[0012] The αvβ6 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 αvβ6 is elevated in liver and bile duct of PSC patients.

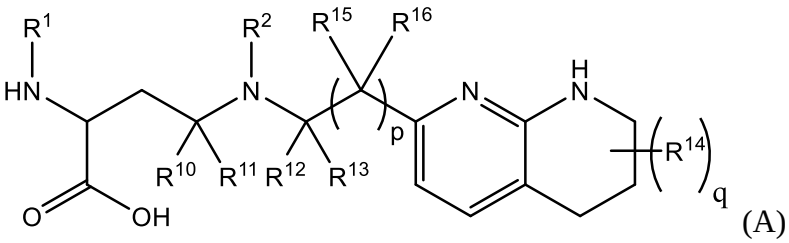
[0014] The present disclosure provides for αvβ6 integrin inhibitors that may be useful for treatment of fibrosis.

BRIEF SUMMARY

[0014a] In an aspect of the present disclosure, there is provided a dosage form configured for daily administration, comprising:

a pharmaceutically acceptable carrier or excipient; and

a unit dose of a compound of formula (A)



(A)

or a salt thereof, wherein:

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;

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;

each R^{10}, R^{11}, R^{12} and R^{13} are independently hydrogen or deuterium;

R^{14} is deuterium;

q is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

each R^{15} is independently selected from hydrogen, deuterium, or halogen;

each R^{16} is independently selected from hydrogen, deuterium, or halogen; and

p is 3, 4, 5, 6, 7, 8, or 9.

[0014b] In another aspect of the present disclosure, there is provided a dosage form configured for daily administration, comprising a pharmaceutically acceptable carrier or excipient and a unit dose of a compound, selected from Compound Nos. 1-780 in **FIG. 1**.

[0014c] In a further aspect of the present disclosure, there is provided a dosage form disclosed herein, for use in treating a fibrotic disease in an individual in need thereof, wherein the dosage form is to be administered to the individual.

[0014d] In another aspect of the present disclosure, thereis provided a use of a dosage form disclosed herein, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof, wherein the dosage form is to be administered to the individual.

[0014e] In a further aspect of the present disclosure, there is provided a kit comprising a dosage form disclosed herein, wherein the kit optionally comprises one or more of the following:

(i) instructions for the treatment of a fibrotic disease;

(ii) instructions for daily administration of the dosage form to an individual in need thereof;

(iii) instructions for administration of the dosage form to an individual in need thereof one, two, three, or four times daily;

(iv) instructions for administration of the dosage form to an individual in need thereof to produce a C_{max} in plasma of the individual 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, or 1500 or a range between any two of the preceding concentrations; or

(v) instructions for administration of the dosage form to an individual in need thereof to produce a C_{max} in ng/mL in plasma of the individual, 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.

[0014f] In another aspect of the present disclosure, there is provided a use of a dosage form disclosed herein, in the manufacture of a medicament for inhibiting $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin in an individual, wherein the dosage form is to be administered to the individual.

[0014g] In a further aspect of the present disclosure, there is provided a dosage form disclosed herein for use in inhibiting TGFβ activation in a cell, wherein the dosage form is to be administered to the cell.

[0014h] In another aspect of the present disclosure, there is provided a use of a dosage form disclosed herein, in the manufacture of a medicament for inhibiting $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin, wherein an effective amount of the dosage form is to be administered to an individual in need thereof to inhibit the $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin.

[0014i] In a further aspect of the present disclosure, there is provided a use of a dosage form disclosed herein, in the manufacture of a medicament for modulating the activity of at least one integrin in a subject in need thereof, wherein an effective amount of the dosage form is to be administered to the subject to modulate the activity of the at least one integrin in the subject, the at least one integrin including at least one of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin.

[0014j] In another aspect of the present disclosure, there is provided a use of a dosage form disclosed herein, in the manufacture of a medicament for treating a subject in need thereof, wherein a therapeutically effective amount of the dosage form is to be administered to the subject, wherein the subject has at least one tissue in need of therapy and the tissue has at least one elevated level of:

$\alpha_V\beta_1$ integrin activity and/or expression;
$\alpha_V\beta_6$ 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.

[0014k] In a further aspect of the present disclosure, there is provided a use of a dosage form disclosed herein, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound in mg of about one of: 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, 175,

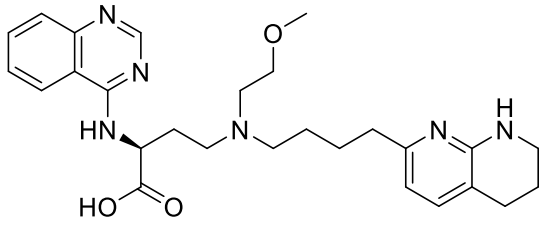
200, 225, or 250, or a range between any two of the preceding amounts is to be administered to the individual.

[0014l] In another aspect of the present disclosure, there is provided a use of a dosage form disclosed herein, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound effective to produce a C_{max} in plasma of the individual 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, or 1500, or a range between any two of the preceding concentrations is to the administered to the individual.

[0014m] In a further aspect of the present disclosure, there is provided a use of a dosage form disclosed herein, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof, wherein an amount of the compoundeffective to produce a C_{max} in ng/mL in plasma of the subject, the C_{max} corresponding to a plasma-adjusted concentration effective to inhibit a percentage of each of $\alpha_V\beta_6$ and/or $\alpha_V\beta_1$ in the subject, each percentage independently selected from 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 is to be administered to the individual.

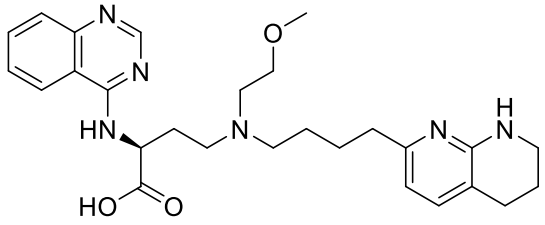
[0014n] In another aspect of the present disclosure, thereis provided a use of the dosage form disclosed herein in the manufacture of a medicament for the treatment of a fibrotic disease in an individual in need thereof, wherein the dosage form is to be administered daily to the individual.

[0014o] In a further aspect of the present disclosure, there is provided a dosage form disclosed herein, wherein the compound 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, for use in the treatment of a fibrotic disease.

[0014p] In another aspect of the present disclosure, there is provided a use of the dosage form disclosed herein, wherein the compound 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, in the manufacture of a medicament for the treatment of a fibrotic disease.

[0014q] In a further aspect of the present disclosure, there is provided a dosage form disclosed herein,

for use in inhibiting $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin in an individual, wherein the dosage form is to be administered to the individual; or

for use in inhibiting $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin, wherein an effective amount of the dosage form is to be administered to an individual in need thereof to inhibit the $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin; or

for use in modulating the activity of at least one integrin in a subject in need thereof, wherein an effective amount of the dosage form is to be administered to the subject to modulate the activity of the at least one integrin in the subject, the at least one integrin including at least one of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin; or

for use in treating a subject in need thereof, wherein a therapeutically effective amount of the dosage form is to be administered to the subject, wherein the subject has at least one tissue in need of therapy and the tissue has at least one elevated level of: $\alpha_V\beta_1$ integrin activity and/or expression; $\alpha_V\beta_6$ 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; or

for use in treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound in mg of about one of: 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, 175, 200, 225, or 250, or a range between any two of the preceding amounts is to be administered to the individual; or

for use in treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound effective to produce a C_{max} in plasma of the individual 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, or 1500, or a range between any two of the preceding concentrations is to the administered to the individual; or

for use in treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound effective to produce a C_{max} in ng/mL in plasma of the subject, the C_{max} corresponding to a plasma-adjusted concentration effective to inhibit a percentage of each of

$\alpha_V\beta_6$ and/or $\alpha_V\beta_1$ in the subject, each percentage independently selected from 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 is to be administered to the individual; or

for use in treating a fibrotic disease in an individual in need thereof, wherein the dosage form is to be administered daily to the individual.

