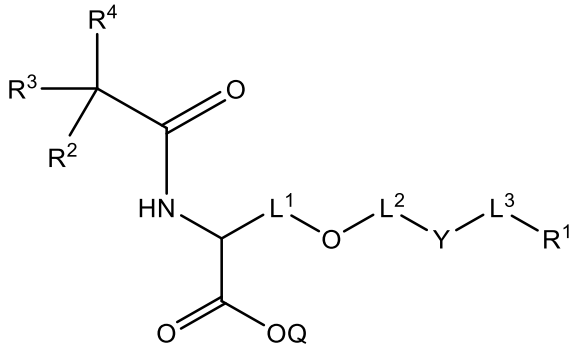
[0018] In one example, provided is a compound of formula (A), or any variation thereof, or a salt thereof (*e.g.*, a pharmaceutically acceptable salt thereof), as detailed herein.

[0018a] In one aspect, provided is a compound of formula (A):



(A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is 5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl optionally substituted by one or more R^{1a}, 1,2,3,4-tetrahydro-1,8-naphthyridin-2-yl optionally substituted by one or more R^{1b}, 6-aminopyridin-2-yl optionally substituted by one or more R^{1c}, or (pyridin-2-yl)amino optionally substituted by one or more R^{1d};

R^2 is H or C_1-C_6 alkyl;

R^3 is H or C_1-C_6 alkyl;

or R^2 and R^3 are taken together with the carbon atom to which they are attached to form a C_3-C_6 cycloalkyl or a 3-to-6-membered heterocyclyl, each of which is optionally substituted by R^{2a};

R^4 is phenyl, 5-to-6-membered heteroaryl, 6-membered heterocyclyl, or C_1-C_6 haloalkyl;

wherein the 5-to-6-membered heteroaryl contains at least one nitrogen atom and is optionally fused to a phenyl group;

wherein the 6-membered heterocyclyl contains at least one nitrogen atom and is optionally fused to a phenyl group;

wherein the phenyl and 5-to-6-membered heteroaryl are optionally substituted by one or more R^{4a}; and

wherein the 6-membered heterocyclyl is optionally substituted by one or more groups selected from the group consisting of R^{4a} and oxo;

or R^2, R^3, and R^4 are taken together to form a 5-membered heteroaryl containing two nitrogen atoms and substituted with phenyl, wherein the phenyl group is optionally substituted by one or more R^{4a};

each R^{4a} is independently halo, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), C_3-C_6 cycloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -$S(O)_2$(C_1-C_6 alkyl), or -C(=O)-NH_2;

or R^{4a} and R^2 are taken together with the atoms to which they are attached to form a 6-membered heterocyclyl, wherein the heterocyclyl contains one oxygen atom;

Q is H or C_1-C_8 alkyl;

L^1 is C_2-C_4 alkylene optionally substituted by one or more L^{1a};

L^2 is a bond or C_1-C_3 alkylene optionally substituted by one or more L^{2a};

L^3 is C_2-C_4 alkylene optionally substituted by one or more L^{3a};

Y is a bond;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{2a}, L^{1a}, L^{2a}, and L^{3a} are each independently selected from R^A;

two R^{1a} groups on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C_3-C_6 cycloalkyl;

two R^{1b} groups on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C_3-C_6 cycloalkyl;

each R^A is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, -CN, $-OR^5$, $-SR^5$, $-NR^6R^7$, $-NO_2$, $-C{=}NH(OR^5)$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)OR^5$, $-C(O)NR^6R^7$, $-NR^5C(O)R^6$, $-NR^5C(O)OR^6$, $-NR^5C(O)NR^6R^7$, $-S(O)R^5$, $-S(O)_2R^5$, $-NR^5S(O)R^6$, $-NR^5S(O)_2R^6$, $-S(O)NR^6R^7$, $-S(O)_2NR^6R^7$, or $-P(O)(OR^5)(OR^6)$, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, C_6-C_{14} aryl, and 5- to 10-membered heteroaryl of R^A are independently optionally substituted by one or more R^{Aa};

each R^{Aa} is independently deuterium, halogen, oxo, $-OR^8$, $-NR^8R^9$, $-C(O)R^8$, $-C(O)OR^8$, $-NR^8C(O)OR^{10}$, -CN, $-S(O)R^8$, $-S(O)_2R^8$, $-P(O)(OR^8)(OR^9)$, 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, wherein the 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, and C_1-C_6 alkyl of R^{Aa} are independently optionally substituted by one or more R^{Ab};

