[0012] The $\alpha_V\beta_6$ integrin is expressed in epithelial cells, and binds to the latency-associated peptide of transforming growth factor-β1 (TGFβ1) and mediates TGFβ1 activation. Its expression level is significantly increased after injury to lung and cholangiocytes, and plays a critical *in vivo* role in tissue fibrosis. Increased levels are also associated with increased mortality in IPF and NSIP patients.

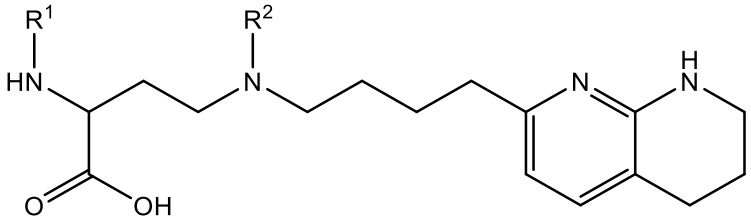
[0013] Primary sclerosing cholangitis (PSC) involves bile duct inflammation, and fibrosis that obliterates the bile ducts. The resulting impediment to the flow of bile to the intestines can lead to cirrhosis of the liver and subsequent complications such as liver failure and liver cancer. Expression of $\alpha_V\beta_6$ is elevated in liver and bile duct of PSC patients.

[0014] The present disclosure provides for $\alpha_V\beta_6$ integrin inhibitors that may be useful for treatment of fibrosis.

BRIEF SUMMARY

[0015] Disclosed are amino acid compounds that are $\alpha_V\beta_6$ integrin inhibitors, compositions containing these compounds and methods for treating diseases mediated by $\alpha_V\beta_6$ integrin such as a fibrotic disease.

[0015a] In an aspect of the present disclosure, there is provided a use of a compound of formula (II):



(II).

or a salt thereof;

in the manufacture of a medicament for treating a subject for a disease, wherein the compound of formula (II) is to be administered to the subject, and at least a second drug that is selected from the group consisting of: pirfenidone and nintedanib, or a salt thereof is to be further administered to the subject;

wherein in the compound of Formula (II):

R^1 is C_6-C_{14} aryl or 5- to 10-membered heteroaryl wherein the C_6-C_{14} aryl and 5- to 10-membered heteroaryl are optionally substituted by R^{1a};

R^2 is hydrogen; deuterium; C_1-C_6 alkyl optionally substituted by R^{2a}; -OH; -O-C_1-C_6 alkyl optionally substituted by R^{2a}; C_3-C_6 cycloalkyl optionally

substituted by R^{2b}; -O-C_3-C_6 cycloalkyl optionally substituted by R^{2b}; 3- to 12-membered heterocyclyl optionally substituted by R^{2c}; or -$S(O)_2R^{2d}$; with the proviso that any carbon atom bonded directly to a nitrogen atom is optionally substituted with an R^{2a} moiety other than halogen;

each R^{1a} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_4-C_8 cycloalkenyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, deuterium, halogen, -CN, -OR^3, -SR^3, -NR^4R^5, -NO_2, -C=NH(OR^3), -$C(O)R^3$, -$OC(O)R^3$, -$C(O)OR^3$, -$C(O)NR^4R^5$, -$NR^3C(O)R^4$, -$NR^3C(O)OR^4$, -$NR^3C(O)NR^4R^5$, -$S(O)R^3$, -$S(O)_2R^3$, -$NR^3S(O)R^4$, -$NR^3S(O)_2R^4$, -$S(O)NR^4R^5$, -$S(O)_2NR^4R^5$, or -$P(O)(OR^4)(OR^5)$, wherein each R^{1a} is, where possible, independently optionally substituted by deuterium, halogen, oxo, -OR^6, -NR^6R^7, -$C(O)R^6$, -CN, -$S(O)R^6$, -$S(O)_2R^6$, -$P(O)(OR^6)(OR^7)$, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, or C_1-C_6 alkyl optionally substituted by deuterium, oxo, -OH or halogen;

each R^{2a}, R^{2b}, R^{2c}, R^{2e}, and R^{2f} is independently oxo or R^{1a};

R^{2d} is C_1-C_6 alkyl optionally substituted by R^{2e} or C_3-C_5 cycloalkyl optionally substituted by R^{2f};

R^3 is independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl and 3- to 12-membered heterocyclyl of R^3 are independently optionally substituted by halogen, deuterium, oxo, -CN, -OR^8, -NR^8R^9, -$P(O)(OR^8)(OR^9)$, or C_1-C_6 alkyl optionally substituted by deuterium, halogen, -OH or oxo;

R^4 and R^5 are each independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 6-membered heteroaryl or 3- to 6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl of R^4 and R^5 are independently optionally substituted by deuterium, halogen, oxo, -CN, -OR^8, -NR^8R^9 or C_1-C_6 alkyl optionally substituted by deuterium, halogen, -OH or oxo;

or R^4 and R^5 are taken together with the atom to which they attached to form a 3- to 6-membered heterocyclyl optionally substituted by deuterium, halogen, oxo, -OR^8, -NR^8R^9 or C_1-C_6 alkyl optionally substituted by deuterium, halogen, oxo or -OH;

R^6 and R^7 are each independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by deuterium, halogen, or oxo;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3- to 6-membered heterocyclyl optionally substituted by deuterium, halogen, oxo or C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo; and

R^8 and R^9 are each independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by deuterium, halogen or oxo, or C_2-C_6 alkynyl optionally substituted by deuterium, halogen, or oxo;

or R^8 and R^9 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by deuterium, halogen, oxo or C_1-C_6 alkyl optionally substituted by deuterium, oxo, or halogen.

[0016] In one example, provided is a compound of formula (A), or any variation thereof, or a salt thereof (*e.g.*, a pharmaceutically acceptable salt thereof), as detailed herein.

[0017] Further provided is a pharmaceutical composition comprising a compound of formula (A), or any variation thereof detailed herein, or a salt thereof (*e.g.*, a pharmaceutically acceptable salt thereof), and a pharmaceutically acceptable carrier or excipient.

[0018] In another example, provided is a method of treating a fibrotic disease in an individual (such as a human) in need thereof comprising administering to the individual a therapeutically effective amount of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof. In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis (such as PBC). In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, psoriasis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis (such as PBC). In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF). In some examples, the fibrotic disease is liver fibrosis. In some examples, the fibrotic disease is skin fibrosis. In some examples, the fibrotic disease is psoriasis. In some

examples, the fibrotic disease is scleroderma. In some examples, the fibrotic disease is cardiac fibrosis. In some examples, the fibrotic disease is renal fibrosis. In some examples, the fibrotic disease is gastrointestinal fibrosis. In some examples, the fibrotic disease is primary sclerosing cholangitis. In some examples, the fibrotic disease is biliary fibrosis (such as PBC).

[0019] In another example, provided is a method of delaying the onset and/or development of a fibrotic disease in an individual (such as a human) who is at risk for developing a fibrotic disease comprising administering to the individual a therapeutically effective amount of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof. In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or PBC. In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, psoriasis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis (such as PBC). In some examples, the fibrotic disease is psoriasis. In some examples, the individual at risk of developing a fibrotic disease has or is suspected of having NAFLD, NASH, CKD, scleroderma, Crohn's Disease, NSIP, PSC, PBC, or is an individual who has had or is suspected of having had a myocardial infarction. In some examples, the individual at risk of developing a fibrotic disease has or is suspected of having psoriasis.

[0020] Also provided is a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutical composition thereof, for the treatment of a fibrotic disease.

[0021] Also provided is use of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising any of the foregoing, in the manufacture of a medicament for the treatment of a fibrotic disease.

[0022] Further provided is a kit comprising a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof. In some examples, the kit comprises instructions for use according to a method described herein, such as a method of treating a fibrotic disease in an individual.

[0023] In another example, provided is a method of making a compound of formula (A) or any variation thereof, or a pharmaceutically acceptable salt thereof. Also provided are compound intermediates useful in synthesis of a compound of formula (A), or any variation thereof.

[0024] In one example, provided is a compound of formula (I), or any variation thereof, or a salt thereof (*e.g.*, a pharmaceutically acceptable salt thereof), as detailed herein.

[0025] Further provided is a pharmaceutical composition comprising a compound of formula (I), or any variation thereof detailed herein, or a salt thereof (*e.g.*, a pharmaceutically acceptable salt thereof), and a pharmaceutically acceptable carrier or excipient.

[0026] In another example, provided is a method of treating a fibrotic disease in an individual (such as a human) in need thereof comprising administering to the individual a therapeutically effective amount of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof. In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis (such as PBC). In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, psoriasis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis (such as PBC). In some examples, the fibrotic disease is psoriasis.

