, 1H), 1.58 (m, 1H), 0.93 (d, *J* = 13.6 Hz, 1H), 0.76 (dt, *J* = 13.0, 2.0 Hz, 1H), 0.46–0.40 (m, 3H), 0.32 (m, 1H); UHPLC-MS (ESI): *m/z* 339.1 [M]⁺.

EXAMPLE 50

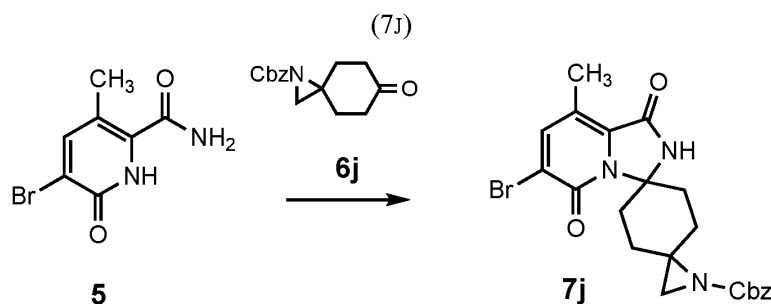
SYNTHESIS OF ETHYL 6''-BROMO-8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-2-CARBOXYLATE (7r)



The title compound (7r) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (141 mg, 0.61 mmol), ethyl 6-oxospiro[2.5]octane-1-carboxylate (6r, 240 mg, 1.22 mmol), H₂SO₄ (0.016 mL, 0.31 mmol), and 1,4-dioxane (1.22 mL) except that the reaction was conducted for 3 hours. Ethyl 6''-bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-2-carboxylate (7r) yield: (123 mg, 0.30 mmol, 50%). ¹H NMR (400 MHz, CDCl₃) δ 7.73 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.37 (m, 2H), 2.46 (s, 3H), 2.25 – 1.34 (m, 7H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.11 – 0.90 (m, 2H). UHPLC-MS (ESI): Rt 0.77 min, *m/z* 409.0 [M]⁺.

EXAMPLE 51

SYNTHESIS OF BENZYL 6''-BROMO-8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[AZIRIDINE-2,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1-CARBOXYLATE (7j)

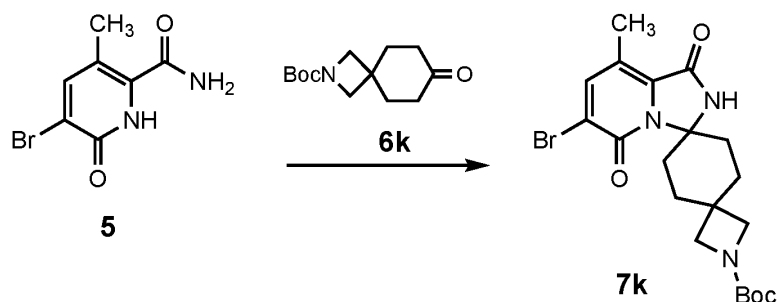


The title compound (7j) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (205 mg, 0.89 mmol), benzyl 6-oxo-1-azaspiro[2.5]octane-1-carboxylate (6j, 345 mg, 1.33 mmol), H₂SO₄ (0.024 mL, 0.44 mmol), and 1,4-dioxane (9.0 mL). Benzyl 6''-bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[aziridine-2,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-1-carboxylate (7j) yield: (187 mg, 0.40 mmol, 46%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.02 (s, 1H), 8.04 (s, 1H), 7.41–7.23 (m, 5H), 5.04 (s, 2H), 3.62 (m, 2H), 3.01 (m, 2H), 2.39 (s, 3H), 2.21 (m, 2H), 1.93 (m, 1H), 1.58 (m, 1H), 1.26 (m, 1H), 0.86 (m, 1H). UHPLC-MS (ESI): Rt 0.76 min, m/z 337.1 [M]⁺.

10

EXAMPLE 52

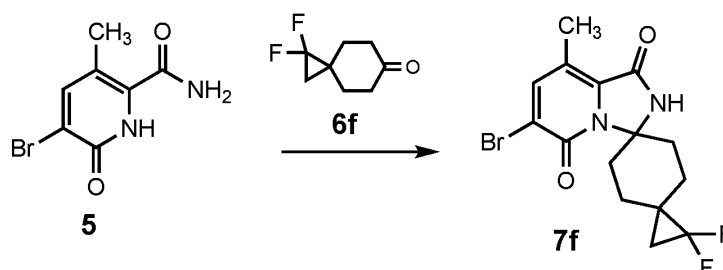
SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[AZETIDINE-3,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7k).



The title compound (7k) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (100 mg, 0.43 mmol), tert-butyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (6k, 414 mg, 1.73 mmol), H₂SO₄ (0.012 mL, 0.22 mmol), and 1,4-dioxane (4.0 mL). 6''-Bromo-8''-methyl-2''H-dispiro[azetidine-3,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-1'',5''-dione (7k) yield: (101 mg, 0.29 mmol, 66%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (s, 1H), 7.78 (s, 1H), 3.05 – 2.80 (m, 4H), 2.37 (s, 3H), 2.00 – 1.92 (m, 4H), 1.41 (dd, *J* = 25.2, 12.9 Hz, 4H). UHPLC-MS (ESI): Rt 0.59 min, m/z 352.2 [M]⁺.

EXAMPLE 53

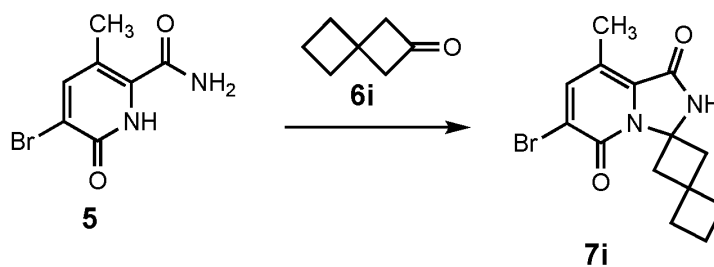
SYNTHESIS OF 6''-BROMO-2,2-DIFLUORO-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7f)



5 The title compound (7f) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (125 mg, 0.54 mmol), 1,1-difluorospiro[2.5]octan-6-one (6f, 86 mg, 0.54 mmol), H₂SO₄ (0.01 mL, 0.27 mmol), and 1,4-dioxane (1.1 mL). 6''-Bromo-2,2-difluoro-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-1'',5''-dione (7f)
10 yield: (39 mg, 0.10 mmol, 19%). UHPLC-MS (ESI): Rt 0.80 min, m/z 373.0 [M]⁺.

EXAMPLE 54

SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOBUTANE-1,1'-CYCLOBUTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7i)



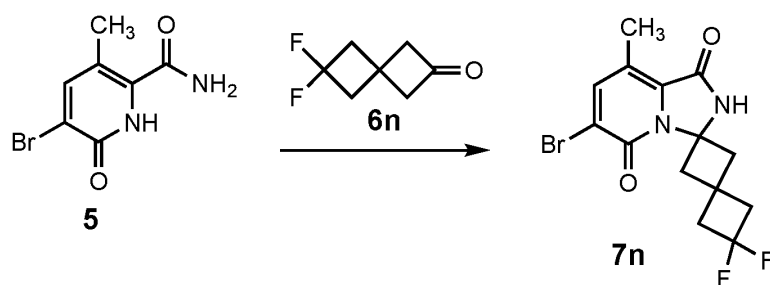
15 The title compound (7i) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (100 mg, 0.43 mmol), spiro[3.3]heptan-2-one (6i, 191 mg, 1.73 mmol), H₂SO₄ (0.012 mL, 0.22 mmol), and 1,4-dioxane (4.0 mL). 6''-Bromo-8''-methyl-2''H-dispiro[cyclobutane-1,1'-cyclobutane-3',3''-imidazo[1,5-a]pyridine]-1'',5''-dione (7i) yield: (101 mg, 0.31 mmol, 72%). ¹H
20 NMR (400 MHz, DMSO-d₆) δ 10.26 (s, 1H), 8.02 (s, 1H), 3.56 (d, *J* = 14.2 Hz, 2H),

2.38 (s, 3H), 2.35 – 2.29 (m, 2H), 2.23 – 2.12 (m, 4H), 1.80 (dt, $J = 14.7, 7.2$ Hz, 2H).

UHPLC-MS (ESI): Rt 0.76 min, m/z 323.1 $[M]^+$.

EXAMPLE 55

SYNTHESIS OF 6''-BROMO-3,3-DIFLUORO-8''-METHYL-2''H-DISPIRO[CYCLOBUTANE-1,1'-
CYCLOBUTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7n)

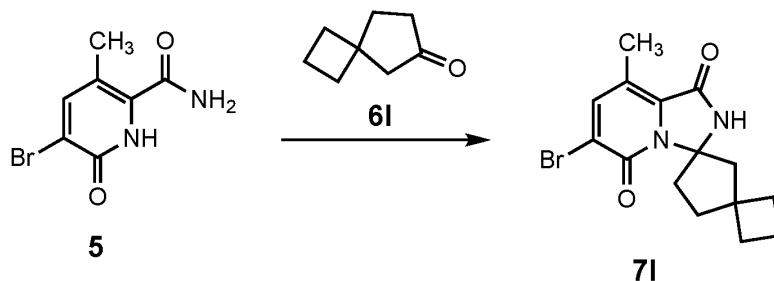


The title compound (7n) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (100 mg, 0.43 mmol), 6,6-difluorospiro[3.3]heptan-2-one (6n, 108 mg, 0.74 mmol), H_2SO_4 (0.012 mL, 0.22 mmol), and 1,4-dioxane (4.0 mL). 6''-Bromo-3,3-difluoro-8''-methyl-2''H-dispiro[cyclobutane-1,1'-cyclobutane-3',3''-imidazo[1,5-a]pyridine]-1'',5''-dione (7n) yield: (93 mg, 0.26 mmol, 60%). 1H NMR (400 MHz, $DMSO-d_6$) δ 10.26 (s, 1H), 8.02 (s, 1H), 3.53 (d, $J = 14.7$ Hz, 2H), 2.78 (dt, $J = 33.0, 12.7$ Hz, 4H), 2.52 (s, 1H), 2.49 (s, 1H), 2.34 (s, 3H). UHPLC-MS (ESI): Rt 0.77 min, m/z 358.8 $[M]^+$.

15

EXAMPLE 56

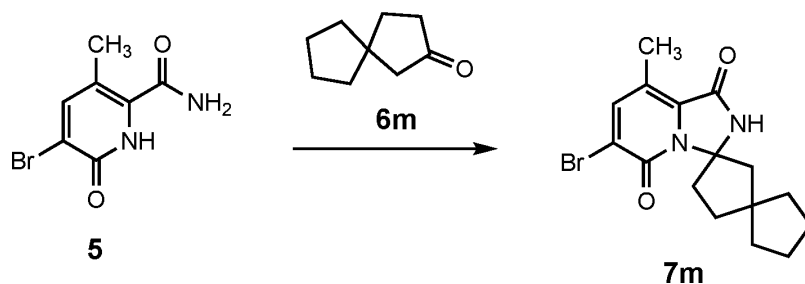
SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOBUTANE-1,1'-CYCLOPENTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7l)



The title compound (7l) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (100 mg, 0.43 mmol), spiro[3.4]octan-6-one (6l, 107 mg, 0.866 mmol), H₂SO₄ (0.012 mL, 0.22 mmol), and 1,4-dioxane (3.0 mL). 6''-Bromo-8''-methyl-2''H-dispiro[cyclobutane-1,1'-cyclopentane-3',3''-imidazo[1,5-a]pyridine]-1'',5''-dione (7l) yield: (101 mg, 69%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.05 (s, 1H), 7.99 (s, 1H), 2.82 (d, *J* = 13.8 Hz, 1H), 2.70 (dt, *J* = 13.1, 8.1 Hz, 1H), 2.34 (s, 3H), 2.16 – 1.61 (m, 9H). UHPLC-MS (ESI): Rt 0.82 min, *m/z* 339.2 [M]⁺.

EXAMPLE 57

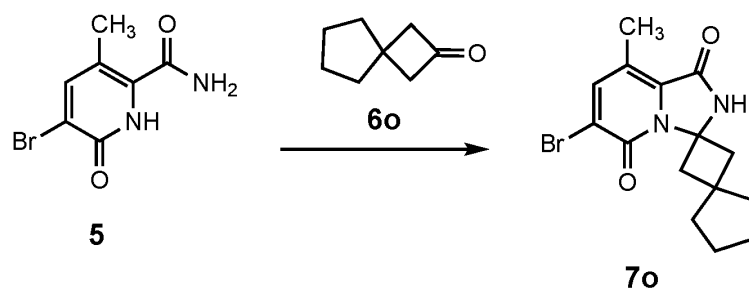
10 SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOPENTANE-1,1'-CYCLOPENTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7m)



The title compound (7m) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (100 mg, 0.43 mmol), spiro[4.4]nonan-2-one (6m, 120 mg, 0.866 mmol), H₂SO₄ (0.012 mL, 0.22 mmol), and 1,4-dioxane (3.0 mL). 6''-Bromo-8''-methyl-2''H-dispiro[cyclopentane-1,1'-cyclopentane-3',3''-imidazo[1,5-a]pyridine]-1'',5''-dione (7m) yield: (91 mg, 59mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.15 (s, 1H), 7.99 (s, 1H), 2.88 – 2.76 (m, 2H), 2.35 (s, 3H), 1.95 – 1.86 (m, 1H), 1.81 – 1.74 (m, 1H), 1.74 – 1.66 (m, 3H), 1.64 – 1.52 (m, 8H). UHPLC-MS (ESI): Rt 0.86 min, *m/z* 351.1 [M]⁺.

EXAMPLE 58

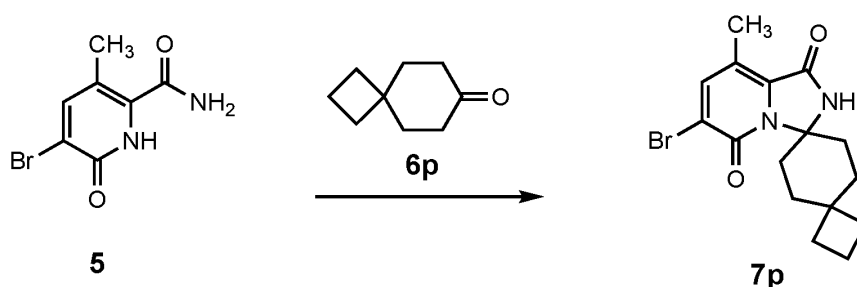
SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOPENTANE-1,1'-CYCLOBUTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7o)



- 5 The title compound (7o) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (100 mg, 0.43 mmol), spiro[3.4]octan-2-one (6o, 215 mg, 1.73 mmol), H₂SO₄ (0.012 mL, 0.22 mmol), and 1,4-dioxane (4.0 mL). 6''-Bromo-8''-methyl-2''H-dispiro[cyclopentane-1,1'-cyclobutane-3',3''-imidazo[1,5-a]pyridine]-1'',5''-dione (7o) yield: (100 mg, 0.3 mmol, 69%). ¹H
- 10 NMR (400 MHz, DMSO-d₆) δ 10.38 (s, 1H), 8.00 (s, 1H), 3.42 (d, *J* = 13.5 Hz, 2H), 2.35 (s, 3H), 2.07 (d, *J* = 13.6 Hz, 2H), 1.91 – 1.82 (m, 2H), 1.82 – 1.73 (m, 2H), 1.63 – 1.41 (m, 4H). UHPLC-MS (ESI): Rt 0.85 min, *m/z* 337.1 [M]⁺.

EXAMPLE 59

SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOBUTANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7p)

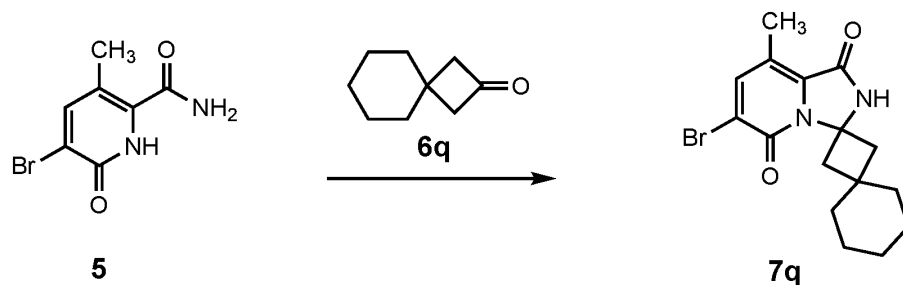


The title compound (7p) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (100 mg, 0.43 mmol), spiro[3.5]nonan-7-one (6p, 120 mg, 0.87 mmol), H₂SO₄ (0.012 mL, 0.22 mmol), and

1,4-dioxane (4.0 mL). 6"-Bromo-8"-methyl-2"H-dispiro[cyclobutane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione (7p) yield: (73 mg, 0.21 mmol, 48%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.32 (s, 1H), 7.99 (s, 1H), 2.97 (t, *J* = 11.7 Hz, 2H), 2.36 (s, 3H), 1.82 (s, 4H), 1.78 – 1.56 (m, 6H), 1.26 (d, *J* = 12.3 Hz, 2H). UHPLC-MS (ESI): Rt 0.86 min, *m/z* 351.2 [M]⁺.

EXAMPLE 60

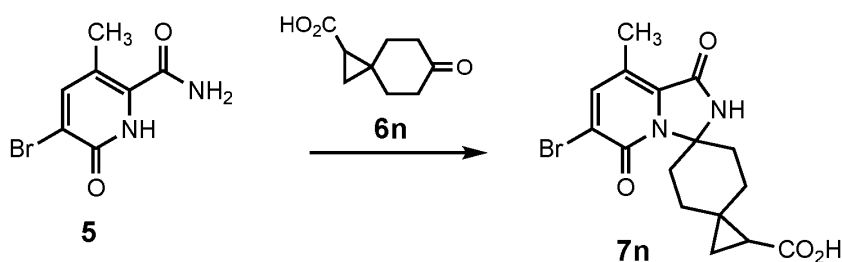
SYNTHESIS OF 6"-BROMO-8"-METHYL-2"H-DISPIRO[CYCLOHEXANE-1,1'-CYCLOBUTANE-3',3"-IMIDAZO[1,5-A]PYRIDINE]-1",5"-DIONE (7Q)



The title compound (7q) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (100 mg, 0.43 mmol), spiro[3.5]nonan-2-one (6q, 120 mg, 0.87 mmol), H₂SO₄ (0.012 mL, 0.22 mmol), and 1,4-dioxane (4.0 mL). 6"-Bromo-8"-methyl-2"H-dispiro[cyclohexane-1,1'-cyclobutane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione (7q) yield: (95 mg, 0.27 mmol, 63%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.27 (s, 1H), 8.00 (s, 1H), 3.23 (d, *J* = 13.6 Hz, 2H), 2.35 (s, 3H), 1.95 (d, *J* = 13.7 Hz, 2H), 1.86 – 1.75 (m, 2H), 1.73 – 1.60 (m, 2H), 1.43 – 1.31 (m, 6H). UHPLC-MS (ESI): Rt 0.89 min, *m/z* 351.1 [M]⁺.