[0015] Disclosed are amino acid compounds that are αvβ6 integrin inhibitors, compositions containing these compounds and methods for treating diseases mediated by αvβ6 integrin such as a fibrotic disease.

[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.

BRIEF DESCRIPTION OF THE FIGURES

[0032] **FIG. 1** shows compounds 1-780 as disclosed herein.

[0033] **FIG. 2** shows Table B-3, with biological data for various compounds disclosed herein.

[0034] **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.

[0035] **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.

[0036] **FIG. 4A** is a graph of PSMAD3/SMAD3 in lung tissue from healthy mice administered PBS vehicle and varying levels of compound 5 for 4 days.

[0037] **FIG. 4B** is a graph of PSMAD3/SMAD3 in BALF drawn from the same healthy mice administered PBS vehicle and varying levels of compound 5 for 4 days.

[0038] **FIG. 4C** is a graph showing that compared to the healthy mice, lung tissue in the vehicle-treated mice experienced a substantial increase in SMAD3 phosphorylation.

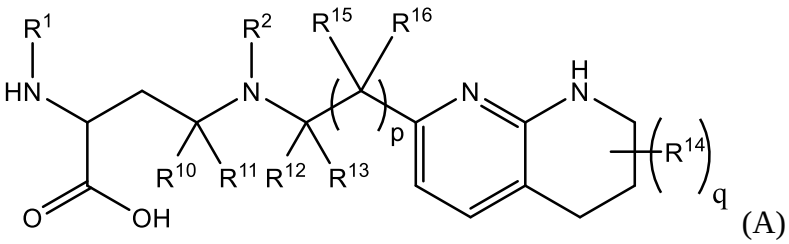
[0039] **FIG. 4D** is a graph showing that compared to the healthy mice, lung tissue in the vehicle-treated mice experienced a substantial accumulation of new collagen as evidenced by the percentage of lung collagen containing ^2H-labeled hydroxyproline.

[0040] **FIG. 4E** shows that compared to the healthy mice, the vehicle-treated mice experienced a significant increase in total pulmonary collagen, as measured by μg of hydroxyproline.

CLAIMS

What is claimed as new and desired to be protected is:

1. A dosage form configured for daily administration, comprising:
a pharmaceutically acceptable carrier or excipient; and
a unit dose of a compound of formula (A)



(A)

or a salt thereof, wherein:

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;

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;

each R^{10}, R^{11}, R^{12} and R^{13} are independently hydrogen or deuterium;

R^{14} is deuterium;

q is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

each R^{15} is independently selected from hydrogen, deuterium, or halogen;

each R^{16} is independently selected from hydrogen, deuterium, or halogen; and

p is 3, 4, 5, 6, 7, 8, or 9.

2. The dosage form of claim 1, wherein:

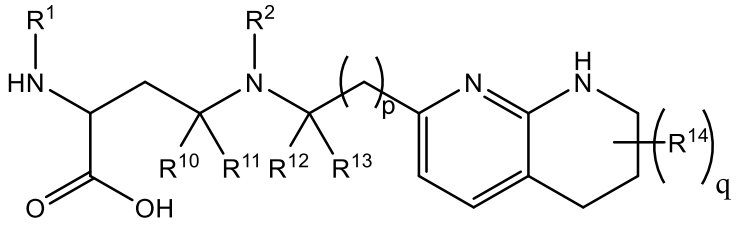
R^2 is C_1-C_6 alkyl optionally substituted by R^{2a}; C_3-C_6 cycloalkyl optionally substituted by R^{2b}; 3- to 12-membered heterocyclyl optionally substituted by R^{2c}; or $-S(O)_2R^{2d}$;

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 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^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;

each R^{15} is hydrogen; and

each R^{16} is hydrogen;

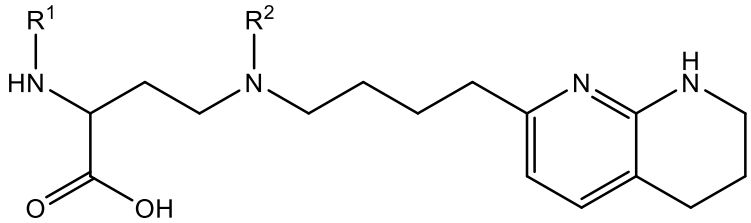
and wherein the compound of formula (A) is represented by Formula (I):



(I).

3. The dosage form of claim 1 or claim 2, wherein at least one of R^{1a}, R^{2a}, R^{2b}, R^{2c}, R^{2e}, R^{2f}, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, or R^{13} is deuterium.

4. The dosage form of claim 1 or claim 2, wherein R^{10}, R^{11}, R^{12}, and R^{13} are hydrogen; p is 3; q is 0; and wherein the compound of formula (A) is represented by formula (II):



(II).

5. The dosage form of any one of claims 1-4,

wherein:

R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a};

or wherein

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 wherein

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 wherein

R^1 is pyrimidin-4-yl optionally substituted by R^{1a};

or wherein

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 wherein

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

or wherein

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

or wherein

R^1 is quinazolin-4-yl optionally substituted by R^{1a};

or wherein

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

R^1 is quinazolin-4-yl optionally substituted by fluoro, chloro, methyl, trifluoromethyl or methoxy.

6. The dosage form of any one of claims 1, 3, 4 or 5, wherein

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

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;

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

7. The dosage form of any one of claims 1-5, wherein R^2 is:

(i) C_1-C_6 alkyl optionally substituted by R^{2a};

optionally 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 optionally wherein R^{2a} is: fluoro; cyclobutyl substituted by fluoro; pyrazolyl substituted by methyl; or $-S(O)_2CH_3$;

(ii) C_1-C_6 alkyl optionally substituted by $-OR^3$;

optionally wherein 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 optionally wherein 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;

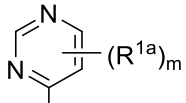
(iii) –$CH_2CH_2OCH_3$;

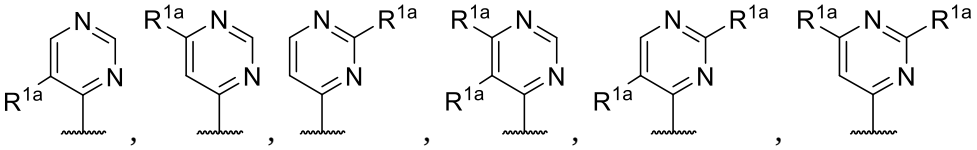
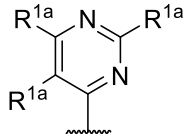
(iv) R^2 is C_1-C_6 alkyl substituted by both halogen and OR^3, wherein R^3 is C_1-C_6 alkyl;.

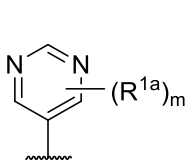
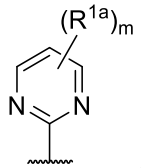
(v) R^2 is C_3-C_6 cycloalkyl optionally substituted by R^{2b}; or

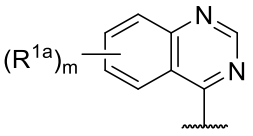
(vi) R^2 is cyclopropyl.