[0027] In another example, provided is a method of delaying the onset and/or development of a fibrotic disease in an individual (such as a human) who is at risk for developing a fibrotic disease comprising administering to the individual a therapeutically effective amount of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof. In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or PBC. In some examples, the fibrotic disease is pulmonary fibrosis (such as IPF), liver fibrosis, skin fibrosis, psoriasis, scleroderma, cardiac fibrosis, renal fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis (such as PBC). In some examples, the fibrotic disease is psoriasis. In some examples, the individual at risk of developing a fibrotic disease has or is suspected of having NAFLD, NASH, CKD, scleroderma, Crohn's Disease, NSIP, PSC, PBC, or is an individual who has had or is suspected of having had a myocardial infarction. In some examples, the individual at risk of developing a fibrotic disease has or is suspected of having psoriasis.

[0028] Also provided is a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutical composition thereof, for the treatment of a fibrotic disease.

[0029] Also provided is use of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition

comprising any of the foregoing, in the manufacture of a medicament for the treatment of a fibrotic disease.

[0030] Further provided is a kit comprising a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof. In some examples, the kit comprises instructions for use according to a method described herein, such as a method of treating a fibrotic disease in an individual.

[0031] In another example, provided is a method of making a compound of formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof. Also provided are compound intermediates useful in synthesis of a compound of formula (I), or any variation thereof.

[0032] In another example, provided is a method of treating a subject for a disease, comprising: administering to the subject a first drug comprising a compound of formula (A) or a salt thereof; and administering to the subject at least a second drug that is selected from the group consisting of pirfenidone and nintedanib, or a salt thereof, whereby the subject is treated for the disease.

[0033] In any of the examples disclosed herein, the compound for use in any of the methods, including methods of treatment of disease or methods of treating a subject in need thereof, can be a compound, salt, or polymorph disclosed in International Patent Application No. WO 2022/109598 or United States Patent Application Publication No. US 2022/0177468.

BRIEF DESCRIPTION OF THE FIGURES

[0034] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0035] **FIG. 1** shows compounds 1-780 as disclosed herein.

[0036] **FIG. 2** shows Table B-3, with biological data for various compounds disclosed herein.

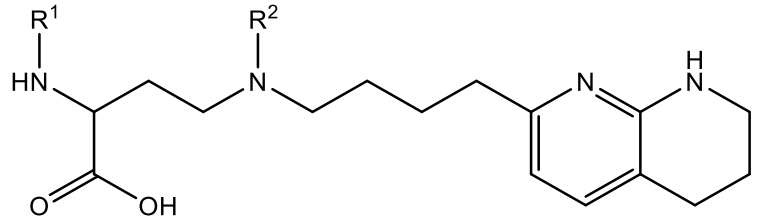
[0037] **FIG. 3A** is a graph showing that compound 5 and the selective antibody $\alpha_V\beta_6$ inhibitor 3G9 both substantially inhibited normal bronchial epithelial cell adhesion to LAP, in contrast with the $\alpha_V\beta_1$-selective small molecule inhibitor.

[0038] **FIG. 3B** shows that compound 5 and the $\alpha_V\beta_1$-selective small molecule inhibitor both substantially inhibited cell adhesion in the IPF-derived lung fibroblasts, in contrast to the selective antibody $\alpha_V\beta_6$ inhibitor, 3G9.

CLAIMS

What is claimed is:

1. Use of a compound of formula (II):



(II).

or a salt thereof;

in the manufacture of a medicament for treating a subject for a disease, wherein the compound of formula (II) is to be administered to the subject, and at least a second drug that is selected from the group consisting of: pirfenidone and nintedanib, or a salt thereof is to be further administered to the subject;

wherein in the compound of Formula (II):

R^1 is C_6-C_{14} aryl or 5- to 10-membered heteroaryl wherein the C_6-C_{14} aryl and 5- to 10-membered heteroaryl are optionally substituted by R^{1a};

R^2 is hydrogen; deuterium; C_1-C_6 alkyl optionally substituted by R^{2a}; -OH; -O-C_1-C_6 alkyl optionally substituted by R^{2a}; C_3-C_6 cycloalkyl optionally substituted by R^{2b}; -O-C_3-C_6 cycloalkyl optionally substituted by R^{2b}; 3- to 12-membered heterocyclyl optionally substituted by R^{2c}; or -$S(O)_2R^{2d}$; with the proviso that any carbon atom bonded directly to a nitrogen atom is optionally substituted with an R^{2a} moiety other than halogen;

each R^{1a} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_4-C_8 cycloalkenyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, deuterium, halogen, -CN, -OR^3, -SR^3, -NR^4R^5, -NO_2, -C=NH(OR^3), -$C(O)R^3$, -$OC(O)R^3$, -$C(O)OR^3$, -$C(O)NR^4R^5$, -$NR^3C(O)R^4$, -$NR^3C(O)OR^4$, -$NR^3C(O)NR^4R^5$, -$S(O)R^3$, -$S(O)_2R^3$, -$NR^3S(O)R^4$, -$NR^3S(O)_2R^4$, -$S(O)NR^4R^5$, -$S(O)_2NR^4R^5$, or -$P(O)(OR^4)(OR^5)$, wherein each R^{1a} is, where possible, independently optionally substituted by deuterium, halogen, oxo, -OR^6, -NR^6R^7, -$C(O)R^6$, -CN, -$S(O)R^6$, -$S(O)_2R^6$, -$P(O)(OR^6)(OR^7)$, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, or C_1-C_6 alkyl optionally substituted by deuterium, oxo, -OH or halogen;

each R^{2a}, R^{2b}, R^{2c}, R^{2e}, and R^{2f} is independently oxo or R^{1a};

R^{2d} is C_1-C_6 alkyl optionally substituted by R^{2e} or C_3-C_5 cycloalkyl optionally substituted by R^{2f};

R^3 is independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl or 3- to 12-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl and 3- to 12-membered heterocyclyl of R^3 are independently optionally substituted by halogen, deuterium, oxo, -CN, -OR^8, -NR^8R^9, -$P(O)(OR^8)(OR^9)$, or C_1-C_6 alkyl optionally substituted by deuterium, halogen, -OH or oxo;

R^4 and R^5 are each independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 6-membered heteroaryl or 3- to 6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl of R^4 and R^5 are independently optionally substituted by deuterium, halogen, oxo, -CN, -OR^8, -NR^8R^9 or C_1-C_6 alkyl optionally substituted by deuterium, halogen, -OH or oxo;

or R^4 and R^5 are taken together with the atom to which they attached to form a 3- to 6-membered heterocyclyl optionally substituted by deuterium, halogen, oxo, -OR^8, -NR^8R^9 or C_1-C_6 alkyl optionally substituted by deuterium, halogen, oxo or -OH;

R^6 and R^7 are each independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by deuterium, halogen, or oxo;

or R^6 and R^7 are taken together with the atom to which they attached to form a 3- to 6-membered heterocyclyl optionally substituted by deuterium, halogen, oxo or C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo; and

R^8 and R^9 are each independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by deuterium, halogen or oxo, or C_2-C_6 alkynyl optionally substituted by deuterium, halogen, or oxo;

or R^8 and R^9 are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by deuterium, halogen, oxo or C_1-C_6 alkyl optionally substituted by deuterium, oxo, or halogen.

2. The use of claim 1, wherein in the compound of Formula (II) or a salt thereof, R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}.

3. The use of claim 1 or claim 2, wherein in the compound of Formula (II), or a salt thereof, R^1 is:

pyrimidinyl, quinazolinyl, pyrazolopyrimidinyl, pyrazinyl, quinolinyl, pyridopyrimidinyl, thienopyrimidinyl, pyridinyl, pyrrolopyrimidinyl, quinoxalinyl, indazolyl, benzothiazolyl, naphthalenyl, purinyl, or isoquinolinyl; and is optionally substituted by deuterium, hydroxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 perhaloalkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_3-C_8 halocycloalkyl, C_3-C_8 cycloalkoxyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, cyano, amino, alkylamino, or dialkylamino; or

R^1 is pyrimidin-2-yl, pyrimidin-4-yl, quinazolin-4-yl, 1H-pyrazolo[3,4-d]pyrimidine-4-yl, 1H-pyrazolo[4,3-d]pyrimidine-7-yl, pyrazin-2-yl, quinoline-4-yl, pyrido[2,3-d]pyrimidin-4-yl, pyrido[3,2-d]pyrimidin-4-yl, pyrido[3,4-d]pyrimidin-4-yl, thieno[2,3-d]pyrimidin-4-yl, thieno[3,2-d]pyrimidin-4-yl, thienopyrimidin-4-yl, pyridin-2-yl, pyridin-3-yl, 7H-pyrrolo[2,3-d]pyrimidin-4-yl, quinoxalin-2-yl, 1H-indazol-3-yl, benzo[d]thiazol-2-yl, naphthalen-1-yl, 9H-purin-6-yl, or isoquinolin-1-yl; and is optionally substituted by: one or more deuterium; methyl; cyclopropyl; fluoro; chloro; bromo; difluoromethyl; trifluoromethyl; methyl and fluoro; methyl and trifluoromethyl; methoxy; cyano; dimethylamino; phenyl; pyridin-3-yl; or pyridin-4-yl; or R^1 is pyrimidin-4-yl optionally substituted by R^{1a} ; or

R^1 is pyrimidin-4-yl optionally substituted by R^{1a} wherein R^{1a} is 5- to 10-membered heteroaryl or C_1-C_6 alkyl optionally substituted by halogen; or

R^1 is pyrimidin-4-yl optionally substituted by pyrazolyl, methyl, difluoromethyl, or trifluoromethyl; or

R^1 is pyrimidin-4-yl substituted by both methyl and trifluoromethyl.