EXAMPLE 61

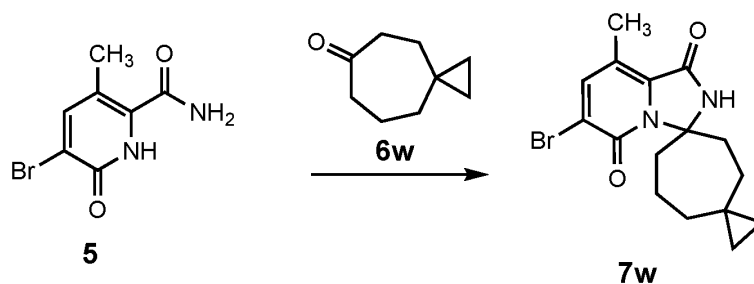
SYNTHESIS OF 6''-BROMO-8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-2-CARBOXYLIC ACID (7n)



The title compound (7n) was prepared according to General Procedure G using 5-bromo-3-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide (460 mg, 1.99 mmol), 6-oxospiro[2.5]octane-1-carboxylic acid (6n, 668 mg, 3.97 mmol), H₂SO₄ (0.05 mL, 0.1 mmol), and 1,4-dioxane (4.0 mL). 6''-Bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-2-carboxylic acid (7n) yield: (210 mg, 0.55 mmol, 28%). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (s, 1H), 3.49 – 3.25 (m, 2H), 2.46 (s, 3H), 2.24 – 1.44 (m, 7H), 1.30 – 1.04 (m, 2H). UHPLC-MS (ESI): Rt 0.67 min, m/z 381.0 [M]⁺.

EXAMPLE 62

SYNTHESIS OF 6''-BROMO-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEPTANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (7w)

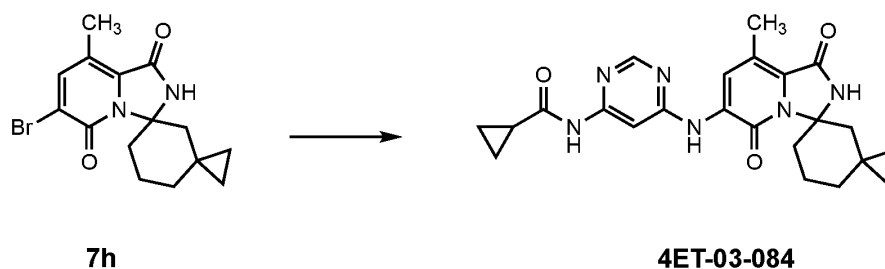


To a stirred solution of 5 (25 mg, 0.108 mmol) in dry isopropanol was added ketone 6w (18 mg, 0.130 mmol) followed by Ti(iOPr)₄ (46 mg, 0.162 mmol). The

mixture was sealed and heated at 100 °C for 12 hours. Purification via flash column chromatography (gradient elution, 5% to 50% hexanes/ethyl acetate) afforded 8 mg 7w (28%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.29 (s, 1H), 8.00 (s, 1H), 2.99 – 2.69 (m, 2H), 2.37 (s, 3H), 1.89 (s, 1H), 1.81 (dd, *J* = 14.8, 10.8 Hz, 1H), 1.68 (dd, *J* = 14.4, 9.2 Hz, 2H), 1.59 (dd, *J* = 14.0, 8.0 Hz, 2H), 1.36 (dd, *J* = 14.4, 8.0 Hz, 2H), 0.31 (d, *J* = 7.6 Hz, 4H).

EXAMPLE 63

SYNTHESIS OF N-(6-((8"-METHYL-1",5"-DIOXO-1",5"-DIHYDRO-2"H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-3',3'"-IMIDAZO[1,5-A]PYRIDIN]-6"-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-084)



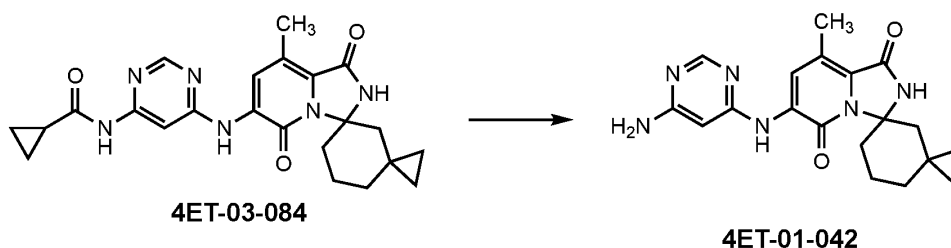
A mixture of 6"-bromo-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3'"-imidazo[1,5-a]pyridine]-1",5"-dione (7h) (60 mg, 0.18 mmol), *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide (38.0 mg, 0.21 mmol), Cs₂CO₃ (174.0 mg, 0.53 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (21.2 mg, 0.04 mmol) and Pd(OAc)₂ (4.0 mg, 0.02 mmol) in 1,4-dioxane (4.0 mL) was purged with inert gas (nitrogen or argon) for 20 minutes. The reaction vessel was sealed and heated at 95 °C for 12 hours, and then cooled to 23 °C and concentrated under reduced pressure. The resulting crude material was purified through a Biotage flash chromatography (gradient elution, 0% to 10% MeOH in CH₂Cl₂) to afford 4ET-03-084 (48.0 mg, 0.11 mmol, 63%) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.86 (s, 1H), 9.92 (s, 1H), 9.11 (s, 1H), 8.53 (s, 1H), 8.47 (s, 1H), 7.85 (s, 1H), 3.49 (d, *J* = 12.8 Hz, 1H), 3.03 (dt, *J* = 4.2, 13.3 Hz, 1H), 2.44 (s, 3H), 2.02 (pent, *J* = 6.2 Hz, 1H), 1.90 (m, 1H), 1.79–1.70 (m, 2H), 1.52 (m, 1H), 0.89 (m, 1H), 0.84 (m, 4H), 0.75 (d, *J* =

12.2 Hz, 1H), 0.43 (m, 2H), 0.28 (m, 1H), 0.19 (m, 1H); UHPLC-MS (ESI): m/z 435.3 $[M+H]^+$

EXAMPLE 64

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-

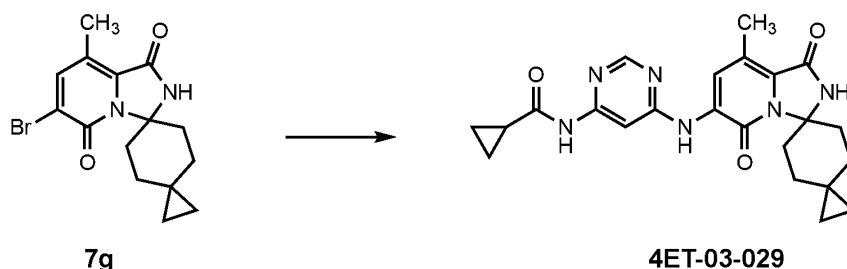
5 DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-
DIONE (4ET-01-042)



To a suspension of 4ET-03-084 (30 mg, 0.07 mmol) in EtOH/THF/H₂O (1 mL, v:v:v/2:1:1) was added 6N KOH aqueous solution (0.23 mL, 1.38 mmol). The mixture
10 was stirred at 23 °C for 16 hours and additional 6N KOH aqueous solution (0.23 mL, 1.38 mmol) was added and stirred for another 6 hours until HPLC/MS showed the complete consumption of the starting material. The reaction was concentrated under reduced pressure and the resulting crude material was purified through a Biotage flash chromatography (gradient elution, 0% to 15% 3M NH₃/MeOH in CH₂Cl₂) to afford
15 4ET-01-042 (19 mg, 0.05 mmol, 75%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 9.86 (s, 1H), 8.62 (s, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 6.57 (br, 2H), 6.16 (s, 1H), 3.49 (d, J = 12.8 Hz, 1H), 3.04 (dt, J = 4.2, 13.3 Hz, 1H), 2.42 (s, 3H), 1.89 (m, 1H), 1.78–1.70 (m, 2H), 1.51 (m, 1H), 0.89 (m, 1H), 0.74 (d, J = 13.0 Hz, 1H), 0.43 (m, 2H), 0.27 (m, 1H), 0.18 (m, 1H); UHPLC-MS (ESI): m/z 367.2 $[M+H]^+$.

EXAMPLE 65

SYNTHESIS OF N-(6-((8"-METHYL-1",5"-DIOXO-1",5"-DIHYDRO-2"H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]PYRIDIN]-6"-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-029)



5

The title compound was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide except that 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione is replaced with 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione to provide the title compound 4ET-03-029. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.86 (s, 1H), 10.12 (s, 1H), 9.17 (s, 1H), 8.54 (s, 1H), 8.48 (s, 1H), 7.84 (s, 1H), 3.22 (dt, *J* = 13.4, 4.4 Hz, 2H), 2.45 (s, 3H), 2.15 (t, *J* = 13.6 Hz, 2H), 2.02 (pent, *J* = 6.4 Hz, 1H), 1.42 (d, *J* = 12.4 Hz, 2H), 0.90 (d, *J* = 13.4 Hz, 2H), 0.83 (m, 4H), 0.39 (m, 2H), 0.30 (m, 2H). UHPLC-MS (ESI): *R*_t 0.77 min, *m/z* 435.3 [*M*+*H*]⁺.

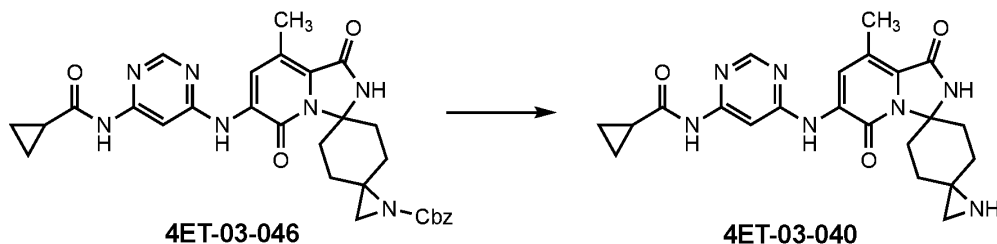
10

15

EXAMPLE 66

SYNTHESIS OF N-(6-((8"-METHYL-1",5"-DIOXO-1",5"-DIHYDRO-2"H-DISPIRO[AZIRIDINE-2,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]PYRIDIN]-6"-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-040)

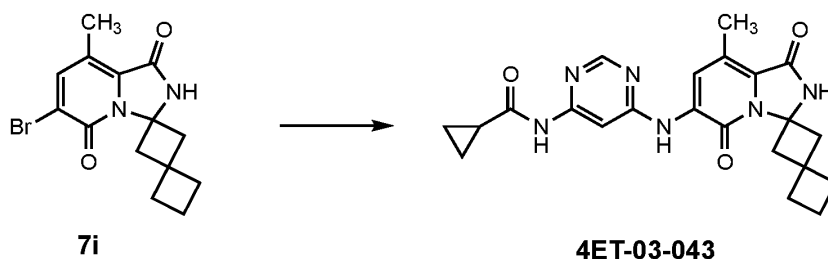
20



To a solution of N-(6-((8"-methyl-1",5"-dioxo-1-(2-oxo-2-phenyl-112-ethyl)-1",5"-dihydro-2"H-dispiro[aziridine-2,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide (4ET-03-046) (50 mg, 0.087 mmol) in ethanol (1 mL) was added Pd/C (10% activated on charcoal, 10 mg, 0.0087 mmol). The suspension was degassed and re-purged with hydrogen gas (this process was repeated three times). The reaction was stirred under hydrogen atmosphere at 23 °C for 16 hours. The reaction was filtered through Celite and washed with 1M NH₃/MeOH solution until full recovery of the desired product (TLC analysis 10% 1M NH₃/MeOH in CH₂Cl₂). The filtrate was concentrated and purified by Biotage flash chromatography (gradient elution, 0 to 25% 3M NH₃/MeOH in CH₂Cl₂) to obtain the desired compound 4ET-03-040 as white powders (11 mg, 0.025 mmol, 30%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.85 (br, 1H), 9.14 (br, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 7.87 (s, 1H), 5.53 (m, 1H), 3.70 (m, 1H), 3.10 (m, 4H), 2.35–2.19 (m, 3H), 2.02 (pent, *J* = 6.2 Hz, 1H), 1.93 (m, 1H), 1.57 (m, 1H), 0.85 (d, *J* = 6.2 Hz, 4H). UHPLC-MS (ESI): Rt 0.61 min, *m/z* 436.3 [M+H]⁺.

EXAMPLE 67

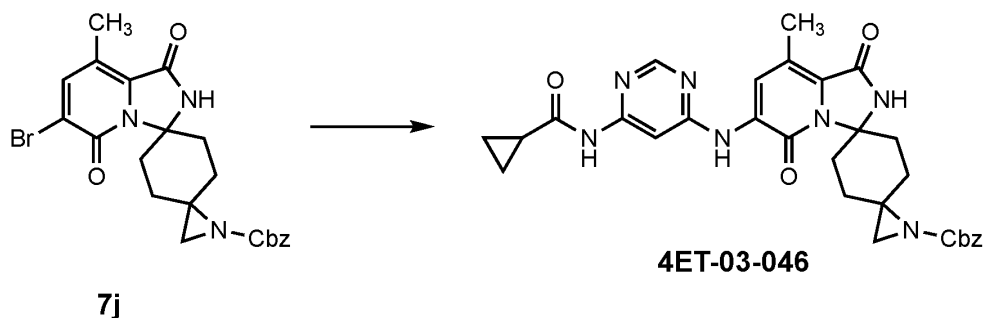
SYNTHESIS OF N-(6-((8"-METHYL-1",5"-DIOXO-1",5"-DIHYDRO-2"H-DISPIRO[CYCLOBUTANE-1,1'-CYCLOBUTANE-3',3"-IMIDAZO[1,5-A]PYRIDIN]-6"-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-043)



The title compound was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide except that 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione is replaced with 6"-Bromo-8"-methyl-2"*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione to provide the title compound 4ET-03-043. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.82 (s, 1H), 9.96 (s, 1H), 9.27 (s, 1H), 8.50 (d, *J* = 16.6 Hz, 2H), 7.89 (s, 1H), 3.55 (d, *J* = 13.8 Hz, 2H), 2.40 (s, 3H), 2.32 (d, *J* = 13.6 Hz, 2H), 2.24 – 2.11 (m, 4H), 2.07 – 1.96 (m, 1H), 1.79 (dt, *J* = 14.9, 7.6 Hz, 2H), 0.83 (d, *J* = 6.1 Hz, 4H). UHPLC-MS (ESI): *R*_t 0.77 min, *m/z* 421.3 [M+H]⁺.

EXAMPLE 68

SYNTHESIS OF *N*-(6-((8"-METHYL-1",5"-DIOXO-1-(2-OXO-2-PHENYL-1L2-ETHYL)-1",5"-DIHYDRO-2"*H*-DISPIRO[AZIRIDINE-2,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]PYRIDIN]-6"-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-046)



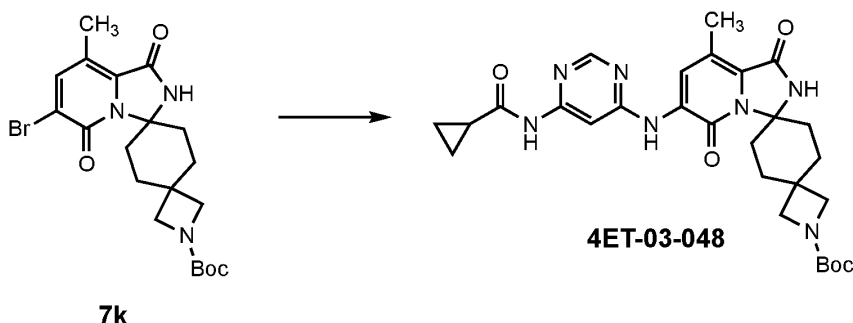
The title compound was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione is replaced with benzyl 6"-bromo-8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[aziridine-2,1'-cyclohexane-4',3"-imidazo[1,5-*a*]pyridine]-1-carboxylate to provide the title compound 4ET-03-046. ¹H NMR (400 MHz, DMSO-*d*₆)

δ 10.85 (s, 1H), 9.70 (br, 1H), 9.14 (s, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 7.87 (s, 1H), 7.40–7.21 (m, 5H), 5.04 (s, 2H), 3.73–3.59 (m, 3H), 3.07 (m, 2H), 2.45 (s, 3H), 2.25 (m, 2H), 2.02 (pent, $J = 6.2$ Hz, 1H), 1.94 (m, 1H), 1.58 (m, 2), 0.84 (d, $J = 6.2$ Hz, 4H). UHPLC-MS (ESI): Rt 0.78 min, m/z 570.4 $[M+H]^+$.

5

EXAMPLE 69

SYNTHESIS OF TERT-BUTYL 6''-((6-(CYCLOPROPANECARBOXAMIDO)PYRIMIDIN-4-YL)AMINO)-8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[AZETIDINE-3,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1-CARBOXYLATE (4ET-03-048)



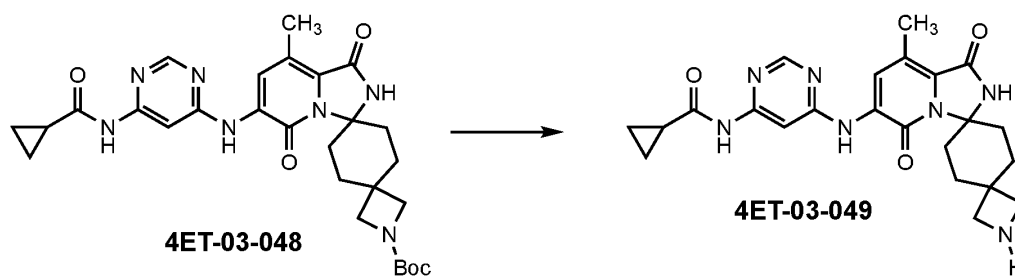
10 The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridin)-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione is replaced with tert-butyl 6''-bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[azetidine-3,1'-cyclohexane-4',3''-imidazo[1,5-*a*]pyridine]-1-carboxylate (7k) to provide the title compound 4ET-03-048. ^1H NMR (400 MHz, DMSO- d_6) δ 10.81 (s, 1H), 10.06 (s, 1H), 9.20 (s, 1H), 8.49 (d, $J = 13.1$ Hz, 2H), 7.84 (s, 1H), 3.73 – 3.57 (m, 2H), 3.57 – 3.41 (m, 2H), 3.09 – 2.97 (m, 2H), 2.41 (s, 3H), 1.93 – 1.73 (m, 4H), 1.45 – 1.31 (m, 10H), 1.19 – 1.08 (m, 2H), 0.87 – 0.77 (m, 4H).