each R^{Ab} is independently deuterium, oxo, -OH, $-O(^2H)$, halogen, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, -OH, $-O(^2H)$, or oxo;

each R^5 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 10-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 10-membered heterocyclyl of R^5 are each independently optionally substituted by one or more R^{5a};

each R^{5a} is independently halogen, deuterium, oxo, -CN, $-OR^{10}$, $-NR^{11}R^{12}$, $-P(O)(OR^{11})(OR^{12})$, 3- to 12-membered heterocyclyl, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, -OH, $-O(^2H)$, or oxo;

each R^6 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 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 10-membered heteroaryl, and 3- to 6-membered heterocyclyl of R^6 are independently optionally substituted by one or more of deuterium, halogen, oxo, -CN, $-OR^{10}$, $-NR^{11}R^{12}$, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, -OH, $-O(^2H)$, or oxo;

each R^7 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 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 10-membered heteroaryl, and 3- to 6-membered heterocyclyl of R^7 are independently optionally substituted by one or more of deuterium, halogen, oxo, -CN, $-OR^{10}$, $-NR^{11}R^{12}$, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, -OH, $-O(^2H)$, or oxo;

or R^6 and R^7 are taken together with the atom to which they are attached to form a 3- to 10-membered heterocyclyl optionally substituted by one or more of deuterium, halogen, oxo, $-OR^{10}$, $-NR^{11}R^{12}$, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, oxo, -OH, or $-O(^2H)$;

each R^8 is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo;

each R^9 is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo;

each R^{10} is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo;

each R^{11} is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo; and

each R^{12} is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo;

or R^{11} and R^{12} are taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by one or more of deuterium, halogen, oxo or C_1-C_6 alkyl optionally substituted by one or more of deuterium, oxo, or halogen.

[0019] 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.

[0020] 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.

[0020a] In one aspect, provided is a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0021] 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.

[0022] Also 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), a checkpoint inhibitor, and a pharmaceutically acceptable carrier or excipient.

[0023] Also 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), a checkpoint inhibitor, and a pharmaceutically acceptable carrier or excipient.

[0024] In another example, provided is a method of treating a fibrotic disease or condition 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 another example, provided is a method of treating a fibrotic disease or condition 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 or condition is pulmonary, liver, renal, cardiac, dermal, or gastrointestinal fibrosis. In other examples the fibrotic disease or condition is idiopathic pulmonary fibrosis, 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, primarily biliary cholangitis (also known as primary biliary cirrhosis), systemic sclerosis associated interstitial lung disease, scleroderma (also known as systemic

sclerosis), diabetic nephropathy, diabetic kidney disease, focal segmental glomerulosclerosis, chronic kidney disease, biliary atresia, and Crohn's Disease. In one aspect, provided is use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a fibrotic disease in an individual in need thereof, optionally wherein the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis, cardiac fibrosis, kidney fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis.

[0025] In another example, provided is a method of delaying the onset and/or development of a fibrotic disease or condition in an individual (such as a human) who is at risk for developing a fibrotic disease or condition 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 another example, provided is a method of delaying the onset and/or development of a fibrotic disease or condition in an individual (such as a human) who is at risk for developing a fibrotic disease or condition 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 disease or condition is pulmonary, liver, renal, cardiac, dermal, or gastrointestinal fibrosis. In other examples the fibrotic disease or condition is idiopathic pulmonary fibrosis, 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, primarily biliary cholangitis (also known as primary biliary cirrhosis), systemic sclerosis associated interstitial lung disease, scleroderma (also known as systemic sclerosis), diabetic nephropathy, diabetic kidney disease, focal segmental glomerulosclerosis, chronic kidney disease, biliary atresia, and Crohn's Disease.

[0026] 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.

[0027] 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.

[0028] Also provided is use of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament 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, in the manufacture of a medicament for the treatment of a fibrotic disease.

[0030] Further 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 thereof, for the treatment of a disease mediated by cells that express $\alpha_V\beta_1$and/or

$\alpha_V\beta_8$. Further 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 thereof, for the treatment of a disease mediated by cells that express $\alpha_V\beta_1$and/or $\alpha_V\beta_8$. In some examples, the cells are associated with the intrahepatic biliary system. In some examples, the cells are associated with the extrahepatic biliary system. In some examples, the cells are associated with the intrahepatic biliary system and the extrahepatic biliary system.