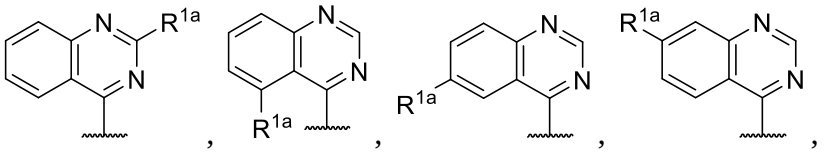
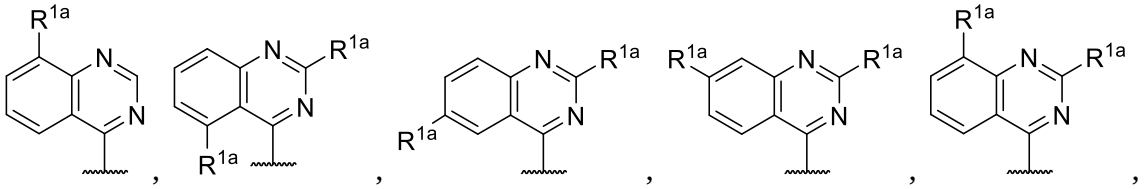
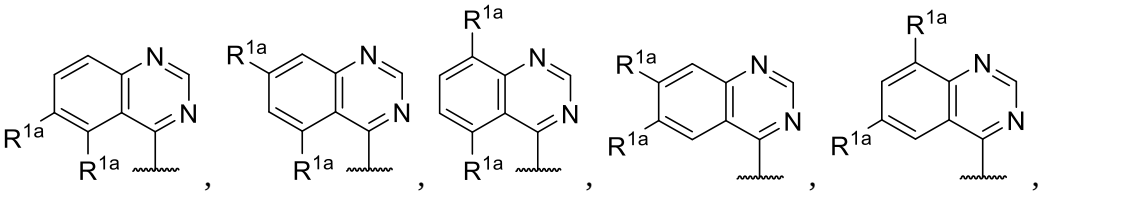
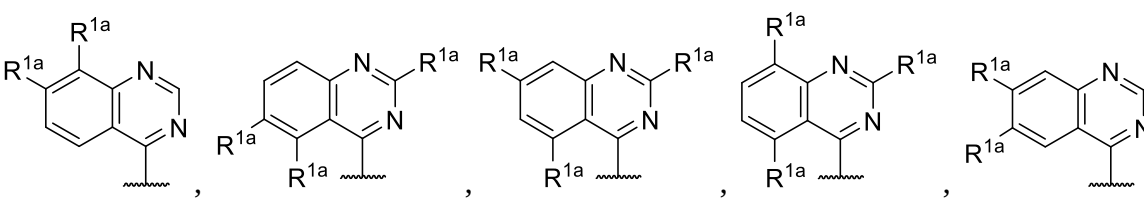
8. The dosage form of any one of claims 1-4, wherein

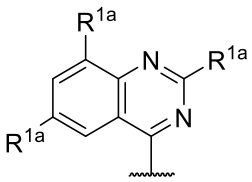
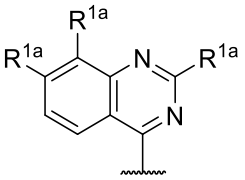
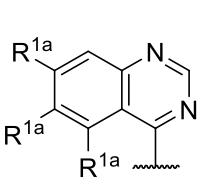
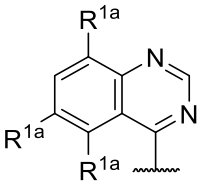
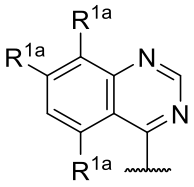
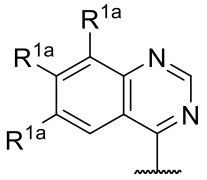
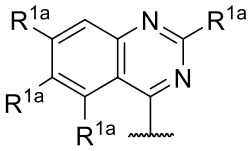
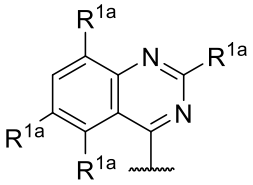
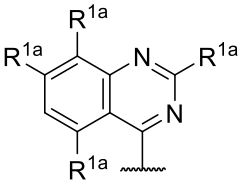
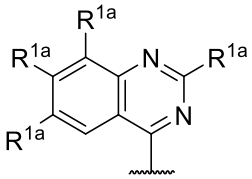
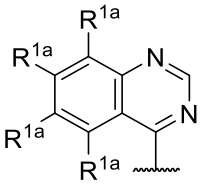
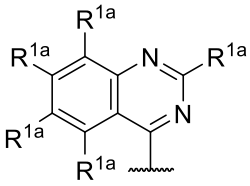
(a) R^1 is , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium;

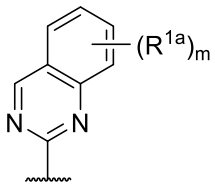
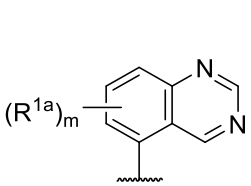
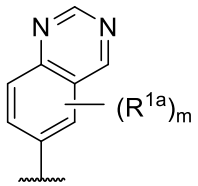
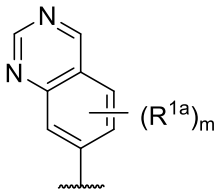
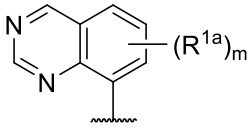
(b) R^1 is , or , wherein each R^{1a} is independently deuterium, alkyl, haloalkyl, or heteroaryl;

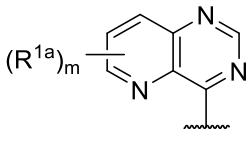
(c) R^1 is  or , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium;

(d) 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;

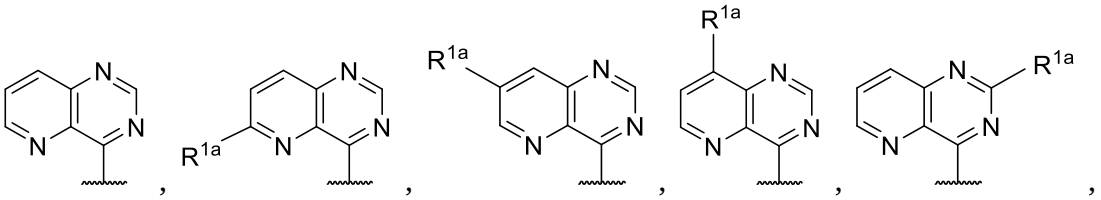
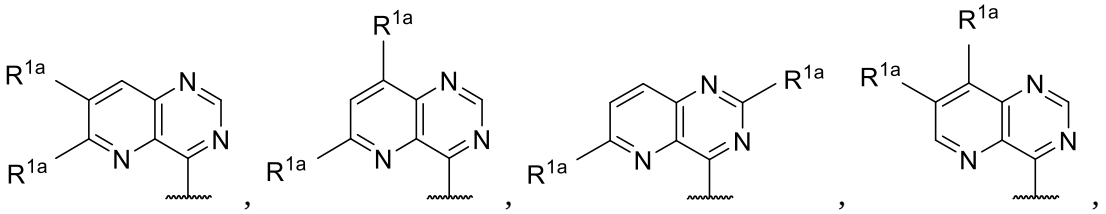
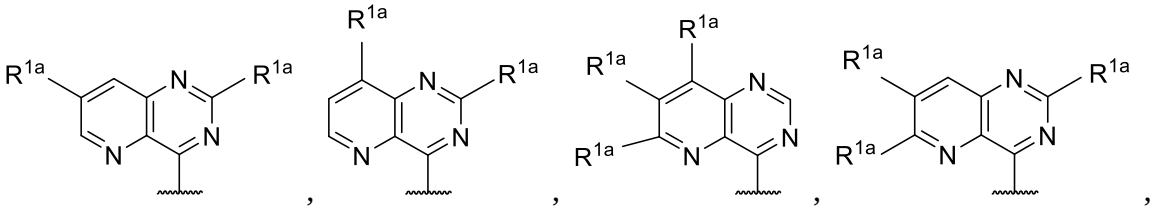
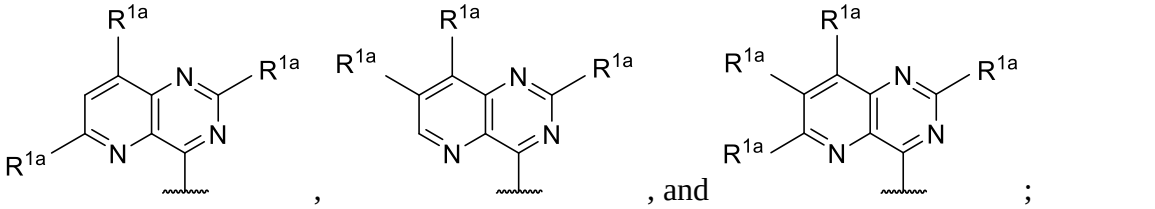
optionally wherein R^1 is , , , , .