15 UHPLC-MS (ESI): Rt 0.78 min, m/z 550.4 $[M+H]^+$.

20

EXAMPLE 70

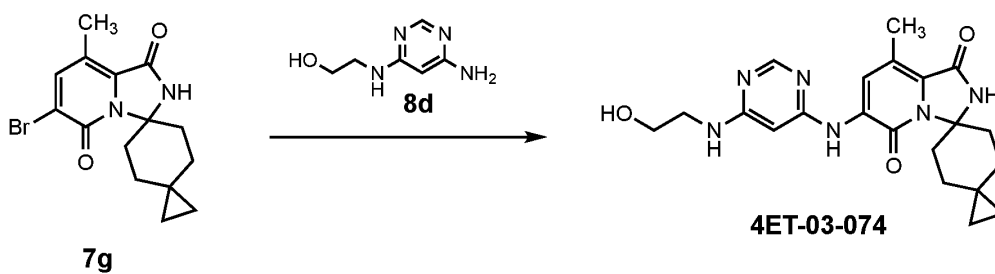
SYNTHESIS OF N-((6''-(8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[AZETIDINE-3,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDIN]-6''-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (4ET-03-049)



A solution of tert-butyl 6''-((6-(cyclopropanecarboxamido)pyrimidin-4-yl)amino)-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[azetidine-3,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-1-carboxylate (4ET-03-048) (12.5 mg, 0.023 mmol) in trifluoroacetic acid/CH₂Cl₂ [70:30] (1mL) stirred at 23 °C for 1 hour. The reaction was concentrated and purified via strong cation exchange (SCX) flash column, eluting with CH₂Cl₂, MeOH, and finally 1M NH₃ in MeOH to generate the title compound 4ET-03-049 (8 mg, 0.018 mmol, 78%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.82 (s, 1H), 9.21 (s, 1H), 8.50 (d, *J* = 15.6 Hz, 2H), 7.85 (s, 1H), 3.48 – 3.39 (m, 2H), 3.12 – 2.95 (m, 2H), 2.43 (s, 3H), 2.08 – 1.95 (m, *J* = 6.7 Hz, 4H), 1.84 – 1.71 (m, 2H), 1.45 – 1.31 (m, *J* = 12.7 Hz, 2H), 0.83 (d, *J* = 5.8 Hz, 4H). UHPLC-MS (ESI): Rt 0.61 min, m/z 450.3 [M+H]⁺.

EXAMPLE 71

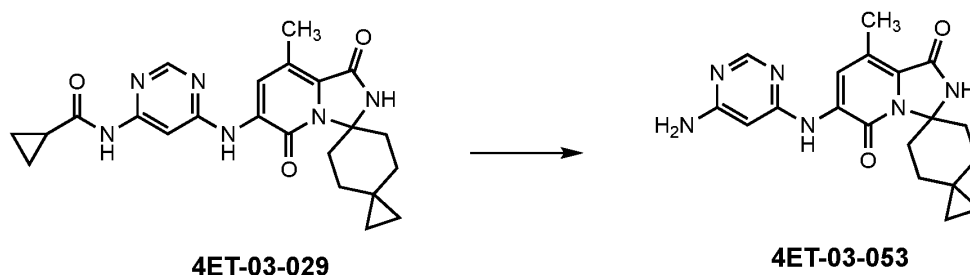
SYNTHESIS OF 6''-((6-((2-HYDROXYETHYL)AMINO)PYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-03-074)



The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-a]pyridin)-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-a]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-1'',5''-dione and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 2-((6-aminopyrimidin-4-yl)amino)ethan-1-ol (8d) to provide the title compound 4ET-03-074. ¹H NMR (400 MHz, DMSO-d₆) δ 10.03 (s, 1H), 8.61 (s, 1H), 8.37 (s, 1H), 8.19 (s, 1H), 6.97 (s, 1H), 6.24 (s, 1H), 4.68 (t, *J* = 5.6 Hz, 1H), 3.53 – 3.43 (m, 2H), 3.24 – 3.11 (m, 4H), 2.41 (s, 3H), 2.18 – 2.05 (m, 2H), 1.39 (d, *J* = 11.7 Hz, 2H), 0.87 (d, *J* = 13.9 Hz, 2H), 0.37 (d, *J* = 7.9 Hz, 2H), 0.28 (d, *J* = 7.7 Hz, 2H). UHPLC-MS (ESI): Rt 0.66 min, *m/z* 411.3 [M+H]⁺.

EXAMPLE 72

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-03-053)



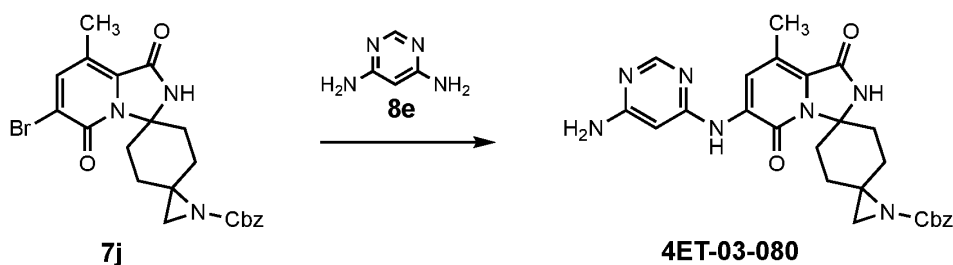
5

The title compound was prepared according to the procedure of 6''-((6-Aminopyrimidin-4-yl)amino)-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-a]pyridine]-1'',5''-dione except that *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-a]pyridin]-6''-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide was replaced with *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridin]-6''-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide (4ET-03-029) to provide the title compound 4ET-03-053 (12 mg, 0.033 mmol, 75%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.04 (s, 1H), 8.62 (s, 1H), 8.40(s, 1H), 8.17 (s, 1H), 6.50 (br, 2H), 6.15 (s, 1H), 3.23 (td, *J* = 13.4, 4.4 Hz, 2H), 2.43 (s, 3H), 2.15 (t, *J* = 13.4 Hz, 2H), 1.41 (m, 2H), 0.89 (m, 2H), 0.40 (m, 2H), 0.29 (m, 2H). UHPLC-MS (ESI): *R*_t 0.61 min, *m/z* 367.3 [M+H]⁺.

15

EXAMPLE 73

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-1-(2-OXO-2-PHENYL-1L2-ETHYL)-2''H-DISPIRO[AZIRIDINE-2,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-03-080)



5

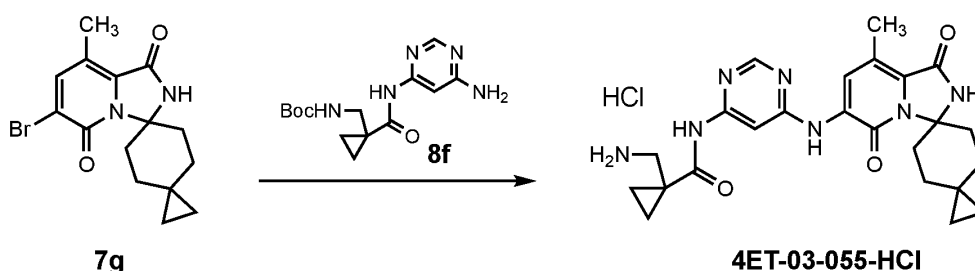
10

15

The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridin-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione is replaced with benzyl 6''-bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[aziridine-2,1'-cyclohexane-4',3''-imidazo[1,5-*a*]pyridine]-1-carboxylate (7j) and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with pyrimidine-4,6-diamine (8e) to provide the title compound 4ET-03-080. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.59 (s, 1H), 8.41 (s, 1H), 8.16 (s, 1H), 7.44–7.23 (m, 5H), 6.50 (br, 2H), 6.18 (s, 1H), 5.55 (s, 1H), 5.04 (s, 2H), 3.73–3.55 (m, 2H), 3.14–2.90 (m, 2H), 2.43 (s, 3H), 2.30 (m, 1H), 2.18 (m, 1H), 1.93 (m, 1H), 1.58 (m, 1H), 1.42 (m, 2H). UHPLC-MS (ESI): Rt 0.66 min, *m/z* 502.3 [M+H]⁺.

EXAMPLE 74

SYNTHESIS OF 1-(AMINOMETHYL)-N-(6-((8"-METHYL-1",5"-DIOXO-1",5"-DIHYDRO-2"H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]PYRIDIN]-6"-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANE-1-CARBOXAMIDE (4ET-03-055-HCl)



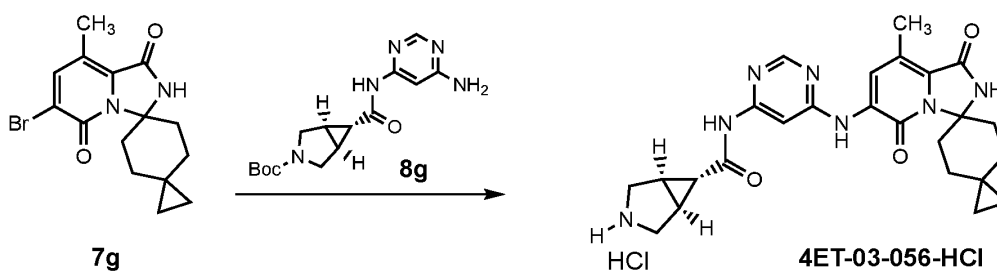
5 **7g** **4ET-03-055-HCl**

tert-butyl ((1-((6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)carbamoyl)cyclopropyl)methyl)carbamate was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6"-bromo-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione is replaced with 6"-bromo-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione (7g) (70 mg, 0.21 mmol), and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with tert-butyl ((1-((6-aminopyrimidin-4-yl)carbamoyl)cyclopropyl)methyl)carbamate (8f) (83 mg, 0.27 mmol), Cs₂CO₃ (203 mg, 0.62 mmol), bis(diphenylphosphino)-9,9-dimethylxanthene (24 mg, 0.041 mmol), Pd(OAc)₂ (4.7 mg, 0.027 mmol), and 1,4-dioxane (2.0 mL) generated the Boc-protected intermediate tert-butyl ((1-((6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)carbamoyl)cyclopropyl)methyl)carbamate (110 mg, 0.19 mmol, 95%). The Boc-protected intermediate was dissolved in CH₂Cl₂/Methanol (v:v/1:1, 2 mL) and added HCl (0.15 mL, 4M solution in 1,4-dioxane). The reaction was diluted with diethyl ether (30 mL) upon reaction completion as determined by monitoring by HPLC/MS. The resulting precipitates were collected through filtration

and washed with diethyl ether to give the title compound 4ET-03-055 as hydrochloride salt (98 mg, 0.19 mmol, 93%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.15 (s, 1H), 10.02 (m, 1H), 9.36 (m, 1H), 8.58 (s, 1H), 8.49 (s, 1H), 7.96 (br s, 2H), 7.87 (s, 1H), 3.26–3.15 (m, 4H), 2.45 (s, 3H), 2.15 (m, 2H), 1.43 (m, 4H), 1.11 (m, 2H), 0.90 (m, 2H), 0.40 (m, 2H), 0.29 (m, 2H). UHPLC-MS (ESI): Rt 0.63 min, m/z 464.3 [M+H]⁺.

EXAMPLE 75

SYNTHESIS OF (1R,5S,6R)-N-(6-((8"-METHYL-1",5"-DIOXO-1",5"-DIHYDRO-2"H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]PYRIDIN]-6"-YL)AMINO)PYRIMIDIN-4-YL)-3-AZABICYCLO[3.1.0]HEXANE-6-CARBOXAMIDE (4ET-03-056-HCl)



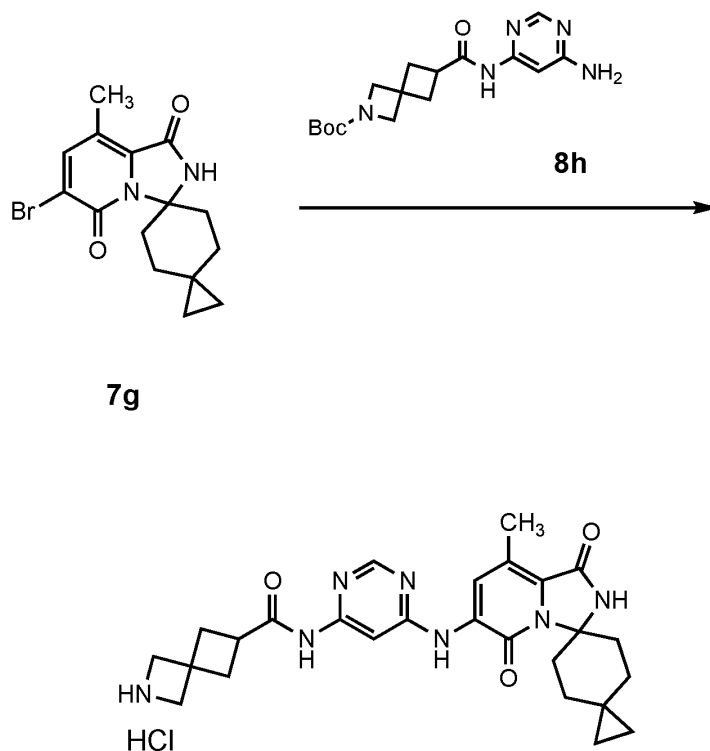
tert-Butyl (1R,5S,6r)-6-((6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)carbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-a]pyridine]-6"-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6"-bromo-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione is replaced with and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 6"-bromo-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione (7g) (70 mg, 0.21 mmol), tert-butyl-(1R,5S,6r)-6-((6-aminopyrimidin-4-yl)carbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (8g) (86 mg, 0.27 mmol), Cs₂CO₃ (203 mg, 0.62 mmol), bis(diphenylphosphino)-9,9-dimethylxanthene (24 mg, 0.041 mmol), Pd(OAc)₂ (4.7 mg, 0.027 mmol), and 1,4-

dioxane (2.0 mL) generated the Boc-protected intermediate tert-butyl (1R,5S,6r)-6-((6-
((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-
4',3"-imidazo [1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)carbamoyl)-3-
azabicyclo[3.1.0]hexane-3-carboxylate (115 mg, 0.20 mmol, 96%). The Boc-protected
5 intermediate was dissolved in CH₂Cl₂/Methanol (v:v/1:1, 2 mL) and added HCl (0.15
mL, 4M solution in 1,4-dioxane). The reaction was diluted with diethyl ether (30 mL)
upon reaction completion as determined by monitoring by HPLC/MS, the resulting
precipitates were collected through filtration and washed with diethyl ether to give the
title compound 4ET-03-056 as hydrochloride salt (95 mg, 0.19 mmol, 88%). ¹H NMR
10 (400 MHz, DMSO-d₆) δ 11.09 (s, 1H), 10.14 (s, 1H), 9.67 (br, 1H), 9.31 (s, 1H), 9.10
(br, 1H), 8.56 (s, 1H), 8.46 (s, 1H), 7.80 (s, 1H), 3.37 (m, 4H), 3.21 (dt, *J* = 14.0, 4.4
Hz, 2H), 2.45 (s, 3H), 2.22 (m, 2H), 2.15 (t, *J* = 14.0 Hz, 2H), 2.09 (t, *J* = 3.2 Hz, 1H),
1.42 (d, *J* = 12.0 Hz, 2H), 0.89 (d, *J* = 13.2 Hz, 2H), 0.40 (m, 2H), 0.29 (m, 2H).
UHPLC-MS (ESI): Rt 0.64 min, m/z 476.4 [M+H]⁺.

EXAMPLE 76

SYNTHESIS OF N-(6-((8"-METHYL-1",5"-DIOXO-1",5"-DIHYDRO-2"H-
DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]PYRIDIN]-6"-
YL)AMINO)PYRIMIDIN-4-YL)-2-AZASPIRO[3.3]HEPTANE-6-CARBOXAMIDE (4ET-03-057-
HCl)

5

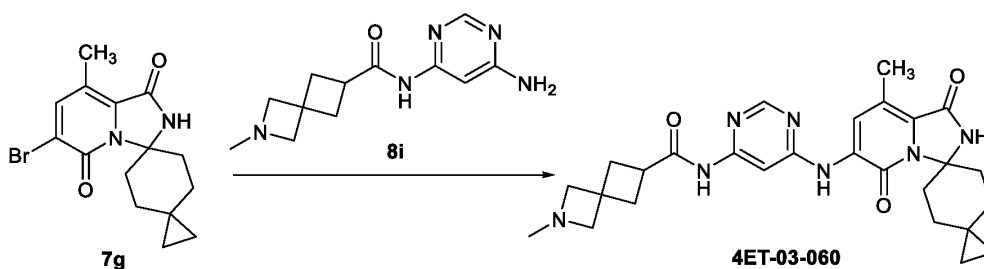


tert-Butyl 6-((6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-
dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-
10 yl)amino)pyrimidin-4-yl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate was
prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-
2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-a]pyridin]-6"-
yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6"-bromo-8"-methyl-
2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione is
15 replaced with 6"-bromo-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-

imidazo[1,5-a]pyridine]-1'',5''-dione (7g) (70 mg, 0.21 mmol), and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with tert-butyl 6-((6-aminopyrimidin-4-yl)carbamoyl)-2-azaspiro[3.3]heptane-2-carboxylate 8h (90 mg, 0.27 mmol), Cs₂CO₃ (203 mg, 0.62 mmol), bis(diphenylphosphino)-9,9-dimethylxanthene (24 mg, 0.041 mmol), Pd(OAc)₂ (4.7 mg, 0.027 mmol), and 1,4-dioxane (2.0 mL) generated the Boc-protected intermediate tert-butyl 6-((6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3'']-imidazo[1,5-a]pyridin)-6''-yl)amino)pyrimidin-4-yl)carbamoyl)-2-azaspiro[3.3] heptane-2-carboxylate (92 mg, 0.15 mmol, 75%). The Boc-protected intermediate was dissolved in CH₂Cl₂/Methanol (v:v/1:1, 2 mL) and added HCl (0.15 mL, 4M solution in 1,4-dioxane). The reaction was diluted with diethyl ether (30 mL) upon reaction completion as determined by monitoring by HPLC/MS, the resulting precipitates were collected through filtration and washed with diethyl ether to give the title compound 4ET-03-057 as hydrochloride salt (77 mg, 0.14 mmol, 94%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.59 (br, 1H), 10.14 (s, 1H), 9.33 (br, 1H), 8.92 (br, 1H), 8.54 (s, 1H), 8.46 (s, 1H), 8.12 (m, 1H), 7.86 (s, 1H), 3.93 (m, 4H), 3.21 (m, 3H), 2.45 (s, 3H), 2.41 (m, 2H), 2.21 (m, 2H), 2.15 (m, 2H), 1.42 (d, *J* = 12.0 Hz, 2H), 0.90 (d, *J* = 13.6 Hz, 2H), 0.40 (m, 2H), 0.30 (m, 2H). UHPLC-MS (ESI): Rt 0.65 min, m/z 490.4 [M+H]⁺.