[0031] Further provided is a kit comprising a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof. 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. In some examples, the kit comprises instructions for use according to a method described herein, such as a method of treating a cancer in an individual. In one aspect, provided is a kit comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, optionally further comprising instructions for the treatment of a fibrotic disease, or further comprising instructions directing a user to treat cancer in a subject in need thereof, the instructions comprising directing the user to administer to the subject the compound or the pharmaceutically acceptable salt thereof.

[0032] Also provided is a kit comprising a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, and a checkpoint inhibitor. Also provided is a kit comprising a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, and a checkpoint inhibitor. 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. In some examples, the kit comprises instructions for use according to a method described herein, such as a method of treating a cancer in an individual.

[0033] Further provided is a method of inhibiting $\alpha_V\beta_8$ integrin in an individual comprising administering a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof.

[0034] Further provided is a method of inhibiting $\alpha_V\beta_8$ integrin in an individual comprising administering a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof.

[0035] Also provided is a method of inhibiting one or more of $\alpha_V\beta_1$, $\alpha_V\beta_6$, or $\alpha_V\beta_8$ integrin in an individual in need thereof, comprising administering to the individual a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0036] Also provided is a method of inhibiting one or more of $\alpha_V\beta_1$, $\alpha_V\beta_6$, or $\alpha_V\beta_8$ integrin in an individual in need thereof, comprising administering to the individual a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0037] Further provided is a method of inhibiting TGFβ activation in a cell comprising administering to the cell a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0038] Further provided is a method of inhibiting TGFβ activation in a cell comprising administering to the cell a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0039] Also provided is the use of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a fibrotic disease.

[0040] Also provided is the use of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a fibrotic disease.

[0041] Also provided is the use of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment of a disease mediated by cells that express one or more of: $\alpha_V\beta_1$; $\alpha_V\beta_6$; and $\alpha_V\beta_8$. Also provided is the use of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment of a disease mediated by cells that express one or more of: $\alpha_V\beta_1$; $\alpha_V\beta_6$; and $\alpha_V\beta_8$. For example, in some examples the disease is mediated by cells that express $\alpha_V\beta_1$. In some examples, the disease is mediated by cells that express $\alpha_V\beta_6$. In some examples, the disease is mediated by cells that express $\alpha_V\beta_8$. In some examples, the disease is mediated by cells that express $\alpha_V\beta_1$ and $\alpha_V\beta_6$. In some examples, the disease is mediated by cells that express $\alpha_V\beta_1$ and $\alpha_V\beta_8$. In some examples, the fibrotic disease is mediated by cells that express $\alpha_V\beta_6$ and $\alpha_V\beta_8$. In some examples, the fibrotic disease is mediated by cells that express $\alpha_V\beta_1$, $\alpha_V\beta_6$, and $\alpha_V\beta_8$.

[0042] In another example provided is a method of treating cancer in an individual in need thereof, comprising administering to the individual a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a

pharmaceutical composition thereof. In some examples, the method further comprises administering to the individual a checkpoint inhibitor.

[0043] In another example provided is a method of treating cancer in an individual in need thereof, comprising administering to the individual a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some examples, the method further comprises administering to the individual a checkpoint inhibitor.

[0044] Also provided is the use of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment of a cancer. In one aspect, provided is use of a composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of as disclosed herein, in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, optionally wherein the cancer comprises a solid tumor; the cancer is selected from the group consisting of melanoma, colon cancer, non-small cell lung cancer, head and neck squamous cell carcinoma, squamous cell lung cancer, renal cell carcinoma, cutaneous squamous cell carcinoma (CSCC), urothelial carcinoma, metastatic Merkel cell carcinoma, gastric cancer, lung cancer, pancreatic cancer, and mesothelioma; the cancer is breast cancer; or the cancer is pancreatic ductal adenocarcinoma (PDAC).

[0045] Also provided is the use of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment of a cancer.

[0046] Also provided is the use of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and a checkpoint inhibitor, together in the manufacture of a medicament for the treatment of a disease mediated by cells that express one or more of: $\alpha_V\beta_1$; $\alpha_V\beta_6$; and $\alpha_V\beta_8$. Also provided is the use of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and a checkpoint inhibitor, together in the manufacture of a medicament for the treatment of cancer.

[0047] Also provided is the use of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and a checkpoint inhibitor, together in the manufacture of a medicament for the treatment of a disease mediated by cells that express one or more of: $\alpha_V\beta_1$; $\alpha_V\beta_6$; and $\alpha_V\beta_8$. Also provided is the use of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and a checkpoint inhibitor, together in the manufacture of a medicament for the treatment of cancer.