4. The use of any one of claims 1-3, wherein in the compound of Formula (II), or a salt thereof, R^1 is quinazolin-4-yl optionally substituted by R^{1a} ; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is quinazolin-4-yl optionally substituted by halogen, C_1-C_6 alkyl optionally substituted by halogen, or C_1-C_6 alkoxy; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is quinazolin-4-yl optionally substituted by fluoro, chloro, methyl, trifluoromethyl or methoxy.

5. The use of any one of claims 1-4, wherein in the compound of Formula (II), or a salt thereof, R^2 is:

hydrogen;

deuterium;

hydroxy; or

C_1-C_6 alkyl or C_1-C_6 alkoxyl optionally substituted with: deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxyl, C_3-C_8 cycloalkyl, C_3-C_8 halocycloalkyl, C_3-C_8 cycloalkoxyl, C_6-C_{14} aryl, C_6-C_{14} aryloxy, 5- to 10-membered heteroaryl, 5- to 10-membered heteroaryloxy, 3- to 12-membered heterocyclyl optionally substituted with oxo, $-C(O)NR^4R^5$, $-NR^3C(O)R^4$, or $-S(O)_2R^3$; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is:

methyl, methoxy, ethyl, ethoxy, propyl, cyclopropyl, or cyclobutyl;

each of which is optionally substituted with one or more of: hydroxy, methoxy, ethoxy, acetamide, fluoro, fluoroalkyl, phenoxy, dimethylamide, methylsulfonyl, cyclopropoxyl, pyridin-2-yloxy, optionally methylated or fluorinated pyridine-3-yloxy, N-morpholinyl, N-pyrrolidin-2-onyl, dimethylpyrazol-1-yl, dioxiran-2-yl, morpholin-2-yl, oxetan-3-yl, phenyl, tetrahydrofuran-2-yl, thiazol-2-yl; that is

each of which is substituted with 0, 1, 2, or 3 of deuterium, hydroxy, methyl, fluoro, cyano, or oxo; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} ; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} wherein R^{2a} is: halogen; C_3-C_8 cycloalkyl optionally substituted by halogen; 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl; $-NR^4R^5$; $-NR^3C(O)R^4$; $-S(O)_2R^3$; or oxo; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} wherein R^{2a} is: fluoro; cyclobutyl substituted by fluoro; pyrazolyl substituted by methyl; or $-S(O)_2CH_3$; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by $-OR^3$; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is: hydrogen; C_1-C_6 alkyl optionally substituted by halogen; C_3-C_6 cycloalkyl optionally substituted by halogen; C_6-C_{14} aryl optionally substituted by halogen; or 5- to 6-membered heteroaryl optionally substituted by halogen or C_1-C_6 alkyl; or

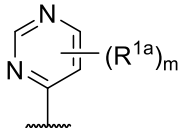
wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is: hydrogen; methyl; ethyl; difluoromethyl; -CH_2CHF_2; -CH_2CF_3; cyclopropyl substituted by fluoro; phenyl optionally substituted by fluoro; or pyridinyl optionally substituted by fluoro or methyl.

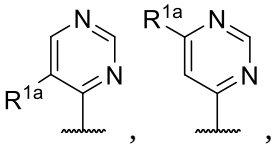
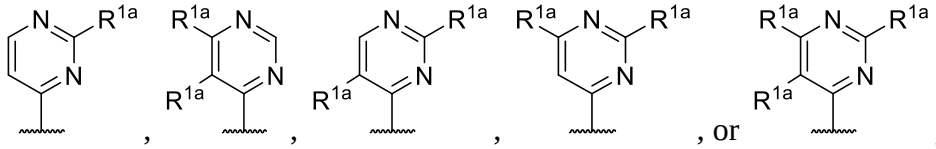
6. The use of any one of claims 1-5, wherein in the compound of Formula (II), or a salt thereof, R^2 is –$CH_2CH_2OCH_3$.

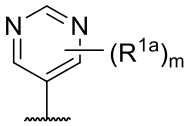
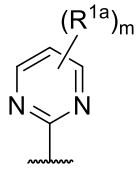
7. The use of any one of claims 1-4, wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by both halogen and OR^3, wherein R^3 is C_1-C_6 alkyl; or

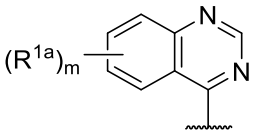
wherein in the compound of Formula (II), or a salt thereof, R^2 is C_3-C_6 cycloalkyl optionally substituted by R^{2b} ; or

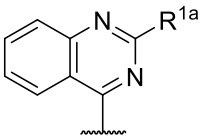
wherein in the compound of Formula (II), or a salt thereof, R^2 is cyclopropyl.

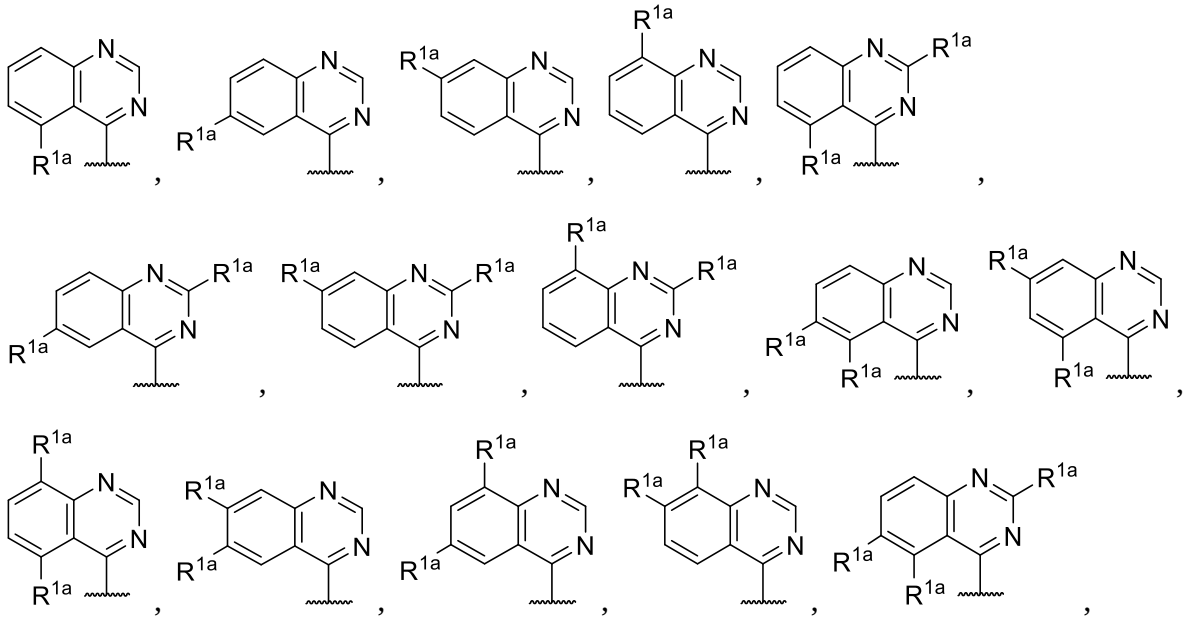
8. The use of any one of claims 1 or 5-7, wherein in the compound of Formula (II), or a salt thereof, R^1 is  , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or

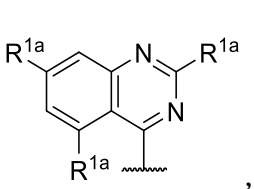
wherein in the compound of Formula (II), or a salt thereof, R^1 is  ,  , or , wherein each R^{1a} is independently deuterium, alkyl, haloalkyl, or heteroaryl; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is  or  , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is  , wherein m is 0, 1, 2, 3, 4, or 5 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is  ,