EXAMPLE 77

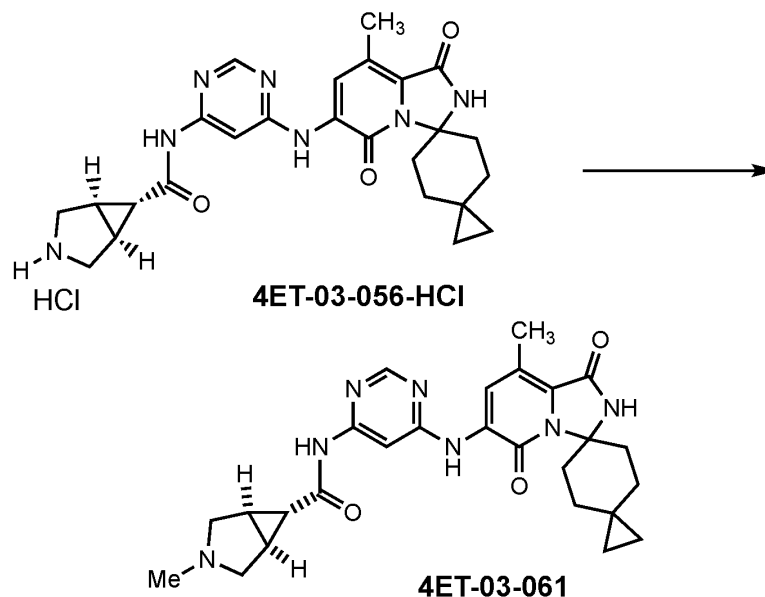
SYNTHESIS OF 2-METHYL-N-(6-((8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3'']-IMIDAZO[1,5-A]PYRIDIN)-6''-YL)AMINO)PYRIMIDIN-4-YL)-2-AZASPIRO[3.3]HEPTANE-6-CARBOXAMIDE (4ET-03-060)



The title compound was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3'-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3'-imidazo[1,5-*a*]pyridine]-1",5"-dione is replaced with 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-4',3'-imidazo[1,5-*a*]pyridine]-1",5"-dione (7g) (48 mg, 0.19 mmol), and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with *N*-(6-aminopyrimidin-4-yl)-2-methyl-2-azaspiro[3.3]heptane-6-carboxamide (8i) (50 mg, 0.14 mmol), Cs₂CO₃ (145 mg, 0.44 mmol), bis(diphenylphosphino)-9,9-dimethylxanthene (17.1 mg, 0.029 mmol), Pd(OAc)₂ (3.3 mg, 0.014 mmol), and 1,4-dioxane (1.5 mL) generated the title compound 4ET-03-060 (18 mg, 0.035 mmol, 24%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.39 (s, 1H), 10.12 (s, 1H), 9.18 (s, 1H), 8.51 (s, 1H), 8.48 (s, 1H), 7.90 (s, 1H), 3.22 (m, 4H), 3.13 (m, 3H), 2.45 (s, 3H), 2.26 (m, 4H), 2.21 (s, 3H), 2.15 (m, 2H), 1.42 (d, *J* = 12.0 Hz, 2H), 0.91 (d, *J* = 13.2 Hz, 2H), 0.40 (m, 2H), 0.30 (m, 2H). UHPLC-MS (ESI): Rt 0.65 min, *m/z* 504.4 [M+H]⁺.

EXAMPLE 78

SYNTHESIS OF (1R,5S,6R)-3-METHYL-N-(6-((8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDIN]-6''-YL)AMINO)PYRIMIDIN-4-YL)-3-AZABICYCLO[3.1.0]HEXANE-6-CARBOXAMIDE (4ET-03-061)



To a solution of (1R,5S,6r)-N-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridin]-6''-yl)amino)pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide HCl (4ET-03-056-HCl) (50 mg, 0.10 mmol) in CH₂Cl₂/methanol (v:v/2:1, 1.5 mL) was added formaldehyde (40% aq. 0.10 mL, 1.57 mmol) and acetic acid (3.15 mg, 0.052 mmol) and the reaction was cooled to 0 °C before adding NaCNBH₃ (13.2 mg, 0.21 mmol). The reaction was stirred at 0 °C for 2 hours and concentrated under the reduced pressure and the resulting material was purified by Biotage flash chromatography (silica gel, 0% to 20% 3M NH₃/MeOH in CH₂Cl₂) to give the title compound 4ET-03-061 (32 mg, 0.065 mmol, 63%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.69 (br, 1H), 10.12 (s, 1H), 9.15 (s, 1H), 8.52 (s, 1H), 8.48 (s, 1H), 7.82 (s, 1H), 3.22 (dt, *J* = 13.2, 4.2 Hz, 2H), 2.98 (m, 3H), 2.45 (s, 3H), 2.36 (m, 2H), 2.28 (m, 3H), 2.15 (m, 2H), 1.90 (m, 2H),

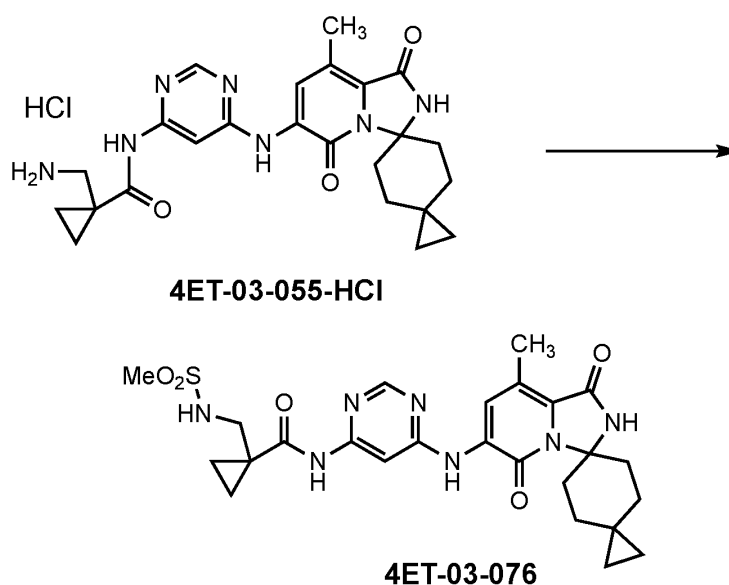
1.42 (d, $J = 12.0$ Hz, 2H), 0.90 (d, $J = 13.2$ Hz, 2H), 0.40 (m, 2H), 0.30 (m, 2H).

UHPLC-MS (ESI): Rt 0.65 min, m/z 504.4 $[M+H]^+$.

EXAMPLE 79

SYNTHESIS OF N-(6-((8"-METHYL-1",5"-DIOXO-1",5"-DIHYDRO-2"H-

5 DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]PYRIDIN]-6"-
YL)AMINO)PYRIMIDIN-4-YL)-1-(METHYLSULFONAMIDO METHYL)CYCLOPROPANE-1-
CARBOXAMIDE (4ET-03-076)

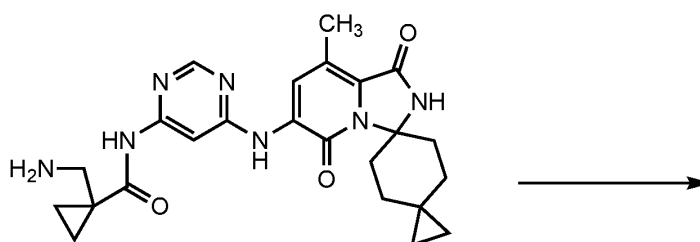


10 To a stirred solution of 1-(aminomethyl)-N-(6-((8"-methyl-1",5"-dioxo-1",5"-
dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3'-imidazo[1,5-a]pyridin]-6"-
yl)amino)pyrimidin-4-yl)cyclopropane-1-carboxamide HCl (4ET-03-055-HCl) (20 mg,
0.037 mmol) in anhydrous acetonitrile (2.0 mL) under inert atmosphere at 23 °C was
added trimethylamine (0.026 mL, 0.187 mmol) and methanesulfonyl chloride (0.009
15 mL, 0.112 mmol). After 3 hours, pyridine (0.5 mL) and additional methanesulfonyl
chloride (0.010 mL). After stirring for 16 hours, the mixture was diluted with methylene
chloride (3 mL) and subjected to a strong cation exchange (SCX) SPE cartridge (2 gram
SCX, CH₂Cl₂/MeOH, then 1M NH₃ in MeOH). The product was in the CH₂Cl₂ and
MeOH fractions along with pyridine. Those fractions were combined, preadsorbed onto

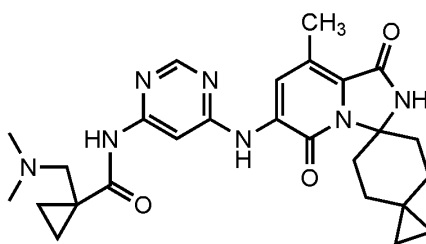
silica and purified by flash chromatography (4g SiO₂, CH₂Cl₂:ethyl acetate 10-100% gradient) to give the title compound 4ET-03-076 (1.1 mg, 6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.10 (s, 1H), 9.70 (s, 1H), 9.24 (s, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 7.84 (d, *J* = 1.1 Hz, 1H), 7.34 (t, *J* = 6.3 Hz, 1H), 3.27 (s, 2H), 3.26 – 3.13 (m, 2H), 2.92 (s, 3H), 2.43 (s, 4H), 2.13 (t, *J* = 13.4 Hz, 2H), 1.40 (d, *J* = 12.1 Hz, 2H), 1.16 (d, *J* = 2.9 Hz, 3H), 0.93 – 0.81 (m, 3H), 0.45 – 0.22 (m, 4H). UHPLC-MS (ESI): Rt 0.770 min, *m/z* 542.3 [M+H]⁺.

EXAMPLE 80

SYNTHESIS OF 1-((DIMETHYLAMINO)METHYL)-N-(6-((8"-METHYL-1",5"-
 10 DIHYDRO-2"H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-
 A]PYRIDIN]-6"-YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANE-1-CARBOXAMIDE (4ET-03-
 081)



4ET-03-055



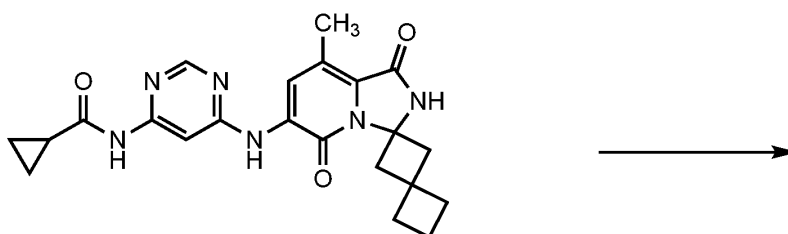
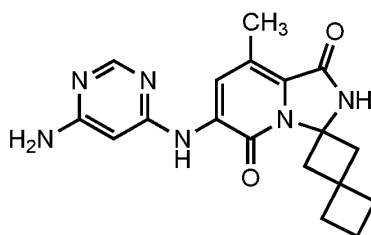
4ET-03-081

15 To a stirred solution of 1-(aminomethyl)-N-(6-((8"-methyl-1",5"-dioxo-1",5"-
 dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-
 yl)amino)pyrimidin-4-yl)cyclopropane-1-carboxamide (4ET-03-055) (15 mg, 0.034
 mmol) in CH₂Cl₂ (2.0 mL) cooled to 0°C was added acetic acid (0.010 mL, 0.172

mmol) and 40% formaldehyde (0.039 mL, 0.517 mmol). The mixture was treated with sodium triacetoxyborohydride (9 mg, 0.138 mmol) and left to gradually warm to 23 °C. After stirring for 16 hours, the solvent was removed and the residue was taken up with trifluoroethanol (2.0 mL) and treated with sodium borohydride (6.4 mg, 0.170 mmol) in one portion at 23 °C. After 1 hour, the mixture was diluted with MeOH (3.0 mL) and subjected to a strong cation exchange (SCX) SPE cartridge (2 gram SCX) and eluted with methanol then dichloromethane then 1M NH₃ in methanol to give the title compound 4ET-03-081 (4.3 mg, 27%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 8.55 (s, 1H), 8.22 (s, 1H), 8.02 (s, 1H), 7.64 (s, 1H), 3.34 (td, *J* = 14.0, 12.8, 4.5 Hz, 2H), 2.57 (s, 3H), 2.51 (s, 2H), 2.41 (s, 6H), 2.02 (td, *J* = 13.3, 12.0, 3.7 Hz, 2H), 1.55 (d, *J* = 11.3 Hz, 2H), 1.39 (q, *J* = 4.0 Hz, 2H), 1.07 (d, *J* = 13.9 Hz, 2H), 0.67 (q, *J* = 4.0 Hz, 2H), 0.45 (s, 4H). UHPLC-MS (ESI): Rt 0.65 min, *m/z* 492.3 [M+H]⁺.

EXAMPLE 81

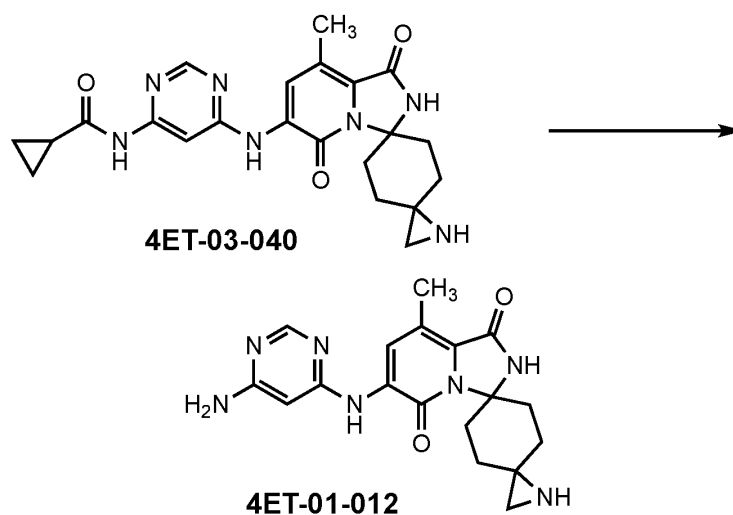
SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-DISPIRO[CYCLOBUTANE-1,1'-CYCLOBUTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-01-009)

**4ET-03-043****4ET-01-009**

The title compound was prepared according to the procedure of 6"-((6-Aminopyrimidin-4-yl)amino)-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione except that *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide was replaced with *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide (4ET-03-043) to provide the title compound 4ET-01-009 (8 mg, 0.023 mmol, 87%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.89 (s, 1H), 8.71 (s, 1H), 8.42 (s, 1H), 8.16 (s, 1H), 6.49 (s, 2H), 6.21 (s, 1H), 3.56 (d, *J* = 14.2 Hz, 2H), 2.38 (s, 3H), 2.35 – 2.29 (m, 2H), 2.24 – 2.12 (m, 4H), 1.80 (dt, *J* = 14.7, 7.2 Hz, 2H). UHPLC-MS (ESI/): Rt 0.63 min, *m/z* 353.3 [M+H]⁺.

EXAMPLE 82

SYNTHESIS OF 6"-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8"-METHYL-2"*H*-DISPIRO[AZIRIDINE-2,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]PYRIDINE]-1",5"-DIONE (4ET-01-012)



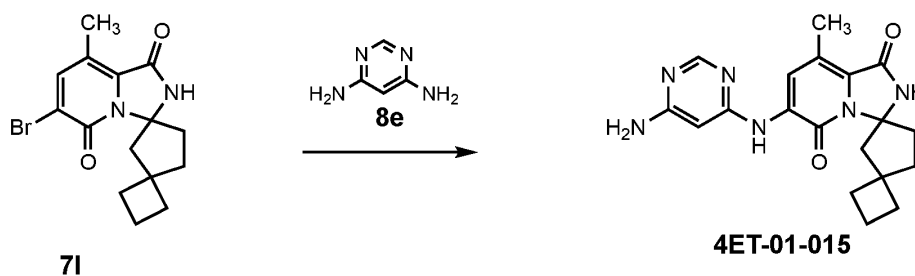
The title compound was prepared according to the procedure of 6"-((6-Aminopyrimidin-4-yl)amino)-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-

3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione except that *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide was replaced with *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[aziridine-2,1'-cyclohexane-4',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide (4ET-03-040) to provide the title compound 4ET-01-012 (7 mg, 0.019 mmol, 38%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 (s, 1H), 8.41 (s, 1H), 8.16 (s, 1H), 6.51 (br, 2H), 6.17 (s, 1H), 5.62 (m, 1H), 3.72 (m, 1H), 3.21 (br, 1H), 3.10 (m, 2H), 2.43 (s, 3H), 2.29 (m, 2H), 1.96 (m, 2H), 1.60 (m, 2H). UHPLC-MS (ESI): Rt 0.55 min, m/z 368.3 [M+H]⁺.

10

EXAMPLE 83

SYNTHESIS OF 6"-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8"-METHYL-2"*H*-DISPIRO[CYCLOPROPANE-1,1'-CYCLOPENTANE-3',3"-IMIDAZO[1,5-A]PYRIDINE]-1",5"-DIONE (4ET-01-015)



15

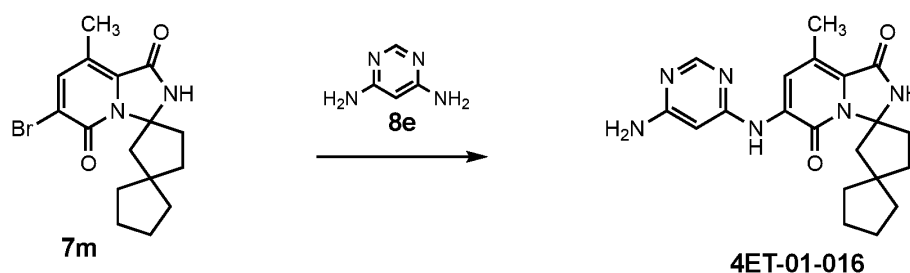
The title compound was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide except that 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione is replaced with, 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclopentane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione (71) and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-Diaminopyrimidine (8e) to provide the title compound 4ET-01-015 (16 mg, 37%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.14 (s, 1H), 6.47 (s, 2H), 6.16 (d, *J* = 1.0 Hz, 1H), 2.90 (d, *J* = 13.7 Hz, 1H), 2.75 (dt, *J* = 13.1, 7.9

Hz, 1H), 2.38 (s, 3H), 2.22 – 2.01 (m, 2H), 1.99 – 1.64 (m, 5H). UHPLC-MS (ESI): Rt 0.64 min, m/z 367.3 [M+H]⁺.