[0048] Further provided is a method of treating a subject in need thereof. In some examples, the method includes providing the subject. In some examples, the subject includes at least one tissue in need of therapy. In some examples, the at least one tissue is characterized by at least one value that is elevated compared to a healthy value in a healthy

state of the tissue. In some examples, the tissue includes an elevated value of $\alpha_V\beta_1$ integrin activity and/or expression. In some examples, the tissue includes an elevated value of $\alpha_V\beta_6$ integrin activity and/or expression. In some examples, the tissue includes an elevated value of $\alpha_V\beta_8$ integrin activity and/or expression. In some examples, the tissue includes an elevated value of a pSMAD/SMAD ratio. In some examples, the tissue includes an elevated value of new collagen formation or accumulation. In some examples, the tissue includes an elevated value of total collagen. In some examples, the tissue includes an elevated value of Type I Collagen gene Col1a1 expression. In some examples, the tissue includes an elevated value of perforin. In some examples, the tissue includes an elevated value of Granzyme B. In some examples, the tissue includes an elevated value of interferon γ. In some examples, the method includes administering to the subject a therapeutically effective amount of a compound of formula (A), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some examples, the method includes administering to the subject a therapeutically effective amount of a compound of formula (I), or any variation thereof detailed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0049] Also provided is a method of characterizing anticancer activity of a small molecule inhibitor in a subject. In some examples, the method includes providing a first live cell sample from the subject. In some examples, the first live cell sample is characterized by the presence of at least one integrin capable of activating transforming growth factor β (TGF-β) from latency associated peptide-TGF-β. In some examples, the method includes determining a first value in the first live cell sample. In some examples, the first value is a pSMAD2/SMAD2 ratio. In some examples, the first value is a pSMAD3/SMAD3 ratio. In some examples, the first value is a perforin level. In some examples, the first value is a granzyme B level. In some examples, the first value is an interferon γ level. In some examples, the method includes administering the small molecule to the subject. In some examples, the method includes providing a second live cell sample from the subject. In some examples, the second live cell sample is drawn from the same tissue in the subject as the first live cell sample. In some examples, the method includes determining a second value in the second live cell sample. In some examples, the second value corresponds to the pSMAD2/SMAD2 ratio, pSMAD3/SMAD3 ratio, perforin level, granzyme B level, or interferon γ level of the first

value. In some examples, the method includes characterizing the anticancer activity of the small molecule in the subject by comparing the second value to the first value.

[0050] In another example, provided is a method of making a compound of formula (A) or any variation thereof. Also provided are compound intermediates useful in synthesis of a compound of formula (A), or any variation thereof.

[0051] In another example, provided is a method of making a compound of formula (I) or any variation thereof. Also provided are compound intermediates useful in synthesis of a compound of formula (I), or any variation thereof.

[0052] In another example, provided is a compound of formula (A) or any variation thereof produced by a process disclosed herein.

[0053] In another example, provided is a compound of formula (I) or any variation thereof produced by a process disclosed herein.

[0054] It is understood that examples and variations described herein also include "consisting of" and/or "consisting essentially of" examples and variations.

BRIEF DESCRIPTION OF THE FIGURES

[0055] **FIG. 1** is a diagram illustrating aspects of integrin-mediated TGF-β activation in tumor adaptive immunity.

[0056] **FIG. 2A** is a diagram illustrating an initial experiment in mice.

[0057] **FIG. 2B** is a graph showing that EMT6 cell proliferation was not affected by anti-$\alpha_V\beta_8$ or IgG control *in vitro*.

[0058] **FIG. 3A** is a graph showing tumor volume as a function of time for the short arm of the study of Example B3.

[0059] **FIG. 3B** is a graph showing tumor volume as a function of time for the long arm of the study of Example B3.

[0060] **FIG. 4A** is a graph showing tumor volume versus time for mice in Group 1.

[0061] **FIG. 4B** is a graph showing tumor volume versus time for mice in Group 2.

[0062] **FIG. 4C** is a graph showing tumor volume versus time for mice in Group 3.

[0063] **FIG. 4D** is a graph showing tumor volume versus time for mice in Group 4.

[0064] **FIG. 4E** is a graph showing tumor volume versus time for mice in Group 5.

[0065] **FIG. 5** is a graph of percent survival versus time over 5 weeks, showing that long term survival was significantly improved by the combination of the anti-PD1 and anti-$\alpha_V\beta_8$ antibodies in Group 4.