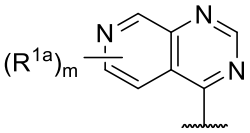

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, or

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

(e) R^1 is

,

,

,

, or

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;

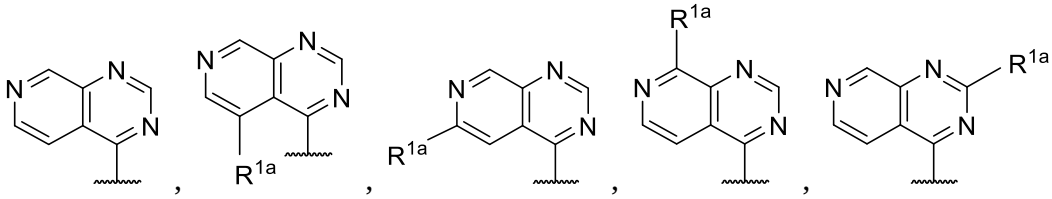
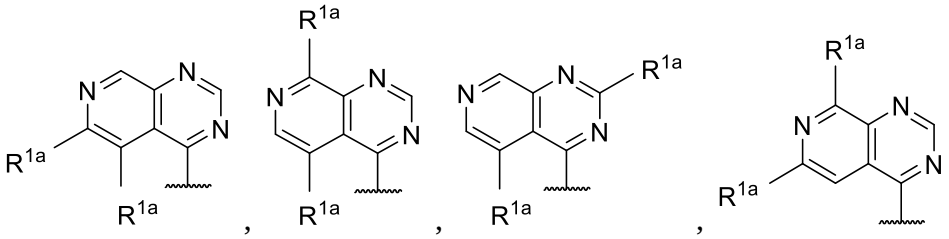
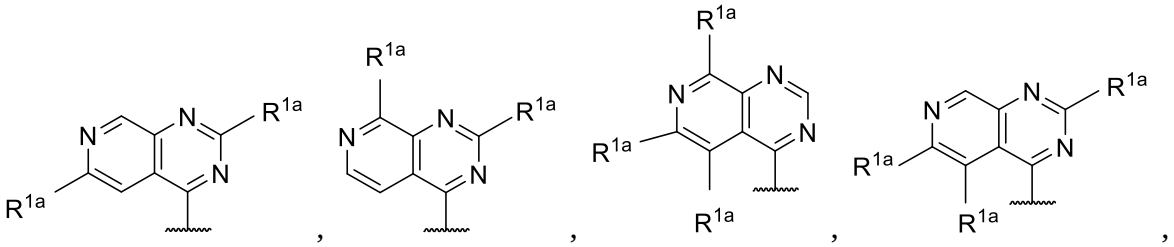
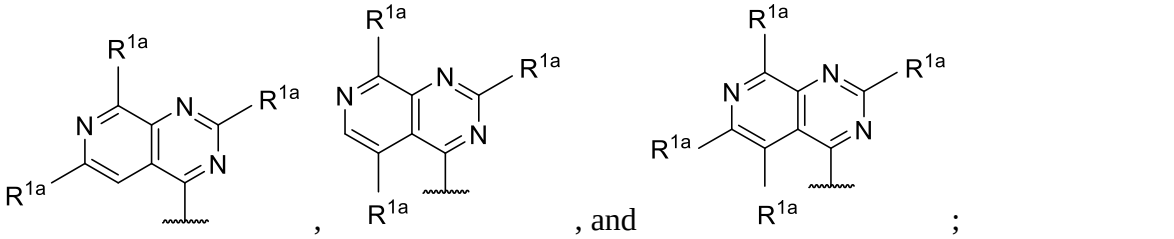
(f) R^1 is

, 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;

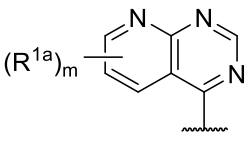
optionally wherein R^1 is selected from the group consisting of

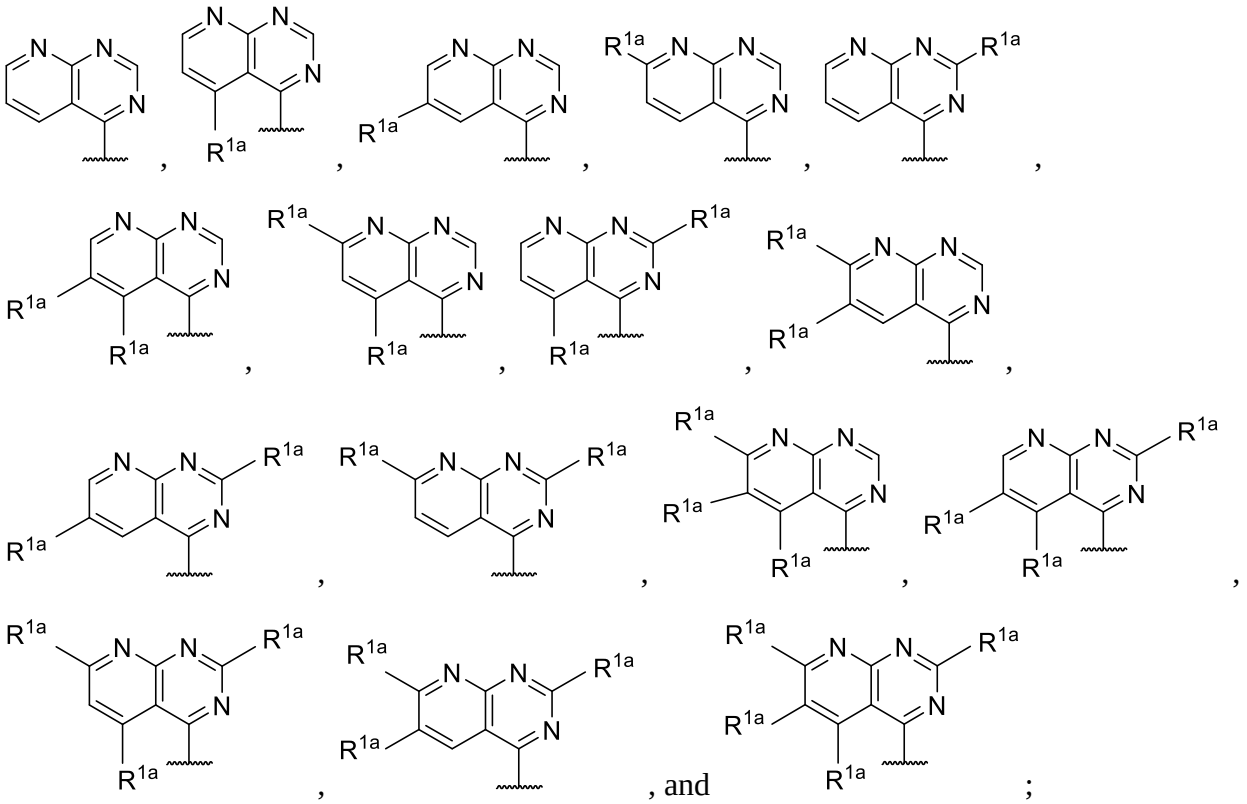
(g) R^1 is , wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium;

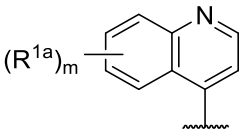
optionally wherein R^1 is selected from the group consisting of

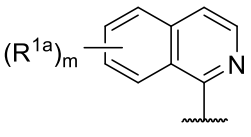




, and ;

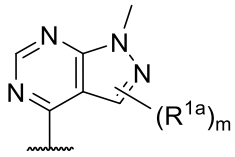
(h) R^1 is , wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium;