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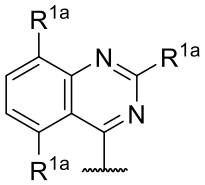
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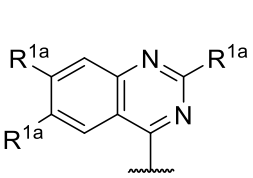
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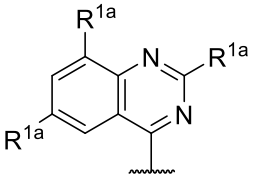
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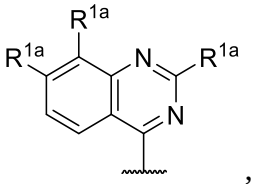
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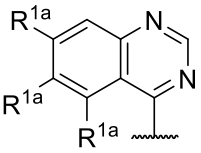
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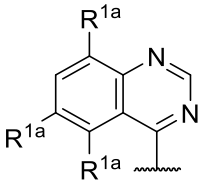
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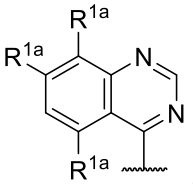
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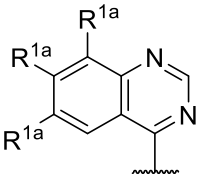
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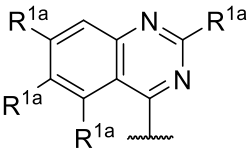
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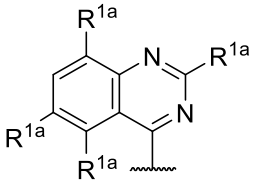
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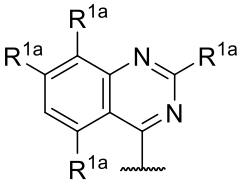
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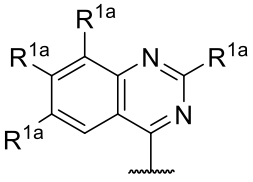
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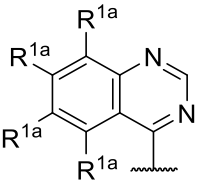
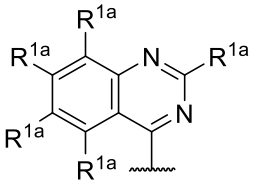
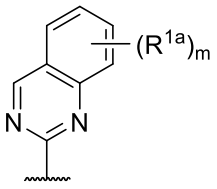


, or

, wherein each R^{1a} is independently deuterium, halogen, alkyl, haloalkyl, or alkoxy; or.

wherein in the compound of Formula (II), or a salt thereof, R^1 is

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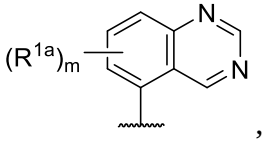
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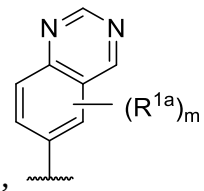
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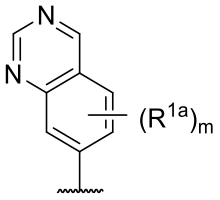
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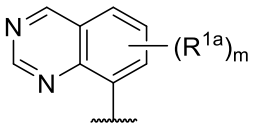
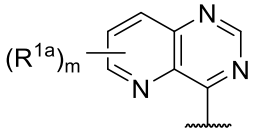
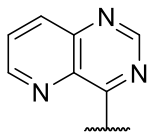
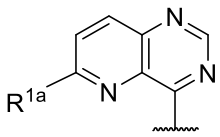
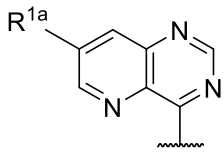
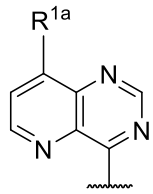
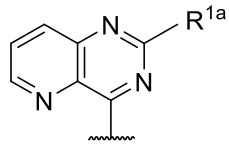
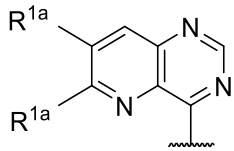
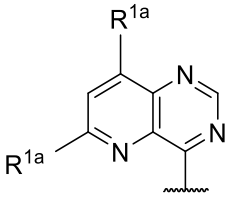
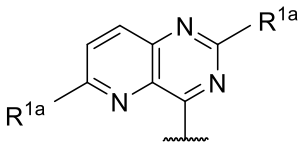
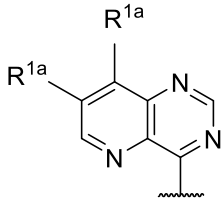

wherein m is 0, 1, 2, 3, 4, or 5 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or

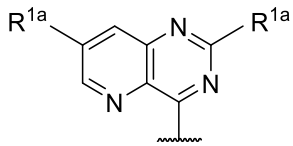
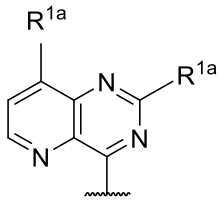
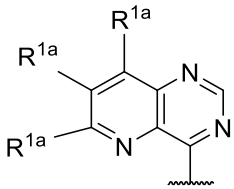
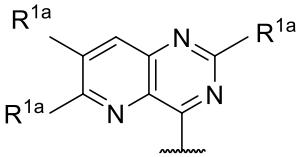
wherein in the compound of Formula (II), or a salt thereof, R^1 is

,
wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium,

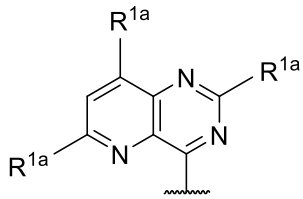
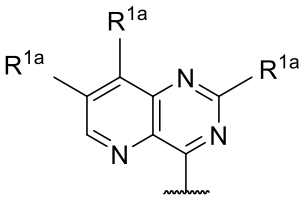
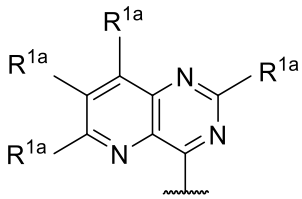
halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or.

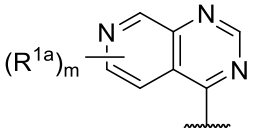
wherein in the compound of Formula (II), or a salt thereof, R^1 is selected from the group consisting of

 ,  ,  ,  ,  ,

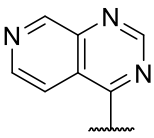
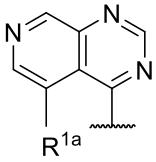
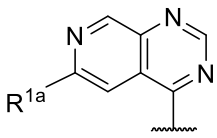
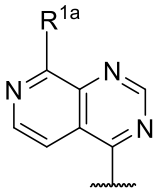
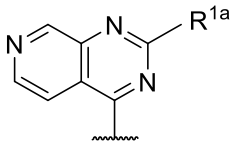
 ,  ,  ,  ,

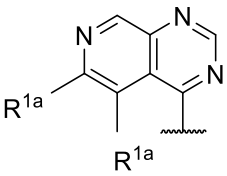
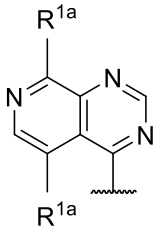
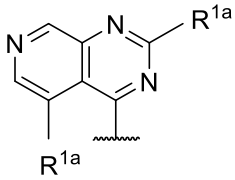
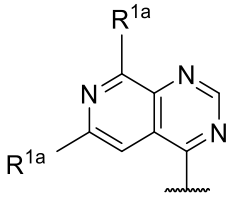
 ,  ,  ,  ,

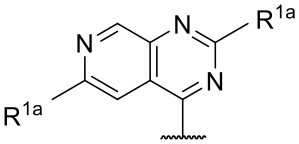
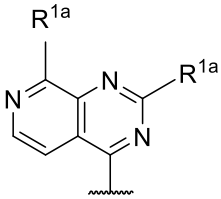
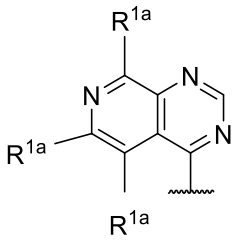
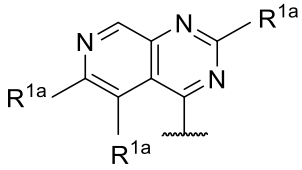
 ,  , and  ; or

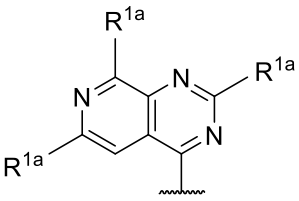
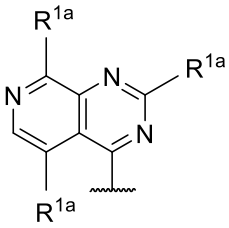
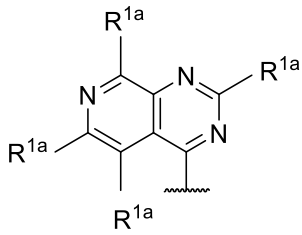
wherein in the compound of Formula (II), or a salt thereof, R^1 is  , wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or

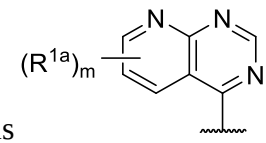
wherein in the compound of Formula (II), or a salt thereof, R^1 is selected from the group consisting of

 ,  ,  ,  ,  ,

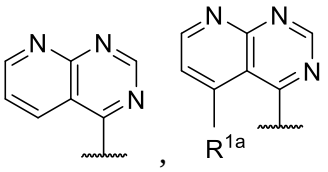
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  , and  ; or