EXAMPLE 84

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-

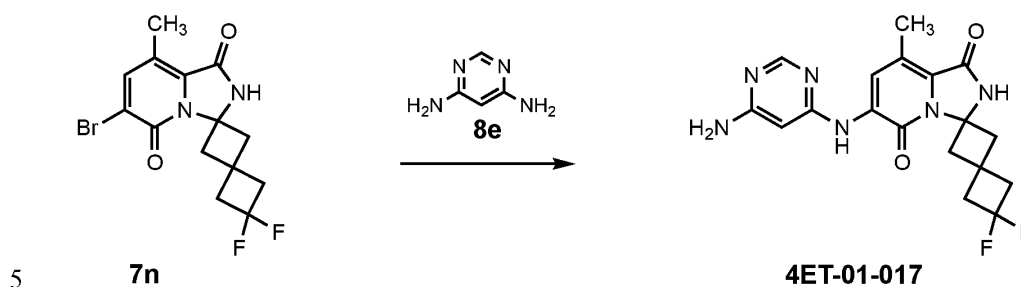
5 DIspiRO[CYCLOPENTANE-1,1'-CYCLOPENTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-01-016)



The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridin)-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except
 10 that 6''-bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''H-dispiro[cyclopentane-1,1'-cyclopentane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-diaminopyrimidine (8e) to provide
 15 the title compound 4ET-01-016. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.77 (s, 1H), 8.68 (s, 1H), 8.41 (s, 1H), 8.14 (d, *J* = 0.9 Hz, 1H), 6.46 (s, 2H), 6.18 (d, *J* = 1.0 Hz, 1H), 2.91 (d, *J* = 14.0 Hz, 1H), 2.88 – 2.80 (m, 0H), 2.39 (s, 3H), 2.03 – 1.91 (m, 1H), 1.86 – 1.68 (m, 2H), 1.60 (t, *J* = 10.1 Hz, 9H). UHPLC-MS (ESI): Rt 0.66 min, m/z 381.3 [M+H]⁺.

EXAMPLE 85

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-3,3-DIFLUORO-8''-METHYL-2''H-DISPIRO[CYCLOBUTANE-1,1'-CYCLOBUTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-01-017)



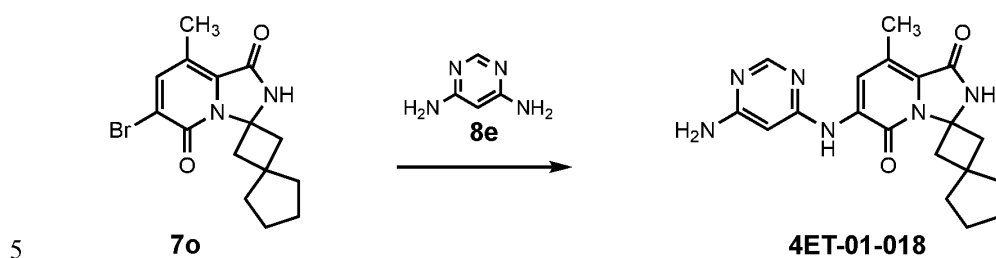
The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*α*]pyridin)-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*α*]pyridine]-1'',5''-dione is replaced with 6''-bromo-3,3-difluoro-8''-methyl-2''*H*-dispiro[cyclobutane-1,1'-cyclobutane-3',3''-imidazo[1,5-*α*]pyridine]-1'',5''-dione (7n) and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-diaminopyrimidine 8e to provide the title compound 4ET-01-017. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.91 (s, 1H), 8.71 (s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 6.48 (s, 2H), 6.20 (s, 1H), 3.61 (d, *J* = 14.4 Hz, 2H), 2.88 – 2.69 (m, 4H), 2.36 (s, 3H), 2.02 – 1.92 (m, 2H). UHPLC-MS (ESI): Rt 0.63 min, *m/z* 381.3 [M+H]⁺.

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EXAMPLE 86

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-DISPIRO[CYCLOPENTANE-1,1'-CYCLOBUTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-01-018)



The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*α*]pyridin-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*α*]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''H-dispiro[cyclopentane-1,1'-cyclobutane-3',3''-imidazo[1,5-*α*]pyridine]-1'',5''-dione (7o) and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-

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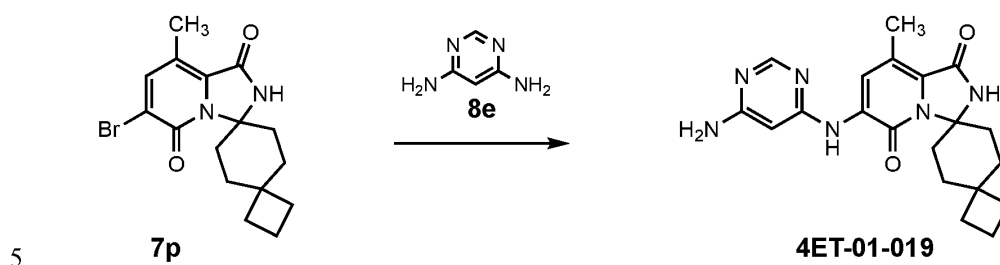
diaminopyrimidine (8e) to provide the title compound 4ET-01-018 ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.00 (s, 1H), 8.72 (s, 1H), 8.43 (s, 1H), 8.17 (s, 1H), 6.50 (s, 2H), 6.21 (s,

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1H), 3.51 (d, *J* = 13.7 Hz, 2H), 2.40 (s, 3H), 2.11 (d, *J* = 13.6 Hz, 2H), 1.97 – 1.87 (m, 2H), 1.86 – 1.77 (m, 2H), 1.61 – 1.53 (m, 4H). UHPLC-MS (ESI): *R*_t 0.73 min, *m/z* 367.3 [M+H]⁺.

EXAMPLE 87

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-DISPIRO[CYCLOBUTANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-01-019)



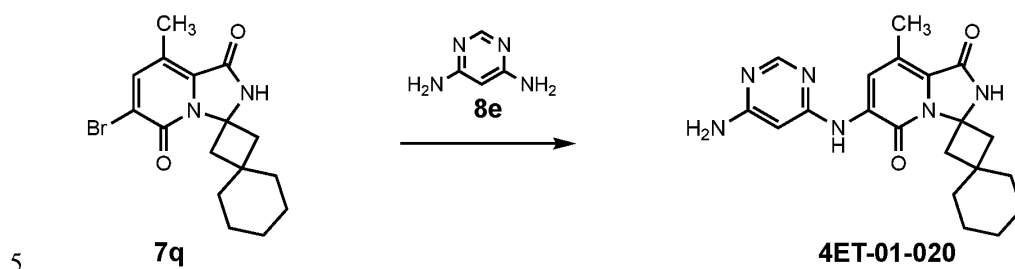
The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridin)-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''*H*-dispiro[cyclobutane-1,1'-cyclohexane-4',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione (7p) and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-diaminopyrimidine (8e) to provide the title compound 4ET-01-019. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.95 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 8.14 (s, 1H), 6.47 (s, 2H), 6.15 (s, 1H), 3.14 – 3.00 (m, 2H), 2.39 (s, 3H), 1.88 – 1.81 (m, 3H), 1.80 – 1.60 (m, *J* = 12.9 Hz, 5H), 1.32 – 1.19 (m, 4H). UHPLC-MS (ESI): Rt 0.66 min, *m/z* 381.3 [M+H]⁺.

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EXAMPLE 88

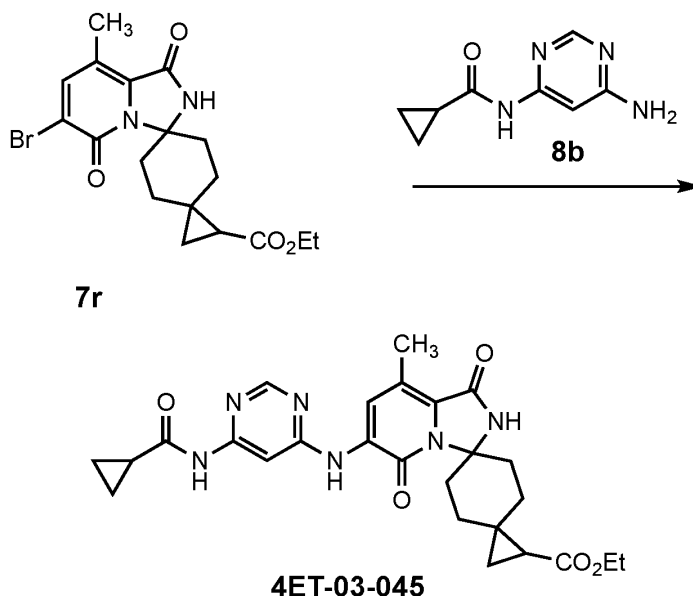
SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-DISPIRO[CYCLOHEXANE-1,1'-CYCLOBUTANE-3',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-01-020):



The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*α*]pyridin-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*α*]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''*H*-dispiro[cyclohexane-1,1'-cyclobutane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione (7q) and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-
 10 a]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''*H*-dispiro[cyclohexane-1,1'-cyclobutane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione (7q) and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-
 diaminopyrimidine (8e) to provide the title compound 4ET-01-020 (18 mg, 0.05 mmol, 33%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.94 – 9.87 (m, 1H), 8.69 (s, 1H), 8.43 (s, 1H),
 15 8.17 (s, 1H), 6.50 (s, 2H), 6.20 (s, 1H), 3.30 – 3.25 (m, 2H), 2.40 (s, 3H), 2.00 (d, *J* = 13.7 Hz, 2H), 1.94 – 1.84 (m, 2H), 1.75 – 1.65 (m, 2H), 1.47 – 1.30 (m, 6H). UHPLC-MS (ESI): Rt 0.67 min, *m/z* 381.2 [*M*+H]⁺.

EXAMPLE 89

SYNTHESIS OF ETHYL 6''-((6-(CYCLOPROPANECARBOXAMIDO)PYRIMIDIN-4-YL)AMINO)-8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-2-CARBOXYLATE (4ET-03-045)

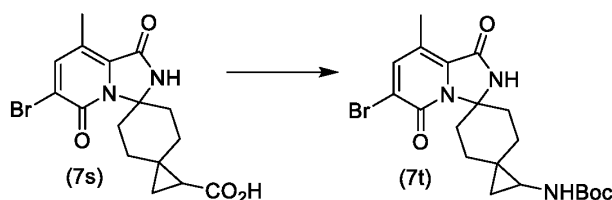


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The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridin)-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except
 10 that 6''-bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione is replaced with ethyl 6''-bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-*a*]pyridine]-2-carboxylate (7r) to provide the title compound 4ET-03-045 (38 mg, 0.075 mmol, 25%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.83 (s, 1H), 10.09 (bs, 1H), 9.12 (s, 1H), 8.50
 15 (s, 1H), 8.44 (s, 1H), 7.82 (s, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.24-3.12 (m, 2H), 2.42 (s, 3H), 2.30 – 2.12 (m, 2H), 1.90 – 1.29 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.08 – 0.92 (m, 2H), 0.82 (d, *J* = 6.1 Hz, 4H). UHPLC-MS (ESI): *R*_t 0.77 min, *m/z* 507.3 [M+H]⁺.

EXAMPLE 90

SYNTHESIS OF TERT-BUTYL (6''-BROMO-8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDIN]-2-
YL)CARBAMATE



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To a solution of 6''-bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridine]-2-carboxylic acid (7s) (210 mg, 0.55 mmol) in toluene (1.8 mL) was added triethylamine (0.12 mL, 0.83 mmol) and diphenyl phosphoryl azide (0.18 mL, 0.83 mmol). The reaction mixture was heated to reflux for 2h. Then, *t*-BuOH (0.06mL, 0.605 mmol) was added and the reaction mixture was refluxed for 16 hours. The solvent was removed under reduced pressure and NaHCO₃ (50 mL) was added. After washed with ethyl acetate (50 mL × 3), the organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting material was purified by Biotage flash chromatography (gradient elution, 0 – 10% MeOH in CH₂Cl₂) to afford a tert-butyl (6''-bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-a]pyridin]-2-yl)carbamate (7t) (14 mg, 0.031 mmol). ¹H NMR (400 MHz, CDCl₃) δ 7.73 (s, 1H), 3.23 (m, 2H), 2.51 (m, 1H), 2.48 (s, 3H), 2.10 (m, 2H), 1.53 (m, 2H), 1.30 (m, 2H), 1.11 (m, 9H), 0.81 (m, 1H), 0.42 (m, 1H). UHPLC-MS (ESI): Rt 0.74 min, m/z 451.1 [M+H]⁺.

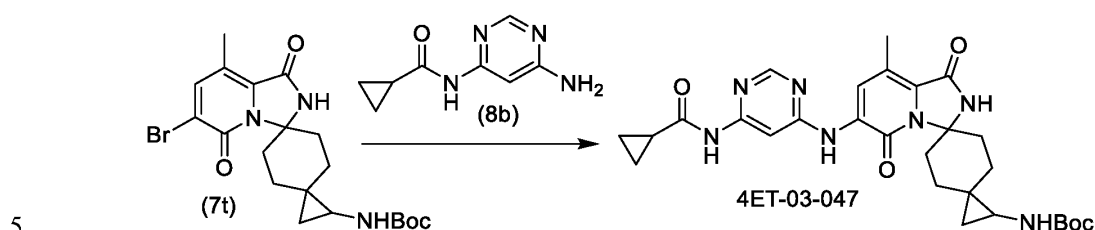
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EXAMPLE 91

SYNTHESIS OF TERT-BUTYL (6''-((6-(CYCLOPROPANECARBOXAMIDO)PYRIMIDIN-4-
YL)AMINO)-8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[CYCLOPROPANE-1,1'-
CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDIN]-2-YL)CARBAMATE (4ET-03-047)



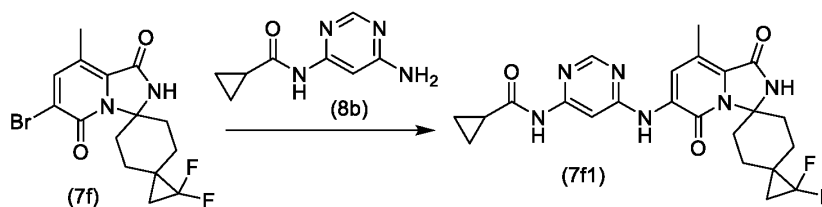
The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridin]-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''H-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione is replaced with tert-butyl (6''-bromo-8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''H-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-*a*]pyridin]-2-yl)carbamate (7t) to provide the title compound 4ET-03-047 (2 mg, 0.004 mmol, 12%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.83 (s, 1H), 10.06 (bs, 1H), 9.16 (s, 1H), 8.51 (s, 1H), 8.46 (s, 1H), 7.82 (s, 1H), 3.23-3.09 (m, 2H), 2.59 (m, 1H), 2.42 (s, 3H), 2.04 – 1.93 (m, 2H), 1.57 (m, 1.0), 1.50 – 1.31 (m, 4H), 0.98-0.82 (m, 11H), 0.53 (m, 2H). UHPLC-MS (ESI): Rt 0.75 min, *m/z* 549.4 [M+H]⁺.

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EXAMPLE 92

SYNTHESIS OF *N*-(6-((2,2-DIFLUORO-8''-METHYL-1'',5''-DIOXO-1'',5''-DIHYDRO-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDIN]-6''-
YL)AMINO)PYRIMIDIN-4-YL)CYCLOPROPANECARBOXAMIDE (7f1)

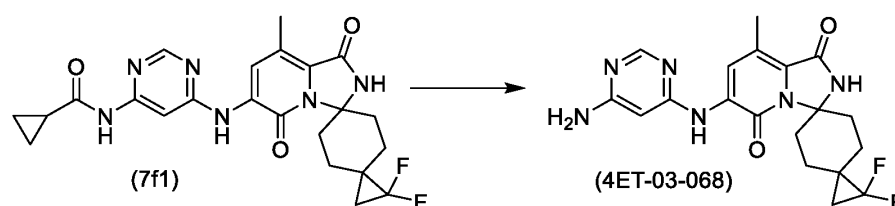
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The title compound was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin)-6"-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione was replaced with 6"-bromo-2,2-difluoro-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione (7f) to provide the title compound (7f1) (21 mg, 0.045 mmol, 43%).

EXAMPLE 93

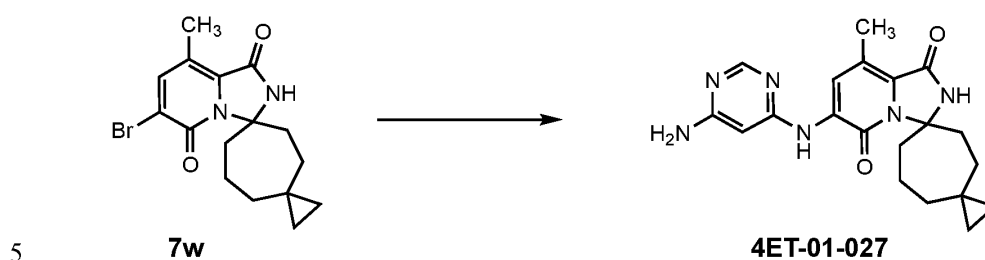
SYNTHESIS OF 6"-((6-AMINOPYRIMIDIN-4-YL)AMINO)-2,2-DIFLUORO-8"-METHYL-2"*H*-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-*A*]PYRIDINE]-1",5"-DIONE (4ET-03-068)



The title compound was prepared according to the procedure of *N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin)-6"-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6"-bromo-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione was replaced with *N*-(6-((2,2-difluoro-8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-*a*]pyridin)-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide (7f1) to provide the title compound 4ET-03-068 (15 mg, 0.037 mmol, 83%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.68 (s, 1H), 8.60 (s, 1H), 8.38 (s, 1H), 8.15 (s, 1H), 6.49 (s, 2H), 6.13 (s, 1H), 3.23 – 3.04 (m, 2H), 2.41 (s, 3H), 2.18 – 1.97 (m, 2H), 1.50 (d, *J* = 11.5 Hz, 2H), 1.39 (d, *J* = 12.9 Hz, 2H), 1.31 (t, *J* = 8.3 Hz, 2H). UHPLC-MS (ESI): *R*_t 0.65 min, *m/z* 403.3 [M+H]⁺.

EXAMPLE 94

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEPTANE-4',3''-IMIDAZO[1,5-A]PYRIDINE]-1'',5''-DIONE (4ET-01-027)



The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridin]-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''*H*-dispiro[cyclopropane-1,1'-cycloheptane-4',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-diaminopyrimidine: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.91 (s, 1H), 8.69 (s, 1H), 8.40 (s, 1H), 8.17 (s, 1H), 6.50 (br s, 2H), 6.18 (d, *J* = 1.1 Hz, 1H), 3.04 – 2.94 (m, 1H), 2.88 (dd, *J* = 14.2, 10.1 Hz, 1H), 2.41 (s, 3H), 2.0-1.97 (m, 1H), 1.90 – 1.80 (m, 1H), 1.71 (dd, *J* = 14.4, 9.3 Hz, 2H), 1.59 (dd, *J* = 14.0, 7.7 Hz, 2H), 1.35 (dt, *J* = 15.5, 8.5 Hz, 2H), 0.32 (d, *J* = 6.2 Hz, 4H); UHPLC-MS (ESI): Rt: 0.98 min, *m/z* 381.4 [M+H]⁺.