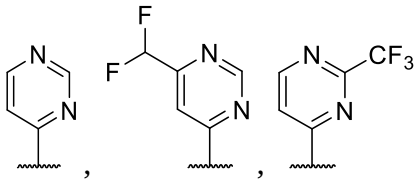
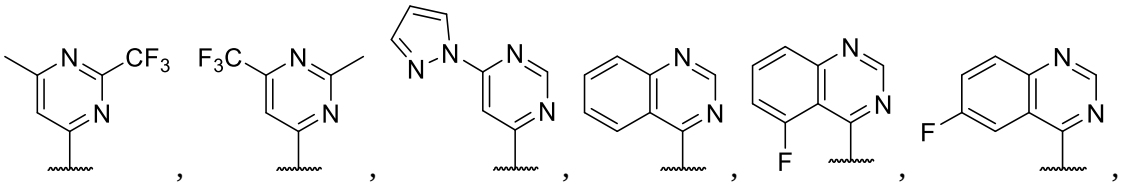
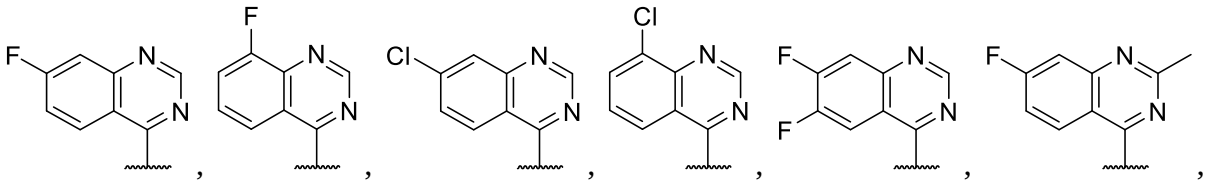
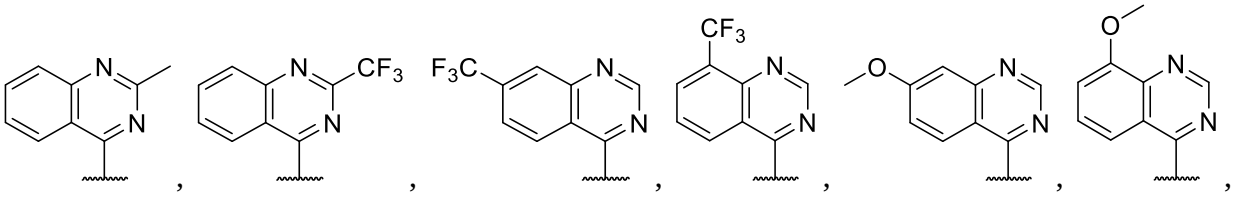
optionally wherein R^1 is selected from the group consisting of

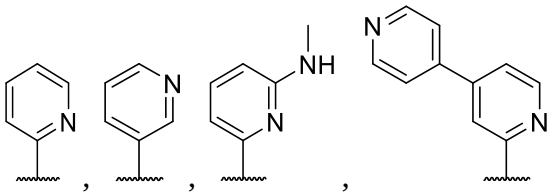
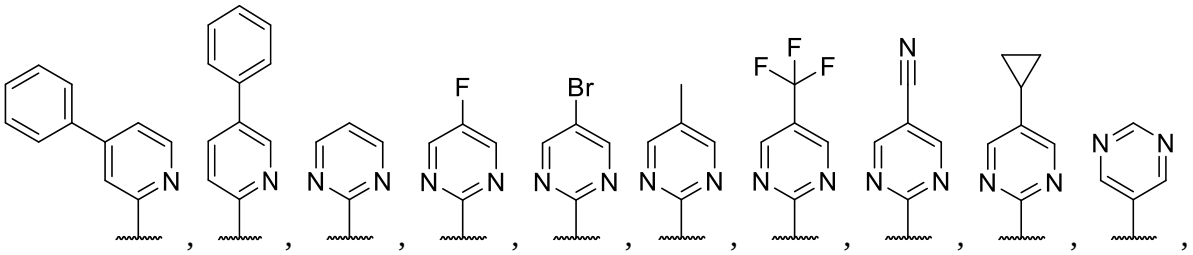
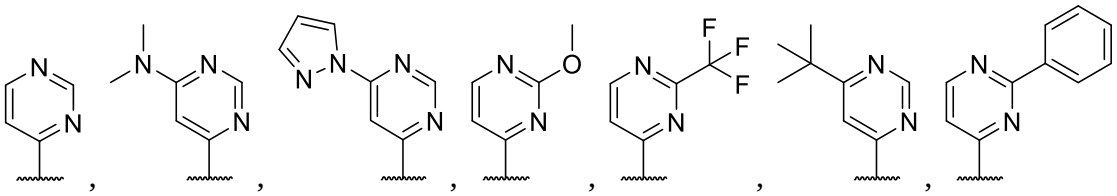
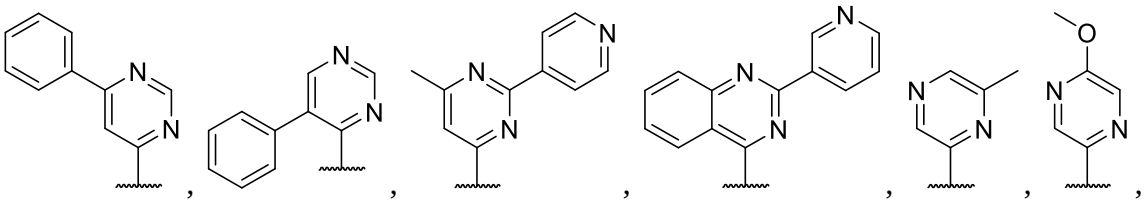
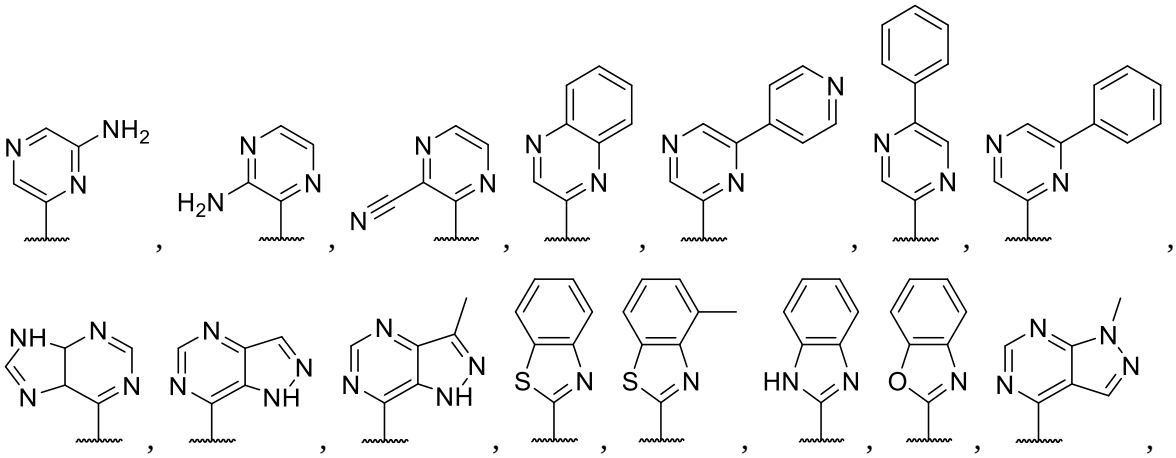