 ,

wherein in the compound of Formula (II), or a salt thereof, R^1 is wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or wherein in the compound of Formula (II), or a salt thereof, R^1 is selected from the group consisting of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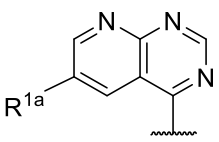
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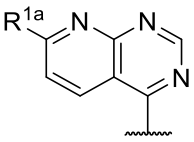
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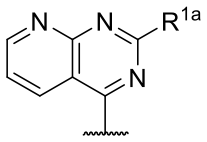
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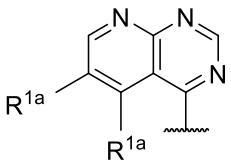
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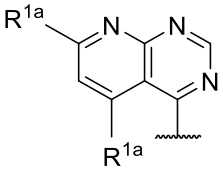
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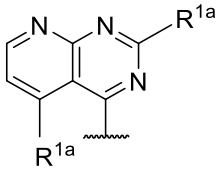
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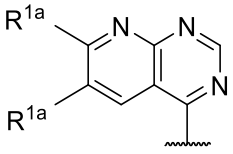
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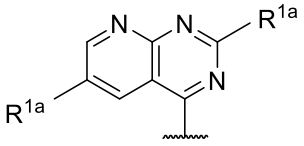
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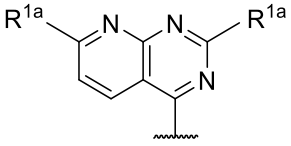
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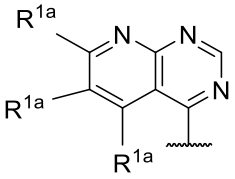
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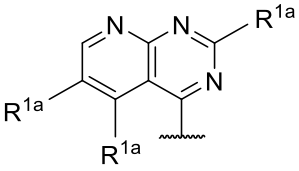
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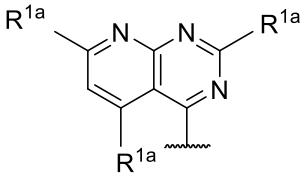
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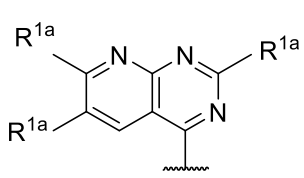
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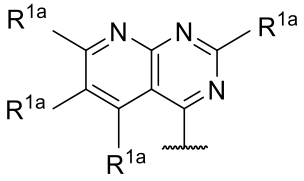
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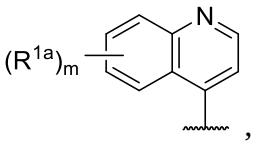
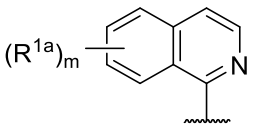

,

wherein in the compound of Formula (II), or a salt thereof, R^1 is , wherein m is 0, 1, 2, 3, 4, 5, or 6 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or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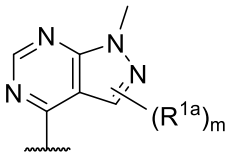
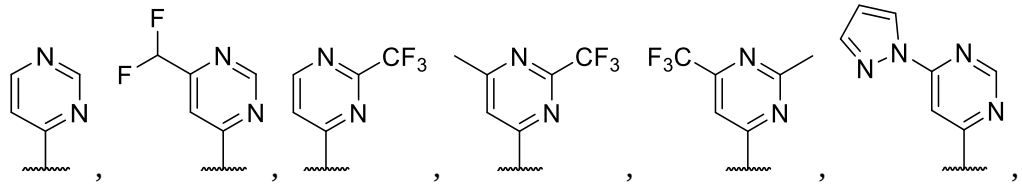
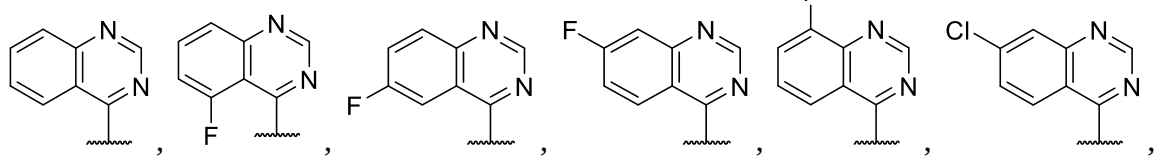
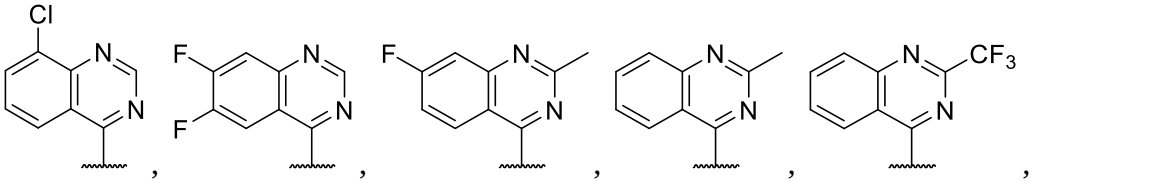
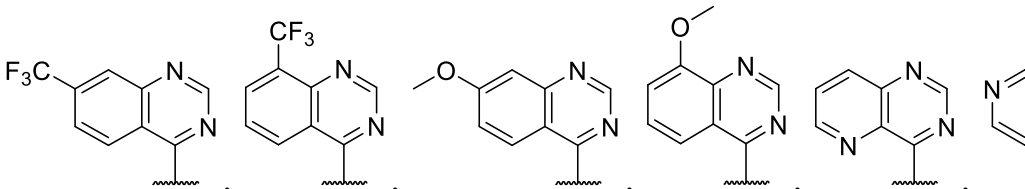
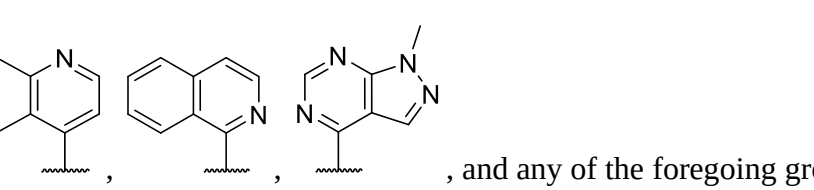
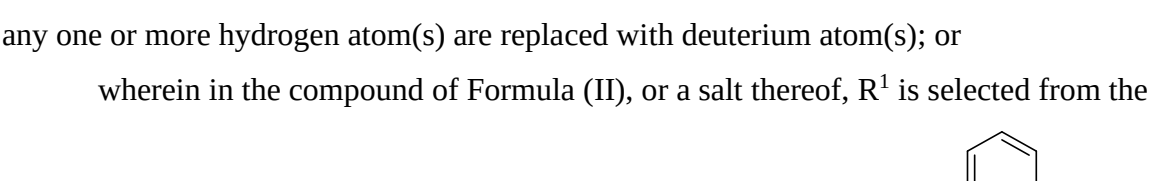
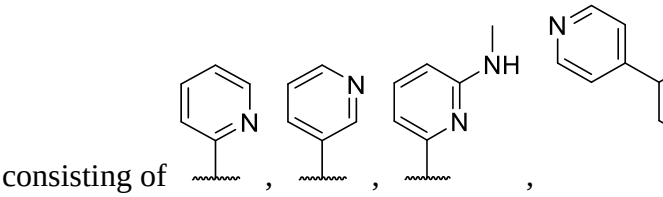
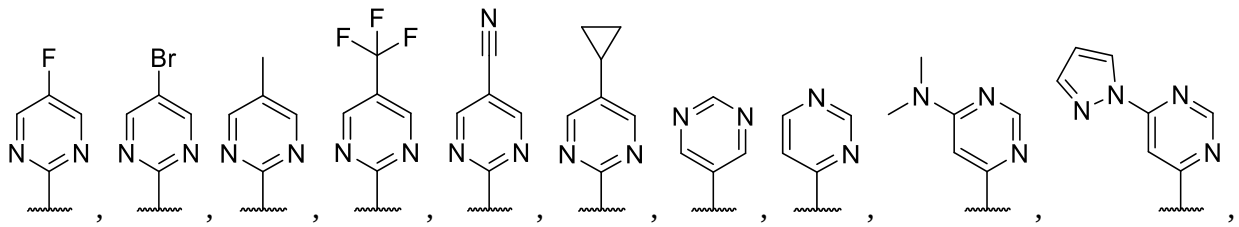
wherein in the compound of Formula (II), or a salt thereof, R^1 is , wherein m is 0, 1, 2, 3, 4, 5, or 6 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or

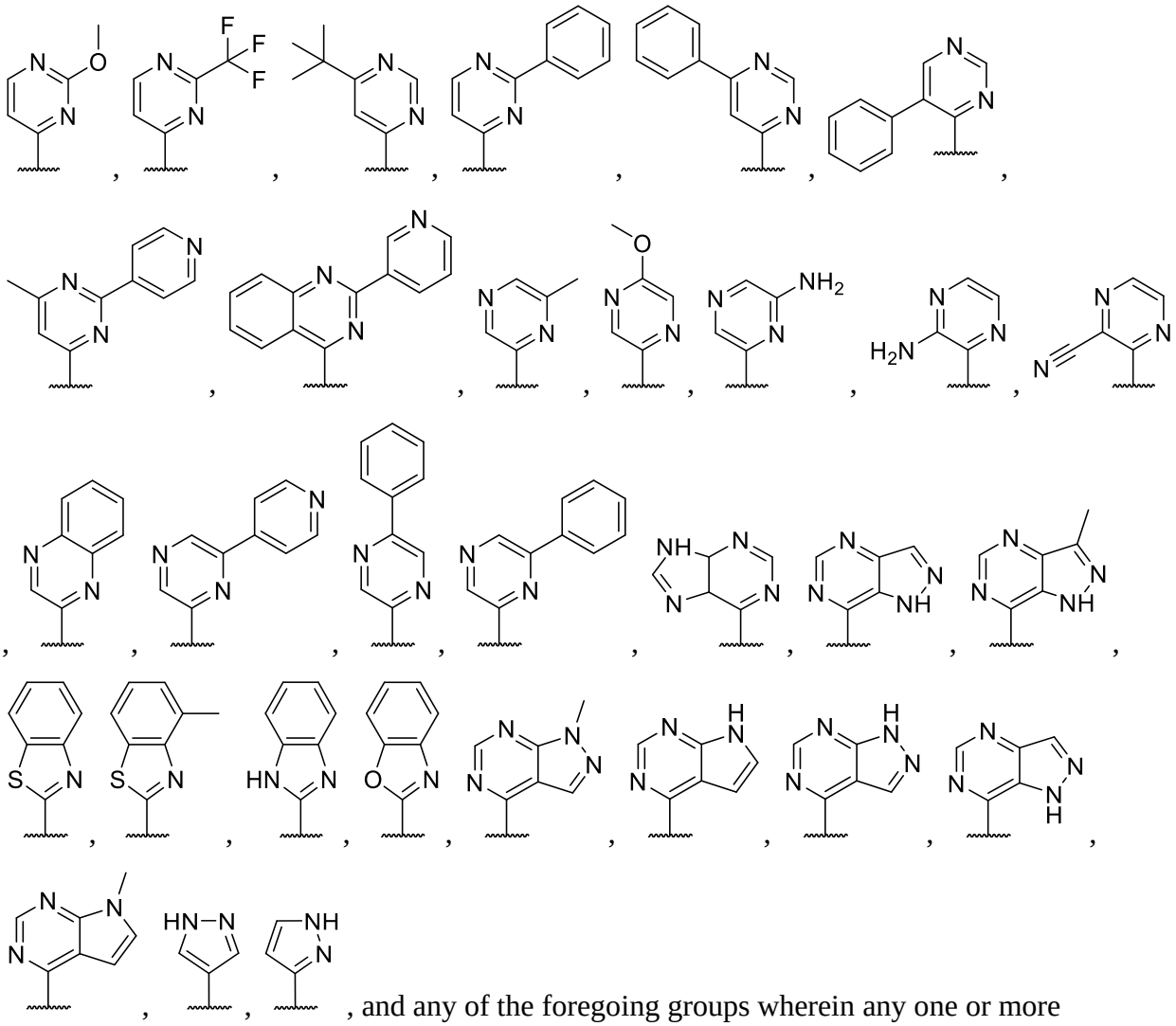

,

wherein in the compound of Formula (II), or a salt thereof, R^1 is , wherein m is 0, 1, or 2 and each R^{1a} is, where applicable, independently deuterium, halogen,

alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium; or

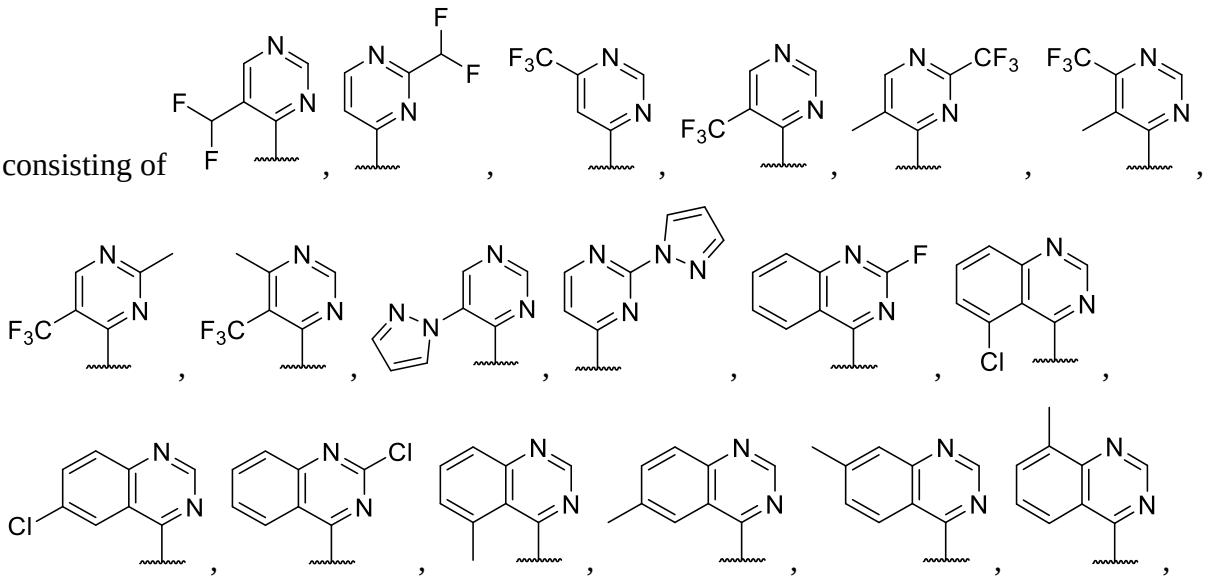
wherein in the compound of Formula (II), or a salt thereof, R^1 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s); or

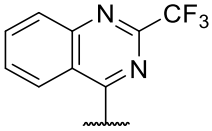
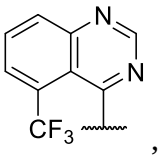
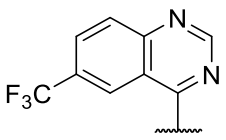
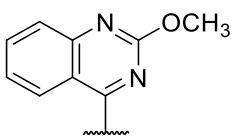
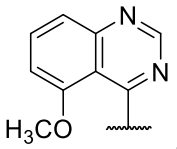
wherein in the compound of Formula (II), or a salt thereof, R^1 is selected from the group consisting of ,  ,

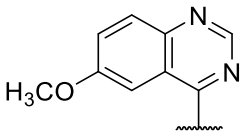
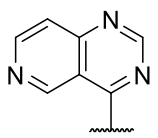
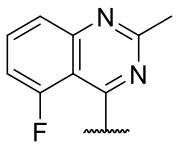
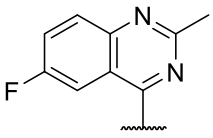
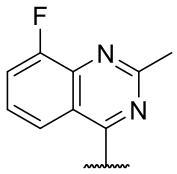


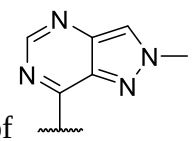
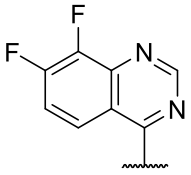
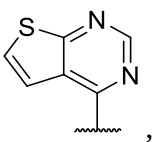
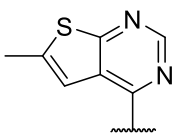
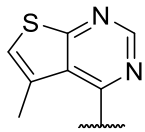
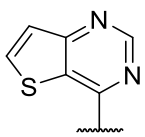
, and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s); or

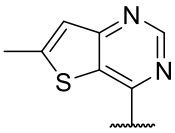
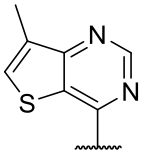
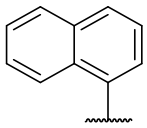
wherein in the compound of Formula (II), or a salt thereof, R^1 is selected from the group consisting of

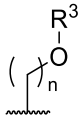


 ,  ,  ,  ,  ,

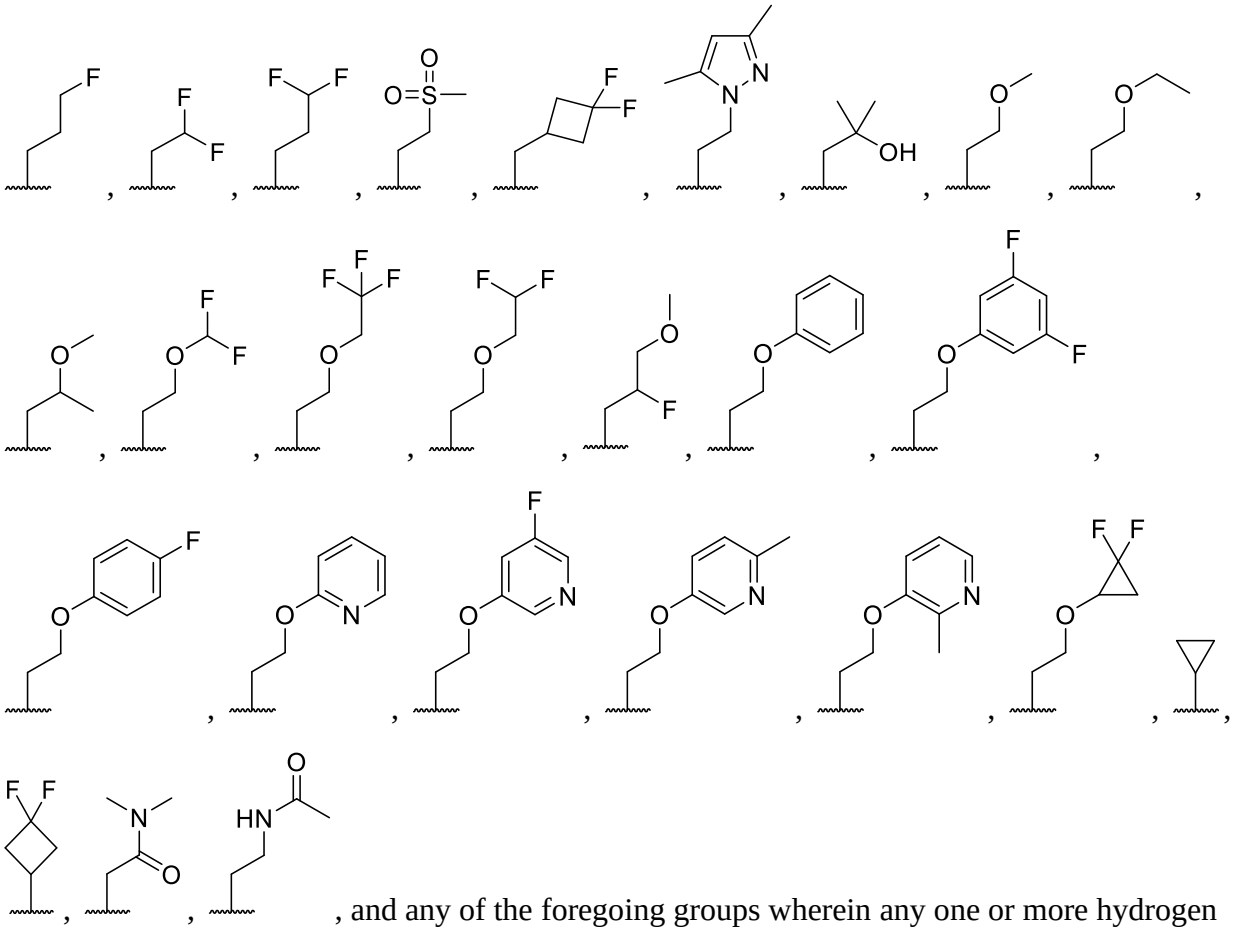
 ,  ,  ,  ,  , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s); or

wherein in the compound of Formula (II), or a salt thereof, R^1 is selected from the group consisting of  ,  ,  ,  ,  ,  ,

 ,  ,  , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s).

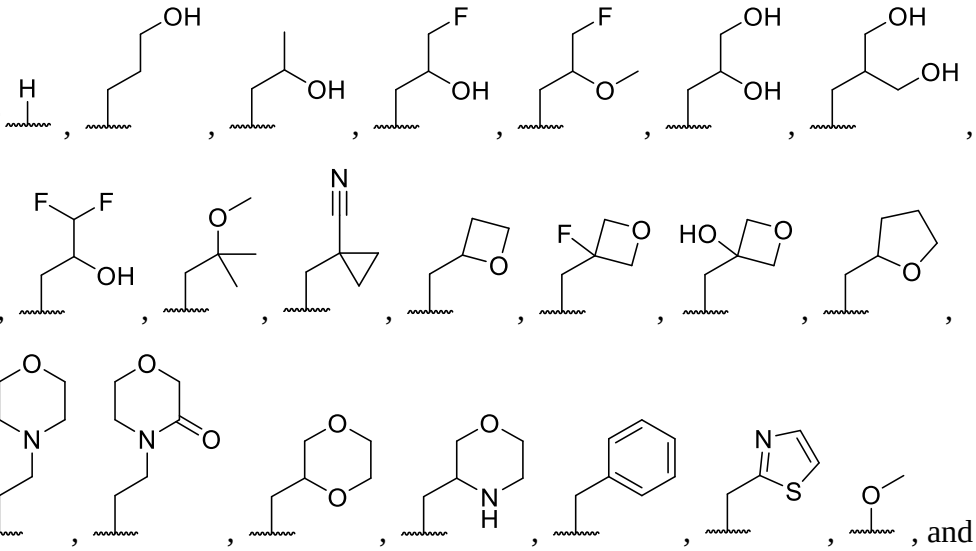
9. The use of any one of claims 1-4 or 8, wherein in the compound of Formula (II), or a salt thereof, R^2 is  , wherein n is 1, 2, 3, 4, 5, or 6, and R^3 is C_1-C_2 alkyl optionally substituted by fluoro; phenyl optionally substituted by fluoro; pyridinyl optionally substituted by fluoro or methyl; or cyclopropyl optionally substituted by fluoro; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is selected from the group consisting of



, and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s); or

wherein in the compound of Formula (II), or a salt thereof, R^2 is selected from the group consisting of



, and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s); or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_3-C_5 alkyl substituted by both fluorine and -OCH_3 ; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is phenyl optionally substituted by fluorine; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is pyridinyl optionally substituted by fluorine or methyl; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is halogen; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is deuterium; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 3- to 12-membered heterocyclyl optionally substituted by oxo; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 4- to 5-membered heterocyclyl optionally substituted by oxo; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is C_6-C_{14} aryl optionally substituted by halogen or –OR^6 ; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is phenyl optionally substituted by halogen or –OR^6 ; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is pyrazolyl optionally substituted by methyl; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is C_3-C_8 cycloalkyl optionally substituted by -CN, halogen, or –OR^6 ; or

wherein in the compound of Formula (II), or a salt thereof, R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is -$S(O)_2R^3$; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is pyridyl optionally substituted by R^{1a} ; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is indazolyl optionally substituted by R^{1a} ; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is 1*H*-pyrrolopyridyl optionally substituted by R^{1a} ; or

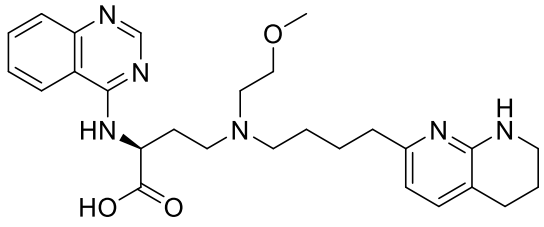
wherein in the compound of Formula (II), or a salt thereof, R^1 is quinolinyl optionally substituted by R^{1a} ; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is phenyl optionally substituted by R^{1a} ; or

wherein in the compound of Formula (II), or a salt thereof, R^1 is indanyl optionally substituted by R^{1a}.

10. The use of claim 1, wherein the compound of Formula (II), or a salt thereof, is selected from Compound Nos. 1-780.

11. The use of claim 1, wherein the compound of Formula (II), or a salt thereof, is (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid:



, or a salt thereof.

12. The use of any one of claims 1-11, wherein an amount in milligrams of about 1, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 150, 160, 175, 200, 225, 250, 320, 400, 480, 560, 640, 720, 800, 880, 960, or 1040, or a range between any two of the preceding values, of the compound of Formula (II) is to be administered; or
wherein the compound of Formula (II), or a salt thereof, is to be administered in an amount effective to produce a C_{max} in plasma of the subject in ng/mL of at least about one of 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, or 2500, or a range between any two of the preceding concentrations; or
the compound of Formula (II), or a salt thereof, is to be administered in an amount effective to produce a C_{max} in plasma of the subject in ng/mL, the C_{max} corresponding to a plasma-adjusted concentration effective to inhibit a percentage of $\alpha_V\beta_6$ or $\alpha_V\beta_1$ in the individual of at least about one of 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100, or a range between any two of the preceding percentages.

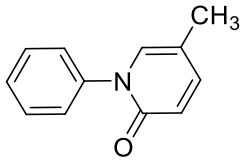
13. The use of any one of claims 1-12, wherein the compound of Formula (II) is to be administered one time, two times, three times, or four times daily.

14. The use of any one of claims 1-13, wherein the disease is a pulmonary disease, a fibrotic disease, or a pulmonary fibrotic disease.

15. The use of any one of claims 1-13, wherein the disease is selected from the group consisting of: idiopathic pulmonary fibrosis, an interstitial lung disease, radiation-induced pulmonary fibrosis, systemic scleroderma or systemic sclerosis associated interstitial lung disease, and nonspecific interstitial pneumonia.

16. The use of any one of claims 1-13, wherein the disease is idiopathic pulmonary fibrosis.

17. The use of any one of claims 1-16, wherein the second drug is pirfenidone, represented by:

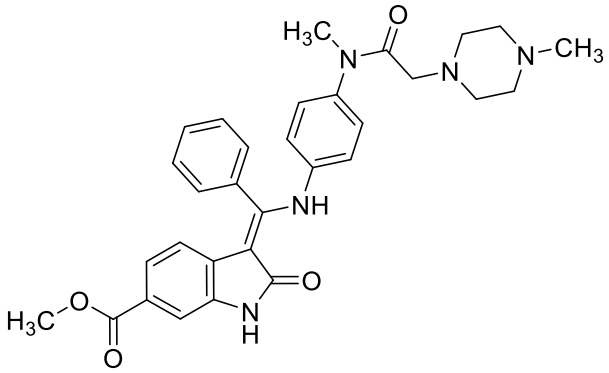


, or a salt thereof; or

the systematic chemical name 5-methyl-1phenyl-2-1(H)-pyridone, or a salt thereof.

18. The use of claim 17, whereinabout 267 mg, 534 mg, or 801 mg, or a range between any two of the preceding values, of pirfenidone is to be orally administered to the subject in a single administration event.

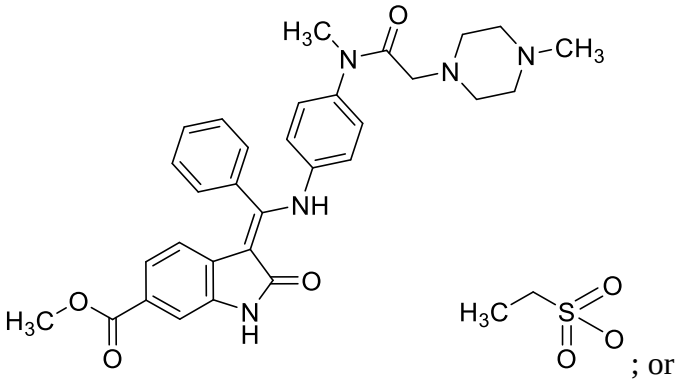
19. The use of any one of claims 1-16, wherein the second drug is nintedanib or a salt thereof, and is represented by:



, or a salt thereof; or

by the systematic chemical name 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone, or a salt thereof; or

by:



; or

by the systematic chemical name 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate.

20. The use of claim 19, wherein the nintedanib or a salt thereof is to be orally administered to the subject via at least one of a lipid dosage form and a capsule dosage form.

21. The use of claim 20, wherein at least one of:

the lipid dosage form is characterized by an amount of the nintedanib or salt thereof equivalent to, or equivalent to about, 100 mg or 150 mg of nintedanib, or a range between about 100 mg to about 150 mg of nintedanib; or

about, 100 mg or 150 mg of nintedanib, or a range between about 100 mg to about 150 mg of nintedanib, or salt thereof is to be orally administered to the subject via the lipid dosage form in a single administration event; or

the lipid dosage form is characterized by an amount of nintedanib ethane sulfonate of, or of about 120.40 mg or 180.60 mg, or a range between about 120.40 mg to about 180.60 mg of nintedanib ethane sulfonate, respectively equivalent to, or equivalent to about, 100 mg or 150 mg of nintedanib, or a range between about 100 mg to about 150 mg of nintedanib; or

an amount per capsule of nintedanib ethane sulfonate of, or of about 120.40 mg or 180.60 mg, or a range between about 120.40 mg to about 180.60 mg of nintedanib ethane sulfonate, respectively equivalent to, or equivalent to about, 100 mg or 150 mg of nintedanib, or a range between about 100 mg to about 150 mg of nintedanib, or salt thereof, is to be orally administered to the subject via the lipid dosage form in a single administration event; or

an amount per capsule of the nintedanib or salt thereof equivalent to, or equivalent to about, 100 mg or 150 mg of nintedanib, or a range between about 100 mg to about 150 mg of nintedanib, or salt thereof, is to be orally administered to the subject via the capsule dosage form; or

about, 100 mg or 150 mg of nintedanib, or a range between about 100 mg to about 150 mg of nintedanib, or salt thereof, is to be orally administered to the subject via the capsule dosage form in a single administration event; or

an amount per capsule of nintedanib ethane sulfonate of, or of about 120.40 mg or 180.60 mg, or a range between about 120.40 mg to about 180.60 mg of nintedanib ethane sulfonate, respectively equivalent to, or equivalent to about, 100 mg or 150 mg of nintedanib, or a range between about 100 mg to about 150 mg of nintedanib, or salt thereof, is to be orally administered to the subject via the capsule dosage form; or

an amount per capsule of nintedanib ethane sulfonate of, or of about 120.40 mg or 180.60 mg, or a range between about 120.40 mg to about 180.60 mg of nintedanib ethane sulfonate, respectively equivalent to, or equivalent to about, 100 mg or 150 mg of nintedanib, or a range between about 100 mg to about 150 mg of nintedanib, or salt thereof, is to be orally administered to the subject via the capsule dosage form in a single administration event.

22. The use of claim 21, wherein the capsule shell of the capsule dosage form comprises 1, 2, 3, 4, 5, or 6 of: gelatin, glycerol, titanium dioxide, red ferric oxide, yellow ferric oxide, and black ink.

23. The use of any one of claims 1-16 or 19-22, wherein the second drug is nintedanib or a salt thereof and is to be administered to the subject twice daily in a dosage of the nintedanib or a salt thereof equivalent to, or equivalent to about, 100 mg of nintedanib, for a total daily dose equivalent to, or equivalent to about, 200 mg of nintedanib; or
the second drug is nintedanib or a salt thereof and is to be administered to the subject twice daily in a dosage of the nintedanib or a salt thereof equivalent to, or equivalent to about, 150 mg of nintedanib, for a total daily dose equivalent to, or equivalent to about, 300 mg of nintedanib.

24. The use of any one of claims 1-23, wherein the disease is an interstitial lung disease including chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.

25. The use of any one of claims 1-23, wherein the disease includes systemic sclerosis-associated interstitial lung disease, and treating the subject includes slowing the rate of decline in pulmonary function in the subject associated with the systemic sclerosis-associated interstitial lung disease.

26. The use of any one of claims 1-25, wherein the first drug is effective to modulate at least one integrin in the subject.

27. The use of any one of claims 1-25, wherein the subject has at least one tissue in need of therapy and the tissue has at least one elevated level of:

at least one integrin activity and/or expression;
a pSMAD/SMAD value;
new collagen formation or accumulation;
total collagen; and
Type I Collagen gene Col1a1 expression;

and wherein the level is elevated compared to a healthy state of the tissue.

28. The use of claim 26 or claim 27, wherein the first drug is effective to inhibit the at least one integrin in the subject; or
wherein the at least one integrin in the subject comprises α_V; or
wherein the at least one integrin in the subject is selected from the group consisting of $\alpha_V\beta_6$ integrin and $\alpha_V\beta_1$ integrin; or

wherein the at least one integrin in the subject comprises both $\alpha_V\beta_6$ integrin and $\alpha_V\beta_1$ integrin; or
wherein the first drug is effective to inhibit one or both of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin in the subject; or
wherein the use selectively reduces $\alpha_V\beta_1$ integrin activity and/or expression compared to $\alpha_V\beta_6$ integrin activity and/or expression in the subject; or
wherein the use selectively reduces $\alpha_V\beta_6$ integrin activity and/or expression compared to $\alpha_V\beta_1$ integrin activity and/or expression in the subject; or
wherein the use reduces both $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin activity and/or expression compared to at least one other α_V-containing integrin in the subject; or
wherein the activity of $\alpha_V\beta_1$ integrin in one or more fibroblasts is reduced in the subject; or
wherein the activity of $\alpha_V\beta_6$ integrin in one or more epithelial cells is reduced in the subject; or
wherein the at least one tissue in the subject comprises one or more of: lung tissue, liver tissue, skin tissue, cardiac tissue, kidney tissue, gastrointestinal tissue, gall bladder tissue, and bile duct tissue; or
wherein the tissue has an elevated pSMAD2/SMAD2 value or an elevated pSMAD3/SMAD3 value compared to the healthy state of the tissue.

29. The use of any one of claims 1-28, wherein the first drug and/or the second drug are to be administered orally to the subject; or
wherein the first drug and/or the second drug are to be administered to the subject with food; or
wherein the first drug and the second drug are to be administered to the subject at the same time or on a same schedule; or
wherein the first drug and the second drug are to be administered to the subject at different times or on a different schedule; or
wherein the second drug is to be administered to the subject over a period of days, weeks, months, or years before the first drug is to be administered to the subject; or
wherein after the first and second drugs is to be administered to the subject over a period of days, weeks, months, or years, the dose of the second drug is to be decreased in amount or frequency; or
wherein after the first and second drugs is to be administered to the subject over a period of days, weeks, months, or years, the second drug is discontinued; or

wherein the second drug is to be decreased in amount or frequency or is discontinued after the subject experiences a stabilization, improvement, or remission in the disease.

30. The use of any of claims 1-29, wherein the subject is human.