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Enantiomers of *rac*-4ET-01-027 ("Enantiomer 1 of 4ET-01-027" and "Enantiomer 2 of 4ET-01-027") were obtained via separation using chiral analytical and preparative HPLC. The separation was performed at Averica Discovery (Milford Massachusetts). Details of the analytical and preparative methods are provided below.

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Analytical Super Critical Fluid (SFC) method details:

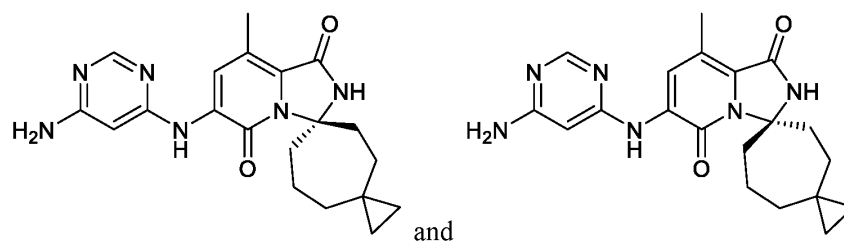
Column	4.6 × 100 mm Chiralcel OD-H from Chiral Technologies (West Chester, PA)
CO ₂ Co-solvent (Solvent B)	Methanol/Acetonitrile (1:3) with 0.1% Isopropylamine
Gradient Method	5-65% Co-solvent at 4 mL/min
System Pressure	125 bar

Column Temperature	40°C
Sample Diluent	Methanol: Dichloromethane (1:1)

Preparative SFC method details:

Column	2.1 × 25.0 cm Chiralcel OX-H from Chiral Technologies (West Chester, PA)
CO ₂ Co-solvent (Solvent B)	Methanol/Acetonitrile (1:3) with 0.25% Isopropylamine
Isocratic Method	40% Co-solvent at 80 g/min
System Pressure	100 bar
Column Temperature	25°C
Sample Diluent	Methanol: Dichloromethane (1:1)

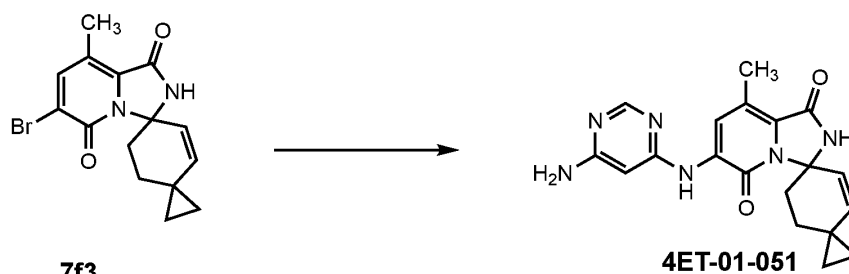
The structures of Enantiomer 1 of 4ET-01-027 and Enantiomer 2 of 4ET-01-027
 5 are as follows (stereochemistry is not assigned):



The first eluting peak had a retention time of 3.24 minutes, a peak height of 25,518, and peak area of 1333.80 using a diode array at 254 nm (see, *e.g.*, FIG. 1). The second eluting peak had a retention time of 3.43 minutes, a peak height of 9,144, and
 10 peak area of 628.45 using a diode array at 254 nm (see, *e.g.*, FIG. 2).

EXAMPLE 95

SYNTHESIS OF 6''-((6-AMINOPYRIMIDIN-4-YL)AMINO)-8''-METHYL-2''H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3''-IMIDAZO[1,5-A]PYRIDIN]-2'-ENE-1'',5''-DIONE (4ET-01-051):



5

The title compound was prepared according to the procedure of *N*-(6-((8''-methyl-1'',5''-dioxo-1'',5''-dihydro-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridin]-6''-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6''-bromo-8''-methyl-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3''-imidazo[1,5-*a*]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-*a*]pyridin]-2'-ene-1'',5''-dione and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-

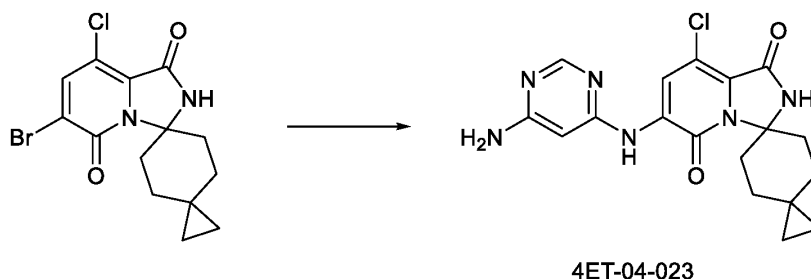
10 a]pyridine]-1'',5''-dione is replaced with 6''-bromo-8''-methyl-2''*H*-dispiro[cyclopropane-1,1'-cyclohexane-4',3''-imidazo[1,5-*a*]pyridin]-2'-ene-1'',5''-dione and *N*-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-

diaminopyrimidine; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.79 (s, 1H), 8.63 (s, 1H), 8.39 (s, 1H), 8.17 (s, 1H), 6.50 (s, 2H), 6.13 (s, 1H), 5.44 (d, *J* = 9.8 Hz, 1H), 5.36 (d, *J* = 9.8

15 Hz, 1H), 3.28 – 3.20 (m, 1H), 2.42 (s, 3H), 2.30 (t, *J* = 13.0 Hz, 1H), 1.60 (d, *J* = 12.4 Hz, 1H), 1.23 (d, *J* = 11.8 Hz, 1H), 0.75 – 0.51 (m, 4H). UHPLC-MS (ESI): *R*_t 0.88 min, *m/z* 365.3 [M+H]⁺.

EXAMPLE 96

SYNTHESIS OF 6'-((6-AMINOPYRIMIDIN-4YL)AMINO-8"-CHLORO-2"H-DISPIRO[CYCLOPROPANE-1,1'-CYCLOHEXANE-4',3"-IMIDAZO[1,5-A]-PYRIDINE]-1",5"-DIONE (4ET-04-023)



5 The title compound was prepared according to the procedure of N-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropane carboxamide except that 6"-bromo-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione is replaced with 6"-bromo-8"-chloro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione and N-(6-aminopyrimidin-4-yl)cyclopropanecarboxamide is replaced with 4,6-diaminopyrimidine: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.23 (s, 1H), 8.90 (s, 1H), 8.62 (s, 1H), 8.12 (s, 1H), 6.57 (br s, 2H), 6.21 (s, 1H), 3.21-3.11 (m, 2H), 2.12 (t, *J* = 13.4 Hz, 2H), 1.49-1.44 (m, 2H), 0.91-15 0.86 (m, 2H), 0.41-0.37 (m, 2H), 0.29-0.26 (m, 2H). UHPLC-MS (ESI): Rt 1.32 min, *m/z* 387.2 [M+H]⁺.

BIOLOGICAL EXAMPLE 1

IC₅₀ TESTING MNK INHIBITORS

20 The ability of MNK inhibitors described herein to inhibit activity of MNK1 was tested using the recombinant human kinase, MNK1, in a substrate phosphorylation assay. IC₅₀ data is provided in Table 5 below. The ability of MNK inhibitors described herein to inhibit activity of MNK2 was tested using the recombinant human kinase, MNK2, in a substrate phosphorylation assay. IC₅₀ data is provided in Table 5 below.

The ability of MNK inhibitors described herein to inhibit eIF4E phosphorylation at Serine 209 in the human embryonic kidney (HEK) 293 cell line was tested by exposing the cells to compound for 2 hours and then measuring eIF4E phosphorylation with a phosphorylation-specific antibody in a fluorescent plate reader. IC₅₀ data is provided in Table 5. These experiments were done with HEK-293 cells plated on 96 well plates. Following treatment, cells were fixed with ice cold methanol for 10 min and then washed in 1× phosphate buffered saline (PBS) and the permeabilized with 0.02% Triton X-100 in 10% normal goat serum made up in PBS. Primary antibody was applied overnight at a concentration dilution of 1:2000 (p-eIF4E antibody from Cell Signaling ab76256). Following washing, cells were then exposed to secondary antibody conjugated to alexa-fluor 488 and then visualized on a Synergy HTX plate reader. Fluorescence for p-eIF4E was measured and normalized to total DAPI fluorescence to determine the percentage of eIF4E phosphorylation in each well. Data were plotted in Graphpad Prism V8 to determine concentration-response effects and calculate IC₅₀ values. IC₅₀ data is provided in Table 5 below.

The ability of MNK inhibitors described herein to inhibit eIF4E phosphorylation at Serine 209 in Karpas 299, Human Non-Hodgkin's Ki-positive Large Cell Lymphoma cell line was tested by sandwich enzyme linked immune-absorbance assay. IC₅₀ data is provided in Table 5 below.

The ability of MNK inhibitors described herein to inhibit eIF4E phosphorylation at Serine 209 in the human osteosarcoma (U2OS) cell line was tested by exposing the cells to compound for 2 hours and then measuring eIF4E phosphorylation with a phosphorylation-specific antibody in a fluorescent plate reader. IC₅₀ data is provided in Table 5 below.

Table 5. MNK1, MNK2, HEK293 Cell, Karpas 299 Cell, and U2OS Cell IC₅₀ values for representative compounds of the disclosure

Compound	MNK1(nM)	MNK2(nM)	HEK 293 cell (nM)	Karpas 299cell (nM)	U2OS cell (nM)
4ET-01-001	81.3	2.9	10.9	-	-
4ET-01-002	27.9	2.6	18.5	33	6.9
4ET-01-003	28.2	2.0	10.5	35	-

Compound	MNK1(nM)	MNK2(nM)	HEK 293 cell (nM)	Karpas 299cell (nM)	U2OS cell (nM)
4ET-01-004	103.7	8.2	33.6	-	-
4ET-01-005	9.8	1.2	8.2	26	8.2
4ET-01-009	13.1	0.8	3.6	-	-
4ET-01-010A	73.4	9.24	35.4	-	-
4ET-01-010B	348	96.6	71.3	-	-
4ET-01-012	27.9	3.0	57.1	-	-
4ET-01-014A	26.0	4.0	28.4	-	-
4ET-01-014B	24.5	4.6	67.4	-	-
4ET-01-015	30.9	2.6	3.9	-	-
4ET-01-016	33.0	3.5	8.9	-	-
4ET-01-017	69.2	7.9	41.6	-	-
4ET-01-018	41.8	4.1	4.1	-	-
4ET-01-019	43.9	4.2	4.9	-	-
4ET-01-020	36.0	3.0	4.3	-	-
4ET-01-021	38.7	5.8	6.0	-	-
4ET-01-023	63.8	3.0	36.7	-	-
4ET-01-025	73.3	5.5	4.4	-	-
<i>rac</i> -4ET-01-027	35.2	1.6	12.6	-	-
Enantiomer 1 of 4ET-01-027	73.4	2.4	11.6	-	-
Enantiomer 2 of 4ET-01-027	177.0	9.7	25.4	-	-
4ET-01-030	48.0	2.3	9.9	-	-
4ET-01-035	22.7	1.8	0.9	-	-
4ET-01-036	48.4	3.5	52.2	-	-
4ET-01-038	66.2	4.2	6.0	-	-
4ET-01-039	96.6	4.4	9.7	-	-
4ET-01-042	16.5	2.0	0.8	-	-
4ET-01-051	58.6	3.1	7.3	-	-
4ET-01-058	58.4	6.5	10.9	-	-
4ET-02-001	39.6	1.6	7.1	17	-
4ET-02-002	inactive	inactive	-	-	-
4ET-02-003	139.6	4.1	1.4	-	-
4ET-02-004	61.7	2.1	30.7	-	30
4ET-02-005	45.1	10.4	22.5	-	-
4ET-02-006	346.0	14.4	-	-	-
4ET-02-007	89.0	3.6	-	-	-
4ET-03-001	118.6	11.9	47.0	-	-
4ET-03-002	133.0	6.5	5.3	-	-
4ET-03-003	80.2	22.6	110.2	-	-
4ET-03-004	84.5	7.7	86.6	-	-
4ET-03-005	20.5	1.8	2.6	6.4	5.1
4ET-03-006	64.6	5.9	53	-	-
4ET-03-007	96.7	4.9	10.0	-	-

Compound	MNK1(nM)	MNK2(nM)	HEK 293 cell (nM)	Karpas 299cell (nM)	U2OS cell (nM)
4ET-03-008	65.5	7.4	52.6	-	-
4ET-03-009	31.3	2.6	1.7	6.2	1.7
4ET-03-010	381.8	84.8	164.1	-	
4ET-03-011	203.3	27.8	32.4	-	-
4ET-03-012	441.4	273.2	-	-	-
4ET-03-013	204.6	8.0	inactive	-	inactive
4ET-03-014	107.0	32.8	-	-	-
4ET-03-015	19.1	1.4	2.7	3.0	2.4
4ET-03-016	-	-	-	-	-
4ET-03-017	74.3	3.0	0.9	1.0	0.4
4ET-03-035	128.1	4.30	8.7	-	-
4ET-03-036	117.8	5.65	8.6	-	-
4ET-03-039	31.6	1.62	2.6	-	-
4ET-03-040	38.6	2.0	27.4	-	-
4ET-03-043	44.9	1.7	0.9	-	-
4ET-03-045	130.8	12.1	17.7	-	-
4ET-03-046	49.8	1.7	6.4	-	-
4ET-03-047	-	-	-	-	-
4ET-03-048	144.9	5.2	6.1	-	-
4ET-03-049	80.0	2.8	110.5	-	-
4ET-03-050A	35.0	1.32	2.6	-	-
4ET-03-050B	40.9	6.84	149.9	-	-
4ET-03-052A	4.71	0.50	19.2	-	-
4ET-03-052B	19.9	1.63	11.7	-	-
4ET-03-053	214.9	20.9	10.1	-	-
4ET-03-054	117.8	5.7	8.6	-	-
4ET-03-055	126.7	29.5	44.0	-	-
4ET-03-056	51.8	3.5	11.1	-	-
4ET-03-057	61.6	3.4	8.7	-	-
4ET-03-060	31.0	1.7	6.5	-	-
4ET-03-061	36.2	1.7	5.2	-	-
4ET-03-063	35.0	3.0	17.0	-	-
4ET-03-066A	47.9	3.4	6.5	-	-
4ET-03-068	25.3	1.5	3.4	-	-
4ET-03-074	45.9	3.1	11.3	-	-
4ET-03-076	37.5	12.2	-	-	-
4ET-03-081	30.3	10.1	-	-	-
4ET-04-023	36.8	1.86	1.2		

- indicates compound was not tested

It was observed that many of the compounds had similar inhibition across multiple cell lines.

BIOLOGICAL EXAMPLE 2

IN VIVO TESTING

Animals

Female and male MNK1 KO mice were a gift of the Sonenberg laboratory at
5 McGill University and bred at the University of Texas at Dallas (UTD) to generate
experimental animals (Ueda T, *et al.*, MNK2 and MNK1 are essential for constitutive
and inducible phosphorylation of eukaryotic initiation factor 4E but not for cell growth
or development. *Mol Cell Biol.* Aug 2004). Genotype was confirmed at weaning using
DNA from ear clips. Experimental C57BL/6 J wild-type (WT) animals were obtained
10 from an internally maintained C57BL/6 J colony at the University of Texas at Dallas.
For pharmacological studies, female and male ICR (CD-1) mice aged 6-8 weeks (~25-
30 g) were outbred and purchased from Envigo. All mice were housed in groups of four
animals per cage on a 12-hour light-dark cycle and had access to food and water *ad*
libitum. Upon arrival to the animal care facility, animals were allowed a minimum of 72
15 hours to acclimate to their new environment before being handled for experiments. All
experiments were performed between the hours of 9:00 AM and 5:00 PM. All
procedures were conducted with prior approval of the Institutional Animal Care and
Use Committee at the University of Texas at Dallas.

20 *Small molecule MNK inhibitors, protein and reagents*

For dural injections, human recombinant interleukin-6 (IL-6) protein (R&D
Systems) stock solution (100 mg/mL) was prepared in sterile 0.1% BSA and diluted to
1 ng/mL in synthetic interstitial fluid (SIF) consisting of 135 mM NaCl, 5 mM KCl, 10
mM HEPES, 2 mM CaCl₂, 10 mM glucose, 1 mM MgCl₂ (pH 7.4, 310 mOsm). Sodium
25 nitroprusside (SNP) (Sigma-Aldrich) was prepared fresh in sterile phosphate buffered
saline (PBS) at the time of use and was kept away from light. To test for the presence of
hyperalgesic priming, mice were given a 150 µL IP injection of 0.1 mg/kg of SNP or a
5 µL dural injection of SIF solution that was brought to a pH of 7.0, as previously
described (Avona A., *et al.*, Repetitive stress in mice causes migraine-like behaviors
30 and CGRP-dependent hyperalgesic priming to a migraine trigger. *Pain.* (2020); Burgos-

Vega C.C. *et al.*, Non-invasive dural stimulation in mice: A novel preclinical model of migraine. *Cephalalgia*. (2019)). For our pharmacological studies with small molecule MNK inhibitors, eFT508 was provided by eFFECTOR Therapeutics, and *rac*-4ET-01-027, Enantiomer 1 of 4ET-01-027 and 4ET-04-023 were provided by 4E Therapeutics, Inc. The MNK inhibitors were prepared for *in vivo* dosing by dissolution in 10% 1-methyl-2-pyrrolidinone (NMP; Sigma Cat# 328634) and 90% propylene glycol (PG; Fisher Cat# P355-1), with ~1 eq. of HCl. MNK inhibitors were given orally to WT mice at 10 mg/kg approximately 1 hr prior to dural IL-6 or dural pH 7.0.

10 *Mouse dural injections*

Mouse dural injections were performed as previously described (Burgos-Vega C.C. *et al.*, Non-invasive dural stimulation in mice: A novel preclinical model of migraine. *Cephalalgia*. (2019)). Mice were anesthetized under isoflurane for <2 min with <2.5–3% isoflurane via a chamber and given a 5 μ L injection via a modified internal cannula (Invivo1, part #8IC313ISPCXC, Internal Cannula, standard, 28 gauge, fit to 0.5 mm). The inner projection of the cannula was used to inject through the soft tissue at the intersection of the lambdoidal and sagittal sutures. Using a caliper, the length of the projection was adjusted to be from 0.6 to 0.7 mm based on animal weight (25–30 g) in order to avoid puncturing the dura mater. Control mice received a 5 μ L dural injection of SIF (pH 7.4, 310 mOsm). Upon completion of injections, mice were placed back into their respective cups in the testing chamber for 1 hr before testing.