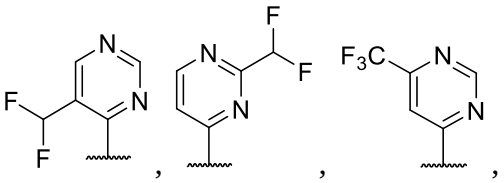
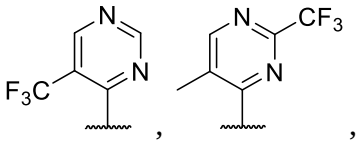
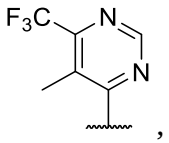
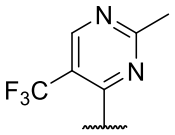
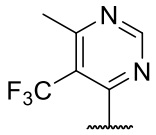
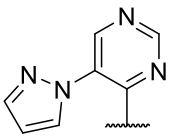
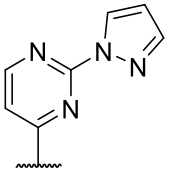
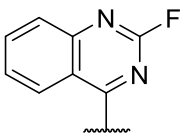
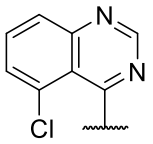
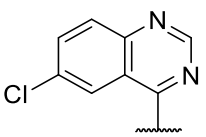
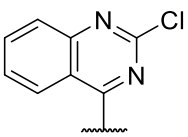
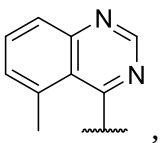
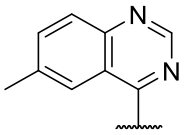
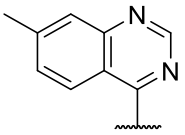
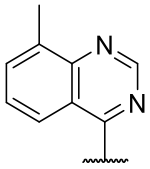
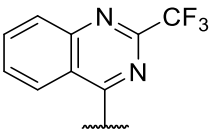
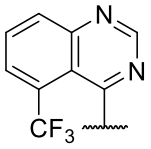
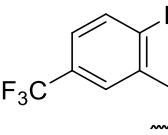
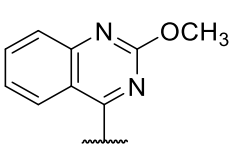
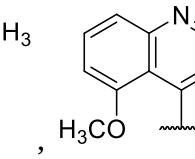
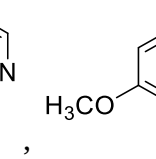
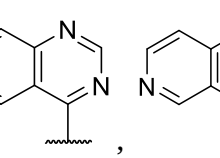
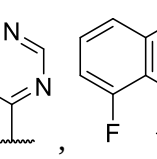
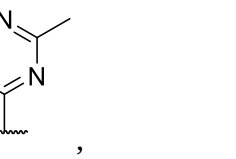
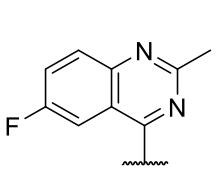
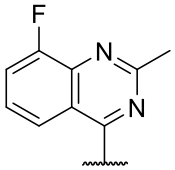
(i) R^1 is , wherein m is 0, 1, 2, 3, 4, 5, or 6 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium;

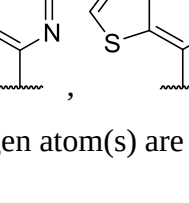
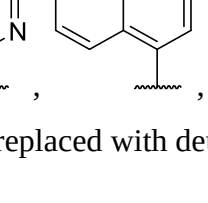
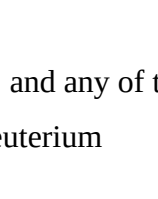
(j) R^1 is , wherein m is 0, 1, 2, 3, 4, 5, or 6 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium;

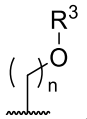
(k) R^1 is , wherein m is 0, 1, or 2 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium;

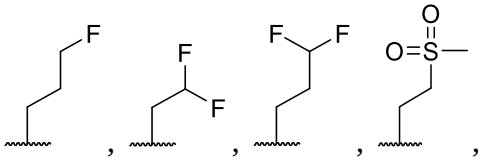
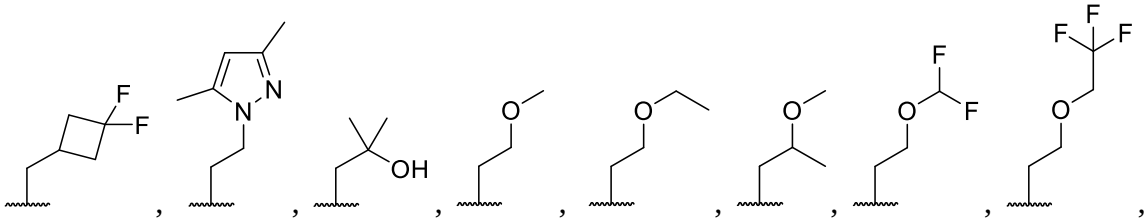
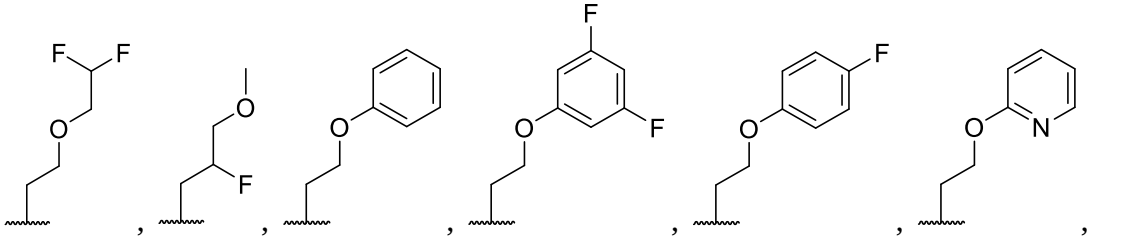
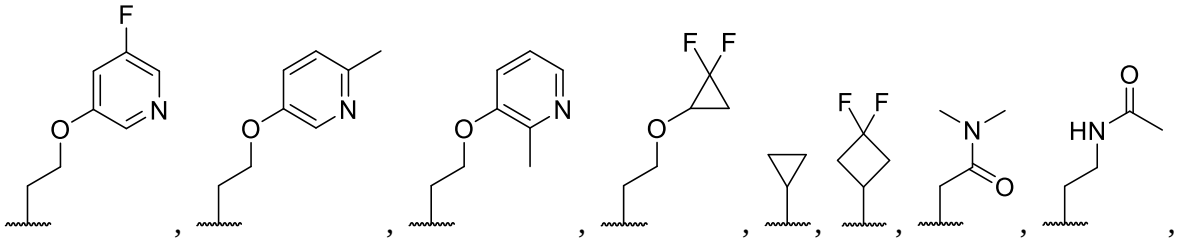
(l) R^1 is selected from the group consisting of , , , , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s);

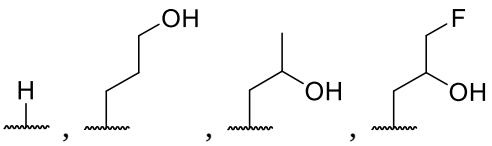
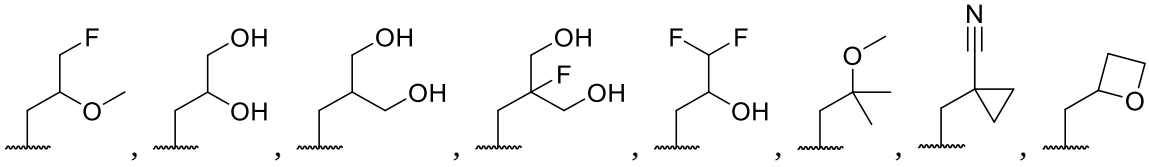
(m) R^1 is selected from the group consisting of , , , , , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s);

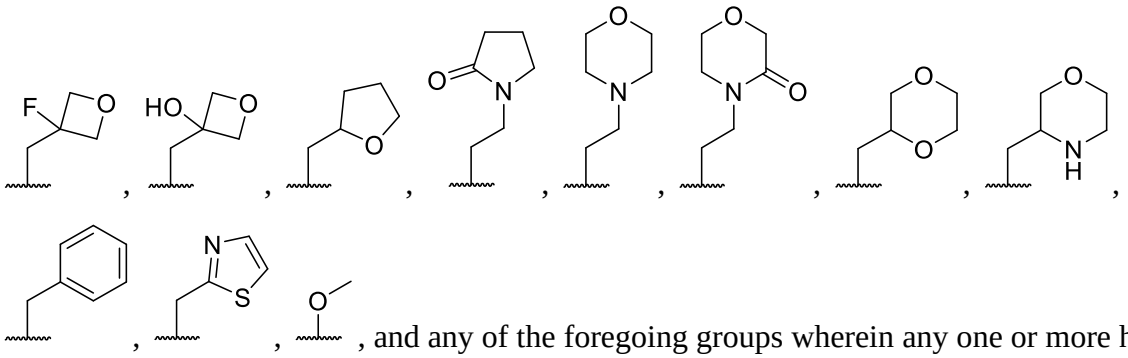
(n) R^1 is selected from the group consisting of , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s); or

(o) 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 dosage form of any one of claims 1 to 5 or 8, wherein 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 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 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 R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is phenyl optionally substituted by fluorine;

or wherein R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, where R^3 is pyridinyl optionally substituted by fluorine or methyl;

or wherein R^2 isC_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is halogen; or

(ii) C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is deuterium; or

(iii) C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 3- to 12-membered heterocyclyl optionally substituted by oxo; or

(iv) C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 4- to 5-membered heterocyclyl optionally substituted by oxo; or

(v) 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

(vi) C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is phenyl optionally substituted by halogen or –OR^6; or

(vii) 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

(viii) C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is pyrazolyl optionally substituted by methyl; or

(ix) 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

(x) C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is -$S(O)_2R^3$.

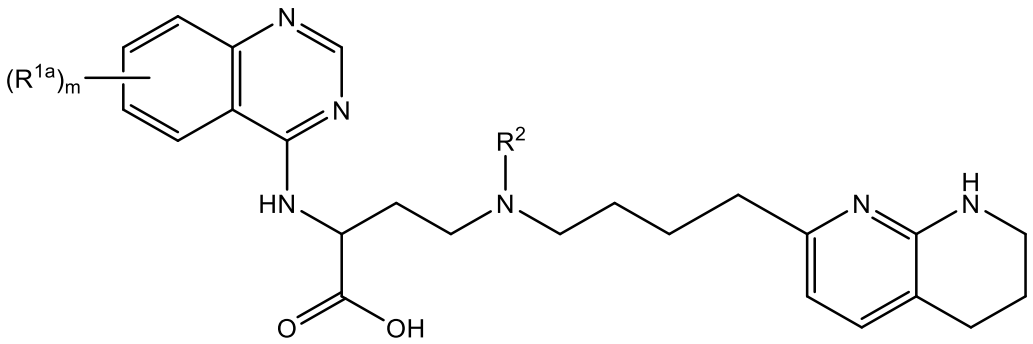
10. The dosage form of any one of claims 1-4,

wherein R1 is pyridyl optionally substituted by R^{1a}; or

wherein R1 is indazolyl optionally substituted by R^{1a}; or
wherein R1 is 1H-pyrrolopyridyl optionally substituted by R^{1a}; or
wherein R1 is quinolinyl optionally substituted by R^{1a}; or
wherein R1 is phenyl optionally substituted by R^{1a}; or
wherein R^1 is indanyl optionally substituted by R^{1a}.

11. A dosage form configured for daily administration, comprising a pharmaceutically acceptable carrier or excipient and a unit dose of a compound, selected from Compound Nos. 1-780 in **FIG. 1**.

12. The dosage form of claim 1, wherein the compound of formula (A) is represented by formula (II-B):



(II-B),

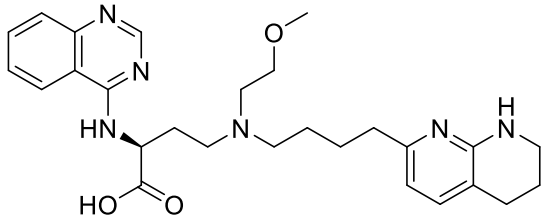
where m is 0, 1, 2, 3, 4, or 5.

13. The dosage form of claim 1, wherein the compound of formula (A) is selected from:
(S)-2-((7-fluoroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;
(S)-2-((7-fluoro-2-methylquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;
(S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((8-(trifluoromethyl)quinazolin-4-yl)amino)butanoic acid;
(S)-2-((6-fluoroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

(S)-2-((6,7-difluoroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;
(S)-2-((7-fluoro-2-methylquinazolin-4-yl)amino)-4-((2-(4-fluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;
(2S)-4-((2-(2,2-difluorocyclopropoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((7-fluoro-2-methylquinazolin-4-yl)amino)butanoic acid;
(S)-4-(((S)-3-fluoro-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-methylquinazolin-4-yl)amino)butanoic acid;
(S)-2-((8-fluoroquinazolin-4-yl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;
(S)-2-((7-fluoroquinazolin-4-yl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;
(S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((8-methylquinazolin-4-yl)amino)butanoic acid;
(S)-2-((7,8-difluoroquinazolin-4-yl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;
(S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;
(S)-4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;
(S)-4-((2-(3,5-difluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;
(S)-4-((2-(pyridin-2-yloxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;
(S)-4-((2-(2,2-difluoroethoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;
(S)-4-((2-((6-methylpyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;
(S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;
(S)-4-((2-hydroxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

(S)-4-(((R)-2-hydroxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid; and
(S)-4-(((S)-2,3-dihydroxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid,
or a pharmaceutically acceptable salt thereof.

14. The dosage form of claim 1, wherein the compound 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 pharmaceutically acceptable salt thereof.

15. The dosage form of any one of claims 1-14, comprising an amount of the compound in mg of about one of: 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, 175, 200, 225, or 250, or a range between any two of the preceding amounts.

16. The dosage form of any one of claims 1-14, comprising the compound in an amount effective on administration to an individual to produce a C_{max} in plasma of the individual 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, or 1500, or a range between any two of the preceding concentrations.

17. The dosage form of any one of claims 1-14, comprising the compound in an amount effective on administration to an individual to produce a C_{max} in ng/mL in plasma of the individual, 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.

18. The dosage form of any one of claims 1-17, for use in treating a fibrotic disease in an individual in need thereof, wherein the dosage form is to be administered to the individual.

19. Use of a dosage form of any one of claims 1-17, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof, wherein the dosage form is to be administered to the individual.

20. The dosage form for use of claim 18, or the use of claim 19, wherein the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis, cardiac fibrosis, kidney fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis.

21. The dosage form for use, or the use of any one of claims 18-20, wherein the dosage form is to be administered one time, two times, three times, or four times daily.

22. The dosage form for use of claim 18, or the use of claim 19, wherein the dosage form administered to the individual is effective to produce a C_{max} of the compound in plasma of the individual 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, or 1500, or a range between any two of the preceding concentrations.

23. The dosage form for use of claim 18, or the use of claim 19, wherein the dosage form administered to the individual is effective to produce a C_{max} in ng/mL in plasma of the individual, 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.

24. A kit comprising a dosage form of any one of claims 1 to 14, wherein the kit optionally comprises one or more of the following:

(i) instructions for the treatment of a fibrotic disease;

(ii) instructions for daily administration of the dosage form to an individual in need thereof;

(iii) instructions for administration of the dosage form to an individual in need thereof one, two, three, or four times daily;

(iv) instructions for administration of the dosage form to an individual in need thereof to produce a C_{max} in plasma of the individual 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, or 1500 or a range between any two of the preceding concentrations; or

(v) instructions for administration of the dosage form to an individual in need thereof to produce a C_{max} in ng/mL in plasma of the individual, 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.

25. Use of a dosage form of any one of claims 1 to 14, in the manufacture of a medicament for inhibiting $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin in an individual, wherein the dosage form is to be administered to the individual.

26. The use of claim 25, wherein the dosage form administered to the individual is effective to produce a C_{max} of the compound in plasma of the individual 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, or 1500 or a range between any two of the preceding concentrations.

27. The use of claim 25, wherein the dosage form administered to the individual is effective to produce a C_{max} in ng/mL in plasma of the individual, 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.

28. The dosage form of any one of claims 1 to 14 for use in inhibiting TGFβ activation in a cell, wherein the dosage form is to be administered to the cell.

29. The dosage form for use of claim 28, wherein the dosage form administered to the cell is effective to produce a C_{max} of the compound at the cell 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, or 1500 or a range between any two of the preceding concentrations.

30. The dosage form for use of claim 28, wherein the dosage form administered to the cell is effective to produce a C_{max} in ng/mL in the cell, the C_{max} corresponding to a concentration effective to inhibit a percentage of $\alpha_V\beta_6$ or $\alpha_V\beta_1$ of the cell 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.

31. Use of a dosage form of any of claims 1-14, in the manufacture of a medicament for inhibiting $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin, wherein an effective amount of the dosage form is to be administered to an individual in need thereof to inhibit the $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin.

32. The use of claim 31, wherein the dosage form administered to the individual is effective to produce a C_{max} of the compound in plasma of the individual 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, or 1500, or a range between any two of the preceding concentrations.

33. The use of claim 31, wherein the dosage form administered to the individual is effective to produce a C_{max} in ng/mL in plasma of the individual, 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.

34. Use of a dosage form of any one of claims 1-14, in the manufacture of a medicament for modulating the activity of at least one integrin in a subject in need thereof, wherein an effective amount of the dosage form is to be administered to the subject to modulate the activity of the at least one integrin in the subject, the at least one integrin including at least one of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin.

35. The use of claim 34, the use the use comprising inhibiting the activity of one or both of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin in the subject.

36. The use of claim 34 or 35, wherein the subject has or is at risk of a fibrotic disease selected from the group consisting of: idiopathic pulmonary fibrosis (IPF), interstitial lung

disease, radiation-induced pulmonary fibrosis, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), alcoholic liver disease induced fibrosis, Alport syndrome, primary sclerosing cholangitis (PSC), primary biliary cholangitis, biliary atresia, systemic sclerosis associated interstitial lung disease, scleroderma, diabetic nephropathy, diabetic kidney disease, focal segmental glomerulosclerosis, chronic kidney disease, and Crohn's Disease; and

wherein the use comprises inhibiting the activity of one or both of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin in the subject, thereby treating the fibrotic disease in the subject.

37. The use of claim 34 or 35, wherein the subject has or is at risk of psoriasis, and wherein the use comprises inhibiting the activity of one or both of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin in the subject, thereby treating the fibrotic disease in the subject.

38. The use of claim 34 or 35, wherein the subject is in need of treatment for NASH, wherein the amount of the dosage form administered to the subject is effective to inhibit the activity of at least $\alpha_V\beta_1$ integrin, thereby treating the subject for NASH.

39. The use of claim 34 or 35, the subject being in need of treatment for IPF, wherein the amount of the dosage form administered to the subject is effective to inhibit the activity of at least $\alpha_V\beta_6$ integrin, thereby treating the subject for IPF.

40. The use of claim 34 or 35, the subject being in need of treatment for PSC, wherein the amount of the dosage form administered to the subject is effective to inhibit the activity of at least one of $\alpha_V\beta_6$ integrin and $\alpha_V\beta_1$ integrin, thereby treating the subject for PSC.

41. The use of claim 34 or 35, wherein the dosage form administered to the individual is effective to produce a C_{max} of the compound in plasma of the individual 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, or 1500, or a range between any two of the preceding concentrations.

42. The use of claim 34 or 35 wherein the dosage form administered to the individual is effective to produce a C_{max} in ng/mL in plasma of the individual, 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.

43. Use of a dosage form of any one of claims 1-14, in the manufacture of a medicament for treating a subject in need thereof, wherein a therapeutically effective amount of the dosage form is to be administered to the subject, wherein the subject has at least one tissue in need of therapy and the tissue has at least one elevated level of:

$\alpha_V\beta_1$ integrin activity and/or expression;

$\alpha_V\beta_6$ 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.

44. The use of claim 43, 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.

45. The use of claim 43, 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.

46. The use of claim 43, 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.

47. The use of claim 44 or 45, wherein the activity of $\alpha_V\beta_1$ integrin in one or more fibroblasts is reduced in the subject.

48. The use of claim 44 or 45, wherein the activity of $\alpha_V\beta_6$ integrin in one or more epithelial cells is reduced in the subject.

49. The use of any one of claims 43-48, 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.

50. The use of any one of claims 43-49, wherein the tissue has an elevated pSMAD2/SMAD2 value or an elevated pSMAD3/SMAD3 value compared to the healthy state of the tissue.

51. The use of any one of claims 43-49, wherein the dosage form administered to the subject is effective to produce a C_{max} of the compound 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, or 1500, or a range between any two of the preceding concentrations.

52. Use of a dosage form recited in any of claims 1-14, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound in mg of about one of: 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, 175, 200, 225, or 250, or a range between any two of the preceding amounts is to be administered to the individual.

53. Use of a dosage form recited in any of claims 1-14, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound effective to produce a C_{max} in plasma of the individual 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, or 1500, or a range between any two of the preceding concentrations is to the administered to the individual.

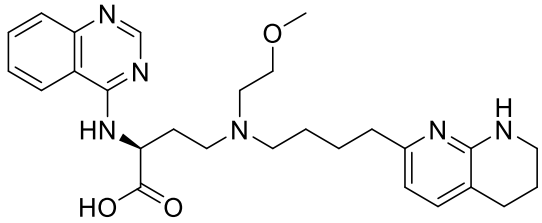
54. Use of a dosage form recited in any of claims 1-14, in the manufacture of a medicament for treating a fibrotic disease in an individual in need thereof, wherein an amount of the compoundeffective to produce a C_{max} in ng/mL in plasma of the subject, the C_{max} corresponding to a plasma-adjusted concentration effective to inhibit a percentage of each of $\alpha_V\beta_6$ and/or $\alpha_V\beta_1$ in the subject, each percentage independently selected from 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 is to be administered to the individual.

55. Use of the dosage form of any one of claims 1 to 14 in the manufacture of a medicament for the treatment of a fibrotic disease in an individual in need thereof, wherein the dosage form is to be administered daily to the individual.

56. The use of claim 55, wherein the fibrotic disease is idiopathic pulmonary fibrosis.

57. The use of claim 55, wherein the fibrotic disease is primary sclerosing cholangitis.

58. The dosage form of claim 1, wherein the compound is (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid:

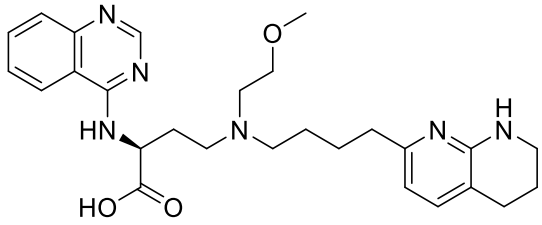


, or a salt thereof, for use in the treatment of a fibrotic disease.

59. The dosage form of claim 58, wherein the fibrotic disease is idiopathic pulmonary fibrosis.

60. The dosage form of claim 58, wherein the fibrotic disease is primary sclerosing cholangitis.

61. Use of the dosage form of claim 1, wherein the compound 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, in the manufacture of a medicament for the treatment of a fibrotic disease.

62. The use of claim 61, wherein the fibrotic disease is idiopathic pulmonary fibrosis.

63. The use of claim 61, wherein the fibrotic disease is primary sclerosing cholangitis.

64. A dosage form of any one of claims 1-14,

for use in inhibiting $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin in an individual, wherein the dosage form is to be administered to the individual; or

for use in inhibiting $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin, wherein an effective amount of the dosage form is to be administered to an individual in need thereof to inhibit the $\alpha_V\beta_6$ or $\alpha_V\beta_1$ integrin; or

for use in modulating the activity of at least one integrin in a subject in need thereof, wherein an effective amount of the dosage form is to be administered to the subject to modulate the activity of the at least one integrin in the subject, the at least one integrin including at least one of $\alpha_V\beta_1$ integrin and $\alpha_V\beta_6$ integrin; or

for use in treating a subject in need thereof, wherein a therapeutically effective amount of the dosage form is to be administered to the subject, wherein the subject has at least one tissue in need of therapy and the tissue has at least one elevated level of: $\alpha_V\beta_1$ integrin activity and/or expression; $\alpha_V\beta_6$ 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; or

for use in treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound in mg of about one of: 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, 175, 200, 225, or 250, or a range between any two of the preceding amounts is to be administered to the individual; or

for use in treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound effective to produce a C_{max} in plasma of the individual 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, or 1500, or a range between any two of the preceding concentrations is to the administered to the individual; or

for use in treating a fibrotic disease in an individual in need thereof, wherein an amount of the compound effective to produce a C_{max} in ng/mL in plasma of the subject, the C_{max} corresponding to a plasma-adjusted concentration effective to inhibit a percentage of each of $\alpha_V\beta_6$ and/or $\alpha_V\beta_1$ in the subject, each percentage independently selected from 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 is to be administered to the individual; or

for use in treating a fibrotic disease in an individual in need thereof, wherein the dosage form is to be administered daily to the individual.