Repeated restraint stress

Mice were stressed as previously described (Avona A., *et al.*, Repetitive stress in mice causes migraine-like behaviors and CGRP-dependent hyperalgesic priming to a migraine trigger. *Pain*. (2020)). Mice were stressed between the hours of 10:00 AM to 12:00 PM for 2 hours per day for three consecutive days. Mice were placed right-side up into tail vein injection tubes (Stolting #51338) with the nose through the provided breathing hole. The slotted tail piece was tightened so as to prevent the mouse from rotating in the tube, but loose enough to allow the animal to breathe. Mice were

restrained at a level that allowed for adequate respiration and care was taken to avoid any trauma caused by the restraint tube. Control mice were placed into a separate room and deprived of food and water for the same 2 hour interval for three consecutive days. Animals subjected to stress were housed separately from control mice in order to avoid
5 potential transfer of the stress phenotype.

Measuring mechanical hypersensitivity and grimace

Mice were handled and conditioned for a single 5-minute session, approximately 24 hrs before habituation. Mice were habituated to paper cups (Choice 4
10 oz paper cups: 6.5 cm top diameter, 4.5 cm bottom diameter, 72.5 cm length) while in testing chambers for 2 hours per day and for at least 2 days before measuring a baseline. Each mouse typically used their same assigned paper cup for the remainder of the experiment. Animals were given food while in testing chambers. Grimace measurements were recorded for each animal in 10-minute increments using an Apple
15 iPhone 11 Pro video camera (Langford D.J., *et al.*, Coding of facial expressions of pain in the laboratory mouse. *Nat Methods*. (2010) 7(6), 447-9; Avona A., *et al.*, Dural Calcitonin Gene-Related Peptide Produces Female-Specific Responses in Rodent Migraine Models. *J Neurosci*. (2019) 39(22), 4323-4331). Analysis of 5 characterized pain behaviors (orbital tightening, nose bulging, cheek bulging, flattening of whiskers,
20 and flattening of the ears) were scored on a scale from 0 to 2 (0 = not present, 1 = somewhat present, 2 = clearly present). Following grimace measurements, von Frey testing of the periorbital region of the face was used to measure facial hypersensitivity (Burgos-Vega C.C. *et al.*, Non-invasive dural stimulation in mice: A novel preclinical model of migraine. *Cephalalgia*. (2019); Lackovic J., *et al.* De novo protein synthesis is
25 necessary for priming in preclinical models of migraine. *Cephalalgia*. (2021) 41(2), 237-246). Filament thresholds were determined using the Dixon “up-and-down” method. Testing in mice began with 0.07 g on the face and increased in weight to a maximum of 0.6 g on the face. The testing timelines for dural injection experiments and stress experiments have been previously established (Avona A., *et al.*, Repetitive stress
30 in mice causes migraine-like behaviors and CGRP-dependent hyperalgesic priming to a

migraine trigger. *Pain*. (2020); Burgos-Vega C.C. *et al.*, Non-invasive dural stimulation in mice: A novel preclinical model of migraine. *Cephalalgia*. (2019)). In both experimental paradigms, once the mice returned to baseline, a sub-threshold dose of compound was administered either onto the dura (pH 7.0) or intraperitoneally (sodium nitroprusside) to test for hyperalgesic priming. Responses were defined as a mouse removing/swiping the filament away from its face upon brief application of the filament. All animals were randomly allocated to experimental groups by drawing for groups. All experimenters were blinded to animal treatments.

10 Statistical Analysis

Female and male mice were used in all experiments to determine any sex differences. Behavioral data were analyzed for multiple comparisons at each time point via two-way ANOVA followed by Bonferroni *post-hoc* analysis. All investigators were blinded to treatments during testing and scoring. All analyses were performed using Prism version 9.2 for Mac OS X and figures were composed in Prism.

FIG. 3A and 3B show genetic inhibition of MNK partially attenuates facial hypersensitivity and hyperalgesic priming caused by dural IL-6. Female and male WT or MNK1 KO mice were administered 5 μ L of the proinflammatory cytokine, IL-6 (0.1 ng), or vehicle onto their dura mater and tested for acute facial hypersensitivity and grimace measures. Following resolution of acute allodynia, all mice were tested for hyperalgesic priming by administering 5 μ L of SIF (pH = 7.0) and tested again. WT mice were observed to have significantly reduced withdrawal thresholds and increased grimacing compared to MNK1 KO mice, in which these effects were partially attenuated. Likewise, contrary to WT mice, MNK1 KO mice did not prime to dural pH 7.0. No sex differences were observed. Comparisons were made via two-way ANOVA followed by Bonferroni *post-hoc* analysis. Significance shown is between WT/IL-6 and MNK1 KO/IL-6 groups. $n \geq 6$ for all groups; * $p \leq 0.05$, ** $p \leq 0.01$, **** $p \leq 0.0001$.

FIG. 4A and 4B show MNK1 KO mice do not prime to low-dose NO donor following repeated stress. Following three consecutive days of restraint stress, female and male WT and MNK1 KO mice were tested for acute facial hypersensitivity and

grimace measures. Upon resolution of hypersensitivity, mice were administered a low dose of the NO donor, SNP (0.1 mg/kg) (IP), to test for the presence of priming. Following stress, WT and MNK1 KO mice showed similar levels of facial hypersensitivity lasting out to fourteen days, with MNK1 KO mice exhibiting

5 significantly lower grimace scores in the early time points measured. Interestingly, despite becoming acutely hypersensitive, MNK1 KO mice do not prime to low-dose SNP compared to WT, suggesting a role for MNK1 activation in the development of stress-induced hyperalgesic priming. No sex differences were observed. Comparisons were made via two-way ANOVA followed by Bonferroni *post-hoc* analysis.

10 Significance shown is between WT/Stress and MNK1 KO/Stress groups. $n \geq 7$ for all groups; ** $p \leq 0.01$, **** $p \leq 0.0001$.

FIG. 5A and 5B depict eFT508 reduces dural IL-6 -induced facial hypersensitivity and prevents priming to pH 7.0. Female and male WT mice were administered 5 μ L of dural IL-6 (0.1 ng) or vehicle and tested for acute facial

15 hypersensitivity and grimacing. Upon returning to baseline thresholds, mice were tested for priming with a 5 μ L dural injection of SIF (pH = 7.0). Prior to IL-6 or pH 7.0, mice received 100 μ L of the MNK inhibitor, eFT508 (10 mg/kg), or vehicle via oral gavage. In mice that received eFT508, dural IL-6 induced facial hypersensitivity and grimace measures were significantly attenuated compared to the vehicle group and these mice

20 did not prime to dural pH 7.0. Similarly, mice that received eFT508 prior to dural pH 7.0 did not prime to pH 7.0 compared to the vehicle group, suggesting that activation of MNK is critical to transition to a primed state. No sex differences were observed. Comparisons were made via two-way ANOVA followed by Bonferroni *post-hoc* analysis. Significance shown is between IL-6/Vehicle and IL-6/eFT508 groups. $n = 7$

25 for all groups; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$.

FIG. 6 shows *rac*-4ET-01-027, Enantiomer 1 of 4ET-01-027, and 4ET-04-023 reduce dural IL-6 -induced facial grimacing. Female and male WT mice were administered 5 μ L of dural IL-6 (0.1 ng) or vehicle and tested for acute facial grimacing as measured by the grimace score. Prior to IL-6, mice received 100 μ L of either *rac*-

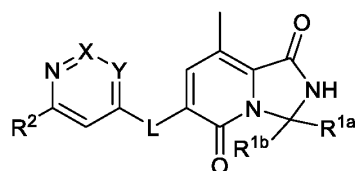
30 4ET-01-027 (10 mg/kg), Enantiomer 1 of 4ET-01-027 (10 mg/kg), 4ET-04-023 (10

mg/kg), or vehicle via oral gavage. In mice that received either *rac*-4ET-01-027, Enantiomer 1 of 4ET-01-027, or 4ET-04-023, dural IL-6 induced facial grimace measures were significantly attenuated compared to the vehicle group. No sex differences were observed. Comparisons were made via two-way ANOVA followed by

5 Bonferroni *post-hoc* analysis. Significance shown is between IL-6/Vehicle and IL-6/*rac*-4ET-01-027, IL-6/Enantiomer 1 of 4ET-01-027, and IL-6/4ET-04-023 groups. n = ≥ 6 for all groups; *p ≤ 0.05 , **p ≤ 0.01 , ***p ≤ 0.001 , ****p ≤ 0.0001 .

CLAIMS

1. A method for treating, preventing, or mitigating the effects of a migraine or symptoms related to a migraine, the method comprising administering a therapeutically effective amount of a compound having the following Structure (II):



(II)

or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof, wherein

R^{1a} is C_1 - C_6 alkyl or aryl;

R^{1b} is C_1 - C_6 alkyl or aryl,

or R^{1a} and R^{1b} , together with the carbon to which they are both attached, join to form cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl;

R^2 is $-NHR^{3a}$, $-NHC(=O)R^{3b}$, $-NHC(=S)R^{3b}$, or $-C(=O)R^{3c}$;

R^{3a} is hydrogen, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl, each of which is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, C_3 - C_6 cycloalkyl, $-NHS(O)_2CH_3$, heterocyclyl, $-C(=O)OH$, $-C(=O)N(R^{3d})R^{3d}$, or $-N(R^{3d})R^{3d}$;

R^{3b} is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, or heterocyclyl each of which is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halo, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $-NHS(O)_2CH_3$, $-N(R^{3d})R^{3d}$, heterocyclyl, $-C(=O)OH$, $-C(=O)N(R^{3d})R^{3d}$, $-NHC(=O)CH_3$, $-CH_2C(=O)OH$,

R^{3c} is $-N(R^{3d})R^{3d}$ or heterocyclyl;

R^{3d} is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, or C_3 - C_6 cycloalkyl;

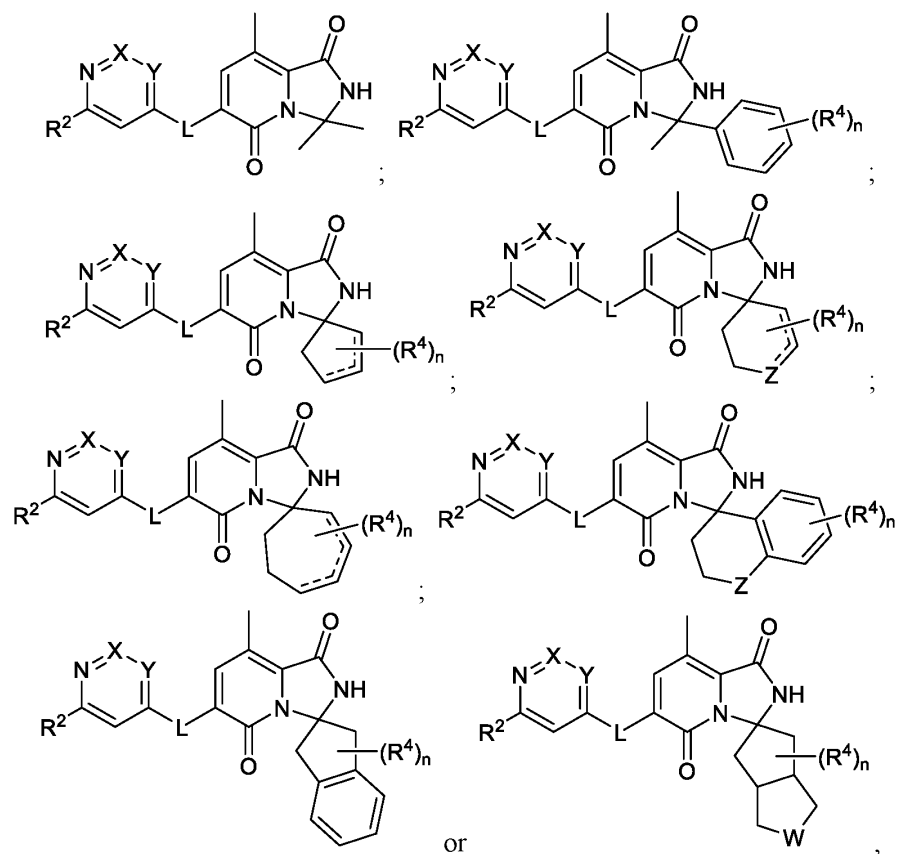
L is $-NH-$ or $-CH_2NH-$; and

X is N and Y is CH or X is CH and Y is N.

2. The method of claim 1, wherein R^{1a} is C_1 - C_6 alkyl.
3. The method of any one of claims 1-2, wherein R^{1a} is methyl.
4. The method of claim 1, wherein R^{1a} is aryl.
5. The method of claim 1, wherein R^{1a} is phenyl.
6. The method of any one of claims 1-5, wherein R^{1b} is C_1 - C_6 alkyl.
7. The method of any one of claims 1-6, wherein R^{1b} is methyl.
8. The method of claim 1, wherein R^{1a} and R^{1b} , together with the carbon to which they are both attached, join to form cycloalkyl.
9. The method of claim 8, wherein the cycloalkyl is cyclopentyl or cyclohexyl.
10. The method of claim 1, wherein R^{1a} and R^{1b} , together with the carbon to which they are both attached, join to form cycloalkenyl.
11. The method of claim 10, wherein the cycloalkenyl is cyclopentenyl, cyclohexenyl, or cycloheptenyl.
12. The method of claim 1, wherein R^{1a} and R^{1b} , together with the carbon to which they are both attached, join to form heterocyclyl.
13. The method of claim 12, wherein R^{1a} and R^{1b} , together with the carbon to which they are both attached, join to form aryl.

14. The method of claim 1, wherein R^{1a} and R^{1b} , together with the carbon to which they are both attached, join to form heteroaryl.

15. The method of any one of claims 1-14, wherein the compound has one of the following structures:



or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof, wherein

==== indicates a double or single bond;

R^4 is, at each occurrence, independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, halo, haloalkyl, hydroxyl, $-NHS(O)_2CH_3$, or $-C(O)OH$,

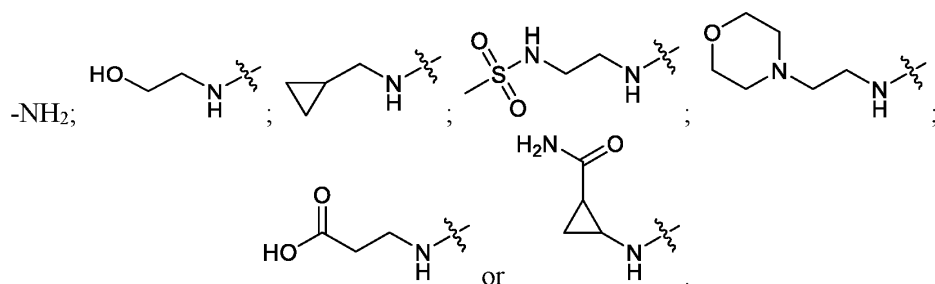
or two R^4 , together with the carbon to which they are both attached, join to form a cycloalkyl;

W is N or O;

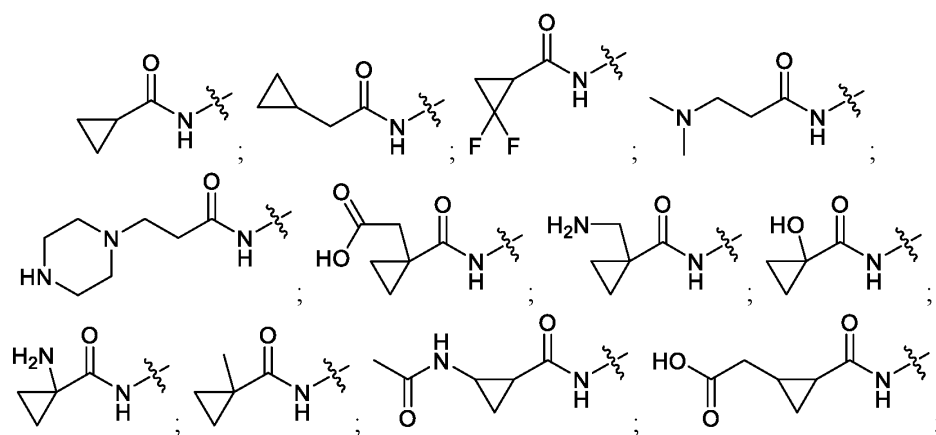
Z is C or O; and

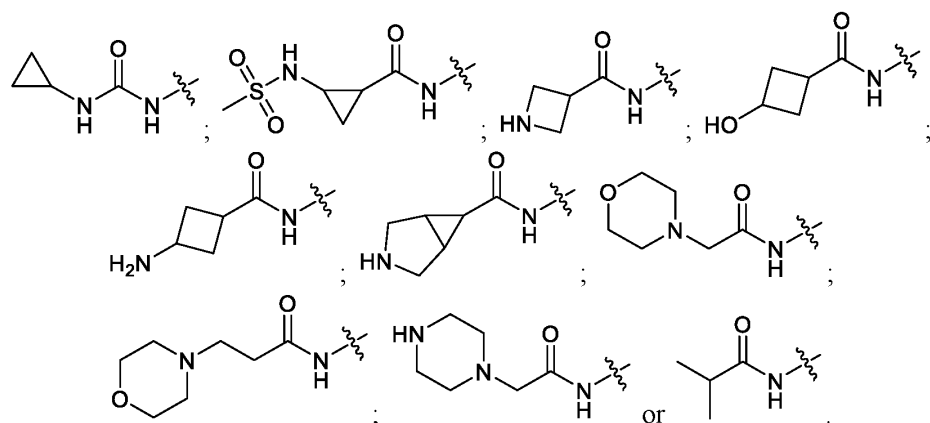
n is 0, 1, 2, 3, or 4.

16. The method of claim 15, wherein n is 0, 1, or 2.
17. The method of any one of claims 1-16, wherein R² is -NHR^{3a}.
18. The method of any one of claims 1-17, wherein R² has one of the structures:



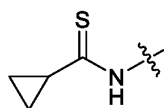
19. The method of any one of claims 1-16, wherein R² is –
NHC(=O)R^{3b}.
20. The method of claim 19, wherein R² has one of the following
structures:





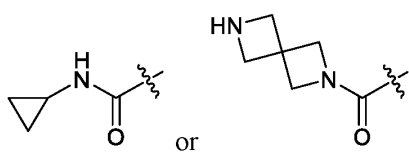
21. The method of any one of claims 1-16, wherein R^2 is –
 $\text{NHC}(=\text{S})R^{3b}$.

22. The method of claim 21, wherein R^2 has the following structure:

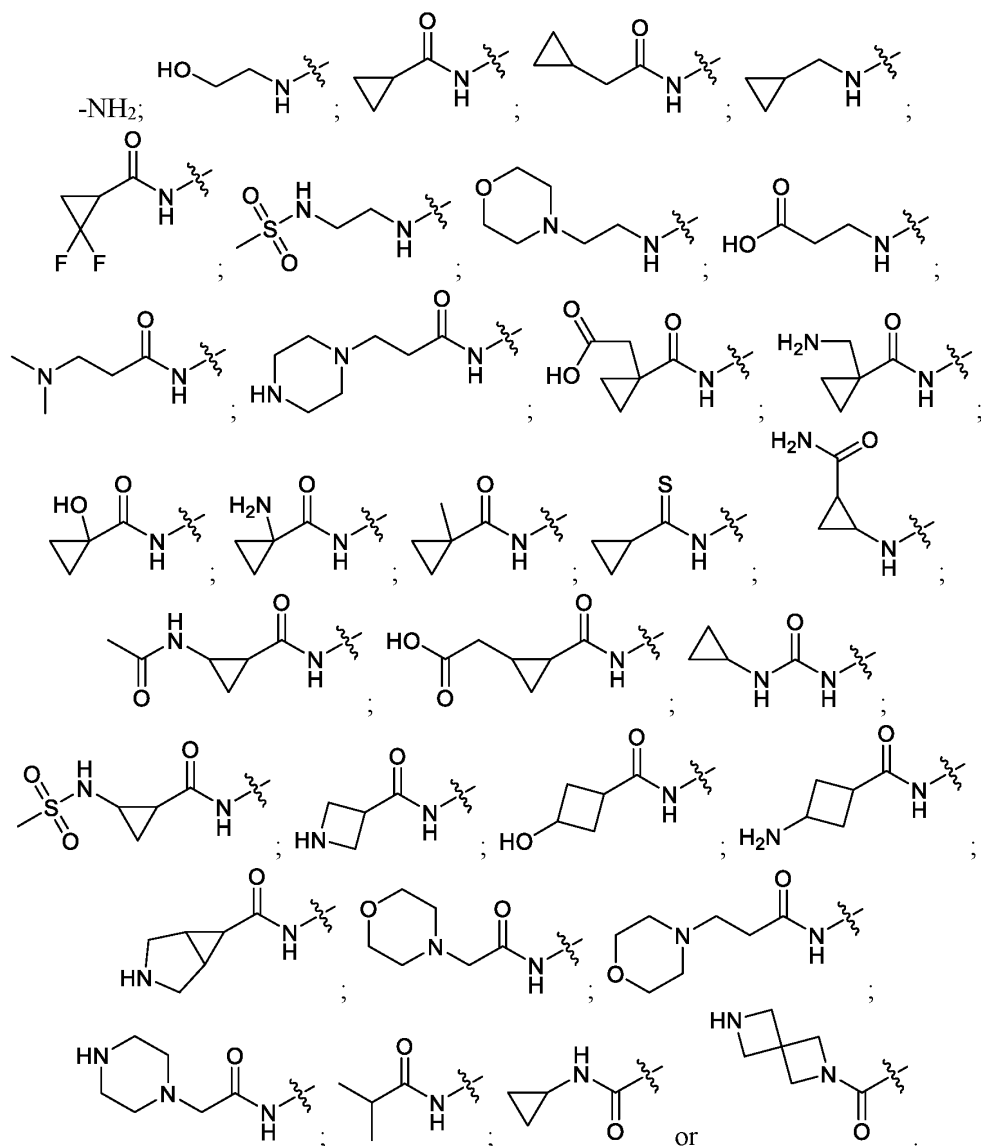


23. The method of any one of claims 1-16, wherein R^2 is $-\text{C}(=\text{O})R^{3c}$.

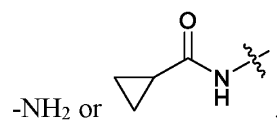
24. The method of claim 23, wherein R^2 has one of the following structures:



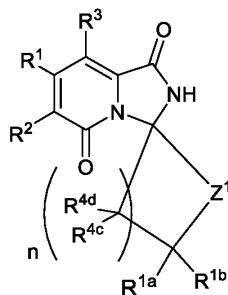
25. The method of any one of claims 1-24, wherein R^2 has one of the following structures:



26. The method of any one of claims 1-16, wherein R^2 has one of the following structures:

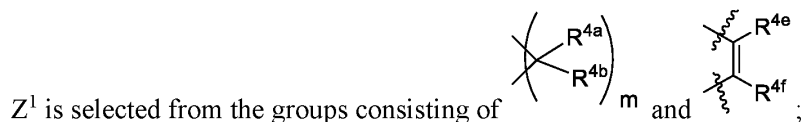


27. The method of any one of claims 1-26, wherein X is CH and Y is N.
28. The method of any one of claims 1-26, wherein X is N and Y is CH.
29. The method of any one of claims 1-26, wherein L is --NH-- .
30. The method of any one of claims 1-26, wherein L is $\text{--CH}_2\text{NH--}$.
31. The method of any one of claims 1-30, wherein the compound is selected from Table 1, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or prodrug thereof.
32. A method for treating, preventing, or mitigating the effects of a migraine or symptoms related to a migraine, the method comprising administering a therapeutically effective amount of a compound having the following Structure (IV):



(IV)

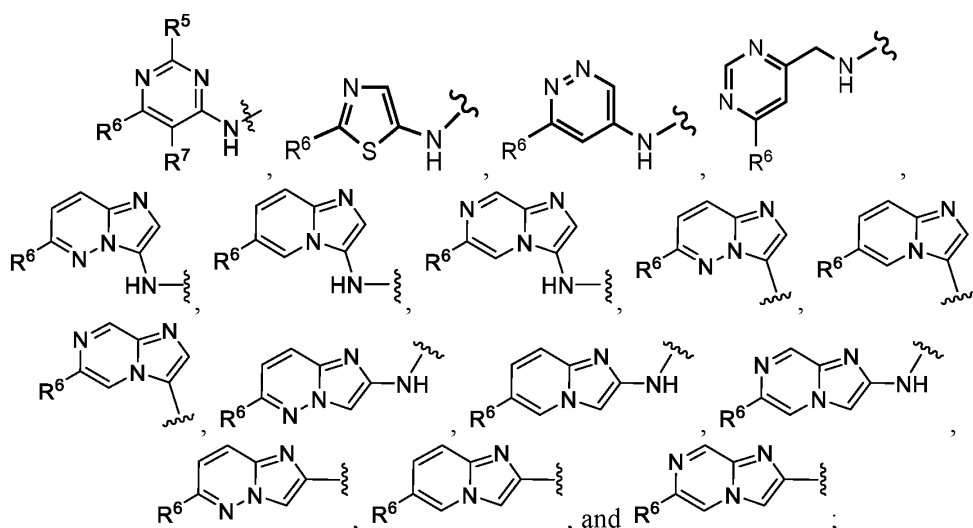
or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:



R^1 is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7}

branched hydroxyalkyl, cyano, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, hydroxy, and C₃₋₆ cycloalkyl that is optionally substituted with 1 to 3 substituents selected from the groups consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ hydroxyalkyl:

R² is selected from the group consisting of:



R³ is selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, cyano, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, hydroxy, and C₃₋₆ cycloalkyl that is optionally substituted with 1 to 3 substituents selected from the groups consisting of halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ hydroxyalkyl:

R^{4a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl):

R^{4b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl)

R^{4c} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl)

R^{4d} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHCO(C₃₋₇ cycloalkyl), NHSO₂(C₁₋₆alkyl), NHSO₂(C₃₋₇ branched alkyl), and NHSO₂(C₃₋₇ cycloalkyl):

R^{4e} is hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, and C₃₋₇ branched haloalkyl;

R^{4f} is hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, and C₃₋₇ branched haloalkyl;

R^{1a} and R^{1b} are taken together to form an optionally substituted 3 to 7 membered ring that optionally contains an X¹ group;

X¹ is selected from the group consisting of CF₂, CHCO₂R¹², O, NH, NR⁸, and SO₂:

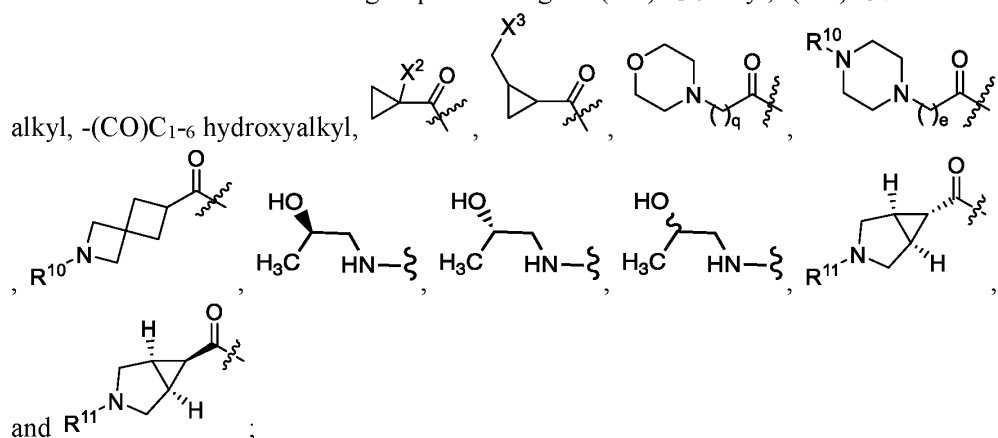
m is 0, 1, or 2;

n is 1, 2, or 3;

R⁵ is selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, and hydroxy:

R⁶ is selected from the group consisting of hydrogen, NH₂, NHR^{6a}, NHCH₂CH₂OH, NHCH₂CH₂NHSO₂Me, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, and hydroxy:

R^{6a} is selected from the group consisting of -(CO)C₁₋₆ alkyl, -(CO)C₃₋₇ branched



q is 1, 2, 3, 4, 5, or 6;

e is 1, 2, 3, 4, 5, or 6;

X² is selected from the group consisting of hydrogen, halogen, C₁₋₆alkyl, C₃₋₇ branched alkyl, C₁₋₆haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₆hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, C₁₋₆alkoxy, C₃₋₇ branched alkoxy, C₁₋₆haloalkoxy, C₃₋₇ branched haloalkoxy, NH₂, NH(C₁₋₆alkyl), N(C₁₋₆alkyl)₂, C₁₋₅(COOH), C₁₋₆(NHSO₂Me);

X³ is selected from the group consisting of hydrogen, halogen, C₁₋₅ alkyl, C₃₋₇ branched alkyl, C₁₋₅ haloalkyl, C₃₋₇ branched haloalkyl, hydroxy, C₁₋₅ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, C₁₋₅ alkoxy, C₃₋₇ branched alkoxy, C₁₋₅ haloalkoxy, C₃₋₇ branched haloalkoxy, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, COOH, C₁₋₅(COOH), NHSO₂Me, C₁₋₅(NHSO₂Me);

R⁷ is selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, and hydroxy:

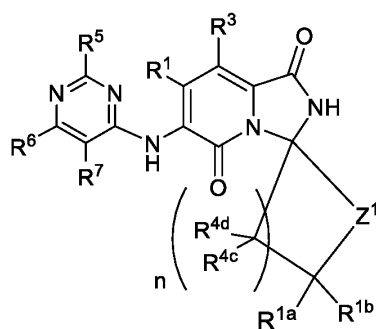
R⁸ is selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, CO(C₁₋₆alkyl), CO(C₃₋₇ branched alkyl), SO₂(C₁₋₆alkyl), and SO₂(C₃₋₇ branched alkyl);

R¹⁰ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, CO(C₁₋₆alkyl), CO(C₃₋₇ branched alkyl), SO₂(C₁₋₆alkyl), and SO₂(C₃₋₇ branched alkyl);

R¹¹ is selected from the group consisting of hydrogen and C₁₋₆ alkyl;

R¹² is selected from the group consisting of hydrogen and C₁₋₆ alkyl.

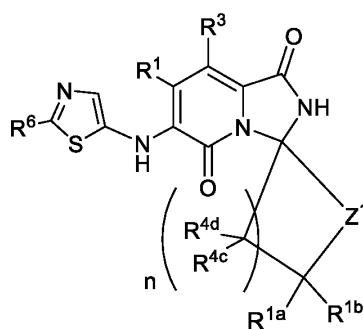
33. The method of claim 32, wherein the compound has the following Structure (V):



(V)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof.

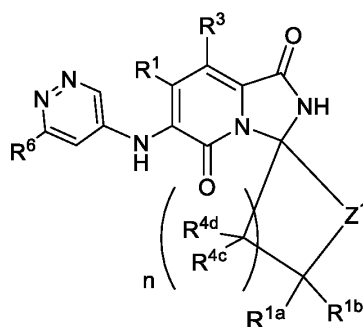
34. The method of claim 32, wherein the compound has the following Structure (VI):



(VI)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof.

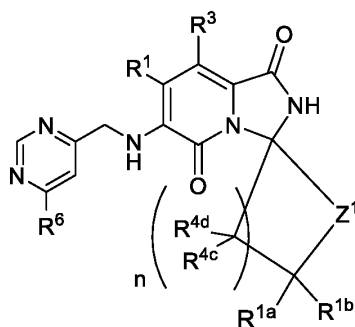
35. The method of claim 32, wherein the compound has the following Structure (VII):



(VII)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof.

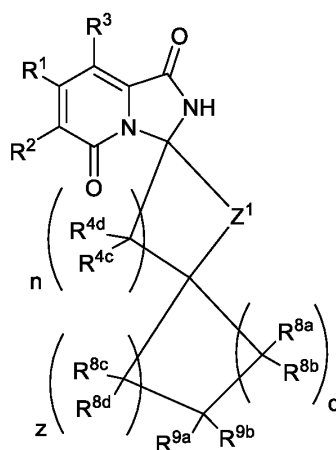
36. The method of claim 32, wherein the compound has the following structure (VIII):



(VIII)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof.

37. The method of claim 32, wherein the compound has the following Structure (IX):



(IX)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:

R^{8a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8c} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{8d} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, C_{3-7} branched alkoxy, $NHCO(C_{1-6}alkyl)$, $NHCO(C_{3-7} branched alkyl)$, $NHSO_2(C_{1-6}alkyl)$, and $NHSO_2(C_{3-7} branched alkyl)$;

R^{9a} is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, and C_{3-7} branched alkoxy;

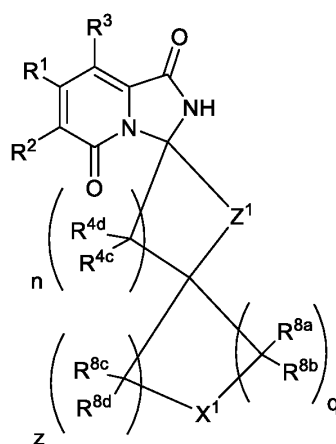
R^{9b} is selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{3-7} branched alkyl, C_{1-6} haloalkyl, C_{3-7} branched haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} branched hydroxyalkyl, hydroxy, C_{1-6} alkoxy, and C_{3-7} branched alkoxy;

R^{9a} and R^{9b} are taken together to form an optionally substituted 3 to 7-membered ring;

q is 1, 2, or 3; and

z is 0, 1, or 2.

38. The method of claim 32, wherein the compound has the following Structure (X):



(X)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein:

R^{8a} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl);

R^{8b} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl);

R^{8c} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl);

R^{8d} is at each occurrence independently selected from the group consisting of hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ branched alkyl, C₁₋₆ haloalkyl, C₃₋₇ branched haloalkyl, C₁₋₆ hydroxyalkyl, C₃₋₇ branched hydroxyalkyl, hydroxy, C₁₋₆ alkoxy, C₃₋₇ branched alkoxy, NHCO(C₁₋₆alkyl), NHCO(C₃₋₇ branched alkyl), NHSO₂(C₁₋₆alkyl), and NHSO₂(C₃₋₇ branched alkyl); q is 1, 2, or 3; and

z is 0, 1, or 2.

39. The method of claim 32, wherein the compound is:

N-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopanecarboxamide;

6"-((6-Aminopyrimidin-4-yl)amino)-8"-methyl-2"*H*-dispiro[cyclopropane-1,1'-cyclohexane-3',3"-imidazo[1,5-*a*]pyridine]-1",5"-dione;

N-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide;

N-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[aziridine-2,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide;

N-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclobutane-1,1'-cyclobutane-3',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide;

N-(6-((8"-methyl-1",5"-dioxo-1-(2-oxo-2-phenyl-112-ethyl)-1",5"-dihydro-2"H-dispiro[aziridine-2,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide;

tert-butyl 6"-((6-(cyclopropanecarboxamido)pyrimidin-4-yl)amino)-8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[azetidine-3,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1-carboxylate;

N-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[azetidine-3,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide;

6"-((6-((2-hydroxyethyl)amino)pyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-Aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-aminopyrimidin-4-yl)amino)-8"-methyl-1-(2-oxo-2-phenyl-112-ethyl)-2"H-dispiro[aziridine-2,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

1-(aminomethyl)-*N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropane-1-carboxamide;

(1R,5S,6R)-*N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

N-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)-2-azaspiro[3.3]heptane-6-carboxamide;

2-methyl-*N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)-2-azaspiro[3.3]heptane-6-carboxamide;

(1R,5S,6R)-3-methyl-*N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

N-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)-1-(methylsulfonamido methyl)cyclopropane-1-carboxamide;

1-((dimethylamino)methyl)-*N*-(6-((8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropane-1-carboxamide;

6"-((6-aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclobutane-1,1'-cyclobutane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[aziridine-2,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclopentane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclopentane-1,1'-cyclopentane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-aminopyrimidin-4-yl)amino)-3,3-difluoro-8"-methyl-2"H-dispiro[cyclobutane-1,1'-cyclobutane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclopentane-1,1'-cyclobutane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclobutane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclohexane-1,1'-cyclobutane-3',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

ethyl 6"-((6-(cyclopropanecarboxamido)pyrimidin-4-yl)amino)-8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-2-carboxylate;

tert-butyl (6"-((6-(cyclopropanecarboxamido)pyrimidin-4-yl)amino)-8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-2-yl)carbamate;

N-(6-((2,2-difluoro-8"-methyl-1",5"-dioxo-1",5"-dihydro-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridin]-6"-yl)amino)pyrimidin-4-yl)cyclopropanecarboxamide;

6"-((6-aminopyrimidin-4-yl)amino)-2,2-difluoro-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-a]pyridine]-1",5"-dione;

6"-((6-Aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cycloheptane-4',3"-imidazo[1,5-*α*]pyridine]-1",5"-dione;

6"-((6-Aminopyrimidin-4-yl)amino)-8"-methyl-2"H-dispiro[cyclopropane-1,1'-cyclohexane-4',3"-imidazo[1,5-*α*]pyridin]-2'-ene-1",5"-dione,

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof.