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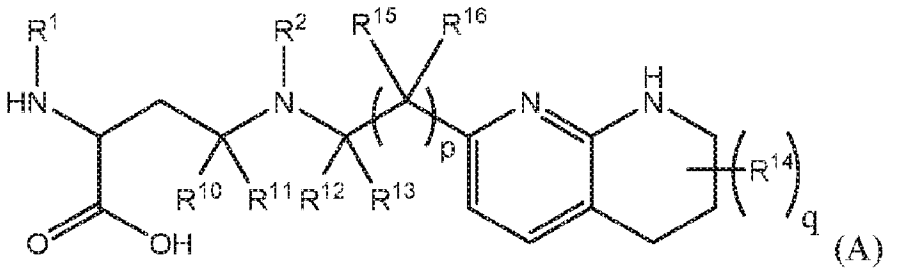
(54) Title: DOSAGE FORMS AND REGIMENS FOR AMINO ACID COMPOUNDS



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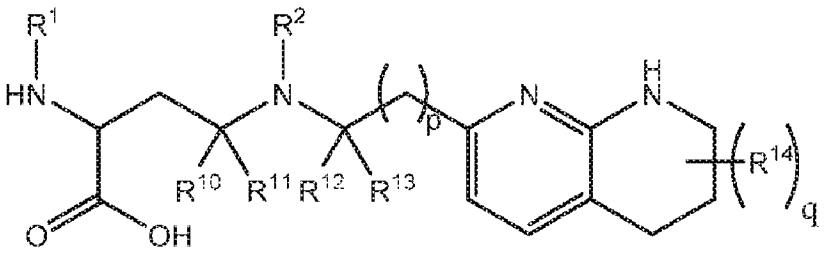

(I).

(57) Abrégé/Abstract:
The invention relates to dosage forms for daily administration of compounds of formula (A) and formula (I): or a salt thereof, wherein R^1, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, q and p are as described herein. Compounds of formula (A), formula (I), and pharmaceutical compositions thereof are αvβ6 integrin inhibitors that are useful for treating fibrosis such as idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP),

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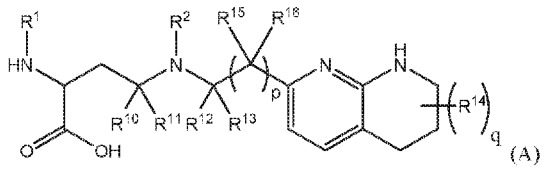
(54) Title: DOSAGE FORMS AND REGIMENS FOR AMINO ACID COMPOUNDS



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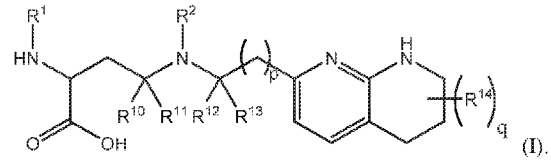

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WO 2020/210404 A1

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WO 2020/210404 A1

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LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 192

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 192

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DOSAGE FORMS AND REGIMENS FOR AMINO ACID COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. Provisional Patent Appl. No. 62/831,060 filed April 8, 2019, of U.S. Provisional Patent Appl. No. 62/850,530 filed May 20, 2019, and of U.S. Provisional Patent Appl. No. 62/899,071 filed September 11, 2019. The entire contents of those patent applications are hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

[0002] Fibrosis, a pathologic feature of many diseases, is caused by a dysfunction in the body's natural ability to repair damaged tissues. If left untreated, fibrosis can result in scarring of vital organs causing irreparable damage and eventual organ failure.

[0003] Patients with nonalcoholic fatty liver disease (NAFLD) may progress from simple steatosis to nonalcoholic steatohepatitis (NASH) and then fibrosis. While liver fibrosis is reversible in its initial stages, progressive liver fibrosis can lead to cirrhosis.

[0004] Fibrosis in the kidney, characterized by glomerulosclerosis and tubulointerstitial fibrosis, is the final common manifestation of a wide variety of chronic kidney diseases (CKD). Irrespective of the initial causes, progressive CKD often results in widespread tissue scarring that leads to destruction of kidney parenchyma and end-stage renal failure, a devastating condition that requires dialysis or kidney replacement.

[0005] Scleroderma encompasses a spectrum of complex and variable conditions primarily characterized by fibrosis, vascular alterations, and autoimmunity. The scleroderma spectrum of disorders share the common feature of fibrosis, resulting in hardening or thickening of the skin. For some patients, this hardening occurs only in limited areas, but for others, it can spread to other major organs.

[0006] Following myocardial infarction, cardiac structural remodeling is associated with an inflammatory reaction, resulting in scar formation at the site of the infarction. This scar formation is a result of fibrotic tissue deposition which may lead to reduced cardiac function and disruption of electrical activity within the heart.

[0007] Crohn's Disease is a chronic disease of unknown etiology tending to progress even in the setting of medical or surgical treatment. Intestinal fibrosis is among the most common

complications of Crohn's disease, resulting in stricture formation in the small intestine and colon.

[0008] Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing disease of unknown etiology, occurring in adults and limited to the lungs. In IPF, the lung tissue becomes thickened, stiff, and scarred. As lung fibrosis progresses, it becomes more difficult for the lungs to transfer oxygen into the bloodstream and the organs do not receive the oxygen needed to function properly. IPF currently affects approximately 200,000 people in the U.S., resulting in 40,000 deaths per year. Patients diagnosed with IPF experience progressive breathlessness and eventually, complete respiratory failure.

[0009] Primary biliary cholangitis (PBC), also known as primary biliary cirrhosis, is a chronic disease of the liver that causes damage and fibrosis in the liver. It results from a slow, progressive destruction of the small bile ducts of the liver, causing bile and other toxins to build up in the liver, a condition called cholestasis. Over time, this leads to scarring and fibrosis in both the liver and biliary tract.

[0010] Nonspecific interstitial pneumonia (NSIP) is a rare disorder that affects the tissue that surrounds and separates the tiny air sacs of the lungs. These air sacs, called the alveoli, are where the exchange of oxygen and carbon dioxide takes place between the lungs and the bloodstream. Interstitial pneumonia is a disease in which the mesh-like walls of the alveoli become inflamed. The pleura (a thin covering that protects and cushions the lungs and the individual lobes of the lungs) might become inflamed as well. There are two primary forms of NSIP - cellular and fibrotic. The cellular form is defined mainly by inflammation of the cells of the interstitium. The fibrotic form is defined by thickening and scarring of lung tissue. This scarring is known as fibrosis and is irreversible. When the lung tissue thickens or becomes scarred, it does not function as effectively. Breathing becomes less efficient, and there are lower levels of oxygen in the blood. (Kim et al., Proc. Am. Thorac. Soc. (2006) 3:285-292; Lynch, D., Radiology (2001) 221:583-584; Kinder et al., Am. J. Respir. Crit. Care Med. (2007) 176:691-697)

[0011] Available courses of treatment are scarce, as there are currently no options on the market proven to have an effect on long-term patient survival or symptomatology. For example, agents such as pirfenidone and nintedanib have been studied for treatment of fibrosis. In the treatment of IPF, pirfenidone and nintedanib have been used, but have shown less therapeutic efficacy than desired while also exhibiting numerous side effects. There remains a need for treatment of fibrotic diseases.

[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 OF THE INVENTION

[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 aspect, 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 aspect, 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 embodiments, 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 embodiments, 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 embodiments, the fibrotic disease is pulmonary fibrosis (such as IPF). In some embodiments, the fibrotic disease is liver fibrosis. In some embodiments, the fibrotic disease is skin fibrosis. In some embodiments, the fibrotic disease is psoriasis. In some

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

[0019] In another aspect, 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 embodiments, 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 embodiments, 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 embodiments, the fibrotic disease is psoriasis. In some embodiments, 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 embodiments, 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 embodiments, 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 aspect, 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 aspect, 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 aspect, 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 embodiments, 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 embodiments, 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 embodiments, the fibrotic disease is psoriasis.

[0027] In another aspect, 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 embodiments, 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 embodiments, 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 embodiments, the fibrotic disease is psoriasis. In some embodiments, 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 embodiments, 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 embodiments, 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 aspect, 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 ^{2}H-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.

[0041] **FIG. 4F** is a high resolution second harmonic generation image of fibrillar collagen (collagen type I and III) taken from formalin-fixed paraffin embedded lung tissue sections from a healthy mouse lung.

[0042] **FIG. 4G** is a high resolution second harmonic generation image of fibrillar collagen (collagen type I and III) taken from formalin-fixed paraffin embedded lung tissue sections from a vehicle-treated mouse lung.

[0043] **FIG. 4H** is a high resolution second harmonic generation image of fibrillar collagen (collagen type I and III) taken from formalin-fixed paraffin embedded lung tissue sections from a test-article treated mouse lung (500 mg/kg BID of compound 5).

[0044] **FIG. 4I** is a graph showing the percent total collagen area in the second harmonic generation mouse lung images of **FIGS. 4F**, **4G**, and **4H**.

[0045] **FIG. 4J** is a graph of sequential measurements in bleomycin-treated mice, which demonstrated a close inverse relationship between pSMAD3 levels in lung vs. plasma drug exposure.

[0046] **FIG. 4K** is a graph of sequential measurements in bleomycin-treated mice, which demonstrated a close inverse relationship between pSMAD3 levels in BALF cells vs. plasma drug exposure.

[0047] **FIG. 5A** is a bar graph, normalized to control slices treated with DMSO, showing that all test treatments reduced Type I Collagen gene Col1a1 expression.

[0048] **FIG. 5B** is a bar graph, normalized to control slices treated with DMSO, showing that all test treatments reduced lung Col1a1 expression.

[0049] **FIG. 6A** is a bar graph showing that compared to the DMSO vehicle control slices, both nintedanib and pirfenidone showed a slight increase in lung Col1a1 expression.

[0050] **FIG. 6B** is a bar graph showing the concentration of compound needed to reduce lung slice Col1a1 expression by 50% compared to DMSO control slices.

[0051] **FIG. 6C** is a bar graph, normalized to control slices treated with DMSO, showing that all test treatments reduced lung Col1a1 expression.

[0052] **FIG. 6D** is a bar graph showing relative expression of COL1A1 in precision cut lung slices (PCLS) from idopathic pulmonary fibrosis (IPF) lung tissue upon exposure to Comopund 5, clinical standard of care compounds nintedanib (Nin) and pirfenidone (Pirf), and an ALK5 inhibitor, all versus DMSO control.

[0053] **FIG. 6E** is a bar graph showing a dose dependent reduction of COL1A1 expression in PCLS from human IPF lung tissue upon treatment with concentrations of compound 5

ranging from 200 pM to 1 μM. COL1A1 expression is also graphed for the PCLS in the presence of 0.1% DMSO control, and an Alk5 inhibitor at 1 μM.

[0054] **FIG. 6F** is a bar graph showing the effect of dual selective $\alpha v\beta_6$ and $\alpha v\beta_1$ inhibition (Compound 5 at 1.82 μM) on the ratio of pSMAD2/SMAD2 in PCLS from human IPF lung tissue samples. The ratio of pSMAD2/SMAD2 is also graphed for the PCLS in the presence of 0.1% DMSO control, and an Alk5 inhibitor at 1 μM

[0055] **FIG. 7A** shows single ascending dose (SAD) study data for administration of 15, 30, 50, and 75 mg of Compound 5.

[0056] **FIG. 7B** shows the multiple ascending dose (MAD) study data for administration of 10, 20, and 40 mg of Compound 5.

[0057] **FIGS. 8A-8F** are a series of graphs showing data for subjects administered 40 mg/day of the selected integrin inhibitor (compound 5). The data in **FIGS. 8A-8F** include the blood plasma concentration ("PK", round dots) of the administered integrin inhibitor and the relative change in pSMAD2:SMAD2 ratio from baseline (Day -1) in BAL (bronchoalveolar lavage) samples ("pSMAD", square dots) through the displayed time course (hours) subsequent to the dose of inhibitor administered on Day 7. The peak of the blood plasma concentration ("PK" curve) is recorded as C_{max}.

[0058] **FIG. 8G** shows the % change in BAL SMAD2 phosphorylation levels (pSMAD2:SMAD2 ratio) on Day 7 compared to baseline levels recorded on Day -1, for subjects receiving placebo treatment, and subjects in which the C_{max} of the integrin inhibitor was measured to be less than 700 ng/mL, from 700 ng/mL to 900 ng/mL, and greater than 900 ng/mL.

[0059] **FIG. 8H** shows the % change in SMAD2 phosphorylation (pSMAD2:SMAD2 ratio) (all timepoints) correlated with C_{max} in subjects administered a 40 mg dose of Compound 5) compared to baseline levels recorded on Day -1.

DETAILED DESCRIPTION OF THE INVENTION

[0060] The present disclosure provides, *inter alia*, compounds of formula (A), and variations thereof, or a salt thereof, pharmaceutical compositions comprising compounds of formula (A) or a salt thereof, and methods of using such compounds and compositions in treating fibrotic diseases.

[0061] The present disclosure provides, *inter alia*, compounds of formula (I), and variations thereof, or a salt thereof, pharmaceutical compositions comprising compounds of

formula (I) or a salt thereof, and methods of using such compounds and compositions in treating fibrotic diseases.

Definitions

[0062] For use herein, unless clearly indicated otherwise, use of the terms "a", "an" and the like refers to one or more.

[0063] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

[0064] As used herein, a "small molecule" is an organic molecule characterized by a mass of less than 900 daltons. Non-limiting examples of small molecules include the compounds depicted in FIG. 1 or a salt thereof.

[0065] "Alkyl" as used herein refers to and includes, unless otherwise stated, a saturated linear (*i.e.*, unbranched) or branched univalent hydrocarbon chain or combination thereof, having the number of carbon atoms designated (*i.e.*, C_1-C_{10} means one to ten carbon atoms). Particular alkyl groups are those having 1 to 20 carbon atoms (a "C_1-C_{20} alkyl"), having 1 to 10 carbon atoms (a "C_1-C_{10} alkyl"), having 6 to 10 carbon atoms (a "C_6-C_{10} alkyl"), having 1 to 6 carbon atoms (a "C_1-C_6 alkyl"), having 2 to 6 carbon atoms (a "C_2-C_6 alkyl"), or having 1 to 4 carbon atoms (a "C_1-C_4 alkyl"). Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like.

[0066] "Alkylene" as used herein refers to the same residues as alkyl, but having bivalency. Particular alkylene groups are those having 1 to 20 carbon atoms (a "C_1-C_{20} alkylene"), having 1 to 10 carbon atoms (a "C_1-C_{10} alkylene"), having 6 to 10 carbon atoms (a "C_6-C_{10} alkylene"), having 1 to 6 carbon atoms (a "C_1-C_6 alkylene"), 1 to 5 carbon atoms (a "C_1-C_5 alkylene"), 1 to 4 carbon atoms (a "C_1-C_4 alkylene") or 1 to 3 carbon atoms (a "C_1-C_3 alkylene"). Examples of alkylene include, but are not limited to, groups such as methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), isopropylene (-$CH_2CH(CH_3)$-), butylene (-$CH_2(CH_2)_2CH_2$-), isobutylene (-$CH_2CH(CH_3)CH_2$-), pentylene (-$CH_2(CH_2)_3CH_2$-), hexylene (-$CH_2(CH_2)_4CH_2$-), heptylene (-$CH_2(CH_2)_5CH_2$-), octylene (-$CH_2(CH_2)_6CH_2$-), and the like.

[0067] "Alkenyl" as used herein refers to and includes, unless otherwise stated, an unsaturated linear (*i.e.*, unbranched) or branched univalent hydrocarbon chain or combination thereof, having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the

formula C=C) and having the number of carbon atoms designated (*i.e.*, C_2-C_{10} means two to ten carbon atoms). An alkenyl group may have "cis" or "trans" configurations, or alternatively have "E" or "Z" configurations. Particular alkenyl groups are those having 2 to 20 carbon atoms (a "C_2-C_{20} alkenyl"), having 6 to 10 carbon atoms (a "C_6-C_{10} alkenyl"), having 2 to 8 carbon atoms (a "C_2-C_8 alkenyl"), having 2 to 6 carbon atoms (a "C_2-C_6 alkenyl"), or having 2 to 4 carbon atoms (a "C_2-C_4 alkenyl"). Examples of alkenyl group include, but are not limited to, groups such as ethenyl (or vinyl), prop-1-enyl, prop-2-enyl (or allyl), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-dienyl, pent-1-enyl, pent-2-enyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, and the like.

[0068] "Alkenylene" as used herein refers to the same residues as alkenyl, but having bivalency. Particular alkenylene groups are those having 2 to 20 carbon atoms (a "C_2-C_{20} alkenylene"), having 2 to 10 carbon atoms (a "C_2-C_{10} alkenylene"), having 6 to 10 carbon atoms (a "C_6-C_{10} alkenylene"), having 2 to 6 carbon atoms (a "C_2-C_6 alkenylene"), 2 to 4 carbon atoms (a "C_2-C_4 alkenylene") or 2 to 3 carbon atoms (a "C_2-C_3 alkenylene"). Examples of alkenylene include, but are not limited to, groups such as ethenylene (or vinylene) (-CH=CH-), propenylene (-CH=CHCH$_2$-), 1,4-but-1-enylene (-CH=CH-CH$_2$CH$_2$-), 1,4-but-2-enylene (-CH$_2$CH=CHCH$_2$-), 1,6-hex-1-enylene (-CH=CH-(CH$_2$)$_3$CH$_2$-), and the like.

[0069] "Alkynyl" as used herein refers to and includes, unless otherwise stated, an unsaturated linear (*i.e.*, unbranched) or branched univalent hydrocarbon chain or combination thereof, having at least one site of acetylenic unsaturation (*i.e.*, having at least one moiety of the formula C≡C) and having the number of carbon atoms designated (*i.e.*, C_2-C_{10} means two to ten carbon atoms). Particular alkynyl groups are those having 2 to 20 carbon atoms (a "C_2-C_{20} alkynyl"), having 6 to 10 carbon atoms (a "C_6-C_{10} alkynyl"), having 2 to 8 carbon atoms (a "C_2-C_8 alkynyl"), having 2 to 6 carbon atoms (a "C_2-C_6 alkynyl"), or having 2 to 4 carbon atoms (a "C_2-C_4 alkynyl"). Examples of alkynyl group include, but are not limited to, groups such as ethynyl (or acetylenyl), prop-1-ynyl, prop-2-ynyl (or propargyl), but-1-ynyl, but-2-ynyl, but-3-ynyl, and the like.

[0070] "Alkynylene" as used herein refers to the same residues as alkynyl, but having bivalency. Particular alkynylene groups are those having 2 to 20 carbon atoms (a "C_2-C_{20} alkynylene"), having 2 to 10 carbon atoms (a "C_2-C_{10} alkynylene"), having 6 to 10 carbon atoms (a "C_6-C_{10} alkynylene"), having 2 to 6 carbon atoms (a "C_2-C_6 alkynylene"), 2 to 4 carbon atoms (a "C_2-C_4 alkynylene") or 2 to 3 carbon atoms (a "C_2-C_3 alkynylene").

Examples of alkynylene include, but are not limited to, groups such as ethynylene (or acetylenylene) (-C≡C-), propynylene (-C≡CCH$_2$-), and the like.

[0071] "Cycloalkyl" as used herein refers to and includes, unless otherwise stated, saturated cyclic univalent hydrocarbon structures, having the number of carbon atoms designated (*i.e.*, C_3-C_{10} means three to ten carbon atoms). Cycloalkyl can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantyl. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or combinations thereof. Particular cycloalkyl groups are those having from 3 to 12 annular carbon atoms. A preferred cycloalkyl is a cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a "C_3-C_8 cycloalkyl"), having 3 to 6 annular carbon atoms (a "C_3-C_6 cycloalkyl"), or having from 3 to 4 annular carbon atoms (a "C_3-C_4 cycloalkyl"). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

[0072] "Cycloalkylene" as used herein refers to the same residues as cycloalkyl, but having bivalency. Cycloalkylene can consist of one ring or multiple rings which may be fused, spiro or bridged, or combinations thereof. Particular cycloalkylene groups are those having from 3 to 12 annular carbon atoms. A preferred cycloalkylene is a cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a "C_3-C_8 cycloalkylene"), having 3 to 6 carbon atoms (a "C_3-C_6 cycloalkylene"), or having from 3 to 4 annular carbon atoms (a "C_3-C_4 cycloalkylene"). Examples of cycloalkylene include, but are not limited to, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, norbornylene, and the like. A cycloalkylene may attach to the remaining structures via the same ring carbon atom or different ring carbon atoms. When a cycloalkylene attaches to the remaining structures via two different ring carbon atoms, the connecting bonds may be cis- or trans- to each other. For example, cyclopropylene may include 1,1-cyclopropylene and 1,2-cyclopropylene (*e.g.*, cis-1,2-cyclopropylene or trans-1,2-cyclopropylene), or a mixture thereof.

[0073] "Cycloalkenyl" refers to and includes, unless otherwise stated, an unsaturated cyclic non-aromatic univalent hydrocarbon structure, having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C) and having the number of carbon atoms designated (*i.e.*, C_3-C_{10} means three to ten carbon atoms). Cycloalkenyl can consist of one ring, such as cyclohexenyl, or multiple rings, such as norbornenyl. A preferred cycloalkenyl is an unsaturated cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a "C_3-C_8 cycloalkenyl"). Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, norbornenyl, and the like.

[0074] "Cycloalkenylene" as used herein refers to the same residues as cycloalkenyl, but having bivalency.

[0075] "Aryl" or "Ar" as used herein refers to an unsaturated aromatic carbocyclic group having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic. Particular aryl groups are those having from 6 to 14 annular carbon atoms (a "C_6-C_{14} aryl"). An aryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, an aryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[0076] "Arylene" as used herein refers to the same residues as aryl, but having bivalency. Particular arylene groups are those having from 6 to 14 annular carbon atoms (a "C_6-C_{14} arylene").

[0077] "Heteroaryl" as used herein refers to an unsaturated aromatic cyclic group having from 1 to 14 annular carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, oxygen and sulfur. A heteroaryl group may have a single ring (*e.g.*, pyridyl, furyl) or multiple condensed rings (*e.g.*, indolizinyl, benzothienyl) which condensed rings may or may not be aromatic. Particular heteroaryl groups are 5 to 14-membered rings having 1 to 12 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, 5 to 10-membered rings having 1 to 8 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, or 5, 6 or 7-membered rings having 1 to 5 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In one variation, particular heteroaryl groups are monocyclic aromatic 5-, 6- or 7-membered rings having from 1 to 6 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In another variation, particular heteroaryl groups are polycyclic aromatic rings having from 1 to 12 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. A heteroaryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, a heteroaryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position. A heteroaryl group may be connected to the parent structure at a ring carbon atom or a ring heteroatom.

[0078] "Heteroarylene" as used herein refers to the same residues as heteroaryl, but having bivalency.

[0079] "Heterocycle", "heterocyclic", or "heterocyclyl" as used herein refers to a saturated or an unsaturated non-aromatic cyclic group having a single ring or multiple condensed rings, and having from 1 to 14 annular carbon atoms and from 1 to 6 annular heteroatoms, such as nitrogen, sulfur or oxygen, and the like. A heterocycle comprising more than one ring may be fused, bridged or spiro, or any combination thereof, but excludes heteroaryl groups. The heterocyclyl group may be optionally substituted independently with one or more substituents described herein. Particular heterocyclyl groups are 3 to 14-membered rings having 1 to 13 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, 3 to 12-membered rings having 1 to 11 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, 3 to 10-membered rings having 1 to 9 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, 3 to 8-membered rings having 1 to 7 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur, or 3 to 6-membered rings having 1 to 5 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In one variation, heterocyclyl includes monocyclic 3-, 4-, 5-, 6- or 7-membered rings having from 1 to 2, 1 to 3, 1 to 4, 1 to 5, or 1 to 6 annular carbon atoms and 1 to 2, 1 to 3, or 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In another variation, heterocyclyl includes polycyclic non-aromatic rings having from 1 to 12 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur.

[0080] "Heterocyclylene" as used herein refers to the same residues as heterocyclyl, but having bivalency.

[0081] "Halo" or "halogen" refers to elements of the Group 17 series having atomic number 9 to 85. Preferred halo groups include the radicals of fluorine, chlorine, bromine and iodine. Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, *e.g.*, dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two ("di") or three ("tri") halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each hydrogen is replaced with a halo group is referred to as a "perhaloalkyl." A preferred perhaloalkyl group is trifluoromethyl ($-CF_3$). Similarly, "perhaloalkoxy" refers to an alkoxy group in which a

halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy (–OCF_3).

[0082] "Carbonyl" refers to the group C=O.

[0083] "Thiocarbonyl" refers to the group C=S.

[0084] "Oxo" refers to the moiety =O.

[0085] "D" refers to deuterium (^2H).

[0086] "T" refers to tritium (^3H).

[0087] An alkyl group in which each hydrogen is replaced with deuterium is referred to as "perdeuterated." An alkyl group in which each hydrogen is replaced with tritium is referred to as "pertritiated."

[0088] "Optionally substituted" unless otherwise specified means that a group may be unsubstituted or substituted by one or more (*e.g.*, 1, 2, 3, 4 or 5) of the substituents listed for that group in which the substituents may be the same of different. In one embodiment, an optionally substituted group has one substituent. In another embodiment, an optionally substituted group has two substituents. In another embodiment, an optionally substituted group has three substituents. In another embodiment, an optionally substituted group has four substituents. In some embodiments, an optionally substituted group has 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, or 2 to 5 substituents. In one embodiment, an optionally substituted group is unsubstituted.

[0089] It is understood that an optionally substituted moiety can be substituted with more than five substituents, if permitted by the number of valences available for substitution on the moiety. For example, a propyl group can be substituted with seven halogen atoms to provide a perhalopropyl group. The substituents may be the same or different.

[0090] Unless clearly indicated otherwise, "an individual" as used herein intends a mammal, including but not limited to a primate, human, bovine, horse, feline, canine, or rodent. In one variation, the individual is a human.

[0091] As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired results include, but are not limited to, one or more of the following: decreasing one more symptoms resulting from the disease, diminishing the extent of the disease, stabilizing the disease (*e.g.*, preventing or delaying the worsening of the disease), preventing or delaying the spread of the disease, delaying the occurrence or recurrence of the disease, delay or slowing the progression of the disease, ameliorating the disease state, providing a remission (whether partial or total) of the disease, decreasing the dose of one or more other medications required to treat the disease,

enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival. Also encompassed by "treatment" is a reduction of pathological consequence of fibrosis. The methods of the invention contemplate any one or more of these aspects of treatment.

[0092] As used herein, the term "effective amount" intends such amount of a compound of the invention which should be effective in a given therapeutic form. As is understood in the art, an effective amount may be in one or more doses, *i.e.*, a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents (*e.g.*, a compound, or pharmaceutically acceptable salt thereof), and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any of the co-administered compounds may optionally be lowered due to the combined action (*e.g.*, additive or synergistic effects) of the compounds.

[0093] A "therapeutically effective amount" refers to an amount of a compound or salt thereof sufficient to produce a desired therapeutic outcome.

[0094] As used herein, "unit dosage form" refers to physically discrete units, suitable as unit dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Unit dosage forms may contain a single or a combination therapy.

[0095] As used herein, the term "controlled release" refers to a drug-containing formulation or fraction thereof in which release of the drug is not immediate, *i.e.*, with a "controlled release" formulation, administration does not result in immediate release of the drug into an absorption pool. The term encompasses depot formulations designed to gradually release the drug compound over an extended period of time. Controlled release formulations can include a wide variety of drug delivery systems, generally involving mixing the drug compound with carriers, polymers or other compounds having the desired release characteristics (*e.g.*, pH-dependent or non-pH-dependent solubility, different degrees of water solubility, and the like) and formulating the mixture according to the desired route of delivery (*e.g.*, coated capsules, implantable reservoirs, injectable solutions containing biodegradable capsules, and the like).

[0096] As used herein, by "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious

manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0097] "Pharmaceutically acceptable salts" are those salts which retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Pharmaceutically acceptable salts can be prepared *in situ* in the manufacturing process, or by separately reacting a purified compound of the invention in its free acid or base form with a suitable organic or inorganic base or acid, respectively, and isolating the salt thus formed during subsequent purification.

[0098] The term "excipient" as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the invention as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, *e.g.*, carbomers, povidone, xanthan gum, etc.; coatings include, *e.g.*, cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, *e.g.*, calcium carbonate, dextrose, fructose dc (dc = "directly compressible"), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, *e.g.*, croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, *e.g.*, maltodextrin, carrageenans, etc.; lubricants include, *e.g.*, magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, *e.g.*, dextrose, fructose dc, lactose

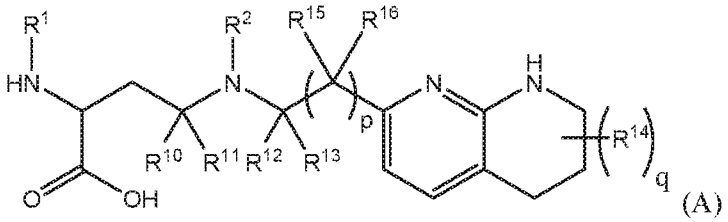
(monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, *e.g.*, carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, *e.g.*, aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, *e.g.*, calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[0099] Unless otherwise stated, "substantially pure" intends a composition that contains no more than 10% impurity, such as a composition comprising less than 9%, 7%, 5%, 3%, 1%, 0.5% impurity.

[00100] It is understood that aspects and embodiments described herein as "comprising" include "consisting of" and "consisting essentially of" embodiments.

Compounds

[00101] In one aspect, provided is 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 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;

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;

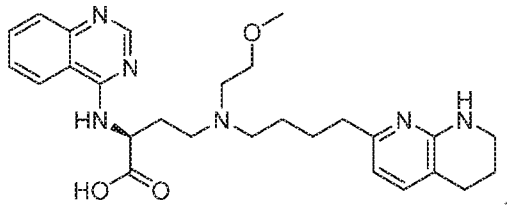
q is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

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

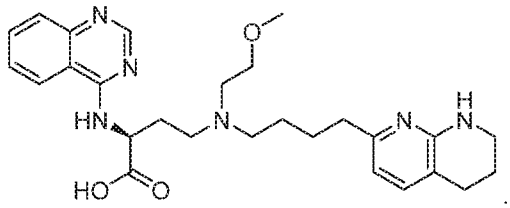
each R^{16} is independently selected from hydrogen, deuterium, or halogen; and

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

[00102] In one variation is provided that the compound of Formula A excludes the free base of (2S)-4-[2-methoxyethyl-[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]amino]-2-(quinazolin-4-ylamino)butanoic acid:



[00103] In various embodiments, the claimed compound excludes a free base of a compound represented by formula A wherein: R^1 is unsubstituted quinazolin-4-yl; R^2 is $-CH_2CH_2OCH_3$; R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, and R^{16} are each H; p is 3; q is 0; and the carbon to which R^1NH- is bonded is in the S configuration, e.g., in some embodiments, the compound of formula A excludes the free base of (2S)-4-[2-methoxyethyl-[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]amino]-2-(quinazolin-4-ylamino)butanoic acid:



[00104] In some embodiments, the claimed compound excludes a free base of a compound represented by formula A wherein R^2 is $-CH_2CH_2OCH_3$; R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, and R^{16} are each H; p is 3; q is 0; the carbon to which R^1NH- is bonded is in the S configuration, and R^1 is one or more of the following separate lettered embodiments (a)-(k). (a) R^1 is unsubstituted quinazolin-4-yl. (b) R^1 is quinazolin-4-yl substituted by R^{1a} wherein R^{1a} is methyl. (c) R^1 is quinazolin-4-yl substituted by R^{1a} wherein R^{1a} is methyl or ethyl. (d) R^1 is quinazolin-4-yl substituted by R^{1a} wherein R^{1a} is C_1-C_6 alkyl. (e) R^1 is quinazolin-4-yl substituted by R^{1a}. (f) R^1 is a 10 membered fused bicyclic heterocycle containing two ring nitrogen atoms, and R^1 is

unsubstituted or substituted by R^{1a}. (g) R^1 is unsubstituted quinazolinyl. (h) R^1 is quinazolinyl substituted by R^{1a} wherein R^{1a} is methyl. (i) R^1 is quinazolinyl substituted by R^{1a} wherein R^{1a} is methyl or ethyl. (j) R^1 is quinazolinyl substituted by R^{1a} wherein R^{1a} is C_1-C_6 alkyl. (k) R^1 is quinazolinyl substituted by R^{1a}.

[00105] In some embodiments, the claimed compound excludes a free base of a compound represented by formula A wherein R^1 is unsubstituted quinazolin-4-yl; R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, and R^{16} are each H; p is 3; q is 0; the carbon to which R^1NH- is bonded is in the S configuration, and R^2 is one or more of the following separate lettered embodiments (l)-(p). (l) R^2 is ethylene 2-substituted by R^{2a} and R^{2a} is methoxy. (m) R^2 is methylene, ethylene, or propylene substituted by R^{2a}, and R^{2a} is methoxy. (n) R^2 is ethylene substituted by R^{2a} and R^{2a} is methoxy or ethoxy. (o) R^2 is ethylene substituted by R^{2a} and R^{2a} is hydroxy. (p) R^2 is methylene, ethylene, or propylene substituted by R^{2a} and R^{2a} is hydroxy, methoxy, or ethoxy.

[00106] In some embodiments, the claimed compound excludes a free base of a compound represented by formula A wherein R^1 is unsubstituted quinazolin-4-yl; R^2 is $-CH_2CH_2OCH_3$; R^{15} and R^{16} are each H; p is 3; q is 0; the carbon to which R^1NH- is bonded is in the S configuration, and R^{10}, R^{11}, R^{12}, and R^{13} together represent one or more of the following separate lettered embodiments (q)-(u). (q) Each of R^{10}, R^{11}, R^{12}, and R^{13} is hydrogen. (r) One of R^{10}, R^{11}, R^{12}, and R^{13} is deuterium and the rest are hydrogen. (s) Two of R^{10}, R^{11}, R^{12}, and R^{13} are deuterium and the rest are hydrogen. (t) Three of R^{10}, R^{11}, R^{12}, and R^{13} are deuterium and the remaining is hydrogen. (u) Each of R^{10}, R^{11}, R^{12}, and R^{13} is deuterium.

[00107] In some embodiments, the claimed compound excludes a free base of a compound represented by formula A wherein R^1 is unsubstituted quinazolin-4-yl; R^2 is $-CH_2CH_2OCH_3$; R^{10}, R^{11}, R^{12}, and R^{13} are each H; p is 3; q is 0; the carbon to which R^1NH- is bonded is in the S configuration, and R^{15} and R^{16} together represent one or more of the following separate lettered embodiments (v)-(aa). (v) Each of R^{15} and R^{16} is hydrogen. (w) R^{15} is hydrogen and R^{16} is deuterium, or R^{15} is deuterium and R^{16} is hydrogen. (x) R^{15} and R^{16} are deuterium. (y) R^{15} is hydrogen and R^{16} is halogen, e.g., fluorine, or R^{15} is halogen, e.g., fluorine, and R^{16} is hydrogen. (z) R^{15} is deuterium and R^{16} is halogen, e.g., fluorine, or R^{15} is halogen, e.g., fluorine, and R^{16} is deuterium. (aa) R^{15} and R^{16} are each halogen, e.g., fluorine.

[00108] In some embodiments, the claimed compound excludes a free base of a compound represented by formula A wherein R^1 is unsubstituted quinazolin-4-yl; R^2 is $-CH_2CH_2OCH_3$; R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, and R^{16} are each H; q is 0; the carbon to which R^1NH- is bonded is in the S configuration; and p is one of the following separate lettered embodiments (ab)-(ad). (ab) p is 3. (ac) p is 4. (ad) p is 5.

[00109] In some embodiments, the claimed compound excludes a free base of a compound represented by formula A wherein R^1 is unsubstituted quinazolin-4-yl; R^2 is $-CH_2CH_2OCH_3$; R^{10}, R^{11}, R^{12}, R^{13}, R^{15}, and R^{16} are each H; p is 3; the carbon to which R^1NH- is bonded is in the S configuration; and q is one of the following separate lettered embodiments (ae)-(ah). (ae) q is 0. (af) q is 1. (ag) q is 2. (ah) q is 3.

[00110] In some embodiments, excluded is a free base of a compound of any combination of the lettered embodiments selected for each of R^1; R^2; R^{10}, R^{11}, R^{12}, and R^{13} together; R^{15} and R^{16} together; variable p; and variable q. For example, selected may be a combination of: R^1 from one of (a)-(k); R^2 from one of (l)-(p); R^{10}, R^{11}, R^{12}, and R^{13} together from one of (q)-(u); R^{15} and R^{16} together from one of (v)-(aa); variable p from among one of (ab)-(ad); and variable q from among one of (ae)-(ah). Exemplary combinations of lettered embodiments may include, for example: (a), (l), (q), (v), (ab), and (ae); (b), (l), (q), (v), (ab), and (ae); (c), (l), (q), (v), (ab), and (ae); (d), (l), (q), (v), (ab), and (ae); (e), (l), (q), (v), (ab), and (ae); (f), (l), (q), (v), (ab), and (ae); (g), (l), (q), (v), (ab), and (ae); (h), (l), (q), (v), (ab), and (ae); (i), (l), (q), (v), (ab), and (ae); (j), (l), (q), (v), (ab), and (ae); (k), (l), (q), (v), (ab), and (ae); (a), (m), (q), (v), (ab), and (ae); (b), (m), (q), (v), (ab), and (ae); (c), (m), (q), (v), (ab), and (ae); (d), (m), (q), (v), (ab), and (ae); (e), (m), (q), (v), (ab), and (ae); (f), (m), (q), (v), (ab), and (ae); (g), (m), (q), (v), (ab), and (ae); (h), (m), (q), (v), (ab), and (ae); (i), (m), (q), (v), (ab), and (ae); (j), (m), (q), (v), (ab), and (ae); (k), (m), (q), (v), (ab), and (ae); (a), (n), (q), (v), (ab), and (ae); (b), (n), (q), (v), (ab), and (ae); (c), (n), (q), (v), (ab), and (ae); (d), (n), (q), (v), (ab), and (ae); (e), (n), (q), (v), (ab), and (ae); (f), (n), (q), (v), (ab), and (ae); (g), (n), (q), (v), (ab), and (ae); (h), (n), (q), (v), (ab), and (ae); (i), (n), (q), (v), (ab), and (ae); (j), (n), (q), (v), (ab), and (ae); (k), (n), (q), (v), (ab), and (ae); (a), (o), (q), (v), (ab), and (ae); (b), (o), (q), (v), (ab), and (ae); (c), (o), (q), (v), (ab), and (ae); (d), (o), (q), (v), (ab), and (ae); (e), (o), (q), (v), (ab), and (ae); (f), (o), (q), (v), (ab), and (ae); (g), (o), (q), (v), (ab), and (ae); (h), (o), (q), (v), (ab), and (ae); (i), (o), (q), (v), (ab), and (ae); (j), (o), (q), (v), (ab), and (ae); (k), (o), (q), (v), (ab), and (ae); (a), (p), (q), (v), (ab), and (ae); (b), (p), (q), (v), (ab), and (ae); (c), (p), (q), (v), (ab), and (ae); (d), (p), (q), (v), (ab), and (ae); (e), (p), (q), (v), (ab), and (ae); (f), (p), (q), (v), (ab), and (ae); (g), (p), (q), (v), (ab), and (ae); (h), (p), (q), (v), (ab), and (ae); (i), (p), (q), (v), (ab), and (ae); (j), (p), (q), (v), (ab), and (ae); (k), (p), (q), (v), (ab), and (ae); any one of the preceding combinations in which (v) is replaced by (y); any one of the preceding combinations in which (v) is replaced by (aa); any one of the preceding combinations in which (ab) is replaced by (ad); or any one of the preceding combinations in which (ab) is replaced by (ae);

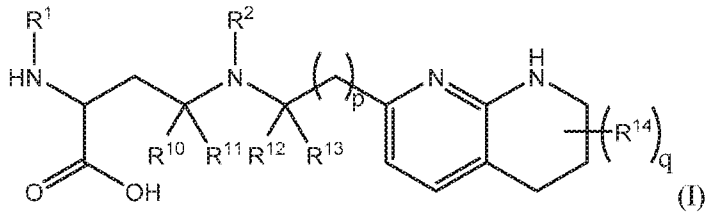
[00111] In some embodiments, excluded are salts of the compound of any one of, or any combination of, the lettered embodiments (a)-(ah) as described above. In some embodiments, excluded are pharmaceutical compositions that include the compound of any one of, or any combination of, the lettered embodiments (a)-(ah) as described above, or salts thereof. In some embodiments, excluded are kits that include the compound of any one of, or any combination of, the lettered embodiments (a)-(ah) as described above, or salts thereof. In some embodiments, excluded are dosage forms that include the compound of any one of, or any combination of, the lettered embodiments (a)-(ah) as described above. In some embodiments, excluded are methods that include the compound of any one of, or any combination of, the lettered embodiments (a)-(ah) as described above, or salts thereof.

[00112] In one variation is provided a compound of the formula (A), or a salt thereof, wherein the carbon bearing the CO_2H and NHR^1 moieties is in the "*S*" configuration. In another variation is provided a compound of the formula (A), or a salt thereof, wherein the carbon bearing the CO_2H and NHR^1 moieties is in the "*R*" configuration. Mixtures of a compound of the formula (A) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

[00113] In one variation of formula (A), R^2 has the proviso that any carbon atom bonded directly to a nitrogen atom is either unsubstituted or is substituted with deuterium.

[00114] In the descriptions herein, it is understood that every description, variation, embodiment or aspect of a moiety may be combined with every description, variation, embodiment or aspect of other moieties the same as if each and every combination of descriptions is specifically and individually listed. For example, every description, variation, embodiment or aspect provided herein with respect to R^1 of formula (A) may be combined with every description, variation, embodiment or aspect of R^2 the same as if each and every combination were specifically and individually listed.

[00115] In one aspect, provided is a compound of formula (I)



(I)

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 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 $-S(O)_2R^{2d}$;

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 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;

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; and

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

[00116] In one variation is provided a compound of the formula (I), or a salt thereof, wherein the carbon bearing the CO_2H and NHR^1 moieties is in the "*S*" configuration. In another variation is provided a compound of the formula (I), or a salt thereof, wherein the carbon bearing the CO_2H and NHR^1 moieties is in the "*R*" configuration. Mixtures of a compound of the formula (I) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

[00117] In one variation of formula (I), R^2 includes the proviso that any carbon atom bonded directly to a nitrogen atom is optionally substituted with an R^{2a} moiety other than halogen. In

one variation of formula (I), R^2 includes the proviso that any carbon atom bonded directly to a nitrogen atom is either unsubstituted or is substituted with deuterium.

[00118] In the descriptions herein, it is understood that every description, variation, embodiment or aspect of a moiety may be combined with every description, variation, embodiment or aspect of other moieties the same as if each and every combination of descriptions is specifically and individually listed. For example, every description, variation, embodiment or aspect provided herein with respect to R^1 of formula (I) may be combined with every description, variation, embodiment or aspect of R^2 the same as if each and every combination were specifically and individually listed.

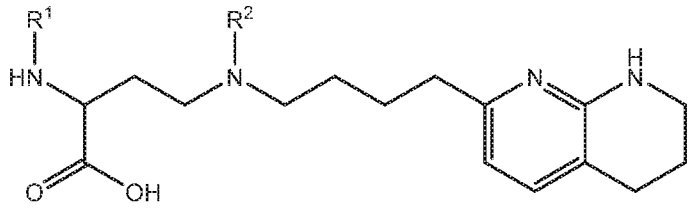
[00119] In some embodiments of the compound of formula (I), or a salt thereof, at least one of R^{1a}, R^{2a}, R^{2b}, R^{2c}, R^{2e}, R^{2f}, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, or R^{16} is deuterium.

[00120] In some embodiments of the compound of formula (I), or a salt thereof, R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}. In some embodiments, R^1 is pyrimidin-4-yl optionally substituted by R^{1a}. In some embodiments, R^1 is pyrimidin-4-yl optionally substituted by R^{1a} wherein R^{1a} is 5- to 10-membered heteroaryl (e.g., pyrazolyl) or C_1-C_6 alkyl optionally substituted by halogen (e.g., methyl, difluoromethyl, and trifluoromethyl). In some embodiments, R^1 is pyrimidin-4-yl optionally substituted by R^{1a} wherein R^{1a} is 5- to 10-membered heteroaryl (e.g., pyrazolyl or pyridinyl) or C_1-C_6 alkyl optionally substituted by halogen (e.g., methyl, difluoromethyl, and trifluoromethyl). In some embodiments, R^1 is pyrimidin-4-yl substituted by both methyl and trifluoromethyl. In some embodiments, R^1 is pyrimidin-4-yl substituted by both methyl and pyridinyl. In some embodiments, R^1 is pyrimidin-4-yl optionally substituted by R^{1a} wherein R^{1a} is C_6-C_{14} aryl (e.g., phenyl). In some embodiments, R^1 is pyrimidin-4-yl optionally substituted by R^{1a} wherein R^{1a} is –CN. In some embodiments, R^1 is pyrimidin-2-yl optionally substituted by R^{1a}. In some embodiments, R^1 is pyrimidin-2-yl optionally substituted by R^{1a} wherein R^{1a} is halogen, C_1-C_6 alkyl optionally substituted by halogen (e.g., methyl or trifluoromethyl), -CN, or C_3-C_8 cycloalkyl (e.g., cyclopropyl). In some embodiments of the compound of formula (I), or a salt thereof, R^1 is quinazolin-4-yl optionally substituted by R^{1a}. In some embodiments, R^1 is quinazolin-4-yl optionally substituted by R^{1a} wherein R^{1a} is halogen (e.g., fluoro and chloro), C_1-C_6 alkyl optionally substituted by halogen (e.g., methyl or trifluoromethyl), or C_1-C_6 alkoxy (e.g., methoxy). In some embodiments, R^1 is quinazolin-4-yl optionally substituted by R^{1a} wherein R^{1a} is 5- to 10-membered heteroaryl (e.g., pyridinyl). In some embodiments, R^1 is pyrazolopyrimidinyl optionally substituted by R^{1a}. In some

embodiments, R^1 is pyrazolopyrimidinyl optionally substituted by R^{1a}, wherein R^{1a} is C_1-C_6 alkyl (e.g., methyl). In some embodiments where R^1 is indicated as optionally substituted by R^{1a}, the R^1 moiety is unsubstituted. In some embodiments where R^1 is indicated as optionally substituted by R^{1a}, the R^1 moiety is substituted by one R^{1a}. In some embodiments where R^1 is indicated as optionally substituted by R^{1a}, the R^1 moiety is substituted by 2 to 6 or 2 to 5 or 2 to 4 or 2 to 3 R^{1a} moieties, which may be the same or different.

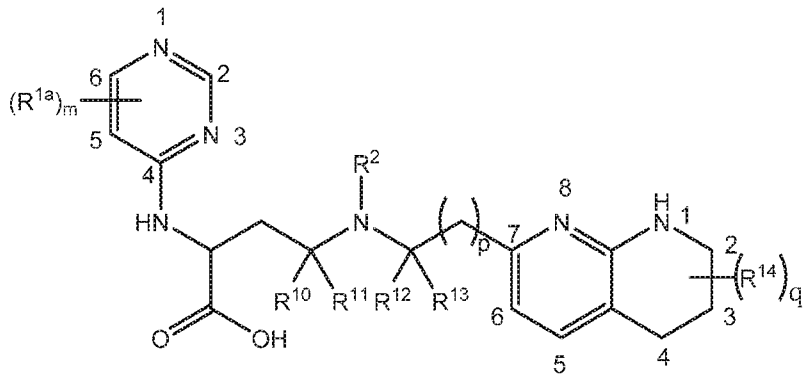
[00121] In some embodiments of formula (I), including the embodiments that describe the R^1 variable, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I), including the embodiments that describe the R^1 variable, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments, including the embodiments that describe the R^1 variable, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

[00122] In some embodiments of formula (I), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II):



(II) or a salt thereof, wherein R^1 and R^2 are as defined for formula (I).

[00123] In some embodiments of the compound of formula (I), wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}, the compound is of the formula (I-A):



(I-A)

or a salt thereof, wherein R^{1a}, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, q and p are as defined for formula (I), m is 0, 1, 2, or 3, and the positions on the pyrimidine ring and tetrahydronaphthyridine ring are as indicated.

[00124] In one embodiment is provided a compound of the formula (I-A), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*S*" configuration. In another

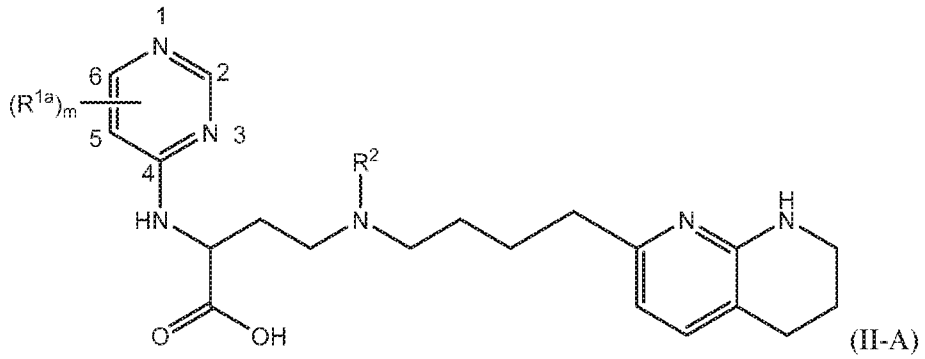
embodiment is provided a compound of the formula (I-A), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*R*" configuration. Mixtures of a compound of the formula (I-A) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

[00125] In some embodiments of the compound of formula (I-A), 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. In a further embodiment of the compound of formula (I-A), m is 0, 1, 2, or 3, and each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium. In some embodiments of formula (I-A), m is 1, 2 or 3.

[00126] In some embodiments of the compound of formula (I-A), m is 0. In some embodiments of the compound of formula (I-A), m is 1, and R^{1a} is at the 2-position. In some embodiments of the compound of formula (I-A), m is 1, and R^{1a} is at the 5-position. In some embodiments of the compound of formula (I-A), m is 1, and R^{1a} is at the 6-position. In some embodiments of the compound of formula (I-A), m is 2, and the R^{1a} groups are at the 2-position and 5-position. In some embodiments of the compound of formula (I-A), m is 2, and the R^{1a} groups are at the 2-position and 6-position. In some embodiments of the compound of formula (I-A), m is 2, and the R^{1a} groups are at the 5-position and 6-position. In some embodiments of the compound of formula (I-A), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 6-position. Whenever more than one R^{1a} group is present, the R^{1a} groups can be chosen independently. In any of these embodiments of the compound of formula (I-A), or a salt thereof, the carbon bearing the CO_2H and NH moieties may be in the "*S*" configuration or the "*R*" configuration.

[00127] In some embodiments of formula (I-A), including the embodiments that describe the R^{1a} and m variables, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I-A), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments of formula (I-A), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

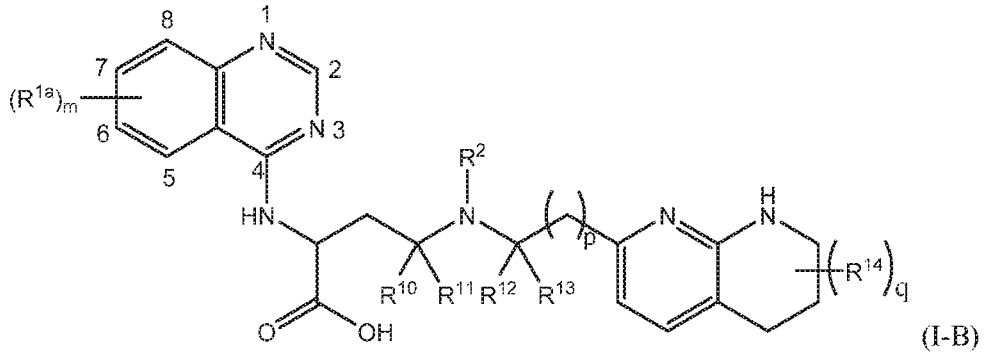
[00128] In some embodiments of formula (I-A), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II-A):



(II-A)

or a salt thereof, wherein R^{1a} and R^2 are as defined for formula (I), m is 0, 1, 2, or 3, and the positions on the pyrimidine ring are as indicated. All descriptions of R^{1a}, R^2 and m with reference to formula (I) apply equally to formulae (I-A) and (II-A).

[00129] In some embodiments of the compound of formula (I), wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}, the compound is of the formula (I-B):



(I-B)

or a salt thereof, wherein R^{1a}, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, q and p are as defined for formula (I), m is 0, 1, 2, 3, 4, or 5, and the positions on the quinazoline ring are as indicated.

[00130] In one embodiment is provided a compound of the formula (I-B), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*S*" configuration. In another embodiment is provided a compound of the formula (I-B), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*R*" configuration. Mixtures of a compound of the formula (I-B) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

[00131] In some embodiments of the compound of formula (I-B), 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

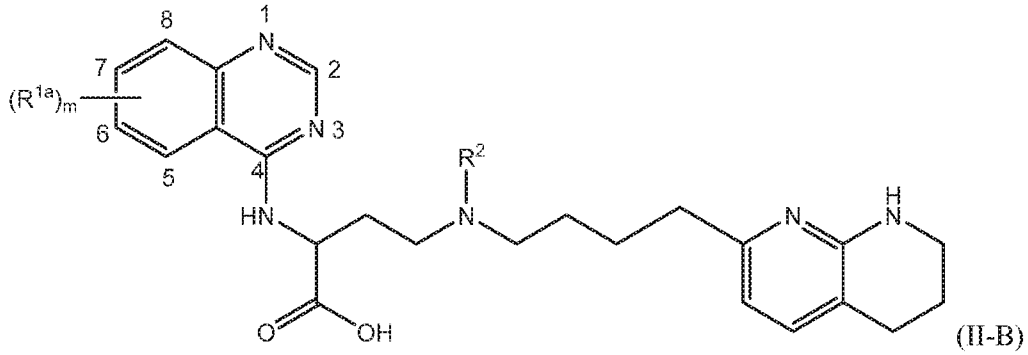
R^{1a} are independently optionally substituted by deuterium. In a further embodiment of the compound of formula (I-B), m is 0, 1, 2, 3, 4, or 5, and each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium. In some embodiments of the compound of formula (I-B), m is 1, 2, 3, 4, or 5.

[00132] In some embodiments of the compound of formula (I-B), m is 0. In some embodiments of the compound of formula (I-B), m is 1, and R^{1a} is at the 2-position. In some embodiments of the compound of formula (I-B), m is 1, and R^{1a} is at the 5-position. In some embodiments of the compound of formula (I-B), m is 1, and R^{1a} is at the 6-position. In some embodiments of the compound of formula (I-B), m is 1, and R^{1a} is at the 7-position. In some embodiments of the compound of formula (I-B), m is 1, and R^{1a} is at the 8-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 2-position and 5-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 2-position and 6-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 2-position and 7-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 2-position and 8-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 5-position and 6-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 5-position and 7-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 5-position and 8-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 6-position and 7-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 6-position and 8-position. In some embodiments of the compound of formula (I-B), m is 2, and the R^{1a} groups are at the 7-position and 8-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 7-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 2-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 2-position, 6-position, and 8-position. In some embodiments of the

compound of formula (I-B), m is 3, and the R^{1a} groups are at the 2-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 3, and the R^{1a} groups are at the 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 4, and the R^{1a} groups are at the 2-position, 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-B), m is 4, and the R^{1a} groups are at the 2-position, 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 4, and the R^{1a} groups are at the 2-position, 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 4, and the R^{1a} groups are at the 2-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 4, and the R^{1a} groups are at the 5-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-B), m is 5, and the R^{1a} groups are at the 2-position, 5-position, 6-position, 7-position, and 8-position. Whenever more than one R^{1a} group is present, the R^{1a} groups can be chosen independently. In any of these embodiments of the compound of formula (I-B), or a salt thereof, the carbon bearing the CO_2H and NH moieties may be in the "*S*" configuration or the "*R*" configuration.

[00133] In some embodiments of formula (I-B), including the embodiments that describe the R^{1a} and m variables, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I-B), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments of formula (I-B), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

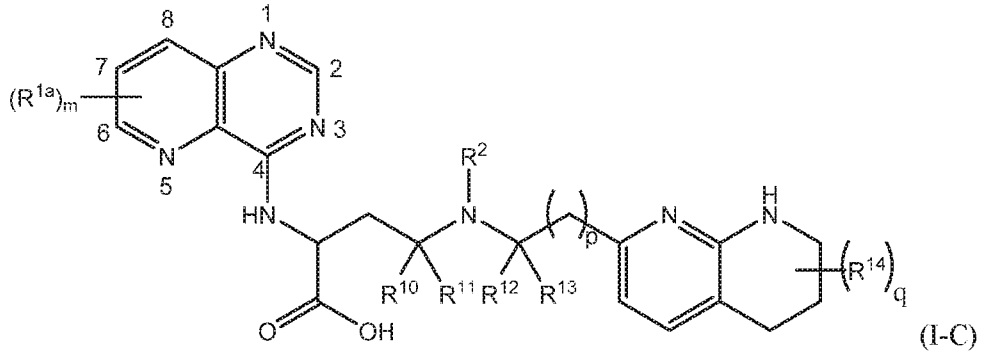
[00134] In some embodiments of formula (I-B), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II-B):



(II-B)

or a salt thereof, wherein R^{1a} and R^2 are as defined for formula (I), m is 0, 1, 2, 3, 4, or 5, and the positions on the quinazoline ring are as indicated. All descriptions of R^{1a}, R^2 and m with reference to formula (I) apply equally to formulae (I-B) and (II-B).

[00135] In some embodiments of the compound of formula (I), wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}, the compound is of the formula (I-C):



(I-C)

or a salt thereof, wherein R^{1a}, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, q and p are as defined for formula (I), m is 0, 1, 2, 3, or 4, and the positions on the pyrido[3,2-*d*]pyrimidine ring are as indicated. In one embodiment is provided a compound of the formula (I-C), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*S*" configuration. In another embodiment is provided a compound of the formula (I-C), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*R*" configuration. Mixtures of a compound of the formula (I-C) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

[00136] In some embodiments of the compound of formula (I-C), 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

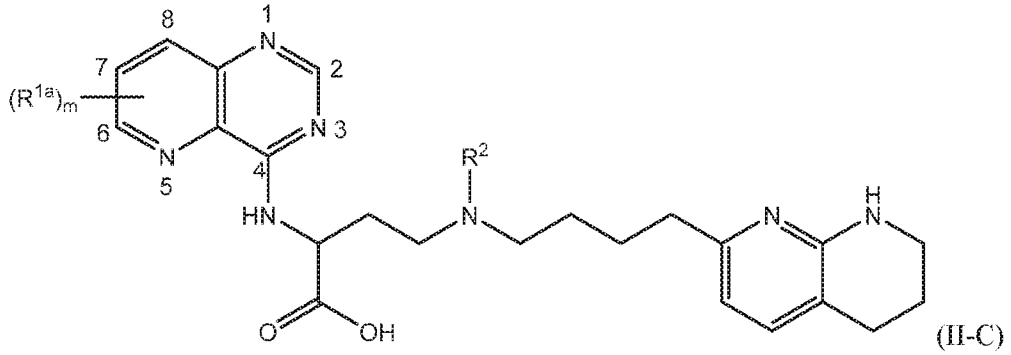
R^{1a} are independently optionally substituted by deuterium. In a further embodiment of the compound of formula (I-C), m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium. In some embodiments of the compound of formula (I-C), m is 1, 2, 3, or 4

[00137] In some embodiments of the compound of formula (I-C), m is 0. In some embodiments of the compound of formula (I-C), m is 1, and R^{1a} is at the 2-position. In some embodiments of the compound of formula (I-C), m is 1, and R^{1a} is at the 6-position. In some embodiments of the compound of formula (I-C), m is 1, and R^{1a} is at the 7-position. In some embodiments of the compound of formula (I-C), m is 1, and R^{1a} is at the 8-position. In some embodiments of the compound of formula (I-C), m is 2, and the R^{1a} groups are at the 2-position and 6-position. In some embodiments of the compound of formula (I-C), m is 2, and the R^{1a} groups are at the 2-position and 7-position. In some embodiments of the compound of formula (I-C), m is 2, and the R^{1a} groups are at the 2-position and 8-position. In some embodiments of the compound of formula (I-C), m is 2, and the R^{1a} groups are at the 6-position and 7-position. In some embodiments of the compound of formula (I-C), m is 2, and the R^{1a} groups are at the 6-position and 8-position. In some embodiments of the compound of formula (I-C), m is 2, and the R^{1a} groups are at the 7-position and 8-position. In some embodiments of the compound of formula (I-C), m is 3, and the R^{1a} groups are at the 2-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-C), m is 3, and the R^{1a} groups are at the 2-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-C), m is 3, and the R^{1a} groups are at the 2-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-C), m is 3, and the R^{1a} groups are at the 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-C), m is 4, and the R^{1a} groups are at the 2-position, 6-position, 7-position, and 8-position. Whenever more than one R^{1a} group is present, the R^{1a} groups can be chosen independently. In any of these embodiments of the compound of formula (I-C), or a salt thereof, the carbon bearing the CO_2H and NH moieties may be in the "*S*" configuration or the "*R*" configuration.

[00138] In some embodiments of formula (I-C), including the embodiments that describe the R^{1a} and m variables, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I-C), including the embodiments that describe the R^{1a} and m variables, and/or the

R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments of formula (I-C), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

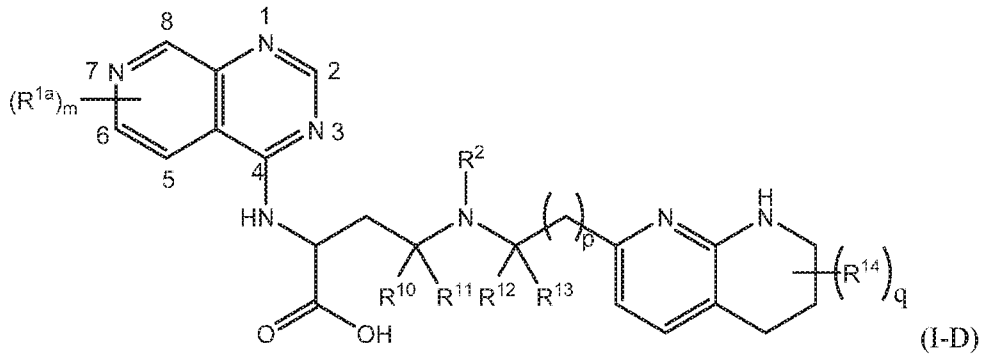
[00139] In some embodiments of formula (I-C), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II-C):



(II-C)

or a salt thereof, wherein R^{1a} and R^2 are as defined for formula (I), m is 0, 1, 2, 3, or 4, and the positions on the pyrido[3,2-*d*]pyrimidine ring are as indicated. All descriptions of R^{1a}, R^2 and m with reference to formula (I) apply equally to formulae (I-C) and (II-C).

[00140] In some embodiments of the compound of formula (I), wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}, the compound is of the formula (I-D):



(I-D)

or a salt thereof, wherein R^{1a}, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, q and p are as defined for formula (I), m is 0, 1, 2, 3, or 4, and the positions on the pyrido[3,4-*d*]pyrimidine ring are as indicated.

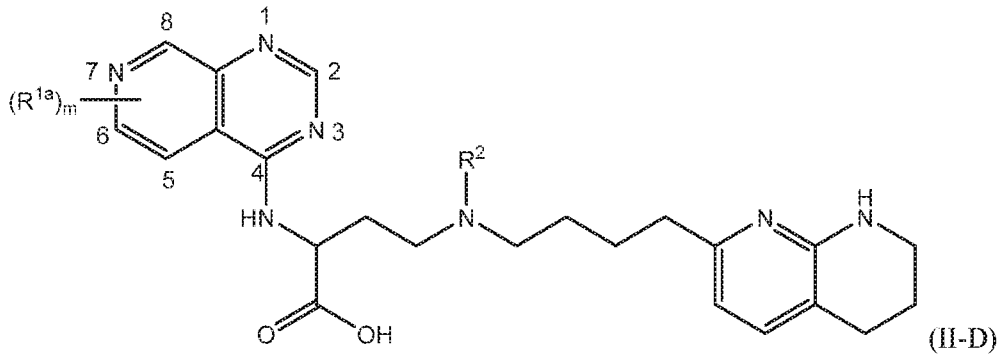
[00141] In one embodiment is provided a compound of the formula (I-D), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*S*" configuration. In another embodiment is provided a compound of the formula (I-D), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*R*" configuration. Mixtures of a compound of the formula (I-D) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

[00142] In some embodiments of the compound of formula (I-D), 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. In a further embodiment of the compound of formula (I-D), m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium. In some embodiments of the compound of formula (I-D), m is 1, 2, 3, or 4.

[00143] In some embodiments of the compound of formula (I-D), m is 0. In some embodiments of the compound of formula (I-D), m is 1, and R^{1a} is at the 2-position. In some embodiments of the compound of formula (I-D), m is 1, and R^{1a} is at the 5-position. In some embodiments of the compound of formula (I-D), m is 1, and R^{1a} is at the 6-position. In some embodiments of the compound of formula (I-D), m is 1, and R^{1a} is at the 8-position. In some embodiments of the compound of formula (I-D), m is 2, and the R^{1a} groups are at the 2-position and 5-position. In some embodiments of the compound of formula (I-D), m is 2, and the R^{1a} groups are at the 2-position and 6-position. In some embodiments of the compound of formula (I-D), m is 2, and the R^{1a} groups are at the 2-position and 8-position. In some embodiments of the compound of formula (I-D), m is 2, and the R^{1a} groups are at the 5-position and 6-position. In some embodiments of the compound of formula (I-D), m is 2, and the R^{1a} groups are at the 5-position and 8-position. In some embodiments of the compound of formula (I-D), m is 2, and the R^{1a} groups are at the 6-position and 8-position. In some embodiments of the compound of formula (I-D), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-D), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 8-position. In some embodiments of the compound of formula (I-D), m is 3, and the R^{1a} groups are at the 2-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-D), m is 3, and the R^{1a} groups are at the 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-D), m is 4, and the R^{1a} groups are at the 2-position, 5-position, 6-position, and 8-position. Whenever more than one R^{1a} group is present, the R^{1a} groups can be chosen independently. In any of these embodiments of the compound of formula (I-D), or a salt thereof, the carbon bearing the CO_2H and NH moieties may be in the "*S*" configuration or the "*R*" configuration.

[00144] In some embodiments of formula (I-D), including the embodiments that describe the R^{1a} and m variables, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I-D), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments of formula (I-D), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

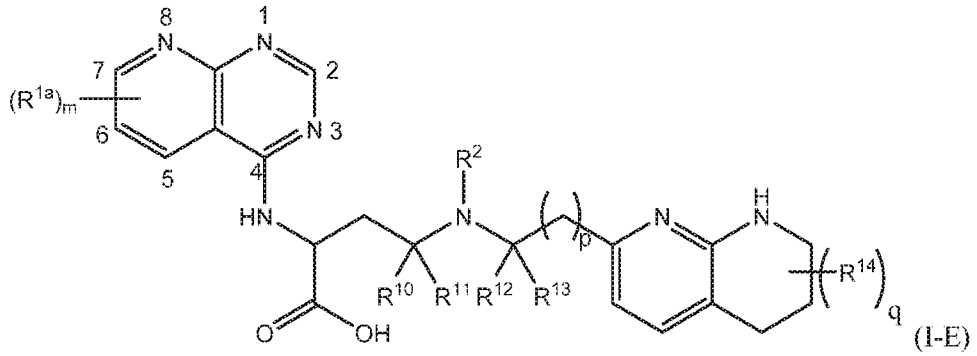
[00145] In some embodiments of formula (I-D), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II-D):



(II-D)

or a salt thereof, wherein R^{1a} and R^2 are as defined for formula (I), m is 0, 1, 2, 3, or 4, and the positions on the pyrido[3,4-*d*]pyrimidine ring are as indicated. All descriptions of R^{1a}, R^2 and m with reference to formula (I) apply equally to formulae (I-D) and (II-D).

[00146] In some embodiments of the compound of formula (I), wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}, the compound is of the formula (I-E):



(I-E)

or a salt thereof, wherein R^{1a}, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, q and p are as defined for formula (I), m is 0, 1, 2, 3, or 4, and the positions on the pyrido[2,3-*d*]pyrimidine ring are as indicated.

[00147] In one embodiment is provided a compound of the formula (I-E), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*S*" configuration. In another embodiment is provided a compound of the formula (I-E), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*R*" configuration. Mixtures of a

compound of the formula (I-E) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

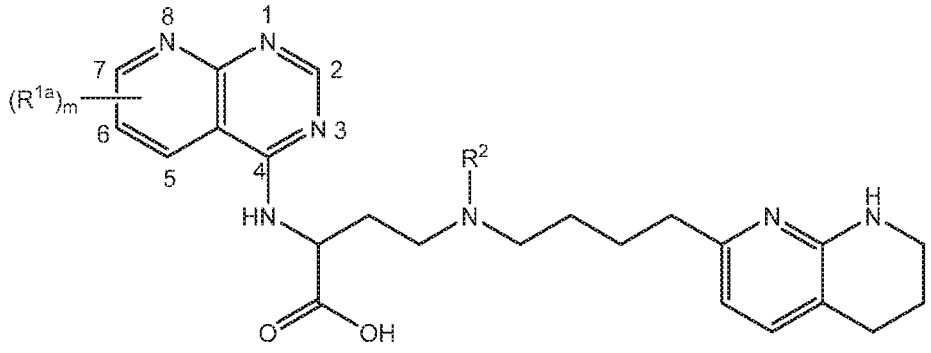
[00148] In some embodiments of the compound of formula (I-E), m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium. In a further embodiment of the compound of formula (I-E), m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium. In some embodiments of the compound of formula (I-E), m is 1, 2, 3, or 4.

[00149] In some embodiments of the compound of formula (I-E), m is 0. In some embodiments of the compound of formula (I-E), m is 1, and R^{1a} is at the 2-position. In some embodiments of the compound of formula (I-E), m is 1, and R^{1a} is at the 5-position. In some embodiments of the compound of formula (I-E), m is 1, and R^{1a} is at the 6-position. In some embodiments of the compound of formula (I-E), m is 1, and R^{1a} is at the 7-position. In some embodiments of the compound of formula (I-E), m is 2, and the R^{1a} groups are at the 2-position and 5-position. In some embodiments of the compound of formula (I-E), m is 2, and the R^{1a} groups are at the 2-position and 6-position. In some embodiments of the compound of formula (I-E), m is 2, and the R^{1a} groups are at the 2-position and 7-position. In some embodiments of the compound of formula (I-E), m is 2, and the R^{1a} groups are at the 5-position and 6-position. In some embodiments of the compound of formula (I-E), m is 2, and the R^{1a} groups are at the 5-position and 7-position. In some embodiments of the compound of formula (I-E), m is 2, and the R^{1a} groups are at the 6-position and 7-position. In some embodiments of the compound of formula (I-E), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-E), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 7-position. In some embodiments of the compound of formula (I-E), m is 3, and the R^{1a} groups are at the 2-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-E), m is 3, and the R^{1a} groups are at the 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-E), m is 4, and the R^{1a} groups are at the 2-position, 5-position, 6-position, and 7-position. Whenever more than one R^{1a} group is present,

the R^{1a} groups can be chosen independently. In any of these embodiments of the compound of formula (I-E), or a salt thereof, the carbon bearing the CO_2H and NH moieties may be in the "*S*" configuration or the "*R*" configuration.

[00150] In some embodiments of formula (I-E), including the embodiments that describe the R^{1a} and m variables, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I-E), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments of formula (I-E), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

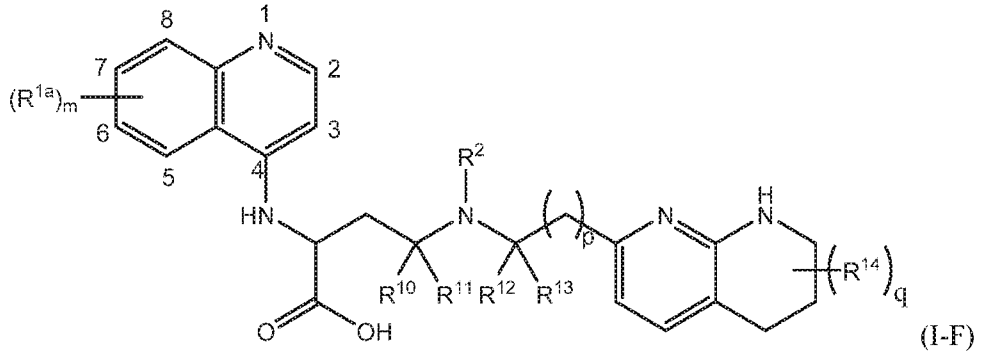
[00151] In some embodiments of formula (I-E), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II-E):



(II-E)

or a salt thereof, wherein R^{1a} and R^2 are as defined for formula (I), m is 0, 1, 2, 3, or 4, and the positions on the pyrido[2,3-*d*]pyrimidine ring are as indicated. All descriptions of R^{1a}, R^2 and m with reference to formula (I) apply equally to formulae (I-E) and (II-E).

[00152] In some embodiments of the compound of formula (I), wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}, the compound is of the formula (I-F):



(I-F)

or a salt thereof, wherein R^{1a}, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, q and p are as defined for formula (I), m is 0, 1, 2, 3, 4, 5, or 6 and the positions on the quinoline ring are as indicated.

[00153] In one embodiment is provided a compound of the formula (I-F), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*S*" configuration. In another embodiment is provided a compound of the formula (I-F), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*R*" configuration. Mixtures of a compound of the formula (I-F) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

[00154] In some embodiments of the compound of formula (I-F), 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. In a further embodiment of the compound of formula (I-F), m is 0, 1, 2, 3, 4, 5, or 6, and each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium. In some embodiments of the compound of formula (I-F), m is 1, 2, 3, 4, 5, or 6.

[00155] In some embodiments of the compound of formula (I-F), m is 0. In some embodiments of the compound of formula (I-F), m is 1, and R^{1a} is at the 2-position. In some embodiments of the compound of formula (I-F), m is 1, and R^{1a} is at the 3-position. In some embodiments of the compound of formula (I-F), m is 1, and R^{1a} is at the 5-position. In some embodiments of the compound of formula (I-F), m is 1, and R^{1a} is at the 6-position. In some embodiments of the compound of formula (I-F), m is 1, and R^{1a} is at the 7-position. In some embodiments of the compound of formula (I-F), m is 1, and R^{1a} is at the 8-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 2-position and 3-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 2-position and 5-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 2-position and 6-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 2-position and 7-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 2-position and 8-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 3-position and 5-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 3-position and 6-position. In some embodiments of the compound of formula (I-F), m is 2, and

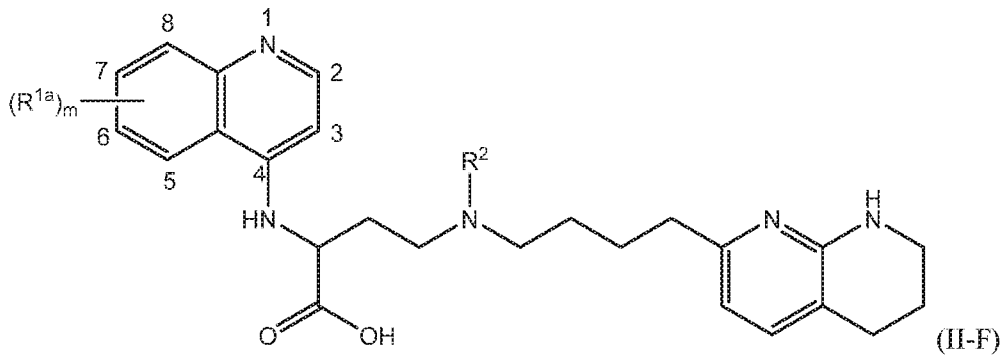
the R^{1a} groups are at the 3-position and 7-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 3-position and 8-position.In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 5-position and 6-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 5-position and 7-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 5-position and 8-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 6-position and 7-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 6-position and 8-position. In some embodiments of the compound of formula (I-F), m is 2, and the R^{1a} groups are at the 7-position and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 3-position, and 5-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 3-position, and 6-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 3-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 3-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 5-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 2-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 3-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 3-position, 5-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 3-position, 5-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 3-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 3-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 3-position, 7-position, and 8-position. In some

embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 3, and the R^{1a} groups are at the 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 3-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 3-position, 5-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 3-position, 5-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 3-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 3-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 3-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 2-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 3-position, 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 3-position, 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 3-position, 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 3-position, 6-position, 7-position, and 8-position.In some embodiments of the compound of formula (I-F), m is 4, and the R^{1a} groups are at the 5-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 5, and the R^{1a} groups are at the 2-position, 3-position, 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-F), m is 5, and the R^{1a} groups are at the 2-position, 3-position, 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-F),

m is 5, and the R^{1a} groups are at the 2-position, 3-position, 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 5, and the R^{1a} groups are at the 2-position, 3-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 5, and the R^{1a} groups are at the 2-position, 5-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 5, and the R^{1a} groups are at the 3-position, 5-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-F), m is 6, and the R^{1a} groups are at the 2-position, 3-position, 5-position, 6-position, 7-position, and 8-position. Whenever more than one R^{1a} group is present, the R^{1a} groups can be chosen independently. In any of these embodiments of the compound of formula (I-F), or a salt thereof, the carbon bearing the CO_2H and NH moieties may be in the "*S*" configuration or the "*R*" configuration.

[00156] In some embodiments of formula (I-F), including the embodiments that describe the R^{1a} and m variables, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I-F), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments of formula (I-F), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

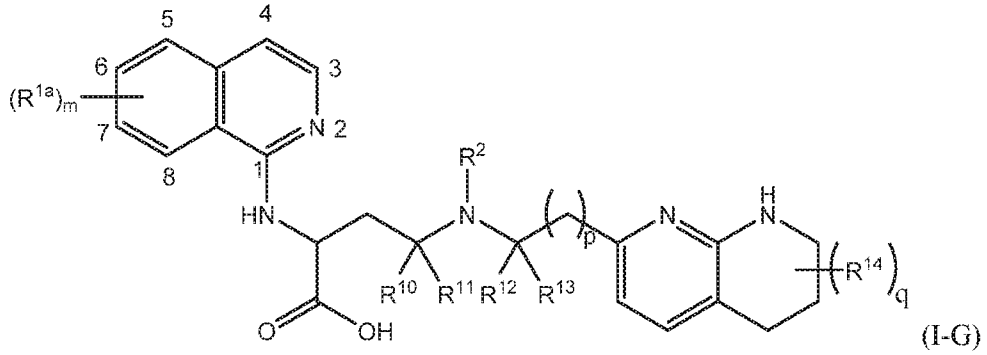
[00157] In some embodiments of formula (I-F), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II-F):



(II-F)

or a salt thereof, wherein R^{1a} and R^2 are as defined for formula (I), m is 0, 1, 2, 3, 4, 5, or 6 and the positions on the quinoline ring are as indicated. All descriptions of R^{1a}, R^2 and m with reference to formula (I) apply equally to formulae (I-F) and (II-F).

[00158] In some embodiments of the compound of formula (I), wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}, the compound is of the formula (I-G):



(I-G)

or a salt thereof, wherein R^{1a}, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, q and p are as defined for formula (I), m is 0, 1, 2, 3, 4, 5, or 6 and the positions on the isoquinoline ring are as indicated.

[00159] In one embodiment is provided a compound of the formula (I-G), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*S*" configuration. In another embodiment is provided a compound of the formula (I-G), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*R*" configuration. Mixtures of a compound of the formula (I-G) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

[00160] In some embodiments of the compound of formula (I-G), 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. In a further embodiment of the compound of formula (I-G), m is 0, 1, 2, 3, 4, 5, or 6, and each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium. In some embodiments of the compound of formula (I-G), m is 1, 2, 3, 4, 5, or 6.

[00161] In some embodiments of the compound of formula (I-G), m is 0. In some embodiments of the compound of formula (I-G), m is 1, and R^{1a} is at the 3-position. In some embodiments of the compound of formula (I-G), m is 1, and R^{1a} is at the 4-position. In some embodiments of the compound of formula (I-G), m is 1, and R^{1a} is at the 5-position. In some embodiments of the compound of formula (I-G), m is 1, and R^{1a} is at the 6-position. In some embodiments of the compound of formula (I-G), m is 1, and R^{1a} is at the 7-position. In some embodiments of the compound of formula (I-G), m is 1, and R^{1a} is at the 8-position. In some

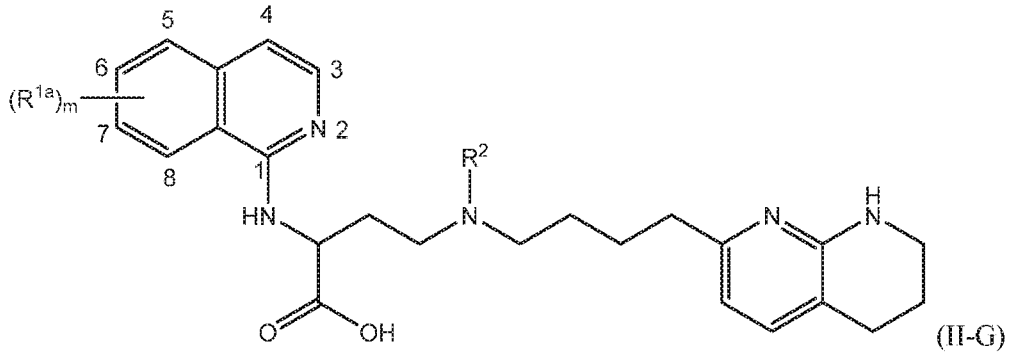
embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 3-position and 4-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 4-position and 5-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 4-position and 6-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 4-position and 7-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 4-position and 8-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 3-position and 5-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 3-position and 6-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 3-position and 7-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 3-position and 8-position.In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 5-position and 6-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 5-position and 7-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 5-position and 8-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 6-position and 7-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 6-position and 8-position. In some embodiments of the compound of formula (I-G), m is 2, and the R^{1a} groups are at the 7-position and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 4-position, and 5-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 4-position, and 6-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 4-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 4-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 4-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 4-position, 5-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 4-position, 5-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 4-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 4-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-G),

m is 3, and the R^{1a} groups are at the 4-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 5-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 5-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 3-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 3, and the R^{1a} groups are at the 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 4-position, 5-position, and 6-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 4-position, 5-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 4-position, 5-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 4-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 4-position, 3-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 4-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 4-position, 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 4-position, 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 4-position, 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 4-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 5-position, 6-position, and 7-position. In some embodiments of the compound of

formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 3-position, 6-position, 7-position, and 8-position.In some embodiments of the compound of formula (I-G), m is 4, and the R^{1a} groups are at the 5-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 5, and the R^{1a} groups are at the 3-position, 4-position, 5-position, 6-position, and 7-position. In some embodiments of the compound of formula (I-G), m is 5, and the R^{1a} groups are at the 3-position, 4-position, 5-position, 6-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 5, and the R^{1a} groups are at the 3-position, 4-position, 5-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 5, and the R^{1a} groups are at the 3-position, 4-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 5, and the R^{1a} groups are at the 4-position, 5-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 5, and the R^{1a} groups are at the 3-position, 5-position, 6-position, 7-position, and 8-position. In some embodiments of the compound of formula (I-G), m is 6, and the R^{1a} groups are at the 3-position, 4-position, 5-position, 6-position, 7-position, and 8-position. Whenever more than one R^{1a} group is present, the R^{1a} groups can be chosen independently. In any of these embodiments of the compound of formula (I-G), or a salt thereof, the carbon bearing the CO_2H and NH moieties may be in the "*S*" configuration or the "*R*" configuration.

[00162] In some embodiments of formula (I-G), including the embodiments that describe the R^{1a} and m variables, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I-G), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments of formula (I-G), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

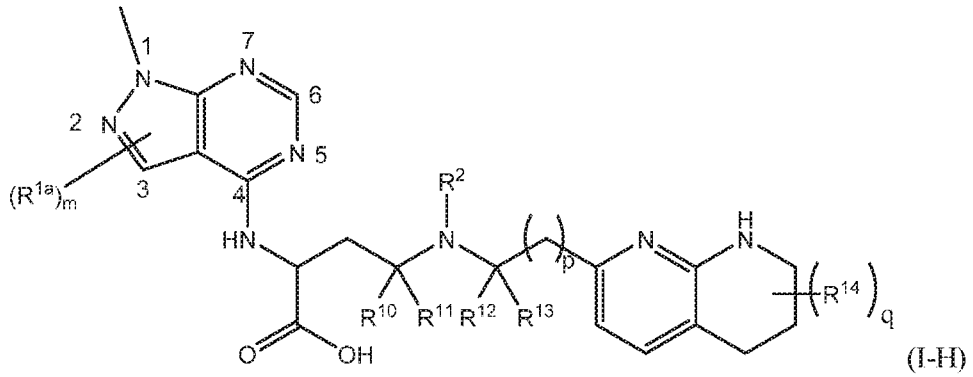
[00163] In some embodiments of formula (I-G), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II-G):



(II-G)

or a salt thereof, wherein R^{1a} and R^2 are as defined for formula (I), m is 0, 1, 2, 3, 4, 5, or 6 and the positions on the isoquinoline ring are as indicated. All descriptions of R^{1a}, R^2 and m with reference to formula (I) apply equally to formulae (I-G) and (II-G).

[00164] In some embodiments of the compound of formula (I), wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}, the compound is of the formula (I-H):



(I-H)

or a salt thereof, wherein R^{1a}, R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, q and p are as defined for formula (I), m is 0, 1, or 2, and the positions on the 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine ring are as indicated.

[00165] In one embodiment is provided a compound of the formula (I-H), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*S*" configuration. In another embodiment is provided a compound of the formula (I-H), or a salt thereof, wherein the carbon bearing the CO_2H and NH moieties is in the "*R*" configuration. Mixtures of a compound of the formula (I-H) are also embraced, including racemic or non-racemic mixtures of a given compound, and mixtures of two or more compounds of different chemical formulae.

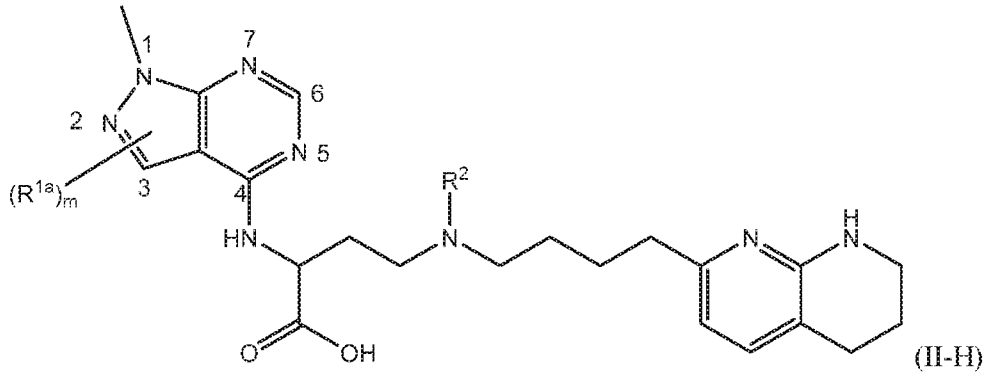
[00166] In some embodiments of the compound of formula (I-H), m is 0, 1, or 2, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy,

hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium. In a further embodiment of the compound of formula (I-H), m is 0, 1, or 2, and each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium. In some embodiments of the compound of formula (I-H), m is 1 or 2.

[00167] In some embodiments of the compound of formula (I-H), m is 0. In some embodiments of the compound of formula (I-H), m is 1, and R^{1a} is at the 3-position. In some embodiments of the compound of formula (I-H), m is 1, and R^{1a} is at the 6-position. In some embodiments of the compound of formula (I-H), m is 2, and the R^{1a} groups are at the 3-position and 6-position. Whenever more than one R^{1a} group is present, the R^{1a} groups can be chosen independently. In any of these embodiments of the compound of formula (I-H), or a salt thereof, the carbon bearing the CO_2H and NH moieties may be in the "*S*" configuration or the "*R*" configuration.

[00168] In some embodiments of formula (I-H), including the embodiments that describe the R^{1a} and m variables, each of R^{10}, R^{11}, R^{12} and R^{13} are hydrogen. In some embodiments of formula (I-H), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables, q is 0. In some embodiments of formula (I-H), including the embodiments that describe the R^{1a} and m variables, and/or the R^{10}, R^{11}, R^{12} and R^{13} variables and/or the q variable, p is 3, 4 or 5.

[00169] In some embodiments of formula (I-H), R^{10}, R^{11}, R^{12} and R^{13} are hydrogen, p is 3, q is 0 and the compound is of the formula (II-H):

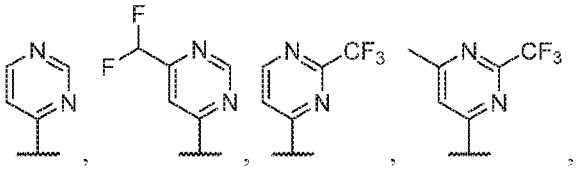


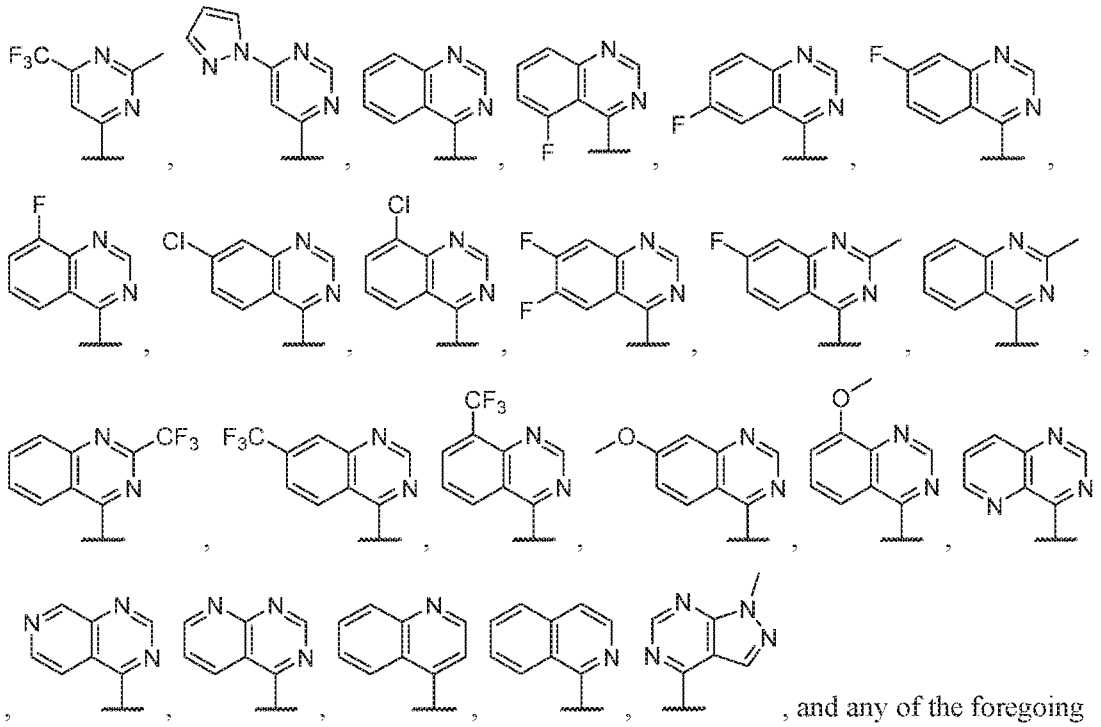
(II-H)

or a salt thereof, wherein R^{1a} and R^2 are as defined for formula (I), m is 0, 1, or 2, and the positions on the 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine ring are as indicated. All

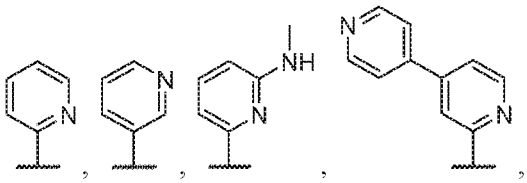
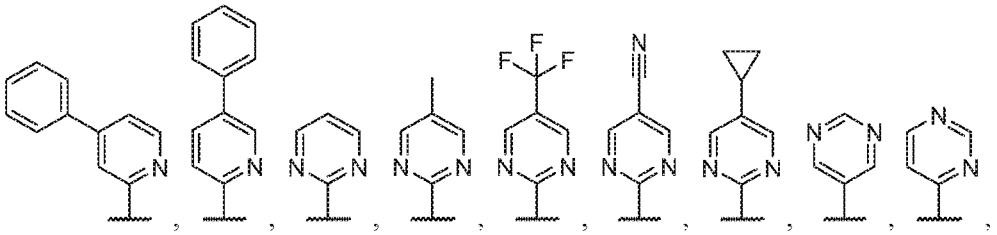
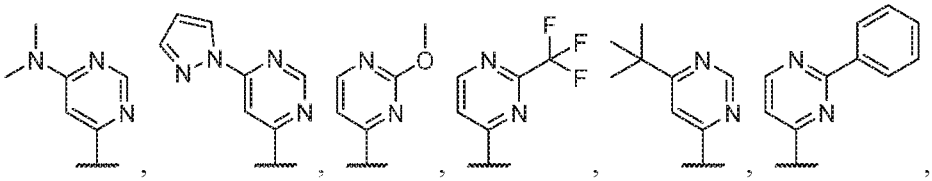
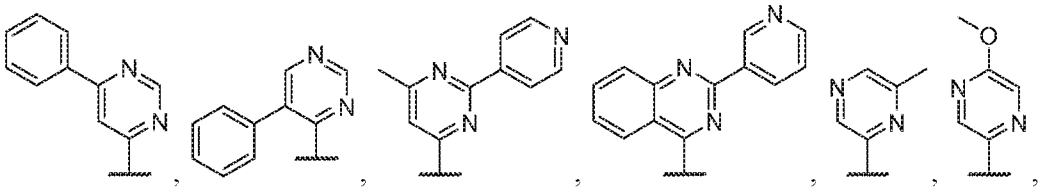
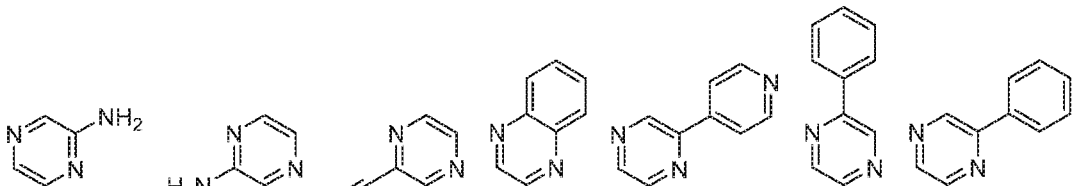
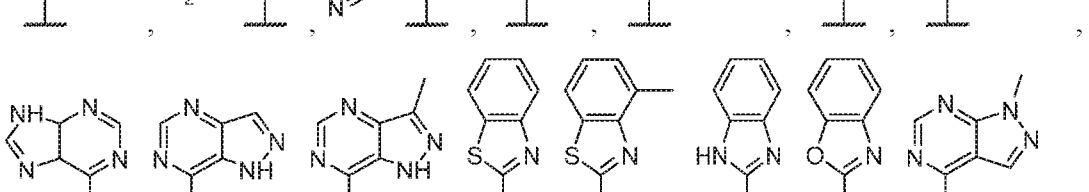
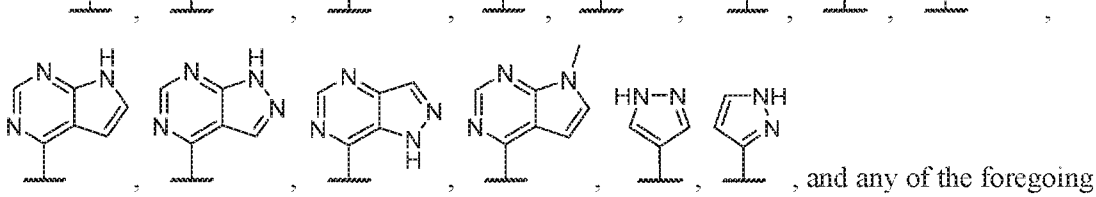
descriptions of R^{1a}, R^2 and m with reference to formula (I) apply equally to formulae (I-H) and (II-H).

[00170] Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}. In some embodiments, R^1 is unsubstituted 5- to 10-membered heteroaryl (e.g., pyridinyl, pyrimidinyl, quinoxalinyl, quinazolinyl, pyrazolopyrimidinyl, quinolinyl, pyridopyrimidinyl, thienopyrimidinyl, pyridinyl, pyrrolopyrimidinyl, benzothiazolyl, isoquinolinyl, purinyl, or benzooxazolyl). In some embodiments, R^1 is 5- to 10-membered heteroaryl substituted by 1, 2, 3, 4, or 5 R^{1a} groups which may be the same or different, wherein each R^{1a} is independently selected from halogen (e.g., fluoro, chloro, or bromo), C_1-C_6 alkyl optionally substituted by halogen (e.g., -CH_3, -CHF_2, -CF_3, or $C(CH_3)_3$), C_3-C_6 cycloalkyl (e.g., cyclopropyl), 5- to 10-membered heteroaryl (e.g., pyridinyl or pyrazolyl), C_6-C_{14} aryl (e.g., phenyl), -CN, -OR^3 (e.g., -OCH_3), and -NR^4R^5 (e.g., -$N(CH_3)_2$). In some embodiments, R^1 is 5-membered heteroaryl (e.g., pyrazolyl) substituted by 1, 2, 3, or 4 R^{1a} groups which may be the same or different and is selected from -CH_3, -CH_2F, -CHF_2, and -CF_3. In some embodiments, R^1 is 6-membered heteroaryl (e.g., pyridinyl, pyrimidinyl, or pyrazinyl) substituted by 1, 2, 3, 4, or 5 R^{1a} groups which may be the same or different and is selected from halogen (e.g., fluoro, chloro, or bromo), C_3-C_6 cycloalkyl (e.g., cyclopropyl), 5- to 6-membered heteroaryl (e.g., pyridinyl or pyrazolyl), C_6-C_{10} aryl (e.g., phenyl), C_1-C_4 alkyl optionally substituted by halogen (e.g., -CH_3, -CF_3 or $C(CH_3)_3$), -CN, -OR^3 (e.g., -OCH_3), and -NR^4R^5 (e.g., -$N(CH_3)_2$). In some embodiments, R^1 is 9-membered heteroaryl (e.g., pyrazolopyrimidinyl, pyrrolopyrimidinyl, thienopyrimidinyl, indazolyl, indolyl, or benzoimidazolyl) substituted by 1, 2, 3, 4, or 5 R^{1a} groups which may be the same or different and is selected from -CH_3, -CH_2F, -CHF_2, and -CF_3. In some embodiments, R^1 is 10-membered heteroaryl (e.g., quinazolinyl) substituted by 1, 2, 3, 4, or 5 R^{1a} groups which may be the same or different and is selected from halogen (e.g., fluoro or chloro), 5- to 6-membered heteroaryl (e.g., pyridinyl), C_1 alkyl optionally substituted by halogen (e.g., -CH_3 or -CF_3), and -OR^3 (e.g., -OCH_3).

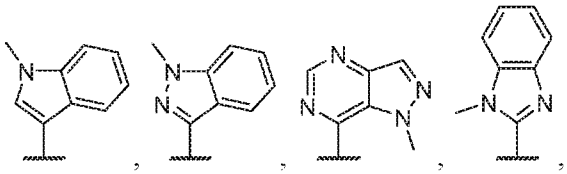
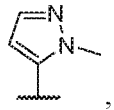
[00171] Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is selected from the group consisting of  ,

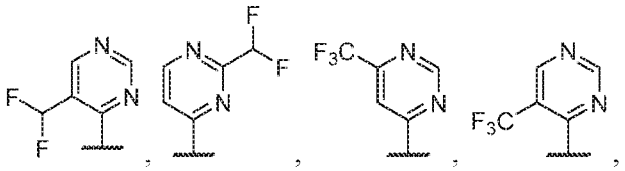
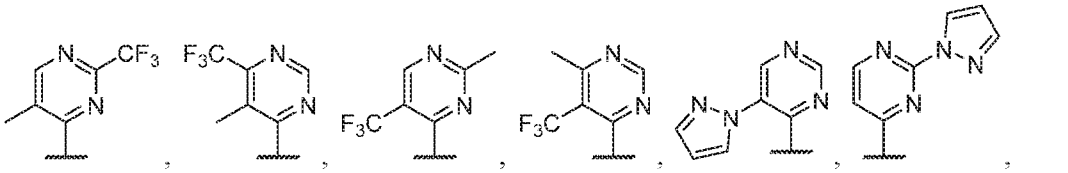
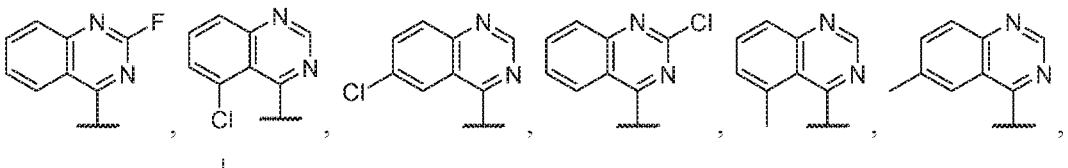
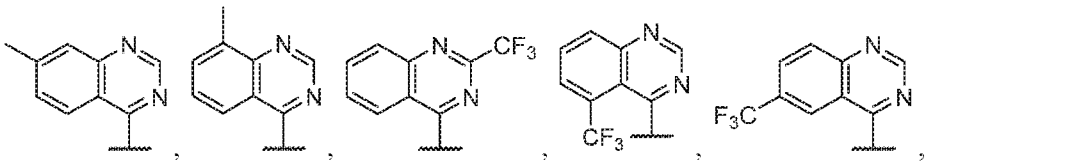
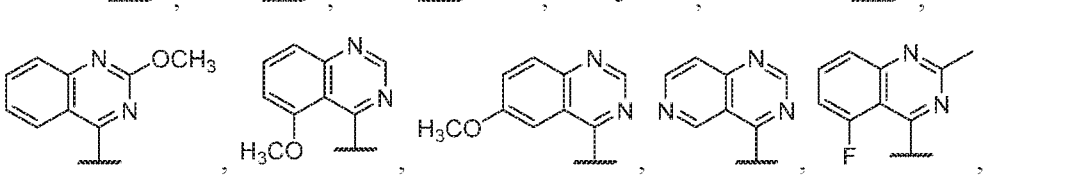
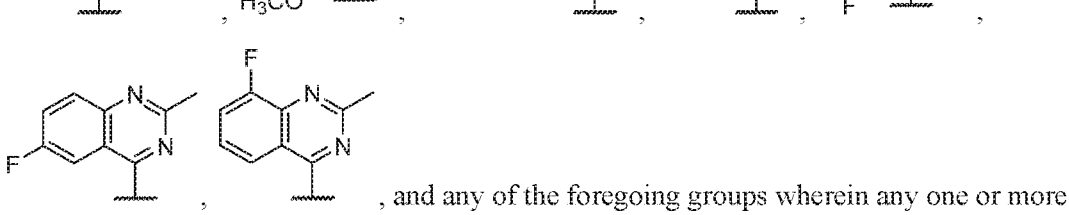


, and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s). Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is selected from any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with tritium atom(s). For example, in some embodiments, each hydrogen bonded to a ring carbon in the foregoing groups may be replaced with a corresponding isotope, e.g., deuterium or tritium. Each hydrogen bonded to an acyclic carbon in the foregoing groups, e.g., methyl or methoxy carbons, may be replaced with a corresponding isotope, e.g., deuterium or tritium. Further, for example, the foregoing groups may be perdeuterated, in which every hydrogen is replaced with deuterium, or pertritiated, in which every hydrogen is replaced with tritium. In some embodiments, one or more ring carbons in the foregoing groups may be replaced with ^{13}C. For example, in polycyclic rings among the foregoing groups, one or more ring carbons in the ring directly bonded to the rest of the compound may be replaced with ^{13}C. In polycyclic rings among the foregoing groups, one or more ring carbons may be replaced with ^{13}C in the ring that substitutes or is fused to the ring bonded to the rest of the compound. Further, for example, every ring carbon in the foregoing groups may be replaced with ^{13}C.

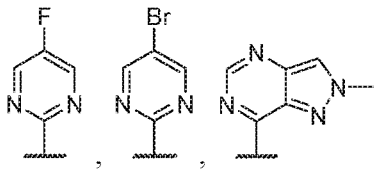
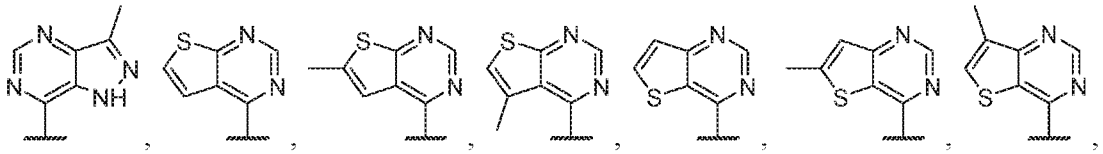
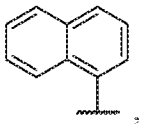
[00172] Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s). Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is selected from any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with tritium atom(s). For example, in some embodiments, each hydrogen bonded to a ring

carbon in the forgoing groups may be replaced with a corresponding isotope, e.g., deuterium or tritium. Each hydrogen bonded to an acyclic carbon in the forgoing groups, e.g., methyl or methoxy carbons, may be replaced with a corresponding isotope, e.g., deuterium or tritium. Further, for example, the forgoing groups may be perdeuterated, in which every hydrogen is replaced with deuterium, or pertritiated, in which every hydrogen is replaced with tritium. In some embodiments, one or more ring carbons in the forgoing groups may be replaced with ^{13}C. For example, in polycyclic rings among the forgoing groups, one or more ring carbons in the ring directly bonded to the rest of the compound may be replaced with ^{13}C. In polycyclic rings among the forgoing groups, one or more ring carbons may be replaced with ^{13}C in the ring that substitutes or is fused to the ring bonded to the rest of the compound. Further, for example, every ring carbon in the forgoing groups may be replaced with ^{13}C.

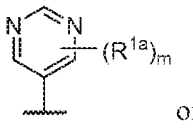
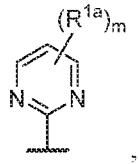
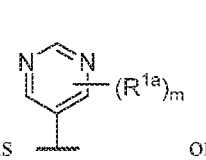
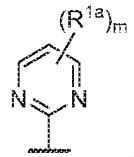
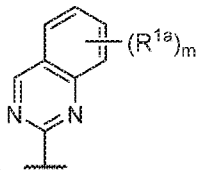
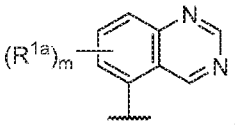
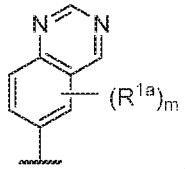
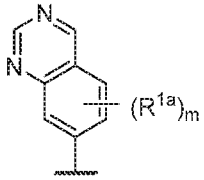
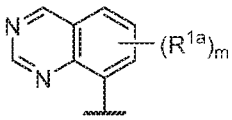
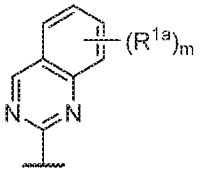
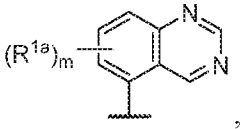
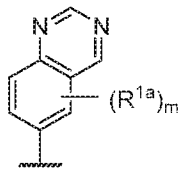
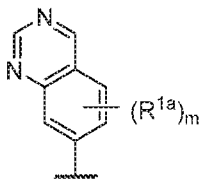
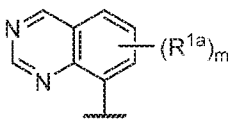
[00173] Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is selected from the group consisting of  ,  , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s). Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is selected from any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with tritium atom(s). For example, in some embodiments, each hydrogen bonded to a ring carbon in the forgoing groups may be replaced with a corresponding isotope, e.g., deuterium or tritium. Each hydrogen bonded to an acyclic carbon in the forgoing groups, e.g., methyl or methoxy carbons, may be replaced with a corresponding isotope, e.g., deuterium or tritium. Further, for example, the forgoing groups may be perdeuterated, in which every hydrogen is replaced with deuterium, or pertritiated, in which every hydrogen is replaced with tritium. In some embodiments, one or more ring carbons in the forgoing groups may be replaced with ^{13}C. For example, in polycyclic rings among the forgoing groups, one or more ring carbons in the ring directly bonded to the rest of the compound may be replaced with ^{13}C. In polycyclic rings among the forgoing groups, one or more ring carbons may be replaced with ^{13}C in the ring that substitutes or is fused to the ring bonded to the rest of the compound. Further, for example, every ring carbon in the forgoing groups may be replaced with ^{13}C.

[00174] Also provided is a compound of formula (I) or (II), or a salt thereof, wherein 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). Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is selected from any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with tritium atom(s). For example, in some embodiments, each hydrogen bonded to a ring carbon in the forgoing groups may be replaced with a corresponding isotope, e.g., deuterium or tritium. Each hydrogen bonded to an acyclic carbon in the forgoing groups, e.g., methyl or methoxy carbons, may be replaced with a corresponding isotope, e.g., deuterium or tritium. Further, for example, the forgoing groups may be perdeuterated, in which every hydrogen is replaced with deuterium, or pertritiated, in which every hydrogen is replaced with tritium. In some embodiments, one or more ring carbons in the forgoing groups may be replaced with ^{13}C. For example, in polycyclic rings among the forgoing groups, one or more ring carbons in the ring directly bonded to the rest of the compound may be replaced with ^{13}C. In polycyclic rings among the

forgoing groups, one or more ring carbons may be replaced with ^{13}C in the ring that substitutes or is fused to the ring bonded to the rest of the compound. Further, for example, every ring carbon in the forgoing groups may be replaced with ^{13}C.

[00175] Also provided is a compound of formula (I) or (II), or a salt thereof, wherein 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). Also provided is a compound of formula (I) or (II), or a salt thereof, wherein R^1 is selected from any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with tritium atom(s). For example, in some embodiments, each hydrogen bonded to a ring carbon in the forgoing groups may be replaced with a corresponding isotope, e.g., deuterium or tritium. Each hydrogen bonded to an acyclic carbon in the forgoing groups, e.g., methyl or methoxy carbons, may be replaced with a corresponding isotope, e.g., deuterium or tritium. Further, for example, the forgoing groups may be perdeuterated, in which every hydrogen is replaced with deuterium, or pertritiated, in which every hydrogen is replaced with tritium. In some embodiments, one or more ring carbons in the forgoing groups may be replaced with ^{13}C. For example, in polycyclic rings among the forgoing groups, one or more ring carbons in the ring directly bonded to the rest of the compound may be replaced with ^{13}C. In polycyclic rings among the forgoing groups, one or more ring carbons may be replaced with ^{13}C in the ring that substitutes or is fused to the ring bonded to the rest of the compound. Further, for example, every ring carbon in the forgoing groups may be replaced with ^{13}C.

[00176] The R^1 groups described herein as moieties (shown with a ~~~ symbol) are shown as attached at specific positions (e.g., pyrimid-4-yl, quinazolin-4-yl, isoquinolin-1-yl) but they can also be attached via any other available valence (e.g., pyrimid-2-yl). In some

embodiments of the compound of formula (I) or (II), or a salt thereof, R^1 is  or  , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium. In a further embodiment of the compound of formula (I) or (II), or a salt thereof, R^1 is  or  , wherein m is 1, 2, or 3 and each R^{1a} is 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. In another embodiment, 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. In a further embodiment of the compound of formula (I) or (II), or a salt thereof, R^1 is  ,  ,  ,  , or  wherein m is 1, 2, 3, 4, or 5 and

each R^{1a} is 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. In a further variation of such embodiments, each R^{1a} is, where applicable, independently deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl (which in one variation may be C_1-C_6 perhaloalky), C_1-C_6 alkoxy, hydroxy, -CN, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, and 5- to 10-membered heteroaryl of R^{1a} are independently optionally substituted by deuterium.

[00177] In some embodiments of the compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a}. In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} where R^{2a} is: halogen (e.g., fluoro); C_3-C_8 cycloalkyl optionally substituted by halogen (e.g., cyclobutyl optionally substituted by fluoro); 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl (e.g., pyrazolyl optionally substituted by methyl); $-S(O)_2R^3$; $-NR^4R^5$; $-NR^3C(O)R^4$; oxo; or $-OR^3$. In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} where R^{2a} is: halogen (e.g., fluoro); C_3-C_8 cycloalkyl optionally substituted by halogen (e.g., cyclobutyl optionally substituted by fluoro); 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl (e.g., pyrazolyl optionally substituted by methyl); 3- to 12-membered heterocyclyl optionally substituted by halogen (e.g., oxetanyl optionally substituted by fluoro), $-S(O)_2R^3$; $-NR^4R^5$; $-NR^3C(O)R^4$; oxo; or $-OR^3$. In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by $-OR^3$ wherein R^3 is: hydrogen; C_1-C_6 alkyl optionally substituted by halogen (e.g., methyl, ethyl, difluoromethyl, $-CH_2CHF_2$, and $-CH_2CF_3$); C_3-C_6 cycloalkyl optionally substituted by halogen (e.g., cyclopropyl substituted by fluoro); C_6-C_{14} aryl optionally substituted by halogen (e.g., phenyl optionally substituted by fluoro); or 5- to 6-membered heteroaryl optionally substituted by halogen or C_1-C_6 alkyl (e.g., pyridinyl optionally substituted by fluoro or methyl). In some embodiments, R^2 is $-CH_2CH_2OCH_3$. In some embodiments, R^2 is C_1-C_6 alkyl substituted by both halogen and OR^3. In some embodiments, R^2 is *n*-propyl substituted by both halogen and alkoxy (e.g., $-CH_2CH(F)CH_2OCH_3$). In some embodiments where R^2 is indicated as optionally substituted by R^{2a}, the R^2 moiety is unsubstituted. In some embodiments where R^2 is indicated as optionally substituted by R^{2a}, the R^2 moiety is substituted by one R^{2a}. In some embodiments where R^2 is indicated as optionally substituted by R^{2a}, the R^2 moiety is substituted by 2 to 6 or 2 to 5 or 2 to 4 or 2 to 3 R^{2a} moieties, which may be the same or different.

[00178] In some embodiments of the compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a}. In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} where R^{2a} is: halogen (e.g., fluoro); C_3-C_8 cycloalkyl optionally substituted by halogen (e.g., cyclobutyl optionally substituted by fluoro); 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl (e.g., pyrazolyl optionally substituted by methyl); $-S(O)_2R^3$; $-NR^4R^5$; $-NR^3C(O)R^4$; oxo; or $-OR^3$. In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} where R^{2a} is: halogen (e.g., fluoro); C_3-C_8 cycloalkyl optionally substituted by halogen (e.g., cyclobutyl optionally substituted by fluoro); 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl (e.g., pyrazolyl optionally substituted by methyl); 3- to 12-membered heterocyclyl optionally substituted by halogen (e.g., oxetanyl optionally substituted by fluoro); $-S(O)_2R^3$; $-NR^4R^5$; $-NR^3C(O)R^4$; oxo; or $-OR^3$. In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} where R^{2a} is: halogen (e.g., fluoro); C_3-C_8 cycloalkyl optionally substituted by halogen (e.g., cyclobutyl optionally substituted by fluoro); C_6-C_{14} aryl (e.g., phenyl); 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl (e.g., thiazolyl or pyrazolyl optionally substituted by methyl); 3- to 12-membered heterocyclyl optionally substituted by halogen or oxo (e.g., R^{2a} is: oxetanyl optionally substituted by fluoro; tetrahydrofuranyl; pyrrolidinyl optionally substituted by oxo; morpholinyl optionally substituted by oxo; or dioxanyl); $-S(O)_2R^3$; $-NR^4R^5$; $-NR^3C(O)R^4$; oxo; $-OR^3$; or -CN. In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted by $-OR^3$ wherein R^3 is: hydrogen; C_1-C_6 alkyl optionally substituted by halogen (e.g., methyl, ethyl, difluoromethyl, $-CH_2CHF_2$, and $-CH_2CF_3$); C_3-C_6 cycloalkyl optionally substituted by halogen (e.g., cyclopropyl substituted by fluoro); C_6-C_{14} aryl optionally substituted by halogen (e.g., phenyl optionally substituted by fluoro); or 5- to 6-membered heteroaryl optionally substituted by halogen or C_1-C_6 alkyl (e.g., pyridinyl optionally substituted by fluoro or methyl). In some embodiments, R^2 is $-CH_2CH_2OCH_3$. In some embodiments, R^2 is C_1-C_6 alkyl substituted by both halogen and OR^3. In some embodiments, R^2 is *n*-propyl substituted by both halogen and alkoxy (e.g., $-CH_2CH(F)CH_2OCH_3$). In some embodiments where R^2 is indicated as optionally substituted by R^{2a}, the R^2 moiety is unsubstituted. In some embodiments where R^2 is indicated as optionally substituted by R^{2a}, the R^2 moiety is substituted by one R^{2a}. In some embodiments where R^2 is indicated as optionally substituted by R^{2a}, the R^2 moiety is substituted by 2 to 6 or 2 to 5 or 2 to 4 or 2 to 3 R^{2a} moieties, which may be the same or different. In some embodiments, R^2 is C_1-C_6 alkyl substituted by two halogen groups, which may be the same or

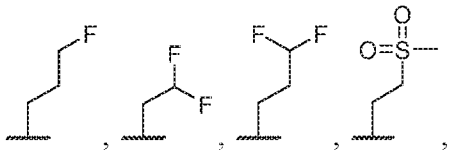
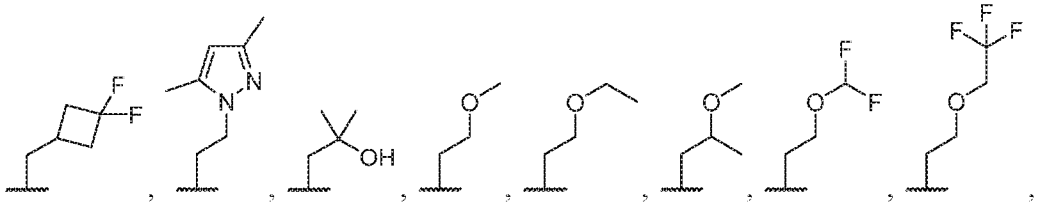
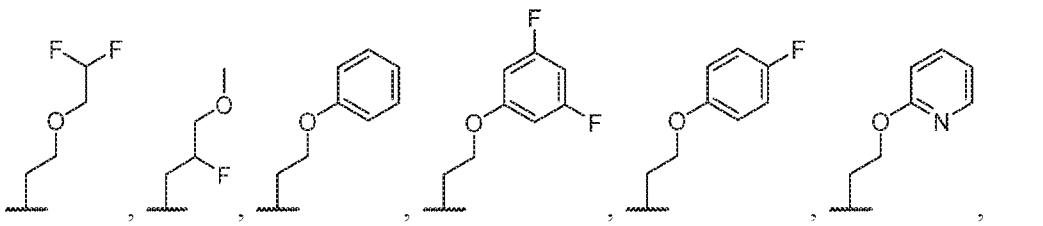
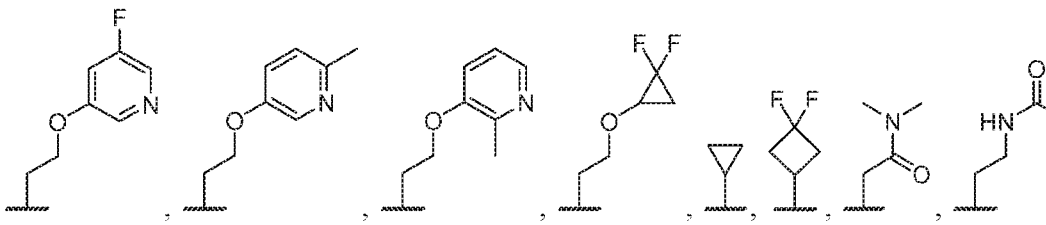
different (e.g., two fluoro groups). In some embodiments, R^2 is C_1-C_6 alkyl substituted by two -OR^3 groups, which may be the same or different (e.g., two –OH groups, one –OH group and one –OCH_3 group, or two –OCH_3 groups). In some embodiments, R^2 is C_1-C_6 alkyl substituted by one halogen group (e.g., fluoro) and one -OR^3 group (e.g., -OH or -OCH_3). In some embodiments, R^2 is C_1-C_6 alkyl substituted by two halogen groups, which may be the same or different (e.g., two fluoro groups), and one -OR^3 group (e.g., -OH or -OCH_3). In some embodiments, R^2 is C_1-C_6 alkyl substituted by one halogen group (e.g., fluoro) and two -OR^3 groups, which may be the same or different (e.g., two –OH groups, one –OH group and one –OCH_3 group, or two –OCH_3 groups).

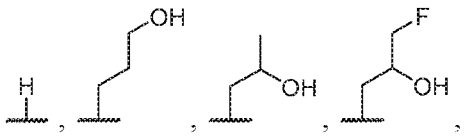
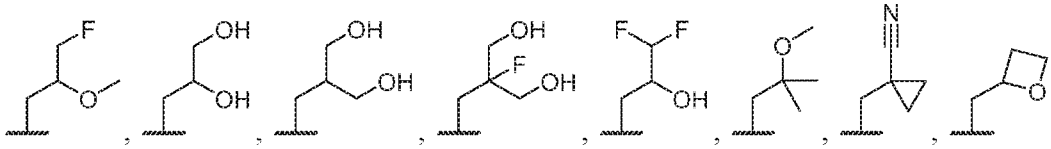
[00179] In some embodiments of the compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, R^2 is C_3-C_6 cycloalkyl optionally substituted by R^{2b}. In some embodiments, R^2 is C_3-C_6 cycloalkyl substituted by 1 or 2 R^{2b} moieties which may be the same or different. In some embodiments, R^2 is C_3-C_4 cycloalkyl optionally substituted by halogen (e.g., unsubstituted cyclopropyl or cyclobutyl optionally substituted by fluoro). In some embodiments, R^2 is C_3-C_4 cycloalkyl optionally substituted by deuterium, or tritium atom(s). For example, in some embodiments, each hydrogen bonded to a ring carbon in the forgoing groups may be replaced with a corresponding isotope, e.g., deuterium or tritium. Each hydrogen bonded to an acyclic carbon in the forgoing groups, e.g., methyl or methoxy carbons, may be replaced with a corresponding isotope, e.g., deuterium or tritium. Further, for example, the forgoing groups may be perdeuterated, in which every hydrogen is replaced with deuterium, or pertritiated, in which every hydrogen is replaced with tritium. In some embodiments, one or more ring carbons in the forgoing groups may be replaced with ^{13}C. For example, in polycyclic rings among the forgoing groups, one or more ring carbons in the ring directly bonded to the rest of the compound may be replaced with ^{13}C. In polycyclic rings among the forgoing groups, one or more ring carbons may be replaced with ^{13}C in the ring that substitutes or is fused to the ring bonded to the rest of the compound. Further, for example, every ring carbon in the forgoing groups may be replaced with ^{13}C.

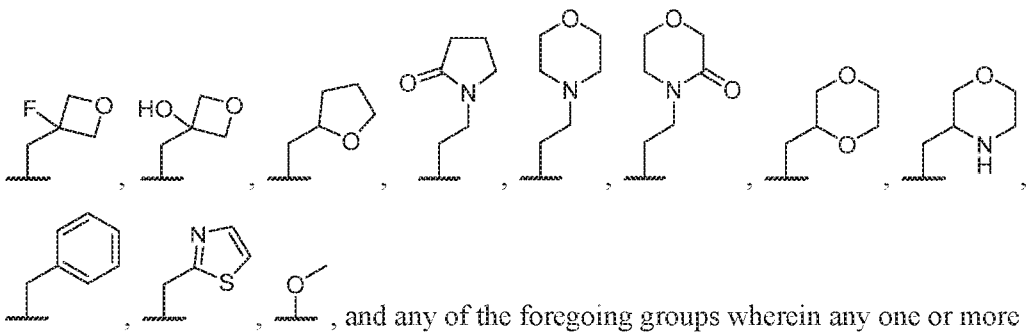
[00180] In some embodiments of the compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, R^2 is hydrogen.

[00181] In some embodiments of the compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt

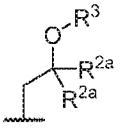
thereof, R^2 is –O-C_1-C_6 alkyl optionally substituted by R^{2a}. In some embodiments, R^2 is –OCH_3.

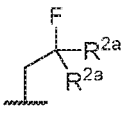
[00182] Also provided is a compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, wherein R^2 is selected from the group consisting of  ,  ,  ,  , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s).

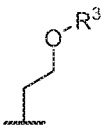
[00183] Also provided is a compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, wherein R^2 is selected from the group consisting of  ,  .



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

[00184] Also provided is a compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, wherein R^2 is  wherein R^3 and each R^{2a} are as defined for formula (I).

[00185] Also provided is a compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, wherein R^2 is  wherein each R^{2a} are as defined for formula (I).

[00186] Also provided is a compound of formula (I), (II), (I-A), (II-A), (I-B), (II-B), (I-C), (II-C), (I-D), (II-D), (I-E), (II-E), (I-F), (II-F), (I-G), (II-G), (I-H) or (II-H), or a salt thereof, wherein R^2 is  wherein R^3 is as defined for formula (I).

[00187] In one embodiment of formula (I), the tetrahydronaphthyridine group is disubstituted with deuterium at the 2-position.

[00188] In one aspect, provided is a compound of formula (I), or a salt thereof (including a pharmaceutically acceptable salt thereof), wherein the compound or salt thereof has any one or more of the following structural features ("SF"):

(SFI) p is 3;

(SFII) each R^{10}, R^{11}, R^{12}, R^{13} is hydrogen;

(SFIII) R^1 is:

(A) unsubstituted 5- to 10-membered heteroaryl;

(B) 5- to 10-membered heteroaryl substituted by 1, 2, 3, 4 or 5 R^{1a} groups which may be the same or different;

wherein the 5- to 10-membered heteroaryl of (III)(A) and (III)(B) is:

(i) pyridinyl;

(ii) pyrimidinyl;

(iii) quinoxalinyl;

(iv) quinazolinyl;

(v) pyrazolopyrimidinyl;

(vi) quinolinyl;

(vii) pyridopyrimidinyl;

(viii) thienopyrimidinyl;

(ix) purinyl;

(x) pyrrolopyrimidinyl;

(xi) benzooxazolyl;

(xii) benzothiazolyl;

(xiii) isoquinolinyl;

(xiv) indolyl;

(xv) benzoimidazolyl;

(xvi) pyrazinyl;

(xvii) indazolyl; or

(xviii) pyrazolyl;

(C) unsubstituted naphthalenyl; or

(D) naphthalenyl substituted by 1, 2, 3, 4 or 5 R^{1a} groups which may be the same or different;

(SFIV) each R^{1a} is:

(A) halogen, such as fluoro, chloro, or bromo;

(B) C_1-C_6 alkyl optionally substituted by halogen, such as -CH_3, -CHF_2, -CF_3, or $C(CH_3)_3$;

(C) C_3-C_6 cycloalkyl, such as cyclopropyl;

(D) 5- to 10-membered heteroaryl, such as pyridinyl or pyrazolyl;

(E) C_6-C_{14} aryl, such as phenyl;

(F) –CN;

(G) –OR^3, such as –OCH_3; or

(H) -NR^4R^5, such as -$N(CH_3)_2$;

(SFV) R^2 is:

(A) unsubstituted C_1-C_6 alkyl, such as C_1-C_2 alkyl;

(B) C_1-C_6 alkyl, such as C_1-C_2 alkyl, each of which is substituted by 1, 2, 3, 4 or 5 R^{2a} groups which may be the same or different;

(C) unsubstituted -O-C_1-C_6 alkyl, such as -O-C_1-C_2 alkyl;

(D) -O-C_1-C_6 alkyl, such as -O-C_1-C_2 alkyl, each of which is substituted by 1, 2, 3, 4 or 5 R^{2a} groups which may be the same or different;

(E) unsubstituted C_3-C_6 cycloalkyl, such as cyclopropyl or cyclobutyl; or

(F) C_3-C_6 cycloalkyl, such as cyclopropyl or cyclobutyl, each of which is substituted by 1, 2, 3, 4 or 5 R^{2b} groups which may be the same or different; and

(SFVI) R^{2a} is:

(A) halogen, such as fluoro;

(B) C_3-C_8 cycloalkyl, such as cyclopropyl or cyclobutyl, each of which is optionally substituted by halogen;

(C) 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl, such as pyrazolyl substituted by methyl;

(D) 3- to 12-membered heterocyclyl optionally substituted by halogen or oxo, such as oxetanyl optionally substituted by fluoro, unsubstituted tetrahydrofuranyl, pyrrolidinyl substituted by oxo, unsubstituted morpholinyl, morpholinyl substituted by oxo, or dioxanyl;

(E) -$S(O)_2R^3$, such as -$S(O)_2CH_3$;

(F) –$C(O)NR^4R^5$, such as –$C(O)N(CH_3)_2$;

(G) -$NR^3C(O)R^4$, such as –$NHC(O)CH_3$; or

(H) -OR^3, wherein R^3 is:

(i) hydrogen;

(ii) -CH_3;

(iii) -CH_2CH_3;

(iv) -CH_2CHF_2;

(v) -CH_2CF_3;

(vi) phenyl substituted by 0-2 fluoro groups; or

(vii) pyridinyl substituted by 0-1 methyl group.

[00189] It is understood that compounds of formula (I) or any variation thereof described herein, or a salt thereof, can in one embodiment have any one or more of the structural features as noted above. For example, compounds of formula (I) or any variation thereof described herein, or a salt thereof, can in one embodiment have the following structural

features: one or two or three or all of (SFI), (SFII), (SFIII) and (SFV). In one such example, a compound of formula (I) or any variation thereof described herein, or a salt thereof, can in one embodiment have the following structural features: (SFI) and any one or two or all of (SFII), (SFIII) and (SFV) or any sub-embodiment thereof. In one such example, a compound of formula (I) or any variation thereof described herein, or a salt thereof, can in one embodiment have the following structural features: (SFII) and any one or two or all of (SFI), (SFIII) and (SFV) or any sub-embodiment thereof. In one such example, a compound of formula (I) or any variation thereof described herein, or a salt thereof, can in one embodiment have the following structural features: (SFIII) and any one or two or all of (SFI), (SFII) and (SFV) or any sub-embodiment thereof. In one such example, a compound of formula (I) or any variation thereof described herein, or a salt thereof, can in one embodiment have the following structural features: (SFV) and any one or two or all of (SFI), (SFII) and (SFIII) or any sub-embodiment thereof. It is understood that the sub-embodiments of structural features can likewise be combined in any manner. Although specific combinations of structural features are specifically noted below, it is understood that each and every combination of features is embraced. In one aspect of this variation, (SFI) and (SFII) apply. In another variation, (SFI) and (SFIII) apply. In another variation, (SFI) and (SFV) apply. In another variation, (SFII) and (SFIII) apply. In another variation, (SFII) and (SFV) apply. In another variation, (SFIII) and (SFV) apply. In another variation, (SFI), (SFII), and (SFIII) apply. In another variation, (SFI), (SFII), and (SFV) apply. In another variation, (SFI), (SFIII), and (SFV) apply. In another variation, (SFII), (SFIII), and (SFV) apply. It is understood that each sub-embodiment of the structural features apply. For example, (SFIII) is (SFIII)(A)(i), (SFIII)(A)(ii),(SFIII)(A)(iii), (SFIII)(A)(iv), (SFIII)(A)(v), (SFIII)(A)(vi), (SFIII)(A)(vii), (SFIII)(A)(viii), (SFIII)(A)(ix), (SFIII)(A)(x), (SFIII)(A)(xi), (SFIII)(A)(xii), (SFIII)(A)(xiii), (SFIII)(A)(xiv), (SFIII)(A)(xv), (SFIII)(A)(xvi), (SFIII)(A)(xvii), (SFIII)(A)(xviii), (SFIII)(B)(i), (SFIII)(B)(ii), (SFIII)(B)(iii), (SFIII)(B)(iv), (SFIII)(B)(v), (SFIII)(B)(vi), (SFIII)(B)(vii), (SFIII)(B)(viii), (SFIII)(B)(ix), (SFIII)(B)(x), (SFIII)(B)(xi), (SFIII)(B)(xii), (SFIII)(B)(xiii), (SFIII)(B)(xiv), (SFIII)(B)(xv), (SFIII)(B)(xvi), (SFIII)(B)(xvii), (SFIII)(B)(xviii), (SFIII)(C), or (SFIII)(D). In one aspect of this variation, (SFV) is (SFV)(A), (SFV)(B), (SFV)(C), (SFV)(D), (SFV)(E), or (SFV)(F).

[00190] In another variation, (SFI), (SFII), (SFIII)(A)(i), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ii), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iii), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iv), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI),

(SFII), (SFIII)(A)(v), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vi), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vii), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(viii), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ix), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(x), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xi), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xii), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xiii), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(A), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(C), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(D), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(E), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(F), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(G), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(H), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(A), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(C), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(D), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(E), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(F), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(G), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(H), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(A), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(C), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(D), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(E), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(F), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(G), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(H), (SFV)(B), and (SFVI)(A) apply. In

another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(A), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(C), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(D), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(E), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(F), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(G), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(H), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(v), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(viii), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(x), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xii), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xiv), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xv), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvii), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xviii), (SFIV)(B), (SFV)(B), and (SFVI)(A) apply.

[00191] In another variation, (SFI), (SFII), (SFIII)(A)(i), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ii), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iii), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iv), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(v), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vi), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vii), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(viii), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ix), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(x), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xi), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xii), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xiii), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(A), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(C), (SFV)(B), and (SFVI)(H)(ii)

apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(D), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(E), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(F), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(G), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(H), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(A), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(C), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(D), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(E), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(F), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(G), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(H), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(A), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(C), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(D), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(E), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(F), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(G), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(H), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(A), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(C), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(D), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(E), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(F), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(G), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(H), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(v), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII),

(SFIII)(B)(viii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(x), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xiv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xviii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(ii) apply.

[00192] In another variation, (SFI), (SFII), (SFIII)(A)(i), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ii), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iii), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iv), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(v), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vi), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vii), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(viii), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ix), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(x), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xi), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xii), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xiii), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(A), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(C), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(D), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(E), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(F), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(G), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(H), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(A), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(C), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(D), (SFV)(B), and (SFVI)(H)(v)

apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(E), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(F), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(G), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(H), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(A), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(C), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(D), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(E), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(F), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(G), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(H), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(A), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(C), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(D), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(E), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(F), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(G), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(H), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(v), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(viii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(x), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xiv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xviii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(v) apply.

[00193] In another variation, (SFI), (SFII), (SFIII)(A)(i), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ii), (SFV)(B), and (SFVI)(H)(vi) apply.

In another variation, (SFI), (SFII), (SFIII)(A)(iii), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iv), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(v), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vi), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vii), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(viii), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ix), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(x), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xi), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xii), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xiii), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(A), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(C), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(D), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(E), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(F), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(G), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(H), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(A), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(C), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(D), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(E), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(F), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(G), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(H), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(A), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(C), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(D), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(E), (SFV)(B), and

(SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(F), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(G), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(H), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(A), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(C), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(D), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(E), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(F), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(G), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(H), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(v), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(viii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(x), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xiv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xviii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vi) apply.

[00194] In another variation, (SFI), (SFII), (SFIII)(A)(i), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ii), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iii), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(iv), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(v), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vi), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(vii), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(viii), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(ix), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(x), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xi), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(A)(xii), (SFV)(B), and (SFVI)(H)(vii) apply. In

another variation, (SFI), (SFII), (SFIII)(A)(xiii), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(A), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(C), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(D), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(E), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(F), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(G), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(ii), (SFIV)(H), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(A), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(C), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(D), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(E), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(F), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(G), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(iv), (SFIV)(H), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(A), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(C), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(D), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(E), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(F), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(G), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(vii), (SFIV)(H), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(A), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(C), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(D), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(E), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII),

(SFIII)(B)(xvi), (SFIV)(F), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(G), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvi), (SFIV)(H), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(v), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(viii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(x), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xiv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xv), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xvii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply. In another variation, (SFI), (SFII), (SFIII)(B)(xviii), (SFIV)(B), (SFV)(B), and (SFVI)(H)(vii) apply.

[00195] Any variations or combinations recited herein for compounds of formula (I) also apply to formula (A), with the addition of any possible combinations of R^{15} and R^{16}.

[00196] Representative compounds are listed in **FIG. 1**.

[00197] In some embodiments, provided is a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof (including a mixture of two or more stereoisomers thereof), or a salt thereof. In some embodiments, the compound is a salt of a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof.

[00198] In some embodiments, provided is a compound selected from Compound Nos. 1-147, or a stereoisomer thereof (including a mixture of two or more stereoisomers thereof), or a salt thereof. In some embodiments, the compound is a salt of a compound selected from Compound Nos. 1-147, or a stereoisomer thereof.

[00199] In some embodiments, provided is a compound selected from Compound Nos. 1-665, or a stereoisomer thereof (including a mixture of two or more stereoisomers thereof), or a salt thereof. In some embodiments, the compound is a salt of a compound selected from Compound Nos. 1-665, or a stereoisomer thereof.

[00200] In some embodiments, provided is a compound selected from Compound Nos. 1-780, or a stereoisomer thereof (including a mixture of two or more stereoisomers thereof), or a salt thereof. In some embodiments, the compound is a salt of a compound selected from Compound Nos. 1-780, or a stereoisomer thereof.

[00201] In one variation, the compound detailed herein is selected from the group consisting of:

4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((6-(difluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrimidin-4-ylamino)butanoic acid;

4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)butanoic acid;

4-((2-hydroxy-2-methylpropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrimidin-4-ylamino)butanoic acid;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

2-((7-fluoroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((3,3-difluorocyclobutyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-methylquinazolin-4-yl)amino)butanoic acid;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrido[2,3-d]pyrimidin-4-ylamino)butanoic acid;

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;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((7-(trifluoromethyl)quinazolin-4-yl)amino)butanoic acid;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)quinazolin-4-yl)amino)butanoic acid;

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;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-ylamino)butanoic acid;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrido[3,4-d]pyrimidin-4-ylamino)butanoic acid;

2-((5-fluoroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((6-fluoroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((8-fluoroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

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;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

2-((6-(difluoromethyl)pyrimidin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((6-methyl-2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

4-((2-(methylsulfonyl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((3,3-difluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((3-fluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

2-((7-fluoro-2-methylquinazolin-4-yl)amino)-4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-(((3,3-difluorocyclobutyl)methyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((7-fluoro-2-methylquinazolin-4-yl)amino)butanoic acid;

2-(isoquinolin-1-ylamino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-(difluoromethoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinolin-4-ylamino)butanoic acid;

2-((7-chloroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((8-chloroquinazolin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-(quinazolin-4-ylamino)-4-((4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)(2-(2,2,2-trifluoroethoxy)ethyl)amino)butanoic acid;

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;

4-((3-fluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((7-methoxyquinazolin-4-yl)amino)butanoic acid;

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;

4-((3-fluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((8-methoxyquinazolin-4-yl)amino)butanoic acid;

2-((6-(1H-pyrazol-1-yl)pyrimidin-4-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-(((S)-2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-methylquinazolin-4-yl)amino)butanoic acid;

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;

2-((8-chloroquinazolin-4-yl)amino)-4-((2-(pyridin-2-yloxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

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;

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;

2-(pyrido[3,2-d]pyrimidin-4-ylamino)-4-((4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)(2-(2,2,2-trifluoroethoxy)ethyl)amino)butanoic acid;

4-((2-((2-methylpyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

2-((7-fluoro-2-methylquinazolin-4-yl)amino)-4-((2-((2-methylpyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-((2-methylpyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-ylamino)butanoic acid;

4-((2-ethoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

2-((7-fluoro-2-methylquinazolin-4-yl)amino)-4-((2-((6-methylpyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-((6-methylpyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-ylamino)butanoic acid;

4-((2-((5-fluoropyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

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;

4-((2-((5-fluoropyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-ylamino)butanoic acid;

2-((7-fluoro-2-methylquinazolin-4-yl)amino)-4-((2-((5-fluoropyridin-3-yl)oxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((2-acetamidoethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((2-(dimethylamino)-2-oxoethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

2-((7-fluoro-2-methylquinazolin-4-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid; and

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-methylquinazolin-4-yl)amino)butanoic acid.

[00202] In another variation, the compound detailed herein is selected from the group consisting of:
2-((3-cyanopyrazin-2-yl)amino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((5-cyanopyrimidin-2-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

2-((5-bromopyrimidin-2-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-phenylpyrimidin-4-yl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)butanoic acid;

4-((2-hydroxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

2-((3-cyanopyrazin-2-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((6-(1H-pyrazol-1-yl)pyrimidin-4-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((5-fluoropyrimidin-2-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((1H-pyrazolo[4,3-d]pyrimidin-7-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((6-phenylpyrimidin-4-yl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-phenylpyrimidin-4-yl)amino)butanoic acid;

2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((5-bromopyrimidin-2-yl)amino)-4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((5-cyanopyrimidin-2-yl)amino)-4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

2-((5-bromopyrimidin-2-yl)amino)-4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)butanoic acid;

4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((6-(1H-pyrazol-1-yl)pyrimidin-4-yl)amino)-4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((6-phenylpyrimidin-4-yl)amino)butanoic acid;

4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(pyridin-3-yl)quinazolin-4-yl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

2-((5-bromopyrimidin-2-yl)amino)-4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

2-((6-(1H-pyrazol-1-yl)pyrimidin-4-yl)amino)-4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(pyridin-3-yl)quinazolin-4-yl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(pyridin-3-yl)quinazolin-4-yl)amino)butanoic acid;

2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-4-((2-(methylsulfonyl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-(methylsulfonyl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

2-((5-bromopyrimidin-2-yl)amino)-4-((2-(methylsulfonyl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-(methylsulfonyl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)butanoic acid;

4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrimidin-4-ylamino)butanoic acid;

4-((2-(methylsulfonyl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(pyridin-3-yl)quinazolin-4-yl)amino)butanoic acid;

2-((6-(1H-pyrazol-1-yl)pyrimidin-4-yl)amino)-4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(pyridin-3-yl)quinazolin-4-yl)amino)butanoic acid;

4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-phenylpyrimidin-4-yl)amino)butanoic acid;

2-((5-cyanopyrimidin-2-yl)amino)-4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((5-cyclopropylpyrimidin-2-yl)amino)-4-((2-phenoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((5-cyanopyrimidin-2-yl)amino)-4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-phenylpyrimidin-4-yl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrimidin-4-ylamino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-fluoropyrimidin-2-yl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((6-methyl-2-(pyridin-4-yl)pyrimidin-4-yl)amino)butanoic acid;

4-((2-(4-fluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)butanoic acid;

2-((5-cyclopropylpyrimidin-2-yl)amino)-4-((2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-4-((2-(methylsulfonyl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((6-(1H-pyrazol-1-yl)pyrimidin-4-yl)amino)-4-((2-(methylsulfonyl)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(pyrimidin-4-ylamino)butanoic acid;

4-((2-fluoro-3-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((6-phenylpyrimidin-4-yl)amino)butanoic acid;

4-((oxetan-2-ylmethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

4-((3-hydroxy-2-(hydroxymethyl)propyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid;

2-((5-bromopyrimidin-2-yl)amino)-4-((3,3-difluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((3,3-difluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

4-((3,3-difluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)butanoic acid;

4-((3,3-difluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

2-((5-cyclopropylpyrimidin-2-yl)amino)-4-((3,3-difluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((3-fluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)butanoic acid;

4-((3-fluoropropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

2-((5-cyanopyrimidin-2-yl)amino)-4-((2-(4-fluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-(4-fluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

4-((2-(dimethylamino)-2-oxoethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)butanoic acid;

4-((2-(dimethylamino)-2-oxoethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)butanoic acid;

4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((6-phenylpyrimidin-4-yl)amino)butanoic acid;

2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-4-((2-(4-fluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

2-((5-bromopyrimidin-2-yl)amino)-4-((2-(4-fluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid;

4-((2-(dimethylamino)-2-oxoethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl)amino)butanoic acid;

2-((5-cyclopropylpyrimidin-2-yl)amino)-4-((2,2-difluoroethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid; and

4-(((3-fluorooxetan-3-yl)methyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinazolin-4-ylamino)butanoic acid.

[00203] In some embodiments, a composition, such as a pharmaceutical composition, is provided wherein the composition comprises a compound selected from the group consisting of one or more of Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof (including a mixture of two or more stereoisomers thereof), or a salt thereof. In some embodiments, the composition comprises a compound selected from the group consisting of a salt of one or more of Compound Nos. 1-66. In one aspect, the composition is a pharmaceutical composition that further comprises a pharmaceutically acceptable carrier.

[00204] In some embodiments, a composition, such as a pharmaceutical composition, is provided wherein the composition comprises a compound selected from the group consisting of one or more of Compound Nos. 1-147, or a stereoisomer thereof (including a mixture of two or more stereoisomers thereof), or a salt thereof. In some embodiments, the composition comprises a compound selected from the group consisting of a salt of one or more of Compound Nos. 1-147. In one aspect, the composition is a pharmaceutical composition that further comprises a pharmaceutically acceptable carrier.

[00205] In some embodiments, a composition, such as a pharmaceutical composition, is provided wherein the composition comprises a compound selected from the group consisting of one or more of Compound Nos. 1-665, or a stereoisomer thereof (including a mixture of two or more stereoisomers thereof), or a salt thereof. In some embodiments, the composition comprises a compound selected from the group consisting of a salt of one or more of Compound Nos. 1-665. In one aspect, the composition is a pharmaceutical composition that further comprises a pharmaceutically acceptable carrier.

[00206] In some embodiments, a composition, such as a pharmaceutical composition, is provided wherein the composition comprises a compound selected from the group consisting

of one or more of Compound Nos. 1-780, or a stereoisomer thereof (including a mixture of two or more stereoisomers thereof), or a salt thereof. In some embodiments, the composition comprises a compound selected from the group consisting of a salt of one or more of Compound Nos. 1-780. In one aspect, the composition is a pharmaceutical composition that further comprises a pharmaceutically acceptable carrier.

[00207] The invention also includes all salts of compounds referred to herein, such as pharmaceutically acceptable salts. The invention also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of the compounds described. Unless stereochemistry is explicitly indicated in a chemical structure or name, the structure or name is intended to embrace all possible stereoisomers of a compound depicted. In addition, where a specific stereochemical form is depicted, it is understood that other stereochemical forms are also described and embraced by the invention. All forms of the compounds are also embraced by the invention, such as crystalline or non-crystalline forms of the compounds. It is also understood that prodrugs, solvates and metabolites of the compounds are embraced by this disclosure. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form thereof. Compositions comprising a mixture of compounds of the invention in any ratio are also embraced by the invention, including mixtures of two or more stereochemical forms of a compound of the invention in any ratio, such that racemic, non-racemic, enantioenriched and scalemic mixtures of a compound are embraced. Where one or more tertiary amine moiety is present in the compound, the N-oxides are also provided and described.

[00208] Compounds described herein are αvβ6 integrin inhibitors. In some instances, it is desirable for the compound to inhibit other integrins in addition to αvβ6 integrin. In some embodiments, the compound inhibits αvβ6 integrin and one or more of αvβ1, αvβ3, αvβ5, α2β1, α3β1, α6β1, α7β1 and α11β1 integrin. In some embodiments, the compound inhibits αvβ6 integrin and αvβ1 integrin. In some embodiments, the compound inhibits αvβ6 integrin, αvβ3 integrin and αvβ5 integrin. In some embodiments, the compound inhibits αvβ6 integrin and α2β1 integrin. In some embodiments, the compound inhibits αvβ6 integrin, α2β1 integrin and α3β1 integrin. In some embodiments, the compound inhibits αvβ6 integrin and α6β1 integrin. In some embodiments, the compound inhibits αvβ6 integrin and α7β1 integrin. In some embodiments, the compound inhibits αvβ6 integrin and α11β1 integrin.

[00209] In some instances, it is desirable to avoid inhibition of other integrins. In some embodiments, the compound is a selective αvβ6 integrin inhibitor. In some embodiments, the compound does not inhibit substantially α4β1, αvβ8 and/or α2β3 integrin. In some embodiments, the compound inhibits αvβ6 integrin but does not inhibit substantially α4β1 integrin. In some embodiments, the compound inhibits αvβ6 integrin but does not inhibit substantially αvβ8 integrin. In some embodiments, the compound inhibits αvβ6 integrin but does not inhibit substantially α2β3 integrin. In some embodiments, the compound inhibits αvβ6 integrin but does not inhibit substantially the αvβ8 integrin and the α4β1 integrin.

[00210] The invention also intends isotopically-labeled and/or isotopically-enriched forms of compounds described herein. The compounds herein may contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. In some embodiments, the compound is isotopically-labeled, such as an isotopically-labeled compound of the formula (I) or variations thereof described herein, where one or more atoms are replaced by an isotope of the same element. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C ^{13}N, ^{15}O, ^{17}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl. Incorporation of heavier isotopes such as deuterium (^{2}H or D) can afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life, or reduced dosage requirements and, hence may be preferred in some instances. As used herein, each instance of replacement of a hydrogen by deuterium is also a disclosure of replacing that hydrogen with tritium. As used herein, each instance of enrichment, substitution, or replacement of an atom with corresponding isotope of that atom encompasses isotopic enrichment levels of one of about: 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99,6%, 99.7%, 99.8%, 99.9%, or 100%, or a range between any two of the preceding percentages.

[00211] Isotopically-labeled compounds of the present invention can generally be prepared by standard methods and techniques known to those skilled in the art or by procedures similar to those described in the accompanying Examples substituting appropriate isotopically-labeled reagents in place of the corresponding non-labeled reagent.

[00212] In various embodiments, for each of the compounds named or depicted herein, specifically disclosed are corresponding isotopically substituted compounds according to the following description. For example, disclosed are corresponding isotopically substituted compounds in which the groups corresponding to structural variables R^1 and R^{1a} may be independently deuterated, e.g., structural variables R^1 and R^{1a} may be perdeuterated such that

every hydrogen therein may be independently replaced with deuterium. Further disclosed are corresponding isotopically substituted compounds in which one or more hydrogens in the group corresponding to structural variable R^1, but not in optional substituent R^{1a}, may be independently replaced with deuterium. For example, disclosed are corresponding isotopically substituted compounds in which every hydrogen bonded to a ring in the group corresponding to R^1, but not in optional substituent R^{1a}, may be replaced with deuterium. Also disclosed are corresponding isotopically substituted compounds in which one or more hydrogens in R^{1a} may be independently replaced with deuterium, e.g., every hydrogen in the group corresponding to R^{1a} may be replaced with deuterium.

[00213] Further disclosed, for example, are corresponding isotopically substituted compounds in which the groups corresponding to structural variables R^2 and R^{2a} may be independently deuterated, e.g., structural variables R^2 and R^{2a} may be perdeuterated such that every hydrogen therein may be independently replaced with deuterium. Also disclosed are corresponding isotopically substituted compounds in which one or more hydrogens in the group corresponding to R^2, but not in optional substituent R^{2a}, may be independently replaced with deuterium. Additionally disclosed are corresponding isotopically substituted compounds in which each hydrogen at the 1-position of R^2, the carbon bonding R^2 to the rest of the compound, may be independently replaced with deuterium. For example, for named compounds having $-CH_2CH_2CH_2F$ corresponding to R^2, also disclosed are corresponding isotopically substituted compounds in which R^2 is $-CD_2CH_2CH_2F$; for named compounds having $-CH_2$-cyclopropyl corresponding to R^2, also disclosed are corresponding isotopically substituted compounds in which R^2 is $-CD_2$-cyclopropyl; and the like. Disclosed are corresponding isotopically substituted compounds in which each hydrogen in the group corresponding to R^{2a} may be independently replaced with deuterium. For example, for each compound in which R^{2a} is $-OCH_3$, also disclosed are corresponding isotopically substituted compounds in which R^{2a} may be $-OCD_3$; for each compound in which R^{2a} is $-N(CH_3)_2$, also disclosed are corresponding isotopically substituted compounds in which R^{2a} may be $-N(CD_3)_2$; and the like. Further disclosed are compounds in which the 1-position of R^2 may be di-deuterated and each hydrogen in the group corresponding to R^{2a} may be replaced with deuterium.

[00214] Also disclosed are corresponding isotopically substituted compounds in which R^{10}, R^{11}, R^{12}, R^{13}, and each R^{14} are independently deuterated. For example, disclosed are corresponding isotopically substituted compounds in which R^{10}, R^{11} are deuterium, or R^{12}, R^{13} are deuterium, or R^{10}, R^{11}, R^{12}, and R^{13} are all deuterium. Further disclosed are

compounds in which R^{14} is deuterium and R^{14} substitutes the tetrahydronaphthyridine-2-yl group at the 3-position, the 4-position, or the 3- and 4-positions. Also disclosed are compounds in which R^{14} is deuterium and each R^{14} independently replaces each hydrogen in the tetrahydronaphthyridine-2-yl group at the 5-position, the 6-position, the 7-position, the 5- and 6-positions, the 5- and 7-positions, the 6- and 7-positions, or the 5-, 6-, and 7-positions, e.g., the 7-position may be substituted with two deuterium atoms.

[00215] In some embodiments, disclosed are corresponding isotopically substituted compounds in which: every ring hydrogen in R^1 may be replaced with deuterium; the 1-position of R^2 may be di-deuterated; and R^{2a} may be perdeuterated. Disclosed are corresponding isotopically substituted compounds in which every ring hydrogen in R^1 may be replaced with deuterium. Disclosed are corresponding isotopically substituted compounds in which: every ring hydrogen in R^1 may be replaced with deuterium; the 1-position of R^2 may be di-deuterated; R^{2a} may be perdeuterated; R^{12} and R^{13} may be deuterium; and the 7-position of the tetrahydronaphthyridine-2-yl group may be di-deuterated. Disclosed are corresponding isotopically substituted compounds in which: every ring hydrogen in R^1 may be replaced with deuterium; and each hydrogen in R^{2a} may be independently replaced with deuterium. Disclosed are corresponding isotopically substituted compounds in which: every ring hydrogen in R^1 may be replaced with deuterium; the 1-position of R^2 may be di-deuterated; R^{2a} may be perdeuterated; and R^{12} and R^{13} may be deuterium. Disclosed are corresponding isotopically substituted compounds in which: R^1 and R^{1a} may be perdeuterated; the 1-position of R^2 may be di-deuterated; R^{2a} may be perdeuterated; R^{12} and R^{13} may be deuterium; and the 7-position of the tetrahydronaphthyridine-2-yl group may be di-deuterated. Disclosed are corresponding isotopically substituted compounds in which: every ring hydrogen in R^1 may be replaced with deuterium; the 1-position of R^2 may be di-deuterated; R^{2a} may be perdeuterated; and R^{12} and R^{13} may be deuterium.

[00216] In some embodiments of the named compounds, each hydrogen represented in R^1, R^{1a}, R^2, R^{2a}, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} may independently be tritium. For example, disclosed are corresponding isotopically substituted compounds in which one or more hydrogens in R^1, R^{1a}, or R^1 and R^{1a} may be independently be replaced by tritium. Disclosed are corresponding isotopically substituted compounds in which one or more ring hydrogens in R^1, R^{1a}, or R^1 and R^{1a} may be independently be replaced by tritium. Disclosed are corresponding isotopically substituted compounds in which one or more hydrogens in R^2, R^{2a}, or R^2 and R^{2a} may be independently be replaced by tritium. Disclosed are corresponding isotopically substituted compounds in which one or more hydrogens in R^2, R^{2a}, or R^2 and R^{2a} may be independently

be replaced by tritium. Disclosed are corresponding isotopically substituted compounds in which one of the 3- or 4-positions of the tetrahydronaphthyridine-2-yl group may be tritiated, e.g., the 3-position. Disclosed are corresponding isotopically substituted compounds in which one of the 5-, 6-, or 7-positions of the tetrahydronaphthyridine-2-yl group may be mono- or di-tritiated, e.g., the 7-position may be di-tritiated.

[00217] In some embodiments of the named compounds, disclosed are corresponding isotopically substituted compounds in which one or more carbons may be replaced with ^{13}C. For example, disclosed are corresponding isotopically substituted compounds in which one or more carbons may be replaced with ^{13}C, such as carbons in R^1, R^{1a}, R^2, R^{2a}, the tetrahydronaphthyridine-2-yl ring depicted in the structural formulas herein, and the like. For example, in rings represented by R^1, R^{1a}, R^2, R^{2a}, and/or the tetrahydronaphthyridine-2-yl group, one or more ring carbons may be replaced with ^{13}C. For example, polycyclic rings represented by R^1, R^{1a}, R^2, R^{2a}, and/or the tetrahydronaphthyridine-2-yl group, one or more ring carbons in the ring directly bonded to the rest of the compound may be replaced with ^{13}C; e.g., in the tetrahydronaphthyridine-2-yl group, the ring directly bonded to the rest of the compound is a heteroaromatic ring bonded at the 2-position. In polycyclic rings in the groups corresponding to R^1, R^{1a}, R^2, R^{2a}, and/or the tetrahydronaphthyridine-2-yl group, one or more ring carbons may be replaced with ^{13}C in a ring that substitutes or is fused to the ring bonded to the rest of the compound. For example, in the tetrahydronaphthyridine-2-yl ring, the nonaromatic heterocyclyl ring is fused to the ring bonded to the rest of the compound. Further, for example, every ring carbon, or every carbon in the group corresponding to R^1, R^{1a}, R^2, R^{2a}, and/or the tetrahydronaphthyridine-2-yl ring may be replaced with ^{13}C.

[00218] The invention also includes any or all metabolites of any of the compounds described. The metabolites may include any chemical species generated by a biotransformation of any of the compounds described, such as intermediates and products of metabolism of the compound.

[00219] Articles of manufacture comprising a compound of the invention, or a salt or solvate thereof, in a suitable container are provided. The container may be a vial, jar, ampoule, preloaded syringe, i.v. bag, and the like.

[00220] Preferably, the compounds detailed herein are orally bioavailable. However, the compounds may also be formulated for parenteral (*e.g.*, intravenous) administration.

[00221] One or several compounds described herein can be used in the preparation of a medicament by combining the compound or compounds as an active ingredient with a

pharmacologically acceptable carrier, which are known in the art. Depending on the therapeutic form of the medication, the carrier may be in various forms.

General Synthetic Methods

[00222] The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter (such as the schemes provides in the Examples below). In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

[00223] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, *e.g.*, a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization, and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

[00224] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

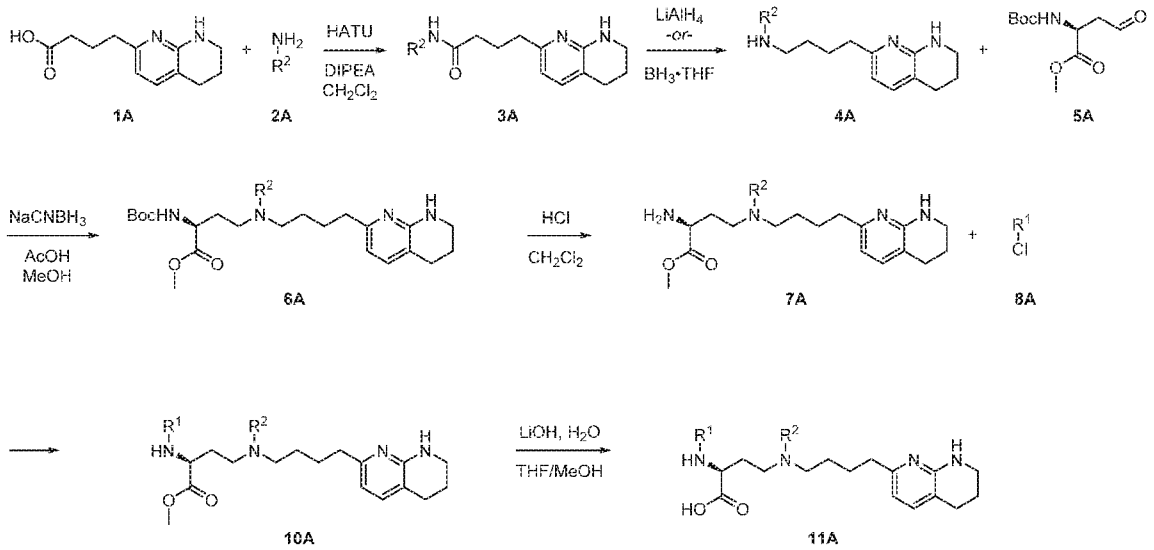
[00225] Solvates and/or polymorphs of a compound provided herein or a pharmaceutically acceptable salt thereof are also contemplated. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and/or solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[00226] Compounds provided herein may be prepared according to General Schemes A, B, C, and D, General Procedures A, B, C, D, E, F, G, H, and P, and the examples herein.

[00227] Compounds provided herein may be prepared according to General Schemes A, B, C, and D, General Procedures A, B, C, D, E, F, G, H, P, Q, R, S, T, and U, and the examples herein.

[00228] Compounds of formula 11A can be prepared according to General Scheme A, wherein R^1 and R^2 are as defined for formula (I), or any applicable variations detailed herein.

General Scheme A



[00229] Coupling of 1A with a compound of formula 2A in the presence of a suitable coupling agent yields a compound of formula 3A, which is reduced to yield a compound of formula 4A. Reductive amination of a compound of formula 4A with compound 5A gives a compound of formula 6A. Removal of the N-Boc protecting group with a compound of formula 6A by exposure to an appropriate acid gives a compound of formula 7A, which can be coupled with a compound of formula 8A to give a compound of formula 10A. Hydrolysis of a compound of formula 10A in the presence of a suitable hydroxide source gives compounds of formula 11A.

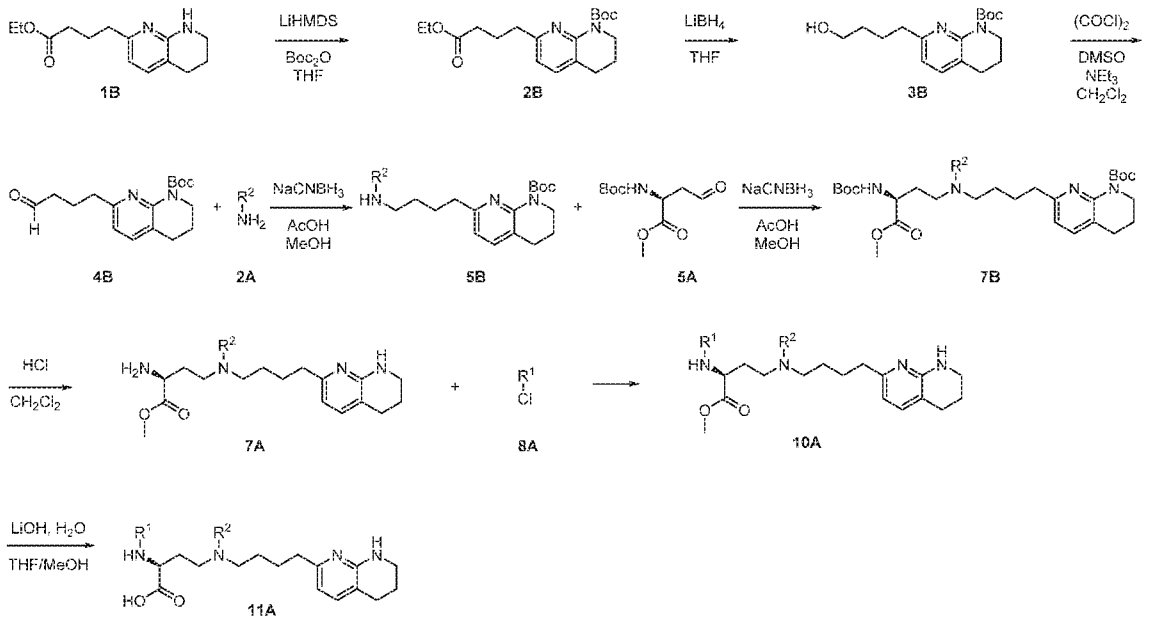
[00230] Reaction conditions for the transformations of General Scheme A are provided in the General Procedures that follow, in particular General Procedures A, D, E, F, G, H, and P.

[00231] General Scheme A can be modified to prepare variants of compounds of formula 11A by beginning with variants of 1A with 5 and 6 carbon linkers between the nitrogen bearing the R^2 group and the tetrahydronaphthyridine group. These variants of compounds of formula 11A can be synthesized by using the route described in General Scheme A substituting 1A with either 5,6,7,8-tetrahydro-1,8-naphthyridine-2-pentanoic acid or 5,6,7,8-tetrahydro-1,8-naphthyridine-2-hexanoic acid. 6-oxoheptanoic acid and 7-oxooctanoic acid

can be converted to 5,6,7,8-tetrahydro-1,8-naphthyridine-2-pentanoic acid and 5,6,7,8-tetrahydro-1,8-naphthyridine-2-hexanoic acid, respectively, by condensation with 2-aminonicotinaldehyde in the presence of an appropriate catalyst followed by hydrogenation of the resulting naphthyridine ring to the 5,6,7,8-tetrahydronaphthyridine ring using procedures known in the chemical literature.

[00232] Compounds of formula 11A can alternatively be prepared according to General Scheme B, wherein R^1 and R^2 are as defined for formula (I), or any applicable variations detailed herein.

General Scheme B



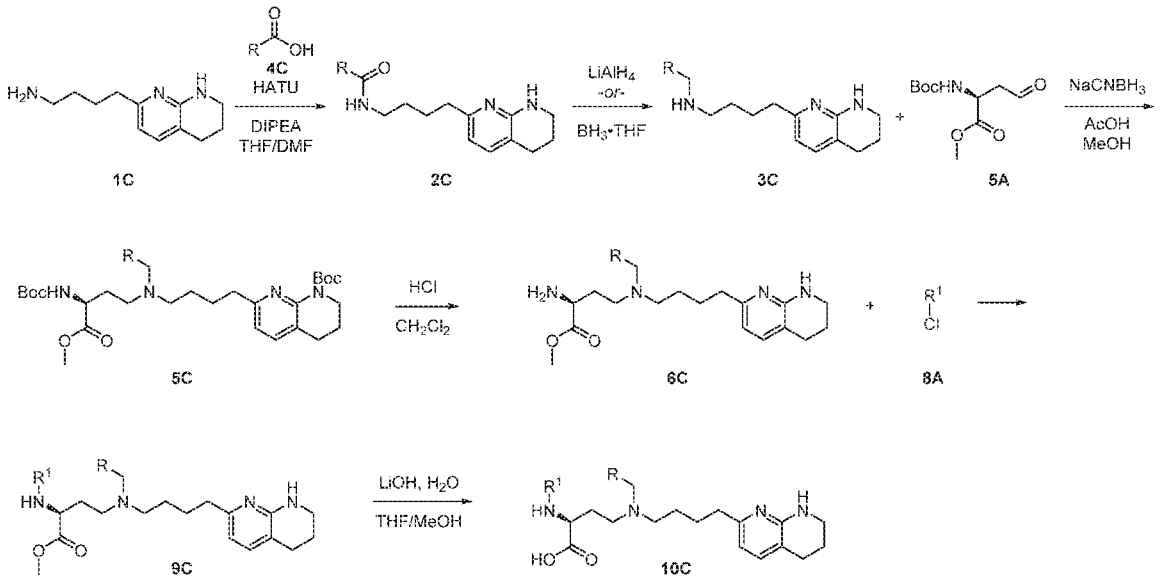
[00233] Installation of a N-Boc group of 1B in the presence of a suitable base and di-tert-butyl decarbonate yields a compound of formula 2B, which is reduced to yield a compound of formula 3B. Oxidation of a compound of formula 3B with a suitable oxidizing agent gives a compound of formula 4B. Reductive amination of a compound of formula 4B with compound 2A gives a compound of formula 5B. Reductive amination of a compound of formula 5B with compound 5A gives a compound of formula 7B. Removal of the N-Boc protecting group with a compound of formula 7B by exposure to an appropriate acid gives a compound of formula 7A, which can be coupled with a compound of formula 8A to give a compound of formula 10A. Hydrolysis of a compound of formula 10A in the presence of a suitable hydroxide source gives compounds of formula 11A.

[00234] Reaction conditions for the transformations of General Scheme B are provided in the General Procedures that follow, in particular General Procedures B, D, F, G, H, and P.

[00235] General Scheme B can be modified to prepare variants of compounds of formula 11A by beginning with variants of 1B with 5 and 6 carbon linkers between the nitrogen bearing the R^2 group and the tetrahydronaphthyridine group. These variants of compounds of formula 11A can be synthesized by using the route described in General Scheme B substituting 1B with either ethyl 5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanoate or ethyl 6-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)hexanoate. Ethyl 6-oxoheptanoate and ethyl 7-oxooctanoate can be converted to ethyl 5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanoate and ethyl 6-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)hexanoate, respectively, by condensation with 2-aminonicotinaldehyde in the presence of an appropriate catalyst followed by hydrogenation of the resulting naphthyridine ring to the 5,6,7,8-tetrahydronaphthyridine ring using procedures known in the chemical literature.

[00236] Compounds of formula 10C can be prepared according to General Scheme C, wherein R is C_1-C_5 alkyl optionally substituted by R^{2a}, and R^1 and R^{2a} are as defined for formula (I), or any applicable variations detailed herein.

General Scheme C



[00237] Coupling of 1C with a compound of formula 4C in the presence of a suitable coupling agent yields a compound of formula 2C, which is reduced to yield a compound of formula 3C. Reductive amination of a compound of formula 3C with compound 5A gives a compound of formula 5C. Global removal of the N-Boc protecting groups with a compound of formula 5C by exposure to an appropriate acid gives a compound of formula 6C, which can be coupled with a compound of formula 8A to give a compound of formula 9C.

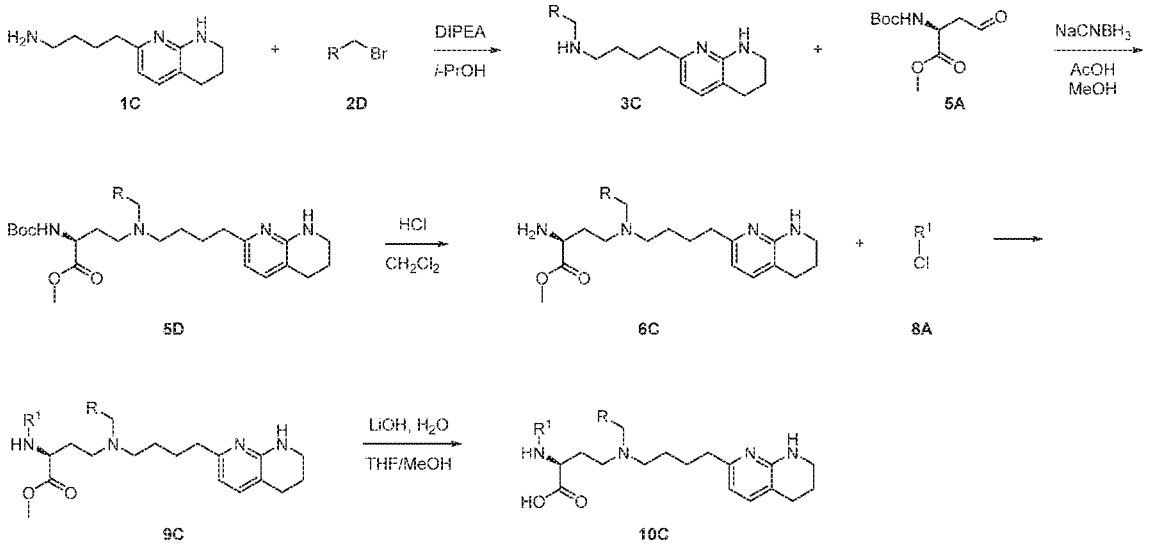
Hydrolysis of a compound of formula 9C in the presence of a suitable hydroxide source gives compounds of formula 10C.

[00238] Reaction conditions for the transformations of General Scheme C are provided in the General Procedures that follow, in particular General Procedures B, D, F, G, H, and P.

[00239] General Scheme C can be modified to prepare variants of compounds of formula 10C by beginning with variants of 1C with 5 and 6 carbon linkers between the nitrogen bearing the -CH_2R group and the tetrahydronaphthyridine group. These variants of compounds of formula 10C can be synthesized by using the route described in General Scheme C substituting 1C with either 5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentan-1-amine or 6-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)hexan-1-amine. 6-oxoheptanoic acid and 7-oxooctanoic acid can be converted to 5,6,7,8-tetrahydro-1,8-naphthyridine-2-pentanoic acid and 5,6,7,8-tetrahydro-1,8-naphthyridine-2-hexanoic acid, respectively, by condensation with 2-aminonicotinaldehyde in the presence of an appropriate catalyst followed by hydrogenation of the resulting naphthyridine ring to the 5,6,7,8-tetrahydronaphthyridine ring using procedures known in the chemical literature. The resulting carboxylic acids can be converted to a primary amine by a two-step procedure that includes coupling of the carboxylic acid with an appropriate ammonia source in the presence of suitable coupling reagents followed by reduction.

[00240] Compounds of formula 10C can alternatively be prepared according to General Scheme D, wherein R is C_1-C_5 alkyl optionally substituted by R^{2a}, and R^1 and R^{2a} are as defined for formula (I), or any applicable variations detailed herein.

General Scheme D



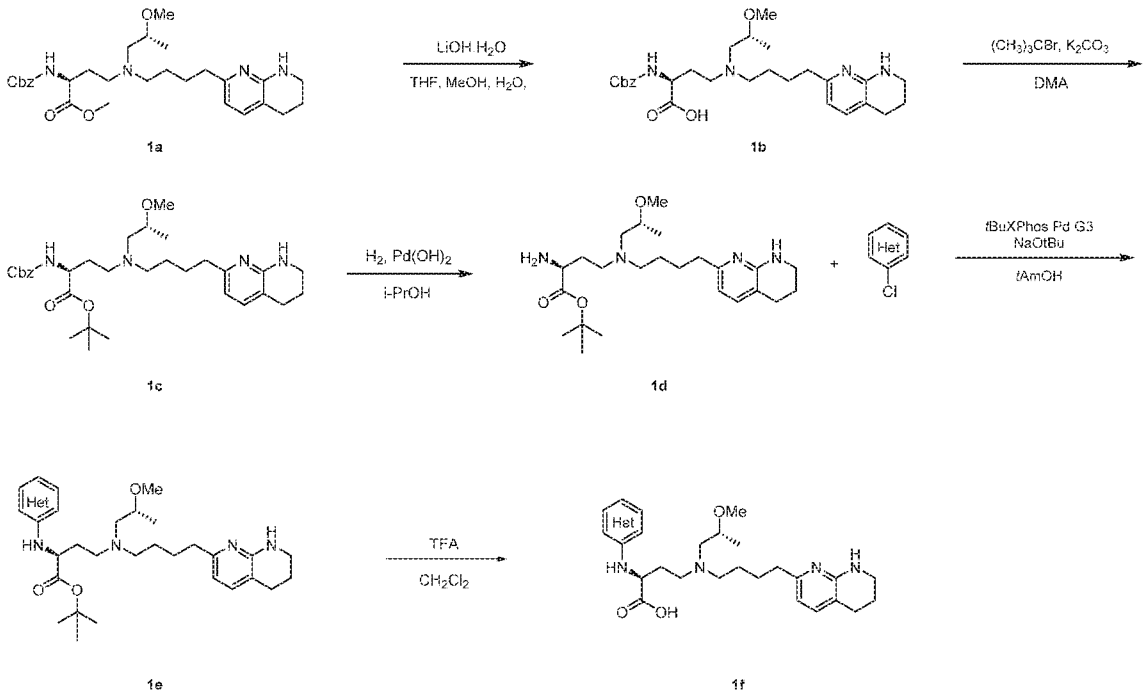
[00241] Alkylation of 1C with a compound of formula 2D in the presence of a suitable alkyl halide yields a compound of formula 3C. Reductive amination of a compound of formula 3C with compound 5A gives a compound of formula 5C. Removal of the N-Boc protecting group with a compound of formula 5C by exposure to an appropriate acid gives a compound of formula 6C, which can be coupled with a compound of formula 9A to give a compound of formula 9C. Hydrolysis of a compound of formula 8A in the presence of a suitable hydroxide source gives compounds of formula 10C.

[00242] Reaction conditions for the transformations of General Scheme D are provided in the General Procedures that follow, in particular General Procedures C, F, G, H, and P.

[00243] General Scheme D can be modified to prepare variants of compounds of formula 10C by beginning with variants of 1C with 5 and 6 carbon linkers between the nitrogen bearing the $-CH_2R$ group and the tetrahydronaphthyridine group. These variants of compounds of formula 10C can be synthesized by using the route described in General Scheme D substituting 1C with either 5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentan-1-amine or 6-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)hexan-1-amine. 6-oxoheptanoic acid and 7-oxooctanoic acid can be converted to 5,6,7,8-tetrahydro-1,8-naphthyridine-2-pentanoic acid and 5,6,7,8-tetrahydro-1,8-naphthyridine-2-hexanoic acid, respectively, by condensation with 2-aminonicotinaldehyde in the presence of an appropriate catalyst followed by hydrogenation of the resulting naphthyridine ring to the 5,6,7,8-tetrahydronaphthyridine ring using procedures known in the chemical literature. The resulting carboxylic acids can be converted to a primary amine by a two-step procedure that includes coupling of the carboxylic acid with an appropriate ammonia source in the presence of suitable coupling reagents followed by reduction.

[00244] Compounds of formula 1f can be prepared according to General Scheme E. It is understood the ring bearing the Het description can be any heteroaromatic ring.

General Scheme E



[00245] Hydrolysis of a compound of formula 1a gives a compound of formula 1b which can be alkylated with a suitable electrophile to give a compound of formula 1c. Deprotection under reductive conditions of a compound of formula 1c gives a compound of formula 1d. Metal catalyzed cross coupling of a halogenated arene with a compound of formula 1d gives a compound of formula 1e, which can be hydrolyzed under acidic conditions to give compound of formula 1f.

[00246] Reaction conditions for the transformations of General Scheme E are provided in the General Procedures that follow, in particular General Procedures Q, R, S, T, and U.

[00247] It is understood that the schemes above may be modified to arrive at various compounds of the invention by selection of appropriate reagents and starting materials. For a general description of protecting groups and their use, see P.G.M. Wuts and T.W. Greene, Greene's Protective Groups in Organic Synthesis 4th edition, Wiley-Interscience, New York, 2006.

[00248] Additional methods of preparing compounds according to Formula (I), and salts thereof, are provided in the Examples. As a skilled artisan would recognize, the methods of preparation taught herein may be adapted to provide additional compounds within the scope of Formula (I), for example, by selecting starting materials which would provide a desired compound.

Pharmaceutical Compositions and Formulations

[00249] Pharmaceutical compositions of any of the compounds detailed herein, including compounds of the formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), or a salt thereof, or any of compounds of **FIG. 1**, or a salt thereof, or mixtures thereof, are embraced by this invention. Pharmaceutical compositions of any of the compounds detailed herein, including compounds of the formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), or a salt thereof, or any of compounds of **FIG. 1**, or a salt thereof, or mixtures thereof, are embraced by this invention. Pharmaceutical compositions of compounds of the formula (A), or a salt thereof, or mixtures thereof, are embraced by this invention. Thus, the invention includes pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation. In one embodiment, the pharmaceutical composition is a composition for controlled release of any of the compounds detailed herein.

[00250] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. In one embodiment, compositions may have no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof, for example, a composition of a compound selected from a compound of **FIG. 1** may contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound of **FIG. 1** or a salt thereof. In one embodiment, compositions may have no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof, for example, a composition of a compound selected from a compound of **FIG. 1** may contain no more than 35% impurity, wherein the impurity denotes a compound other than the compound of **FIG. 1**, or a salt thereof. In one embodiment, compositions may contain no more than 25% impurity. In one embodiment, compositions may contains no more than 20% impurity. In still further embodiments, compositions comprising a compound as detailed herein or a salt thereof are provided as compositions of substantially pure compounds. "Substantially pure" compositions comprise no more than 10% impurity, such as a composition comprising less

than 9%, 7%, 5%, 3%, 1%, or 0.5% impurity. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. In still another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 10% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 9% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 7% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 5% impurity. In another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 3% impurity. In still another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 1% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 0.5% impurity. In yet other variations, a composition of substantially pure compound means that the composition contains no more than 10% or preferably no more than 5% or more preferably no more than 3% or even more preferably no more than 1% impurity or most preferably no more than 0.5% impurity, which impurity may be the compound in a different stereochemical form. For instance, a composition of substantially pure (*S*) compound means that the composition contains no more than 10% or no more than 5% or no more than 3% or no more than 1% or no more than 0.5% of the (*R*) form of the compound.

[00251] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual such as a human. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the invention embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier or excipient. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[00252] A compound detailed herein or salt thereof may be formulated for any available delivery route, including an oral, mucosal (e.g., nasal, sublingual, vaginal, buccal or rectal), parenteral (e.g., intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound or salt thereof may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard

gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (e.g., nasal spray or inhalers), gels, suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[00253] One or several compounds described herein or a salt thereof can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds, or a salt thereof, as an active ingredient with a pharmaceutically acceptable carrier, such as those mentioned above. Depending on the therapeutic form of the system (e.g., transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, e.g., in *Remington: The Science and Practice of Pharmacy*, Lippincott Williams & Wilkins, 21st ed. (2005), which is incorporated herein by reference.

[00254] Compounds as described herein may be administered to individuals (e.g., a human) in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, *etc*. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[00255] In one embodiment, the compounds can be administered in the liquid vehicle ORA-SWEET® from PERRIGO®, Allegan, Michigan, which is a syrup vehicle having ingredients of purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, and flavoring, buffered with citric acid and sodium citrate, preserved with methylparaben (0.03%), potassium sorbate (0.1%), and propylparaben (0.008%); or in a mixture of ORA-SWEET® and water of any proportion, such as a 50:50 mixture of ORA-SWEET® to water. The water used should be a pharmaceutically acceptable grade of water, for example, sterile water.

[00256] Any of the compounds described herein can be formulated in a tablet in any dosage form described, for example, a compound as described herein or a pharmaceutically acceptable salt thereof can be formulated as a 10 mg tablet.

[00257] Compositions comprising a compound provided herein are also described. In one variation, the composition comprises a compound and a pharmaceutically acceptable carrier or excipient. In another variation, a composition of substantially pure compound is provided. In some embodiments, the composition is for use as a human or veterinary medicament. In some embodiments, the composition is for use in a method described herein. In some embodiments, the composition is for use in the treatment of a disease or disorder described herein.

Methods of Use

[00258] Compounds and compositions of the invention, such as a pharmaceutical composition containing a compound of any formula provided herein or a salt thereof and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein. The compounds and compositions may also be used in *in vitro* methods, such as *in vitro* methods of administering a compound or composition to cells for screening purposes and/or for conducting quality control assays.

[00259] In one aspect, provided is a method of treating a fibrotic disease in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound of formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. In one aspect, provided is a method of treating a fibrotic disease in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound of formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-147, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. In one aspect, provided is a method of treating a fibrotic disease in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound of formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-665, or a stereoisomer thereof, or a pharmaceutically

acceptable salt thereof. In one aspect, provided is a method of treating a fibrotic disease in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound of formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. In one aspect, provided is a method of treating a fibrotic disease in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a compound of formula (A), or any variation thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. In one aspect, the individual is a human. The individual, such as human, may be in need of treatment, such as a human who has or is suspected of having a fibrotic disease.

[00260] In another aspect, 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. It is appreciated that delayed development may encompass prevention in the event the individual does not develop the fibrotic disease. An individual at risk of developing a fibrotic disease in one aspect has or is suspected of having one or more risk factors for developing a fibrotic disease. Risk factors for fibrotic disease may include an individual's age (e.g., middle-age or older adults), the presence of inflammation, having one or more genetic component associated with development of a fibrotic disease, medical history such as treatment with a drug or procedure believed to be associated with an enhanced susceptibility to fibrosis (e.g., radiology) or a medical condition believed to be associated with fibrosis, a history of smoking, the presence of occupational and/or environmental factors such as exposure to pollutants associated with development of a fibrotic disease. In some embodiments, the individual at risk for developing a fibrotic disease is an individual who 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 embodiments, the individual at risk for developing a fibrotic disease has or is suspected of having psoriasis.

[00261] In some embodiments, the fibrotic disease is fibrosis of a tissue such as the lung (pulmonary fibrosis), the liver, the skin, the heart (cardiac fibrosis), the kidney (renal fibrosis), or the gastrointestinal tract (gastrointestinal fibrosis).

[00262] In some embodiments, 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 embodiments, 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 embodiments, the fibrotic disease is psoriasis.

[00263] In some embodiments, the fibrotic disease is a pulmonary fibrosis, *e.g.*, idiopathic pulmonary fibrosis (IPF). In some embodiments, the pulmonary fibrosis is, *e.g.*, interstitial lung disease, radiation-induced pulmonary fibrosis, or systemic sclerosis associated interstitial lung disease.

[00264] In some embodiments, the fibrotic disease is a primary sclerosing cholangitis, or biliary fibrosis. In some embodiments, the fibrotic disease is primary biliary cholangitis (also known as primary biliary cirrhosis) or biliary atresia.

[00265] In some embodiments, the fibrotic disease is fibrotic nonspecific interstitial pneumonia (NSIP).

[00266] In some embodiments, the fibrotic disease is a liver fibrosis, *e.g.*, infectious liver fibrosis (from pathogens such as HCV, HBV or parasites such as schistosomiasis), NASH, alcoholic steatosis induced liver fibrosis, and cirrhosis. In some embodiments, the liver fibrosis is nonalcoholic fatty liver disease (NAFLD). In some embodiments, the liver fibrosis is NASH.

[00267] In some embodiments, the fibrotic disease is biliary tract fibrosis.

[00268] In some embodiments, the fibrotic disease is renal fibrosis, *e.g.*, diabetic nephrosclerosis, hypertensive nephrosclerosis, focal segmental glomerulosclerosis ("FSGS"), and acute kidney injury from contrast induced nephropathy. In several embodiments, the fibrotic disease is diabetic nephropathy, diabetic kidney disease, or chronic kidney disease.

[00269] In some embodiments, the fibrotic disease is characterized by one or more of glomerulonephritis, end-stage kidney disease, hearing loss, changes to the lens of the eye, hematuria, or proteinuria. In some embodiments, the fibrotic disease is Alport syndrome.

[00270] In some embodiments, the fibrotic disease is systemic and local sclerosis or scleroderma, keloids and hypertrophic scars, or post surgical adhesions. In some embodiments, the fibrotic disease is scleroderma or systemic sclerosis.

[00271] In some embodiments, the fibrotic disease is atherosclerosis or restenosis.

[00272] In some embodiments, the fibrotic disease is a gastrointestinal fibrosis, *e.g.*, Crohn's disease.

[00273] In some embodiments, the fibrotic disease is cardiac fibrosis, *e.g.*, post myocardial infarction induced fibrosis and inherited cardiomyopathy.

[00274] In some embodiments, the fibrotic disease is psoriasis.

[00275] In some embodiments, methods may include modulating the activity of at least one integrin in a subject in need thereof. For example, the method may include modulating the activity of $\alpha v\beta_6$. The method may include modulating the activity of $\alpha v\beta_1$. The method may include modulating the activity of $\alpha v\beta_1$ and $\alpha v\beta_6$. Modulating the activity of the at least one integrin may include, e.g., inhibiting the at least one integrin. The method may include administering to the subject an amount of the compound or a pharmaceutically acceptable salt thereof effective to modulate the activity of the at least one integrin in the subject, e.g., at least one of $\alpha v\beta_1$ and $\alpha v\beta_6$. The subject in need of modulating the activity of at least one integrin may have any of the fibrotic disease or conditions described herein. For example, the fibrotic disease or condition may include 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, primary biliary cholangitis (also known as primary biliary cirrhosis), biliary atresia, systemic sclerosis associated interstitial lung disease, scleroderma (also known as systemic sclerosis), diabetic nephropathy, diabetic kidney disease, focal segmental glomerulosclerosis, chronic kidney disease, or Crohn's Disease. The fibrotic disease or condition may include psoriasis. The method may include administering to the subject an amount of the compound or a pharmaceutically acceptable salt thereof effective to modulate the activity of the at least one integrin in the subject, e.g., at least one of $\alpha v\beta_1$ and $\alpha v\beta_6$, the subject being in need of treatment for NASH. The method may include administering to the subject an amount of the compound or a pharmaceutically acceptable salt thereof effective to modulate the activity of the at least one integrin in the subject, e.g., at least one of $\alpha v\beta_1$ and $\alpha v\beta_6$, the subject being in need of treatment for IPF.

[00276] The fibrotic disease may be mediated primarily by $\alpha v\beta_6$, for example, the fibrotic disease may include idiopathic pulmonary fibrosis or renal fibrosis. Accordingly, the method may include modulating the activity of $\alpha v\beta_6$ to treat conditions primarily mediated by $\alpha v\beta_6$ such as IPF. The fibrotic disease may be mediated primarily by $\alpha v\beta_1$, for example, the fibrotic disease may include NASH. Accordingly, the method may include modulating the activity of $\alpha v\beta_1$ to treat conditions primarily mediated by $\alpha v\beta_1$, e.g., NASH. The fibrotic disease may be mediated by $\alpha v\beta_1$ and $\alpha v\beta_6$, for example, the fibrotic disease may include PSC or biliary atresia. Accordingly, the method may include modulating the activity of $\alpha v\beta_1$ and $\alpha v\beta_6$ to treat conditions mediated by both $\alpha v\beta_1$ and $\alpha v\beta_6$.

[00277] The compound may be a modulator, e.g., an inhibitor, of $\alpha v\beta_1$. The compound may be a modulator, e.g., an inhibitor, of $\alpha v\beta_6$. The compound may be a dual modulator, such as a dual inhibitor, e.g., dual selective inhibitor, of $\alpha v\beta_1$ and $\alpha v\beta_6$. For example, **Table B-3** demonstrates that some exemplary compounds primarily inhibit $\alpha v\beta_1$ over $\alpha v\beta_6$; some exemplary compounds primarily inhibit $\alpha v\beta_6$ over $\alpha v\beta_1$; and some exemplary compounds inhibit $\alpha v\beta_1$ and $\alpha v\beta_6$, comparably, and may be considered, e.g., "dual $\alpha v\beta_1/\alpha v\beta_6$ inhibitors."

[00278] Modulating or inhibiting the activity of one or both of $\alpha v\beta_1$ integrin and $\alpha v\beta_6$ integrin, thereby treating a subject with a fibrotic disease, indicates that $\alpha v\beta_1$ integrin, $\alpha v\beta_6$ integrin, or $\alpha v\beta_1$ integrin and $\alpha v\beta_6$ integrin are modulated or inhibited to a degree sufficient to treat the fibrotic disease in the subject.

[00279] In one aspect, provided is a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a fibrotic disease.

[00280] In one aspect, provided is a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-147, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a fibrotic disease.

[00281] In one aspect, provided is a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-665, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a fibrotic disease.

[00282] In one aspect, provided is a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment of a fibrotic disease.

[00283] Also provided is use of a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from

Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a fibrotic disease.

[00284] Also provided is use of a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-147, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a fibrotic disease.

[00285] Also provided is use of a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-665, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a fibrotic disease.

[00286] Also provided is use of a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a fibrotic disease.

[00287] In another aspect, provided herein is a method of treating a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a dosage form disclosed herein, wherein the subject has at least one tissue in need of therapy and the tissue has at least one elevated level of: αVβ1 integrin activity and/or expression; αVβ6 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. In some embodiments, 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. In some embodiments, the tissue has an elevated pSMAD2/SMAD2 value or an elevated pSMAD3/SMAD3 value compared to the healthy state of the tissue.

[00288] Methods of determine the values of αVβ1 integrin activity and/or expression; αVβ6 integrin activity and/or expression; a pSMAD/SMAD value; new collagen formation or

accumulation; total collagen; and Type I Collagen gene Col1a1 expression are known in the art and exemplary methods are disclosed in the Examples, such as antibody assays of tissue samples, such as a biopsy sample.

[00289] In some embodiments, the method selectively reduces αVβ1 integrin activity and/or expression compared to αVβ6 integrin activity and/or expression in the subject. In some embodiments, the method 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. In some embodiments, the method reduces both $\alpha v\beta_1$ integrin and $\alpha v\beta_6$ integrin activity and/or expression compared to at least one other αv-containing integrin in the subject. In some embodiments, the activity of αVβ1 integrin in one or more fibroblasts is reduced in the subject. In some embodiments, the activity of αVβ6 integrin in one or more epithelial cells is reduced in the subject.

[00290] In another aspect, provided herein is a method of treating a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a dosage form disclosed herein, wherein the subject has at least one tissue in need of therapy and the tissue has at least one elevated level of: αVβ1 integrin activity and/or expression; αVβ6 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. In some embodiments, 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. In some embodiments, the tissue has an elevated pSMAD2/SMAD2 value or an elevated pSMAD3/SMAD3 value compared to the healthy state of the tissue.

[00291] Methods of determine the values of αVβ1 integrin activity and/or expression; αVβ6 integrin activity and/or expression; a pSMAD/SMAD value; new collagen formation or accumulation; total collagen; and Type I Collagen gene Col1a1 expression are known in the art and exemplary methods are disclosed in the Examples, such as antibody assays of tissue samples, such as a biopsy sample.

[00292] In some embodiments, the method selectively reduces αVβ1 integrin activity and/or expression compared to αVβ6 integrin activity and/or expression in the subject. In some embodiments, the method 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. In some embodiments, the method reduces both $\alpha v\beta_1$ integrin and $\alpha v\beta_6$ integrin activity and/or expression compared to at least one other αv-containing integrin in the subject. In some embodiments, the activity of αVβ1 integrin in one or more fibroblasts is reduced in the subject. In some embodiments, the activity of αVβ6 integrin in one or more epithelial cells is reduced in the subject.

[00293] Also provided herein is a method of characterizing the antifibrotic activity of a small molecule in a subject, comprising: providing a first live cell sample from the subject, the first live cell sample characterized by the presence of at least one integrin capable of activating transforming growth factor β (TGF-β) from latency associated peptide-TGF-β; determining a first pSMAD/SMAD value in the first live cell sample; administering the small molecule to the subject; providing a second live cell sample from the subject, the second live cell sample being drawn from the same tissue in the subject as the first live cell sample; determining a second pSMAD/SMAD value in the second live cell sample; and characterizing the antifibrotic activity of the small molecule in the subject by comparing the second pSMAD/SMAD value to the first pSMAD/SMAD value. In some embodiments, the small molecule is a compound disclosed herein, optionally in a dosage form disclosed herein.

[00294] In some embodiments, each live cell sample is a plurality of cells derived from a tissue of the subject, or a plurality of macrophages associated with the tissue of the subject. In some embodiments, the tissue comprises one of: lung tissue, liver tissue, skin tissue, cardiac tissue, kidney tissue, gastrointestinal tissue, gall bladder tissue, and bile duct tissue. In some embodiments, each live cell sample comprises a plurality of alveolar macrophages derived from a bronchoalveolar lavage fluid of the subject.

[00295] In some embodiments, the method further comprising conducting a bronchoalveolar lavage on a lung of the subject effective to produce a bronchoalveolar lavage fluid that comprises the plurality of macrophages as a plurality of alveolar macrophages.

[00296] In some embodiments, the subject has 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. In some embodiments, the subject has the fibrotic disease psoriasis.

[00297] In some embodiments, the at least one integrin comprises α_V. In some embodiments, the at least one integrin comprises $\alpha_V\beta_1$. In some embodiments, the at least one integrin comprises $\alpha_V\beta_6$.

[00298] In some embodiments, determining the first pSMAD/SMAD value in the at least one live cell comprises determining a pSMAD2/SMAD2 value or a pSMAD3/SMAD3 value; and determining the second pSMAD/SMAD value in the at least one live cell after contacting the at least one live cell with the small molecule comprises determining a pSMAD2/SMAD2 value or a pSMAD3/SMAD3 value.

[00299] Also provided herein is a method of treating a fibrotic disease in a subject in need thereof, comprising: providing a first live cell sample from the subject, the first live cell sample having at least one integrin capable of activating transforming growth factor β (TGF-β) from latency associated peptide-TGF-β; determining a first pSMAD/SMAD value in the first live cell sample; administering a small molecule to the subject; providing a second live cell sample from the subject, the second live cell sample being drawn from the same tissue in the subject as the first live cell sample; determining a second pSMAD/SMAD value in the second live cell sample; comparing the second pSMAD/SMAD value to the first pSMAD/SMAD value; and administering the small molecule to the subject if the second pSMAD/SMAD value is lower than the first pSMAD/SMAD value. In some embodiments, the small molecule is a compound disclosed herein or a salt thereof, optionally in a dosage form disclosed herein. In some embodiments, the first live cell sample is obtained from the subject prior to treatment with a small molecule.

[00300] In some embodiments, each live cell sample is a plurality of cells derived from a tissue of the subject, or a plurality of macrophages associated with the tissue of the subject. In some embodiments, the tissue comprises one of: lung tissue, liver tissue, skin tissue, cardiac tissue, kidney tissue, gastrointestinal tissue, gall bladder tissue, and bile duct tissue. In some embodiments, each live cell sample comprises a plurality of alveolar macrophages derived from a bronchoalveolar lavage fluid of the subject. In some embodiments, the method further comprising conducting a bronchoalveolar lavage on a lung of the subject effective to produce a bronchoalveolar lavage fluid that comprises the plurality of macrophages as a plurality of alveolar macrophages.

[00301] In some embodiments, the subject is characterized by having 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. In some embodiments, the subject is characterized by having psoriasis.

[00302] In some embodiments, the at least one integrin comprises αv. In some embodiments, the at least one integrin comprises $\alpha v\beta_1$. In some embodiments, the at least one integrin comprises $\alpha v\beta_6$.

[00303] In some embodiments, determining the first pSMAD/SMAD value in the first live cell sample comprises determining a pSMAD2/SMAD2 value or a pSMAD3/SMAD3 value; and determining the second pSMAD/SMAD value in the at least one live cell after contacting the first live cell sample with the small molecule comprises determining a pSMAD2/SMAD2 value or a pSMAD3/SMAD3 value.

[00304] In another aspect, provided is a method of inhibiting $\alpha v\beta 6$ integrin in an individual comprising administering a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a stereoisomer thereof, or a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a pharmaceutically acceptable salt thereof.

[00305] In another aspect, provided is a method of inhibiting $\alpha v\beta 6$ integrin in an individual comprising administering a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a stereoisomer thereof, or a compound selected from Compound Nos. 1-147, or a pharmaceutically acceptable salt thereof.

[00306] In another aspect, provided is a method of inhibiting $\alpha v\beta 6$ integrin in an individual comprising administering a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a stereoisomer thereof, or a compound selected from Compound Nos. 1-665, or a pharmaceutically acceptable salt thereof.

[00307] In another aspect, provided is a method of inhibiting $\alpha v\beta 6$ integrin in an individual comprising administering a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a stereoisomer thereof, or a compound selected from Compound Nos. 1-780, or a pharmaceutically acceptable salt thereof.

[00308] Also provided is a method of inhibiting TGFβ activation in a cell comprising administering to the cell a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[00309] Also provided is a method of inhibiting TGFβ activation in a cell comprising administering to the cell a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-147, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[00310] Also provided is a method of inhibiting TGFβ activation in a cell comprising administering to the cell a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-665, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[00311] Also provided is a method of inhibiting TGFβ activation in a cell comprising administering to the cell a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[00312] Also provided is a method of inhibiting αvβ6 integrin in an individual in need thereof, comprising administering to the individual a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. Also provided is a method of inhibiting αvβ6 integrin in an individual in need thereof, comprising administering to the individual a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-147, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. Also provided is a method of inhibiting αvβ6 integrin in an individual in need thereof, comprising administering to the individual a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-

F), (II-G), or (II-H), a compound selected from Compound Nos. 1-665, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. Also provided is a method of inhibiting αvβ6 integrin in an individual in need thereof, comprising administering to the individual a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. In one such method, the compound is a selective αvβ6 integrin inhibitor. In another such method, the compound does not inhibit substantially α4β1, αvβ8 and/or α2β3 integrin. In yet another such method, the compound inhibits αvβ6 integrin but does not inhibit substantially α4β1 integrin. In still another such method, the compound inhibits αvβ6 integrin but does not inhibit substantially αvβ8 integrin. In a further such method, the compound inhibits αvβ6 integrin but does not inhibit substantially α2β3 integrin. In one embodiment is provided a method of inhibiting αvβ6 integrin and one or more of αvβ1, αvβ3, αvβ5, α2β1, α3β1, α6β1, α7β1 and α11β1 integrin in an individual in need thereof. In another embodiment is provided a method of inhibiting αvβ6 integrin and αvβ1 integrin. In another embodiment is provided a method of inhibiting αvβ6 integrin, αvβ3 integrin and αvβ5 integrin. In another embodiment is provided a method of inhibiting αvβ6 integrin and α2β1 integrin. In another embodiment is provided a method of inhibiting αvβ6 integrin, α2β1 integrin and α3β1 integrin. In another embodiment is provided a method of inhibiting αvβ6 integrin and α6β1 integrin. In another embodiment is provided a method of inhibiting αvβ6 integrin and α7β1 integrin. In another embodiment is provided a method of inhibiting αvβ6 integrin and α11β1 integrin. In all such embodiments, in one aspect the method of inhibition is for an individual in need thereof, such as an individual who has or is suspected of having a fibrotic disease, and wherein the method comprises administering to the individual a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-66 in **FIG. 1**, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. In all such embodiments, in one aspect the method of inhibition is for an individual in need thereof, such as an individual who has or is suspected of having a fibrotic disease, and wherein the method comprises administering to the individual a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-147, or a stereoisomer thereof, or a

pharmaceutically acceptable salt thereof. In all such embodiments, in one aspect the method of inhibition is for an individual in need thereof, such as an individual who has or is suspected of having a fibrotic disease, and wherein the method comprises administering to the individual a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-665, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. In all such embodiments, in one aspect the method of inhibition is for an individual in need thereof, such as an individual who has or is suspected of having a fibrotic disease, and wherein the method comprises administering to the individual a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[00313] Compounds of formula (A) can be used in any of the compositions, methods, and uses recited herein for formula (I) and variations of formula (I).

[00314] In any of the described methods, in one aspect the individual is a human, such as a human in need of the method. The individual may be a human who has been diagnosed with or is suspected of having a fibrotic disease. The individual may be a human who does not have detectable disease but who has one or more risk factors for developing a fibrotic disease.

[00315] Also provided herein are dosage forms configured for daily administration, comprising a pharmaceutically acceptable carrier or excipient; and a unit dose of a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[00316] A unit dose, such as a unit dose for daily administration, can comprise about 1, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, or 125 mg of the compound, or a range between any two of the preceding values, such as about 1-125, 1-5, 2.5-7.5, 5-15, 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-50, 10-75, 15-20, 15-25, 15-30, 15-35, 15-40, 15-50, 15-75, 20-25, 20-30, 20-35, 20-40, 20-50, 20-75, 25-30, 25-35, 25-40, 25-50, 25-75, 30-35, 30-40, 30-50, 30-75, 35-40, 35-50, 35-75, 40-50, 40-75, 50-75, 50-100, 60-85, 70-90, 70-100, 80-125, 90-125, or 100-125 mg.

[00317] A unit dose, such as a unit dose for daily administration, can comprise about 1, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 150, 175, 200, 225, or 250 mg of the compound, or a range between any two of the preceding values, such as about 1-125, 1-250, 1-5, 2.5-7.5, 5-15, 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-50, 10-75, 15-20, 15-25, 15-30, 15-35, 15-40, 15-50, 15-75, 20-25, 20-30, 20-35, 20-40, 20-50, 20-75, 25-30, 25-35, 25-40, 25-50, 25-75, 30-35, 30-40, 30-50, 30-75, 35-40, 35-50, 35-75, 40-50, 40-75, 50-75, 50-100, 50-150, 50-250, 60-85, 70-90, 70-100, 80-125, 90-125, 100-125, 100-150, 100-200, 125-175, 100-225, 100-250, and 150-250 mg. For example, the unit dose may be 10 mg. The unit dose may be 15 mg. The unit dose may be 20 mg. The unit dose may be 30 mg. The unit dose may be 40 mg. The unit dose may be 50 mg. The unit dose may be 60 mg. The unit dose may be 70 mg. The unit dose may be 75 mg. The unit dose may be 80 mg. The unit dose may be 90 mg. The unit dose may be 100 mg. The unit dose may be 110 mg. The unit dose may be 120 mg. The unit dose may be 125 mg. The unit dose may be 150 mg. The unit dose may be 175 mg. The unit dose may be 200 mg. The unit dose may be 225 mg. The unit dose may be 250 mg.

[00318] A unit dose, such as a unit dose for daily administration, can comprise 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, or greater than 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, such as 700-1500, 700-900, 800-1300, 750-950, 800-1000, 850-950, 850-1050, 900-1400, 900-1300, 900-1200, 900-1100, 950-1050, 950-1400, 950-1150, 1000-1400, 1000-1300, 1000-1200, and the like. For example, C_{max} can be about 700 ng/mL or greater. C_{max} can be about 750 ng/mL or greater. C_{max} can be about 800 ng/mL or greater. C_{max} can be about about 850 ng/mL or greater. C_{max} can be 900 ng/mL or greater. C_{max} can be about 950 ng/mL or greater. C_{max} can be about 1000 ng/mL or greater. C_{max} can be about 1050 ng/mL or greater. C_{max} can be about 1100 ng/mL or greater. C_{max} can be about 1200 ng/mL or greater. C_{max} can be about 1300 ng/mL or greater. C_{max} can be about 1400 ng/mL or greater.C_{max} can be about 1500 ng/mL or greater.

[00319] A unit dose, such as a unit dose for daily administration, can comprise 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, for example, 50-100, 60-90, 70-90, 75-95, and the like. In some embodiments,

the compound may be a dual $\alpha v\beta_6$ and $\alpha v\beta_1$ inhibitor, and the C_{max} can correspond to a plasma-adjusted concentration effective to inhibit a percentage of each of $\alpha v\beta_6$ and $\alpha v\beta_1$ in the individual, each percentage independently selected from the preceding percentages, or a range between any two of the preceding percentages. For example, the plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_6$ by at least about 50%. The plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_6$ by at least about 60%. The plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_6$ by at least about 70%. The plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_6$ by at least about 80%. The plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_6$ by at least about 90%. Further, for example, the plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_1$ by at least about 50%. The plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_1$ by at least about 60%. The plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_1$ by at least about 70%. The plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_1$ by at least about 80%. The plasma-adjusted concentration can be effective to inhibit $\alpha v\beta_1$ by at least about 90%. The recitation "percentage of each of $\alpha v\beta_6$ and/or $\alpha v\beta_1$ in the subject, each percentage independently selected" means, in the alternative, a single $\alpha v\beta_6$ inhibitor and corresponding percentage, a single $\alpha v\beta_1$ inhibitor and corresponding percentage, or a dual $\alpha v\beta_6/\alpha v\beta_6$ inhibitor and corresponding independently selected percentages.

[00320] The dosage form for daily administration can be administered to an individual in need thereof once daily. That is, the total amount of a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, which is to be administered each day, can be administered all together at one time daily. Alternatively, if it is desirable that the total amount of a compound of formula (A), formula (I), or any variation thereof, *e.g.*, a compound of formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (II), (II-A), (II-B), (II-C), (II-D), (II-E), (II-F), (II-G), or (II-H), a compound selected from Compound Nos. 1-780, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, is to be administered in two or more portions daily, the dosage form containing the appropriate amount of compound can be administered two times or more daily, such as twice a day, three times a day, or four times a day.

Kits

[00321] The invention further provides kits for carrying out the methods of the invention, which comprises one or more compounds described herein, or a salt thereof, or a pharmacological composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein or a pharmaceutically acceptable salt thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for use in the treatment of a fibrotic disease.

[00322] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. One or more components of a kit may be sterile and/or may be contained within sterile packaging.

[00323] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein (*e.g.*, a therapeutically effective amount) and/or a second pharmaceutically active compound useful for a disease detailed herein (*e.g.*, fibrosis) to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[00324] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present invention. The instructions included with the kit generally include information as to the components and their administration to an individual.

[00325] The kits may optionally further comprise instructions for daily administration of the dosage form to an individual in need thereof, such as instructions for administration of the dosage form to an individual in need thereof one, two, three, or four times daily, for example, instructions for administration of the dosage form to an individual in need thereof once daily.

GENERAL PROCEDURES

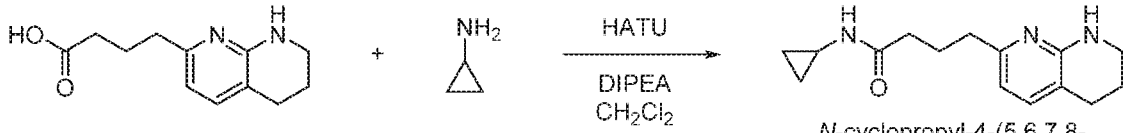
[00326] Compounds provided herein may be prepared according to General Schemes, as exemplified by the General Procedures and Examples. Minor variations in temperatures, concentrations, reaction times, and other parameters can be made when following the General Procedures, which do not substantially affect the results of the procedures.

[00327] When a specific stereoisomer, or an unspecified stereoisomer, or a mixture of stereoisomers is shown in the following general procedures, it is understood that similar chemical transformations can be performed on other specific stereoisomers, or an unspecified stereoisomer, or mixtures thereof. For example, a hydrolysis reaction of a methyl (*S*)-4-amino-butanoate to an (*S*)-4-amino-butanoic acid can also be performed on a methyl (*R*)-4-amino-butanoate to prepare an (*R*)-4-amino-butanoic acid, or on a mixture of a methyl (*S*)-4-amino-butanoat and a methyl (*R*)-4-amino-butanoate to prepare a mixture of an (*S*)-4-amino-butanoic acid and an (*R*)-4-amino-butanoic acid.

[00328] Some of the following general procedures use specific compounds to illustrate a general reaction (*e.g.*, deprotection of a compound having a Boc-protected amine to a compound having a deprotected amine using acid). The general reaction can be carried out on other specific compounds having the same functional group (*e.g.*, a different compound having a protected amine where the Boc-protecting group can be removed using acid in the same manner) as long as such other specific compounds do not contain additional functional groups affected by the general reaction (i.e., such other specific compounds do not contain acid-sensitive functional groups), or if the effect of the general reaction on those additional functional groups is desired (*e.g.*, such other specific compounds have another group that is affected by acid, and the effect of the acid on that other group is a desirable reaction).

[00329] Where specific reagents or solvents are specified for reactions in the general procedures, the skilled artisan will recognize that other reagents or solvents can be substituted as desired. For example, where hydrochloric acid is used to remove a Boc group, trifluoroacetic acid can be used instead. As another example, where HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate) is used as a coupling reagent, BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate) or PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate) can be used instead.

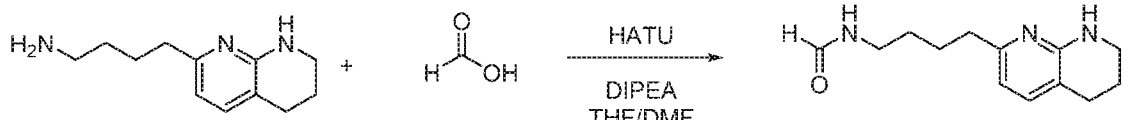
General Procedure A



4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanoic acid | cyclopropanamine | *N*-cyclopropyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanamide

[00330] ***N-cyclopropyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanamide.*** To a mixture of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanoic acid hydrochloride (5.0 g, 19.48 mmol) and cyclopropanamine (1.51 mL, 21.42 mmol) in CH_2Cl_2 (80 mL) at rt was added DIPEA (13.57 mL, 77.9 mmol). To this was then added HATU (8.1 g, 21.42 mmol) and the resulting mixture was stirred at rt for 2 hrs. The reaction mixture was concentrated *in vacuo* and purified by normal phase silica gel chromatography to give N-cyclopropyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanamide.

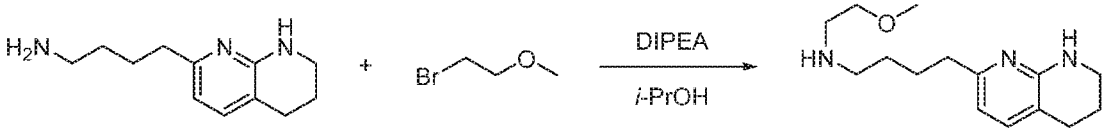
General Procedure B



4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine | N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)formamide

[00331] ***N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)formamide.*** To a mixture of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine (351 mg, 1.71 mmol) and formic acid (0.09 mL, 2.22 mmol) in 4:1 THF/DMF (5 mL) was added HATU (844 mg, 2.22 mmol) followed by DIPEA (0.89 mL, 5.13 mmol) and the reaction was allowed to stir at rt for 1 hr. The reaction mixture was concentrated *in vacuo* and purified by normal phase silica gel chromatography to give N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)formamide.

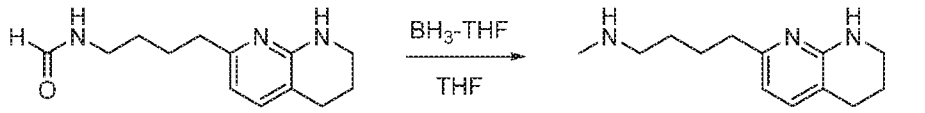
General Procedure C



[00332] ***N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine.*** A mixture of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine (300 mg, 1.46 mmol), 1-bromo-2-methoxyethane (0.11 mL, 1.17 mmol) and DIPEA (0.25 mL, 1.46 mmol) in *i*-PrOH (3 mL) was heated to 70 °C for 18 hr. The reaction mixture was allowed to cool to rt

and then concentrated *in vacuo* and purified by normal phase silica gel chromatography to give N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine.

General Procedure D

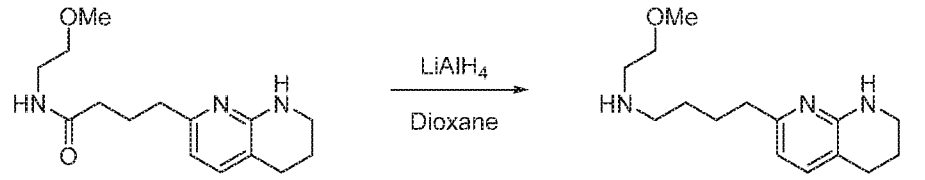


N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)formamide

N-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine

[00333] ***N-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine***. To a solution of N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)formamide (200 mg, 0.86 mmol) in THF (2 mL) at rt was added borane tetrahydrofuran complex solution (1.0M in THF, 4.0 mL, 4.0 mmol) dropwise. The resulting mixture was then heated to 60 °C for 2 hr and then allowed to cool to rt. The reaction mixture was diluted with MeOH and concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give N-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine.

General Procedure E



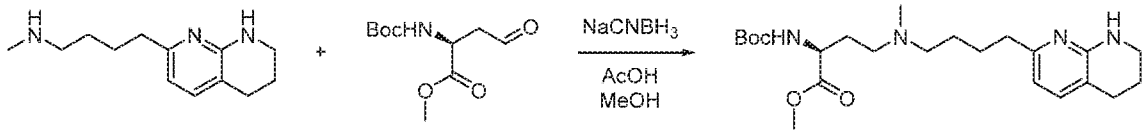
N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanamide

N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine

[00334] ***N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine*** **(5)**. To a solution of N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanamide (15.5 g, 1.0 equiv) in 1,4-dioxane (124 mL) at rt was slowly added $LiAlH_4$ (1.0 M in THF, 123 mL, 2.2 equiv) and the resulting mixture was heated to reflux for 20 hours and then cooled to 0 °C. To this solution was added H_2O (4.7 mL), then 1M NaOH (4.7 mL) then H_2O (4.7 mL) and warmed to room temperature and stirred for 30 minutes, at which time, solid $MgSO_4$ was added and stirred for an additional 30 minutes. The resulting mixture was filtered and the filter cake was washed with THF. The filtrate were concentrated

in vacuo to give N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine.

General Procedure F



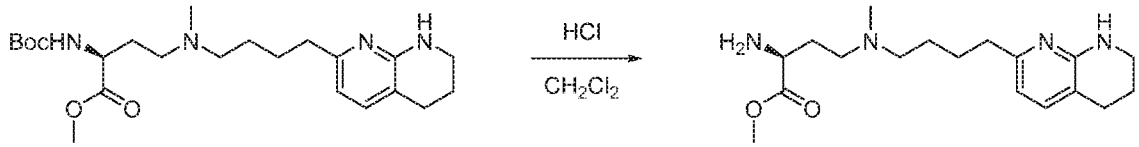
N-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine

methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate

methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

[00335] ***methyl (S)-2-((tert-butoxycarbonyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate***. To a mixture of N-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine (5) (187 mg, 0.85mmol) in MeOH (5 mL) at rt was added acetic acid (0.12 mL, 2.05 mmol) followed by methyl (S)-2-((tert-butoxycarbonyl)amino)-4-oxobutanoate (217 mg, 0.94 mmol). The resulting mixture was allowed to stir at rt for 15 min, at which time, sodium cyanoborohydride (80 mg, 1.28 mmol) was added to the reaction mixture and stirred for 30 min and then concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give methyl (S)-2-((tert-butoxycarbonyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate.

General Procedure G

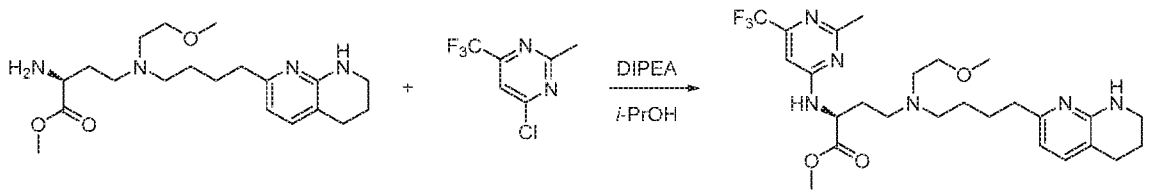


methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

methyl (*S*)-2-amino-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

[00336] ***methyl (S)-2-amino-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate***. To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (152 mg, 0.35mmol) in CH_2Cl_2 (2 mL) at rt was added 4N HCl in 1,4-dioxane (1 mL, 4 mmol) and the resulting mixture was allowed to stir for 2 hr. The reaction mixture was concentrated *in vacuo* to give methyl (S)-2-amino-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate as the trihydrochloride salt.

General Procedure H



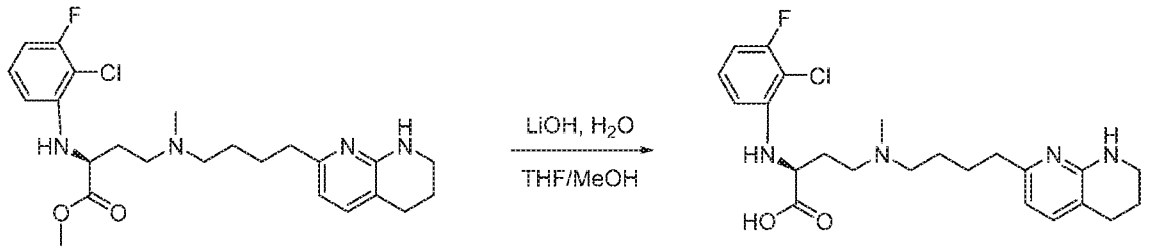
methyl (*S*)-2-amino-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

4-chloro-2-methyl-6-(trifluoromethyl)pyrimidine

methyl (*S*)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl)amino)butanoate

[00337] A solution of methyl (S)-2-amino-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate trihydrochloride (80 mg, 0.16 mmol), 4-chloro-2-methyl-6-(trifluoromethyl)pyrimidine (64 mg, 0.33 mmol) and DIPEA (0.23 mL, 1.31 mmol) in *i*-PrOH (1 mL) was heated at 60 °C overnight. The reaction was allowed to cool to rt and then concentrated *in vacuo*. The resulting crude residue was purified by normal phase silica gel chromatography to give methyl (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl)amino)butanoate.

General Procedure P

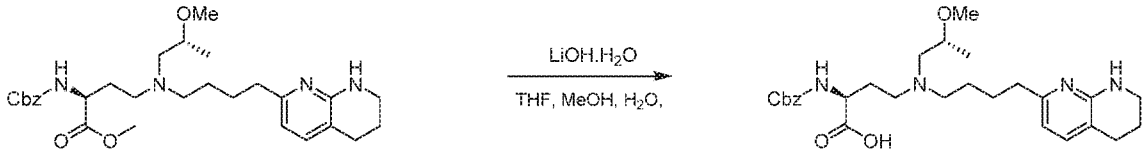


methyl (*S*)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

(*S*)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid

[00338] ***(S)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid*** To a solution of methyl (S)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate in 4:1:1 THF/MeOH/H_2O at rt was added lithium hydroxide (approximately four equivalents) and the resulting mixture was stirred for 30 min. The reaction mixture was concentrated *in vacuo* and the resulting crude residue purified by reverse phase HPLC to give (S)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid, as the trifluoroacetate salt.

General Procedure Q

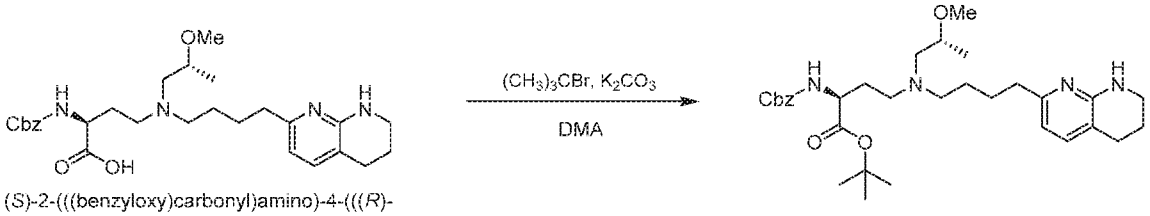


methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

(*S*)-2-(((benzyloxy)carbonyl)amino)-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid

[00339] (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid. A mixture of methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (1 g, 1.90 mmol) in H_2O (3 mL) and THF (3 mL) and MeOH (3 mL) was added $LiOH{\bullet}H_2O$ (159.36 mg, 3.80 mmol) and then the mixture was stirred at room temperature for 1 h and the resulting mixture was concentrated in vacuo. The mixture was adjusted to pH=6 by AcOH (2 mL) and the residue was concentrated in vacuo to give a residue to yield compound (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid. LCMS (ESI+): m/z = 513.5 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d): δ ppm 7.25 - 7.37 (m, 5 H) 7.00 (d, J=7.28 Hz, 1 H) 6.81 (br d, J=7.50 Hz, 1 H) 6.22 (d, J=7.28 Hz, 1 H_6) 4.93 - 5.05 (m, 2 H) 3.68 - 3.77 (m, 1 H) 3.25 - 3.34 (m, 1 H) 3.15 - 3.24 (m, 5 H) 2.58 (br t, J=6.06 Hz, 2 H) 2.29 - 2.49 (m, 8 H) 2.16 (br dd, J=12.90, 6.06 Hz, 1 H) 1.69 - 1.78 (m, 2 H) 1.58 - 1.68 (m, 1 H) 1.53 (quin, J=7.39 Hz, 2 H) 1.28 - 1.40 (m, 2 H) 1.00 (d, J=5.95 Hz, 3 H).

General Procedure R



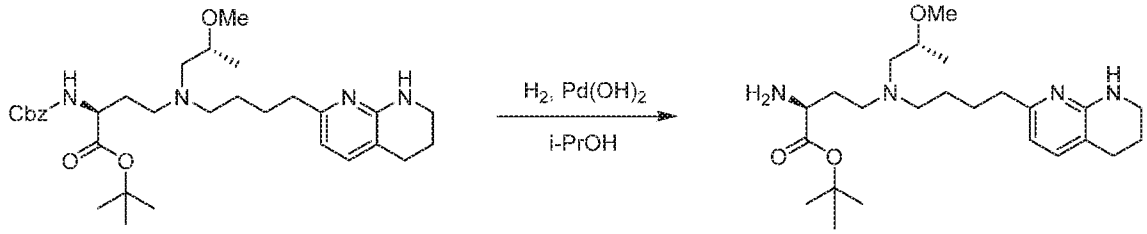
(*S*)-2-(((benzyloxy)carbonyl)amino)-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid

tert-butyl (*S*)-2-(((benzyloxy)carbonyl)amino)-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

[00340] tert-butyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate: A solution of (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid (300 mg, 523.84 umol, HOAc salt) in DMA (4 mL) was added N-benzyl-N,N-diethylethanaminium chloride (119.32 mg, 523.84 umol),

K_2CO_3 (1.88 g, 13.62 mmol), 2-bromo-2-methylpropane (3.45 g, 25.14 mmol,). The mixture was stirred for 18 h at the 55 °C and then allowed to cool to room temperature. The reaction mixture was concentrated in vacuo and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by prep-TLC to give tert-butyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate. LCMS (ESI+): m/z = 569.3 $(M+H)^+$.

General Procedure S

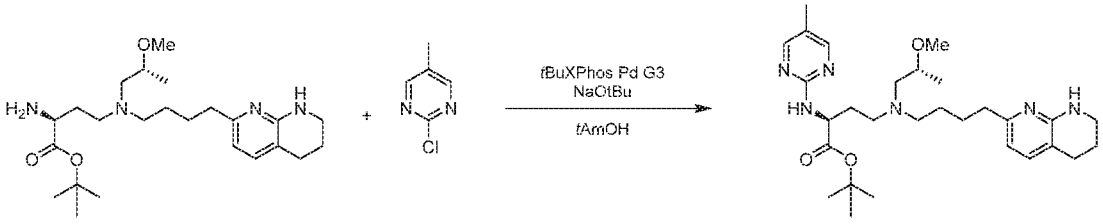


tert-butyl (*S*)-2-(((benzyloxy)carbonyl)amino)-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

tert-butyl (*S*)-2-amino-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

[00341] ***tert-butyl (S)-2-amino-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate***. To a solution of tert-butyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (107 mg, 188.13 umol) in *i*-PrOH (2 mL) was added $Pd(OH)_2$ (26 mg) under an N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at room temperature for 15 h. The mixture was filtered and concentrated *in vacuo* to give tert-butyl (S)-2-amino-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate. LCMS (ESI+): m/z = 435.5 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.06 (d, *J*=7.34 Hz, 1 H) 6.34 (d, *J*=7.34 Hz, 1 H) 4.98 (br s, 1 H) 3.38 - 3.44 (m, 4 H) 3.34 (s, 3 H) 2.69 (t, *J*=6.30 Hz, 2 H) 2.51 - 2.59 (m, 5 H) 2.31 (dd, *J*=13.39, 5.56 Hz, 1 H) 1.86 - 1.94 (m, 5 H) 1.49 - 1.69 (m, 6 H) 1.47 (s, 9 H) 1.13 (d, *J*=6.11 Hz, 3 H).

General Procedure T

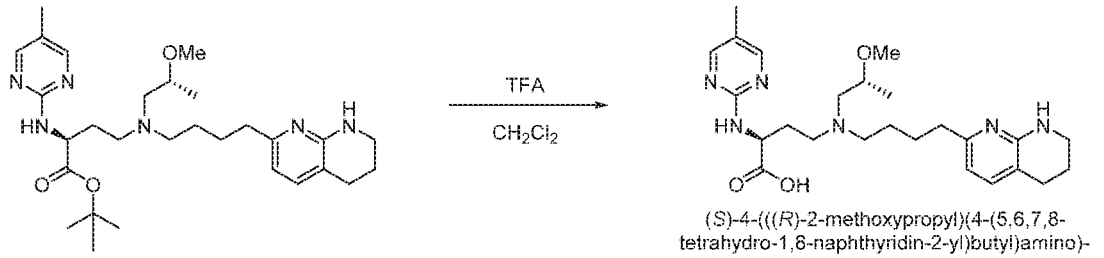


tert-butyl (*S*)-2-amino-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

tert-butyl (*S*)-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoate

[00342] tert-butyl (S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoate. To a solution of (S)-tert-butyl 2-amino-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate tert-butyl (S)-2-amino-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (100 mg, 230.09 umol) and 2-chloro-5-methyl-pyrimidine (24.65 mg, 191.74 umol) in 2-methyl-2-butanol (2 mL) was added t-BuONa (2 M in THF, 191.74 uL) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (15.23 mg, 19.17 umol), and the resulting mixture was stirred at 100 °C for 14 h. The mixture was concentrated in vacuo to give (S)-tert-butyl 4-(((S)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoate. LCMS (ESI+): m/z = 527.3 $(M+H)^+$.

General Procedure U



tert-butyl (*S*)-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoate

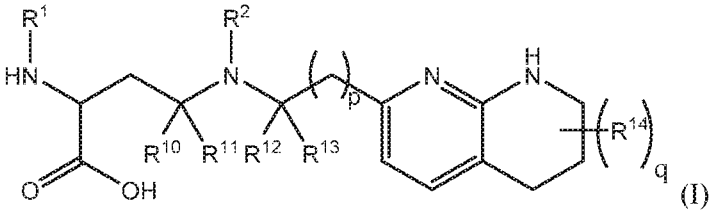
(*S*)-4-(((*R*)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoic acid

[00343] (S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoic acid. To a solution of tert-butyl (S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoate (80 mg, 151.89 umol) in DCM (2 mL) was added TFA (254.14 mg, 2.23 mmol) at 0 °C. The mixture was stirred at room temperature for 6 h. The mixture was concentrated in vacuo and the resulting crude residue was purified by prep-HPLC to give compound (S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoic acid. LCMS (ESI+): m/z = 471.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.57 (br s, 2 H) 7.60 (d, J=7.28 Hz, 1 H) 6.67 (d, J=7.28 Hz, 1 H) 4.81 - 4.86 (m, 1 H) 3.86 (br s, 1 H) 3.41 - 3.59 (m, 4 H) 3.39 (s, 3 H) 3.33 - 3.38 (m, 1 H) 3.12 - 3.30 (m, 3 H) 2.76 - 2.86 (m, 4 H) 2.54 (br s, 1 H) 2.39 (br d, J=8.82 Hz, 1 H) 2.30 (s, 3 H) 1.76 - 1.99 (m, 6 H) 1.22 (d, J=5.95 Hz, 3 H).

ENUMERATED EMBODIMENTS

[00344] The following enumerated embodiments are representative of some aspects of the invention.

Embodiment 1. A compound of formula (I)



(I)

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 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 $-S(O)_2R^{2d}$;

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 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;

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;

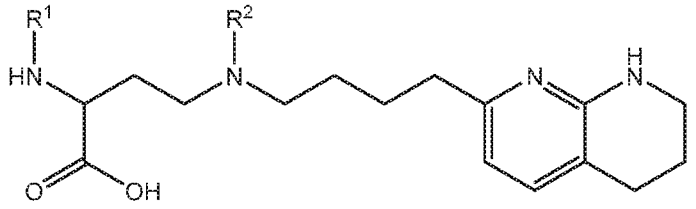
R^{14} is deuterium;

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

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

Embodiment 2. The compound of embodiment 1, or a salt thereof, 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}, R^{13}, or R^{14} is deuterium.

Embodiment 3. The compound of embodiment 1 or a salt thereof, wherein R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are hydrogen; p is 3; and is represented by the compound of formula (II):



(II).

Embodiment 4. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}.

Embodiment 5. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is pyrimidin-4-yl optionally substituted by R^{1a}.

Embodiment 6. The compound of embodiment 1, 2, or 3, or a salt thereof, 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.

Embodiment 7. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is pyrimidin-4-yl optionally substituted by pyrazolyl, methyl, difluoromethyl, or trifluoromethyl.

Embodiment 8. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is pyrimidin-4-yl substituted by both methyl and trifluoromethyl.

Embodiment 9. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is quinazolin-4-yl optionally substituted by R^{1a}.

Embodiment 10. The compound of embodiment 1, 2, or 3, or a salt thereof, 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.

Embodiment 11. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is quinazolin-4-yl optionally substituted by fluoro, chloro, methyl, trifluoromethyl or methoxy.

Embodiment 12. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by R^{2a}.

Embodiment 13. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} wherein R^{2a} is: halogen; C_3-C_8 cycloalkyl optionally substituted by halogen; 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl; $-NR^4R^5$; $-NR^3C(O)R^4$; $-S(O)_2R^3$; or oxo.

Embodiment 14. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} wherein R^{2a} is: fluoro; cyclobutyl substituted by fluoro; pyrazolyl substituted by methyl; or $-S(O)_2CH_3$.

Embodiment 15. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by $-OR^3$.

Embodiment 16. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by $-OR^3$, and R^3 is: hydrogen; C_1-C_6 alkyl optionally substituted by halogen; C_3-C_6 cycloalkyl optionally substituted by halogen; C_6-C_{14} aryl optionally substituted by halogen; or 5- to 6-membered heteroaryl optionally substituted by halogen or C_1-C_6 alkyl.

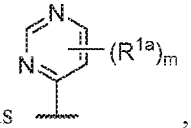
Embodiment 17. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by $-OR^3$, and R^3 is: hydrogen; methyl; ethyl; difluoromethyl; $-CH_2CHF_2$; $-CH_2CF_3$; cyclopropyl substituted by fluoro; phenyl optionally substituted by fluoro; or pyridinyl optionally substituted by fluoro or methyl.

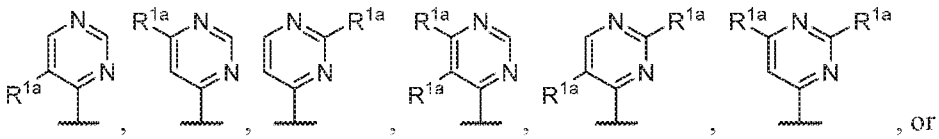
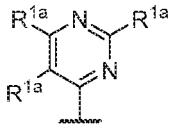
Embodiment 18. The compound of any one of embodiments 1 to 11, wherein R^2 is $-CH_2CH_2OCH_3$.

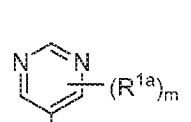
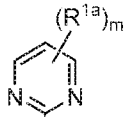
Embodiment 19. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by both halogen and OR^3, wherein R^3 is C_1-C_6 alkyl.

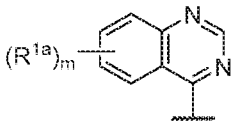
Embodiment 20. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_3-C_6 cycloalkyl optionally substituted by R^{2b}.

Embodiment 21. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is cyclopropyl.

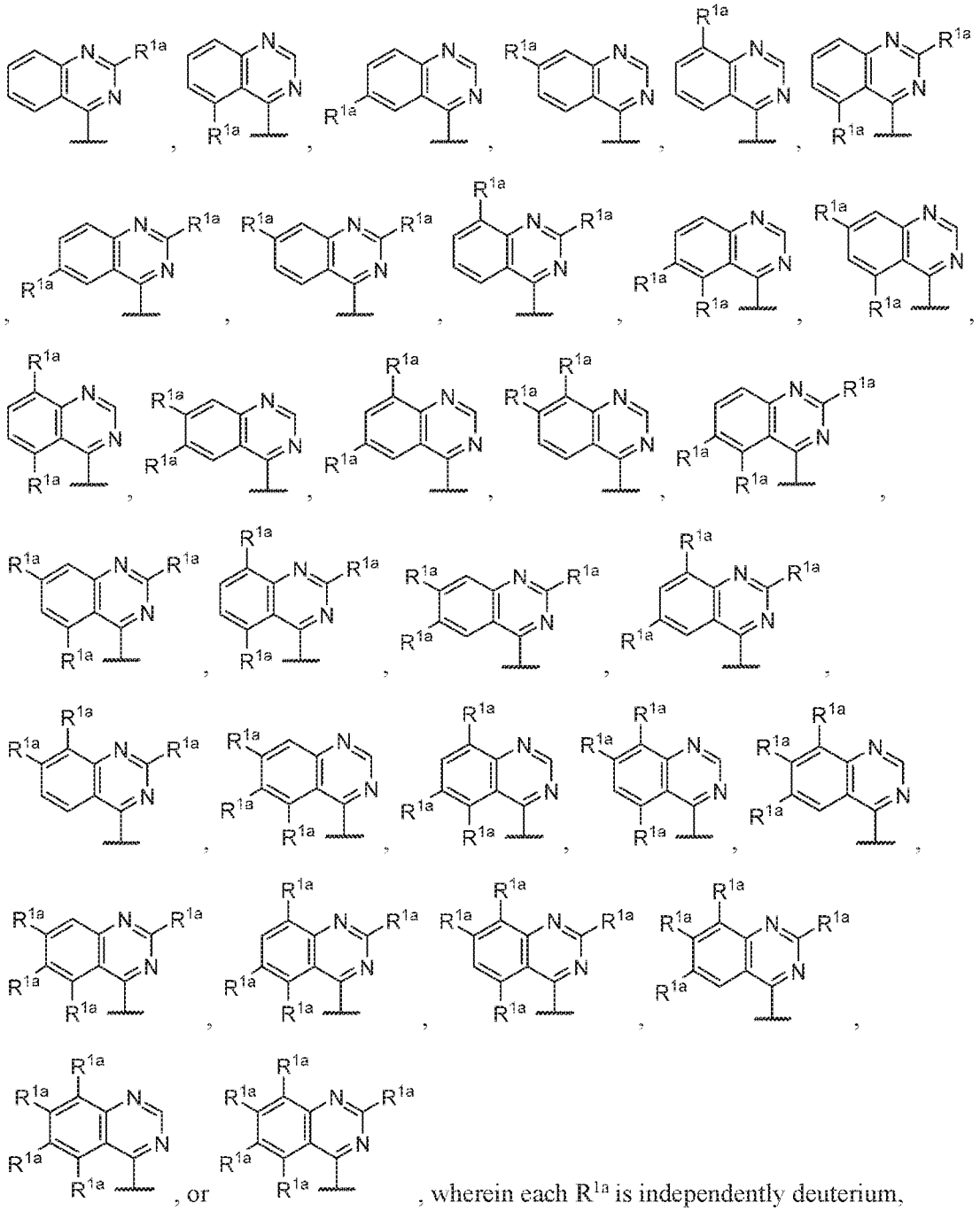
Embodiment 22. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

Embodiment 23. The compound of embodiment 22, or a salt thereof, wherein R^1 is  , or  , wherein each R^{1a} is independently deuterium, alkyl, haloalkyl, or heteroaryl.

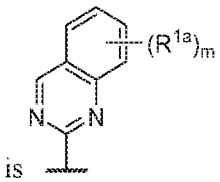
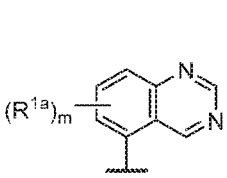
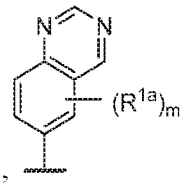
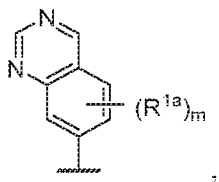
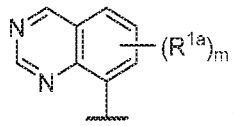
Embodiment 24. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is  or  , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

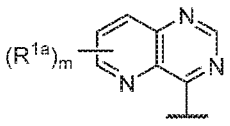
Embodiment 25. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, 3, 4, or 5 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

Embodiment 26. The compound of embodiment 25, or a salt thereof, wherein R^1 is

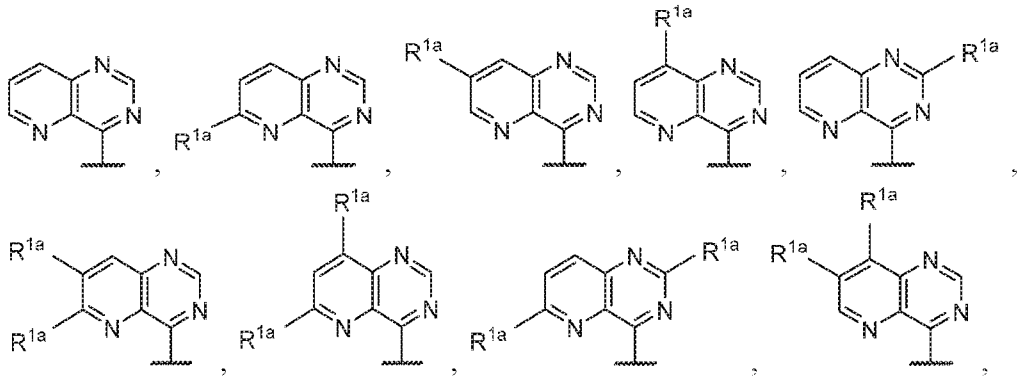


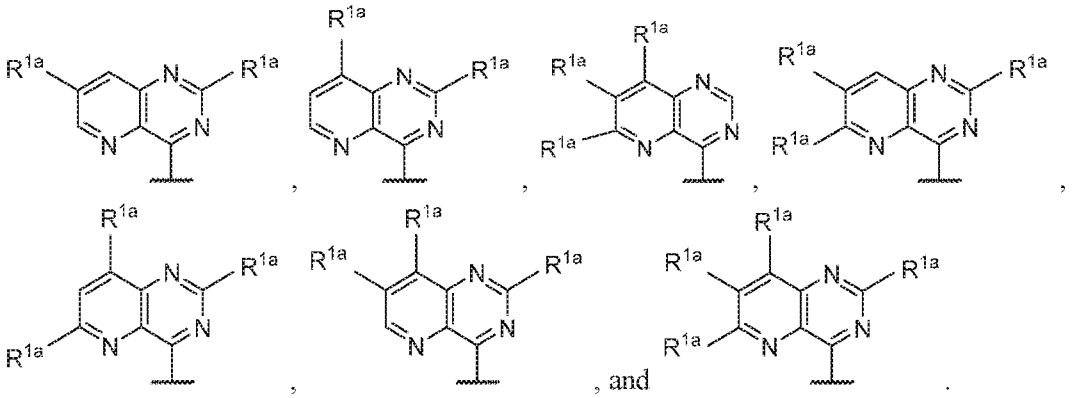
, wherein each R^{1a} is independently deuterium, halogen, alkyl, haloalkyl, or alkoxy.

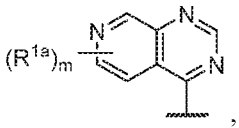
Embodiment 27. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is  ,  ,  ,  , or  wherein m is 0, 1, 2, 3, 4, or 5 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

Embodiment 28. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein 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.

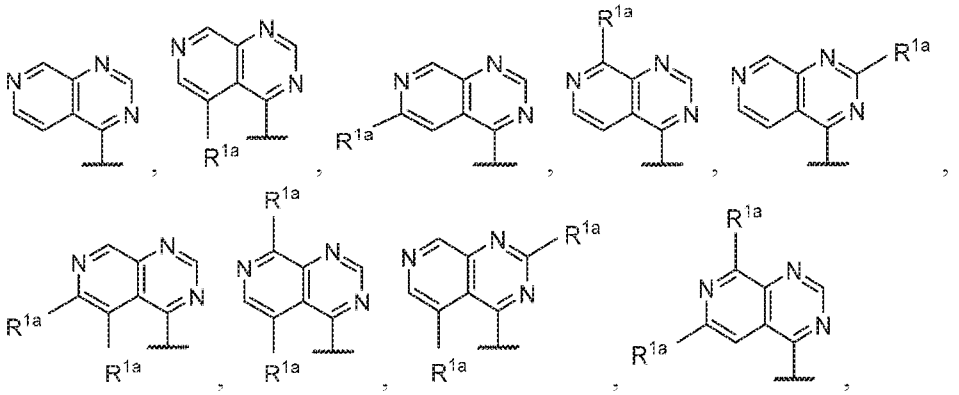
Embodiment 29. The compound of embodiment 28, or a salt thereof, wherein R^1 is selected from the group consisting of

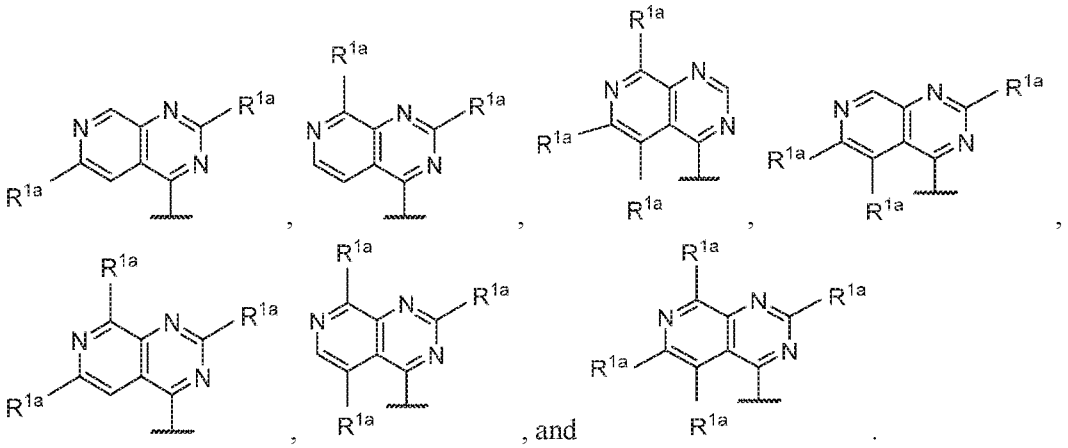


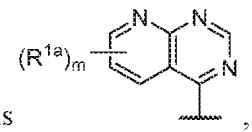


Embodiment 30. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

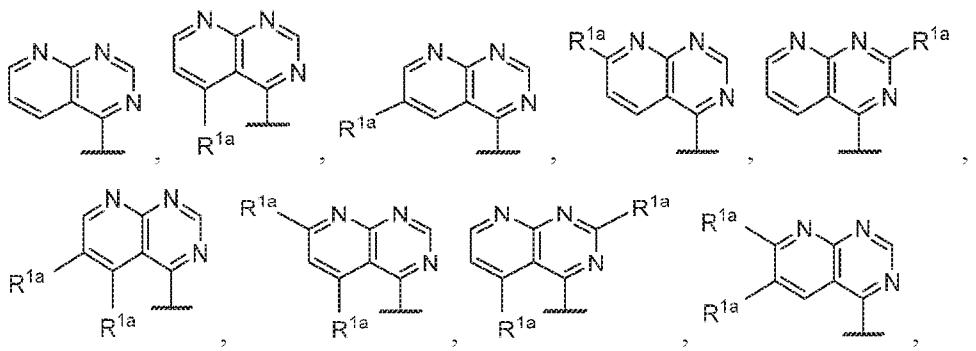
Embodiment 31. The compound of embodiment 30, or a salt thereof, wherein R^1 is selected from the group consisting of

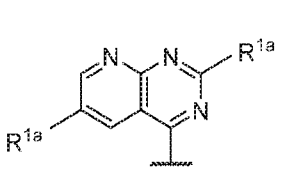
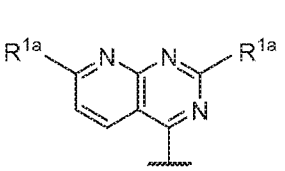
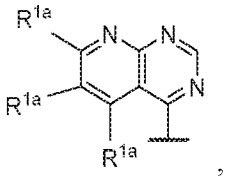
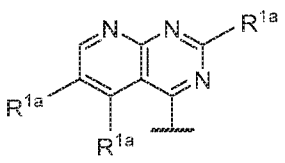
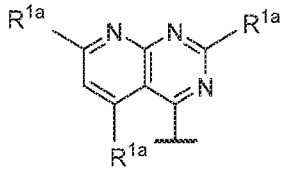
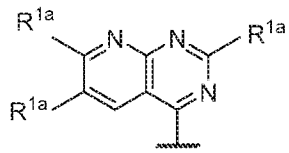
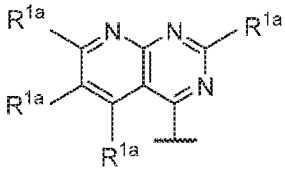


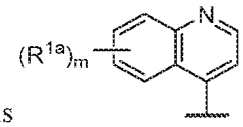


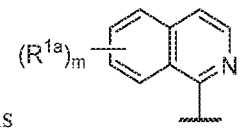
Embodiment 32. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

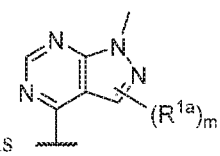
Embodiment 33. The compound of embodiment 32, or a salt thereof, wherein R^1 is selected from the group consisting of



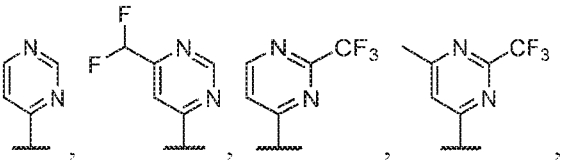
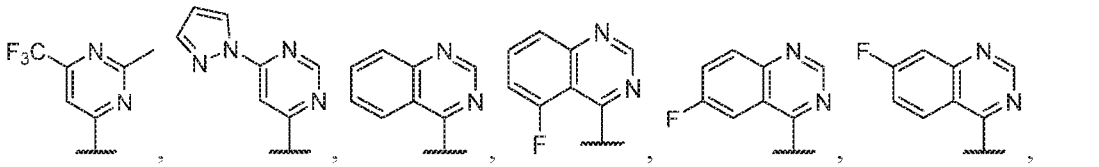
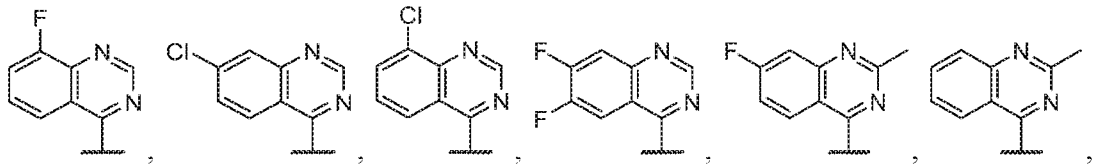
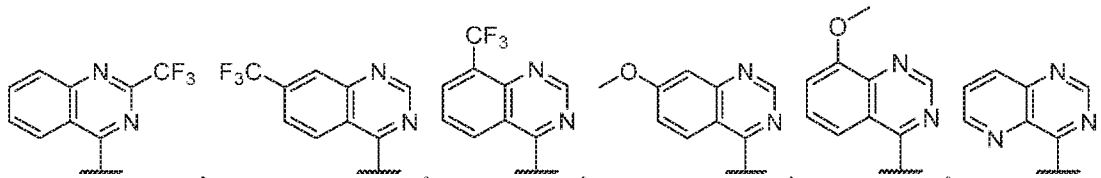
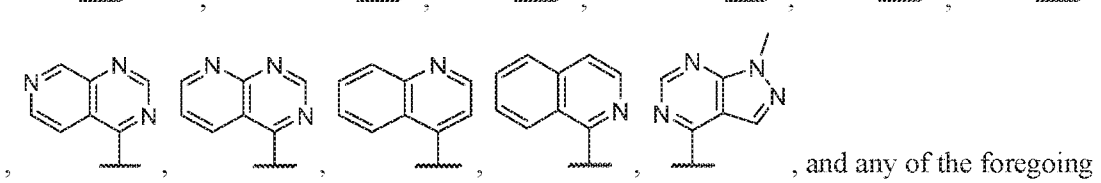
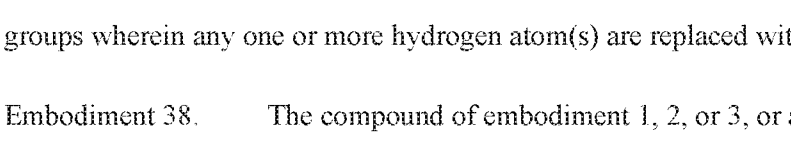

,

,

,

,

,

, and

.

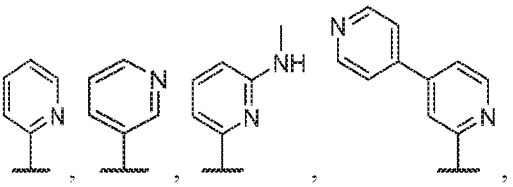
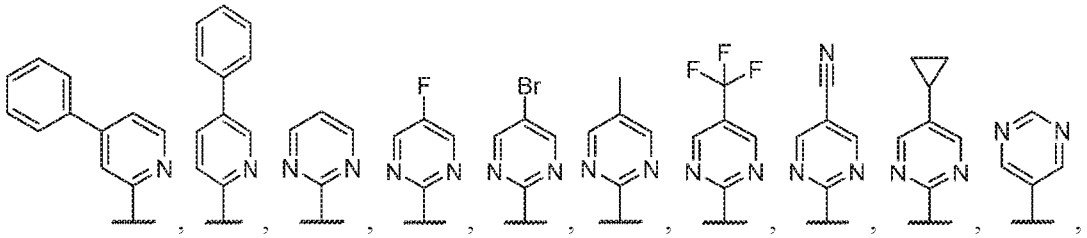
Embodiment 34. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, 3, 4, 5, or 6 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

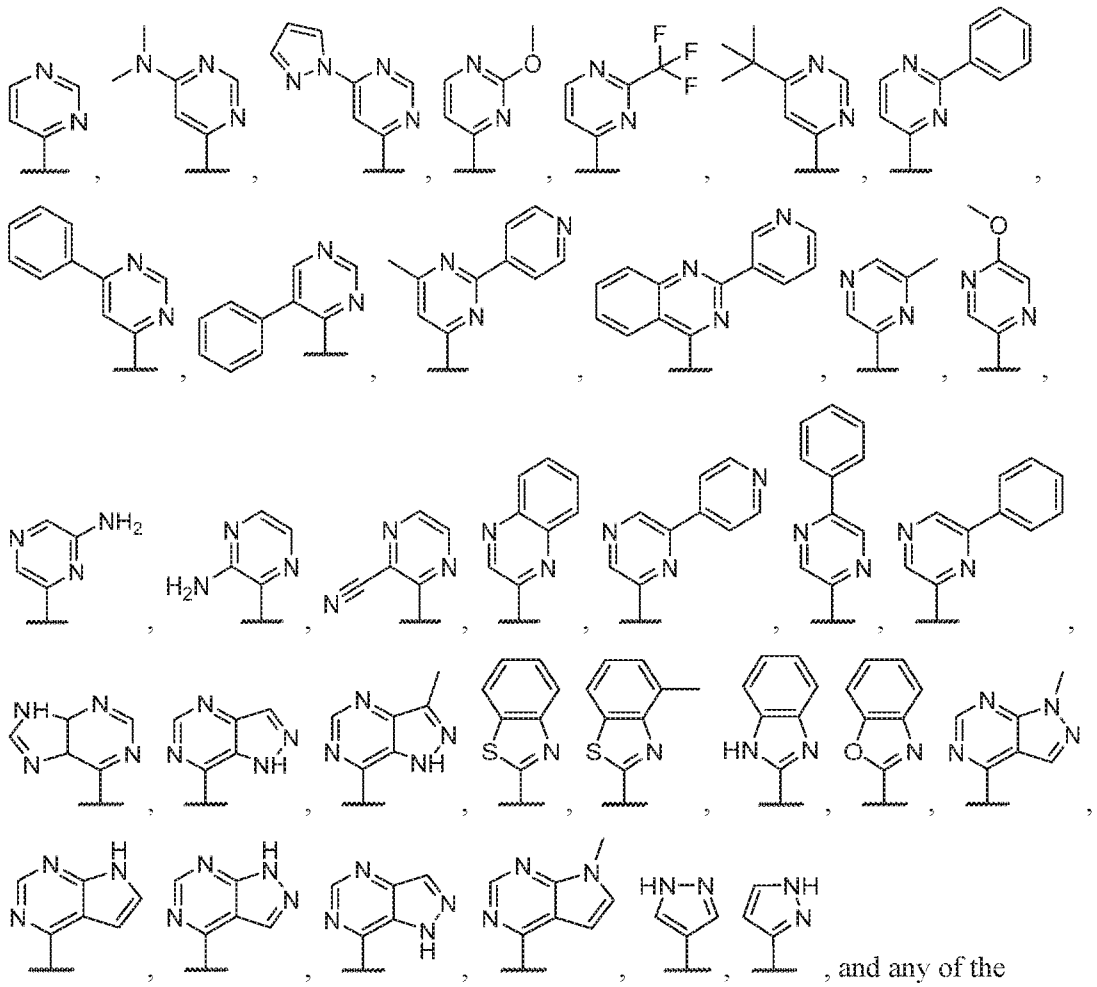
Embodiment 35. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, 3, 4, 5, or 6 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

Embodiment 36. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein 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.

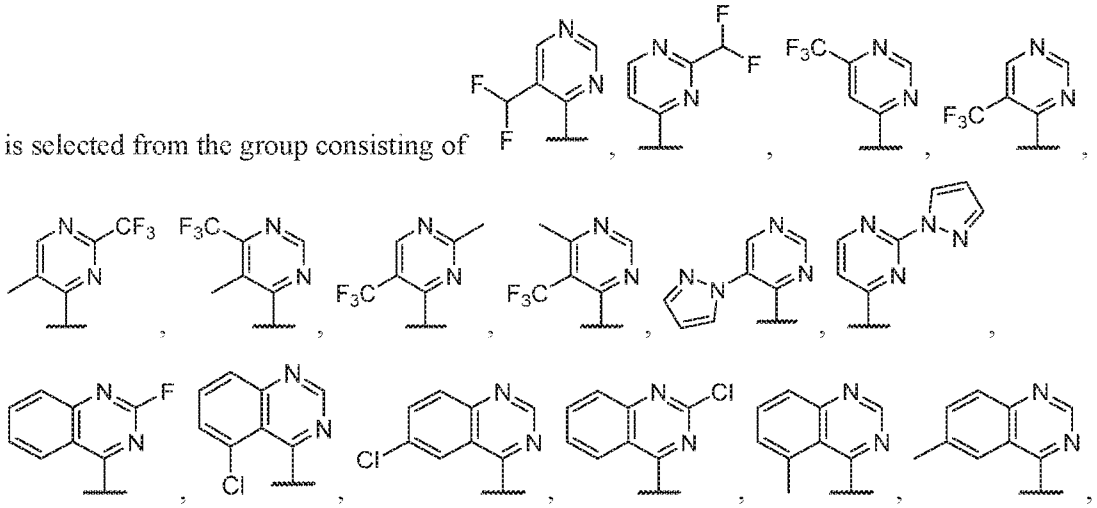
Embodiment 37. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is selected from the group consisting of  ,  ,  ,  ,  ,  , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s).

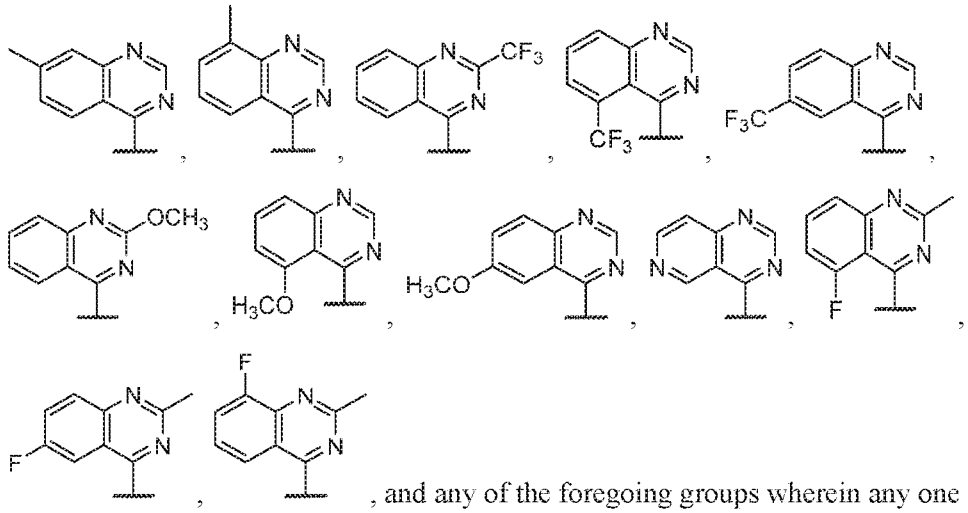
Embodiment 38. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is selected from the group consisting of  ,  ,



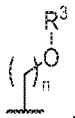
, and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s).

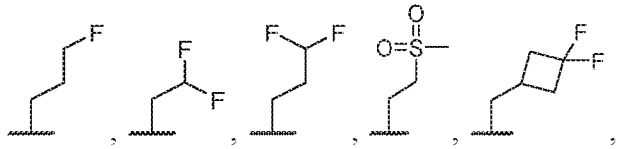
Embodiment 39. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is selected from the group consisting of

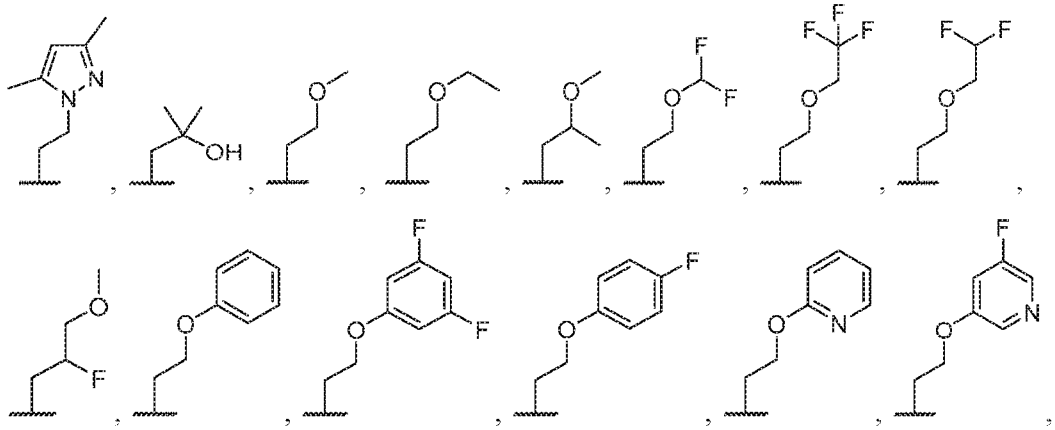


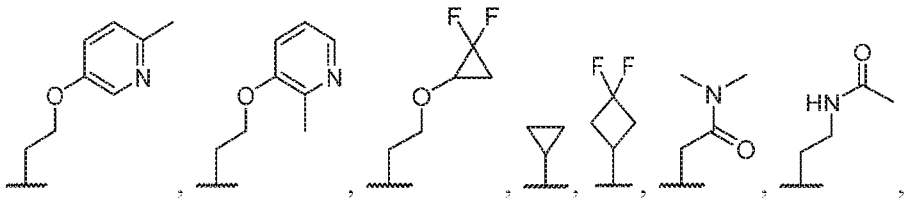


, and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s).

Embodiment 40. The compound of any one of embodiments 1 to 11, or a salt thereof, 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.

Embodiment 41. The compound of embodiment 1, 2, or 3, or a salt thereof, 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).

Embodiment 42. A compound, or a salt thereof, selected from Compound Nos. 1-66 in FIG 1.

Embodiment 43. A compound, or a salt thereof, selected from Compound Nos. 1-147.

Embodiment 44. A compound, or a salt thereof, selected from Compound Nos. 1-665.

Embodiment 45. A pharmaceutical composition comprising a compound of any one of embodiments 1 to 44, or a salt thereof, and a pharmaceutically acceptable carrier or excipient.

Embodiment 46. A method of treating a fibrotic disease in an individual in need thereof comprising administering a compound of any one of embodiments 1 to 44 or a pharmaceutically acceptable salt thereof.

Embodiment 47. The method of embodiment 46, wherein the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis, cardiac fibrosis, kidney fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis.

Embodiment 48. A kit comprising a compound of any one of embodiments 1 to 44, or a pharmaceutically acceptable salt thereof.

Embodiment 49. The kit of embodiment 48, further comprising instructions for the treatment of a fibrotic disease.

Embodiment 50. A method of inhibiting αvβ6 integrin in an individual comprising administering a compound of any one of embodiments 1 to 44 or a pharmaceutically acceptable salt thereof.

Embodiment 51. A method of inhibiting TGFβ activation in a cell comprising administering to the cell a compound of any one of embodiments 1 to 44 or a pharmaceutically acceptable salt thereof.

Embodiment 52. Use of a compound of any one of embodiments 1 to 44 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fibrotic disease.

Embodiment 53. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_3-C_5 alkyl substituted by both fluorine and -OCH_3.

Embodiment 54. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is phenyl optionally substituted by fluorine.

Embodiment 55. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is pyridinyl optionally substituted by fluorine or methyl.

Embodiment 56. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is halogen.

Embodiment 57. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is deuterium.

Embodiment 58. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 3- to 12-membered heterocyclyl optionally substituted by oxo.

Embodiment 59. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 4- to 5-membered heterocyclyl optionally substituted by oxo.

Embodiment 60. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is C_6-C_{14} aryl optionally substituted by halogen or –OR^6.

Embodiment 61. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is phenyl optionally substituted by halogen or –OR^6.

Embodiment 62. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl.

Embodiment 63. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is pyrazolyl optionally substituted by methyl.

Embodiment 64. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is C_3-C_8 cycloalkyl optionally substituted by -CN, halogen, or $-OR^6$.

Embodiment 65. The compound of any one of embodiments 1 to 11, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is $-S(O)_2R^3$.

Embodiment 66. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is pyridyl optionally substituted by R^{1a}.

Embodiment 67. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is indazolyl optionally substituted by R^{1a}.

Embodiment 68. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is 1*H*-pyrrolopyridyl optionally substituted by R^{1a}.

Embodiment 69. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is quinolinyl optionally substituted by R^{1a}.

Embodiment 70. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is phenyl optionally substituted by R^{1a}.

Embodiment 71. The compound of embodiment 1, 2, or 3, or a salt thereof, wherein R^1 is indanyl optionally substituted by R^{1a}.

SYNTHETIC EXAMPLES

[00345] The chemical reactions in the Synthetic Examples described can be readily adapted to prepare a number of other compounds of the invention, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention can be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, or by making routine modifications of reaction

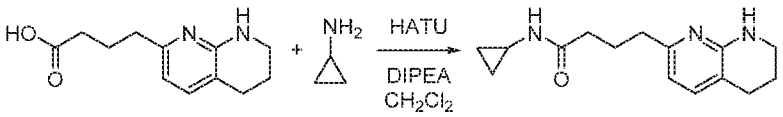
conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

[00346] For the examples described herein, reference to a General Procedure indicates that the reaction was prepared using similar reaction conditions and parameters as the General Procedures stated above.

PROCEDURES

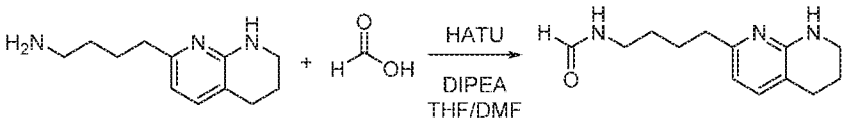
[00347] Compounds provided herein may be prepared according to Schemes, as exemplified by the Procedures and Examples. Minor variations in temperatures, concentrations, reaction times, and other parameters can be made when following the Procedures, which do not substantially affect the results of the procedures.

Procedure A



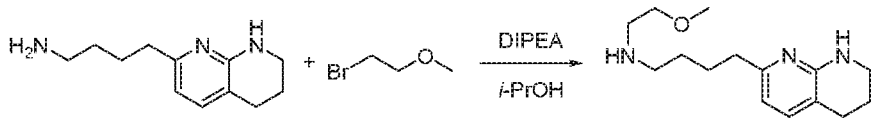
[00348] N-cyclopropyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanamide.To a mixture of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanoic acid hydrochloride (5.0 g, 19.48 mmol) and cyclopropanamine (1.51 mL, 21.42 mmol) in CH_2Cl_2 (80 mL) at rt was added DIPEA (13.57 mL, 77.9 mmol). To this was then added HATU (8.1 g, 21.42 mmol) and the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated in vacuo and purified by normal phase silica gel chromatography to give N-cyclopropyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanamide.

Procedure B



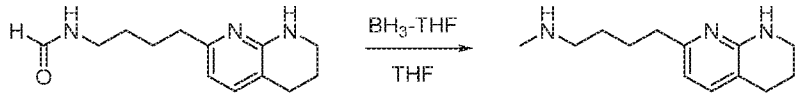
[00349] N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)formamide. To a mixture of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine (351 mg, 1.71 mmol) and formic acid (0.09 mL, 2.22 mmol) in 4:1 THF/DMF (5 mL) was added HATU (844 mg, 2.22 mmol) followed by DIPEA (0.89 mL, 5.13 mmol) and the reaction was allowed to stir at rt for 1 h. The reaction mixture was concentrated in vacuo and purified by normal phase silica gel chromatography to give N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)formamide.

Procedure C



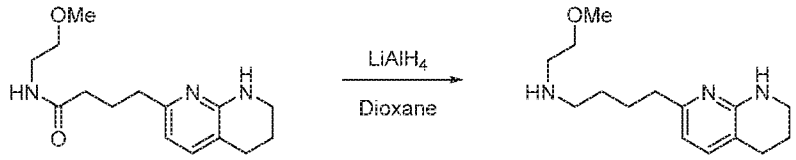
[00350] N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine. A mixture of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine (300 mg, 1.46 mmol), 1-bromo-2-methoxyethane (0.11 mL, 1.17 mmol) and DIPEA (0.25 mL, 1.46 mmol) in i-PrOH (3 mL) was heated to 70° C for 18 h. The reaction mixture was allowed to cool to rt and then concentrated in vacuo and purified by normal phase silica gel chromatography to give N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine.

Procedure D



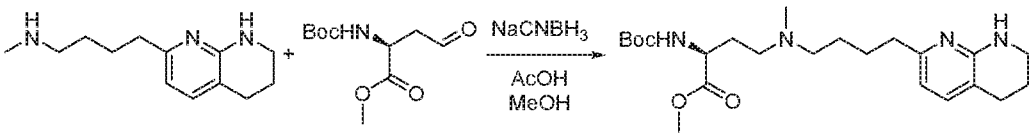
[00351] N-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine. To a solution of N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)formamide (200 mg, 0.86 mmol) in THF (2 mL) at rt was added borane tetrahydrofuran complex solution (1.0M in THF, 4.0 mL, 4.0 mmol) dropwise. The resulting mixture was then heated to 60° C for 2 h and then allowed to cool to rt. The reaction mixture was diluted with MeOH and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography to give N-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine.

Procedure E



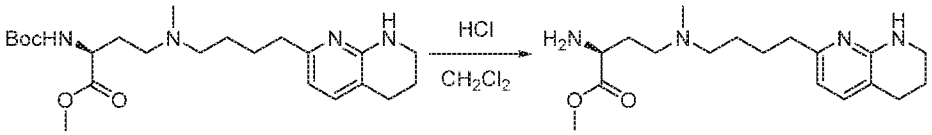
[00352] N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine (5). To a solution of N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanamide (15.5 g, 1.0 equiv) in 1,4-dioxane (124 mL) at rt was slowly added $LiAlH_4$ (1.0 M in THF, 123 mL, 2.2 equiv) and the resulting mixture was heated to reflux for 20 hours and then cooled to 0° C. To this solution was added H_2O (4.7 mL), then 1M NaOH (4.7 mL) then H_2O (4.7 mL) and warmed to room temperature and stirred for 30 minutes, at which time, solid $MgSO_4$ was added and stirred for an additional 30 minutes. The resulting mixture was filtered and the filter cake was washed with THF. The filtrate were concentrated in vacuo to give N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine.

Procedure F



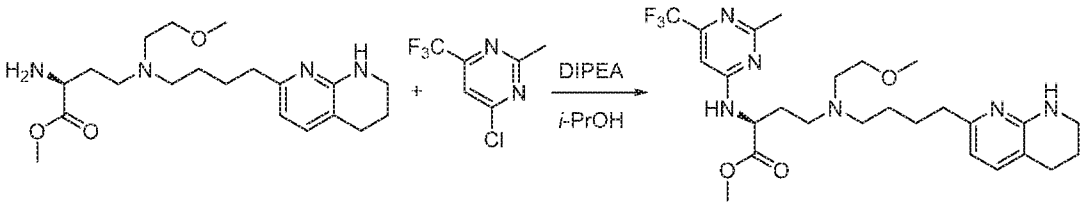
[00353] methyl (S)-2-((tert-butoxycarbonyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate. To a mixture of N-methyl-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butan-1-amine (5) (187 mg, 0.85mmol) in MeOH (5 mL) at rt was added acetic acid (0.12 mL, 2.05 mmol) followed by methyl (S)-2-((tert-butoxycarbonyl)amino)-4-oxobutanoate (217 mg, 0.94 mmol). The resulting mixture was allowed to stir at rt for 15 min, at which time, sodium cyanoborohydride (80 mg, 1.28 mmol) was added to the reaction mixture and stirred for 30 min and then concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography to give methyl (S)-2-((tert-butoxycarbonyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate.

Procedure G



[00354] methyl (S)-2-amino-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate. To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (152 mg, 0.35mmol) in CH_2Cl_2 (2 mL) at rt was added 4N HCl in 1,4-dioxane (1 mL, 4 mmol) and the resulting mixture was allowed to stir for 2 h. The reaction mixture was concentrated in vacuo to give methyl (S)-2-amino-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate as the trihydrochloride salt.

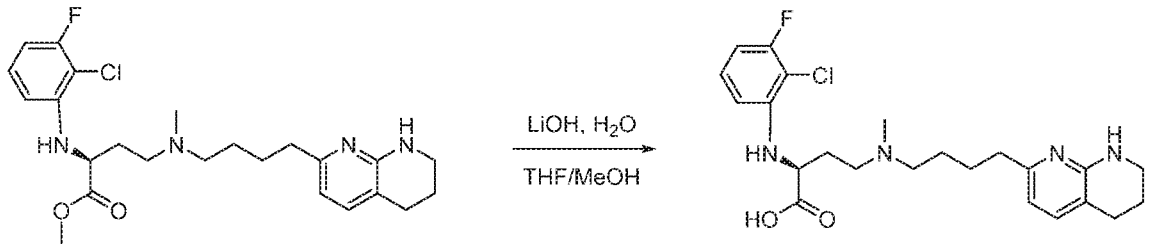
Procedure H



[00355] A solution of methyl (S)-2-amino-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate trihydrochloride (80 mg, 0.16 mmol), 4-chloro-2-methyl-6-(trifluoromethyl)pyrimidine (64 mg, 0.33 mmol) and DIPEA (0.23 mL, 1.31 mmol)

in i-PrOH (1 mL) was heated at 60° C overnight. The reaction was allowed to cool to rt and then concentrated in vacuo. The resulting crude residue was purified by normal phase silica gel chromatography to give methyl (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl)amino)butanoate.

Procedure P

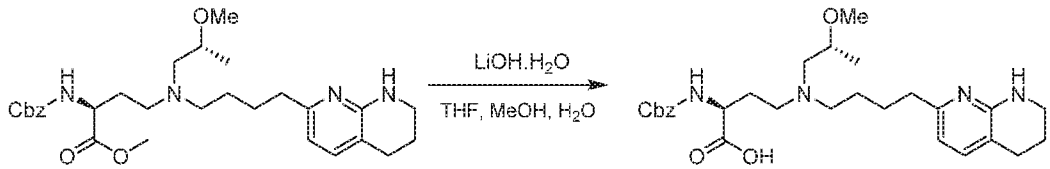


methyl (*S*)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate

(*S*)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid

[00356] ***(S)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid*** To a solution of methyl (S)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate in 4:1:1 THF/MeOH/H_2O at rt was added lithium hydroxide (approximately four equivalents) and the resulting mixture was stirred for 30 min. The reaction mixture was concentrated *in vacuo* and the resulting crude residue purified by reverse phase HPLC to give (S)-2-((2-chloro-3-fluorophenyl)amino)-4-(methyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid.

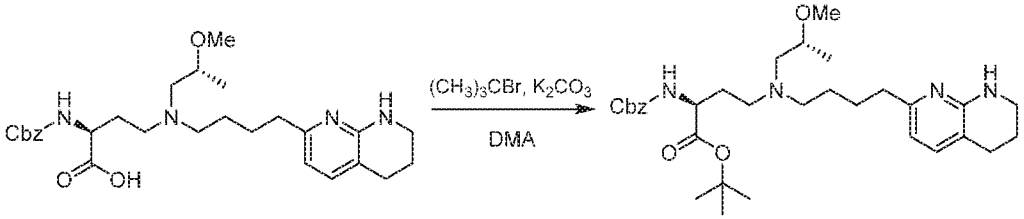
Procedure Q



[00357] (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid. A mixture of methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (1 g, 1.90 mmol) in H_2O (3 mL) and THF (3 mL) and MeOH (3 mL) was added $LiOH{\cdot}H_2O$ (159.36 mg, 3.80 mmol) and then the mixture was stirred at room temperature for 1 h and the resulting mixture was concentrated in vacuo. The mixture was adjusted to pH=6 by AcOH (2 mL) and the residue was concentrated in vacuo to

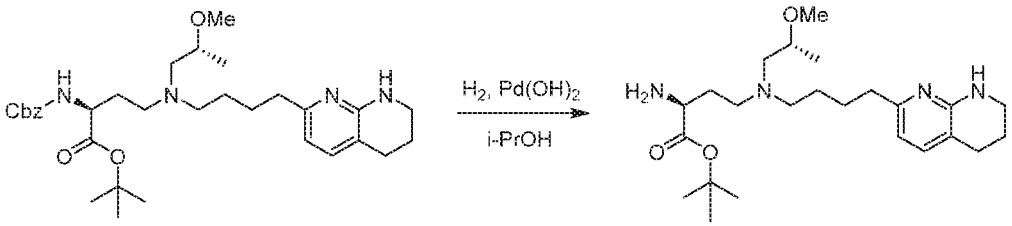
give a residue to yield compound (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid. LCMS (ESI+): m/z = 513.5 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d): δ ppm 7.25 - 7.37 (m, 5 H) 7.00 (d, J=7.28 Hz, 1 H) 6.81 (br d, J=7.50 Hz, 1 H) 6.22 (d, J=7.28 Hz, 1 H_6) 4.93 - 5.05 (m, 2 H) 3.68 - 3.77 (m, 1 H) 3.25 - 3.34 (m, 1 H) 3.15 - 3.24 (m, 5 H) 2.58 (br t, J=6.06 Hz, 2 H) 2.29 - 2.49 (m, 8 H) 2.16 (br dd, J=12.90, 6.06 Hz, 1 H) 1.69 - 1.78 (m, 2 H) 1.58 - 1.68 (m, 1 H) 1.53 (quin, J=7.39 Hz, 2 H) 1.28 - 1.40 (m, 2 H) 1.00 (d, J=5.95 Hz, 3 H).

Procedure R



[00358] tert-butyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate: A solution of (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid (300 mg, 523.84 µmol, HOAc salt) in DMA (4 mL) was added N-benzyl-N,N-diethylethanaminium chloride (119.32 mg, 523.84 µmol), K_2CO_3 (1.88 g, 13.62 mmol), 2-bromo-2-methylpropane (3.45 g, 25.14 mmol,). The mixture was stirred for 18 h at the 55° C and then allowed to cool to room temperature. The reaction mixture was concentrated in vacuo and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by prep-TLC to give tert-butyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate. LCMS (ESI+): m/z = 569.3 $(M+H)^+$.

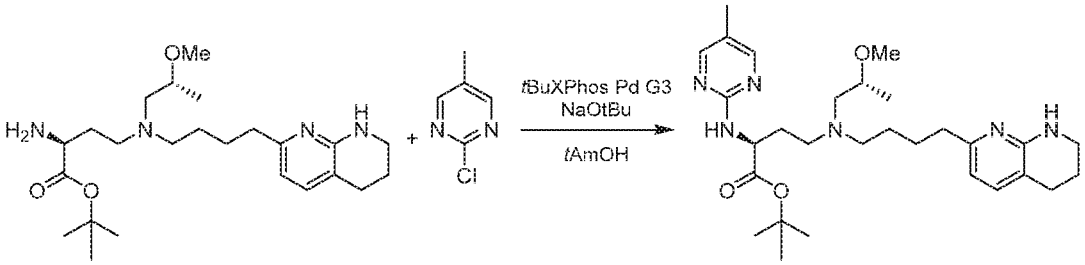
Procedure S



[00359] tert-butyl (S)-2-amino-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate. To a solution of tert-butyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-

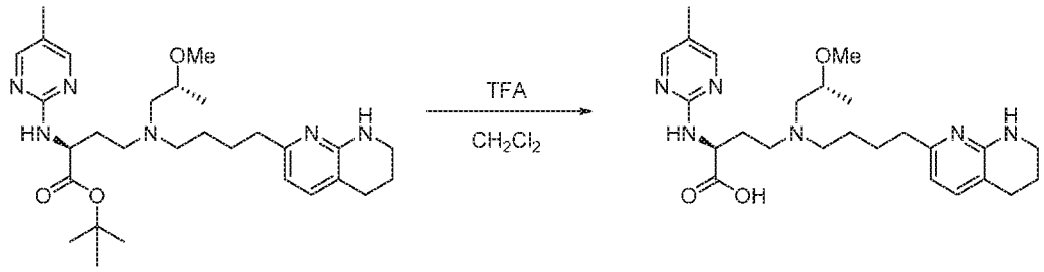
naphthyridin-2-yl)butyl)amino)butanoate (107 mg, 188.13 μmol) in i-PrOH (2 mL) was added $Pd(OH)_2$ (26 mg) under an N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at room temperature for 15 h. The mixture was filtered and concentrated in vacuo to give tert-butyl (S)-2-amino-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate. LCMS (ESI+): m/z = 435.5 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.06 (d, *J*=7.34 Hz, 1 H) 6.34 (d, *J*=7.34 Hz, 1 H) 4.98 (br s, 1 H) 3.38 - 3.44 (m, 4 H) 3.34 (s, 3 H) 2.69 (t, *J*=6.30 Hz, 2 H) 2.51 - 2.59 (m, 5 H) 2.31 (dd, *J*=13.39, 5.56 Hz, 1 H) 1.86 - 1.94 (m, 5 H) 1.49 - 1.69 (m, 6 H) 1.47 (s, 9 H) 1.13 (d, *J*=6.11 Hz, 3 H).

Procedure T



[00360] tert-butyl (S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoate. To a solution of (S)-tert-butyl 2-amino-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate tert-butyl (S)-2-amino-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (100 mg, 230.09 μmol) and 2-chloro-5-methyl-pyrimidine (24.65 mg, 191.74 μmol) in 2-methyl-2-butanol (2 mL) was added t-BuONa (2 M in THF, 191.74 uL) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;ditert-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (15.23 mg, 19.17 μmol), and the resulting mixture was stirred at 100° C for 14 h. The mixture was concentrated in vacuo to give (S)-tert-butyl 4-(((S)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoate. LCMS (ESI+): m/z = 527.3 $(M+H)^+$.

Procedure U



[00361] (S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoic acid. To a solution of tert-butyl (S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methyl pyrimidin-2-yl)amino)butanoate (80 mg, 151.89 μmol) in DCM (2 mL) was added TFA (254.14 mg, 2.23 mmol) at 0° C. The mixture was stirred at room temperature for 6 h. The mixture was concentrated in vacuo and the resulting crude residue was purified by prep-HPLC to give compound (S)-4-(((R)-2-methoxypropyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((5-methylpyrimidin-2-yl)amino)butanoic acid. LCMS (ESI+): m/z = 471.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.57 (br s, 2 H) 7.60 (d, J=7.28 Hz, 1 H) 6.67 (d, J=7.28 Hz, 1 H) 4.81 - 4.86 (m, 1 H) 3.86 (br s, 1 H) 3.41 - 3.59 (m, 4 H) 3.39 (s, 3 H) 3.33 - 3.38 (m, 1 H) 3.12 - 3.30 (m, 3 H) 2.76 - 2.86 (m, 4 H) 2.54 (br s, 1 H) 2.39 (br d, J=8.82 Hz, 1 H) 2.30 (s, 3 H) 1.76 - 1.99 (m, 6 H) 1.22 (d, J=5.95 Hz, 3 H).

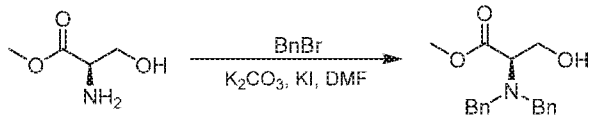
SYNTHETIC EXAMPLES

[00362] The chemical reactions in the Synthetic Examples described can be readily adapted to prepare a number of other compounds of the invention, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention can be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

[00363] For the examples described herein, reference to a Procedure indicates that the reaction was prepared using similar reaction conditions and parameters as the Procedures stated above.

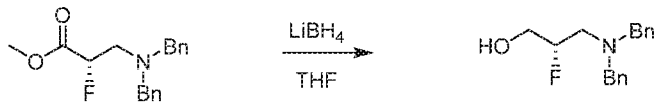
Example A1

Synthesis of (S)-2-fluoro-3-methoxypropan-1-amine

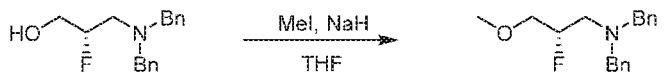


[00364] Methyl dibenzyl-D-serinate. To a mixture of methyl D-serinate hydrochloride (100 g, 642.76 mmol) and K_2CO_3 (177.67 g, 1.29 mol) and KI (53.35 g, 321.38 mmol) in DMF (1.5 L) was added benzyl bromide (241.85 g, 1.41 mol) at 0° C. The mixture was stirred at 25° C for 12 h. The mixture was quenched with H_2O (3000 mL) and EtOAc (1 L x 3). The organic layer was washed with brine (1 L), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by normal phase silica gel chromatographyto give methyl dibenzyl-D-serinate.

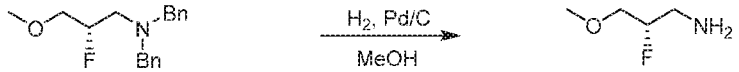
[00365] Methyl (S)-3-(dibenzylamino)-2-fluoropropanoate. To a solution of methyl dibenzyl-D-serinate (155 g, 517.77 mmol) in THF (1.2 L) was added DAST (102.65 g, 636.85 mmol, 84.14 mL) dropwise at 0° C and the reaction mixture was stirred for 14 h at rt. The reaction mixture was quenched with saturated aq. NaHCO3 (1 L) at 0° C and extracted with EtOAc (500 mL x 3). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by normal phase silica gel chromatography to give methyl (S)-3-(dibenzylamino)-2-fluoropropanoate.



[00366] (S)-3-(dibenzylamino)-2-fluoropropan-1-ol. To a solution of methyl (S)-3-(dibenzylamino)-2-fluoropropanoate (103 g, 341.79 mmol) in THF (1 L) was added $LiBH_4$ (14.89 g, 683.58 mmol) at 0° C. The mixture was stirred at 40° C for 12 h. The mixture was poured into aq. NH_4Cl (500 mL) at 0° C. The aqueous phase was extracted with ethyl acetate (300 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give (S)-3-(dibenzylamino)-2-fluoropropan-1-ol that was used without further purification.



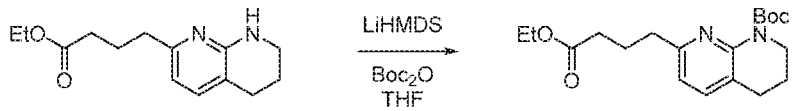
[00367] (S)-N,N-dibenzyl-2-fluoro-3-methoxypropan-1-amine. To a solution of (S)-3-(dibenzylamino)-2-fluoropropan-1-ol (51 g, 186.58 mmol) in THF (400 mL) was added NaH (60% dispersion in mineral oil, 11.19 g, 279.87 mmol) at 0° C and the resulting mixture was stirred at 0° C for 30 min. To this was then added iodomethane (18.58 mL, 298.52 mmol) and the mixture was stirred at rt for 12 h. The mixture was quenched with aq. NH_4Cl (500 mL) at 0° C. The aqueous phase was extracted with EtOAc (500 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude residue was purified by normal phase silica gel chromatography to give (S)-N,N-dibenzyl-2-fluoro-3-methoxypropan-1-amine.



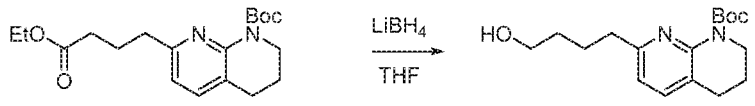
[00368] (S)-2-fluoro-3-methoxypropan-1-amine. To a solution of (S)-N,N-dibenzyl-2-fluoro-3-methoxypropan-1-amine (15 g, 52.20 mmol) in MeOH (200 mL) was added Pd/C (3 g). The suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred under H_2 (50 psi) at 50° C for 12 h. The reaction mixture was filtered through a pad of Celite and the filtrate was treated with HCl/EtOAc (50 mL) and then concentrated in vacuo to give (S)-2-fluoro-3-methoxypropan-1-amine hydrochloride that was used without further purification.

Example A2

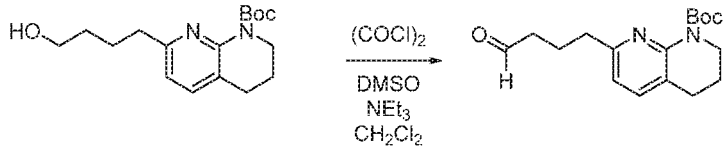
Synthesis of tert-butyl 7-(4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate



[00369] tert-Butyl 7-(4-ethoxy-4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate. To a solution of ethyl 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butanoate (5.25g, 21.1 mmol) and di-tert-butyl dicarbonate (5.89 mL, 25.4 mmol in THF (70 mL) was added lithium bis(trimethylsilyl)amide (25.4 mL, 25.4 mmol) was added at 0° C. After 2 h, the reaction was diluted with EtOAc (50 mL) and was quenched with sat NH_4Cl (50 mL). After 30 min of stirring, the layers were separated and the organic layer was washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting crude residue was purified by normal phase silica gel chromatography to give tert-butyl 7-(4-ethoxy-4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate.



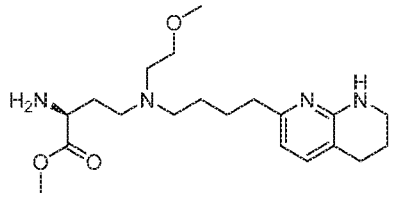
[00370] tert-Butyl 7-(4-hydroxybutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate. To a solution of tert-butyl 7-(4-ethoxy-4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (6.81 g, 19.5 mmol) in THF (50 mL) was added $LiBH_4$ (1.0M in THF, 19.5 mL, 19.5 mmol) at rt. The mixture was stirred overnight and then quenched with sat. NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude residue was purified by normal phase silica gel chromatography to give tert-butyl 7-(4-hydroxybutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate.



[00371] tert-Butyl 7-(4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate. A solution of oxalyl chloride (2.57 mL, 29.3 mmol) in CH_2Cl_2 (69 mL) was cooled to -78° C for 5 minutes, at which time, dimethyl sulfoxide (4.2 mL, 58.6 mmol) was added and the mixture was stirred for 30 min. A solution of tert-butyl 7-(4-hydroxybutyl)-3,4-dihydro-2H-1,8-naphthyridine-1-carboxylate (6.9 g, 22.6 mmol) in CH_2Cl_2 (10.5 mL) was added and stirred at -78° C for 1 h. Triethylamine (10.5 mL, 75.1 mmol) was then added to the reaction mixture and stirred for 30 mins. The reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was collected and dried over sodium sulfate. The organic layer was concentrate to give tert-butyl 7-(4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate that was used without further purification.

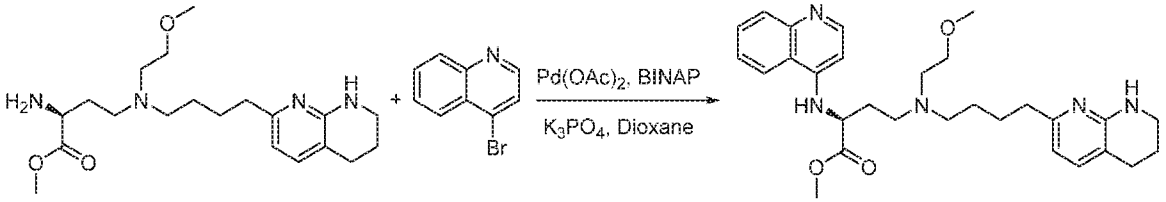
Example A3

Synthesis of methyl (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinolin-4-ylamino)butanoate



[00372] Methyl (S)-2-amino-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)butanoate. Prepared according to Scheme A using Procedure A with 2-methoxyethylamine, then Procedure E, Procedure F, and Procedure G to give methyl (S)-2-

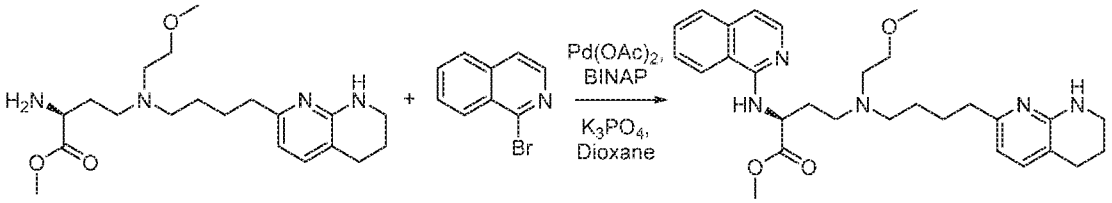
amino-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate.



[00373] Methyl (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinolin-4-ylamino)butanoate. A microwave vial containing methyl (S)-2-amino-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (125 mg, 0.3 mmol) was charged with 4-bromoquinoline (65 mg, 0.3 mmol), $Pd(OAc)_2$ (6.3 mg, 0.03 mmol), *rac*-BINAP (35 mg, 0.6 mmol), and K_3PO_4 (210 mg, 1.0 mmol) and then diluted with Dioxane (2 mL). The mixture was degassed and then sealed and heated to 100° C for 1 h. The reaction mixture was allowed to cool to rt and then filtered and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography to give methyl (S)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-(quinolin-4-ylamino)butanoate.

Example A4

Synthesis of methyl (S)-2-(isoquinolin-1-ylamino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate



[00374] Methyl (S)-2-(isoquinolin-1-ylamino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate. A microwave vial containing methyl (S)-2-amino-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoate (125 mg, 0.3 mmol) was charged with 1-bromoisoquinoline (65 mg, 0.3 mmol), $Pd(OAc)_2$ (6.3 mg, 0.03 mmol), *rac*-BINAP (35 mg, 0.6 mmol), and K_3PO_4 (210 mg, 1.0 mmol) and then diluted with Dioxane (2 mL). The mixture was degassed and then sealed and heated to 100° C for 1 h. The reaction mixture was allowed to cool to rt and then filtered and concentrated in vacuo. The crude residue was purified by normal phase silica gel chromatography to give methyl (S)-2-(isoquinolin-1-ylamino)-4-((2-methoxyethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino) butanoate.

[00375] In the following examples, compounds without specific synthetic descriptions may be synthesized by procedures described herein, for example, analogous to that for compound 2, Scheme 1; compound 81, Scheme 5; and Compound 213, Scheme 24.

[00376] For example, (S)-2-((3-cyanopyrazin-2-yl)amino)-4-((2-(3,5-difluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)butanoic acid (compound 597) may be prepared by slight modification of the procedures from Scheme 1. In step 1, 2-(3,5-difluorophenoxy)ethan-1-amine may be substituted for cyclopropylamine which may afford the analogous amine product. The amine product may then undergo a Boc deprotection as in step 2 followed by a reductive amination as in step 3 to afford an analogous tertiary amine product. This tertiary amine may then undergo a base mediated hydrolysis as in step 4 followed by deprotection of the benzyl carbamate under reductive conditions as in step 5 to afford an analogous amino acid product. This amino acid may then be reacted with a suitably activated heterocycle in an S_NAr reaction, such as 3-chloropyrazine-2-carbonitrile to give the described compound. Similarly, the analogous free amino acid product from step 5 may be reacted with an analogous activated heterocycle as depicted in step 6 and then subjected to either reducing conditions as shown in step 7 of Scheme 1 or cross-coupling conditions as shown in step 2 of Scheme 5 to afford further prophetic compounds described.

[00377] The tertiary amine products arising from step 3 in Scheme 1, if alternative amines were substituted for cyclopropylamine, may alternatively be hydrolyzed as depicted in step 1 of Scheme 24 followed by t-butylation of the acid product with t-butyl bromide under basic conditions as shown in step 2 of Scheme 24. The resulting t-butyl ester product may be deprotected under reductive conditions as in step 3 of Scheme 24 to afford an amino ester product, which may then undergo palladium catalyzed cross-coupling with an appropriate aryl or heteroaryl halide as in step 4 of Scheme 24 to give an ester product that may be exposed to acid to generate a final compound as in step 5 of Scheme 24.

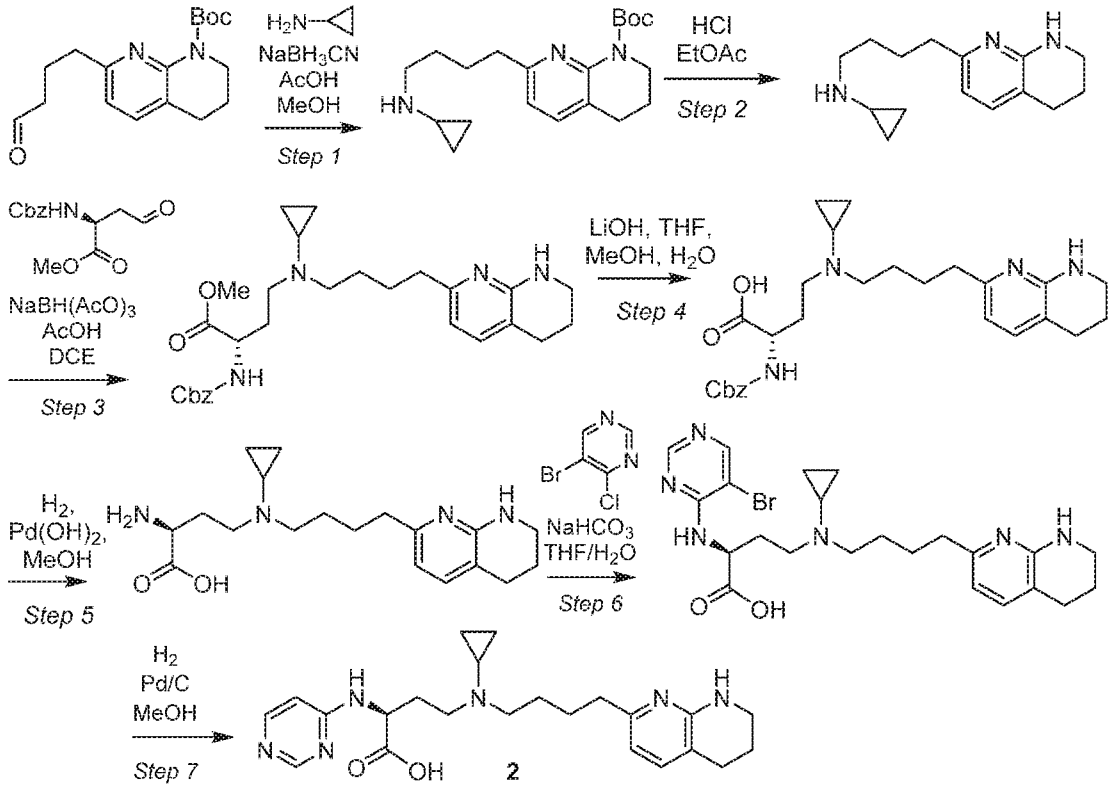
[00378] For example, (S)-4-((2-(3,5-difluorophenoxy)ethyl)(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl)amino)-2-((1-methyl-1H-indazol-3-yl)amino)butanoic acid (compound 624) may be prepared by slight modification of the procedures from Scheme 1. In step 1, 2-(3,5-difluorophenoxy)ethan-1-amine may be substituted for cyclopropylamine which would afford the analogous amine product. This amine product may then undergo a Boc deprotection as in step 2 followed by a reductive amination as in step 3 to afford an analogous tertiary amine product. The tertiary amine product may be hydrolyzed as depicted in step 1 of Scheme 24 followed by t-butylation of the acid product with t-butyl bromide

under basic conditions as shown in step 2 of Scheme 24. The resulting t-butyl ester product may be deprotected under reductive conditions as in step 3 of Scheme 24 to afford an amino ester product, which may then undergo palladium catalyzed cross-coupling substituting 3-bromo-1-methyl-1H-indazole for 6-chloro-N,N-dimethylpyrimidin-4-amine in step 4 of Scheme 24 to give an ester product that may be exposed to acid to generate the described compound.

[00379] Compound 1: ***(S)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((6-(difluoromethyl)pyrimidin-4-yl) amino) butanoic acid***. Prepared according to Scheme A using Procedure A with cyclopropylamine, and Procedure H with 4-chloro-6-(difluoromethyl)pyrimidine. LCMS theoretical m/z = 475.3. [M+H]+, found 475.2.

[00380] Compound 1: ***(S)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((6-(difluoromethyl)pyrimidin-4-yl) amino) butanoic acid***. Prepared according to Scheme A using Procedure A with cyclopropylamine, and Procedure H with 4-chloro-6-(difluoromethyl)pyrimidine. LCMS theoretical m/z = 475.3. [M+H]+, found 475.2.

Scheme 1, Compound 2:



[00381] Step 1: ***tert-butyl 7-(4-(cyclopropylamino) butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate***. To a solution of cyclopropanamine (22.8 mL, 328.5 mmol), AcOH (18.8 mL, 328.5 mmol), and $NaBH_3CN$ (4.13 g, 65.7 mmol) in MeOH (100 mL) at 0° C was added a solution of tert-butyl 7-(4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (10.0 g, 32.9 mmol) in MeOH (100 mL) and the resulting mixture was stirred at rt for 16 h. The mixture was diluted with sat. $NaHCO_3$ and stirred until gas evolution ceased and then concentrated *in vacuo* to remove the volatiles. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by prep-HPLC to give the title compound. LCMS theoretical m/z = 346.3. [M+H]+, found 346.5.

[00382] Step 2: ***N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)cyclopropanamine***. To a solution of tert-butyl 7-(4-(cyclopropylamino)butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (2.5 g, 7.24 mmol) in EtOAc (10 mL) was added 4 M HCl in EtOAc (1.8 mL) and the resulting mixture was stirred at rt for 12 h and then concentrated *in vacuo*. The crude residue was used without further purification. LCMS theoretical m/z = 246.2. [M+H]+, found 246.0.

[00383] Step 3: ***methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate***. To a mixture of methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-oxobutanoate (2.59 g, 9.8 mmol) and N-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)cyclopropanamine hydrochloride (2.5 g, 8.9 mmol) in DCE (40 mL) was added AcOH (761 µL, 13.3 mmol) at 0° C was added $NaBH(OAc)_3$ (2.82 g, 13.3 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with sat. aq. $NaHCO_3$ and stirred until gas evolution ceased and then was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give the title compound. LCMS theoretical m/z = 495.3. [M+H]+, found 495.4.

[00384] Step 4: ***(S)-2-(((benzyloxy)carbonyl)amino)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. To a solution of methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate (4 g, 7.9 mmol) in 1:1:1 THF/MeOH/H_2O (36 mL) was added $LiOH{\bullet}H_2O$ (664 mg, 15.8 mmol) at 0° C and the resulting mixture was stirred at rt for 1 h. The mixture was then adjusted to pH = 6 by the careful addition of 1 N HCl and then concentrated *in vacuo* to give the title compound. LCMS theoretical m/z = 480.3 [M]+, found 480.1.

[00385] Step 5: ***(S)-2-amino-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. A flask containing (S)-2-(((benzyloxy)carbonyl)amino)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (4.5 g, 9.4 mmol) was charged with 20 wt% $Pd(OH)_2/C$ (4.5 g) and then diluted with i-PrOH (300 mL) and stirred under an H_2 atmosphere at 50 psi for 48 h at rt. The reaction mixture was filtered through a pad of CELITE® and rinsed with MeOH and then concentrated *in vacuo*. The crude residue was purified by reverse phase prep-HPLC to give the title compound. LCMS theoretical m/z = 347.2. [M+H]+, found 347.2.

[00386] Step 6: ***(S)-2-((5-bromopyrimidin-4-yl) amino)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. To a solution of (S)-2-amino-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid trifluoroacetate (150 mg, 0.3 mmol) in 4:1 THF/H_2O (3 mL) was added 5-bromo-4-chloro-pyrimidine (69 mg, 0.4 mmol) and $NaHCO_3$ (137 mg, 1.63 mmol) and then was stirred at 70° C for 2 h and then cooled to rt and concentrated *in vacuo*. The crude residue was used without further purification.

[00387] Step 7: ***(S)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrimidin-4-ylamino) butanoic acid***. A flask containing (S)-2-((5-bromopyrimidin-4-yl) amino)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (157 mg, 0.3 mmol) was charged with 20 wt% Pd/C (200 mg) and then diluted with MeOH (20 mL) and the resulting mixture was stirred at rt under an H_2 atmosphere for 4 h and then filtered and concentrated *in vacuo*. The crude residue was purified by reverse phase prep-HPLC to give the title compound. LCMS (ESI+): m/z = 425.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4): δ ppm 8.34 (s, 1 H) 7.96 (br s, 1 H) 7.18 (d, J=7.21 Hz, 1 H) 6.52 (br s, 1 H) 6.39 (d, J=7.21 Hz, 1 H) 3.87 - 4.65 (m, 1 H) 3.34 - 3.42 (m, 2 H) 2.76 - 2.96 (m, 2 H) 2.70 (br t, J=6.11 Hz, 4 H) 2.54 (br t, J=7.03 Hz, 2 H) 2.14 - 2.26 (m, 1 H) 1.96 - 2.08 (m, 1 H) 1.87 (q, J=5.87 Hz, 3 H) 1.62 (br d, J=4.40 Hz, 4 H) 0.37 - 0.59 (m, 4 H). LCMS theoretical m/z = 425.3. [M+H]+, found 425.2.

[00388] **Compound 3:** ***(S)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl) amino) butanoic acid***. To a mixture of (S)-2-amino-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (170 mg, 0.4 mmol) in 4:1 THF/H_2O (2.5 mL) was added 4-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine (75 mg, 0.4 mmol) and $NaHCO_3$ (112 mg, 1.33 mmol) and the resulting mixture was stirred at 70° C for 1 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The resulting crude residue was purified by reverse phase prep-HPLC to give the title compound as the trifluoroacetate salt. ^1H NMR (400 MHz, D_2O): δ ppm 8.32 - 8.47 (m, 2 H) 7.51 (br d, J=6.60 Hz, 1 H) 6.56 (br s, 1 H) 4.85 (br s, 1 H) 4.03 (br s, 3 H) 3.29 - 3.63 (m, 6 H) 2.38 - 2.91 (m, 7 H) 1.64 - 1.95 (m, 6 H) 0.90 - 1.09 (m, 4 H). LCMS theoretical m/z = 479.3. [M+H]+, found 479.2.

[00389] **Compound 4:** ***(S)-4-((2-hydroxy-2-methylpropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrimidin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 1-amino-2-methylpropan-2-ol, Procedure H with 4-chloropyrimidine, and Procedure P. LCMS theoretical m/z = 457.3. [M+H]+, found 457.2.

[00390] **Compound 5:** ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 493.1. [M+H]+, found 493.1.

[00391] **Compound 6:** ***(S)-4-(cyclopropyl(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid***. Prepared according to Scheme A

using Procedure A with cyclopropylamine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 475.3. [M+H]+, found 475.3.

[00392] Compound 7: ***(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***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-7-fluoroquinazoline, and Procedure P. LCMS theoretical m/z = 511.3. [M+H]+, found 511.3.

[00393] Compound 8: ***(S)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2,2-difluoroethan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 499.3. [M+H]+, found 499.3.

[00394] Compound 9: ***(S)-4-((3,3-difluorocyclobutyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 3,3-difluorocyclobutan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 523.3. [M+H]+, found 525.3.

[00395] Compound 10: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-methylquinazolin-4-yl) amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 507.3. [M+H]+, found 507.3.

[00396] Compound 11: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrido[2,3-d]pyrimidin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloropyrido[2,3-d]pyrimidine, and Procedure P. LCMS theoretical m/z = 494.3. [M+H]+, found 494.3.

[00397] Compound 12: ***(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***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 525.3. [M+H]+, found 525.3.

[00398] Compound 13: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((7-(trifluoromethyl)quinazolin-4-yl) amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-7-(trifluoromethyl)quinazoline, and Procedure P. LCMS theoretical m/z = 561.3. [M+H]+, found 561.3.

[00399] Compound 14: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(trifluoromethyl)quinazolin-4-yl) amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-2-(trifluoromethyl)quinazoline, and Procedure P. LCMS theoretical m/z = 561.3. [M+H]+, found 561.3.

[00400] Compound 15: ***(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***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-8-(trifluoromethyl)quinazoline, and Procedure P. LCMS theoretical m/z = 561.3. [M+H]+, found 561.3.

[00401] Compound 16: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloropyrido[3,2-d]pyrimidine, and Procedure P. LCMS theoretical m/z = 494.3. [M+H]+, found 494.3.

[00402] Compound 17: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrido[3,4-d]pyrimidin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloropyrido[3,4-d]pyrimidine, and Procedure P. LCMS theoretical m/z = 494.3. [M+H]+, found 494.3.

[00403] Compound 18: ***(S)-2-((5-fluoroquinazolin-4-yl) amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-5-fluoroquinazoline, and Procedure P. LCMS theoretical m/z = 511.3. [M+H]+, found 511.3.

[00404] Compound 19: ***(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***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-6-fluoroquinazoline, and Procedure P. LCMS theoretical m/z = 511.3. [M+H]+, found 511.3.

[00405] Compound 20: ***(S)-2-((8-fluoroquinazolin-4-yl) amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-8-fluoroquinazoline, and Procedure P. LCMS theoretical m/z = 511.3. [M+H]+, found 511.3.

[00406] Compound 21: ***(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***. Prepared

according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-6,7-difluoroquinazoline, and Procedure P. LCMS theoretical m/z = 529.3. [M+H]+, found 529.3.

[00407] Compound 22: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-methyl-6-(trifluoromethyl)pyrimidin-4-yl) amino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-2-methyl-6-(trifluoromethyl)pyrimidine, and Procedure P. LCMS theoretical m/z = 525.3. [M+H]+, found 525.3.

[00408] Compound 23: ***(S)-2-((6-(difluoromethyl)pyrimidin-4-yl) amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-6-(difluoromethyl)pyrimidine, and Procedure P. LCMS theoretical m/z = 493.3. [M+H]+, found 493.3.

[00409] Compound 24: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl) amino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-2-(trifluoromethyl)pyrimidine, and Procedure P. LCMS theoretical m/z = 511.3. [M+H]+, found 511.3.

[00410] Compound 25: ***(S)-4-(((S)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2-(S)-2-methoxypropan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 507.3. [M+H]+, found 507.4.

[00411] Compound 26: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((6-methyl-2-(trifluoromethyl)pyrimidin-4-yl) amino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-6-methyl-2-(trifluoromethyl)pyrimidine, and Procedure P. LCMS theoretical m/z = 525.3. [M+H]+, found 525.3.

[00412] Compound 27: ***(S)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2-(methylsulfonyl)ethan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 541.3. [M+H]+, found 541.3.

[00413] Compound 28: ***(S)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme D using Procedure C with (2-bromoethoxy)benzene, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 555.3. [M+H]+, found 555.3.

[00414] Compound 29: ***(S)-4-((3,3-difluoropropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 3,3-difluoropropan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 513.3. [M+H]+, found 513.4.

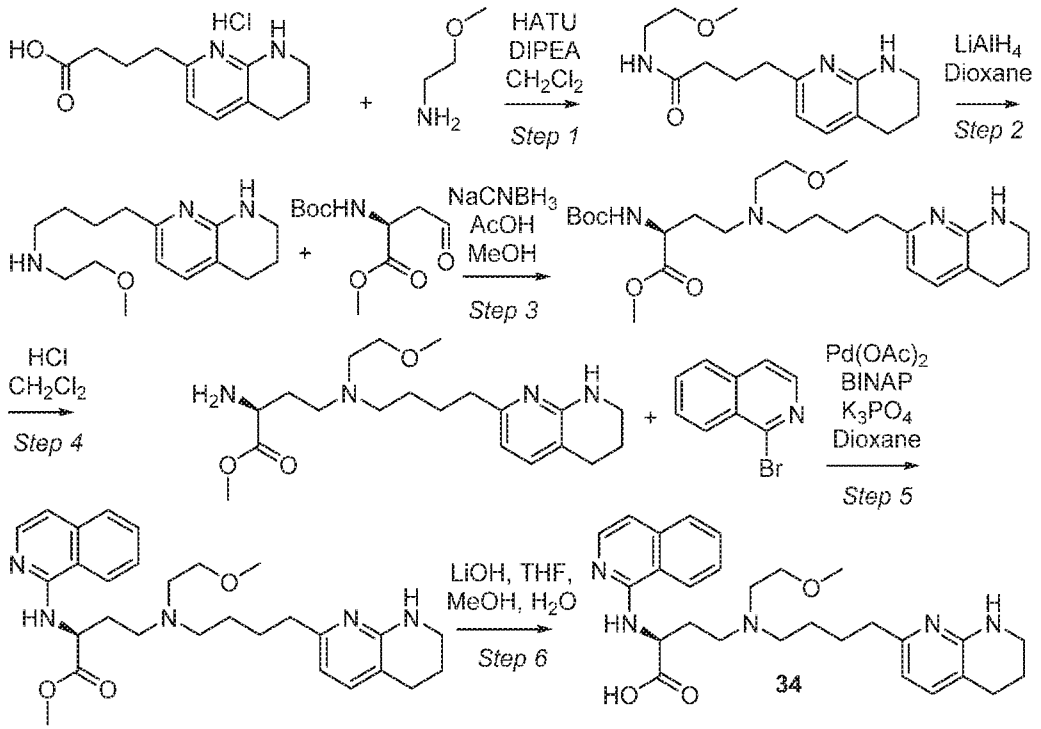
[00415] Compound 30: ***(S)-4-((3-fluoropropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2- 3-fluoropropan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 495.3. [M+H]+, found 495.3.

[00416] Compound 31: ***(S)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme A using Procedure A with (S)-2-fluoro-3-methoxypropan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 525.3. [M+H]+, found 525.3.

[00417] Compound 32: ***(S)-2-((7-fluoro-2-methylquinazolin-4-yl) amino)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** Prepared according to Scheme A using Procedure A with (S)-2-fluoro-3-methoxypropan-1-amine, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 557.3. [M+H]+, found 557.4.

[00418] Compound 33: ***(S)-4-(((3,3-difluorocyclobutyl)methyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((7-fluoro-2-methylquinazolin-4-yl) amino) butanoic acid.*** Prepared according to Scheme D using Procedure C with 3-(bromomethyl)-1,1-difluorocyclobutane, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 571.3. [M+H]+, found 571.3.

Scheme 2, Compound 34:



[00419] Step 1: ***N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanamide***. To a solution of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanoic acid hydrochloride (2.6 g, 10.29 mmol) in CH_2Cl_2 (26 mL) was added 2-methoxyethan-1-amine (1.3 mL, 15.44 mmol), DIPEA (5.4 mL, 30.87 mmol), then HATU (5.67 g, 14.92 mmol) and the resulting mixture was stirred at rt for 2 h and then concentrated *in vacuo*. The resulting crude residue was purified using normal phase silica gel chromatography to give the title compound.

[00420] Step 2: ***N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butan-1-amine***. To a solution of N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanamide (1.1 g, 4.0 mmol) in 1,4-dioxane (11 mL) was added 2.0M $LiAlH_4$ in THF (4 mL, 8.0 mmol) and the resulting mixture was refluxed overnight and then allowed to cool to rt. The solution was carefully neutralized by the cautious addition of H_2O (310 μL), then 1 N NaOH (310 μL), then additional H_2O (310 μL) and the mixture was stirred at rt for 30 min and then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was used without further purification.

[00421] Step 3: ***methyl (S)-2-((tert-butoxycarbonyl)amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate***. To a solution of N-(2-methoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butan-1-amine (927 mg, 3.52

mmol) and methyl (S)-2-((tert-butoxycarbonyl)amino)-4-oxobutanoate (895 mg, 3.87 mmol) in MeOH (10 mL) at rt was added AcOH (222 μL, 3.87 mmol) then $NaCNBH_3$ (243 mg, 3.87 mmol) and the resulting mixture was stirred at rt overnight and then concentrated *in vacuo*. The resulting crude residue was purified by normal phase silica gel chromatography to afford the title compound.

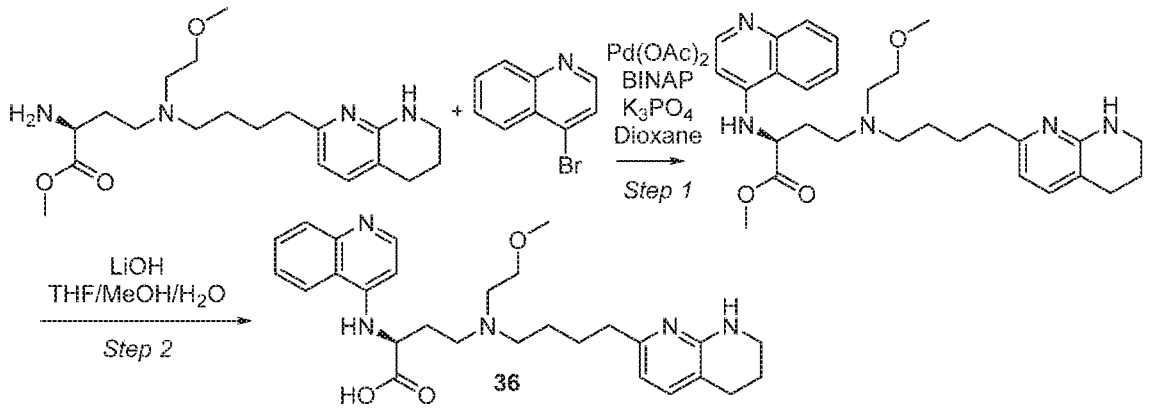
[00422] Step 4: ***methyl (S)-2-amino-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate***. To a solution of methyl (S)-2-((tert-butoxycarbonyl)amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate (700 mg, 1.46 mmol) in CH_2Cl_2 (3 mL) was added 4 N HCl in dioxane (5 mL) and the resulting mixture was stirred at rt for 2 h and concentrated *in vacuo*. The resulting crude residue was used without further purification.

[00423] Step 5: ***methyl (S)-2-(isoquinolin-1-ylamino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate***. A microwave vial containing methyl (S)-2-amino-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate (125 mg, 0.3 mmol) was charged with 1-bromoisoquinoline (65 mg, 0.3 mmol), $Pd(OAc)_2$ (6.3 mg, 0.03 mmol), rac-BINAP (35 mg, 0.6 mmol), and K_3PO_4 (210 mg, 1.0 mmol) and then diluted with dioxane (2 mL). The mixture was degassed and then sealed and heated to 100° C for 1 h. The reaction mixture was allowed to cool to rt and then filtered and concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give the title compound.

[00424] Step 6: ***(S)-2-(isoquinolin-1-ylamino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** To a solution of methyl (S)-2-(isoquinolin-1-ylamino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate (20 mg, 0.04 mmol) in 4:1:1 THF/MeOH/H_2O (1.5 mL) was added LiOH (5 mg, 0.20 mmol) and the resulting mixture was stirred at rt for 1 h and then neutralized with AcOH and concentrated *in vacuo*. The crude residue was purified by reverse phase prep-HPLC to give the title compound. LCMS theoretical m/z = 492.3. [M+H]+, found 492.4.

[00425] **Compound 35:** ***(S)-4-((2-(difluoromethoxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-(difluoromethoxy)ethan-1-amine, Procedure D, Procedure F, Procedure G, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 529.3. [M+H]+, found 529.3.

Scheme 3, Compound 36:



[00426] Step 1: ***methyl (S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinolin-4-ylamino) butanoate***. A microwave vial containing methyl (S)-2-amino-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate (125 mg, 0.3 mmol) was charged with 4-bromoquinoline (65 mg, 0.3 mmol), $Pd(OAc)_2$ (6 mg, 0.03 mmol), rac-BINAP (35 mg, 0.6 mmol), and K_3PO_4 (210 mg, 1.0 mmol) and then diluted with dioxane (2 mL). The mixture was degassed and then sealed and heated to 100° C for 1 h. The reaction mixture was cool to rt and then filtered and concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give methyl (S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinolin-4-ylamino) butanoate.

[00427] Step 2: ***(S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinolin-4-ylamino) butanoic acid***. To a solution of methyl (S)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinolin-4-ylamino) butanoate (54 mg, 0.11 mmol) in 4:1:1 THF/MeOH/H_2O (3 mL) was added LiOH (25.5 mg, 1.1 mmol) and the resulting mixture was stirred at rt for 1 h and then neutralized with AcOH and concentrated *in vacuo*. The resulting crude residue was purified by reverse phase prep-HPLC to give the title compound. LCMS theoretical m/z = 492.3. [M+H]+, found 492.3.

[00428] **Compound 37:** ***(S)-2-((7-chloroquinazolin-4-yl) amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4,7-dichloroquinazoline, and Procedure P. LCMS theoretical m/z = 527.3. [M+H]+, found 527.3.

[00429] **Compound 38:** ***(S)-2-((8-chloroquinazolin-4-yl) amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. Prepared according

to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4,8-dichloroquinazoline, and Procedure P. LCMS theoretical m/z = 527.3. [M+H]+, found 527.3.

[00430] Compound 39: ***(S)-2-(quinazolin-4-ylamino)-4-((4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl) (2-(2,2,2-trifluoroethoxy)ethyl)amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-(2,2,2-trifluoroethoxy)ethan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 561.3. [M+H]+, found 561.3.

[00431] Compound 40: ***(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***. Prepared according to Scheme D using Procedure C with 1-(2-bromoethoxy)-4-fluorobenzene, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 605.3. [M+H]+, found 605.3.

[00432] Compound 41: ***(S)-4-((3-fluoropropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((7-methoxyquinazolin-4-yl) amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 3-fluoropropan-1-amine, Procedure H with 4-chloro-7-methoxyquinazoline, and Procedure P. LCMS theoretical m/z = 525.3. [M+H]+, found 525.3.

[00433] Compound 42: ***(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***. Prepared according to Scheme D using Procedure C with 2-(2-bromoethoxy)-1,1-difluorocyclopropane, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 587.3. [M+H]+, found 587.3.

[00434] Compound 43: ***(S)-4-((3-fluoropropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((8-methoxyquinazolin-4-yl) amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 3-fluoropropan-1-amine, Procedure H with 4-chloro-8-methoxyquinazoline, and Procedure P. LCMS theoretical m/z = 525.3. [M+H]+, found 525.3.

[00435] Compound 44: ***(S)-2-((6-(1H-pyrazol-1-yl) pyrimidin-4-yl) amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 4-chloro-6-(1H-pyrazol-1-yl) pyrimidine and Procedure P. LCMS theoretical m/z = 509.3. [M+H]+, found 509.3.

[00436] Compound 45: ***(S)-4-((2-(3,5-dimethyl-1H-pyrazol-1-yl) ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid***. Prepared according to Scheme D using Procedure C with 1-(2-bromoethyl)-3,5-dimethyl-1H-

pyrazole, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 557.3. [M+H]+, found 557.3.

[00437] Compound 46: ***(S)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-methylquinazolin-4-yl) amino) butanoic acid.*** Prepared according to Scheme A using Procedure A with (S)-2-fluoro-3-methoxypropan-1-amine, Procedure H with 4-chloro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 539.3. [M+H]+, found 539.3.

[00438] Compound 47: ***(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.*** Prepared according to Scheme C using Procedure B with 2-(3,5-difluorophenoxy)acetic acid, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 591.3. [M+H]+, found 591.3.

[00439] Compound 48: ***(S)-2-((8-chloroquinazolin-4-yl) amino)-4-((2-(pyridin-2-yloxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** Prepared according to Scheme C using Procedure B with 2-(pyridin-2-yloxy)acetic acid, Procedure H with 4,8-dichloroquinazoline, and Procedure P. LCMS theoretical m/z = 590.3. [M+H]+, found 590.3.

[00440] Compound 49: ***(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.*** Prepared according to Scheme C using Procedure B with 2-(pyridin-2-yloxy)acetic acid, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 556.3. [M+H]+, found 556.3.

[00441] Compound 50: ***(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.*** Prepared according to Scheme C using Procedure B with 2-(2,2-difluoroethoxy)acetic acid, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 543.3. [M+H]+, found 543.3.

[00442] Compound 51: ***(S)-2-(pyrido[3,2-d]pyrimidin-4-ylamino)-4-((4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl) (2-(2,2,2-trifluoroethoxy)ethyl)amino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2-(2,2,2-trifluoroethoxy)ethan-1-amine, Procedure G, Procedure H with 4-chloropyrido[3,2-d]pyrimidine, and Procedure P. LCMS theoretical m/z = 562.3. [M+H]+, found 562.3.

[00443] Compound 52: ***(S)-4-((2-((2-methylpyridin-3-yl) oxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared

according to Scheme C using Procedure B with 2-((2-methylpyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 570.3. [M+H]+, found 570.3.

[00444] Compound 53: ***(S)-2-((7-fluoro-2-methylquinazolin-4-yl) amino)-4-((2-((2-methylpyridin-3-yl) oxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. Prepared according to Scheme C using Procedure B with 2-((2-methylpyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 602.3. [M+H]+, found 602.3.

[00445] Compound 54: ***(S)-4-((2-((2-methylpyridin-3-yl) oxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-ylamino) butanoic acid***. Prepared according to Scheme C using Procedure B with 2-((2-methylpyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloropyrido[3,2-d]pyrimidine, and Procedure P. LCMS theoretical m/z = 571.3. [M+H]+, found 571.3.

[00446] Compound 55: ***(S)-4-((2-ethoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-ethoxyethan-1-amine, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 507.3. [M+H]+, found 507.3.

[00447] Compound 56: ***(S)-2-((7-fluoro-2-methylquinazolin-4-yl) amino)-4-((2-((6-methylpyridin-3-yl) oxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. Prepared according to Scheme C using Procedure B with 2-((6-methylpyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 602.3. [M+H]+, found 602.3.

[00448] Compound 57: ***(S)-4-((2-((6-methylpyridin-3-yl) oxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-ylamino) butanoic acid***. Prepared according to Scheme C using Procedure B with 2-((6-methylpyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloropyrido[3,2-d]pyrimidine, and Procedure P. LCMS theoretical m/z = 571.3. [M+H]+, found 571.3.

[00449] Compound 58: ***(S)-4-((2-((5-fluoropyridin-3-yl) oxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid***. Prepared according to Scheme C using Procedure B with 2-((5-fluoropyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 574.3. [M+H]+, 574.3.

[00450] Compound 59: ***(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***. Prepared

according to Scheme C using Procedure B with 2-((6-methylpyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 570.3. [M+H]+, found 570.3.

[00451] Compound 60: ***(S)-4-((2-((5-fluoropyridin-3-yl) oxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrido[3,2-d]pyrimidin-4-ylamino) butanoic acid.*** Prepared according to Scheme C using Procedure B with 2-((5-fluoropyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloropyrido[3,2-d]pyrimidine, and Procedure P. LCMS theoretical m/z = 575.3. [M+H]+, found 575.3.

[00452] Compound 61: ***(S)-2-((7-fluoro-2-methylquinazolin-4-yl) amino)-4-((2-((5-fluoropyridin-3-yl) oxy)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** Prepared according to Scheme C using Procedure B with 2-((5-fluoropyridin-3-yl) oxy)acetic acid, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 606.3. [M+H]+, found 606.3.

[00453] Compound 62: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme C using Procedure B with (R)-2-methoxypropanoic acid, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 507.3. [M+H]+, found 507.3.

[00454] Compound 63: ***(S)-4-((2-acetamidoethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme B using Procedure F with N-(2-aminoethyl)acetamide, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 520.3. [M+H]+, found 520.3.

[00455] Compound 64: ***(S)-4-((2-(dimethylamino)-2-oxoethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme B using Procedure F with 2-amino-N,N-dimethylacetamide, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 520.3. [M+H]+, found 520.3

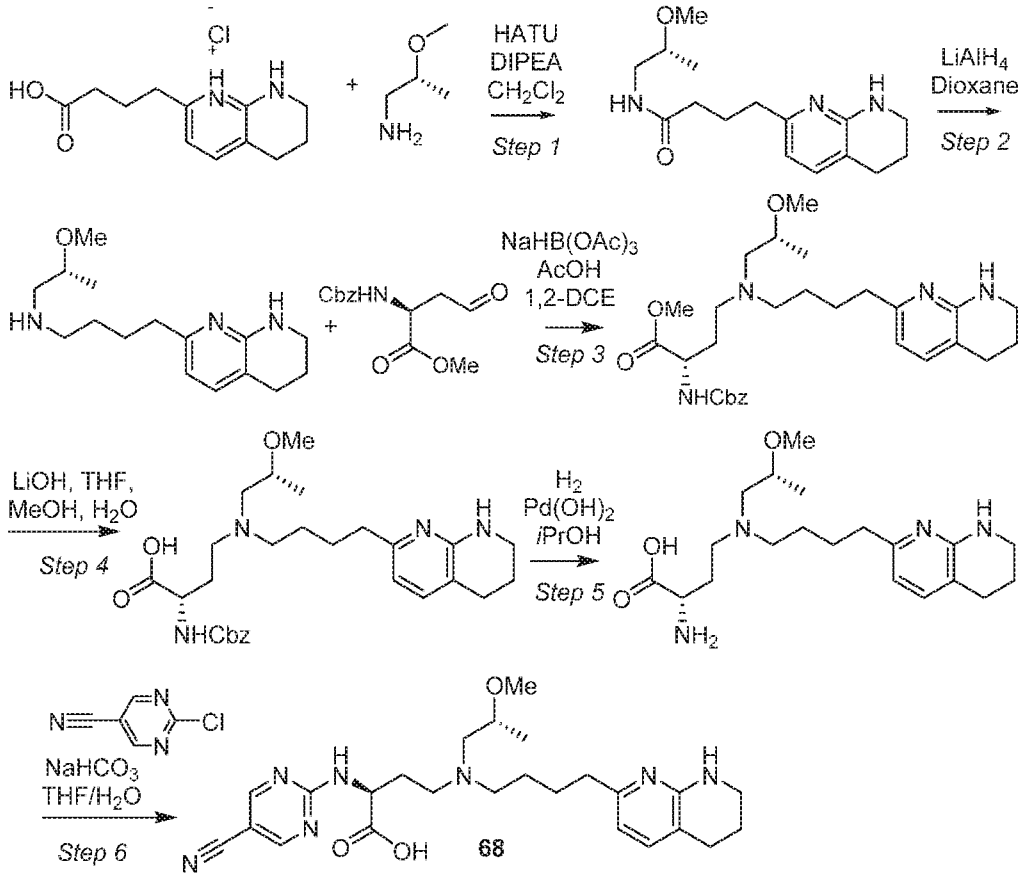
[00456] Compound 65: ***(S)-2-((7-fluoro-2-methylquinazolin-4-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** Prepared according to Scheme C using Procedure B with (R)-2-methoxypropanoic acid, Procedure H with 4-chloro-7-fluoro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 539.3. [M+H]+, found 539.3.

[00457] Compound 66: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-methylquinazolin-4-yl) amino) butanoic acid.***

Prepared according to Scheme C using Procedure B with (R)-2-methoxypropanoic acid, Procedure H with 4-chloro-2-methylquinazoline, and Procedure P. LCMS theoretical m/z = 521.3. [M+H]+, found 521.3.

[00458] Compound 67: ***(S)-2-((3-cyanopyrazin-2-yl) amino)-4-((2-methoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. Prepared according to Scheme A using Procedure A with 2-methoxyethan-1-amine, Procedure H with 3-chloropyrazine-2-carbonitrileand Procedure P. LCMS theoretical m/z = 468.3. [M+H]+, found 468.3.

Scheme 4, Compound 68:



[00459] Step 1: ***(R)-N-(2-methoxypropyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanamide***. To a solution of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanoic acid hydrochloride (2.6 g, 10.29 mmol) in CH_2Cl_2 (26 mL) was added (R)-2-methoxypropan-1-amine (1.38 g, 15.44 mmol), DIPEA (5.4 mL, 30.87 mmol), then HATU (5.67 g, 14.92 mmol) and the resulting mixture was stirred at rt for 2 h and then concentrated *in vacuo*. The resulting crude residue was purified using normal phase silica gel chromatography to give the title compound.

[00460] Step 2: ***(R)-N-(2-methoxypropyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butan-1-amine***. To a solution of (R)-N-(2-methoxypropyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanamide (1.2 g, 4.0 mmol) in 1,4-dioxane (11 mL) was added 2.0M $LiAlH_4$ in THF (4 mL, 8.0 mmol) and the resulting mixture was refluxed overnight and then allowed to cool to rt. The solution was carefully neutralized by the cautious addition of H_2O (310 μL), then 1 N NaOH (310 μL), then additional H_2O (310 μL) and the mixture was stirred at rt for 30 min and then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude residue was used without further purification.

[00461] Step 3: ***methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate***: To a mixture of (R)-N-(2-methoxypropyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butan-1-amine (10 g, 36.05 mmol) and methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-oxobutanoate (10.52 g, 39.65 mmol) in 1,2-DCE (100 mL) at 0° C was added AcOH (3.09 mL, 54.07 mmol) then $NaBH(OAc)_3$ (11.46 g, 54.07 mmol) was added and the resulting mixture was stirred at rt for 1 h. The resulting mixture was diluted with MeOH and then was concentrated *in vacuo*. The residue was taken back up in CH_2Cl_2 and sat. aq. $NaHCO_3$ and then the layers were seperated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by normal phase silica gel chromatography to give the title compound. LCMS (ESI+): m/z = 527.5 $(M+H)^+$.

[00462] Step 4: ***(S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. To a mixture of methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate (6 g, 11.39 mmol) in 1:1:1 THF/MeOH/H_2O (60 mL) was added $LiOH.H_2O$ (956 mg, 22.78 mmol) and the resulting mixture was stirred at rt for 1 h. The mixture was then adjusted to pH = 6 by the addition of AcOH and then concentrated *in vacuo* to give the title compound as the acetate salt that was used without further purification. LCMS (ESI+): m/z = 513.2 $(M+H)^+$.

[00463] Step 5: ***(S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***: To a solution of (S)-2-(((benzyloxy)carbonyl)amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (8 g, 13.97 mmol) in *i*-PrOH (50 mL) was added 20 wt% $Pd(OH)_2/C$ (1.96 g) and the resulting suspension was evacuated and backfilled with H_2 several times. The resulting mixture was stirred under an H_2 atmosphere at

rt for 2 h and then the mixture was filtered and concentrated under reduced pressure to give the title compound as the acetate salt that was used without further purification. LCMS (ESI+): m/z = 379.2 $(M+H)^+$.

[00464] Step 6: ***(S)-2-((5-cyanopyrimidin-2-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. To a solution of (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (100 mg, 228 µmol) in 4:1 THF/ H_2O (2.5 mL) was added solid $NaHCO_3$ (57 mg, 684 µmol) followed by 2-chloropyrimidine-5-carbonitrile (33 mg, 239 µmol). The resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt. The mixture was adjusted to pH = 6 by the addition of aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 482.3 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.48 - 8.64 (m, 2 H) 7.21 (d, *J*=7.28 Hz, 1 H) 6.42 (d, *J*=7.28 Hz, 1 H) 4.41 (dd, *J*=6.62, 4.85 Hz, 1 H) 3.71 (ddd, *J*=9.26, 6.06, 3.20 Hz, 1 H) 3.36 - 3.41 (m, 2 H) 3.32 - 3.34 (m, 1 H) 3.33 (s, 2 H) 3.26 (br dd, *J*=13.78, 6.73 Hz, 1 H) 3.02 - 3.12 (m, 2 H) 2.87 - 3.01 (m, 3 H) 2.71 (t, *J*=6.06 Hz, 2 H) 2.59 (br t, *J*=7.06 Hz, 2 H) 2.22 - 2.32 (m, 1 H) 2.06 - 2.16 (m, 1 H) 1.88 (dt, *J*=11.52, 6.04 Hz, 2 H) 1.72 (br s, 4 H) 1.17 (d, *J*=6.17 Hz, 3 H).

[00465] **Compound 69:** ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl) amino) butanoic acid***. (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (100 mg, 228 µmol) in 4:1 THF/H_2O (2.5 mL) was added solid $NaHCO_3$ (38 mg, 456 µmol) followed by 2-chloro-5-(trifluoromethyl)pyrimidine (44 mg, 239.42 µmol). The resulting mixture was stirred at 70° C for 1 h, cooled to rt, adjusted to pH = 6 by the addition of 1 M HCl, and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 525.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.72 - 10.42 (m, 1 H) 8.65 (s, 2 H) 8.05 - 8.33 (m, 2 H) 7.59 (d, *J*=7.34 Hz, 1 H) 6.62 (d, *J*=7.34 Hz, 1 H) 4.57 (br s, 1 H) 3.88 (ddd, *J*=8.99, 6.11, 3.12 Hz, 1 H) 3.45 (t, *J*=5.56 Hz, 2 H) 3.24 - 3.38 (m, 4 H) 3.06 - 3.23 (m, 5 H) 2.69 - 2.80 (m, 4 H) 2.23 - 2.43 (m, 3 H) 1.81 - 1.90 (m, 2 H) 1.70 - 1.80 (m, 4 H) 1.14 (d, *J*=6.24 Hz, 3 H).

[00466] **Compound 70:** ***(S)-2-((5-bromopyrimidin-2-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (100 mg, 228 µmol) in 4:1 THF/H_2O (2.5 mL) was added solid $NaHCO_3$ (57 mg,

684 μmol) followed by 5-bromo-2-chloro-pyrimidine (46 mg, 239 μmol). The resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt. The mixture was adjusted to pH = 6 by the addition of aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 535.2 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.47 - 8.55 (m, 2 H) 7.59 (d, *J*=7.28 Hz, 1 H) 6.65 (d, *J*=7.50 Hz, 1 H) 4.70 (dt, *J*=8.49, 4.35 Hz, 1 H) 3.82 (br s, 1 H) 3.49 - 3.53 (m, 2 H) 3.37 (d, *J*=12.13 Hz, 4 H) 3.13 - 3.29 (m, 4 H) 2.76 - 2.85 (m, 4 H) 2.41 - 2.51 (m, 2 H) 2.30 (br d, *J*=10.80 Hz, 1 H) 1.90 - 2.00 (m, 2 H) 1.79 (br s, 4 H) 1.21 (t, *J*=5.29 Hz, 3 H).

[00467] Compound 71: ***(S)-2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***. (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (150 mg, 342 μmol) in 4:1 THF/H_2O (2.5 mL) was added $NaHCO_3$ (86 mg, 1.03 mmol) followed by 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (56 mg, 359 μmol). The resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt. The mixture was adjusted to pH = 6 by the addition of aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 497.3 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 14.34 (br s, 1 H) 9.83 - 10.11 (m, 1 H) 8.93 (br s, 1 H) 8.54 (br s, 1 H) 8.11 (br s, 1 H) 7.60 (d, *J*=7.28 Hz, 1 H) 6.63 (d, *J*=7.50 Hz, 1 H) 4.93 (br s, 1 H) 3.88 (br s, 1 H) 3.42 (br s, 2 H) 3.26 - 3.39 (m, 2 H) 3.24 (s, 3 H) 3.17 (br s, 4 H) 2.72 (br d, *J*=5.95 Hz, 4 H) 2.42 (br s, 2 H) 1.64 - 1.86 (m, 6 H) 1.11 (d, *J*=5.95 Hz, 3 H).

[00468] Compound 72: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl) amino) butanoic acid***. (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (100 mg, 228 μmol) in 4:1 THF/H_2O (2.5 mL) was added $NaHCO_3$ (57 mg, 684 μmol) followed by 4-chloro-2-(trifluoromethyl)pyrimidine (44 mg, 239 μmol). The resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt. The mixture was adjusted to pH = 6 by the addition of aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 525.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.27 (br d, *J*=5.51 Hz, 1 H) 7.60 (d, *J*=7.28 Hz, 1 H) 6.96 (d, *J*=6.39 Hz, 1 H) 6.65 (d, *J*=7.28 Hz, 1 H) 4.86 (br s, 1 H) 3.82 (br d, *J*=5.95 Hz, 1 H) 3.42 - 3.55 (m, 3 H) 3.37 (d, *J*=8.38 Hz,

4 H) 3.12 - 3.30 (m, 4 H) 2.72 - 2.86 (m, 4 H) 2.48 (dt, *J*=11.85, 5.87 Hz, 1 H) 2.26 - 2.39 (m, 1 H) 1.95 (q, *J*=5.90 Hz, 2 H) 1.73 - 1.90 (m, 4 H) 1.22 (dd, *J*=6.06, 1.87 Hz, 3 H).

[00469] Compound 73: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-phenylpyrimidin-4-yl) amino) butanoic acid.*** (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (150 mg, 342 µmol), 4-chloro-2-phenylpyrimidine (65 mg, 342 µmol) in DMA (2 mL) was added DIPEA (179 µL, 1.03 mmol) and the resulting mixture was stirred at 100° C for 2 h. The mixture was cooled to rt and then adjusted to pH = 6 by aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to afford the title compound. LCMS (ESI+): m/z = 533.3 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.24 (br d, *J*=5.95 Hz, 2 H) 8.11 (br s, 1 H) 7.37 - 7.48 (m, 3 H) 7.16 (br d, *J*=5.51 Hz, 1 H) 6.49 (br s, 1 H) 6.38 (d, *J*=7.50 Hz, 1 H) 4.65 (br s, 1 H) 3.68 (br d, *J*=5.95 Hz, 1 H) 3.36 (br s, 1 H) 3.23 - 3.30 (m, 5 H) 2.82 - 3.18 (m, 5 H) 2.52 - 2.69 (m, 4 H) 2.35 (br s, 1 H) 2.13 - 2.21 (m, 1 H) 1.62 - 1.86 (m, 6 H) 1.14 (d, *J*=6.17 Hz, 3 H).

[00470] Compound 74: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl) amino) butanoic acid.*** (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (100 mg, 228 µmol) in 4:1 THF/H_2O (2.5 mL) was added $NaHCO_3$ (57 mg, 684 µmol) followed by 4-chloro-1-methyl-pyrazolo[3,4-d]pyrimidine (40 mg, 239 µmol) and the resulting mixture was stirred at 70° C for l h. The mixture was cooled to rt and then adjusted to pH = 6 by aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 511.3 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.60 (br d, *J*=16.54 Hz, 1 H) 8.50 (s, 1 H) 7.59 (d, *J*=7.50 Hz, 1 H) 6.66 (d, *J*=7.28 Hz, 1 H) 5.07 (br dd, *J*=8.05, 5.62 Hz, 1 H) 4.09 (s, 3 H) 3.87 (br s, 1 H) 3.59 (br d, *J*=16.76 Hz, 1 H) 3.43 - 3.53 (m, 4 H) 3.39 (s, 3 H) 3.33 - 3.36 (m, 1 H) 3.15 - 3.29 (m, 2 H) 2.77 - 2.85 (m, 4 H) 2.51 - 2.68 (m, 2 H) 1.78 - 1.98 (m, 6 H) 1.23 (d, *J*=5.95 Hz, 3 H).

[00471] Compound 75: ***(S)-4-((2-hydroxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(quinazolin-4-ylamino) butanoic acid.*** Prepared according to Scheme A using Procedure A with 2-aminoethan-1-ol, Procedure H with 4-chloroquinazoline, and Procedure P. LCMS theoretical m/z = 479.3. [M+H]+, found 479.3.

[00472] Compound 76: ***(S)-2-((3-cyanopyrazin-2-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** (S)-2-amino-4-(((R)-

2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (100 mg, 228 μmol) in *i*-PrOH (2 mL) was added DPIEA (199 μL, 1.14 mmol) and 3-chloropyrazine-2-carbonitrile (35 mg, 250.82 μmol) and the resulting mixture was stirred at 70° C for 12 h. The mixture was cooled to rt and then adjusted to pH = 6 by aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 482.2 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.23 (d, *J*=2.32 Hz, 1 H) 7.87 (d, *J*=2.32 Hz, 1 H) 7.15 (d, *J*=7.34 Hz, 1 H) 6.38 (d, *J*=7.34 Hz, 1 H) 4.40 (t, *J*=5.50 Hz, 1 H) 3.63 - 3.73 (m, 1 H) 3.35 - 3.39 (m, 2 H) 3.31 - 3.32 (m, 3 H) 3.12 - 3.22 (m, 1 H) 2.81 - 3.03 (m, 5 H) 2.69 (t, *J*=6.17 Hz, 2 H) 2.51 - 2.60 (m, 2 H) 2.26 (dq, *J*=14.35, 6.99 Hz, 1 H) 2.06 - 2.16 (m, 1 H) 1.86 (q, *J*=5.90 Hz, 2 H) 1.67 (br s, 4 H) 1.15 (d, *J*=5.99 Hz, 3 H).

[00473] Compound 77: ***(S)-2-((6-(1H-pyrazol-1-yl) pyrimidin-4-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (100 mg, 228 μmol) in DMA (2 mL) was added DIPEA (119 μL, 684 μmol) followed by 4-chloro-6-pyrazol-1-yl-pyrimidine (45 mg, 251 μmol) and the resulting mixture was stirred at 100° C for 2 h. The mixture was cooled to rt and then adjusted to pH = 6 by 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 523.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.51 (d, *J*=2.21 Hz, 1 H) 8.33 (s, 1 H) 7.75 (s, 1 H) 7.16 (d, *J*=7.28 Hz, 1 H) 7.00 (br s, 1 H) 6.52 (d, *J*=1.76 Hz, 1 H) 6.39 (d, *J*=7.28 Hz, 1 H) 4.49 (br s, 1 H) 3.75 (br s, 1 H) 3.33 - 3.42 (m, 6 H) 3.00 - 3.15 (m, 3 H) 2.86 - 2.98 (m, 2 H) 2.67 (br t, *J*=6.17 Hz, 2 H) 2.56 - 2.62 (m, 2 H) 2.23 - 2.35 (m, 1 H) 2.11 (br dd, *J*=14.44, 5.40 Hz, 1 H) 1.85 (q, *J*=5.95 Hz, 2 H) 1.72 (br d, *J*=3.75 Hz, 4 H) 1.18 (d, *J*=5.95 Hz, 3 H).

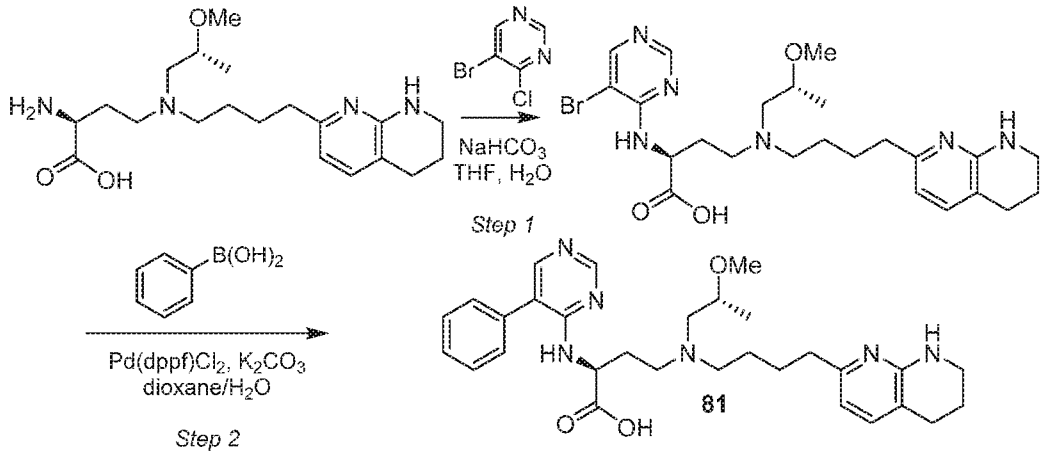
[00474] Compound 78: ***(S)-2-((5-fluoropyrimidin-2-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (150 mg, 342 μmol), 2-chloro-5-fluoropyrimidine (50 mg, 376 μmol) in DMA (2 mL) was added DIPEA (179 μL, 1.03 mmol) and the resulting mixture was stirred at 100° C for 2 h. The mixture was cooled to rt and then adjusted to pH = 6 by aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 475.2 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.33 (s, 2 H) 7.60 (d, *J*=7.28 Hz, 1 H) 6.61 - 6.67 (m, 1 H) 4.57 - 4.66

(m, 1 H) 3.74 - 3.87 (m, 1 H) 3.48 - 3.53 (m, 2 H) 3.39 - 3.48 (m, 1 H) 3.32 - 3.39 (m, 4 H) 3.12 - 3.29 (m, 4 H) 2.80 (dt, *J*=17.81, 6.64 Hz, 4 H) 2.37 - 2.50 (m, 1 H) 2.25 (br dd, *J*=9.04, 3.53 Hz, 1 H) 1.95 (dt, *J*=11.91, 5.95 Hz, 2 H) 1.79 (br d, *J*=5.73 Hz, 4 H) 1.21 (t, *J*=6.28 Hz, 3 H).

[00475] Compound 79: ***(S)-2-((1H-pyrazolo[4,3-d]pyrimidin-7-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (100 mg, 241 µmol) in 4:1 THF/H_2O (2.5 mL) was added $NaHCO_3$ (57 mg, 684 µmol) followed by 7-chloro-1H-pyrazolo[4,3-d]pyrimidine (45 mg, 289 µmol) and the resulting mixture was stirred at 70° C for 12 h. The mixture was cooled to rt and then adjusted to pH = 6 by aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 497.3 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.18 - 8.48 (m, 2 H) 7.60 (d, *J*=7.21 Hz, 1 H) 6.59 (d, *J*=7.21 Hz, 1 H) 4.87 (br s, 1 H) 3.73 (br s, 1 H) 3.41 (br s, 2 H) 3.25 - 3.37 (m, 1 H) 3.19 - 3.24 (m, 3 H) 3.02 - 3.19 (m, 5 H) 2.63 - 2.77 (m, 4 H) 2.33 (br s, 1 H) 2.20 (br d, *J*=10.15 Hz, 1 H) 1.59 - 1.87 (m, 6 H) 1.10 (br d, *J*=5.87 Hz, 3 H).

[00476] Compound 80: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((6-phenylpyrimidin-4-yl) amino) butanoic acid:*** To a solution of (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 241 µmol) and 4-chloro-6-phenyl-pyrimidine (51 mg, 265 µmol) in 4:1 THF/H_2O (2.5 mL) was added $NaHCO_3$ (61 mg, 723 µmol) and the resulting mixture was stirred at 70° C for 12 h. The mixture was cooled to rt and then adjusted to pH = 6 by aq. 1 M HCl and then concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 533.3 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.47 (s, 1 H) 7.81 - 7.92 (m, 2 H) 7.44 - 7.53 (m, 3 H) 7.15 (d, *J*=7.50 Hz, 1 H) 6.93 - 7.05 (m, 1 H) 6.39 (d, *J*=7.50 Hz, 1 H) 4.47 (br s, 1 H) 3.75 (br s, 1 H) 3.32 - 3.39 (m, 6 H) 2.84 - 3.21 (m, 5 H) 2.66 (t, *J*=6.17 Hz, 2 H) 2.56 - 2.62 (m, 2 H) 2.24 - 2.35 (m, 1 H) 2.05 - 2.17 (m, 1 H) 1.84 (q, *J*=5.90 Hz, 2 H) 1.72 (br s, 4 H) 1.18 (d, *J*=6.17 Hz, 3 H).

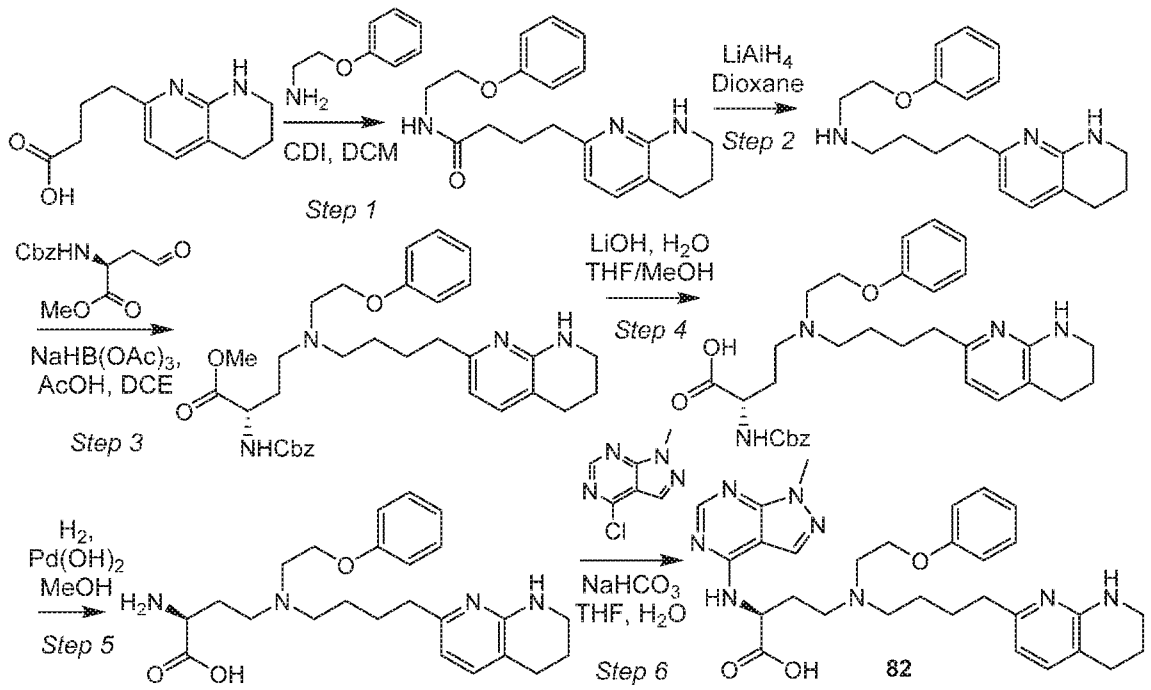
Scheme 5, Compound 81:



[00477] Step 1: ***(S)-2-((5-bromopyrimidin-4-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a solution of (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 241 µmol) and 5-bromo-4-chloropyrimidine (51 mg, 265 µmol) in 4:1 THF/H_2O (2.5 mL) was added $NaHCO_3$ (101 mg, 1.20 mmol) and the resulting mixture was stirred at 70° C for 2 h. The mixture was cooled to rt and then adjusted to pH = 6 by aq. 1 M HCl and then concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 535.3 $(M+H)^+$.

[00478] Step 2: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((5-phenylpyrimidin-4-yl) amino) butanoic acid:*** A mixture of (S)-2-((5-bromopyrimidin-4-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (30 mg, 56 µmol), phenylboronic acid (8 mg, 67 µmol), $Pd(dppf)Cl_2$ (4 mg, 6 µmol), and K_2CO_3 (15 mg, 112 µmol) were diluted in 4:1 dioxane/H_2O (1.25 mL) and the resulting mixture was stirred at 100° C for 2 h. The mixture was cooled to rt and then filtered and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to afford the title compound. LCMS (ESI+): m/z = 533.3 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.86 (s, 1 H) 8.22 (s, 1 H) 7.53 - 7.66 (m, 6 H) 6.66 (br d, *J*=6.84 Hz, 1 H) 5.11 (br s, 1 H) 3.84 (br s, 1 H) 3.48 - 3.54 (m, 2 H) 3.46 (br s, 1 H) 3.34 - 3.39 (m, 3 H) 3.08 - 3.29 (m, 4 H) 2.74 - 2.86 (m, 5 H) 2.56 (br s, 1 H) 2.37 (br s, 1 H) 1.76 - 2.00 (m, 6 H) 1.21 (br d, *J*=5.29 Hz, 3 H).

Scheme 6, Compound 82:



[00479] Step 1: ***N-(2-phenoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanamide:*** To a mixture of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanoic acid (5 g, 15.89 mmol) in DCM (70 mL) was added CDI (2.83 g, 17.48 mmol) at 0° C and the resulting mixture was stirred at rt for 1 h, at which time, 2-phenoxyethanamine (2.40 g, 17.48 mmol) was added and stirred for an additional 1 h at rt. The mixture was diluted with H_2O and the layers were separated. The aqueous layer was extracted with DCM and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 339.9 $(M+H)^+$.

[00480] Step 2: ***N-(2-phenoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butan-1-amine:*** To a mixture of $LiAlH_4$ (1.21 g, 31.79 mmol) in 1,4-dioxane (50 mL) at rt was added N-(2-phenoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanamide (5 g, 14.45 mmol) and the resulting mixture was heated to reflux for 30 min and then allowed to cool to rt. The mixture was carefully neutralized by the dropwise addition of H_2O (1.2 mL), then 1 M aq. NaOH (1.2 mL), and then H_2O (3.6 mL) again, followed by drying over $MgSO_4$. The mixture was filtered and concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 326.1 $(M+H)^+$.

[00481] Step 3: ***methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate:*** To a mixture of N-(2-phenoxyethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butan-1-amine (5 g, 12.84 mmol)

and (S)-methyl 2-(((benzyloxy)carbonyl)amino)-4-oxobutanoate (3.75 g, 14.12 mmol) in DCE (75 mL) at 0° C was added AcOH (1.10 mL, 19.26 mmol) and $NaBH(OAc)_3$ (4.08 g, 19.26 mmol) and the resulting mixture was stirred for 3 h at rt. The mixture was diluted with MeOH (50 mL) and the mixture was concentrated *in vacuo*. The crude product was taken up in DCM and sat. aq. $NaHCO_3$ was added. The layers were separated and the aqueous layer was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give the title compound. LCMS (ESI+): m/z = 575.1 $(M+H)^+$.

[00482] Step 4: ***(S)-2-(((benzyloxy)carbonyl)amino)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a solution of (S)-methyl 2-(((benzyloxy)carbonyl)amino)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate (1 g, 1.74 mmol) in 1:1:1 THF/MeOH/H_2O (9 mL) was added $LiOH•H_2O$ (146 mg, 3.48 mmol) at 0° C and the resulting mixture was stirred at rt for 40 min. The mixture was adjusted to pH = 6 by the addition of AcOH and then was concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 561.1 $(M+H)^+$.

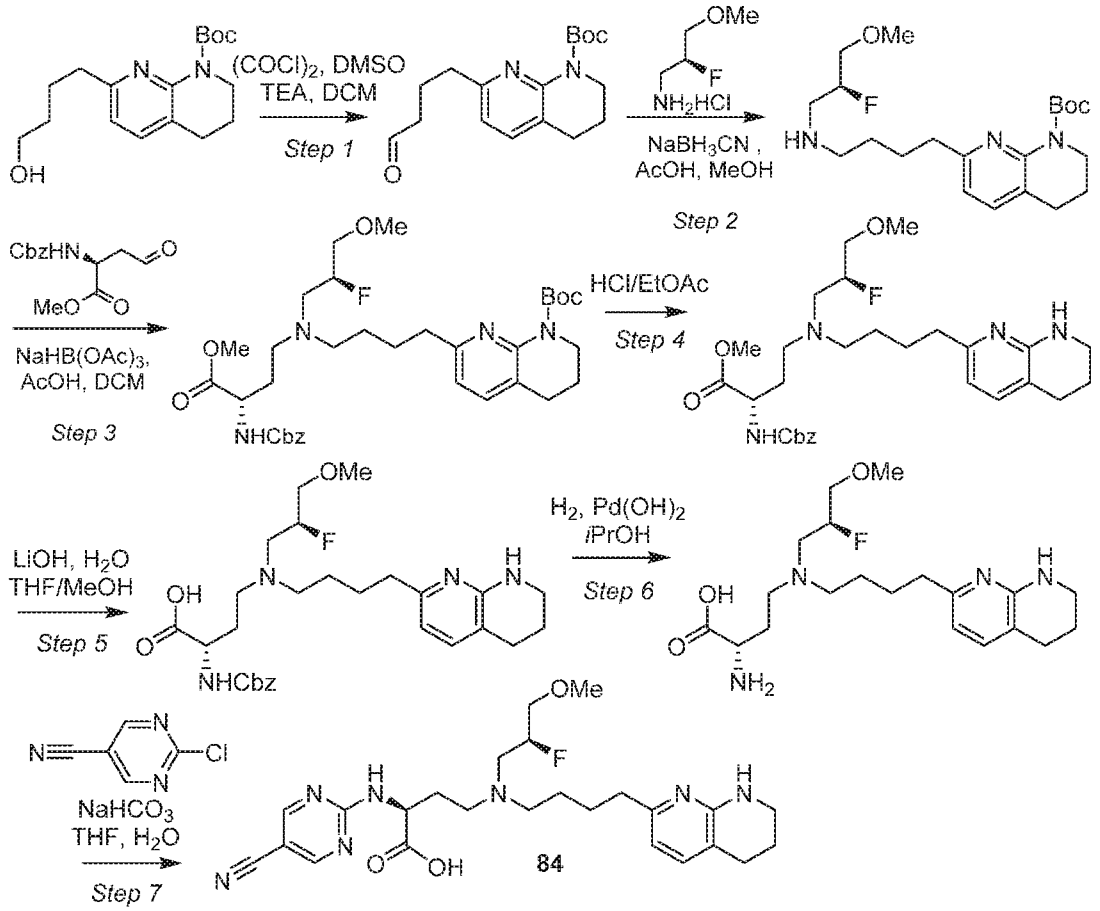
[00483] Step 5: ***(S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a solution of (S)-2-(((benzyloxy)carbonyl)amino)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (3.78 g, 6.74 mmol) in MeOH (300 mL) was added 20 wt% $Pd(OH)_2/C$ (2.9 g) and the resulting mixture was stirred under an H_2 atmosphere for 2 h at rt. The mixture was filtered and concentrated *in vacuo* to give the title compound that was used without further purifcation. LCMS (ESI+): m/z = 427.2 $(M+H)^+$.

[00484] Step 6: ***(S)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl) amino)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***: To a solution of 4-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine (43 mg, 258 μmol) in 4:1 THF/H_2O (2 mL) was added (S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 234 μmol) and $NaHCO_3$ (59 mg, 703 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 559.3 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 14.37 (br s, 1 H) 10.79 - 11.21 (m, 1 H) 9.88 - 10.34 (m, 1 H) 8.64 (s, 1 H) 8.40 (s, 1 H) 8.14 (br s, 1 H) 7.58 (d, J=7.45 Hz, 1 H) 7.20 - 7.32 (m, 2 H) 6.87 - 7.03 (m, 3 H) 6.62

(d, J=7.45 Hz, 1 H) 5.01 (br s, 1 H) 4.37 - 4.51 (m, 2 H) 3.96 (s, 3 H) 3.34 - 3.72 (m, 5 H) 3.26 (br s, 2 H) 2.71 (br t, J=6.14 Hz, 4 H) 2.50 (br s, 3 H) 1.64 - 1.94 (m, 5 H).

[00485] Compound 83: ***(S)-2-((5-bromopyrimidin-2-yl) amino)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 234 µmol) in 4:1 THF/H_2O (2 mL) was added 5-bromo-2-fluoropyrimidine (46 mg, 258 µmol) and $NaHCO_3$ (59 mg, 703 µmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 583.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.16 (s, 2 H) 7.29 (d, J=7.45 Hz, 1 H) 7.16 - 7.25 (m, 2 H) 6.90 (t, J=7.24 Hz, 1 H) 6.84 (d, J=7.89 Hz, 2 H) 6.46 (d, J=7.45 Hz, 1 H) 4.32 (t, J=6.14 Hz, 1 H) 4.18 (t, J=5.26 Hz, 2 H) 3.33 - 3.43 (m, 2 H) 3.05 - 3.27 (m, 4 H) 2.94 (br s, 2 H) 2.59 - 2.75 (m, 4 H) 2.05 - 2.27 (m, 2 H) 1.69 - 1.93 (m, 6 H).

Scheme 7, Compound 84:



[00486] Step 1: ***tert-butyl 7-(4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate:*** To a mixture of oxalyl chloride (16.00 g, 126.04 mmol) in DCM (200 mL) was added DMSO (15.15 g, 193.91 mmol) at -78° C and the resulting mixture was stirred at -78° C for 30 min, at which time, a solution of tert-butyl 7-(4-hydroxybutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (29.71 g, 96.95 mmol) in DCM (100 mL) was added. The reaction mixture was stirred at -78° C for 1 h and then triethylamine (67.5 mL, 484.77 mmol) was added and the mixture was stirred at -78° C for another 30 min and then slowly warmed to -40° C and then diluted with H_2O and allowed to warm to rt. The layers were separated and the aqueous layer was extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound that was used without further purification.

[00487] Step 2: ***tert-butyl (S)-7-(4-((2-fluoro-3-methoxypropyl)amino) butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate***: To a solution of tert-butyl 7-(4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (15 g, 49.28 mmol) in MeOH (50 mL) was

added (S)-2-fluoro-3-methoxypropan-1-amine hydrochloride (10.61 g, 73.92 mmol), AcOH (2.82 mL, 49.28 mmol), and $NaBH_3CN$ (6.19 g, 98.56 mmol) at 0° C and stirred at rt for 12 h. The resulting mixture was concentrated *in vacuo* and then diluted with sat. aq. $NaHCO_3$ and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give the title compound. LCMS (ESI+): m/z = 396.2 $(M+H)^+$.

[00488] Step 3: ***tert-butyl 7-(4-(((S)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl) ((S)-2-fluoro-3-methoxypropyl)amino) butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate***: To a mixture of tert-butyl (S)-7-(4-((2-fluoro-3-methoxypropyl)amino)butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (2.00 g, 6.77 mmol) and methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-oxobutanoate (1.98 g, 7.45 mmol) in DCE (20 mL) was added AcOH (581 µL, 10.16 mmol) and $NaBH(OAc)_3$ (2.15 g, 10.16 mmol) at 0° C and the resulting mixture was stirred at rt for 1 h. The mixture was diluted with MeOH and then concentrated *in vacuo*. The crude residue was diluted with DCM and sat. aq. $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with DCM and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give the title compound. LCMS (ESI+): m/z = 645.5 $(M+H)^+$.

[00489] Step 4: ***methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate***: tert-butyl 7-(4-(((S)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl) ((S)-2-fluoro-3-methoxypropyl)amino)butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (1.8 g, 2.79 mmol) was taken up in 4 M HCl in EtOAc (20 mL) and the mixture was stirred at rt for 15 h and then concentrated *in vacuo* to give the title compound which was used without further purification. LCMS (ESI+): m/z = 545.4 $(M+H)^+$.

[00490] Step 5: ***(S)-2-(((benzyloxy)carbonyl)amino)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***: A mixture of methyl (S)-2-(((benzyloxy)carbonyl)amino)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate hydrochloride (500 mg, 860 µmol), in 1:1:1 THF/H_2O/MeOH (3 mL) was added $LiOH•H_2O$ (72 mg, 1.72 mmol) and the resulting mixture was stirred at rt for 1 h and then diluted with MeOH and adjusted to pH = 6 by the addition of AcOH and then concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 531.4 $(M+H)^+$.

[00491] Step 6: ***(S)-2-amino-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a solution of (S)-2-(((benzyloxy)carbonyl)amino)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid acetate (1 g, 1.69 mmol) in *i*-PrOH (10 mL) was added 20 wt% $Pd(OH)_2/C$ (238 mg) and the resulting mixture was stirred under an H_2 atmosphere for 2 h. The mixture was filtered and concentrated under *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 397.2 $(M+H)^+$.

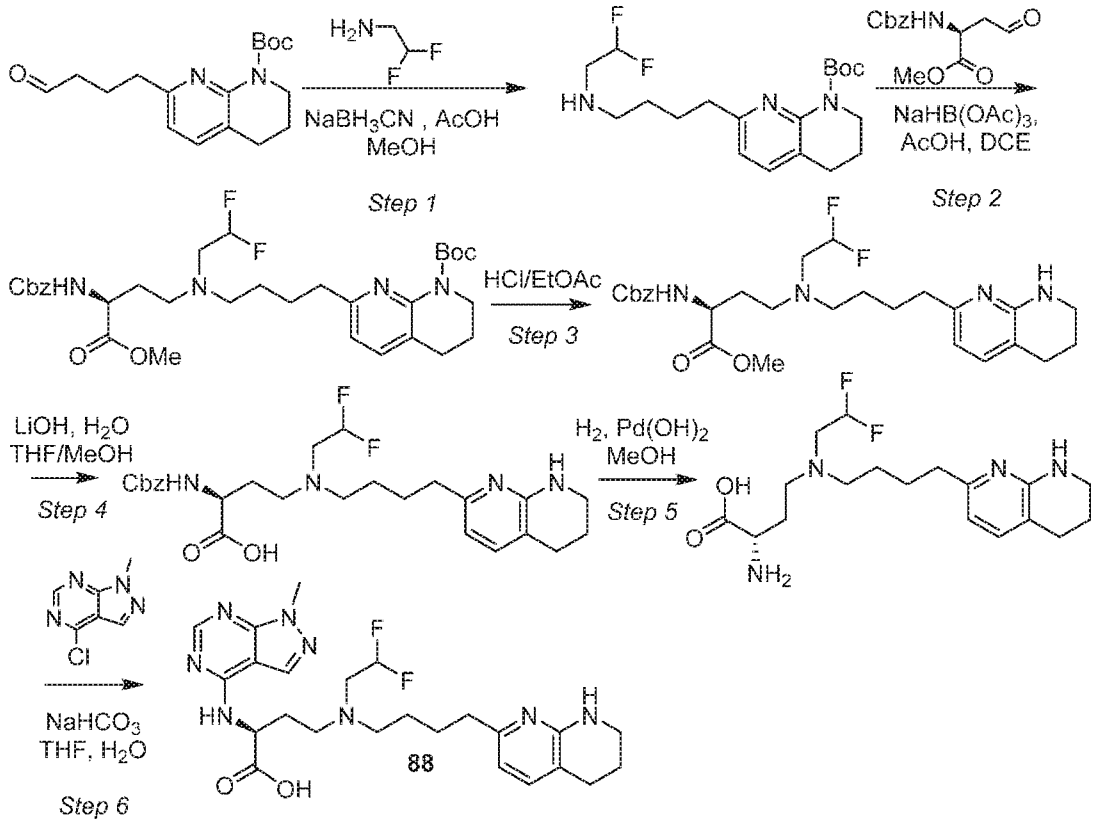
[00492] Step 7: ***(S)-2-((5-cyanopyrimidin-2-yl) amino)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***: To a solution of (S)-2-amino-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (120 mg, 277 μmol) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (70 mg, 831 μmol), and then 2-chloropyrimidine-5-carbonitrile (43 mg, 305 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt. The mixture was adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 500.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.56 (br s, 1 H) 8.45 (br s, 1 H) 7.42 (br d, *J*=7.28 Hz, 1 H) 6.52 (d, *J*=7.50 Hz, 1 H) 4.75 (br d, *J*=3.31 Hz, 1 H) 4.51 (t, *J*=5.84 Hz, 1 H) 3.57 (d, *J*=3.97 Hz, 1 H) 3.49 - 3.53 (m, 1 H) 3.37 - 3.46 (m, 2 H) 3.33 - 3.37 (m, 3 H) 2.84 - 2.96 (m, 2 H) 2.65 - 2.83 (m, 8 H) 2.15 - 2.24 (m, 1 H) 2.04 - 2.14 (m, 1 H) 1.87 - 1.94 (m, 2 H) 1.81 (br dd, *J*=13.78, 6.73 Hz, 2 H) 1.58 - 1.69 (m, 2 H).

[00493] **Compound 85:** ***(S)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl) amino) butanoic acid:*** To a solution of (S)-2-amino-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 252 μmol) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (64 mg, 757 μmol) and then 2-chloro-5-(trifluoromethyl)pyrimidine (51 mg, 277 μmol) and the resulting mixture was stirred at 70° C for 1 h and then cooled to rt. The mixture was adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 543.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.64 (s, 2 H) 7.59 (d, *J*=7.46 Hz, 1 H) 6.65 (d, *J*=7.34 Hz, 1 H) 5.10 - 5.28 (m, 1 H) 4.79 (br s, 1 H) 3.54 - 3.74 (m, 4 H) 3.42 - 3.54 (m, 4 H) 3.40 (s, 3 H) 3.33 - 3.39 (m, 2 H) 2.75 - 2.86 (m, 4 H) 2.43 - 2.57 (m, 1 H) 2.35 (br s, 1 H) 1.74 - 2.00 (m, 6 H).

[00494] Compound 86: ***(S)-2-((5-bromopyrimidin-2-yl) amino)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** (S)-2-amino-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 231 μmol) in THF (1 mL) and H_2O (0.25 mL) was added $NaHCO_3$ (58 mg, 693 μmol) and 5-bromo-2-fluoropyrimidine (49 mg, 277 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt. The mixture was adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 553.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.24 (s, 2 H) 7.40 (d, *J*=7.50 Hz, 1 H) 6.52 (d, *J*=7.28 Hz, 1 H) 4.77 (br d, *J*=3.53 Hz, 1 H) 4.36 (t, *J*=6.17 Hz, 1 H) 3.58 (d, *J*=4.41 Hz, 1 H) 3.52 (d, *J*=4.19 Hz, 1 H) 3.35 - 3.44 (m, 2 H) 3.33 (s, 3 H) 2.83 - 2.95 (m, 4 H) 2.66 - 2.76 (m, 6 H) 2.05 - 2.18 (m, 2 H) 1.84 - 1.91 (m, 3 H) 1.75 - 1.83 (m, 1 H) 1.61 - 1.71 (m, 2 H).

[00495] Compound 87: ***(S)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl) amino) butanoic acid:*** (S)-2-amino-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 231 μmol) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (58 mg, 693 μmol) and 4-chloro-2-(trifluoromethyl)pyrimidine (46 mg, 254 μmol) and the resulting mixture was stirred at 70° C for 1hr and then cooled to rt. The mixture was adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 543.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.06 (br d, *J*=5.26 Hz, 1 H) 7.42 (d, *J*=7.34 Hz, 1 H) 6.66 (br d, *J*=5.62 Hz, 1 H) 6.51 (d, *J*=7.34 Hz, 1 H) 4.71 - 4.78 (m, 1 H) 4.68 (br s, 1 H) 3.46 - 3.61 (m, 2 H) 3.36 - 3.44 (m, 2 H) 3.31 (s, 3 H) 2.95 (br d, *J*=4.89 Hz, 2 H) 2.54 - 2.85 (m, 8 H) 2.23 (br s, 1 H) 2.06 (br d, *J*=4.52 Hz, 1 H) 1.73 - 1.94 (m, 4 H) 1.51 - 1.73 (m, 2 H).

Scheme 8, Compound 88:



[00496] Step 1: ***tert-butyl 7-(4-((2,2-difluoroethyl)amino) butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate:*** To a mixture of 2,2-difluoroethanamine (3.99 g, 49.28 mmol, 1.5 *eq*) in MeOH (80 mL) was added AcOH (1.88 mL, 32.85 mmol), $NaBH_3CN$ (4.13 g, 65.71 mmol), and then a solution of tert-butyl 7-(4-oxobutyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (10 g, 32.85 mmol) in MeOH (30 mL) at 0° C. The resulting mixture was stirred at rt for 3 h and then dilute with sat. aq. $NaHCO_3$ and concentrated *in vacuo* to remove the volatiles. The remaining aqueous phase was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by reverse phase HPLC to give the title compound. LCMS (ESI+): m/z = 370.2.

[00497] Step 2: ***(S)-tert-butyl 7-(4-((3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl) (2,2-difluoroethyl)amino) butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate:*** To a mixture of tert-butyl 7-(4-((2,2-difluoroethyl)amino)butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (5.7 g, 15.43 mmol) and (S)-methyl 2-(((benzyloxy)carbonyl)amino)-4-oxobutanoate (4.50 g, 16.97 mmol) in DCE (60 mL) was added AcOH (1.32 mL, 23.14 mmol), $NaBH(OAc)_3$ (4.90 g, 23.14 mmol) at 0° C and the

resulting mixture was stirred at rt for 1 h. The mixture was diluted with sat. aq. $NaHCO_3$ and DCM and the layers were separated. The aqueous layer was extracted with DCM and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by normal phase silica gel chromatography to give the title compound. LCMS (ESI+): m/z = 619.2.

[00498] Step 3: ***(S)-methyl 2-(((benzyloxy)carbonyl)amino)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate:*** (S)-tert-butyl 7-(4-((3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl) (2,2-difluoroethyl)amino)butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (3 g, 4.85 mmol) was diluted in 4 M HCl in EtOAc (5 mL) and stirred at rt for 16 h and then concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 519.2.

[00499] Step 4: ***(S)-2-(((benzyloxy)carbonyl)amino)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a mixture of (S)-methyl 2-(((benzyloxy)carbonyl)amino)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate hydrochloride (2.7 g, 4.86 mmol) in 1:1:1 THF/H_2O/MeOH (25 mL) was added $LiOH.H_2O$ (408 mg, 9.73 mmol) at 0° C and the resulting mixture was stirred at rt for 1 h. The mixture was adjusted to pH=6 by the addition of 1 M aq. HCl and concentrated *in vacuo* to give the title compound. LCMS (ESI+): m/z = 505.3.

[00500] Step 5: ***(S)-2-amino-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a solution of (S)-2-(((benzyloxy)carbonyl)amino)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (2.9 g, 5.75 mmol) in MeOH (20 mL) was added 20 wt% $Pd(OH)_2/C$ (1.29 g) and the resulting mixture was stirred under an H_2 atmosphere for 2 h. The mixture was filtered and concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 371.4.

[00501] Step 6: ***(S)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl) amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (110 mg, 297 μmol) and 4-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine (55 mg, 327 μmol) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (50 mg, 594 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 503.3. ^1H NMR (400 MHz, Methanol-d_4) δ

ppm 8.63 (s, 1 H) 8.49 (s, 1 H) 7.59 (br d, *J*=6.61 Hz, 1 H) 6.37 - 6.71 (m, 2 H) 5.10 (br s, 1 H) 4.09 (s, 3 H) 3.86 (br t, *J*=14.22 Hz, 2 H) 3.55 - 3.76 (m, 2 H) 3.36 - 3.54 (m, 4 H) 2.82 (br d, *J*=5.95 Hz, 4 H) 2.54 - 2.75 (m, 2 H) 1.76 - 2.00 (m, 6 H).

[00502] Compound 89: ***(S)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl) amino) butanoic acid:*** (S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 234 μmol) in 4:1 THF/H_2O (2 mL) was added 2-chloro-5-(trifluoromethyl)pyrimidine (47 mg, 258 μmol) and $NaHCO_3$ (59 mg, 703 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 573.3 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.57 (s, 2 H) 7.58 (d, J=7.34 Hz, 1 H) 7.30 (br t, J=7.15 Hz, 2 H) 6.93 - 7.05 (m, 3 H) 6.63 (d, J=7.21 Hz, 1 H) 4.79 (dd, J=8.38, 5.07 Hz, 1 H) 4.38 (br s, 2 H) 3.63 - 3.78 (m, 2 H) 3.46 (br s, 3 H) 3.42 - 3.60 (m, 1 H) 3.37 (br d, J=8.80 Hz, 2 H) 2.74 - 2.85 (m, 4 H) 2.51 - 2.62 (m, 1 H) 2.37 (br s, 1 H) 1.75 - 1.99 (m, 6 H).

[00503] Compound 90: ***(S)-2-((1H-pyrazolo[3,4-d]pyrimidin-4-yl) amino)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 234 μmol) in 4:1 THF/H_2O (2 mL) was added 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (40 mg, 258 μmol) and $NaHCO_3$ (59 mg, 703 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 545.0 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.78 (br d, J=19.07 Hz, 1 H) 8.59 (s, 1 H) 7.58 (d, J=7.46 Hz, 1 H) 7.25 (br t, J=7.89 Hz, 2 H) 6.90 - 7.02 (m, 3 H) 6.64 (d, J=7.34 Hz, 1 H) 5.29 (br s, 1 H) 4.40 (br d, J=5.01 Hz, 2 H) 3.73 (br s, 2 H) 3.48 - 3.68 (m, 4 H) 3.42 (br t, J=7.76 Hz, 2 H) 2.75 - 2.85 (m, 4 H) 2.71 (br s, 1 H) 2.54 (br s, 1 H) 1.88 - 2.03 (m, 4 H) 1.71 - 1.87 (m, 2 H).

[00504] Compound 91: ***(S)-2-((6-(1H-pyrazol-1-yl) pyrimidin-4-yl) amino)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a solution of (S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 216 μmol) in DMA (2 mL) was added DIPEA (188 μL, 1.08 mmol) and then 4-chloro-6-(1H-pyrazol-1-yl) pyrimidine (43 mg, 238 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give

the title compound. LCMS (ESI+): m/z = 571.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.46 (d, J=2.44 Hz, 1 H) 8.23 (br s, 1 H) 7.72 (d, J=0.98 Hz, 1 H) 7.24 (br s, 1 H) 7.12 (dd, J=8.56, 7.46 Hz, 2 H) 6.78 - 6.89 (m, 4 H) 6.51 (dd, J=2.57, 1.71 Hz, 1 H) 6.46 (d, J=7.34 Hz, 1 H) 4.56 (br s, 1 H) 4.12 - 4.22 (m, 2 H) 3.08 - 3.29 (m, 7 H) 2.54 - 2.74 (m, 5 H) 2.20 - 2.35 (m, 1 H) 2.04 - 2.16 (m, 1 H) 1.73 - 1.88 (m, 6 H).

[00505] Compound 92: ***(S)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl) amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 234 μmol) in 4:1 THF/H_2O (2 mL) was added 4-chloro-2-(trifluoromethyl)pyrimidine (47 mg, 258 μmol) and $NaHCO_3$ (59 mg, 703 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 573.2 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.21 (br d, J=5.75 Hz, 1 H) 7.57 (d, J=7.34 Hz, 1 H) 7.30 (t, J=7.89 Hz, 2 H) 6.92 - 7.07 (m, 3 H) 6.81 (d, J=6.11 Hz, 1 H) 6.63 (d, J=7.21 Hz, 1 H) 4.81 - 4.85 (m, 1 H) 4.38 (br t, J=4.22 Hz, 2 H) 3.70 (br d, J=3.91 Hz, 2 H) 3.34 - 3.60 (m, 6 H) 2.72 - 2.87 (m, 4 H) 2.49 - 2.63 (m, 1 H) 2.28 - 2.44 (m, 1 H) 1.72 - 2.03 (m, 6 H).

[00506] Compound 93: ***(S)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((6-phenylpyrimidin-4-yl) amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 234 μmol) in 4:1 THF/H_2O (2 mL) was added 4-chloro-6-phenylpyrimidine (49 mg, 258 μmol) and $NaHCO_3$ (59 mg, 703 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 581.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.74 (s, 1 H) 7.83 (br d, J=7.21 Hz, 2 H) 7.62 - 7.74 (m, 3 H) 7.57 (d, J=7.34 Hz, 1 H) 7.18 - 7.31 (m, 3 H) 6.93 - 7.03 (m, 3 H) 6.64 (d, J=7.34 Hz, 1 H) 5.09 (br s, 1 H) 4.40 (br s, 2 H) 3.47 - 3.73 (m, 4 H)) 3.38 - 3.46 (m, 2 H) 2.80 (q, J=5.87 Hz, 4 H) 2.65 (br s, 1 H) 2.45 (br s, 1 H) 1.87 - 2.00 (m, 4 H).

[00507] Compound 94: ***(S)-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(pyridin-3-yl) quinazolin-4-yl) amino) butanoic acid:*** To a solution of (S)-2-amino-4-((2-phenoxyethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 216 μmol) in DMA (2 mL) was added DIPEA (188 μL, 1.08 mmol) and then 4-chloro-2-(pyridin-3-yl) quinazoline (57 mg, 238

μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 632.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 9.52 (d, J=1.35 Hz, 1 H) 8.78 (dt, J=7.98, 1.88 Hz, 1 H) 8.58 (dd, J=4.89, 1.71 Hz, 1 H) 8.03 (d, J=8.44 Hz, 1 H) 7.77 - 7.84 (m, 1 H) 7.68 - 7.76 (m, 1 H) 7.46 (dd, J=7.58, 4.52 Hz, 1 H) 7.35 (t, J=8.13 Hz, 1 H) 7.19 (d, J=6.97 Hz, 1 H) 7.01 - 7.09 (m, 2 H) 6.79 (t, J=7.34 Hz, 1 H) 6.71 (d, J=7.82 Hz, 2 H) 6.36 (d, J=7.21 Hz, 1 H) 5.00 (t, J=5.93 Hz, 1 H) 4.10 - 4.21 (m, 2 H) 2.81 - 3.27 (m, 8 H) 2.60 (br d, J=6.72 Hz, 4 H) 2.46 (br s, 1 H) 2.29 (br dd, J=15.04, 4.89 Hz, 1 H) 1.70 - 1.90 (m, 6 H).

[00508] Compound 95: ***(S)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl) amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (160 mg, 432 μmol) and 2-chloro-5-(trifluoromethyl)pyrimidine (87 mg, 475 μmol) in H_2O (0.5 mL) and THF (2 mL) was added $NaHCO_3$ (73 mg, 864 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 517.2. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.62 (s, 2 H) 7.60 (d, *J*=7.50 Hz, 1 H) 6.65 (d, *J*=7.28 Hz, 1 H) 6.33 - 6.64 (m, 1 H) 4.78 (dd, *J*=8.49, 5.18 Hz, 1 H) 3.83 (td, *J*=15.05, 3.42 Hz, 2 H) 3.35 - 3.62 (m, 6 H) 2.76 - 2.88 (m, 4 H) 2.46 - 2.59 (m, 1 H) 2.30 - 2.43 (m, 1 H) 1.74 - 2.02 (m, 6 H).

[00509] Compound 96: ***(S)-2-((5-bromopyrimidin-2-yl) amino)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid.*** To a mixture of (S)-2-amino-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (160 mg, 432 μmol) and 5-bromo-2-chloropyrimidine (84 mg, 475 μmol) in THF (2 mL), H_2O (0.5 mL) was added $NaHCO_3$ (73 mg, 864 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 527.1. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.55 (s, 2 H) 7.59 (d, *J*=7.28 Hz, 1 H) 6.32 - 6.71 (m, 2 H) 4.73 (dd, *J*=8.38, 5.07 Hz, 1 H) 3.82 (td, *J*=14.88, 3.31 Hz, 2 H) 3.35 - 3.60 (m, 6 H) 2.75 - 2.85 (m, 4 H) 2.46 - 2.60 (m, 1 H) 2.29 - 2.43 (m, 1 H) 1.74 - 2.00 (m, 6 H).

[00510] Compound 97: ***(S)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl) amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)

butyl)amino) butanoic acid (160 mg, 432 μmol) and 4-chloro-2-(trifluoromethyl)pyrimidine (87 mg, 475 μmol) in THF (2 mL), H_2O (0.5 mL) was added $NaHCO_3$ (73 mg, 864 μmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 517.2. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.29 (br d, *J*=6.39 Hz, 1 H) 7.60 (d, *J*=7.50 Hz, 1 H) 6.98 - 7.09 (m, 1 H) 6.31 - 6.70 (m, 2 H) 4.85 - 4.91 (m, 1 H) 3.83 (td, *J*=14.94, 3.20 Hz, 2 H) 3.36 - 3.64 (m, 6 H) 2.76 - 2.85 (m, 4 H) 2.49 - 2.62 (m, 1 H) 2.33 - 2.46 (m, 1 H) 1.75 - 1.99 (m, 6 H).

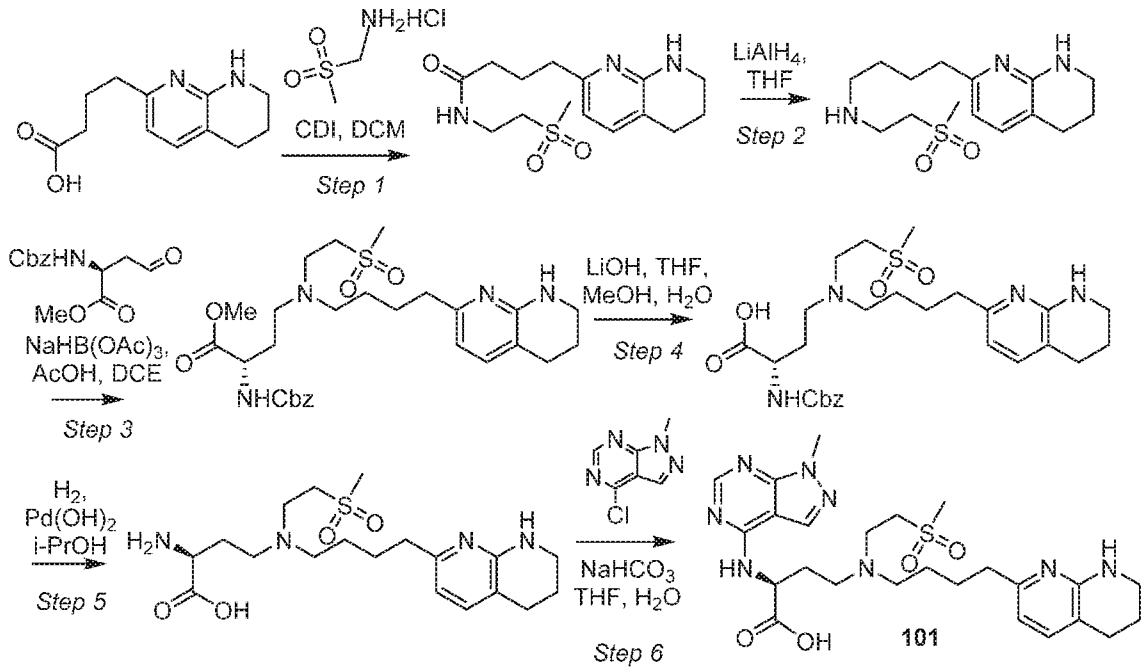
[00511] Compound 98: ***(S)-2-((6-(1H-pyrazol-1-yl) pyrimidin-4-yl) amino)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 270 μmol) and 4-chloro-6-(1H-pyrazol-1-yl) pyrimidine (54 mg, 297 μmol) in DMA (2 mL) was added DIPEA (235 μL, 1.35 mmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 515.2. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.61 (br s, 2 H) 7.93 (s, 1 H) 7.59 (d, *J*=7.28 Hz, 1 H) 7.31 (br s, 1 H) 6.35 - 6.74 (m, 3 H) 4.98 (br s, 1 H) 3.85 (td, *J*=14.99, 3.31 Hz, 2 H) 3.39 - 3.66 (m, 6 H) 2.75 - 2.87 (m, 4 H) 2.36 - 2.70 (m, 2 H) 1.75 - 2.01 (m, 6 H).

[00512] Compound 99: ***(S)-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(pyridin-3-yl) quinazolin-4-yl) amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2,2-difluoroethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 270 μmol) and 4-chloro-2-(pyridin-3-yl) quinazoline (72 mg, 297 μmol) in DMA (2 mL) was added DPIEA (235 μL, 1.35 mmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 576.3. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 9.88 (d, *J*=1.76 Hz, 1 H) 9.52 (d, *J*=8.38 Hz, 1 H) 9.16 (d, *J*=5.51 Hz, 1 H) 8.73 (d, *J*=8.38 Hz, 1 H) 8.35 (dd, *J*=8.27, 5.84 Hz, 1 H) 8.12 - 8.21 (m, 2 H) 7.88 - 7.96 (m, 1 H) 7.59 (d, *J*=7.28 Hz, 1 H) 6.36 - 6.69 (m, 2 H) 5.54 (dd, *J*=8.60, 5.51 Hz, 1 H) 3.59 - 3.93 (m, 4 H) 3.40 - 3.54 (m, 4 H) 2.65 - 2.88 (m, 6 H) 1.75 - 2.01 (m, 6 H).

[00513] Compound 100: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(pyridin-3-yl) quinazolin-4-yl) amino) butanoic acid:*** To a mixture of (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-

naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 264 µmol) in DMA (2 mL) was added DIPEA (171 mg, 1.32 mmol) and 4-chloro-2-(pyridin-3-yl) quinazoline (70 mg, 291 µmol) and the resulting mixture was heated to 100° C for 2 h and then allowed to cool to rt and concentrated *in vacuo*. The resulting crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 584.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 9.57 (s, 1 H) 8.85 (br d, *J*=7.95 Hz, 1 H) 8.63 (d, *J*=4.40 Hz, 1 H) 8.16 (d, *J*=8.19 Hz, 1 H) 7.77 - 7.90 (m, 2 H) 7.51 - 7.59 (m, 2 H) 7.12 (br d, *J*=7.34 Hz, 1 H) 6.32 (d, *J*=7.21 Hz, 1 H) 3.75 (br s, 1 H) 3.37 - 3.49 (m, 1 H) 3.27 (s, 5 H) 2.88 - 3.25 (m, 6 H) 2.64 (br t, *J*=5.93 Hz, 2 H) 2.45 - 2.57 (m, 3 H) 2.32 (br dd, *J*=14.79, 5.14 Hz, 1 H) 1.77 - 1.86 (m, 2 H) 1.71 (br s, 4 H) 1.10 - 1.20 (m, 3 H).

Scheme 9, Compound 101:



[00514] Step 1: ***N-(2-(methylsulfonyl)ethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanamide:*** To a mixture of 4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanoic acid (20 g, 63.56 mmol) in DCM (400 mL) was added CDI (11.34 g, 69.92 mmol) at 0° C and the resulting mixture was stirred at rt for 1 h, at which time, 2-(methylsulfonyl)ethanamine hydrochloride (11.16 g, 69.92 mmol) was added and stirred at rt for an additional 2 h. The mixture was diluted with H_2O and the layers were separated. The aqueous layer was extracted with DCM and the combine organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was re-dissolved in EtOAc (80 mL) and then heated to reflux, at which time, hexanes (20 mL) was added and the mixture was cooled to rt causing

a precipitate to form. The solid was filtered and the filtrate was concentrated *in vacuo* to give the title compound. LCMS (ESI+): m/z = 325.9 $(M+H)^+$.

[00515] Step 2: ***N-(2-(methylsulfonyl)ethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butan-1-amine:*** To a solution of $LiAlH_4$ (1.28 g, 33.80 mmol) in THF (20 mL) at 0° C was added N-(2-(methylsulfonyl)ethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butanamide (5 g, 15.36 mmol) and the resulting mixture was heated to reflux for 12 h and then cooled to rt. The mixture carefully neutralized by the addition of H_2O (1.3 mL), 1 M aq. NaOH (1.3 mL), then H_2O (1.3 mL) again, followed by drying over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure to give the title compound that was used without further purification. LCMS (ESI+): m/z = 311.9 $(M+H)^+$.

[00516] Step 3: ***(S)-methyl 2-(((benzyloxy)carbonyl)amino)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate***: To a mixture of N-(2-(methylsulfonyl)ethyl)-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butan-1-amine (3 g, 9.63 mmol) and (S)-methyl 2-(((benzyloxy)carbonyl)amino)-4-oxobutanoate (2.56 g, 9.63 mmol) in DCE (30 mL) at 0° C was added AcOH (862 µL, 14.45 mmol) then $NaBH(OAc)_3$ (3.06 g, 14.45 mmol) and the resulting mixture was stirred at rt for 1hr. The mixture was diluted with MeOH and then concentrated under reduced pressure. The crude residue was taken up in DCM and sat. aq. $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with DCM and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by normal phase silica gel chromatography to give the title compound. LCMS (ESI+): m/z = 561.4 $(M+H)^+$.

[00517] Step 4: ***(S)-2-(((benzyloxy)carbonyl)amino)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a mixture of (S)-methyl 2-(((benzyloxy)carbonyl)amino)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoate (1 g, 1.78 mmol) in 1:1:1 THF/MeOH/H_2O (9 mL) was added $LiOH.H_2O$ (150 mg, 3.57 mmol) and the resulting mixture was stirred at rt for 1 h. The mixture was adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 547.2 $(M+H)^+$.

[00518] Step 5: ***(S)-2-amino-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***: To a solution of (S)-2-(((benzyloxy)carbonyl)amino)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (1 g, 1.71 mmol) in *i*-PrOH (20 mL) was added 20 wt% $Pd(OH)_2/C$ (241 mg) and the resulting mixture was stirred under an

H_2 atmosphere for 12 h. The mixture was filtered and concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 413.1 $(M+H)^+$.

[00519] Step 6: ***(S)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl) amino)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 242) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (61 mg, 727) followed by 4-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine (49 mg, 291 μmol) and the resulting mixture was stirred at 70° C for 18 h and then allowed to cool to rt and then adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 545.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.61 (s, 1 H) 8.50 (s, 1 H) 7.59 (d, *J*=7.28 Hz, 1 H) 6.67 (d, *J*=7.50 Hz, 1 H) 5.10 (br dd, *J*=8.05, 5.18 Hz, 1 H) 4.10 (s, 3 H) 3.70 - 3.90 (m, 4 H) 3.53 - 3.68 (m, 2 H) 3.49 - 3.53 (m, 2 H) 3.35 - 3.43 (m, 2 H) 3.13 (s, 3 H) 2.77 - 2.86 (m, 4 H) 2.53 - 2.77 (m, 2 H) 1.77 - 2.00 (m, 6 H).

[00520] **Compound 102:** ***(S)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((5-(trifluoromethyl)pyrimidin-2-yl) amino) butanoic acid:*** To a solution of (S)-2-amino-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 242 μmol) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (61 mg, 727 μmol) followed by 2-chloro-5-(trifluoromethyl)pyrimidine (53 mg, 291 μmol) and the resulting mixture was stirred at 70° C for 18 h and then allowed to cool to rt and then adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 559.2 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.60 (s, 2 H) 7.59 (br d, *J*=7.21 Hz, 1 H) 6.65 (d, *J*=7.34 Hz, 1 H) 4.77 (br dd, *J*=8.01, 4.95 Hz, 1 H) 3.67 - 3.82 (m, 4 H) 3.49 - 3.54 (m, 2 H) 3.32 - 3.49 (m, 4 H) 3.13 (s, 3 H) 2.75 - 2.86 (m, 4 H) 2.46 - 2.58 (m, 1 H) 2.36 (br s, 1 H) 1.92 - 1.99 (m, 2 H) 1.84 (br s, 4 H).

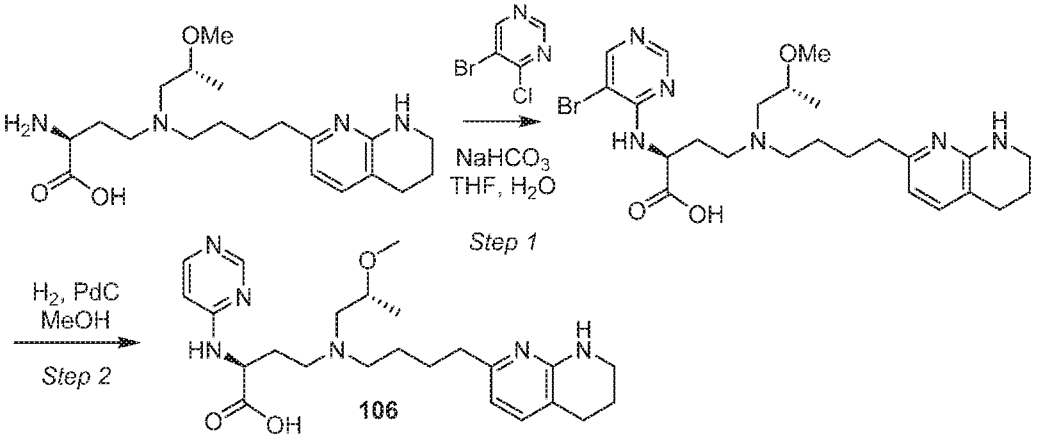
[00521] **Compound 103:** ***(S)-2-((5-bromopyrimidin-2-yl) amino)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 242 μmol) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (61 mg, 727 μmol), followed by 5-bromo-2-chloro-pyrimidine (51 mg, 291 μmol) and the resulting mixture was stirred at 70° C for 18 h and then allowed to

cool to rt and then adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 569.0 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.44 - 8.56 (m, 2 H) 7.59 (d, *J*=7.28 Hz, 1 H) 6.66 (d, *J*=7.28 Hz, 1 H) 4.68 - 4.77 (m, 1 H) 3.68 - 3.82 (m, 4 H) 3.49 - 3.55 (m, 2 H) 3.32 - 3.49 (m, 4 H) 3.13 (s, 3 H) 2.76 - 2.87 (m, 4 H) 2.46 - 2.58 (m, 1 H) 2.28 - 2.43 (m, 1 H) 1.96 (q, *J*=5.90 Hz, 2 H) 1.83 (br s, 4 H).

[00522] Compound 104: ***(S)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(trifluoromethyl)pyrimidin-4-yl) amino) butanoic acid:*** To a mixture of (S)-2-amino-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 242 µmol) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (61 mg, 727 µmol) followed by 4-chloro-2-(trifluoromethyl)pyrimidine (53 mg, 291 µmol) and the resulting mixture was stirred at 70° C for 18 h and then allowed to cool to rt and then adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 559.1 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.26 (br d, *J*=5.95 Hz, 1 H) 7.59 (d, *J*=7.28 Hz, 1 H) 6.92 (d, *J*=6.39 Hz, 1 H) 6.65 (d, *J*=7.50 Hz, 1 H) 4.83 - 4.87 (m, 1 H) 3.69 - 3.80 (m, 4 H) 3.49 - 3.53 (m, 2 H) 3.32 - 3.49 (m, 4 H) 3.12 (s, 3 H) 2.81 (dt, *J*=12.29, 6.31 Hz, 4 H) 2.48 - 2.59 (m, 1 H) 2.30 - 2.42 (m, 1 H) 1.92 - 2.00 (m, 2 H) 1.83 (br s, 4 H).

[00523] Compound 105: ***(S)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl) amino) butanoic acid***: To a solution of (S)-2-amino-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 231 µmol) in THF (2 mL) and H_2O (0.5 mL) was added $NaHCO_3$ (58 mg, 693 µmol), and then 4-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine (43 mg, 254 µmol) and the resulting mixture was stirred at 70° C for 1 h and then allowed to cool to rt. The mixture was adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 529.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.63 (s, 1 H) 8.50 (s, 1 H) 7.59 (d, *J*=7.28 Hz, 1 H) 6.67 (d, *J*=7.50 Hz, 1 H) 5.15 - 5.34 (m, 1 H) 5.08 (br dd, *J*=8.49, 5.40 Hz, 1 H) 4.10 (s, 3 H) 3.63 - 3.74 (m, 4 H) 3.49 - 3.63 (m, 4 H) 3.41 (s, 5 H) 2.76 - 2.88 (m, 4 H) 2.55 - 2.73 (m, 2 H) 1.75 - 2.02 (m, 6 H).

Scheme 10, Compound 106:



[00524] Step1: ***(S)-2-((5-bromopyrimidin-4-yl)amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid:*** To a solution of (S)-2-amino-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (200 mg, 482 µmol) and 5-bromo-4-chloropyrimidine (102 mg, 530 µmol) in THF (4 mL) and H_2O (1 mL) was added $NaHCO_3$ (202 mg, 2.4 mmol) and the resulting mixture was stirred at 70° C for 2 h and then cooled to rt and concentrated *in vacuo* to give the title compound that was used without further purification. LCMS (ESI+): m/z = 535.3 $(M+H)^+$.

[00525] Step 2: ***(S)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-(pyrimidin-4-ylamino) butanoic acid:*** To a solution of (S)-2-((5-bromopyrimidin-4-yl) amino)-4-(((R)-2-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid (150 mg, 280 µmol) in MeOH (2 mL) was added 10 wt% Pd/C (297 mg) and the resulting mixture was stirred under an H_2 atmosphere for 15 h. The mixture was filtered and concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 457.3 $(M+H)^+$. ^1H NMR (400 MHz, Methanol-d_4) δ ppm 8.41 (s, 1 H) 8.03 (br d, *J*=6.11 Hz, 1 H) 7.21 (d, *J*=7.34 Hz, 1 H) 6.63 (br d, *J*=5.99 Hz, 1 H) 6.43 (d, *J*=7.34 Hz, 1 H) 4.43 (br s, 1 H) 3.76 (br s, 1 H) 3.37 - 3.42 (m, 3 H) 3.35 (s, 3 H) 2.91 - 3.18 (m, 5 H) 2.72 (t, *J*=6.11 Hz, 2 H) 2.60 (br s, 2 H) 2.21 - 2.34 (m, 1 H) 2.03 - 2.15 (m, 1 H) 1.89 (dt, *J*=11.74, 5.99 Hz, 2 H) 1.73 (br s, 4 H) 1.20 (d, *J*=6.11 Hz, 3 H).

[00526] **Compound 107:** ***(S)-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(pyridin-3-yl) quinazolin-4-yl) amino) butanoic acid:*** To a solution of (S)-2-amino-4-((2-(methylsulfonyl)ethyl) (4-(5,6,7,8-tetrahydro-1,8-

naphthyridin-2-yl) butyl)amino) butanoic acid (100 mg, 242 µmol) in DMA (2 mL) was added DIPEA (210 µL, 1.21 mmol) and 4-chloro-2-(pyridin-3-yl) quinazoline (59 mg, 242 µmol and the resulting mixture was stirred at 100° C for 2 h and then allowed to cool to rt and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound.). LCMS (ESI+): m/z = 618.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 9.57 (d, *J*=1.47 Hz, 1 H) 8.84 (dt, *J*=8.04, 1.85 Hz, 1 H) 8.61 (dd, *J*=4.89, 1.71 Hz, 1 H) 8.12 (d, *J*=7.70 Hz, 1 H) 7.83 - 7.88 (m, 1 H) 7.76 - 7.82 (m, 1 H) 7.48 - 7.55 (m, 2 H) 7.34 (d, *J*=7.34 Hz, 1 H) 6.45 (d, *J*=7.34 Hz, 1 H) 5.05 (t, *J*=6.05 Hz, 1 H) 3.26 - 3.31 (m, 2 H) 3.24 (t, *J*=5.56 Hz, 2 H) 3.01 - 3.17 (m, 2 H) 2.84 - 2.93 (m, 4 H) 2.61 - 2.77 (m, 7 H) 2.36 - 2.46 (m, 1 H) 2.22 - 2.32 (m, 1 H) 1.76 - 1.91 (m, 4 H) 1.57 - 1.72 (m, 2 H).

[00527] Compound 108: ***(S)-2-((6-(1H-pyrazol-1-yl) pyrimidin-4-yl) amino)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid***: To a mixture of 4-chloro-6-(1H-pyrazol-1-yl) pyrimidine (50 mg, 277 µmol) in DMA (2 mL) and was added DIPEA (201 µL, 1.15 mmol) then (S)-2-amino-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 231 µmol) and the resulting mixture was stirred at 70° C for 18 h and then allowed to cool to rt and then adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 541.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 8.49 (br s, 1 H) 8.28 (br s, 1 H) 7.72 (s, 1 H) 7.26 (br s, 1 H) 6.87 (s, 1 H) 6.42 - 6.53 (m, 2 H) 4.76 (br s, 1 H) 4.66 (br s, 1 H) 3.46 - 3.59 (m, 2 H) 3.32 - 3.32 (m, 3 H) 2.90 (br s, 2 H) 2.65 (br d, *J*=6.60 Hz, 10 H) 2.19 (br s, 1 H) 2.09 (br d, *J*=5.01 Hz, 1 H) 1.82 (br s, 4 H) 1.62 (br d, *J*=6.72 Hz, 2 H).

[00528] Compound 109: ***(S)-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino)-2-((2-(pyridin-3-yl) quinazolin-4-yl) amino) butanoic acid:*** To a mixture of 4-chloro-2-(pyridin-3-yl) quinazoline (67 mg, 277 µmol) in DMA (2 mL) and was added DIPEA (201 µL, 1.15 mmol) then (S)-2-amino-4-(((S)-2-fluoro-3-methoxypropyl) (4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) butyl)amino) butanoic acid hydrochloride (100 mg, 231 µmol) and the resulting mixture was stirred at 70° C for 18 h and then allowed to cool to rt and then adjusted to pH = 6 by the addition of 1 M aq. HCl and then concentrated *in vacuo*. The crude residue was purified by reverse phase *prep*-HPLC to give the title compound. LCMS (ESI+): m/z = 602.3 $(M+H)^+$. ^{1}H NMR (400 MHz, Methanol-d_4) δ ppm 9.56 (d, *J*=1.47 Hz, 1 H) 8.83 (dt, *J*=8.04, 1.85 Hz, 1 H) 8.60 (dd, *J*=4.89, 1.59 Hz, 1 H)

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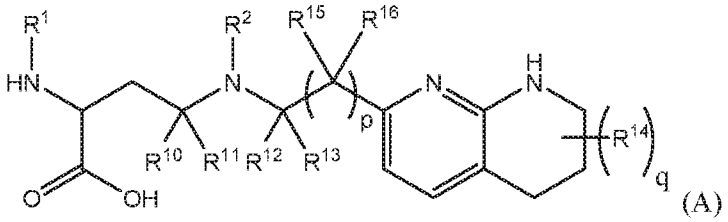
CLAIMS

What is claimed as new and desired to be protected by Letters Patent of the United States 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:

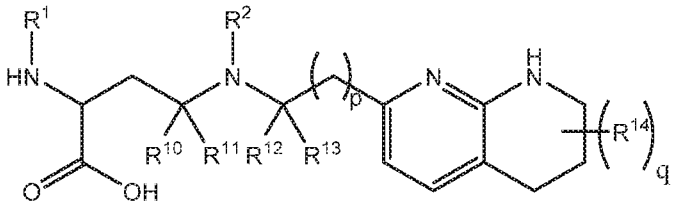
R^2 is C_1-C_6 alkyl optionally substituted by R^{2a}; C_3-C_6 cycloalkyl optionally substituted by R^{2b}; 3- to 12-membered heterocyclyl optionally substituted by R^{2c}; or $-S(O)_2R^{2d}$;

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;

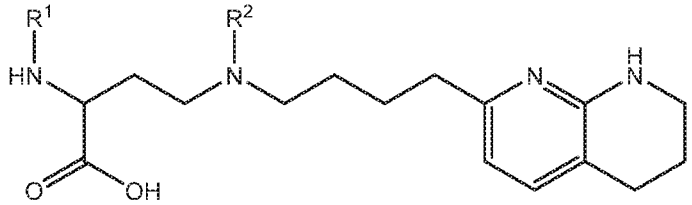
wherein the compound of Formula (A) is represented by Formula (I):



(I).

3. The dosage form of claim 1 or claim 2, or a salt thereof, 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}, R^{13}, or R^{14} is deuterium.

4. The dosage form of claim 1 or claim 2, or a salt thereof, wherein R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are hydrogen; p is 3; and wherein the compound of Formula (A) is represented by the compound of formula (II):



(II).

5. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is 5- to 10-membered heteroaryl optionally substituted by R^{1a}.

6. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is:

pyrimidinyl, quinazolinyl, pyrazolopyrimidinyl, pyrazinyl, quinolinyl, pyridopyrimidinyl, thienopyrimidinyl, pyridinyl, pyrrolopyrimidinyl, quinoxalinyl, indazolyl, benzothiazolyl, naphthalenyl, purinyl, or isoquinolinyl; and

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.

7. The dosage form of any one of claims 1-4, or a salt thereof, 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

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.

8. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is pyrimidin-4-yl optionally substituted by R^{1a}.

9. The dosage form of claim any one of claims 1-4, or a salt thereof, 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.

10. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is pyrimidin-4-yl optionally substituted by pyrazolyl, methyl, difluoromethyl, or trifluoromethyl.

11. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is pyrimidin-4-yl substituted by both methyl and trifluoromethyl.

12. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is quinazolin-4-yl optionally substituted by R^{1a}.

13. The dosage form of any one of claims 1-4, or a salt thereof, 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.

14. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is quinazolin-4-yl optionally substituted by fluoro, chloro, methyl, trifluoromethyl or methoxy.

15. The dosage form of any one of claims 1 or 3-14, or a salt thereof, 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 $-S(O)_2R^3$.

16. The dosage form of any one of claims 1 or 3-14, or a salt thereof, 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; that is

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

17. The dosage form of any one of claims 1-14, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by R^{2a}.

18. The dosage form of any one of claims 1-14, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} wherein R^{2a} is: halogen; C_3-C_8 cycloalkyl optionally substituted by halogen; 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl; -NR^4R^5; -$NR^3C(O)R^4$; -$S(O)_2R^3$; or oxo.

19. The dosage form of any one of claims 1-14, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by R^{2a} wherein R^{2a} is: fluoro; cyclobutyl substituted by fluoro; pyrazolyl substituted by methyl; or -$S(O)_2CH_3$.

20. The dosage form of any one of claims 1-14, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by -OR^3.

21. The dosage form of any one of claims 1-14, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is: hydrogen; C_1-C_6 alkyl optionally substituted by halogen; C_3-C_6 cycloalkyl optionally substituted by halogen; C_6-C_{14} aryl optionally substituted by halogen; or 5- to 6-membered heteroaryl optionally substituted by halogen or C_1-C_6 alkyl.

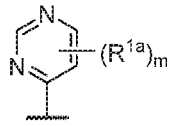
22. The dosage form of any one of claims 1-14, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is: hydrogen; methyl; ethyl; difluoromethyl; -CH_2CHF_2; -CH_2CF_3; cyclopropyl substituted by fluoro; phenyl optionally substituted by fluoro; or pyridinyl optionally substituted by fluoro or methyl.

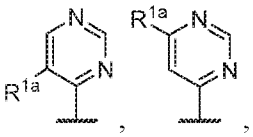
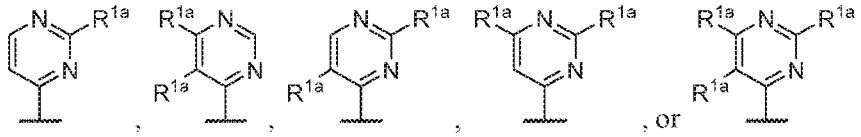
23. The dosage form of any one of claims 1 to 14, or a salt thereof, wherein R^2 is –$CH_2CH_2OCH_3$.

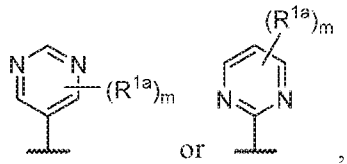
24. The dosage form of any one of claims 1 to 14, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by both halogen and OR^3, wherein R^3 is C_1-C_6 alkyl.

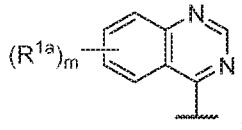
25. The dosage form of any one of claims 1 to 14, or a salt thereof, wherein R^2 is C_3-C_6 cycloalkyl optionally substituted by R^{2b}.

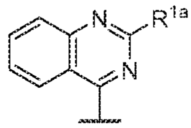
26. The dosage form of any one of claims 1 to 14, or a salt thereof, wherein R^2 is cyclopropyl.

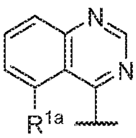
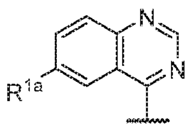
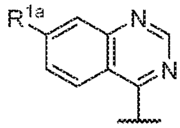
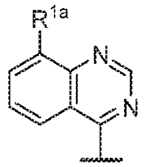
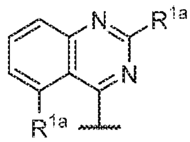
27. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

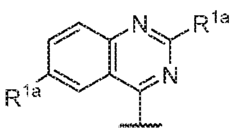
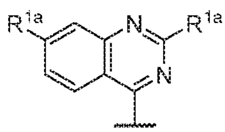
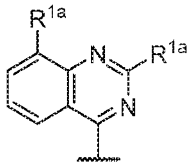
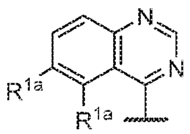
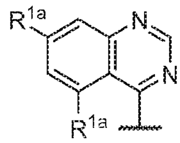
28. The dosage form of claim 27, or a salt thereof, wherein R^1 is  ,  , or , wherein each R^{1a} is independently deuterium, alkyl, haloalkyl, or heteroaryl.

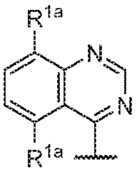
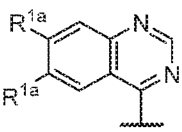
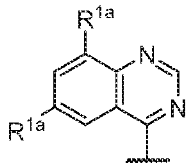
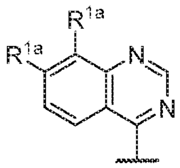
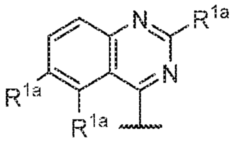
29. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, or 3 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

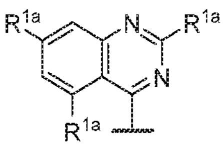
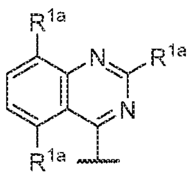
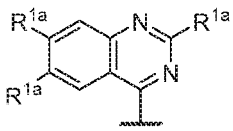
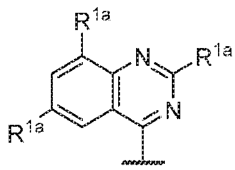
30. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is  , wherein m is 0, 1, 2, 3, 4, or 5 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

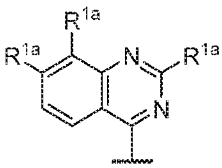
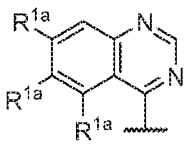
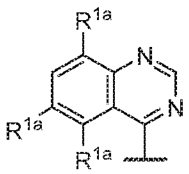
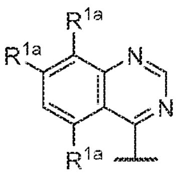
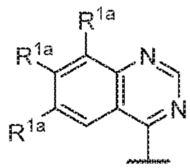
31. The dosage form of claim 30, or a salt thereof, wherein R^1 is  ,

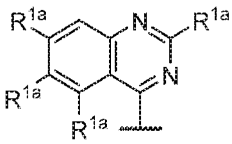
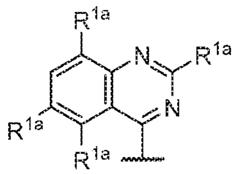
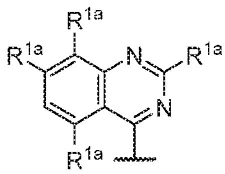
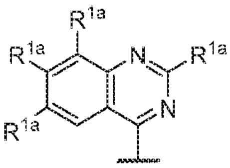
 ,  ,  ,  ,  ,

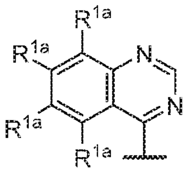
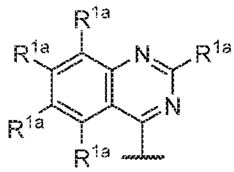
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

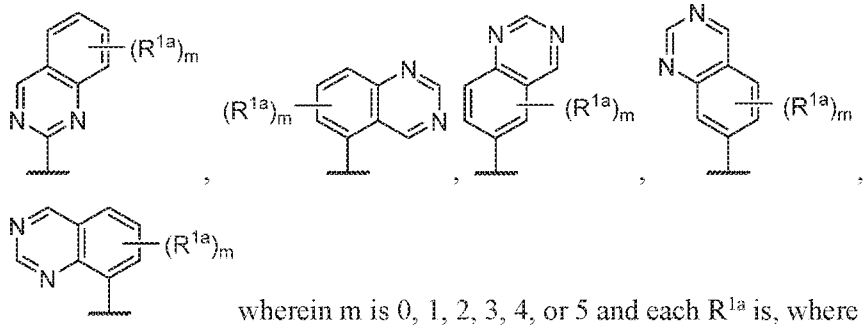
 ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,

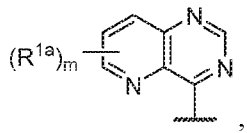
 , or  , wherein each R^{1a} is independently deuterium, halogen, alkyl, haloalkyl, or alkoxy.

32. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is



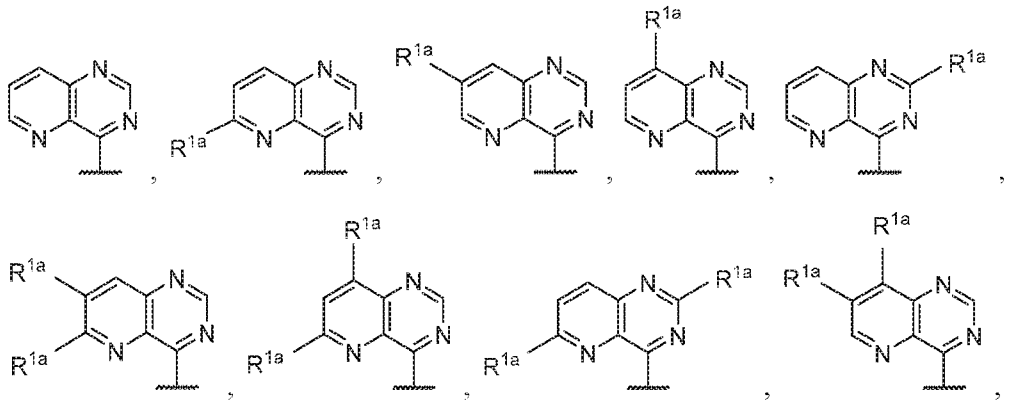
wherein m is 0, 1, 2, 3, 4, or 5 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

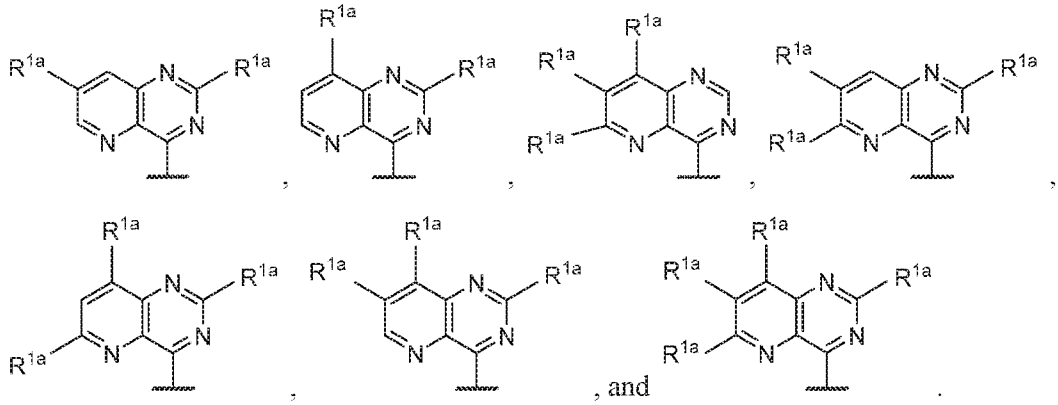
33. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is



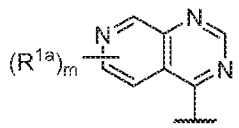
, wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

34. The dosage form of claim 33, or a salt thereof, wherein R^1 is selected from the group consisting of



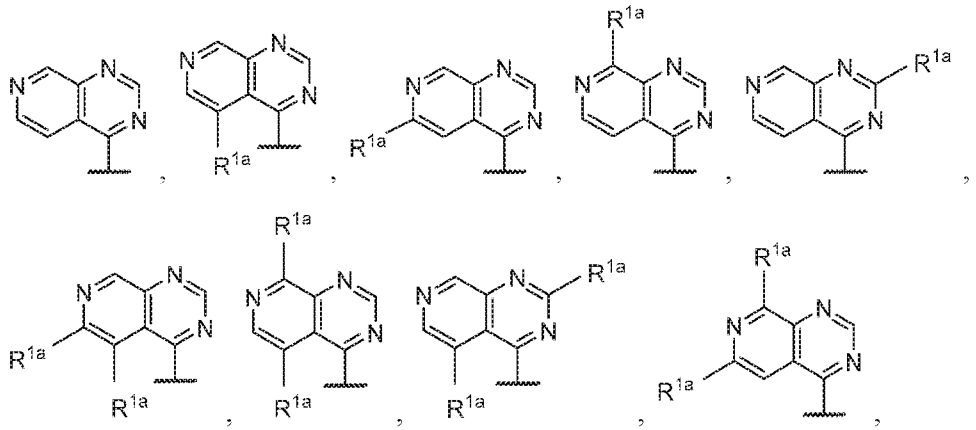


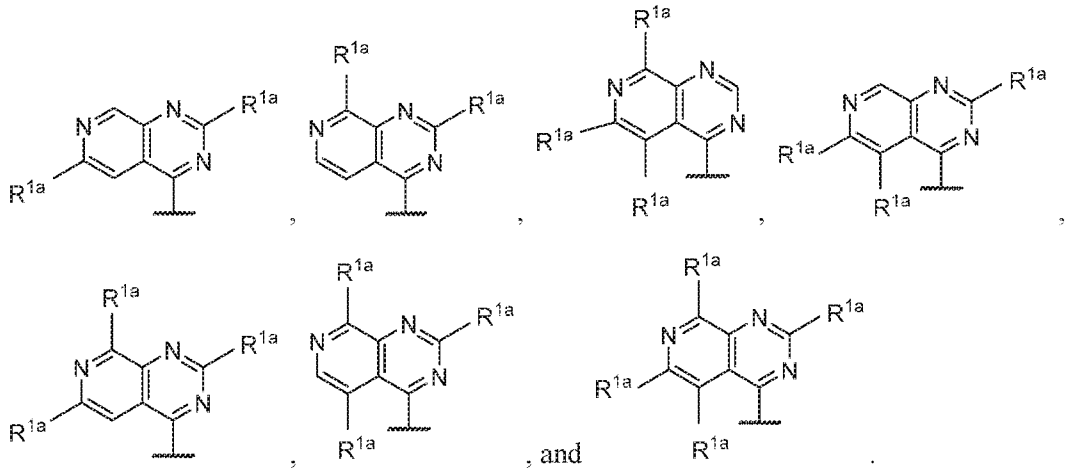
35. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is



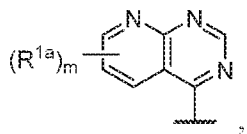
, wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

36. The dosage form of claim 35, or a salt thereof, wherein R^1 is selected from the group consisting of



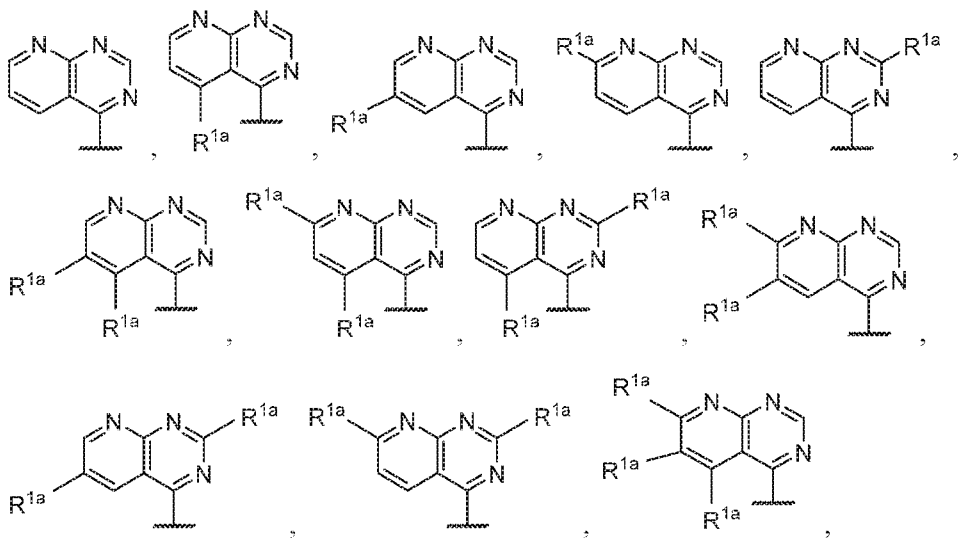


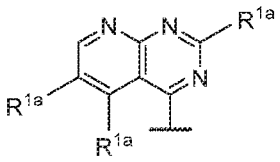
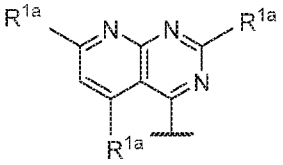
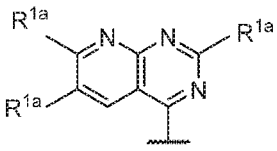
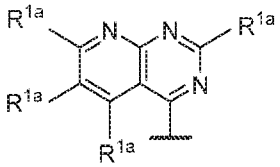
37. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is



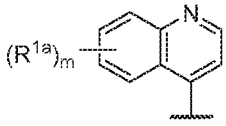
, wherein m is 0, 1, 2, 3, or 4, and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

38. The dosage form of claim 37, or a salt thereof, wherein R^1 is selected from the group consisting of

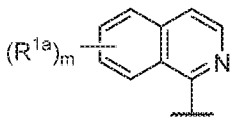





, and


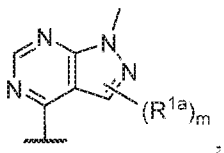
39. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is

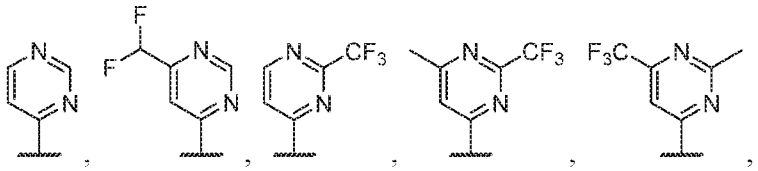
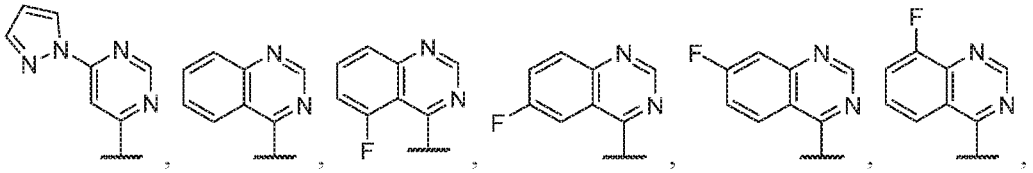
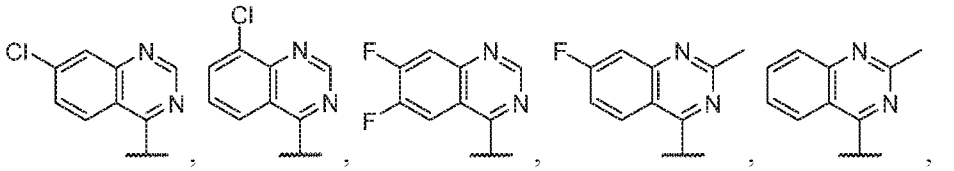
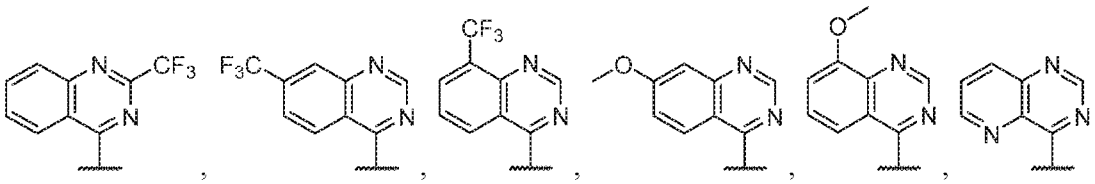
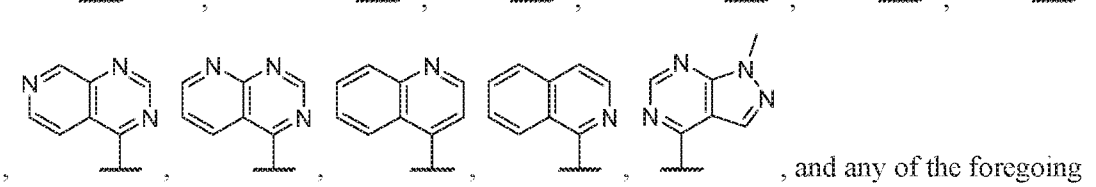
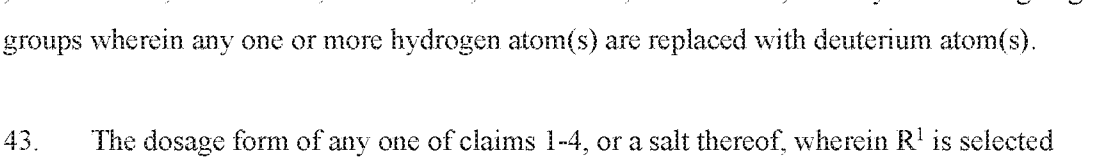

, wherein m is 0, 1, 2, 3, 4, 5, or 6 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

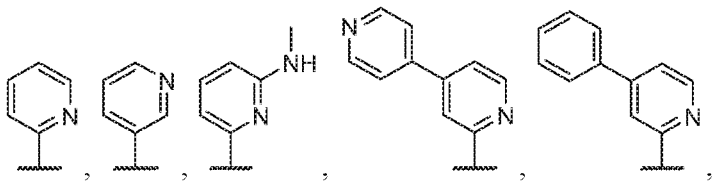
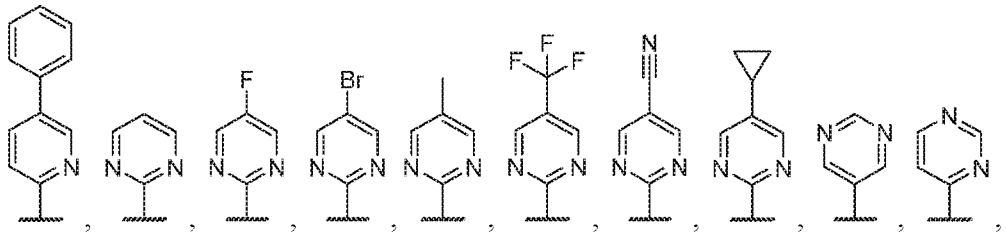
40. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is

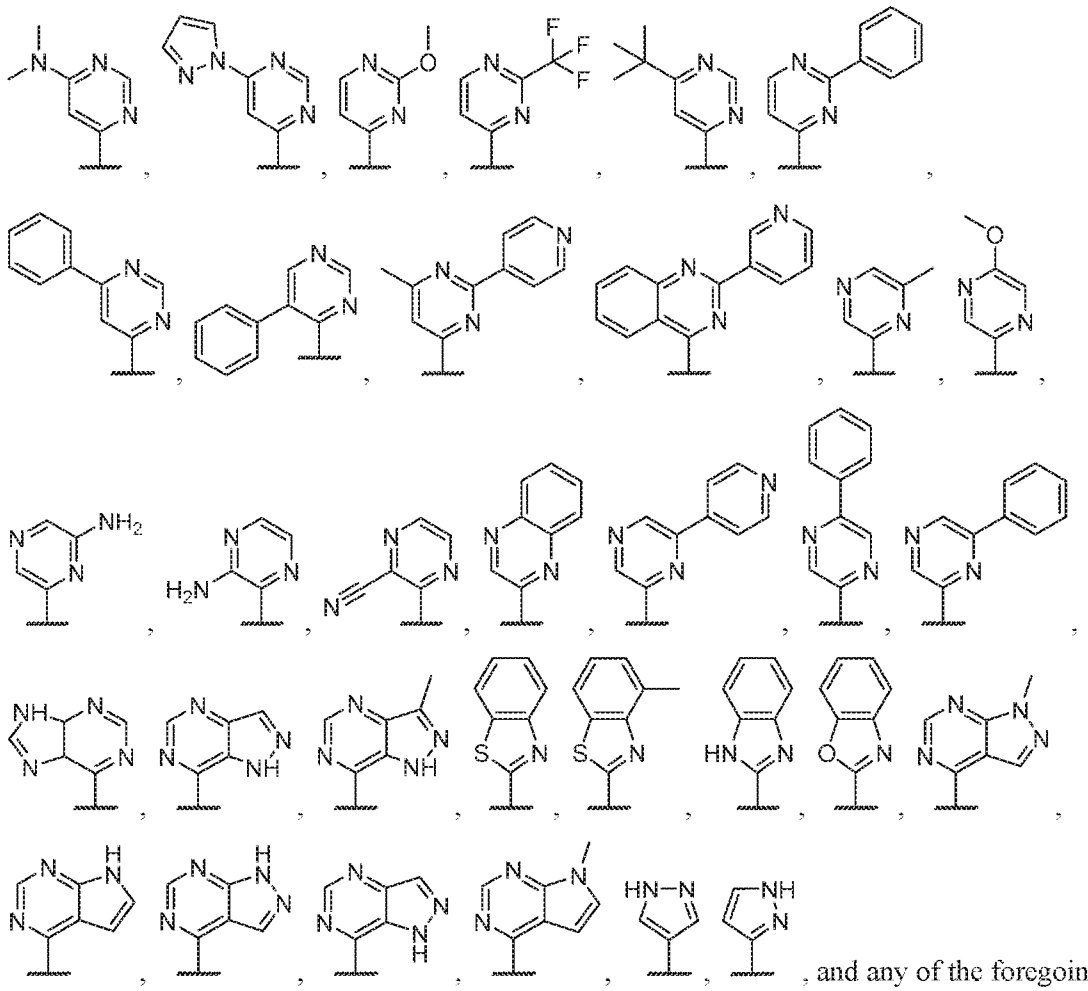

, wherein m is 0, 1, 2, 3, 4, 5, or 6 and each R^{1a} is, where applicable, independently deuterium, halogen, alkyl, haloalkyl, alkoxy, hydroxy, -CN, or heteroaryl, wherein the alkyl, haloalkyl, alkoxy, hydroxy, and heteroaryl of R^{1a} are independently optionally substituted by deuterium.

41. The dosage form of any one of claims 1-4, or a salt thereof, wherein 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.

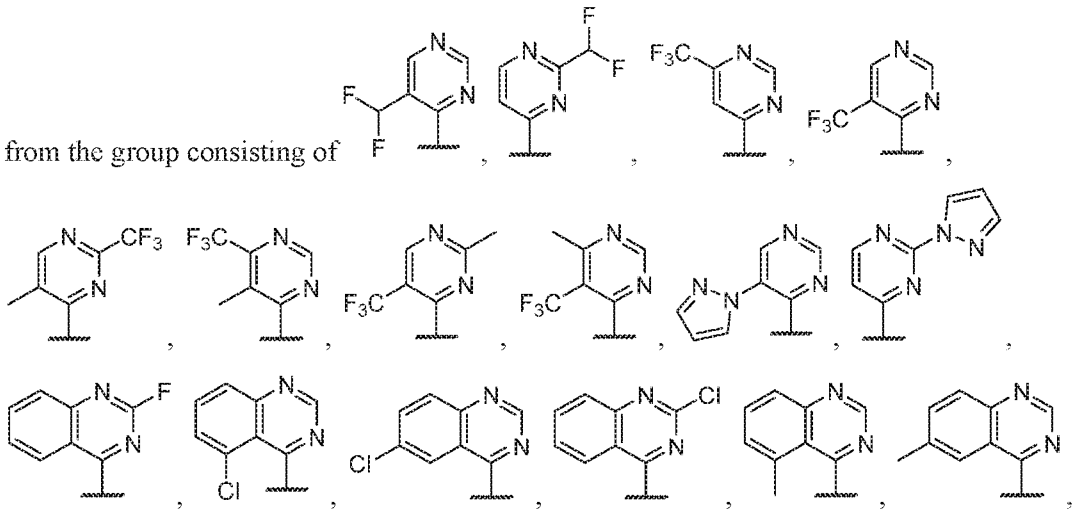
42. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is selected from the group consisting of  ,  ,  ,  ,  ,  , and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s).

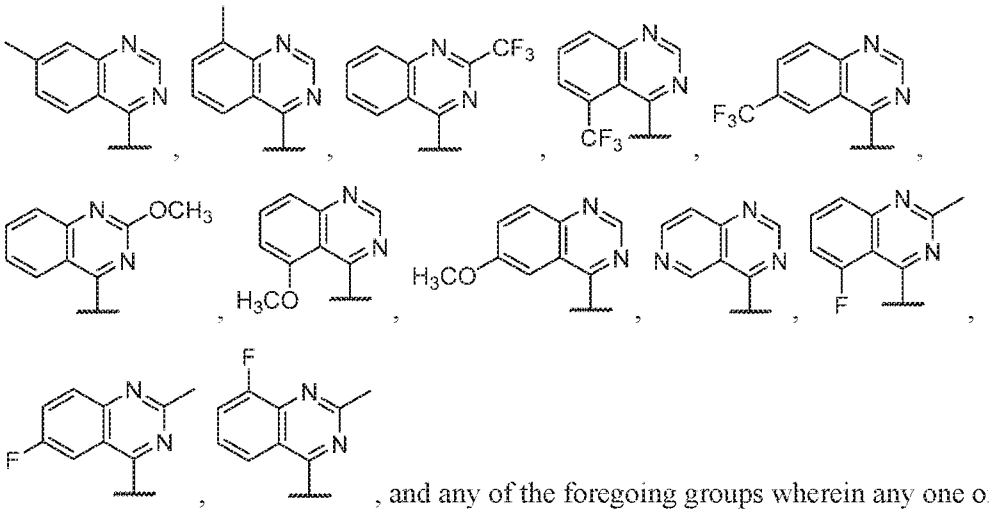
43. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is selected from the group consisting of  ,  .



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

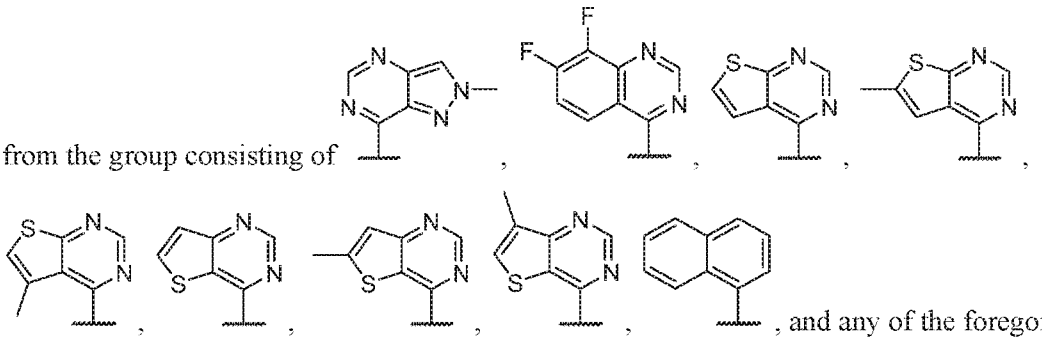
44. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is selected from the group consisting of





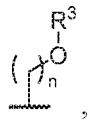
, and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s).

45. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is selected from the group consisting of



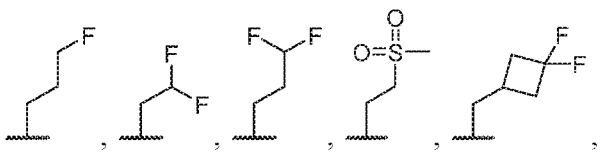
, and any of the foregoing groups wherein any one or more hydrogen atom(s) are replaced with deuterium atom(s).

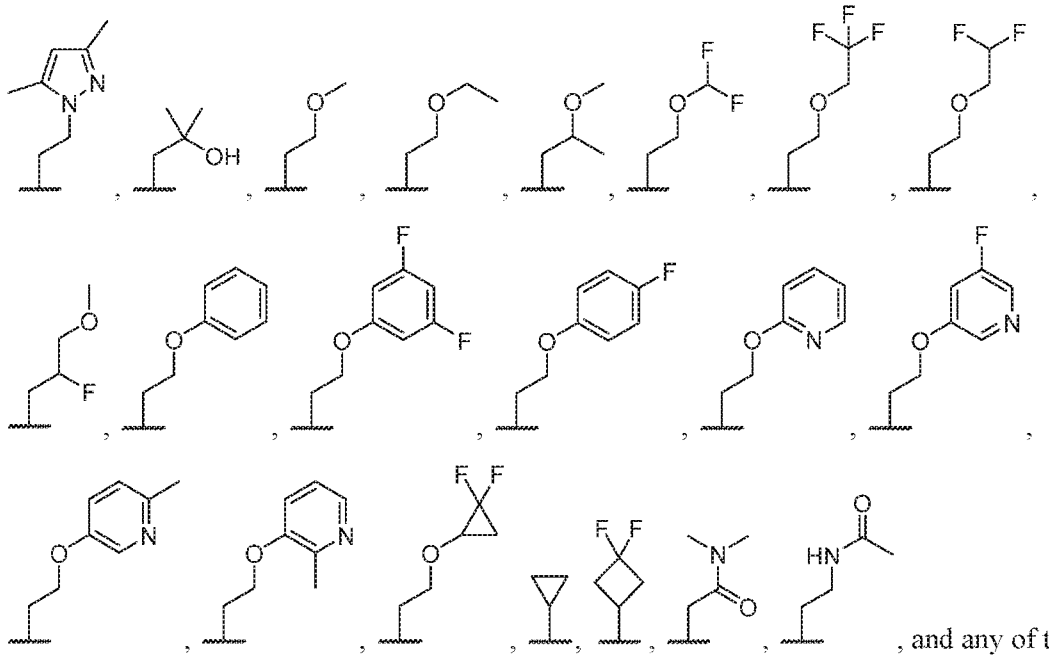
46. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is



, 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.

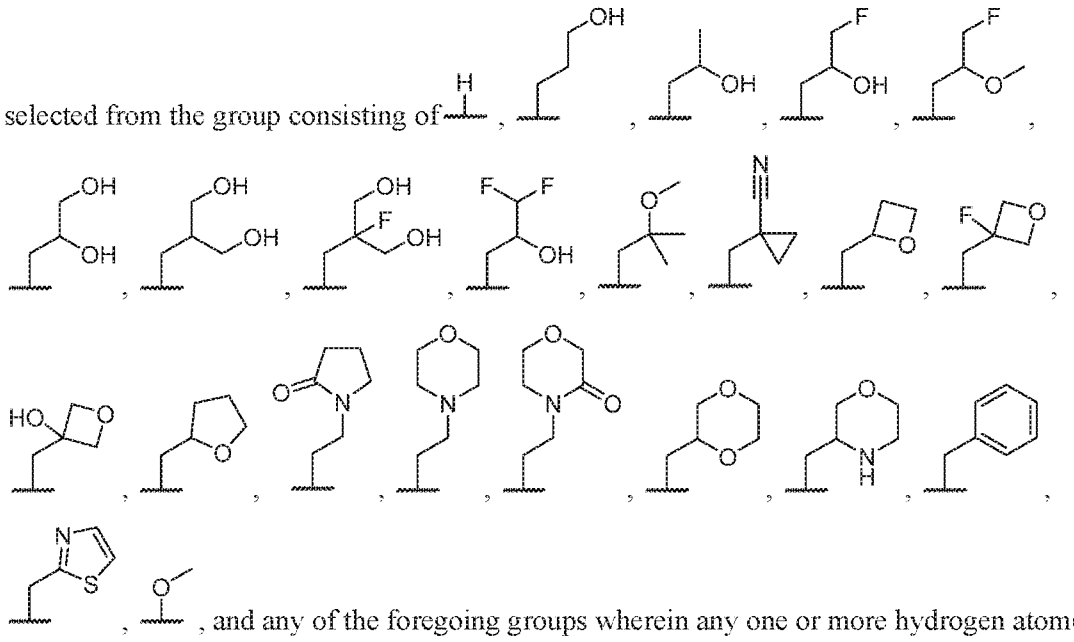
47. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is selected from the group consisting of





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

48. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, 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).

49. The dosage form of any one of claims 1 to 11, or a salt thereof, wherein R^2 is C_3-C_5 alkyl substituted by both fluorine and -OCH_3.

50. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is phenyl optionally substituted by fluorine.

51. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl optionally substituted by -OR^3, and R^3 is pyridinyl optionally substituted by fluorine or methyl.

52. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is halogen.

53. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is deuterium.

54. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 3- to 12-membered heterocyclyl optionally substituted by oxo.

55. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 4- to 5-membered heterocyclyl optionally substituted by oxo.

56. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is C_6-C_{14} aryl optionally substituted by halogen or –OR^6.

57. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is phenyl optionally substituted by halogen or –OR^6.

58. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is 5- to 10-membered heteroaryl optionally substituted by C_1-C_6 alkyl.

59. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is pyrazolyl optionally substituted by methyl.

60. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is C_3-C_8 cycloalkyl optionally substituted by -CN, halogen, or $-OR^6$.

61. The dosage form of any one of claims 1 to 14 or 27-45, or a salt thereof, wherein R^2 is C_1-C_6 alkyl substituted by R^{2a} wherein R^{2a} is $-S(O)_2R^3$.

62. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is pyridyl optionally substituted by R^{1a}.

63. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is indazolyl optionally substituted by R^{1a}.

64. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is 1*H*-pyrrolopyridyl optionally substituted by R^{1a}.

65. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is quinolinyl optionally substituted by R^{1a}.

66. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is phenyl optionally substituted by R^{1a}.

67. The dosage form of any one of claims 1-4, or a salt thereof, wherein R^1 is indanyl optionally substituted by R^{1a}.

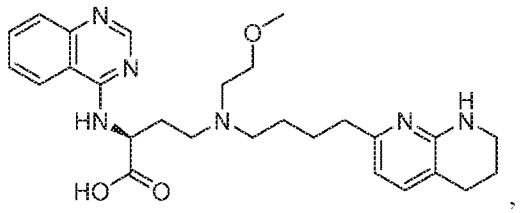
68. A dosage form configured for daily administration, comprising a pharmaceutically acceptable carrier or excipient and a unit dose of a compound, or a salt thereof, selected from Compound Nos. 1-66 in **FIG. 1**.

69. A dosage form configured for daily administration, comprising a pharmaceutically acceptable carrier or excipient and a unit dose of a compound, or a salt thereof, selected from Compound Nos. 1-147.

70. A dosage form configured for daily administration, comprising a pharmaceutically acceptable carrier or excipient and a unit dose of a compound, or a salt thereof, selected from Compound Nos. 1-665.

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

72. 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.

73. The dosage form of any one of claims 1-72, comprising about 1, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, or 125 mg of the compound, or a range between any two of the preceding values.

74. The dosage form of any one of claims 1-72, 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.

75. The dosage form of any one of claims 1-72, 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.

76. The dosage form of any one of claims 1-72, 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.

77. A method of treating a fibrotic disease in an individual in need thereof comprising administering the dosage form of any one of claims 1 to 76 or a pharmaceutically acceptable salt thereof daily to the individual.

78. The method of claim 77, wherein the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis, cardiac fibrosis, kidney fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis.

79. The method of claim 78, wherein the fibrotic disease is liver fibrosis, cardiac fibrosis, primary sclerosing cholangitis, or biliary fibrosis.

80. The method of any one of claims 77-79, wherein the daily administering is given one time, two times, three times, or four times daily.

81. The method of any one of claims 77-79, wherein the daily administering is given once daily.

82. The method of claim 77, comprising administering the dosage form to the individual 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.

83. The method of claim 77, comprising administering the dosage form to the individual 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.

84. A kit comprising a dosage form of any one of claims 1 to 76.

85. The kit of claim 84, further comprising instructions for the treatment of a fibrotic disease.

86. The kit of claim 84, further comprising instructions for daily administration of the dosage form to an individual in need thereof.

87. The kit of claim 84, further comprising instructions for administration of the dosage form to an individual in need thereof one, two, three, or four times daily.

88. The kit of claim 84, further comprising instructions for administration of the dosage form to an individual in need thereof once daily.

89. The kit of claim 84, further comprising 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, or 1400, or a range between any two of the preceding concentrations.

90. The kit of claim 84, further comprising 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.

91. A method of inhibiting $\alpha v\beta_6$ or $\alpha v\beta_1$ integrin in an individual comprising administering the dosage form of any one of claims 1 to 76 or a pharmaceutically acceptable salt thereof.

92. The method of claim 91, comprising administering the dosage form to the individual 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, or 1400, or a range between any two of the preceding concentrations.

93. The method of claim 91, comprising administering the dosage form to the individual 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.

94. A method of inhibiting TGFβ activation in a cell comprising administering to the cell the dosage form of any one of claims 1 to 76 or a pharmaceutically acceptable salt thereof.

95. The method of claim 94, comprising administering the dosage form to the cell 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, or 1400, or a range between any two of the preceding concentrations.

96. The method of claim 94, comprising administering the dosage form to the cell 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.

97. The dosage form of any of claims 1-76 or a salt thereof for use in inhibiting $\alpha v\beta_6$ or $\alpha v\beta_1$ integrin, the use comprising administering the dosage form to an individual in need thereof in an amount effective to inhibit the $\alpha v\beta_6$ or $\alpha v\beta_1$ integrin.

98. The dosage form of claim 97, the use comprising administering the dosage form to the individual 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.

99. The dosage form of claim 97, the use comprising administering the dosage form to the individual 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.

100. A method of modulating the activity of at least one integrin in a subject in need thereof, comprising administering to the subject an amount of the dosage form of any one of claims 1-76 or a pharmaceutically acceptable salt thereof effective 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.

101. The method of claim 100, comprising inhibiting the activity of one or both of $\alpha v\beta_1$ integrin and $\alpha v\beta_6$ integrin in the subject.

102. The method of claim 100 or claim 101, 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 method 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.

103. The method of claim 100 or claim 101, wherein the subject has or is at risk of psoriasis, and wherein the method 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.

104. The method of claim 100 or claim 101, wherein the subject is in need of treatment for NASH, the amount of the dosage form administered to the subject being effective to inhibit the activity of at least $\alpha v\beta_1$ integrin, thereby treating the subject for NASH.

105. The method of claim 100 or claim 101, the subject being in need of treatment for IPF, the amount of the dosage form administered to the subject being effective to inhibit the activity of at least $\alpha v\beta_6$ integrin, thereby treating the subject for IPF.

106. The method of claim 100 or claim 101, the subject being in need of treatment for PSC, the amount of the dosage form administered to the subject being 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.

107. The method of claim 100 or 101, comprising administering the dosage form to the individual 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.

108. The method of claim 100 or 101, comprising administering the dosage form to the individual 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.

109. A method of treating a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form of any one of claims 1-76, 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.

110. The method of claim 109, wherein the method 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.

111. The method of claim 109, wherein the method 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.

112. The method of claim 109, wherein the method reduces both $\alpha v\beta_1$ integrin and $\alpha v\beta_6$ integrin activity and/or expression compared to at least one other αv-containing integrin in the subject.

113. The method of claim 110 or 111, wherein the activity of $\alpha v\beta_1$ integrin in one or more fibroblasts is reduced in the subject.

114. The method of claim 110 or 111, wherein the activity of $\alpha v\beta_6$ integrin in one or more epithelial cells is reduced in the subject.

115. The method of any one of claims 109-114, 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.

116. The method of any one of claims 109-115, wherein the tissue has an elevated pSMAD2/SMAD2 value or an elevated pSMAD3/SMAD3 value compared to the healthy state of the tissue.

117. The method of any one of claims 109-115, comprising administering the dosage form to the subject 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.

118. The method of claim 91, comprising administering the dosage form to the individual 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.

119. A method of characterizing the antifibrotic activity of a small molecule in a subject, comprising:

providing a first live cell sample from the subject, the first live cell sample characterized by the presence of at least one integrin capable of activating transforming growth factor β (TGF-β) from latency associated peptide-TGF-β;

determining a first pSMAD/SMAD value in the first live cell sample;

administering the small molecule to the subject;

providing a second live cell sample from the subject, the second live cell sample being drawn from the same tissue in the subject as the first live cell sample;

determining a second pSMAD/SMAD value in the second live cell sample;

characterizing the antifibrotic activity of the small molecule in the subject by comparing the second pSMAD/SMAD value to the first pSMAD/SMAD value.

120. The method of claim 119, wherein each live cell sample is a plurality of cells derived from a tissue of the subject, or a plurality of macrophages associated with the tissue of the subject.

121. The method of claim 120, wherein the tissue comprises one of: lung tissue, liver tissue, skin tissue, cardiac tissue, kidney tissue, gastrointestinal tissue, gall bladder tissue, and bile duct tissue.

122. The method of claim 120, wherein each live cell sample comprises a plurality of alveolar macrophages derived from a bronchoalveolar lavage fluid of the subject.

123. The method of claim 120, the method further comprising conducting a bronchoalveolar lavage on a lung of the subject effective to produce a bronchoalveolar lavage fluid that comprises the plurality of macrophages as a plurality of alveolar macrophages.

124. The method of claim 120, wherein the subject has 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.

125. The method of claim 120, wherein the subject has psoriasis.

126. The method of claim 119, wherein the at least one integrin comprises α_V.

127. The method of claim 119, wherein the at least one integrin comprises $\alpha_V\beta_1$.

128. The method of claim 119, wherein the at least one integrin comprises $\alpha_V\beta_6$.

129. The method of claim 119, wherein:
determining the first pSMAD/SMAD value in the at least one live cell comprises determining a pSMAD2/SMAD2 value or a pSMAD3/SMAD3 value; and

determining the second pSMAD/SMAD value in the at least one live cell after contacting the at least one live cell with the small molecule comprises determining a pSMAD2/SMAD2 value or a pSMAD3/SMAD3 value.

130. The method of any one of claims 119-128, the administering the small molecule to the subject being effective to produce a C_{max} of the small molecule in 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.

131. The method of any one of claims 119-128, the administering the small molecule to the subject being effective to produce a C_{max} in ng/mL in the subject, the C_{max} corresponding to a 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.

132. The method of any one of claims 119-131, the administering the small molecule to the subject comprising administering the dosage form of any one of claims 1-76 to the subject.

133. A method of treating a fibrotic disease in a subject in need thereof, comprising:
providing a first live cell sample from the subject, the first live cell sample having at least one integrin capable of activating transforming growth factor β (TGF-β) from latency associated peptide-TGF-β;

determining a first pSMAD/SMAD value in the first live cell sample;

administering a small molecule to the subject;

providing a second live cell sample from the subject, the second live cell sample being drawn from the same tissue in the subject as the first live cell sample;

determining a second pSMAD/SMAD value in the second live cell sample;

comparing the second pSMAD/SMAD value to the first pSMAD/SMAD value; and

administering the small molecule to the subject if the second pSMAD/SMAD value is lower than the first pSMAD/SMAD value.

134. The method of claim 133, wherein each live cell sample is a plurality of cells derived from a tissue of the subject, or a plurality of macrophages associated with the tissue of the subject.

135. The method of claim 134, wherein the tissue comprises one of: lung tissue, liver tissue, skin tissue, cardiac tissue, kidney tissue, gastrointestinal tissue, gall bladder tissue, and bile duct tissue.

136. The method of claim 134, wherein each live cell sample comprises a plurality of alveolar macrophages derived from a bronchoalveolar lavage fluid of the subject.

137. The method of claim 134, the method further comprising conducting a bronchoalveolar lavage on a lung of the subject effective to produce a bronchoalveolar lavage fluid that comprises the plurality of macrophages as a plurality of alveolar macrophages.

138. The method of claim 134, the subject characterized by having 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.

139. The method of claim 134, the subject characterized by having psoriasis.

140. The method of claim 134, wherein the at least one integrin comprises αv.

141. The method of claim 133, wherein the at least one integrin comprises $\alpha v\beta_1$.

142. The method of claim 133, wherein the at least one integrin comprises $\alpha v\beta_6$.

143. The method of claim 133, wherein:
determining the first pSMAD/SMAD value in the first live cell sample comprises determining a pSMAD2/SMAD2 value or a pSMAD3/SMAD3 value; and
determining the second pSMAD/SMAD value in the at least one live cell after contacting the first live cell sample with the small molecule comprises determining a pSMAD2/SMAD2 value or a pSMAD3/SMAD3 value.

144. The method of any one of claims 133-143, the administering the small molecule to the subject being effective to produce a C_{max} of the small molecule in 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.

145. The method of any one of claims 133-143, the administering the small molecule to the subject being effective to produce a C_{max} in ng/mL in the subject, the C_{max} corresponding to a 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.

146. The method of any one of claims 133-145, the administering the small molecule to the subject comprising administering the dosage form of any one of claims 1-76 to the subject.

147. A method of treating a fibrotic disease in an individual in need thereof, comprising administering to the individual an amount of a 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, the compound being the compound recited in any of claims 1-76.

148. A method of treating a fibrotic disease in an individual in need thereof, comprising administering to the individual an amount of a 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, the compound being the compound recited in any of claims 1-76.

149. A method of treating a fibrotic disease in an individual in need thereof, comprising administering to the individual an amount of a compound 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 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, the compound being the compound recited in any of claims 1-76.

FIG. 1

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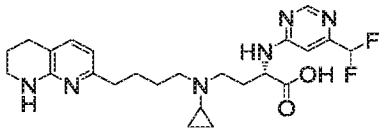
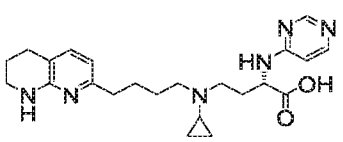
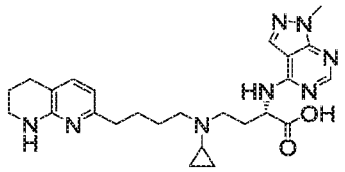
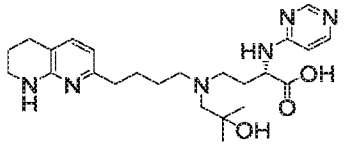
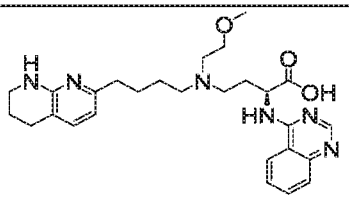
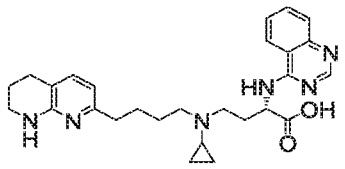
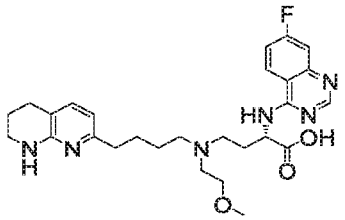
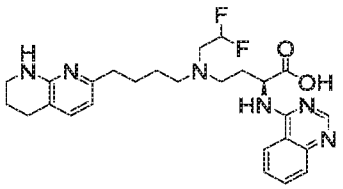
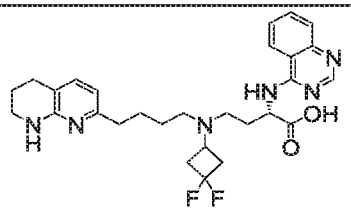
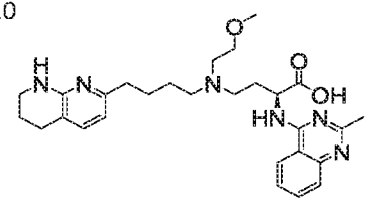
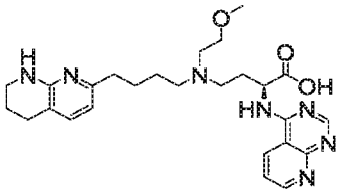
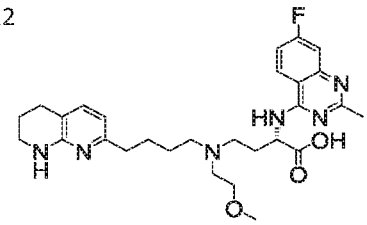
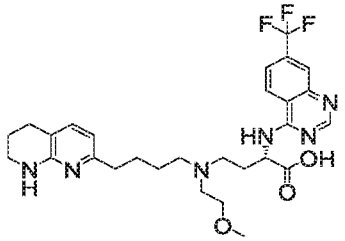
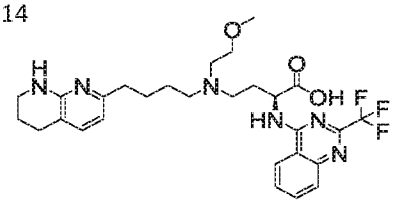
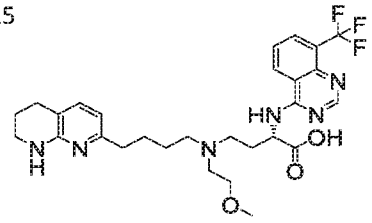
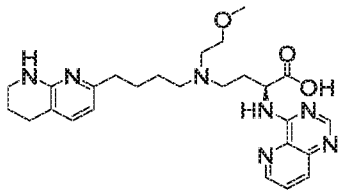
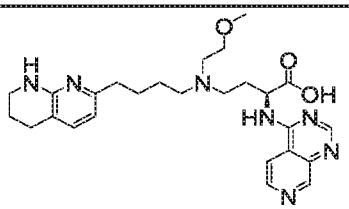
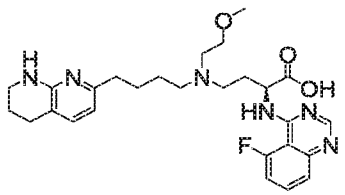
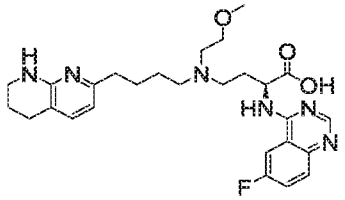
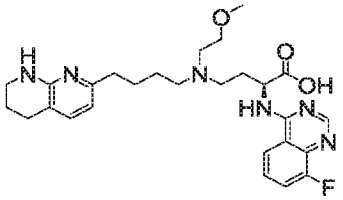
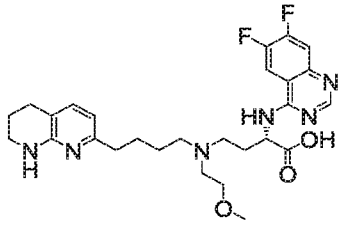
1 	2 	3 
4 	5 	6 
7 	8 	9 
10 	11 	12 
13 	14 	15 
16 	17 	18 
19 	20 	21 

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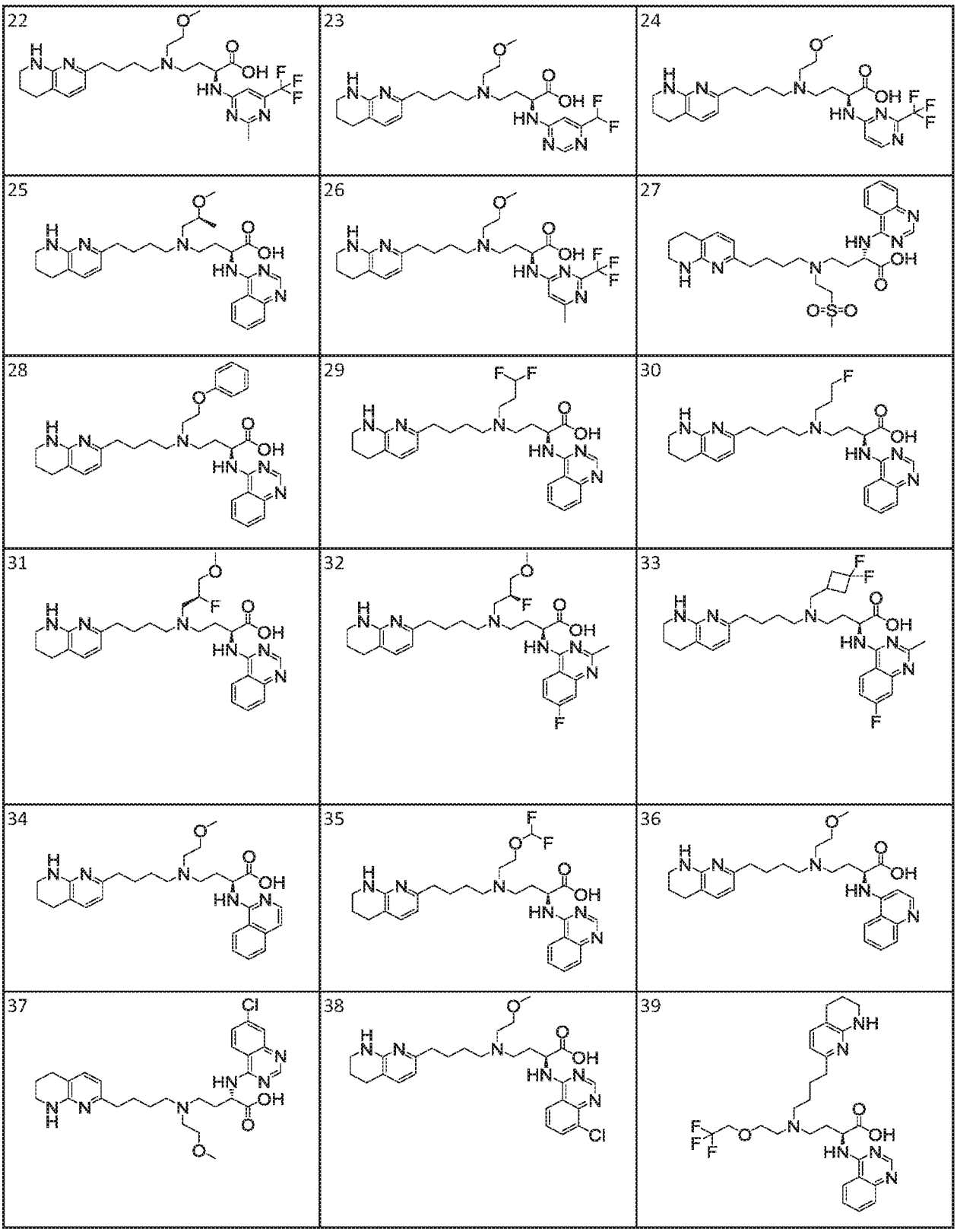

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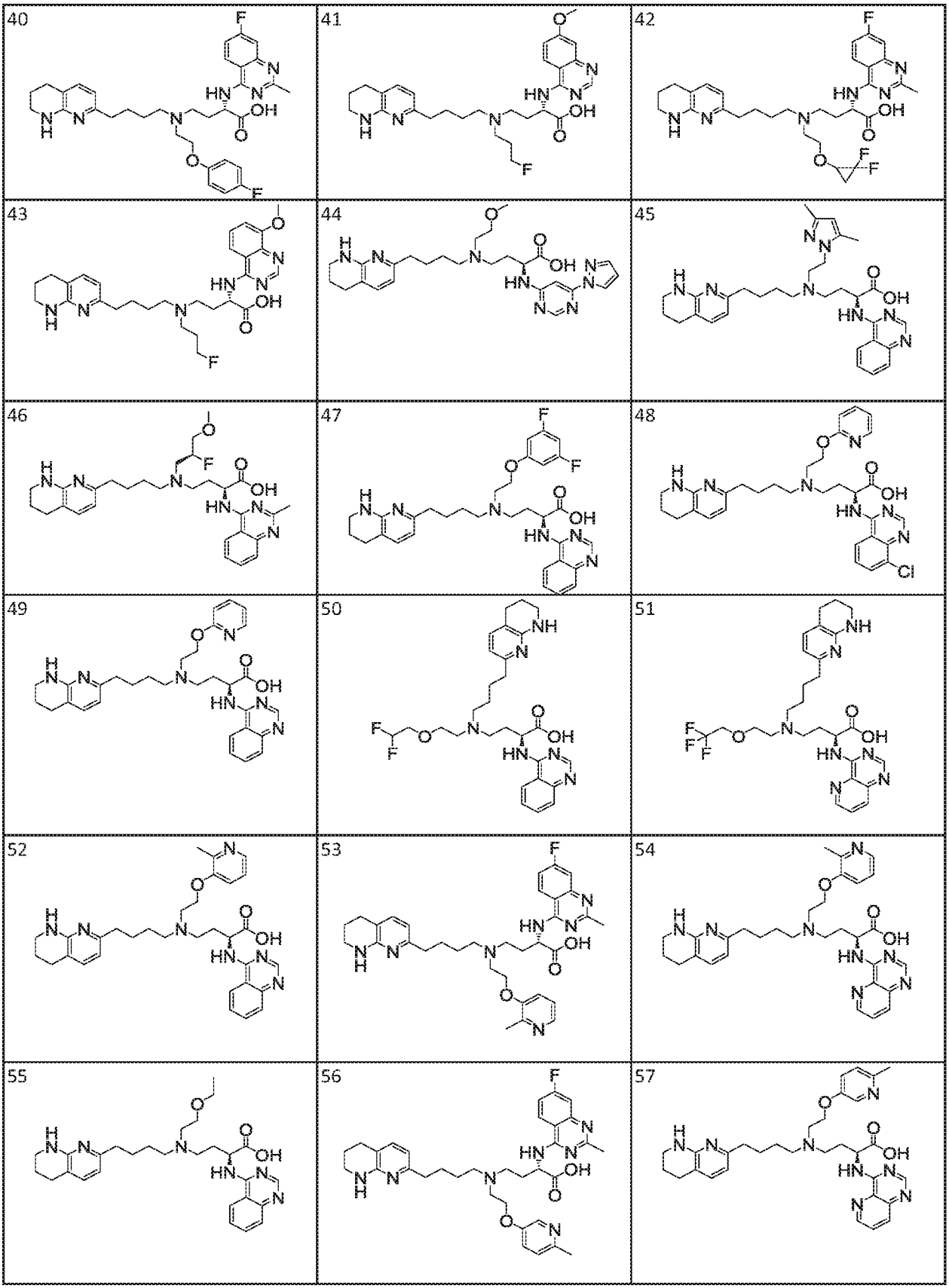

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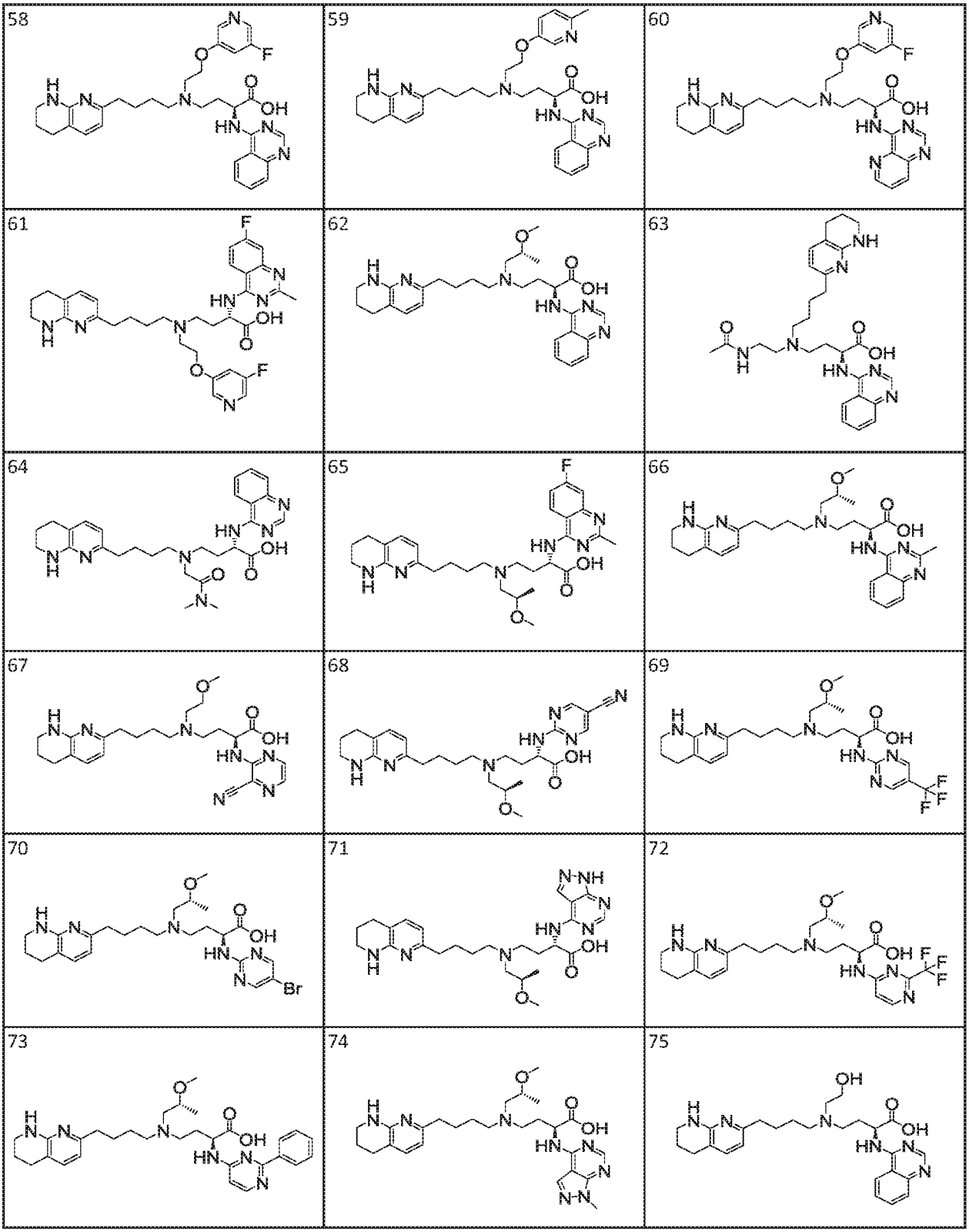

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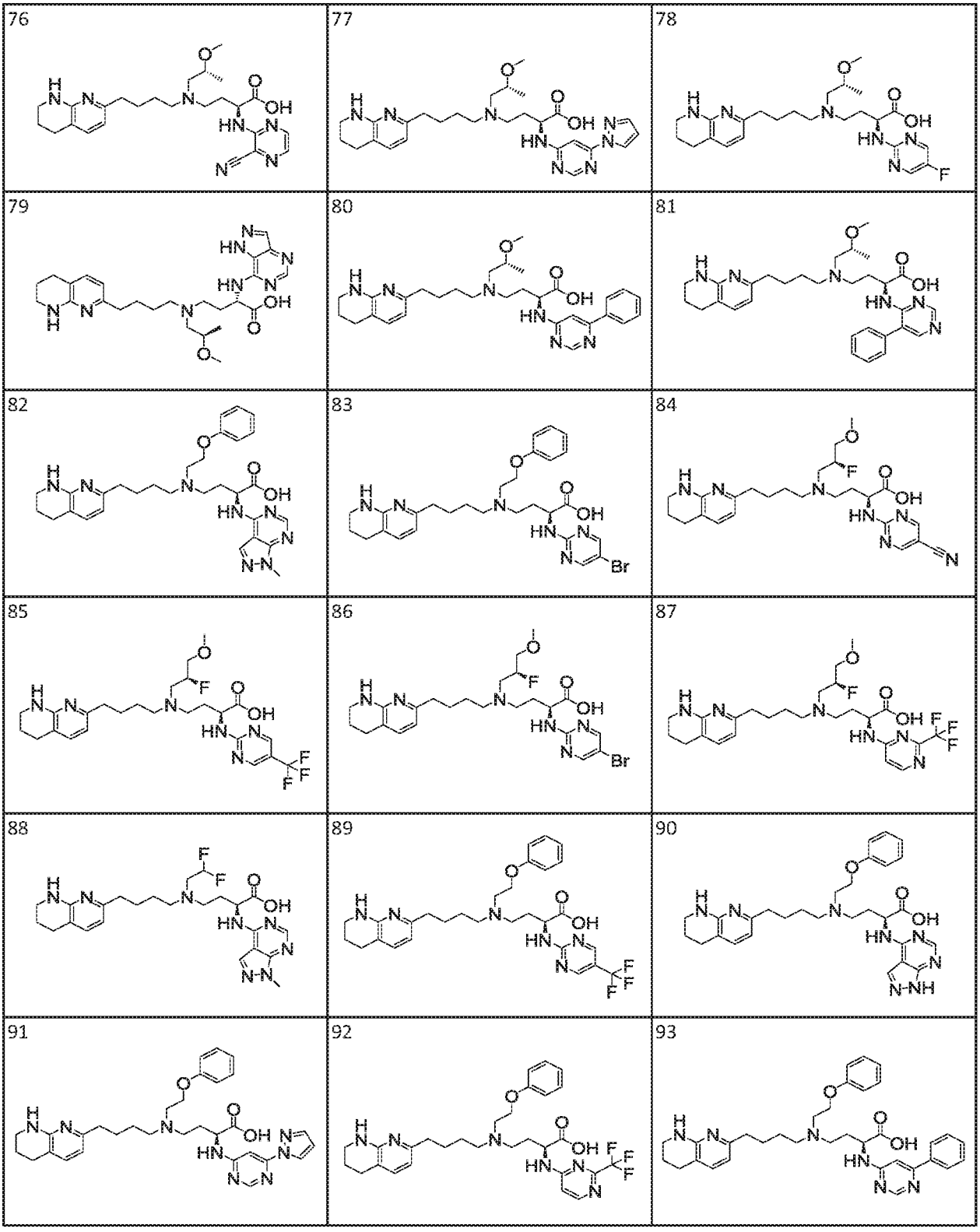

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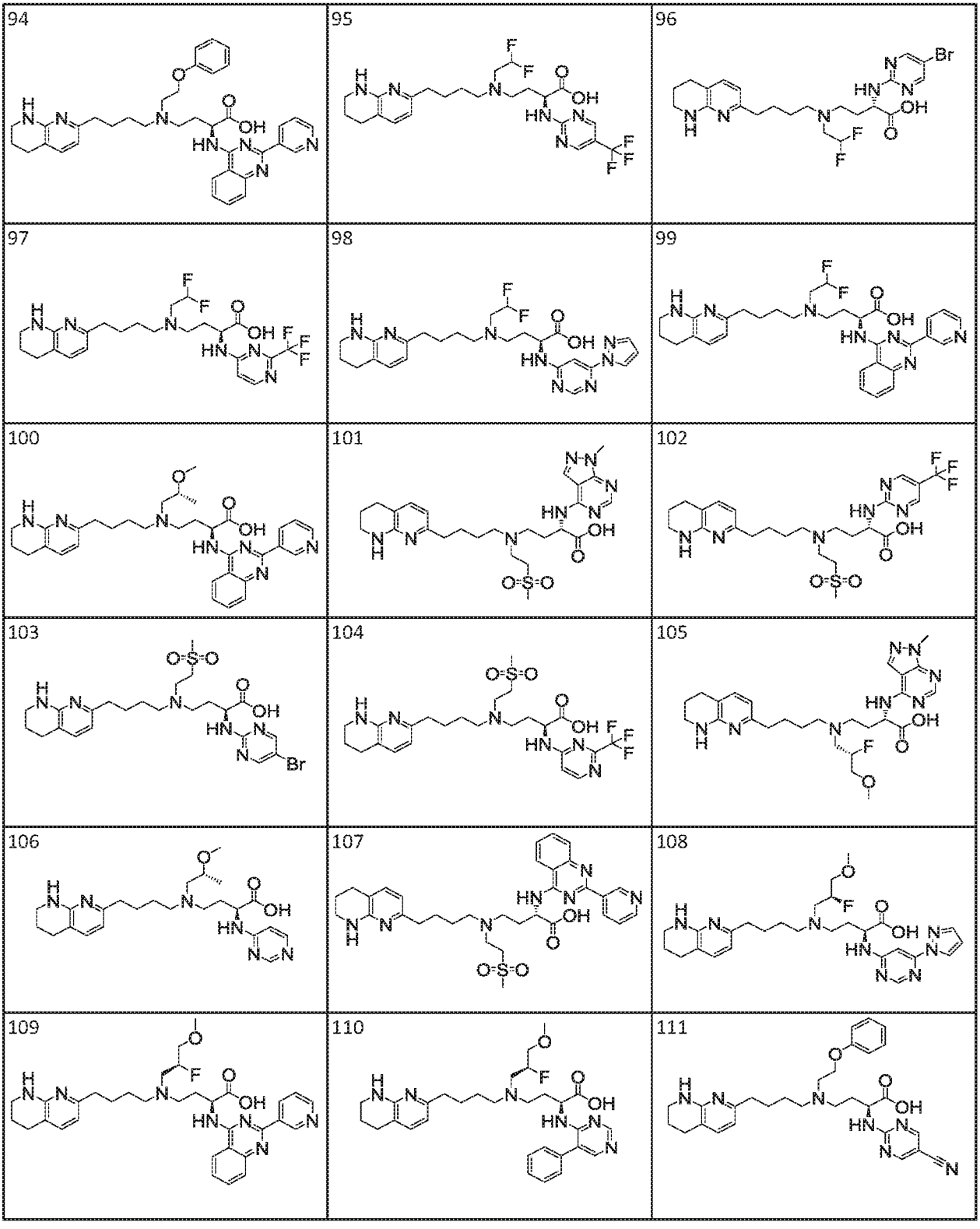

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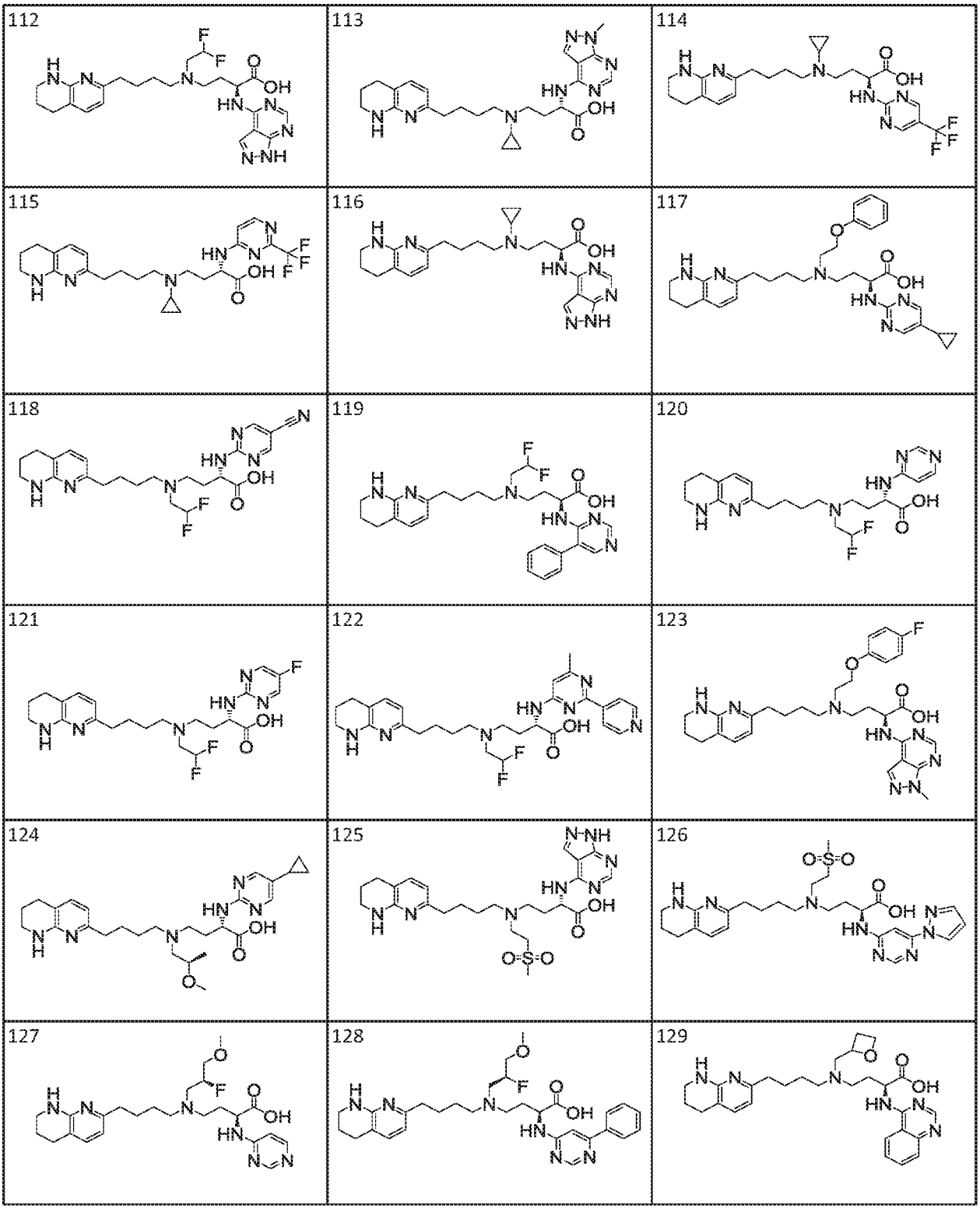
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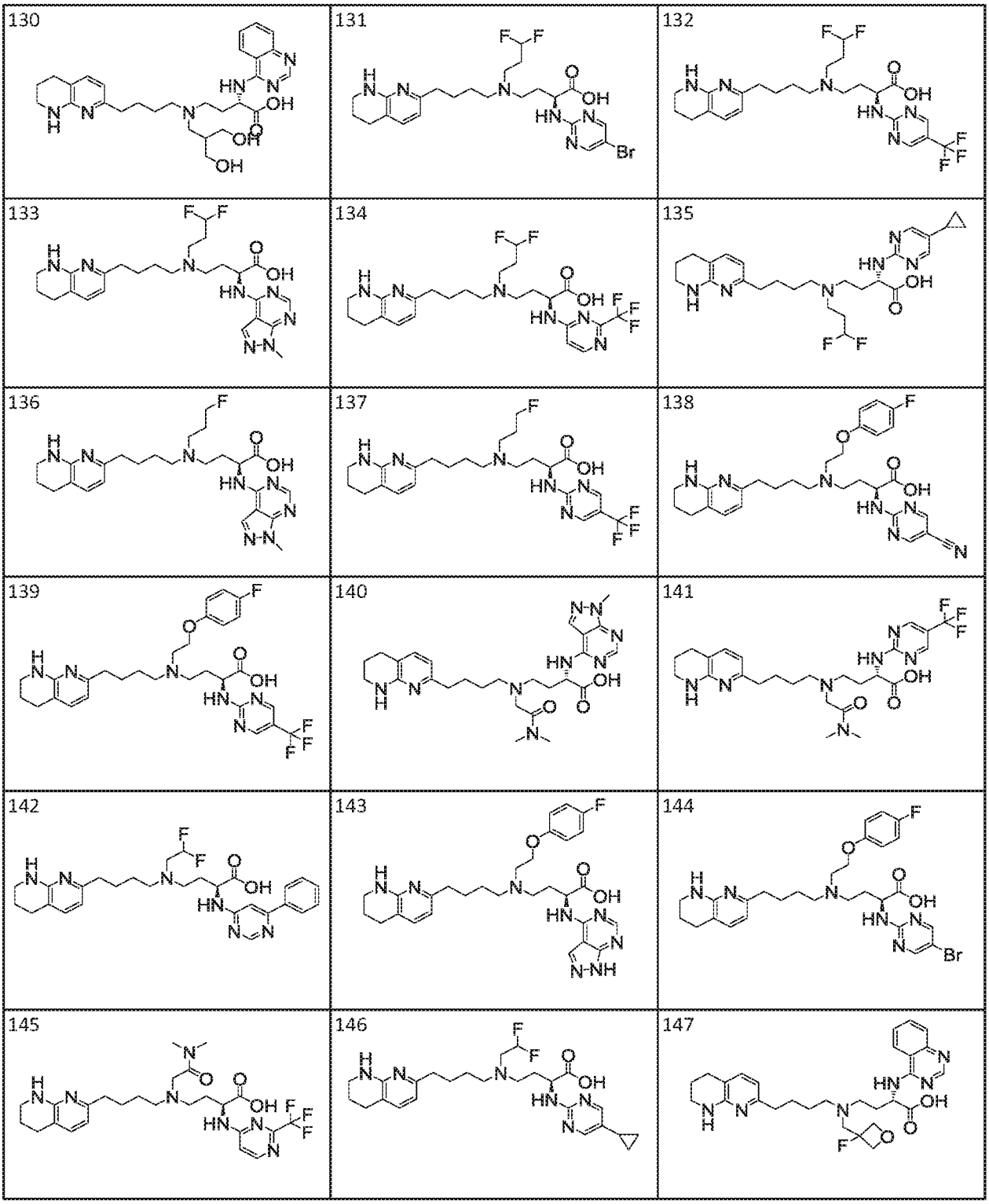
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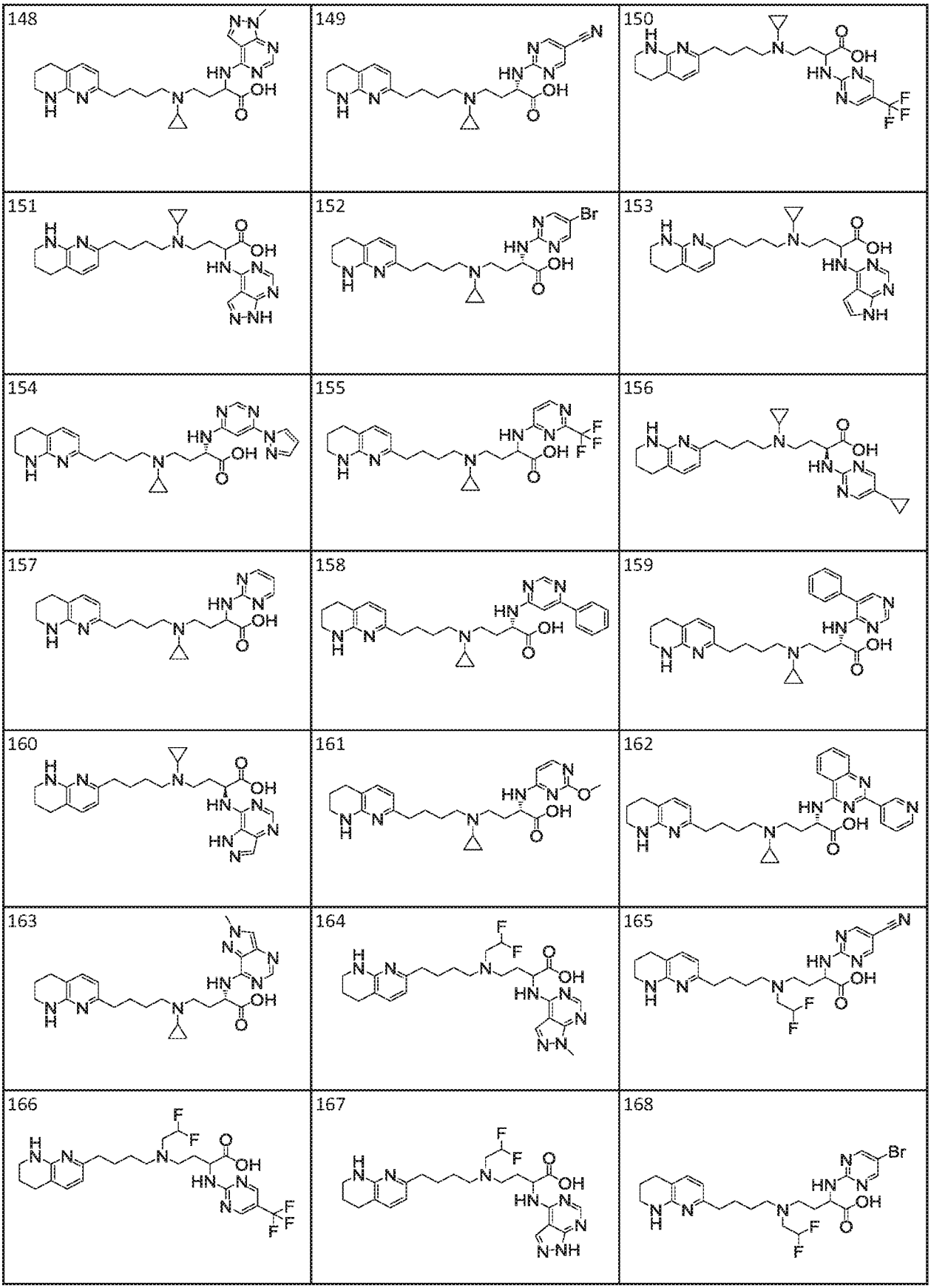
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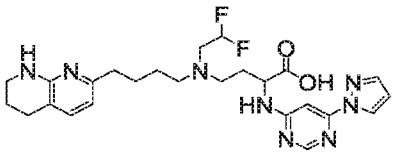
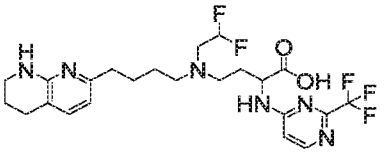
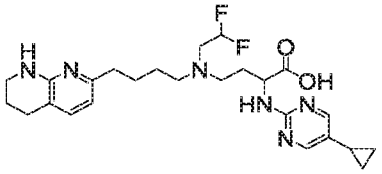
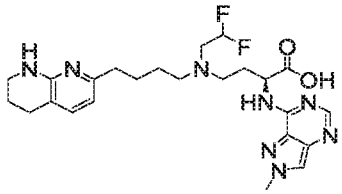
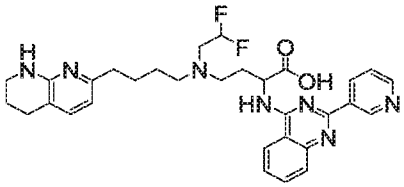
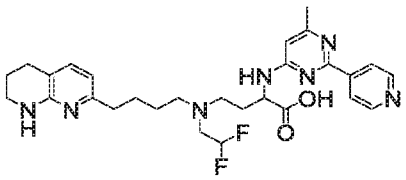
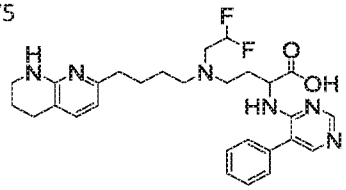
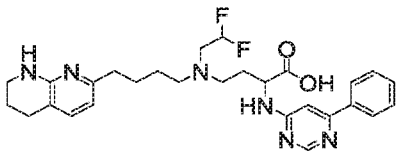
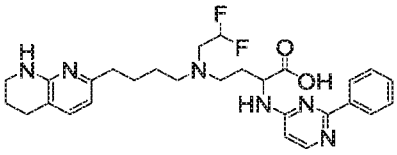
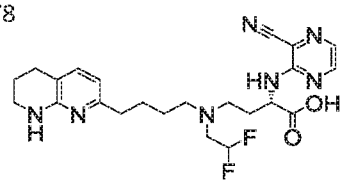
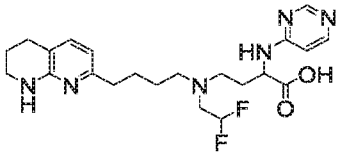
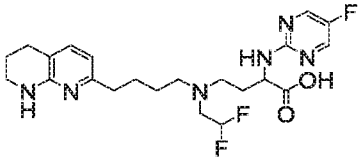
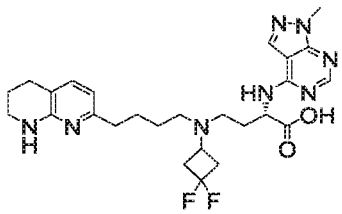
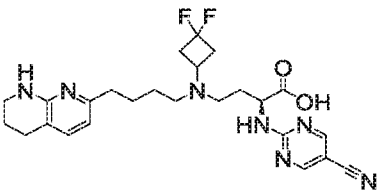
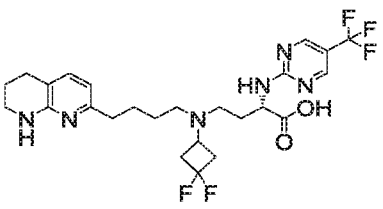
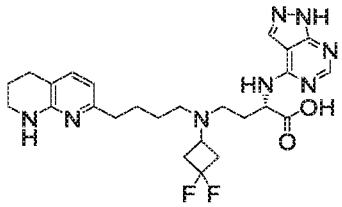
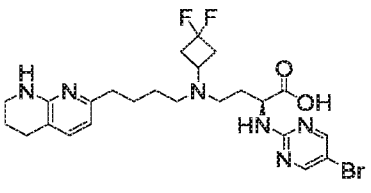
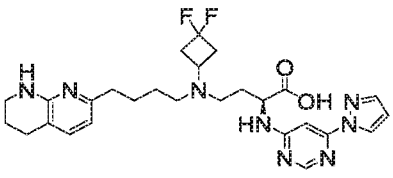
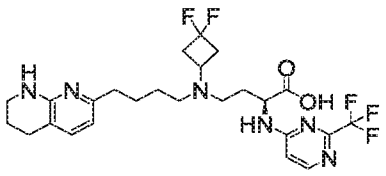
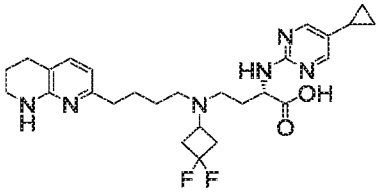
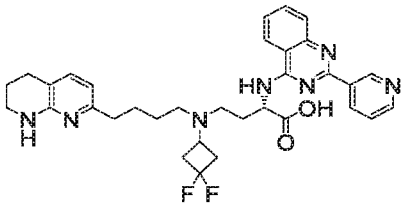
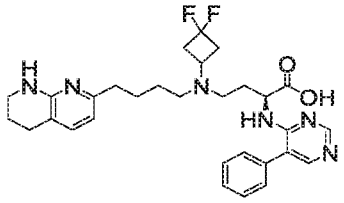
169 	170 	171 
172 	173 	174 
175 	176 	177 
178 	179 	180 
181 	182 	183 
184 	185 	186 

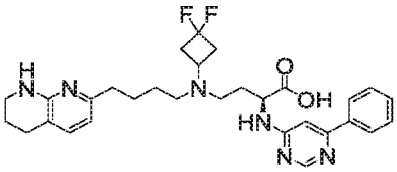
FIG. 1 (cont.)

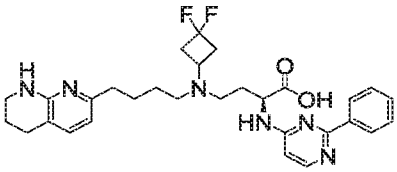
187 

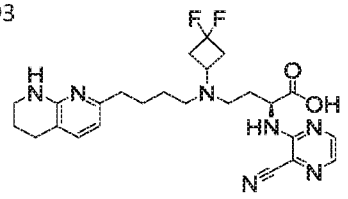
188 

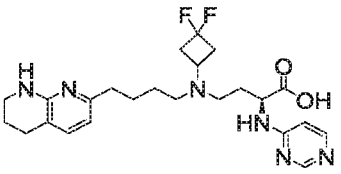
189 

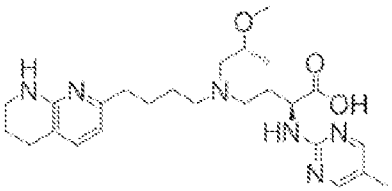
190 

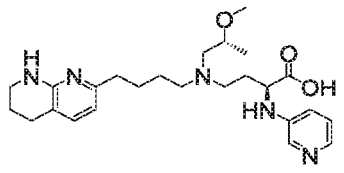
191 

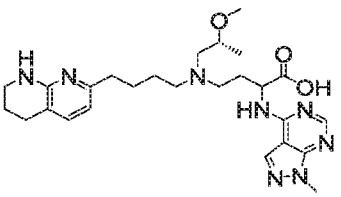
192 

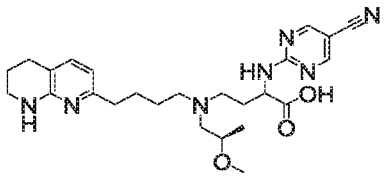
193 

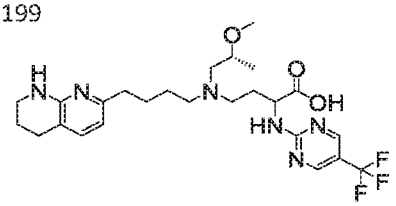
194 

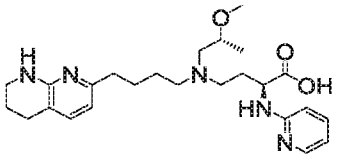
195 

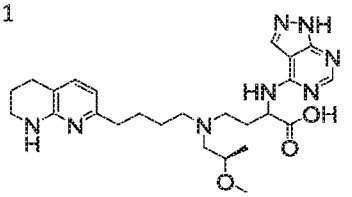
196 

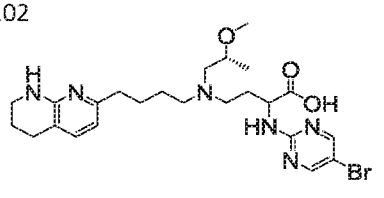
197 

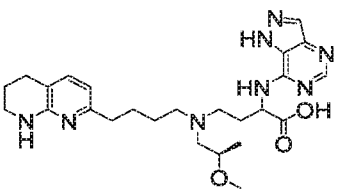
198 

199 

200 

201 

202 

203 

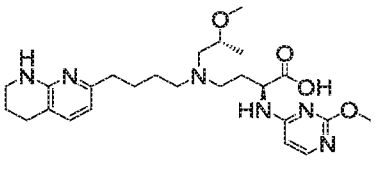
204 

FIG. 1 (cont.)

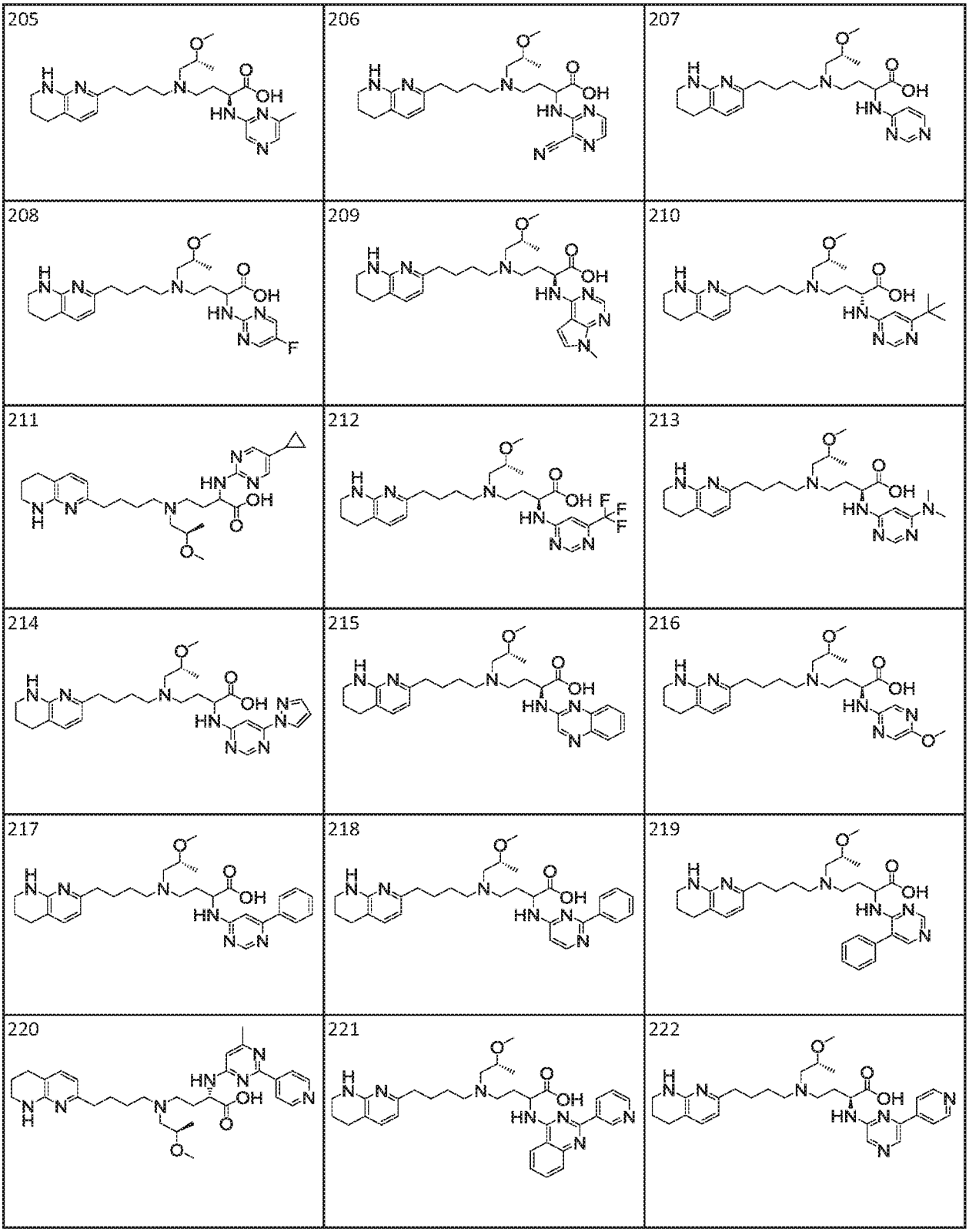

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FIG. 1 (cont.)

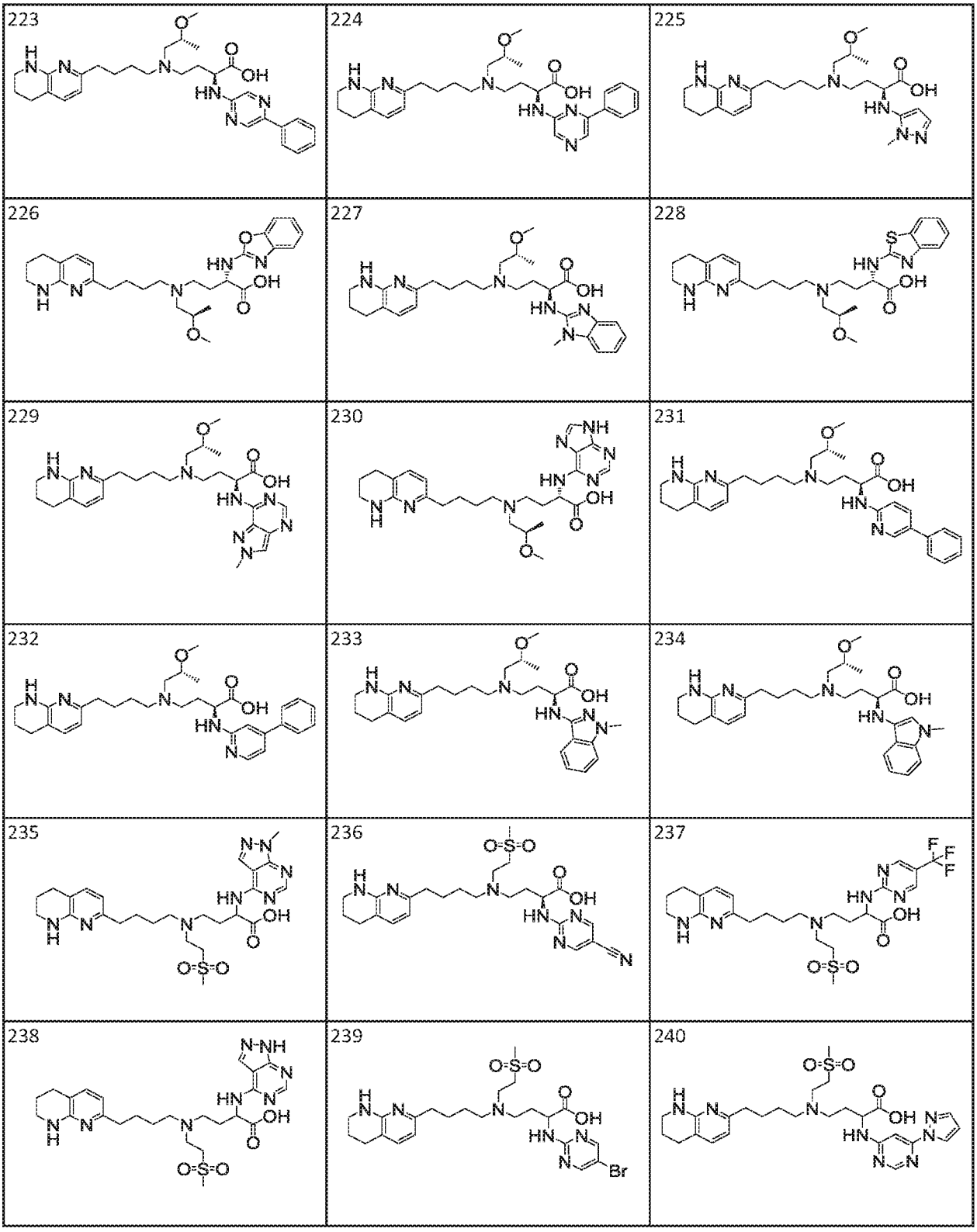
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FIG. 1 (cont.)

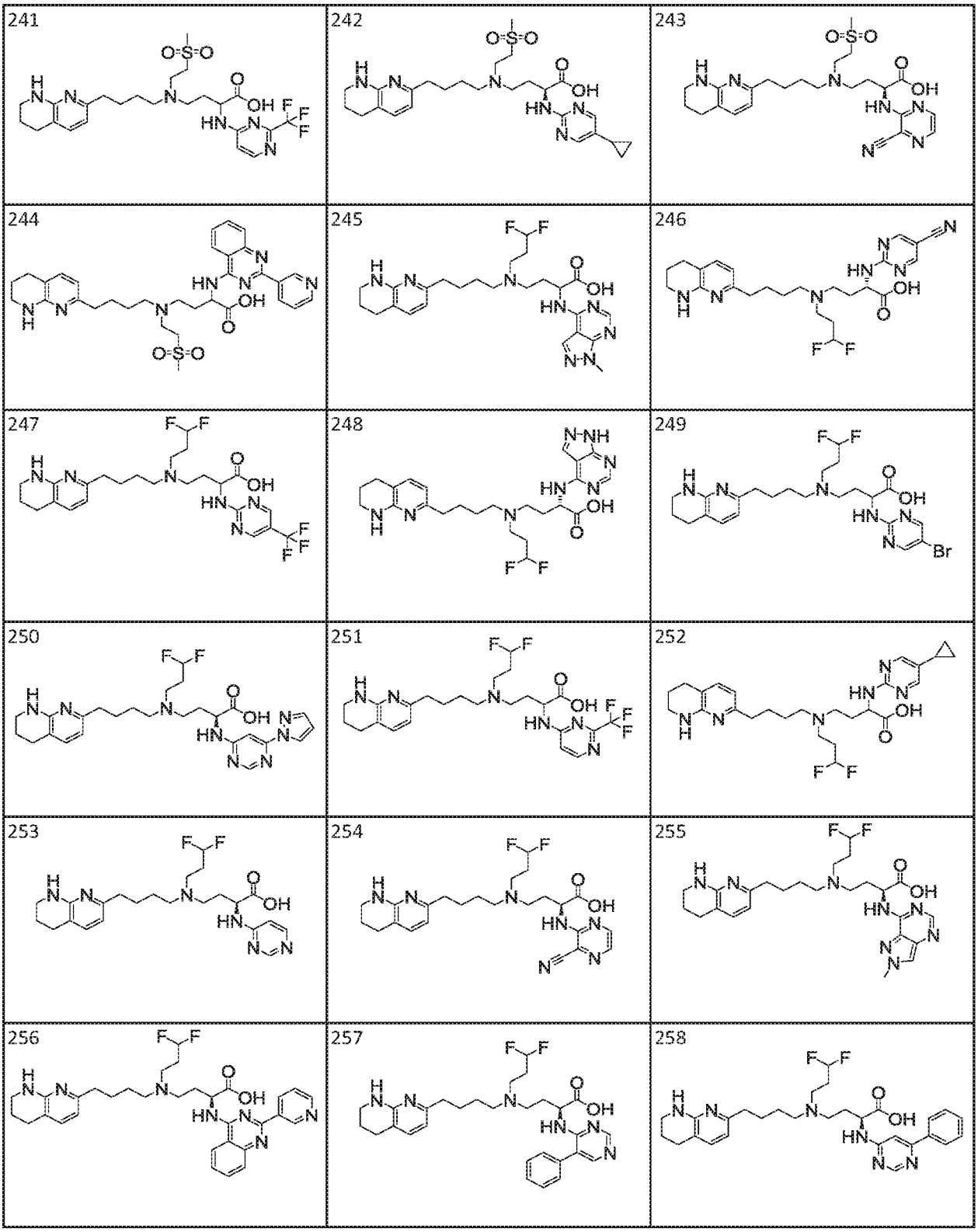
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FIG. 1 (cont.)

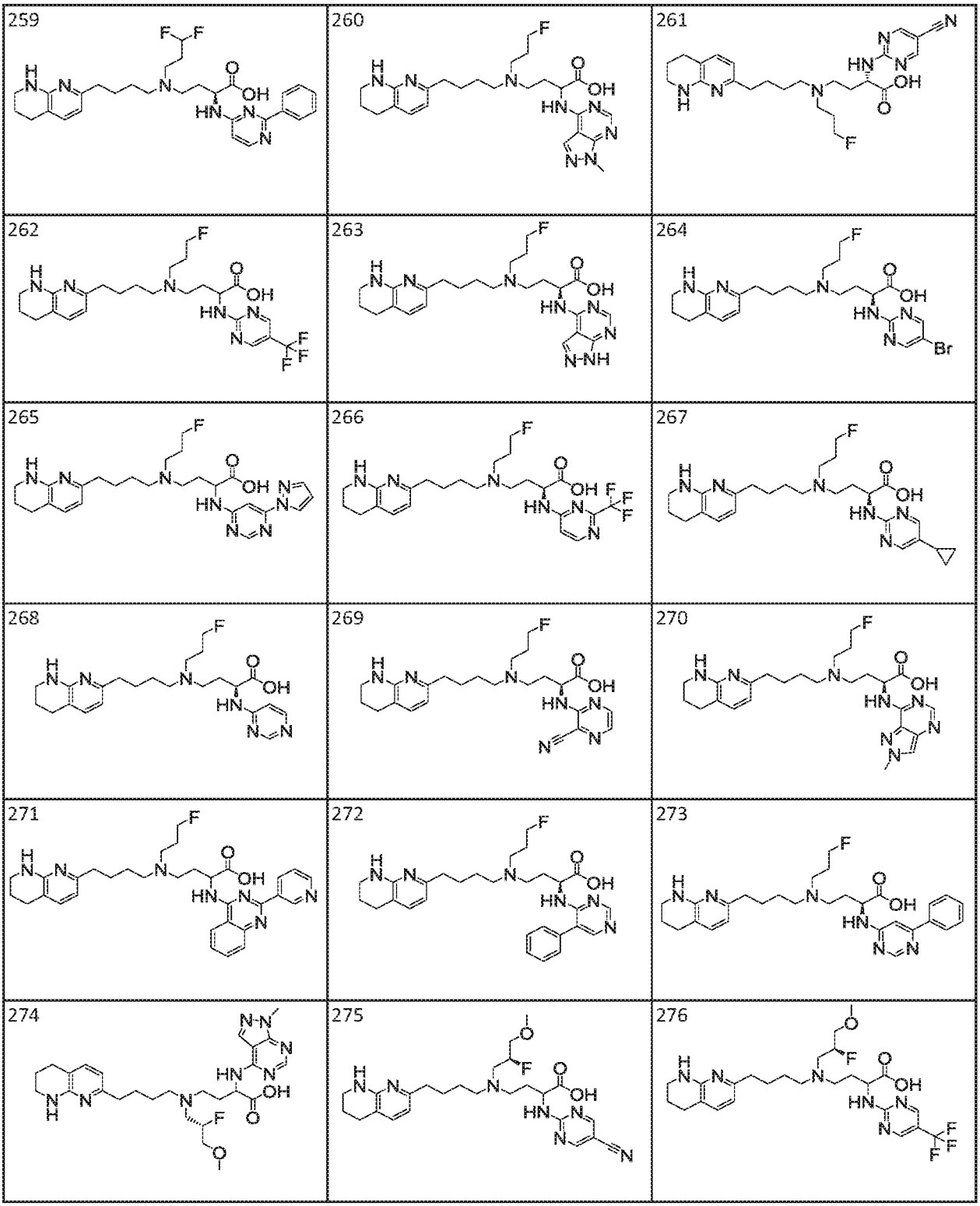
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FIG. 1 (cont.)

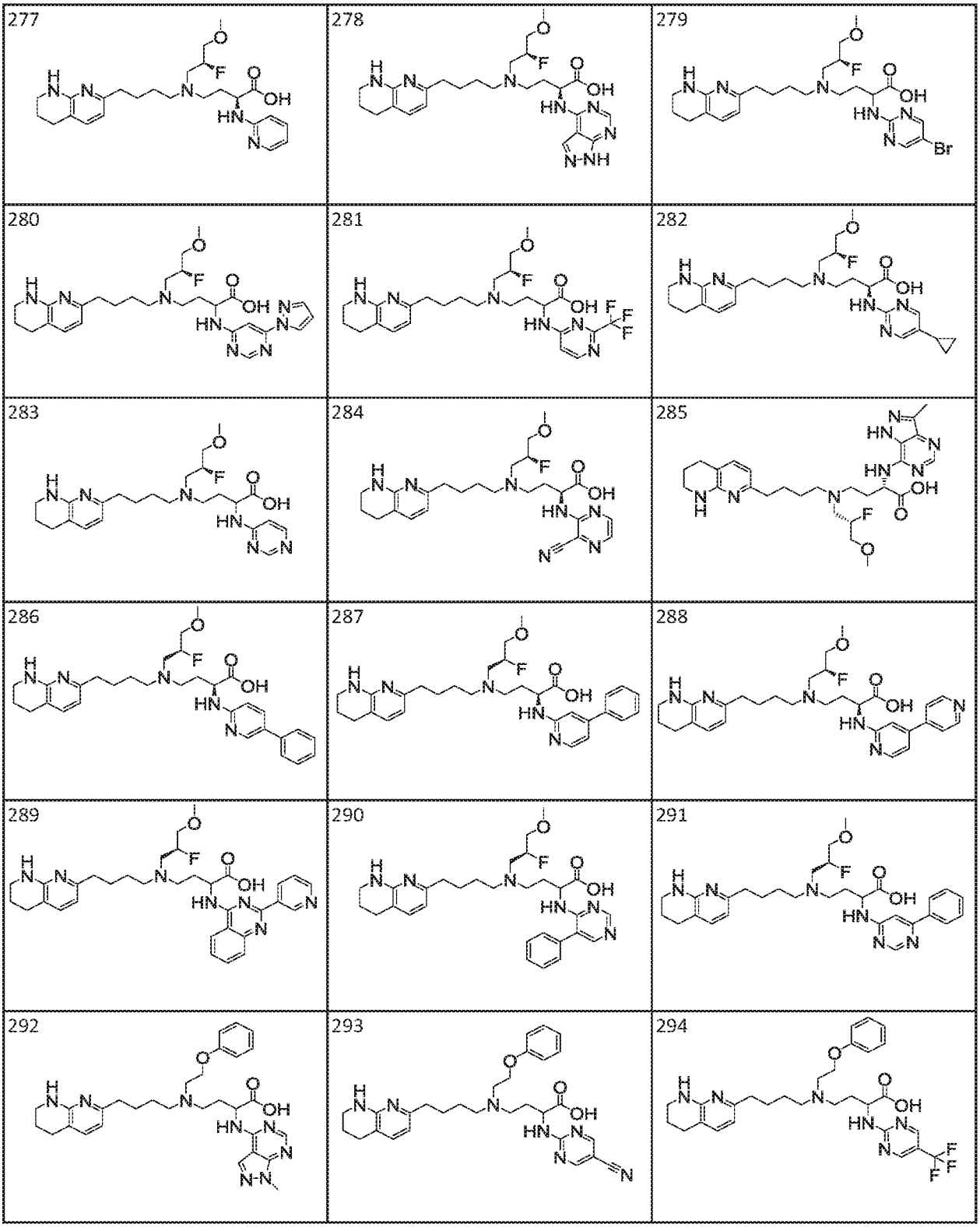
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FIG. 1 (cont.)

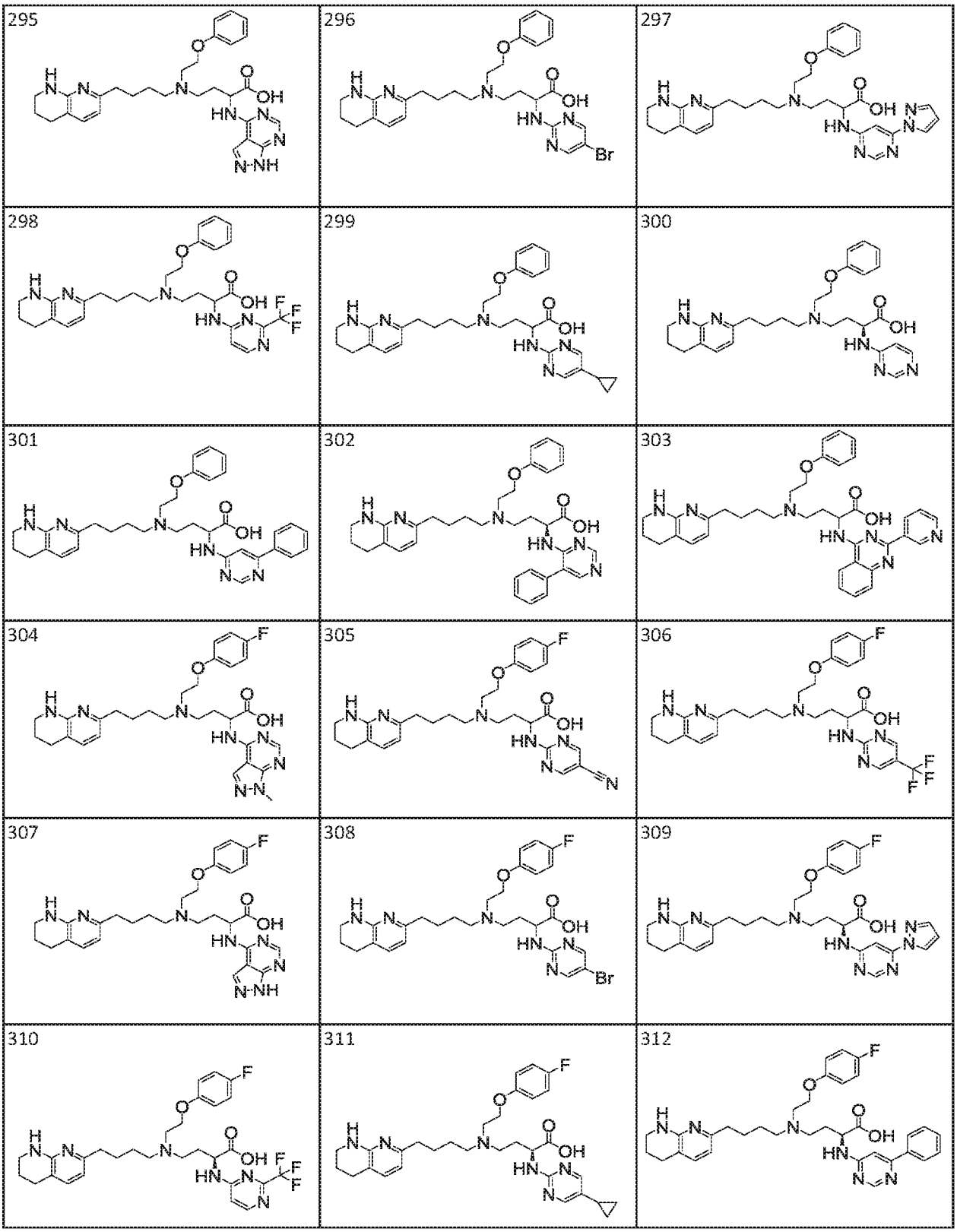
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FIG. 1 (cont.)

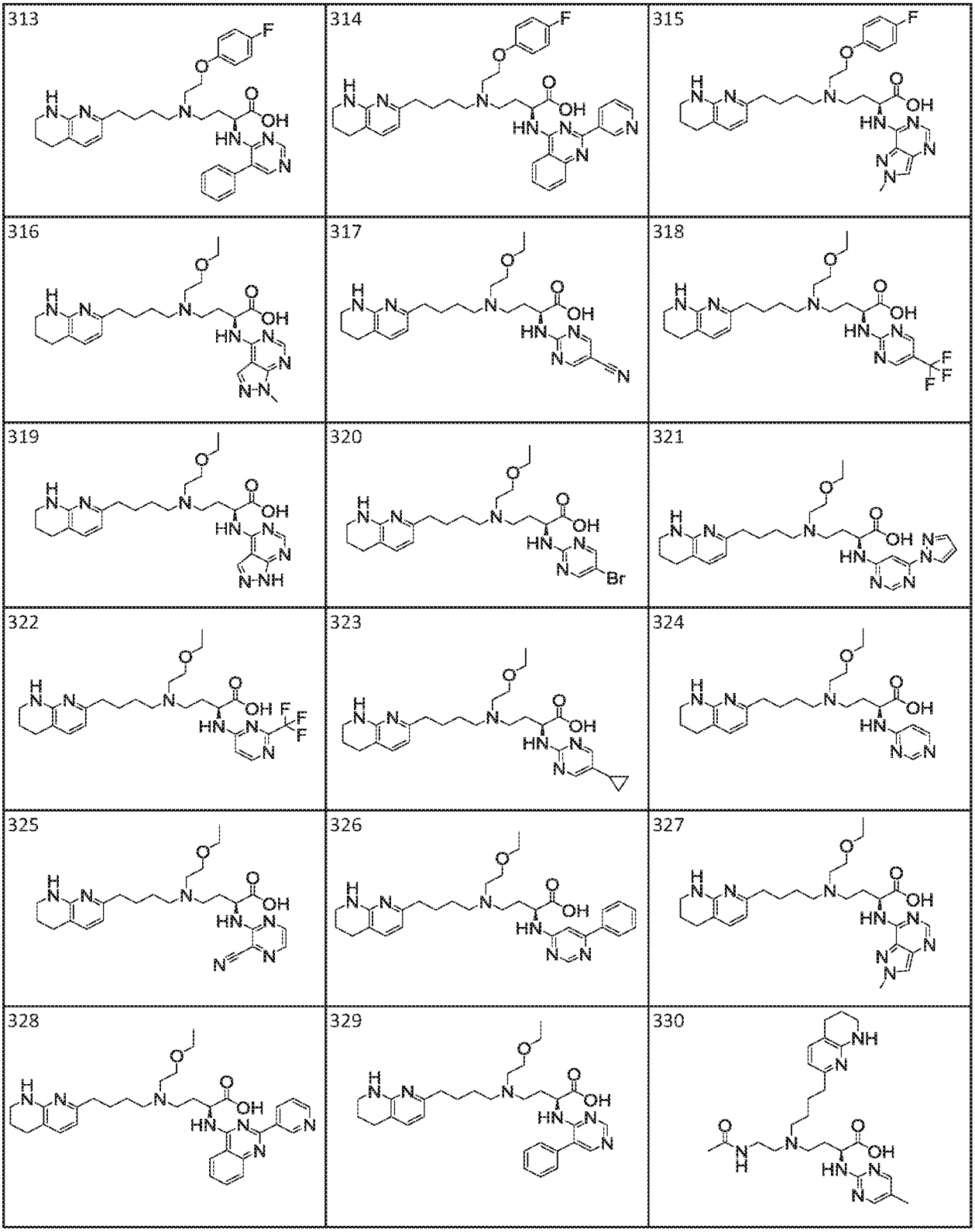
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FIG. 1 (cont.)

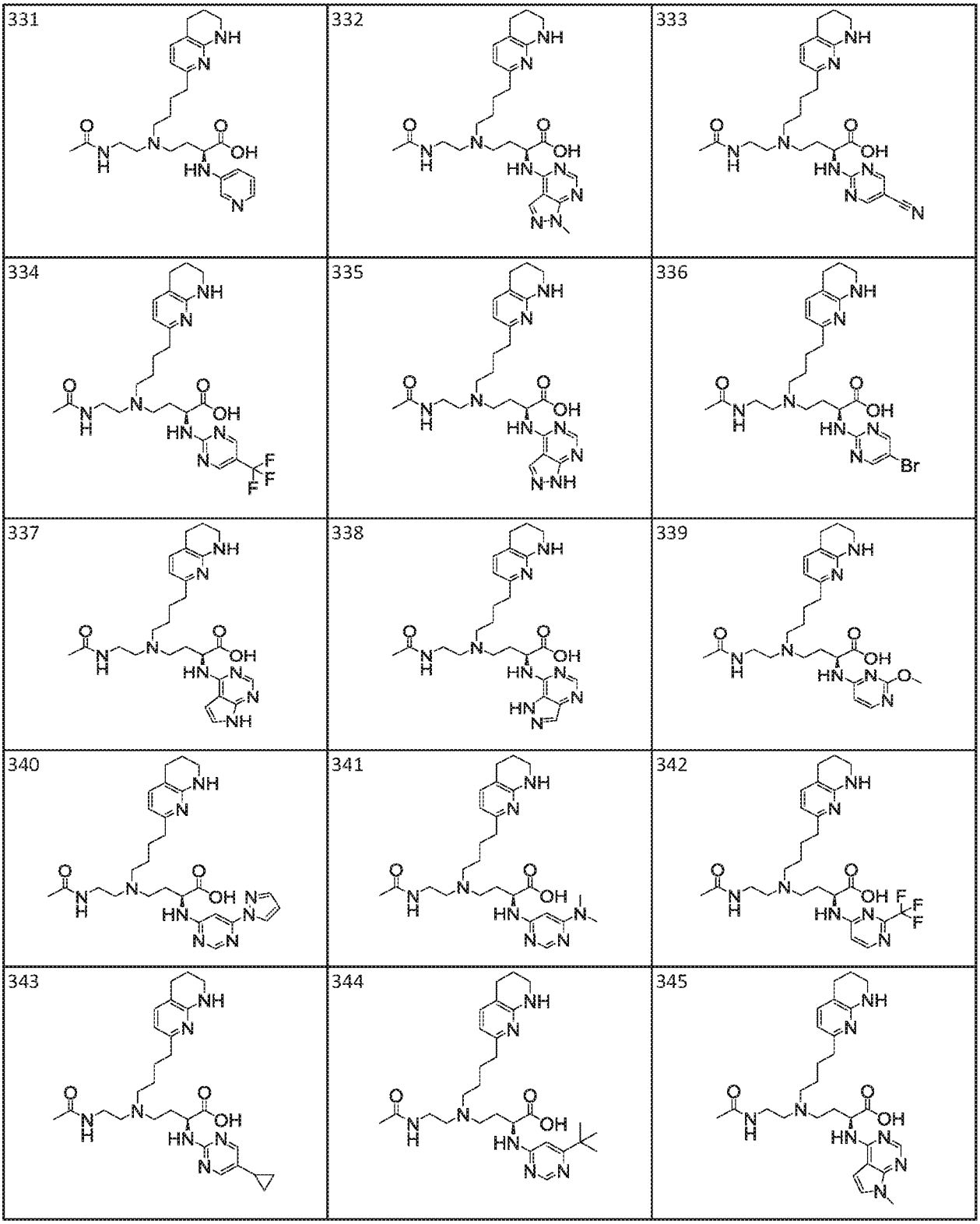


FIG. 1 (cont.)

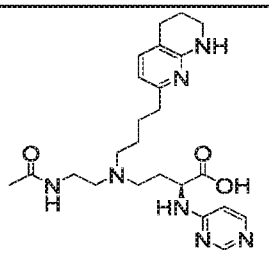
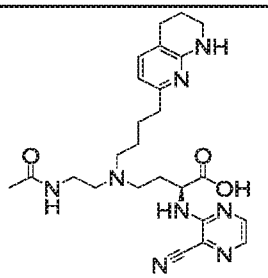
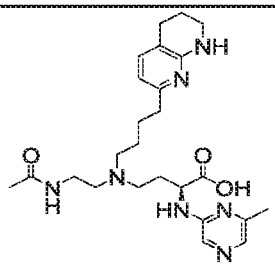
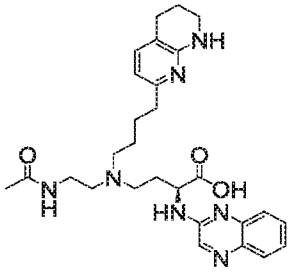
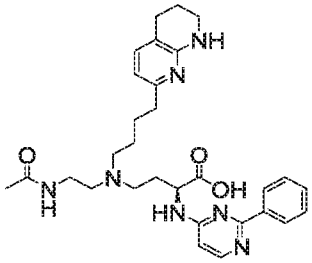
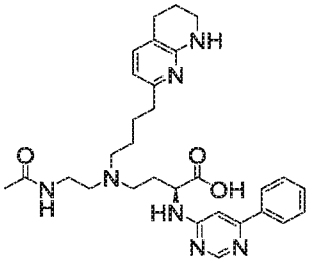
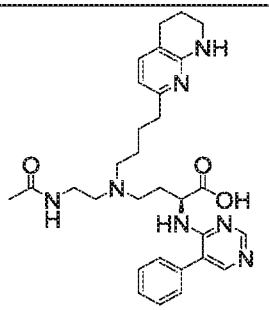
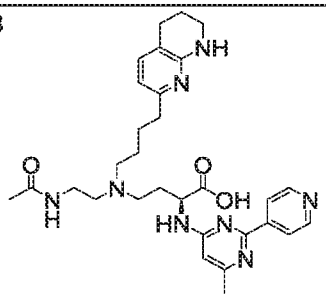
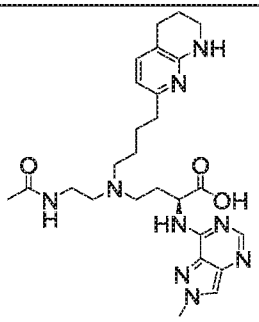
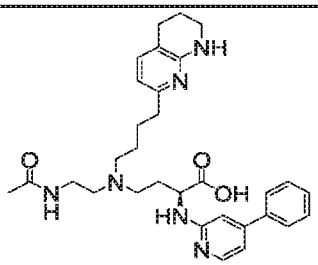
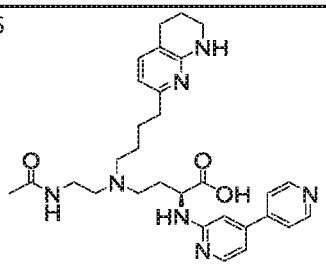
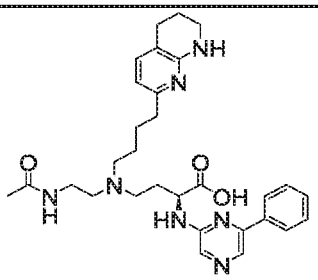
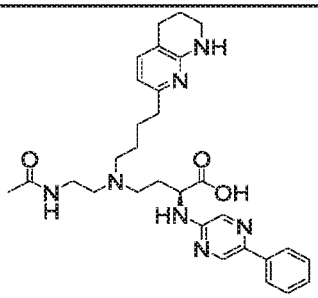
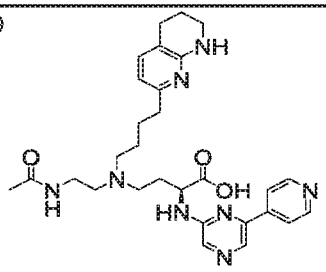
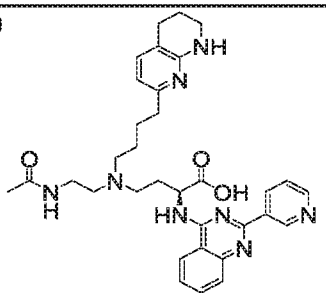
346 	347 	348 
349 	350 	351 
352 	353 	354 
355 	356 	357 
358 	359 	360 

FIG. 1 (cont.)

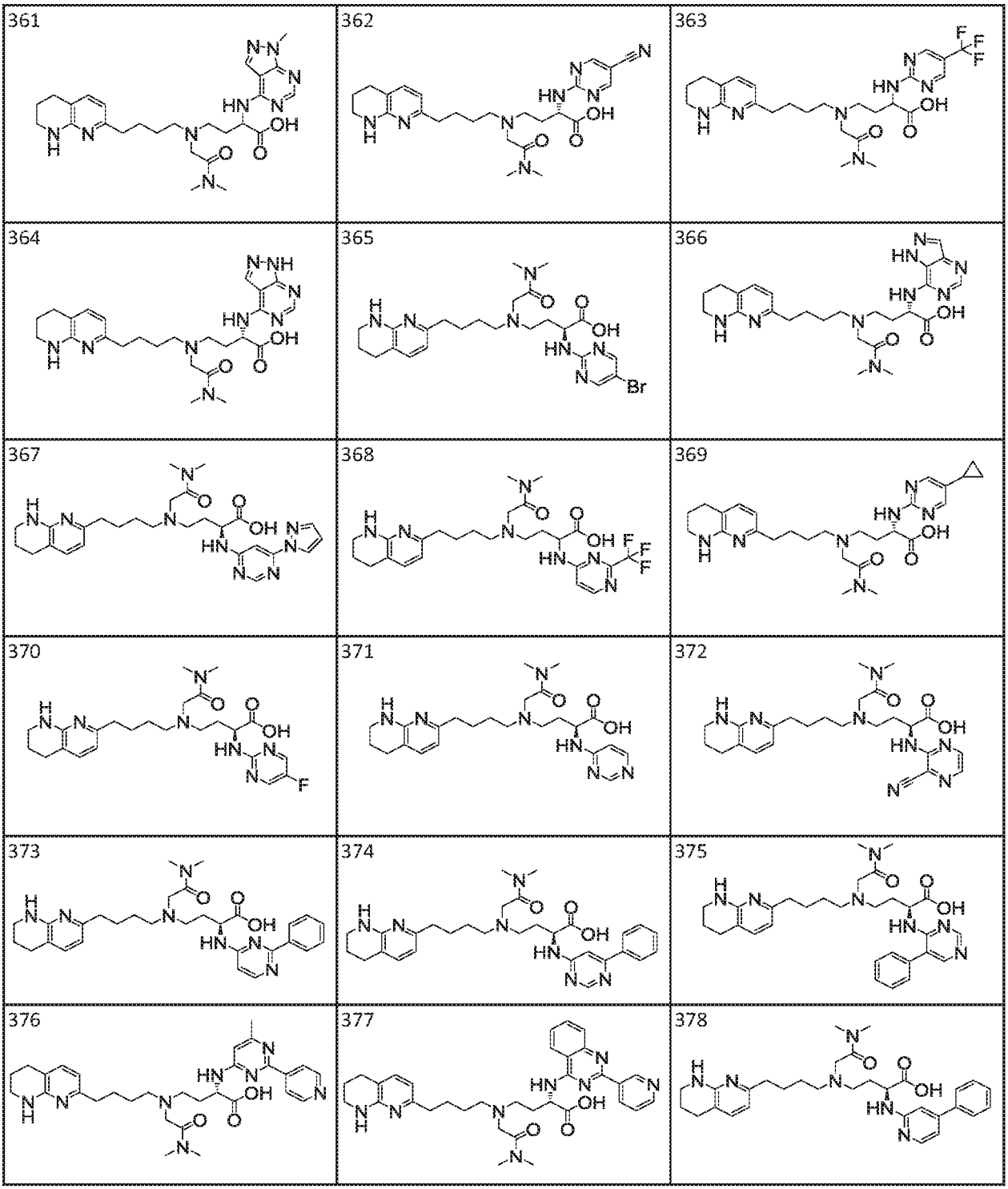

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FIG. 1 (cont.)

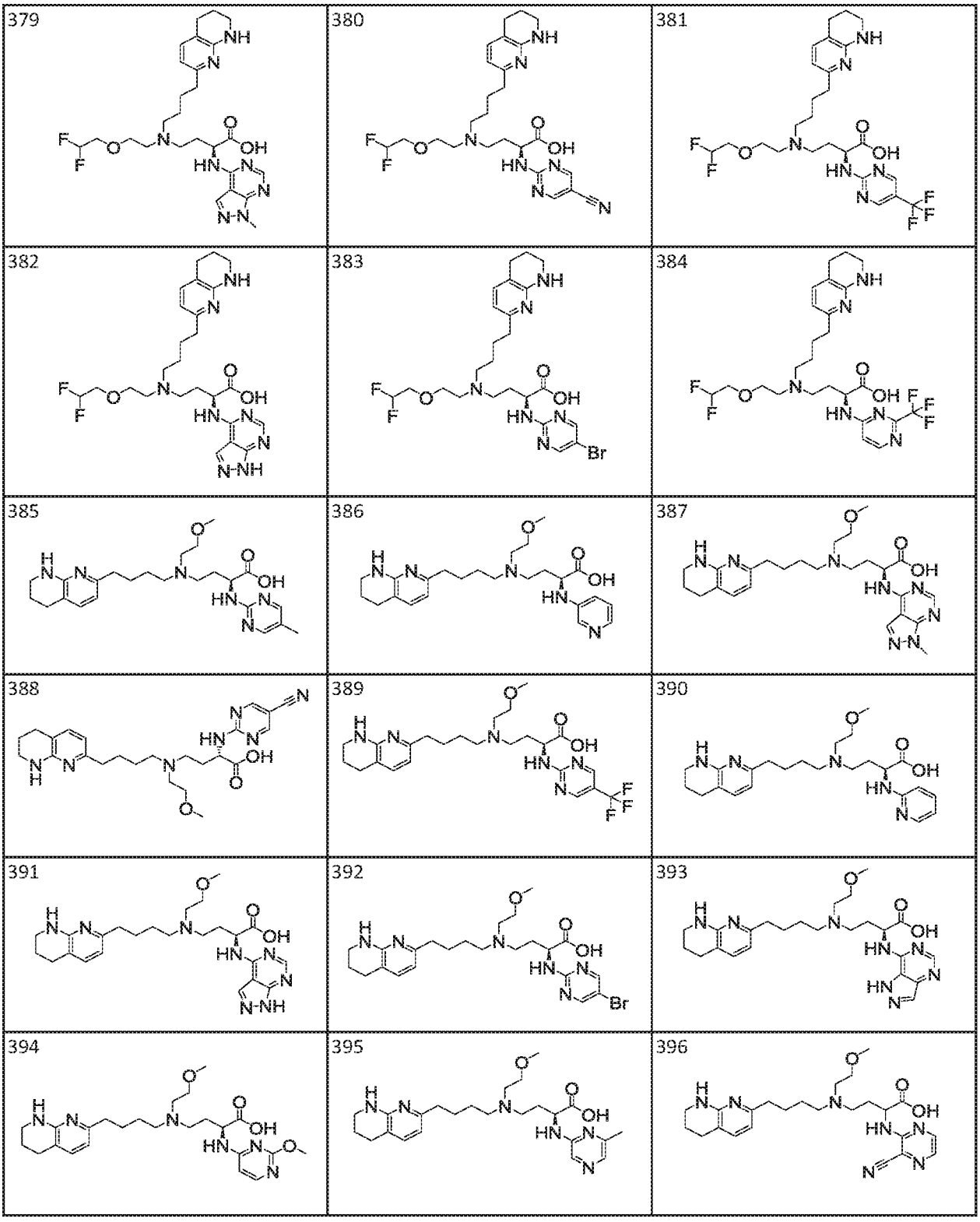
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FIG. 1 (cont.)

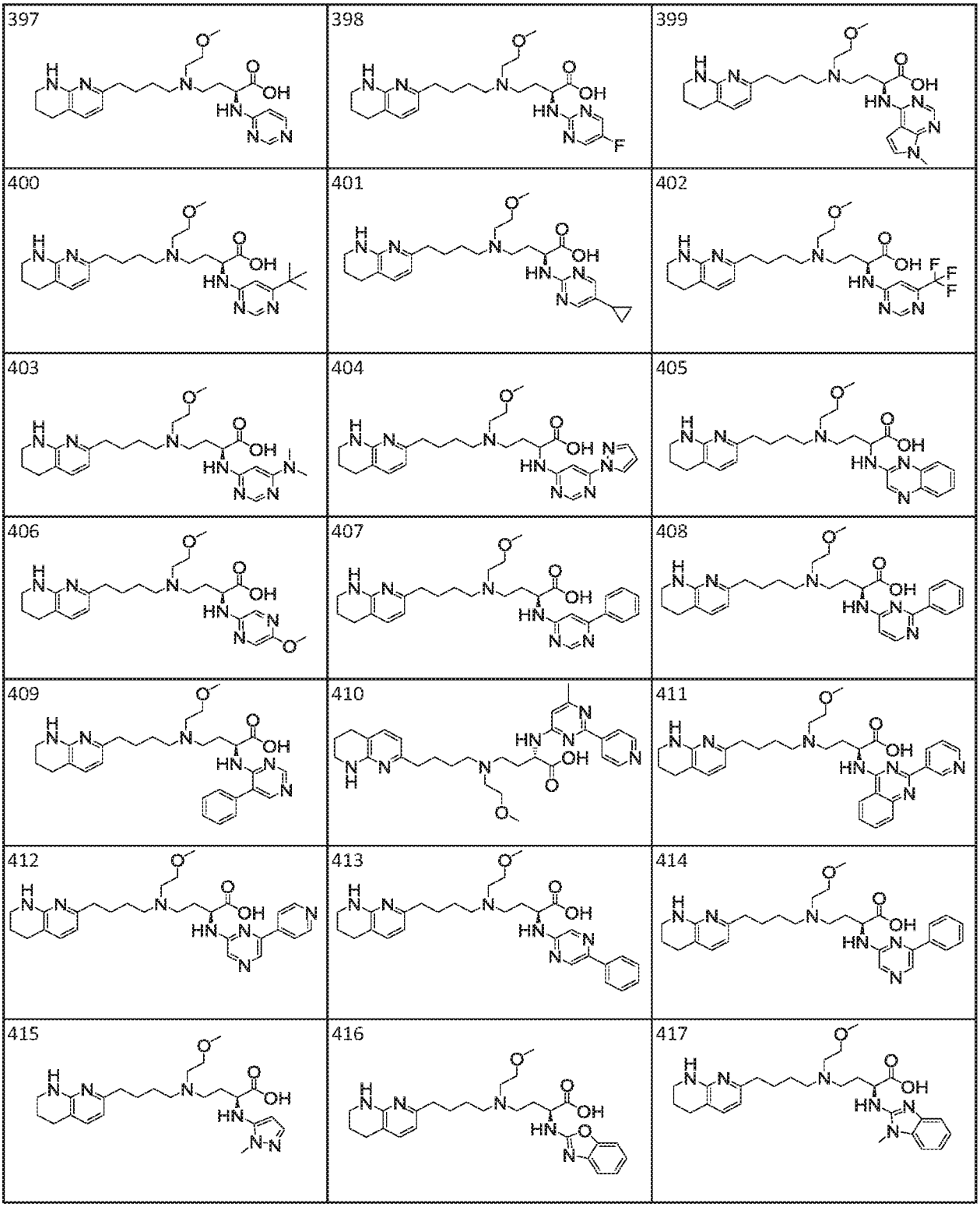
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FIG. 1 (cont.)

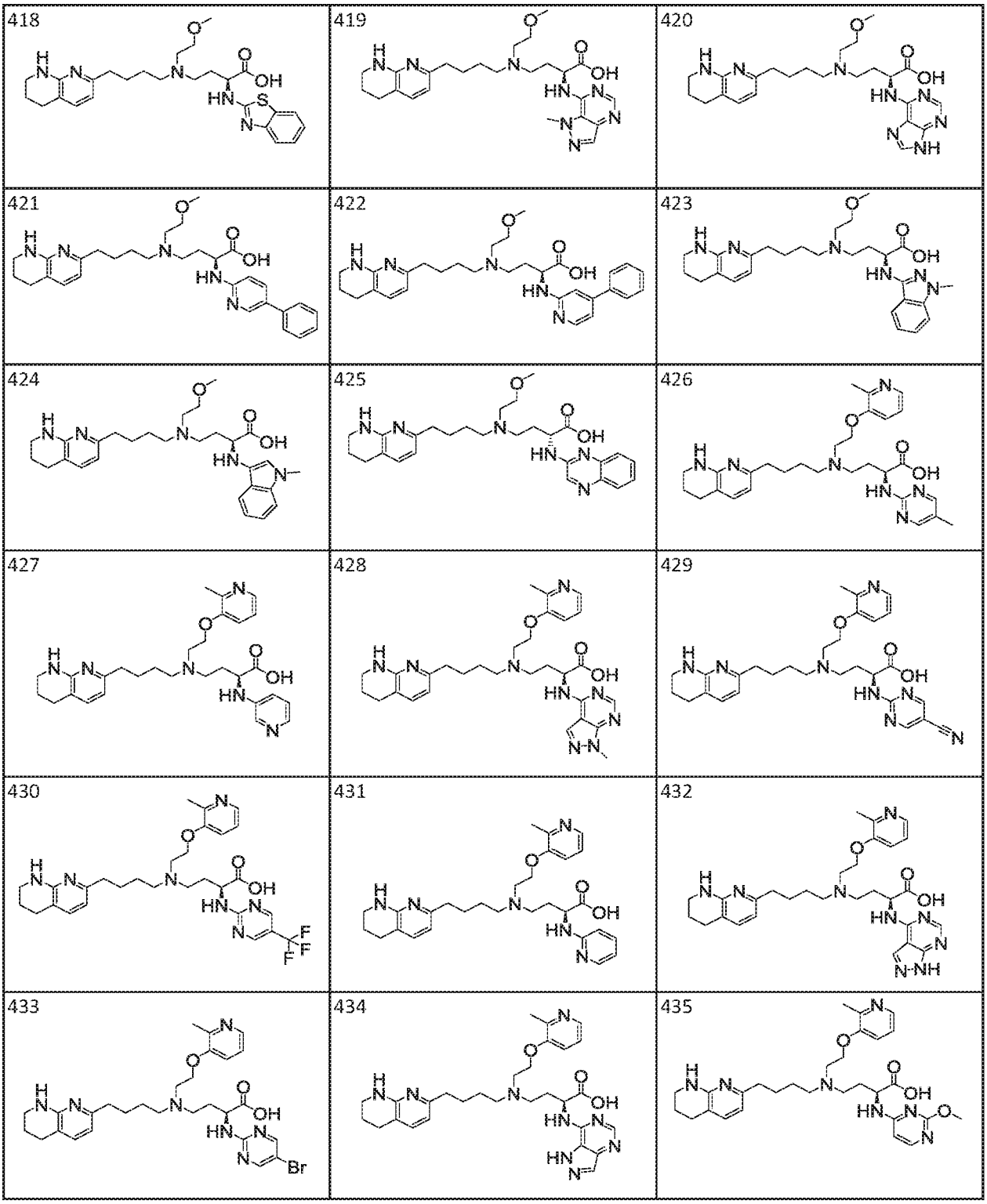
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FIG. 1 (cont.)

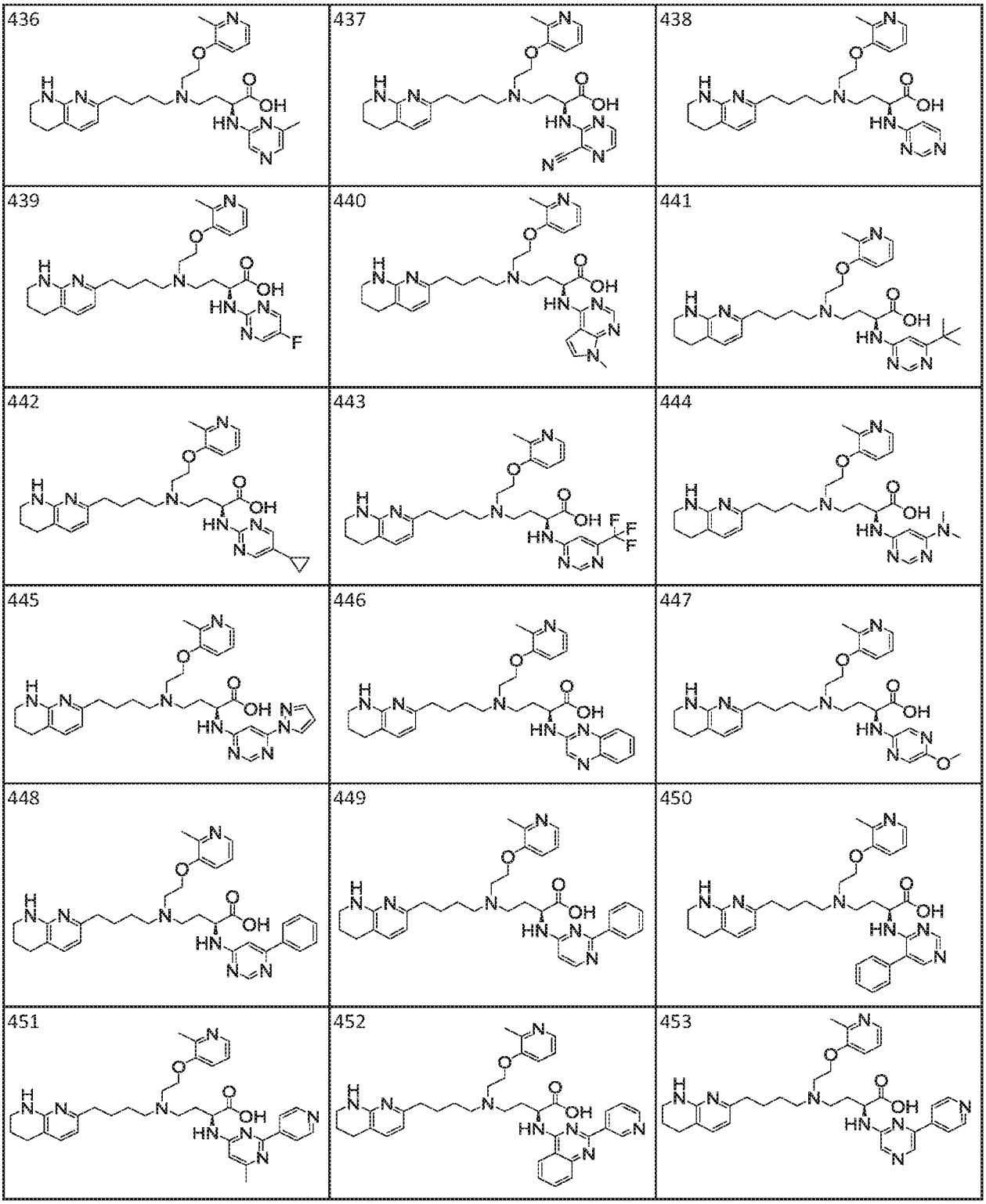
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FIG. 1 (cont.)

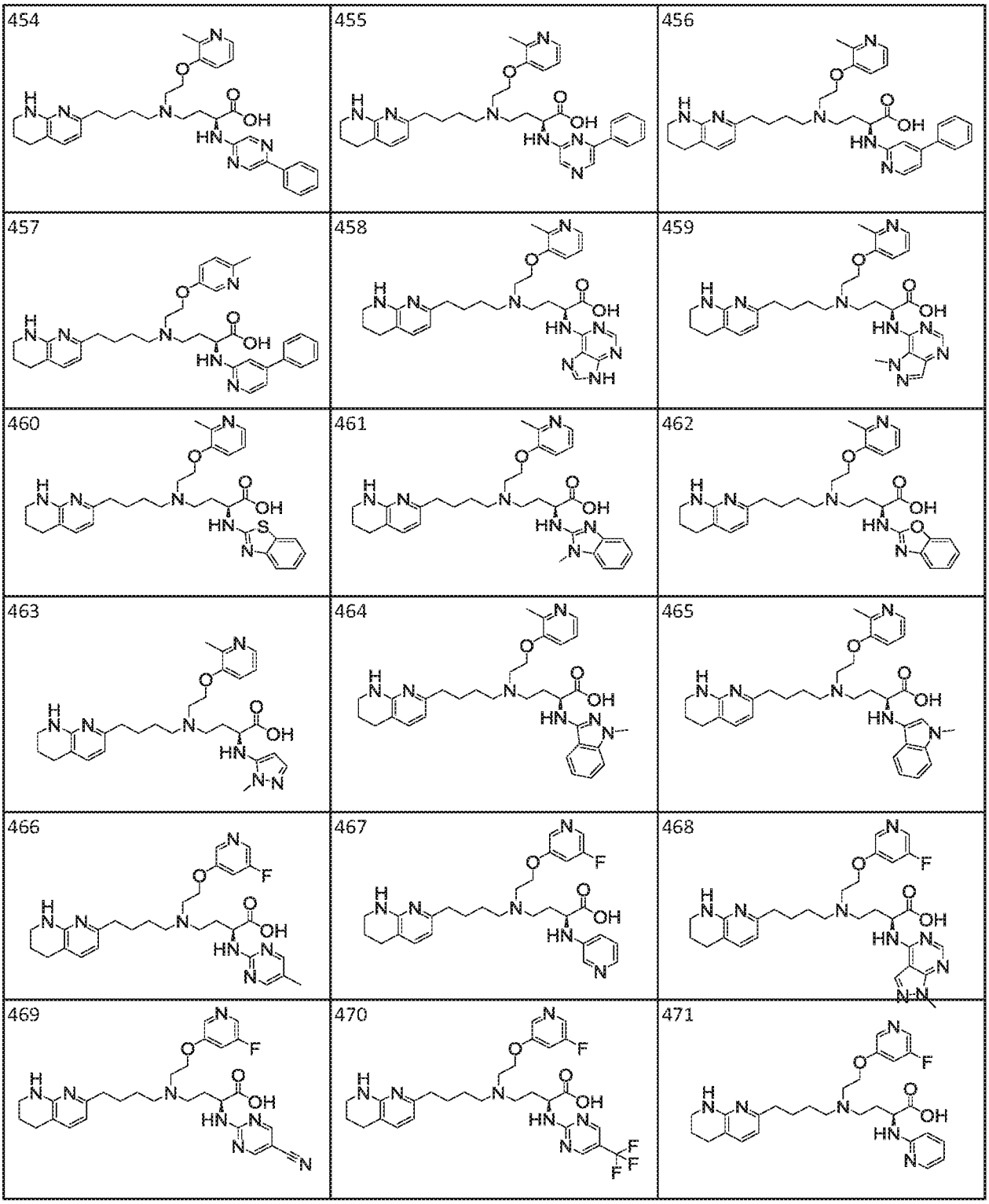
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FIG. 1 (cont.)

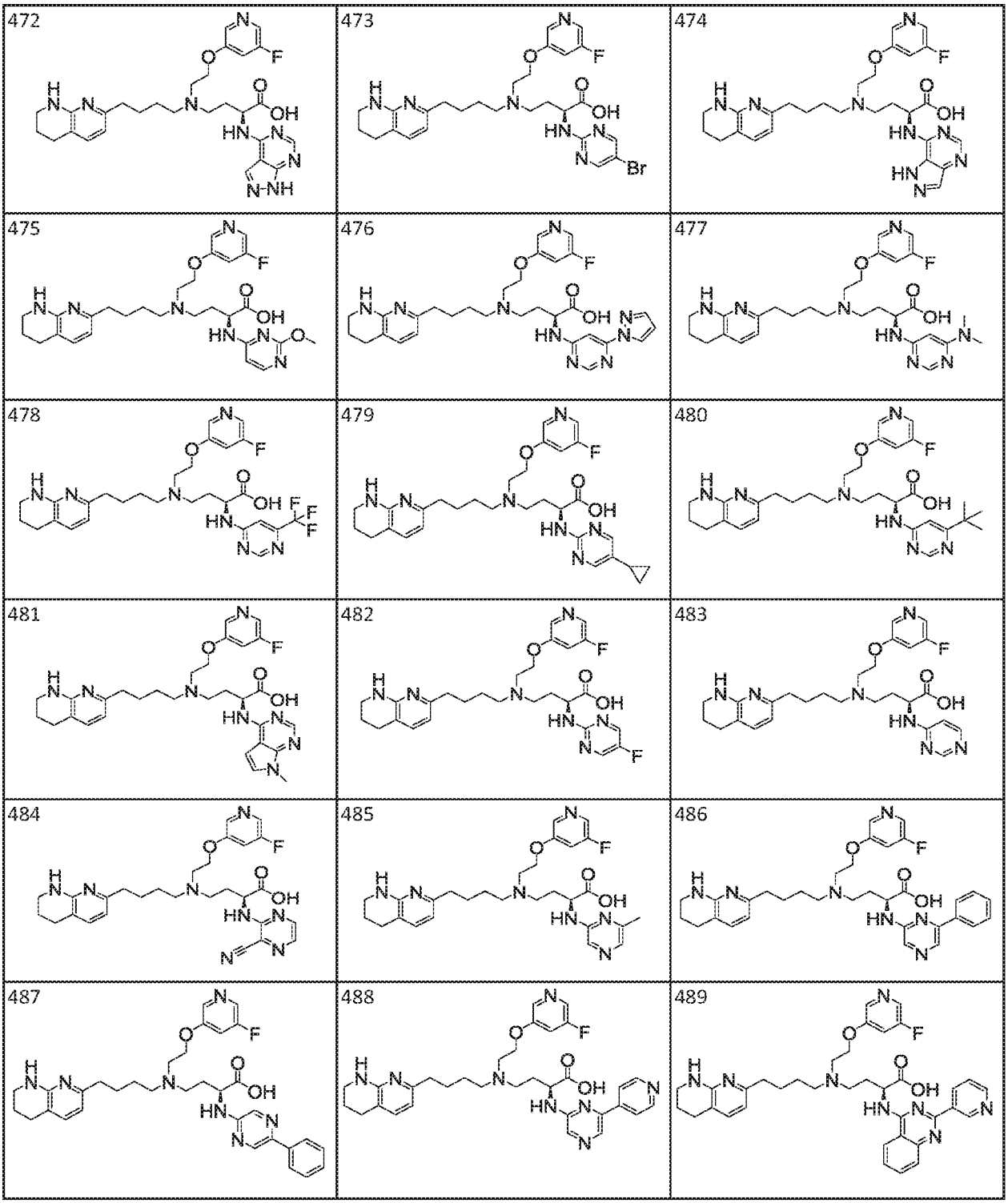
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FIG. 1 (cont.)

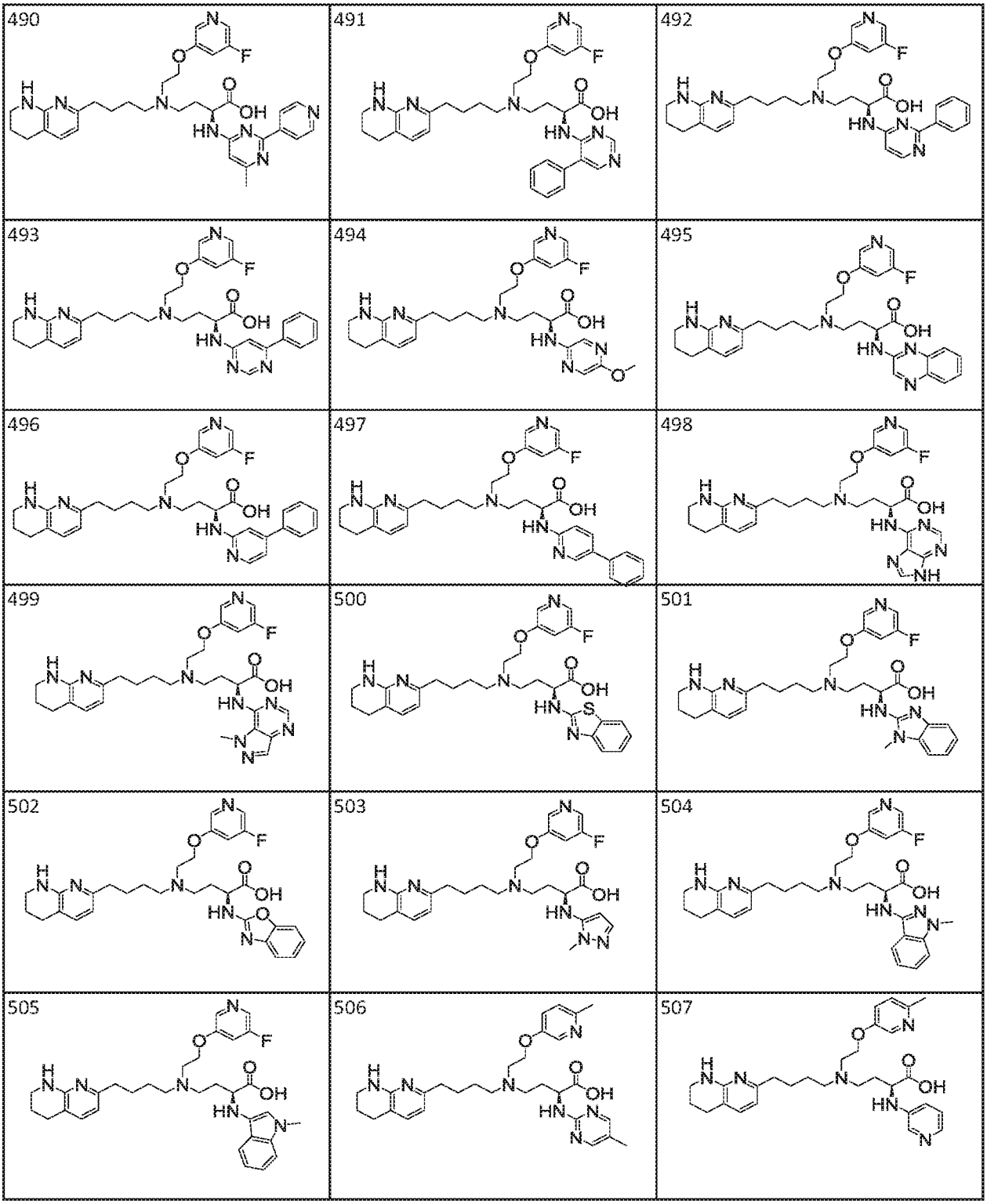
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FIG. 1 (cont.)

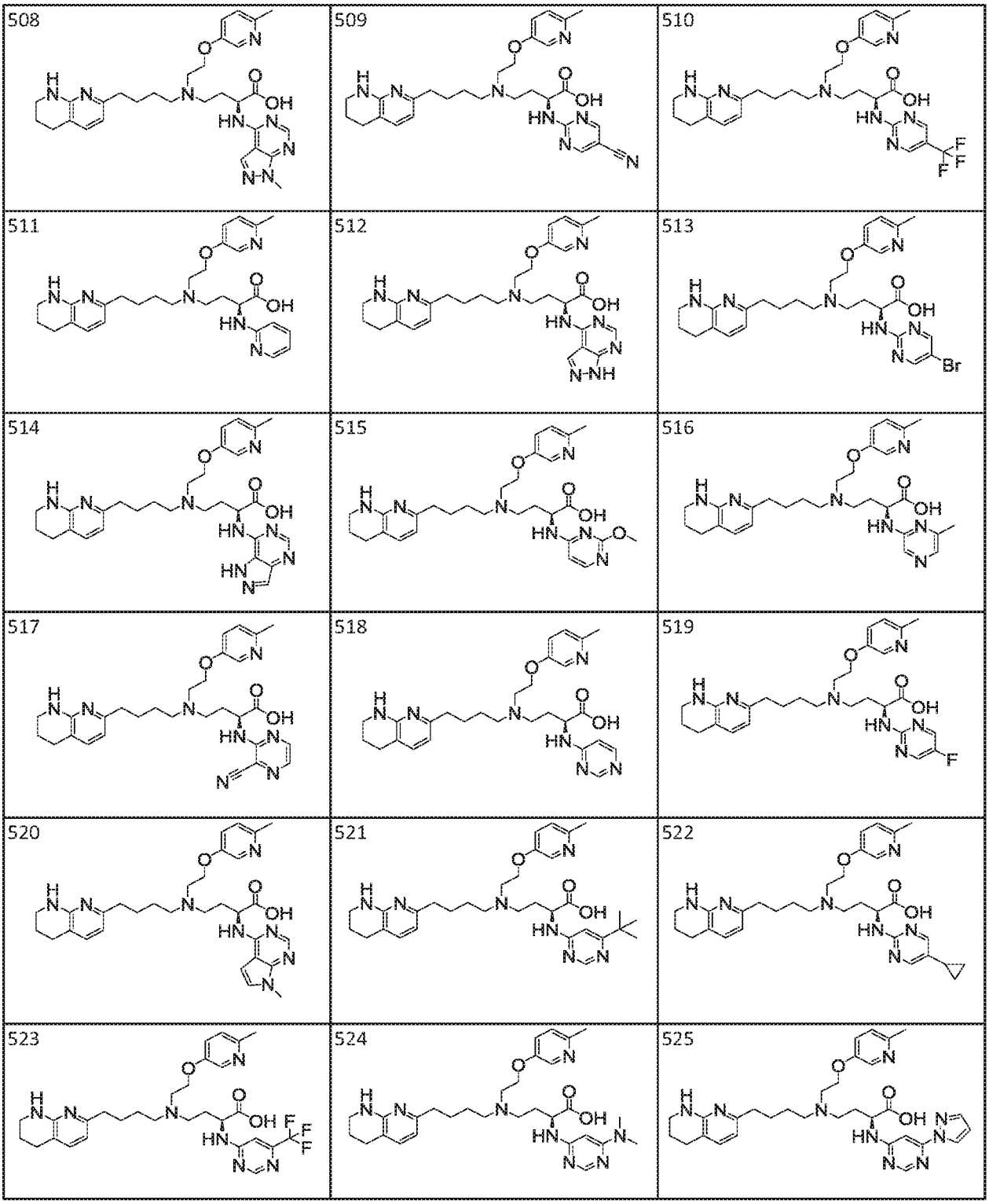
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FIG. 1 (cont.)

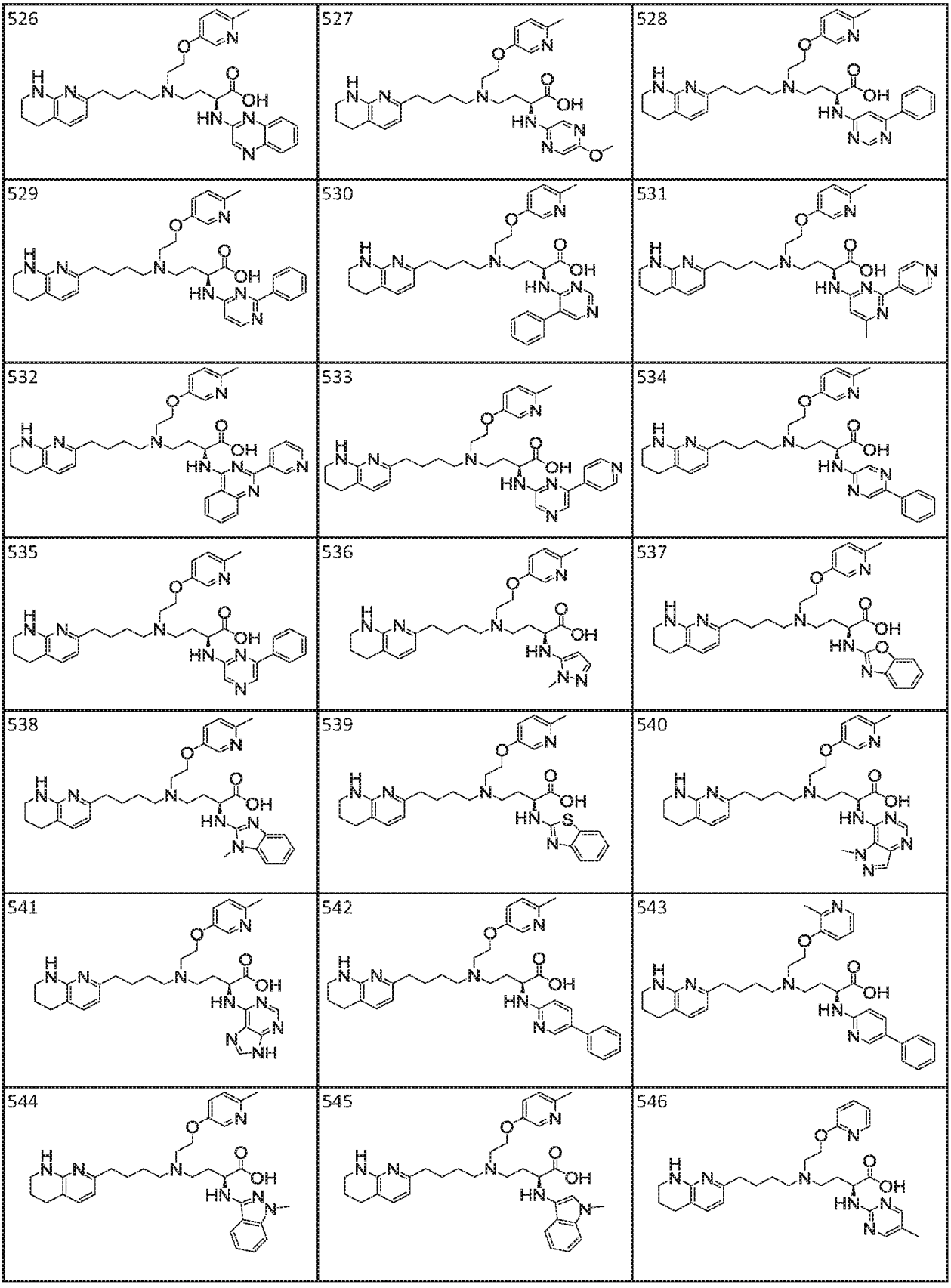
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FIG. 1 (cont.)

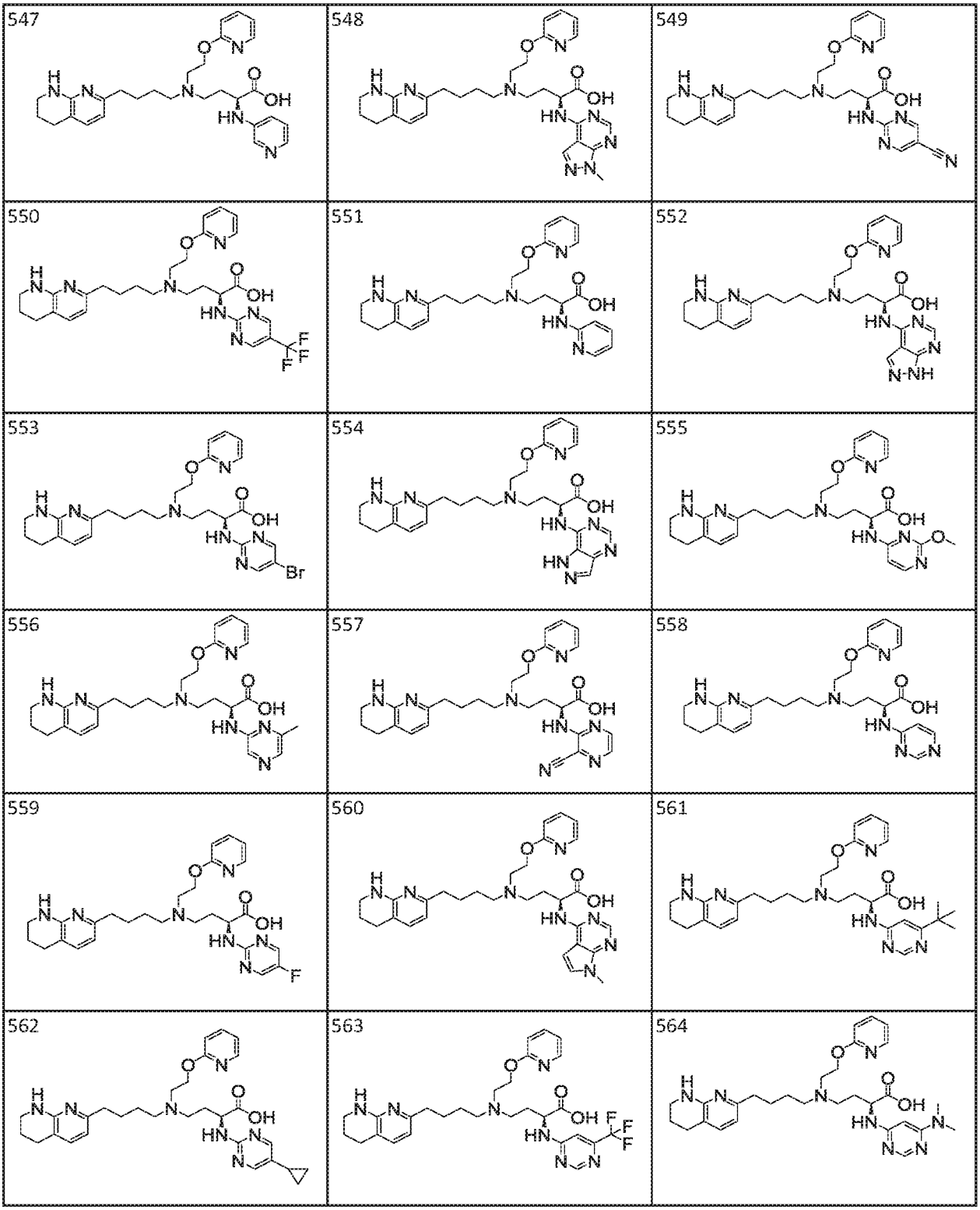
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FIG. 1 (cont.)

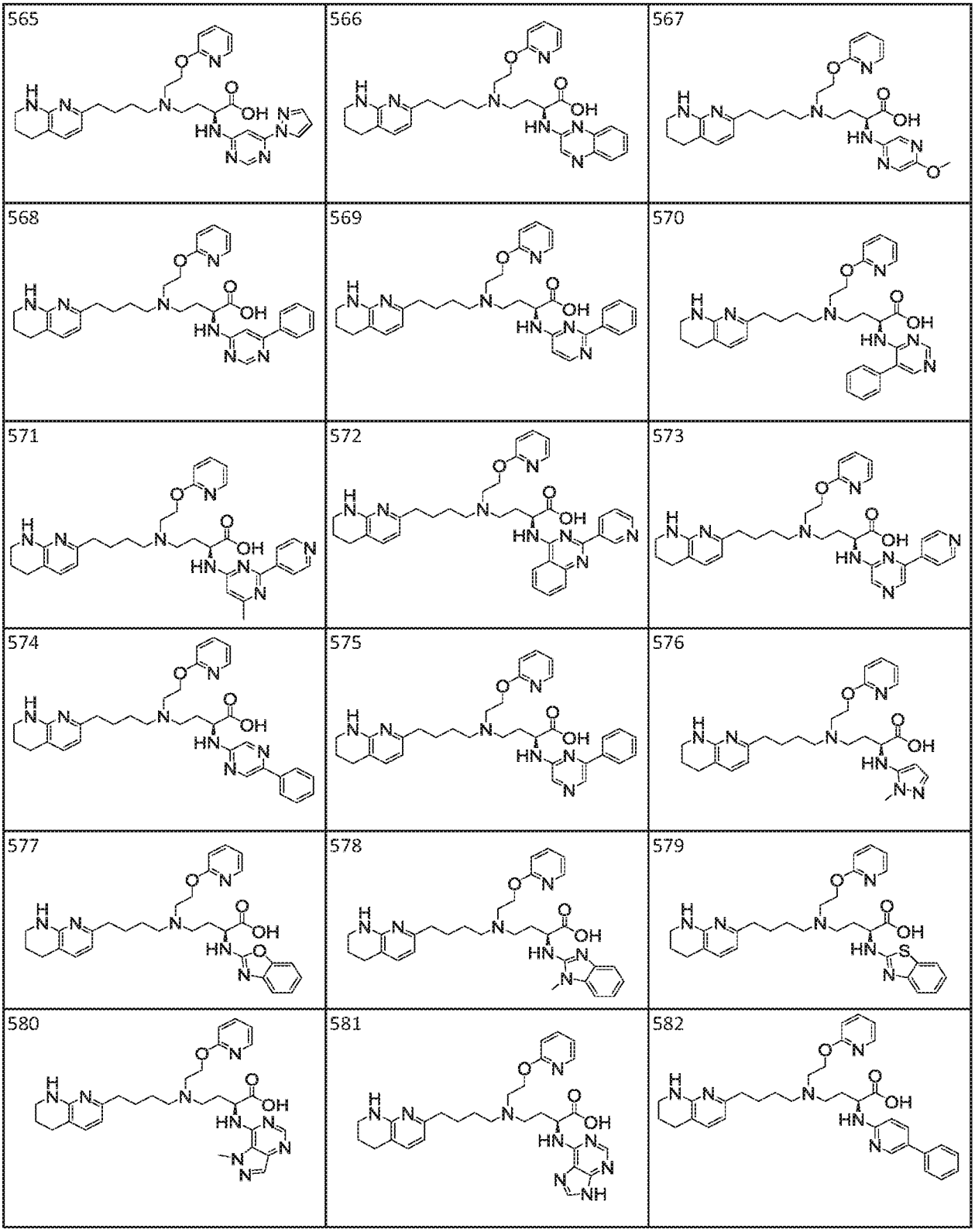
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FIG. 1 (cont.)

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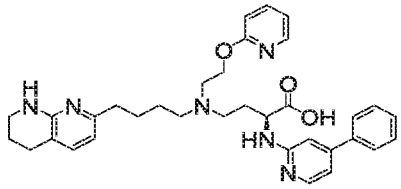

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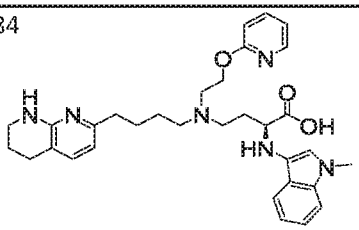

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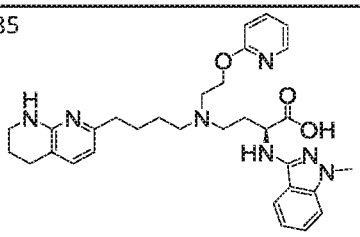

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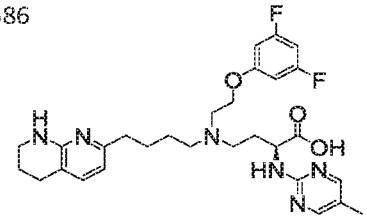

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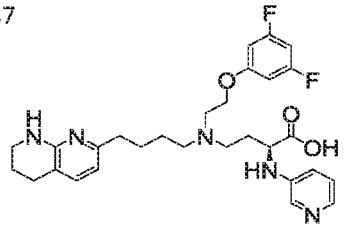

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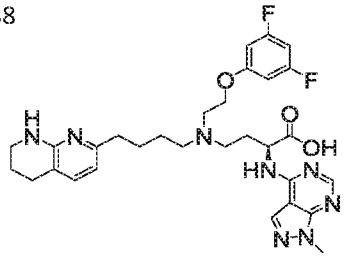

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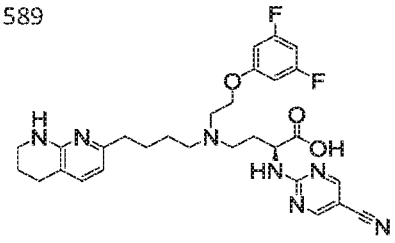

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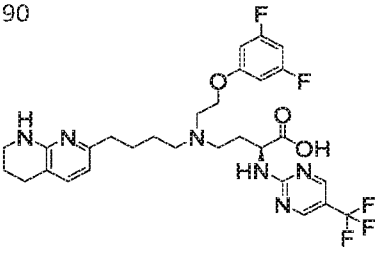

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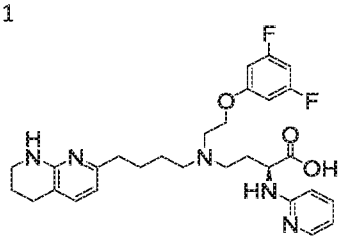

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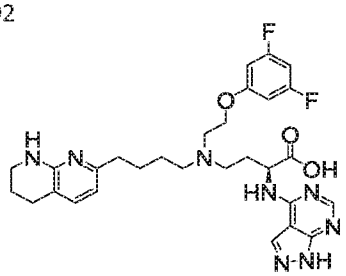

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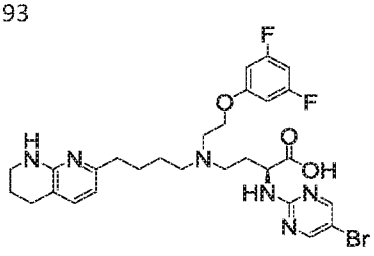

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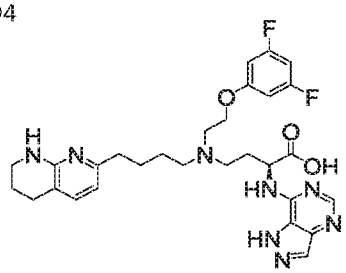

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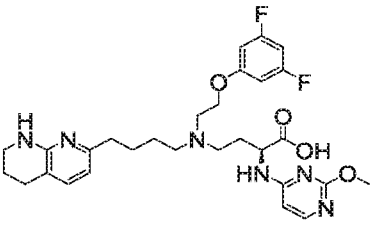

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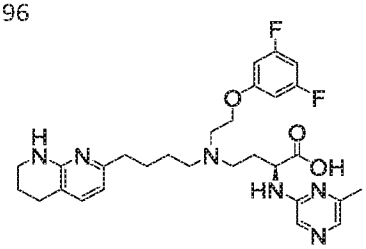

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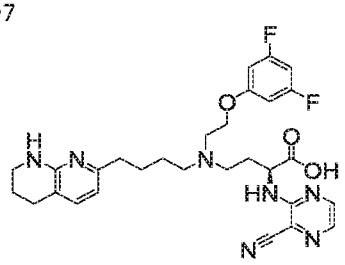

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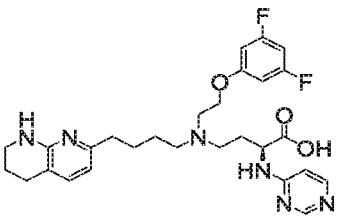

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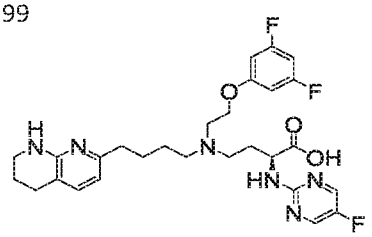

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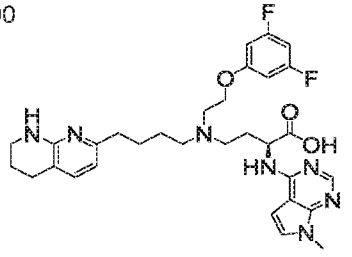

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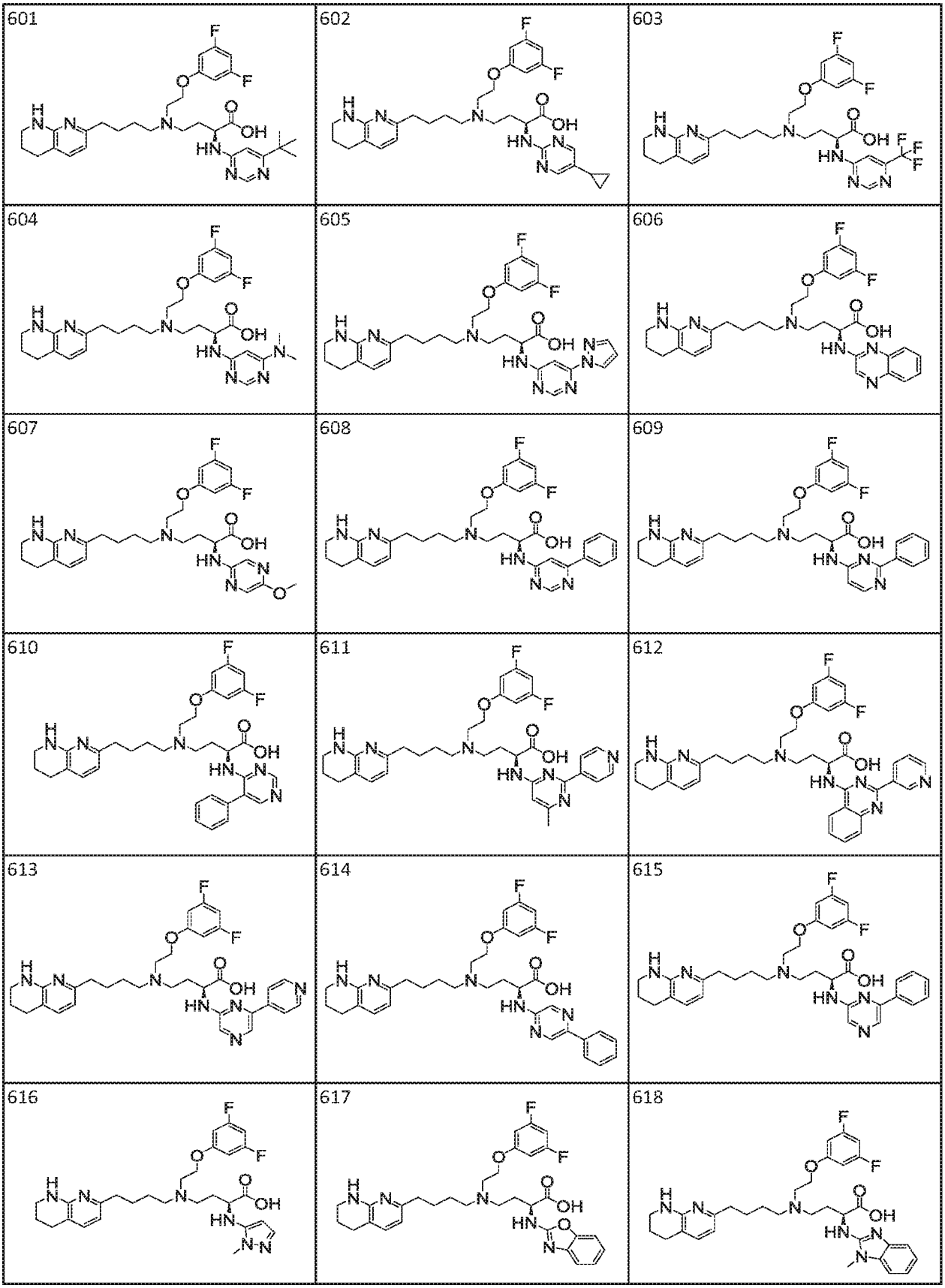
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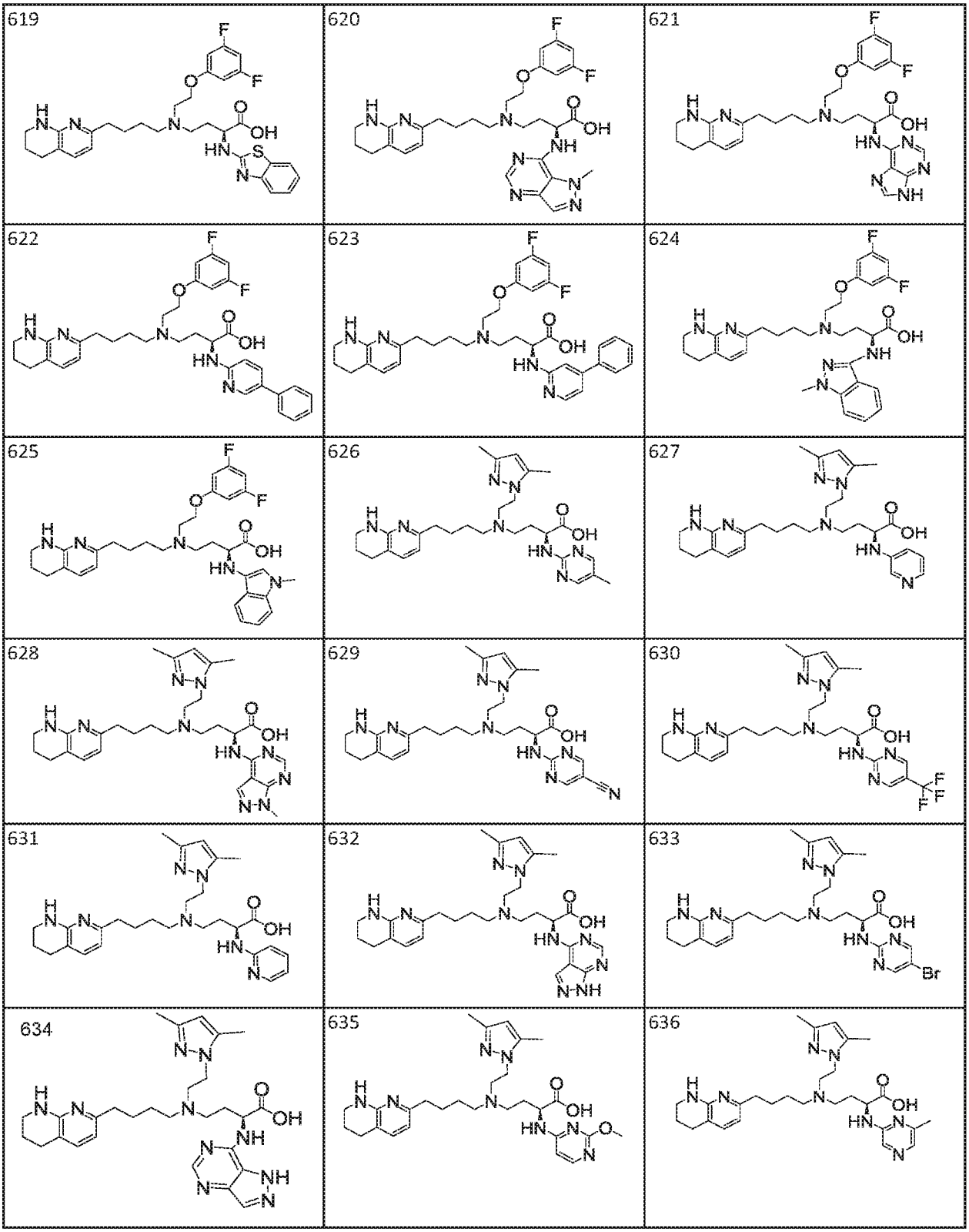
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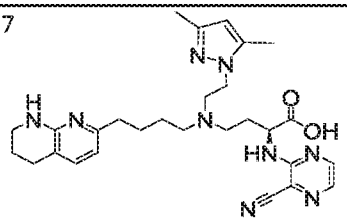
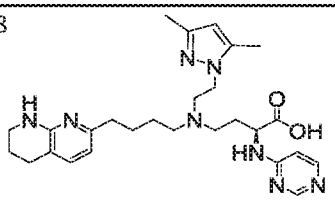
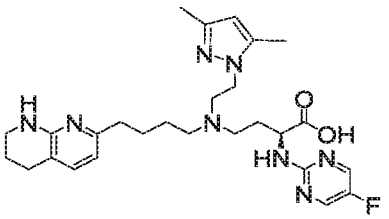
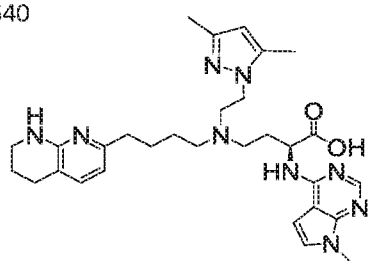
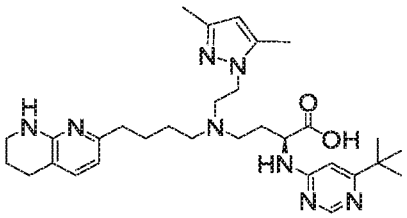
FIG. 1 (cont.)

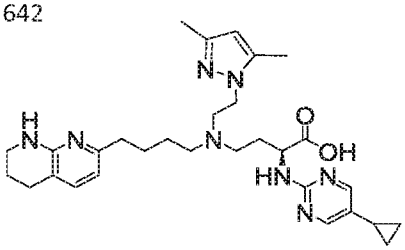
637 

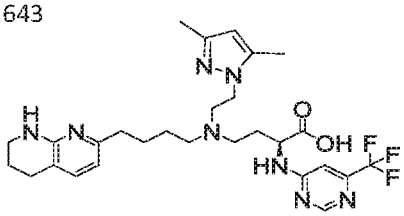
638 

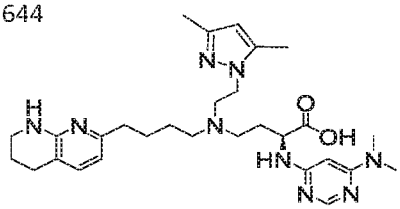
639 

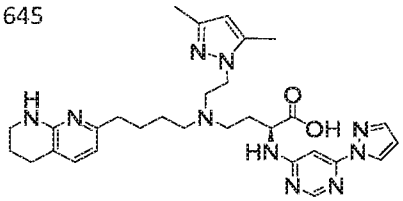
640 

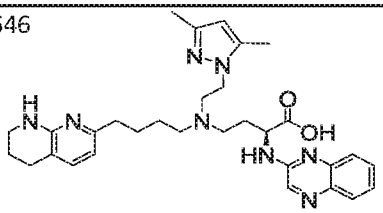
641 

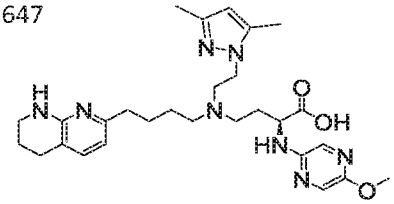
642 

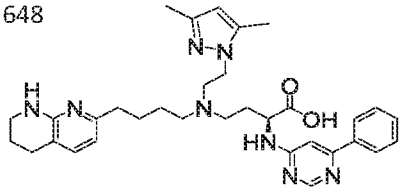
643 

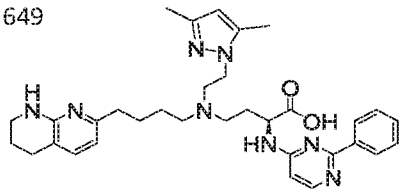
644 

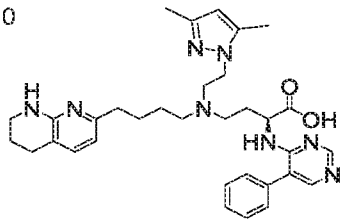
645 

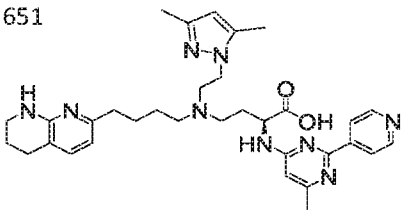
646 

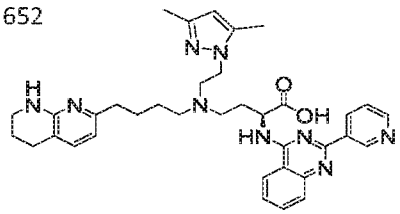
647 

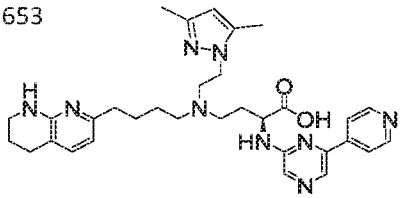
648 

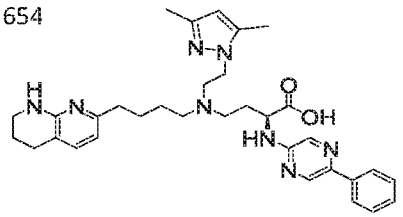
649 

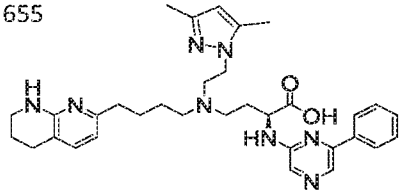
650 

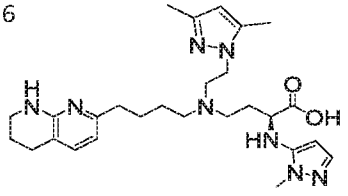
651 

652 

653 

654 

655 

656 

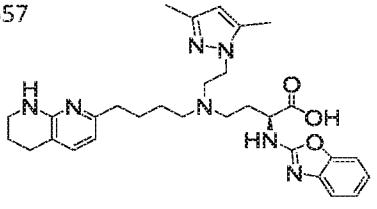
657 

FIG. 1 (cont.)

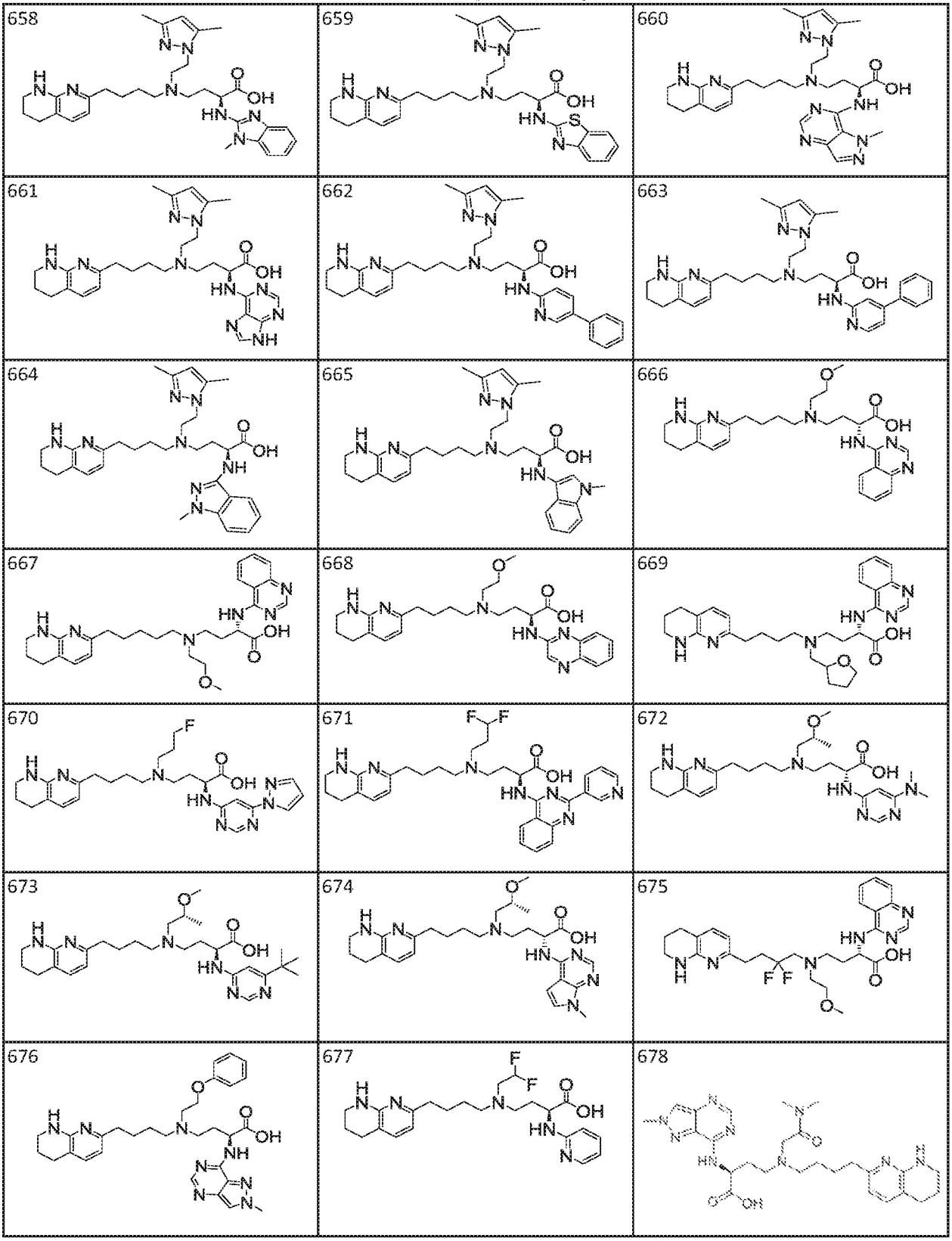

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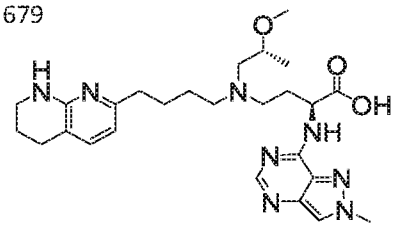
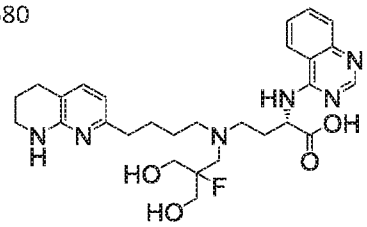
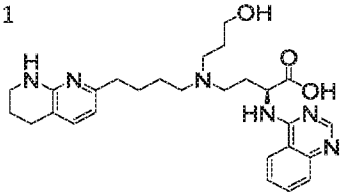
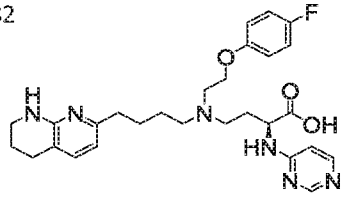
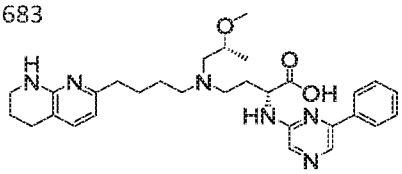
FIG. 1 (cont.)

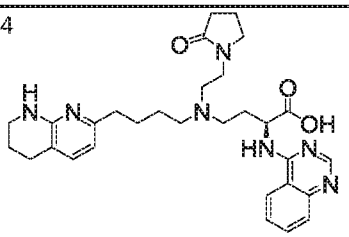
679 

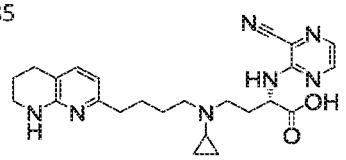
680 

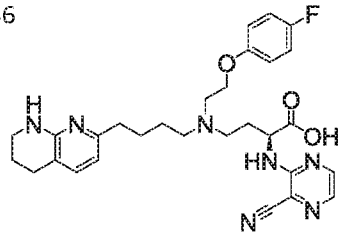
681 

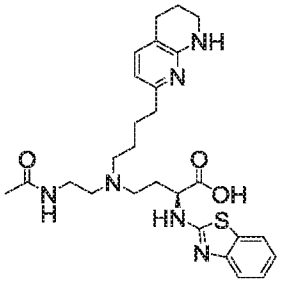
682 

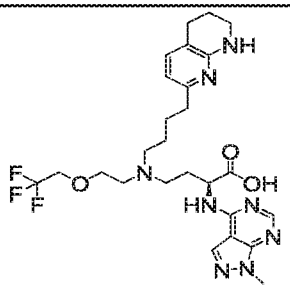
683 

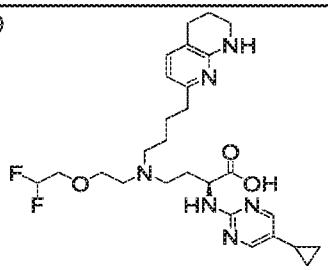
684 

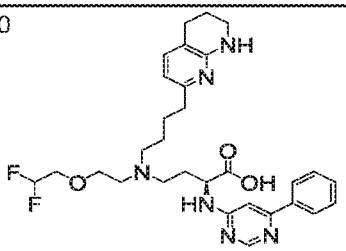
685 

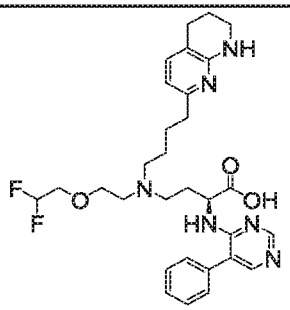
686 

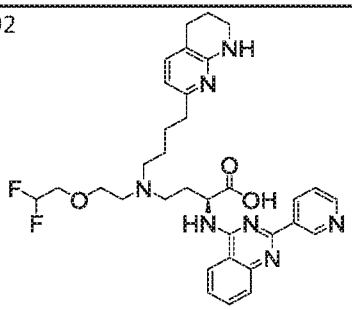
687 

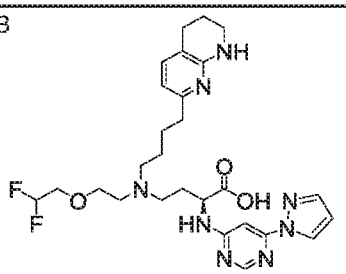
688 

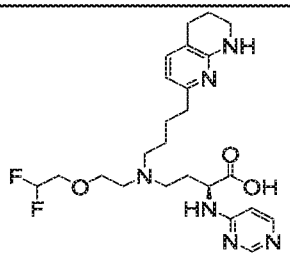
689 

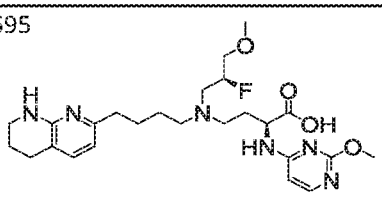
690 

691 

692 

693 

694 

695 

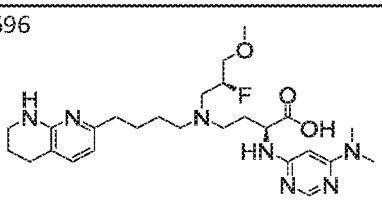
696 

FIG. 1 (cont.)

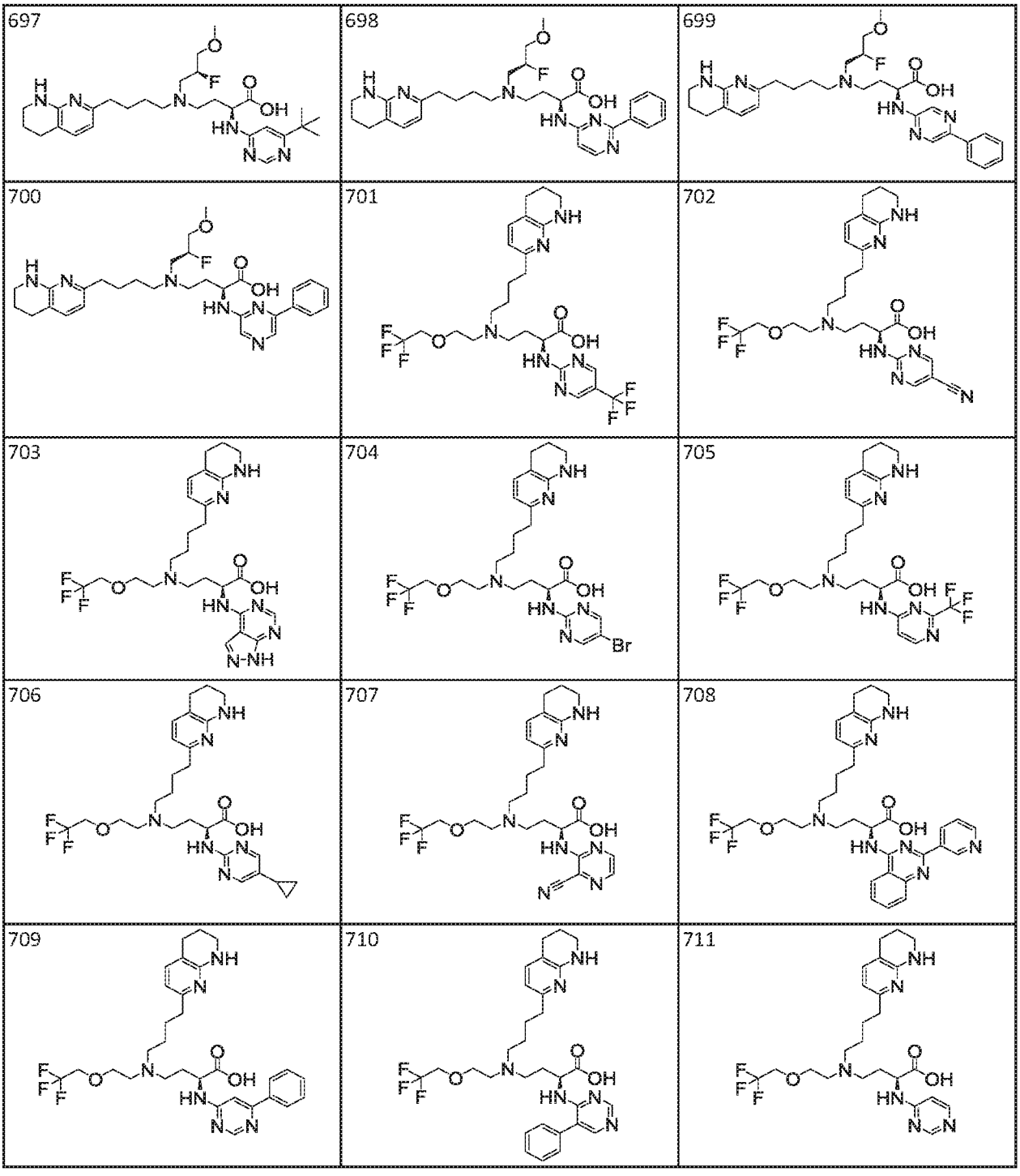


FIG. 1 (cont.)

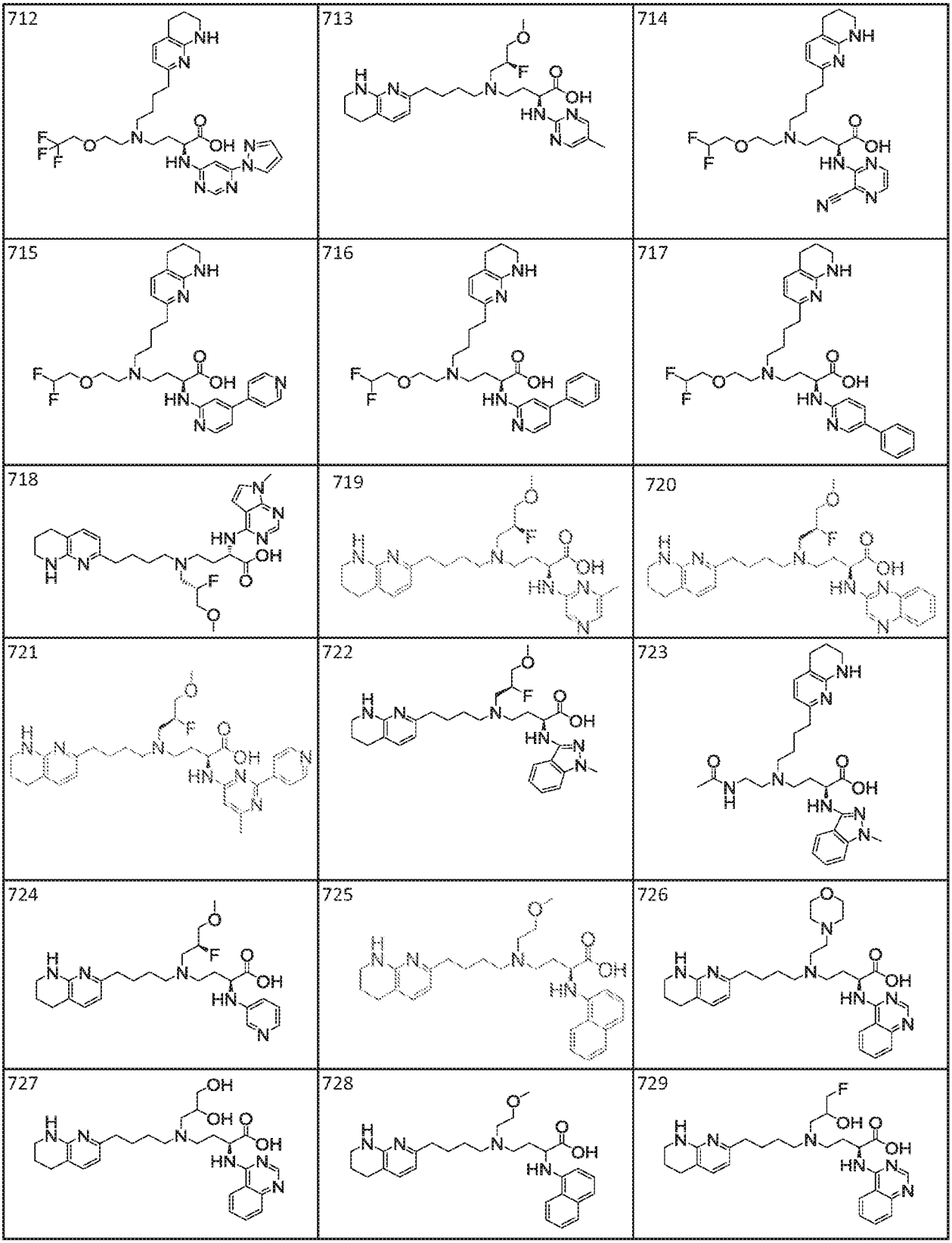

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FIG. 1 (cont.)

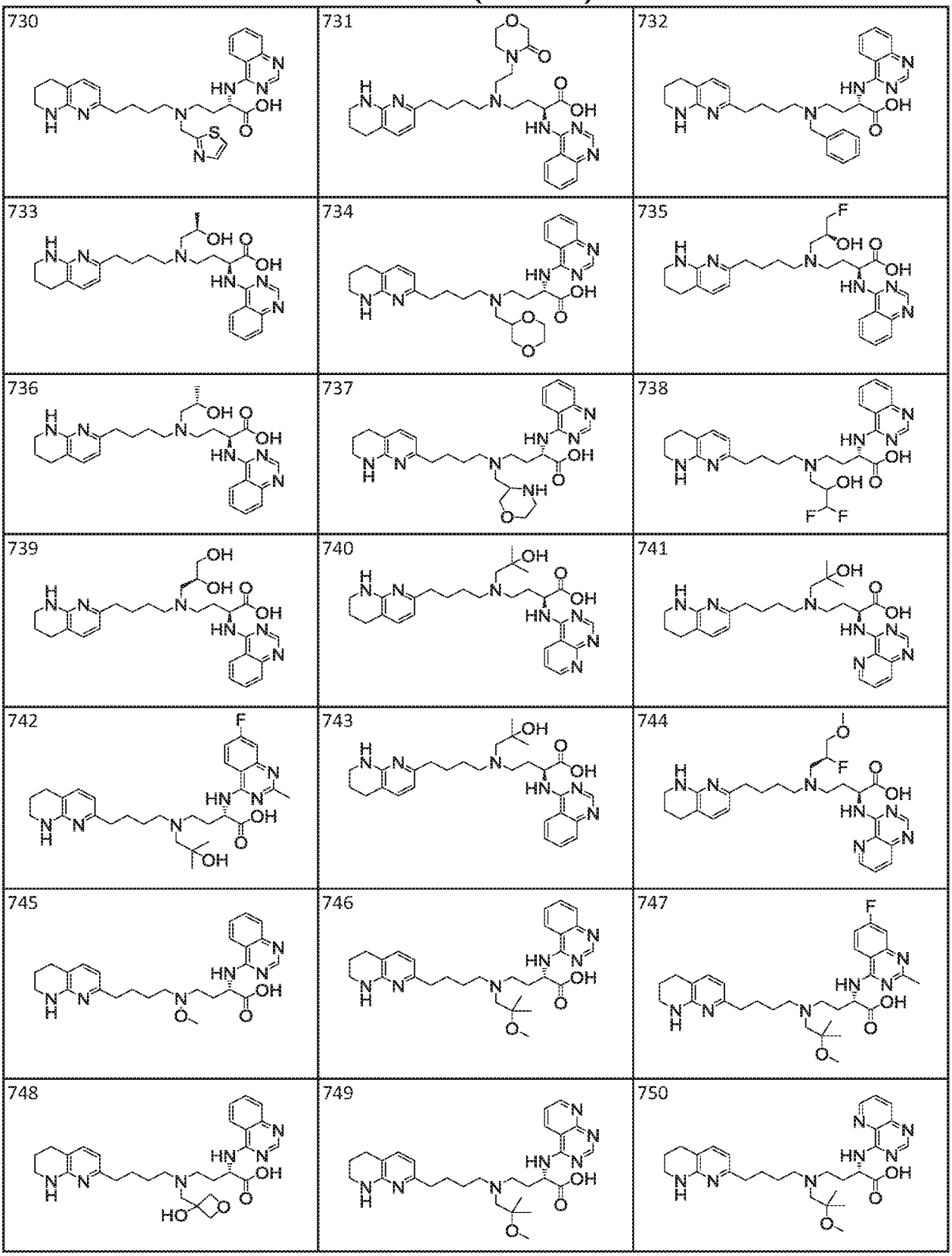
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FIG. 1 (cont.)

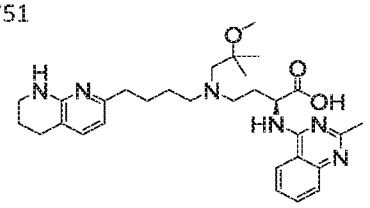
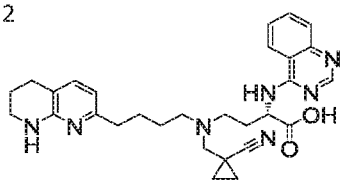
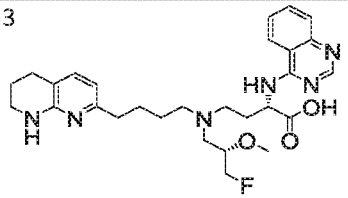
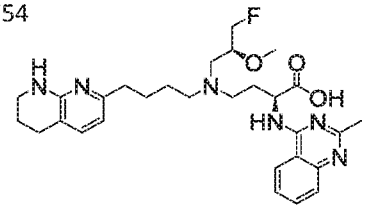
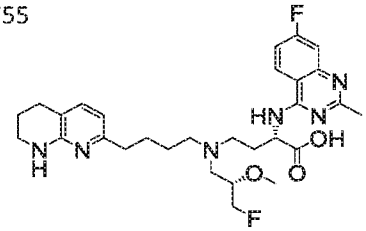
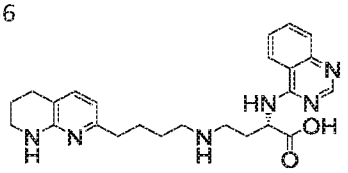
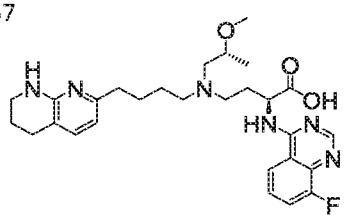
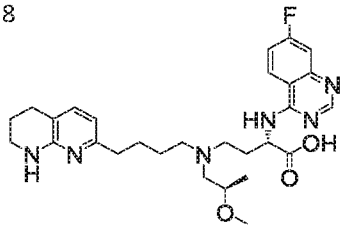
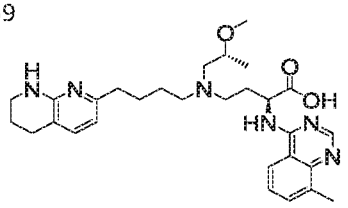
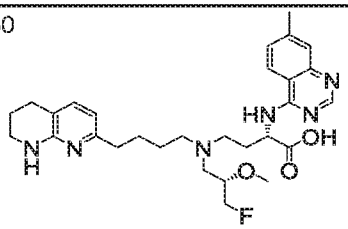
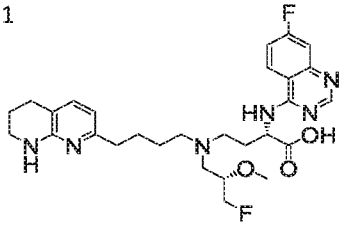
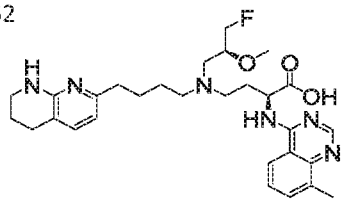
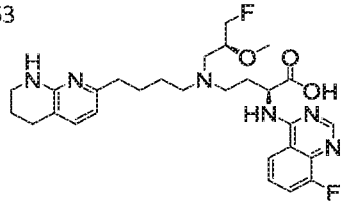
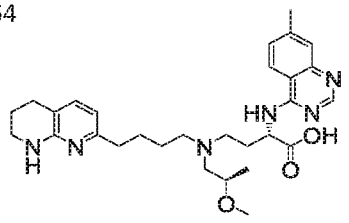
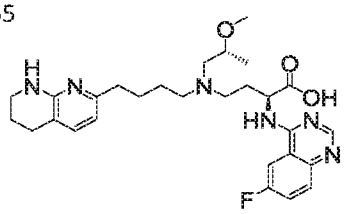
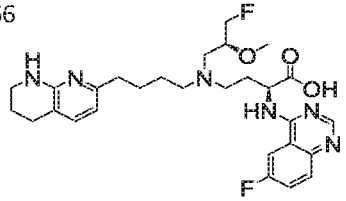
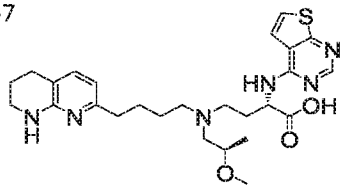
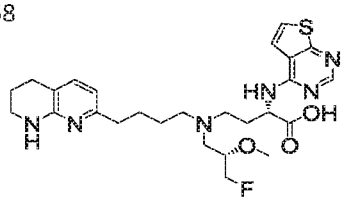
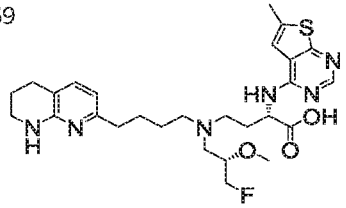
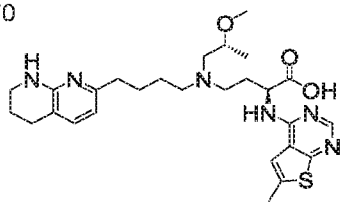
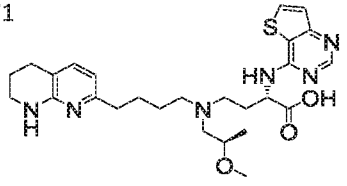
751 	752 	753 
754 	755 	756 
757 	758 	759 
760 	761 	762 
763 	764 	765 
766 	767 	768 
769 	770 	771 

FIG. 1 (cont.)

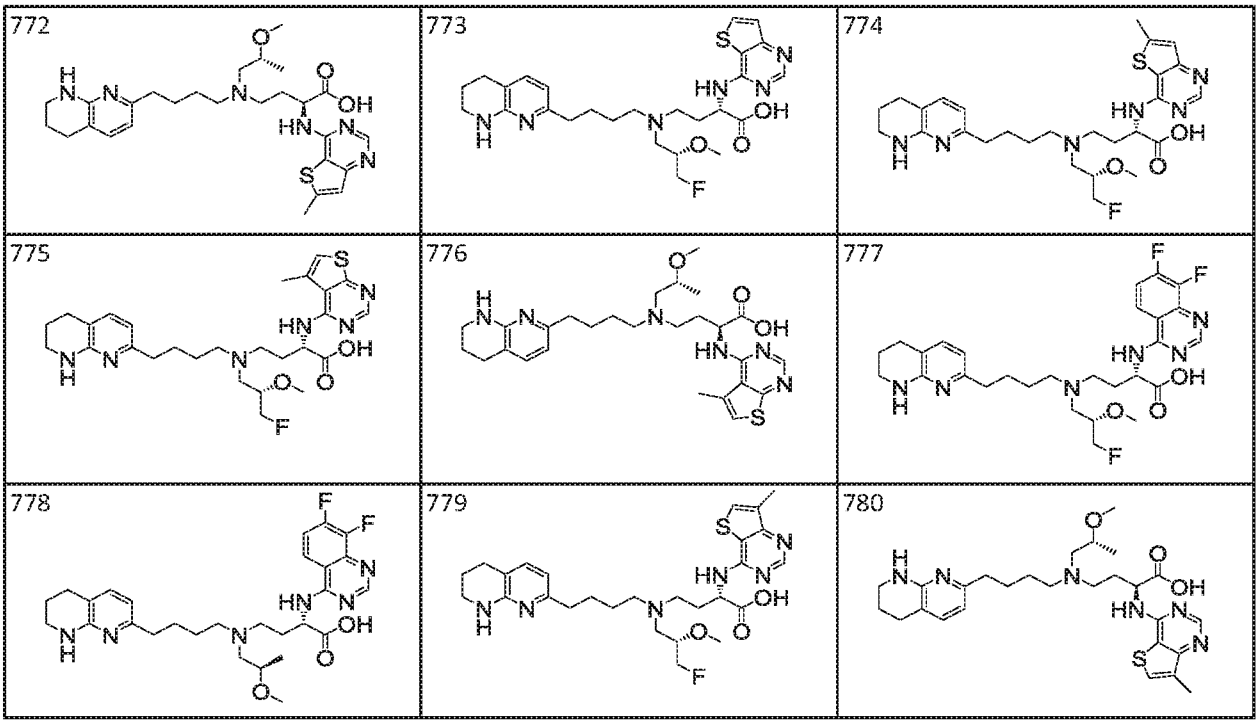


FIG. 2

Table B-3

#	Solid phase assay		Proximity-based assay		#	Solid phase assay		Proximity-based assay	
	$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$		$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$
1	>1000	250-1000		50-250	41		<50		<50
2	>1000	250-1000		>1000	42	<50	<50		<50
3	>1000	50-250		250-1000	43		<50		
4	>1000	50-250	>1000	50-250	44	<50	<50		
5	<50	<50			45	50-250	<50		
6		50-250		<50	46		<50	<50	<50
7		<50		<50	47		<50		<50
8		50-250		<50	48		<50		<50
9		>1000		50-250	49		<50		<50
10	<50	<50			50		<50		<50
11	<50	<50		<50	51		<50		<50
12	<50	<50		<50	52		<50		<50
13		50-250		<50	53		<50	50-250	<50
14		<50		<50	54		<50		<50
15		<50		<50	55		<50		<50
16	<50	<50		<50	56		<50		<50
17		<50		<50	57		<50		<50
18		<50		<50	58		<50		<50
19		<50		<50	59		<50		<50
20		<50		<50	60		<50		<50
21		<50		<50	61		<50		<50
22	<50	<50		<50	62	<50	<50		<50
23	<50	<50		<50	63		<50	50-250	<50
24	250-1000	<50		<50	64		<50		<50
25	250-1000	<50	50-250	<50	65	<50	<50	<50	<50
26		<50		<50	66	<50	<50	<50	<50
27		<50		<50	67	<50	<50		
28	<50	<50		<50	68		<50		<50
29		<50		<50	69		<50		<50
30	50-250	<50		<50	70		<50		<50
31	50-250	<50		<50	71		<50		<50
32	50-250	<50		<50	72		<50		<50
33		<50		<50	73		<50		50-250
34		>1000		>1000	74		<50	<50	<50
35	<50	<50		<50	75		<50		<50
36		>1000		>1000	76		<50		<50
37		50-250		<50	77		<50		<50
38	<50	<50		<50	78		<50		<50
39	<50	<50		<50	79		<50	<50	<50
40	<50	<50		<50	80		<50		<50

FIG. 2 (cont.)

#	Solid phase assay		Proximity-based assay		#	Solid phase assay		Proximity-based assay	
	$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$		$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$
81		<50		<50	121		>1000		>1000
82		<50		<50	122		250-1000		250-1000
83		<50		<50	123		<50		<50
84		250-1000		50-250	124		<50		<50
85		250-1000		<50	125		50-250		<50
86		50-250		50-250	126		>1000		250-1000
87		250-1000		50-250	127		250-1000		50-250
88		>1000		>1000	128		>1000		50-250
89		<50		<50	129		<50	<50	<50
90		<50		<50	130		<50		<50
91		<50		<50	131		50-250		50-250
92		<50			132		50-250		50-250
93		<50			133		50-250		<50
94		<50			134		50-250		250-1000
95		>1000		>1000	135		50-250		50-250
96		>1000		>1000	136		<50		<50
97		>1000		>1000	137		<50		50-250
98		>1000		>1000	138		<50		<50
99		250-1000		250-1000	139		<50		<50
100		<50		<50	140		<50		<50
101		50-250		50-250	141		50-250		50-250
102		>1000		250-1000	142		>1000		
103		>1000		250-1000	143		50-250		
104		>1000		250-1000	144		50-250		
105		<50		<50	145		<50		50-250
106		<50		<50	146		>1000		>1000
107		250-1000		<50	147		50-250		<50
108		>1000		250-1000	149		50-250		250-1000
109		<50		<50	152		>1000		250-1000
110		<50		<50	154		>1000		250-1000
111		<50		<50	156		50-250		250-1000
112		250-1000		250-1000	158		>1000		250-1000
113		250-1000		50-250	159		>1000		50-250
114		<50		250-1000	162		<50		<50
115		50-250		250-1000	163		>1000		50-250
116		50-250		50-250	172		>1000		250-1000
117		<50		<50	178		>1000		250-1000
118		>1000		>1000	181	>1000	>1000		>1000
119		>1000			182	>1000	>1000		>1000
120	>1000	>1000		>1000	183	>1000	>1000		>1000

FIG. 2 (cont.)

#	Solid phase assay		Proximity-based assay		#	Solid phase assay		Proximity-based assay	
	$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$		$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$
185	>1000	>1000		>1000	264	250-1000	>1000		50-250
186	>1000	>1000		>1000	266	>1000	50-250		50-250
187	>1000	>1000		>1000	267		<50		
188	>1000	>1000		>1000	268		50-250		<50
190	>1000	>1000		>1000	269	<50	50-250		<50
191	>1000	>1000		>1000	270		<50		
192	>1000	>1000		50-250	272		250-1000		
193	>1000	>1000		>1000	273		50-250		
194	>1000	>1000		>1000	278		<50		<50
195		<50		<50	282		>1000		
196		>1000		50-250	284		<50		50-250
200		<50		<50	287	250-1000	250-1000		50-250
204	<50	<50		<50	288	50-250	<50		50-250
205		<50		<50	302		<50		<50
209		50-250		50-250	309		50-250		<50
210		<50			310		<50		<50
213		>1000		50-250	311		<50		<50
215		<50		<50	312	<50	50-250		<50
220		<50		<50	313	<50	<50		<50
222		50-250		<50	314		50-250		<50
224		>1000		50-250	315		<50		<50
228	<50	<50		<50	316		<50		<50
229		<50		<50	317	<50	<50		<50
230		<50		<50	318		<50		<50
231		<50		<50	319		<50		<50
232		<50		<50	320		<50		<50
233	>1000	>1000		>1000	321	<50	50-250		<50
236		<50			322	>1000	50-250		<50
243	250-1000	>1000		250-1000	323	<50	<50		<50
246	>1000	250-1000		50-250	324	<50	<50		<50
248		<50		<50	325	<50	<50		<50
250	>1000	50-250		50-250	326	<50	<50		<50
253		50-250		<50	327	<50	<50		<50
254	<50	<50		50-250	328	250-1000	50-250		<50
255		<50		<50	329	<50	<50		<50
256	>1000	50-250		<50	330	>1000	50-250		<50
257		50-250		50-250	332		50-250		<50
258		>1000		50-250	334		50-250		<50
261	>1000	>1000		50-250	335		<50		<50
263		<50		<50	336		50-250		<50

FIG. 2 (cont.)

#	Solid phase assay		Proximity-based assay	
	$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$
340	>1000	50-250		<50
341	>1000	>1000		<50
342		50-250		250-1000
343		50-250		<50
344	250-1000	<50		<50
345	50-250	50-250		<50
346		250-1000		<50
347	50-250	>1000		<50
348	>1000	250-1000		50-250
349	250-1000	50-250		<50
350	>1000	>1000		250-1000
352	>1000	>1000		<50
353	>1000	>1000		50-250
354		<50	<50	<50
357	>1000	>1000		50-250
360	>1000	<50		<50
362	>1000	>1000		50-250
364		<50		<50
365		50-250		50-250
369		50-250		<50
371		50-250		50-250
372		50-250		<50
375		<50		<50
377		<50		<50
379	<50	<50		<50
381	<50	<50	<50	<50
382	<50	<50		<50
383	<50	<50		<50
384	>1000	250-1000		50-250
666	50-250	<50		
667	50-250	<50		
668	<50	<50		<50
669	<50	<50	<50	<50
670	>1000	50-250		<50
671	250-1000	50-250		<50
672		<50		
673		<50		<50
674		<50		
675	>1000	>1000		>1000
676		<50		<50

#	Solid phase assay		Proximity-based assay	
	$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$
677		>1000		250-1000
678		<50		<50
679		<50		<50
680			>1000	<50
681			<50	<50
682	<50	<50	<50	<50
683	50-250	<50		
684	250-1000	<50		<50
685	250-1000	>1000		250-1000
686	<50	<50		<50
687	>1000	>1000		<50
688	<50	<50		<50
689	<50	<50		<50
690	<50	50-250		<50
691	<50	<50		<50
692	>1000	50-250		<50
693	50-250	50-250		<50
694	<50	<50		<50
695	250-1000	50-250		50-250
696	50-250	50-250		50-250
697	50-250	50-250		<50
698	250-1000	>1000		50-250
699	>1000	>1000		50-250
700	>1000	250-1000		50-250
701	<50	<50		<50
702	50-250	<50		<50
703	<50	<50		<50
704	<50	<50		<50
705	>1000	50-250		250-1000
706	<50	<50		<50
707	<50	<50		
708	>1000	<50		
709	<50	<50		
710	<50	<50	<50	<50
711	<50	<50	50-250	<50
712	50-250	<50	50-250	<50
713	250-1000	<50	250-1000	50-250
714	<50	<50	<50	<50
715	<50	<50	<50	<50
716	<50	50-250	50-250	<50

FIG. 2 (cont.)

#	Solid phase assay		Proximity-based assay	
	$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$
717	<50	<50	50-250	<50
718	<50	<50	<50	<50
719	>1000	<50	250-1000	50-250
720	250-1000	<50	250-1000	<50
721	250-1000	<50	50-250	50-250
722	>1000	50-250	>1000	250-1000
723	>1000	50-250	>1000	<50
724	>1000	250-1000	>1000	250-1000
725	>1000	250-1000	250-1000	50-250
726	50-250	<50	50-250	<50
727	<50	<50		<50
728			>1000	50-250
729			<50	<50
730			250-1000	50-250
731			250-1000	<50
732			250-1000	<50
733			<50	<50
734			<50	<50
735			<50	<50
736			<50	<50
737			>1000	50-250
738			50-250	<50
739			<50	<50
740			250-1000	<50
741			250-1000	<50
742			50-250	<50
743				
744				
745			50-250	50-250
746			50-250	<50
747			50-250	<50
748			<50	<50
749			50-250	<50
750			250-1000	<50
751			50-250	<50
752			50-250	<50
753			<50	<50
754			<50	<50
755			<50	<50
756				

#	Solid phase assay		Proximity-based assay	
	$\alpha v\beta_1$	$\alpha v\beta_6$	$\alpha v\beta_1$	$\alpha v\beta_6$
757			<50	<50
758			<50	<50
759			<50	<50
760			<50	<50
761			<50	<50
762			<50	<50
763			<50	<50
764			<50	<50
765			<50	<50
766			<50	<50
767			<50	<50
768			<50	<50
769			50-250	<50
770			<50	<50
771			<50	<50
772			<50	<50
773			<50	<50
774			<50	<50
775			<50	<50
776			<50	<50
777			<50	<50
778			<50	<50
779			<50	<50
780			<50	<50

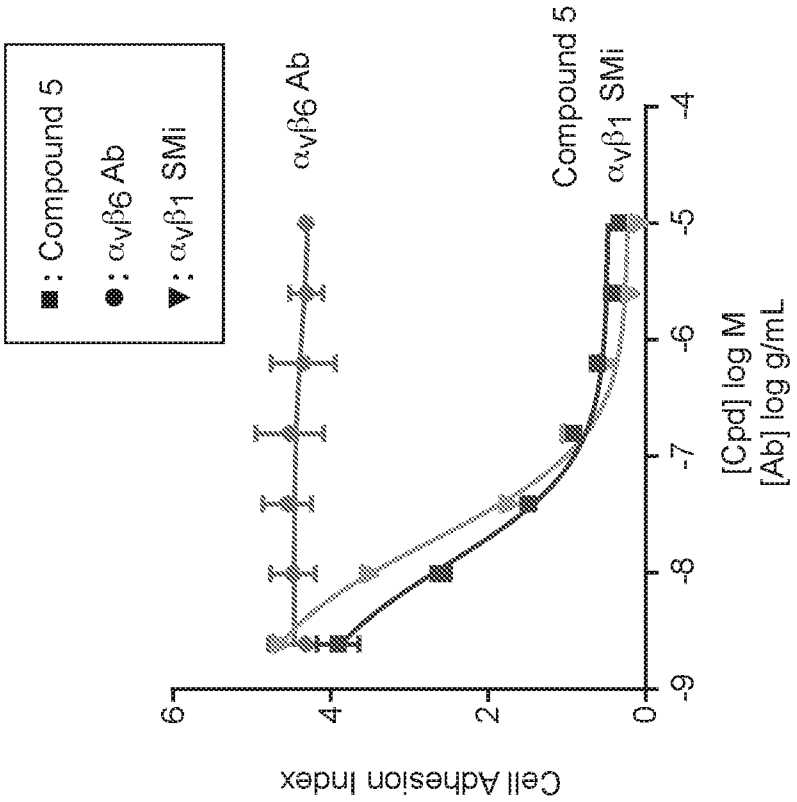

■: Compound 5
●: αvβ6 Ab
▼: αvβ1 SMi
αvβ6 Ab
Compound 5
αvβ1 SMi
Cell Adhesion Index
[Cpd] log M
[Ab] log g/mL

FIG. 3B

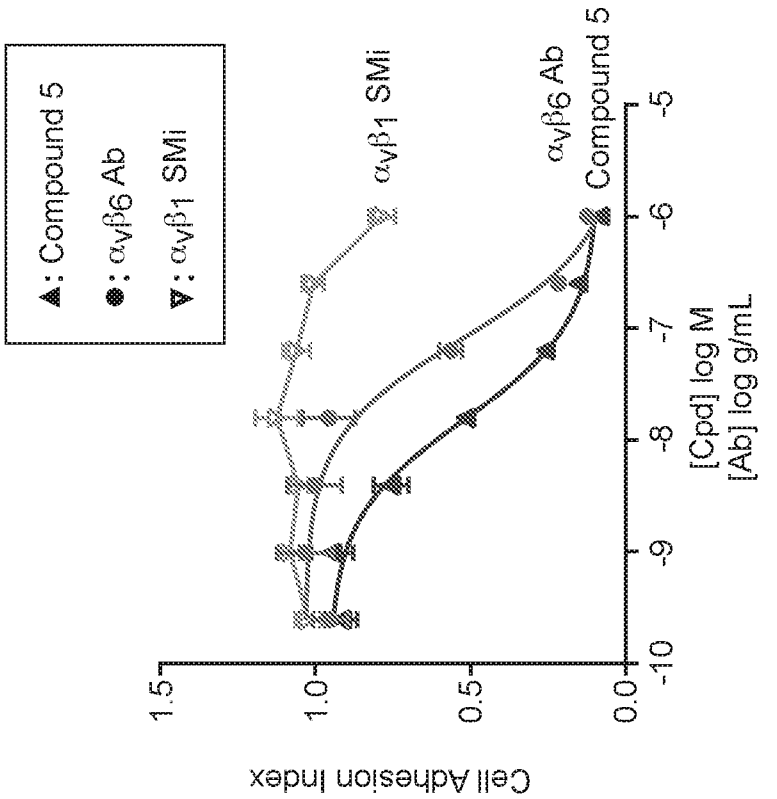

▲: Compound 5
●: αvβ6 Ab
▼: αvβ1 SMi
αvβ1 SMi
αvβ6 Ab
Compound 5
Cell Adhesion Index
[Cpd] log M
[Ab] log g/mL

FIG. 3A

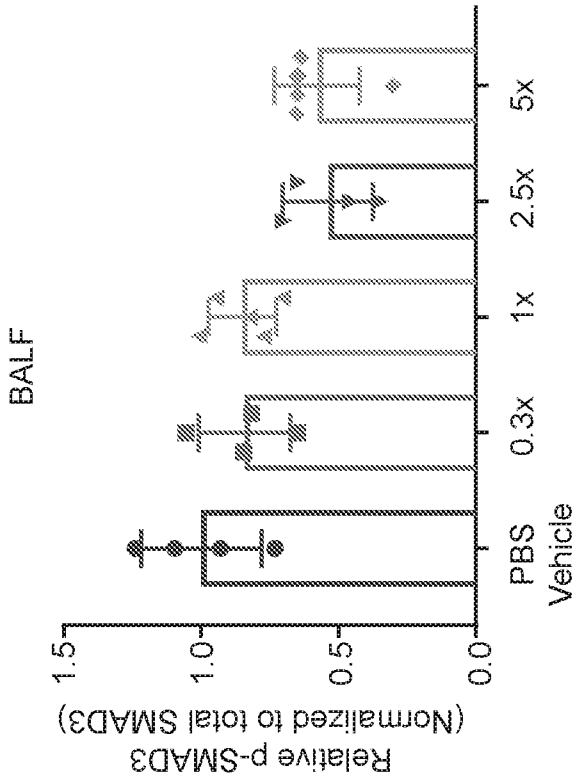

BALF
Relative p-SMAD3
(Normalized to total SMAD3)
1.5
1.0
0.5
0.0
PBS
Vehicle
0.3x
1x
2.5x
5x

FIG. 4B

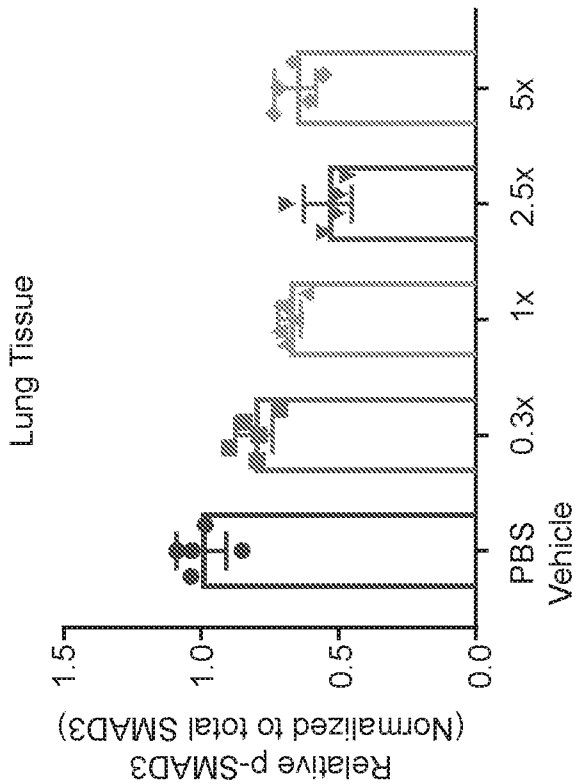

Lung Tissue
Relative p-SMAD3
(Normalized to total SMAD3)
1.5
1.0
0.5
0.0
PBS
Vehicle
0.3x
1x
2.5x
5x

FIG. 4A

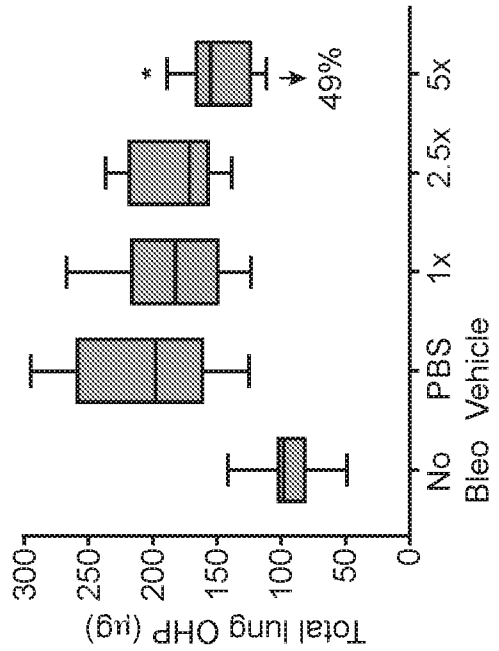


FIG. 4E

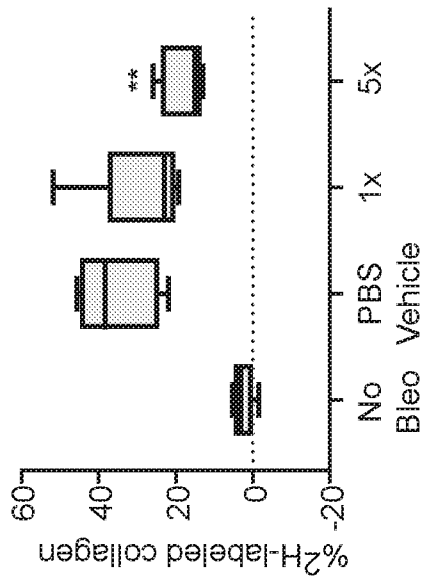


FIG. 4D

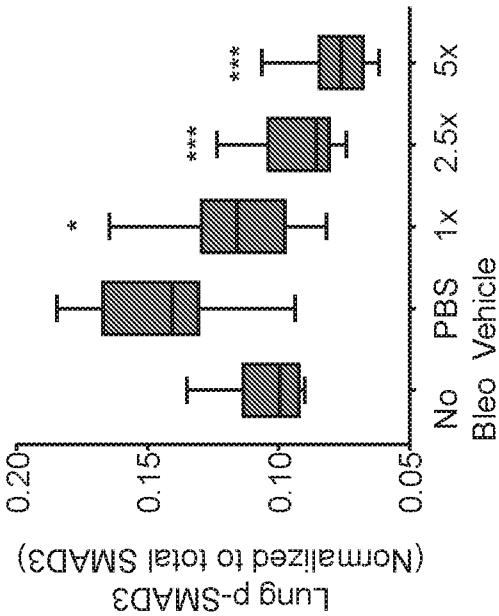


FIG. 4C

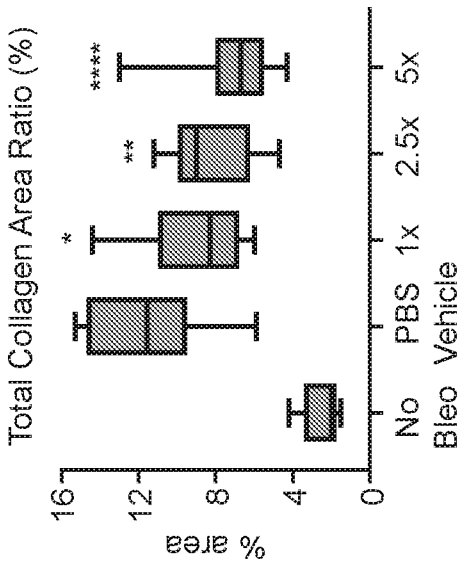


FIG. 4I

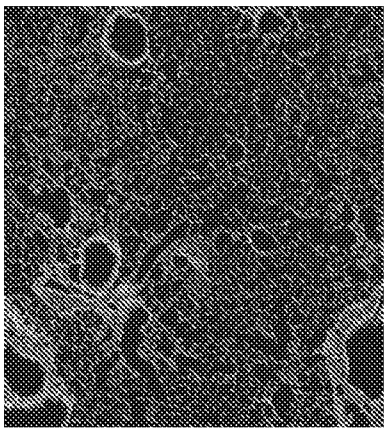


FIG. 4H

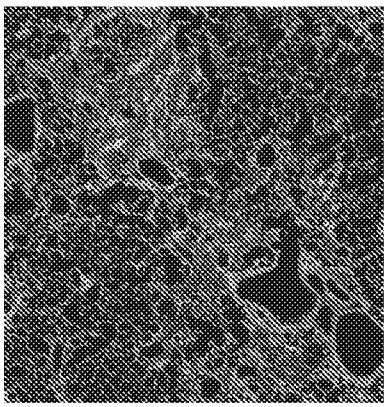


FIG. 4G

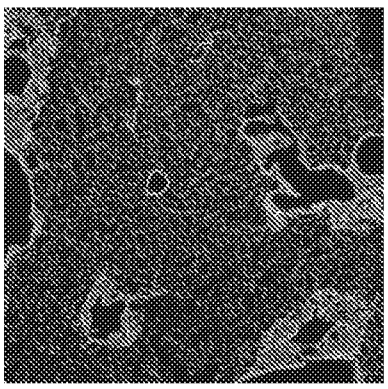


FIG. 4F

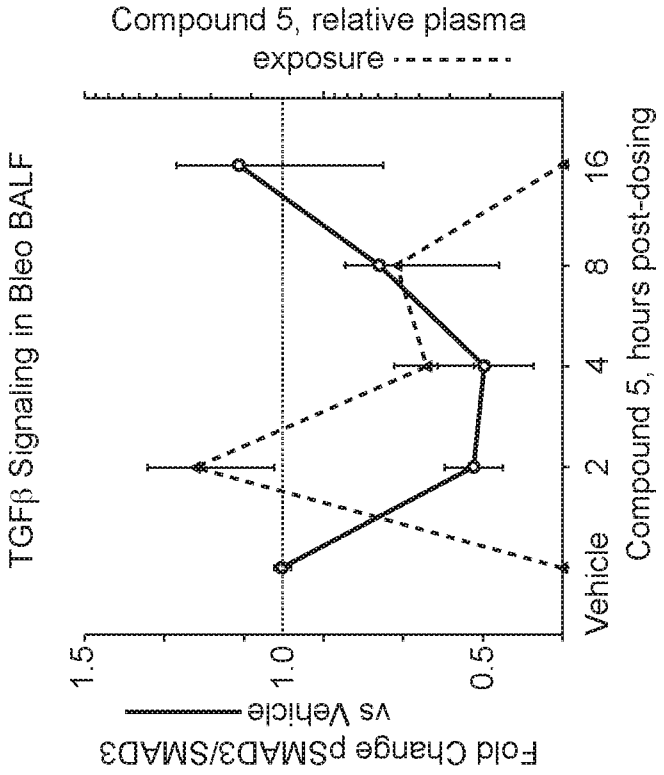

Compound 5, relative plasma exposure
TGFβ Signaling in Bleo BALF
Fold Change pSMAD3/SMAD3 vs Vehicle
1.5
1.0
0.5
Vehicle
2
4
8
16
Compound 5, hours post-dosing

FIG. 4K

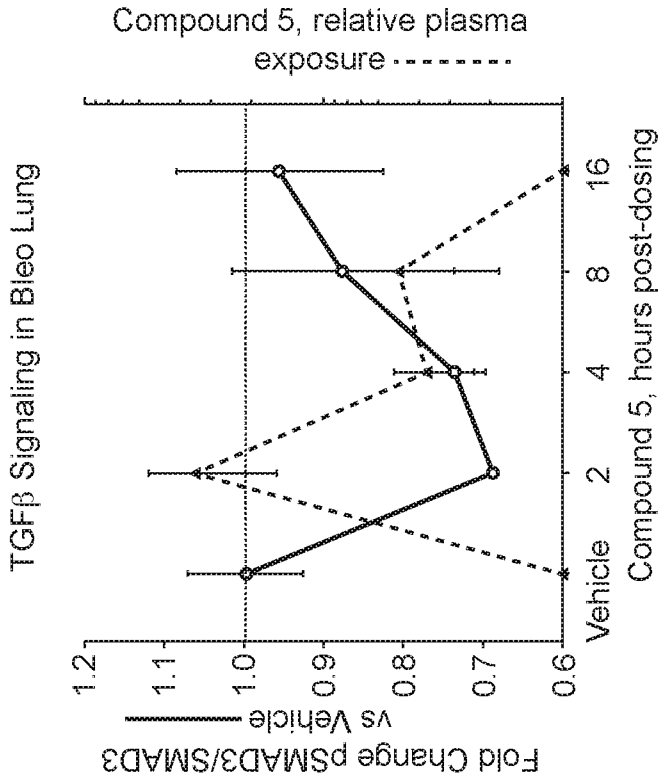

Compound 5, relative plasma exposure
TGFβ Signaling in Bleo Lung
Fold Change pSMAD3/SMAD3 vs Vehicle
1.2
1.1
1.0
0.9
0.8
0.7
0.6
Vehicle
2
4
8
16
Compound 5, hours post-dosing

FIG. 4J

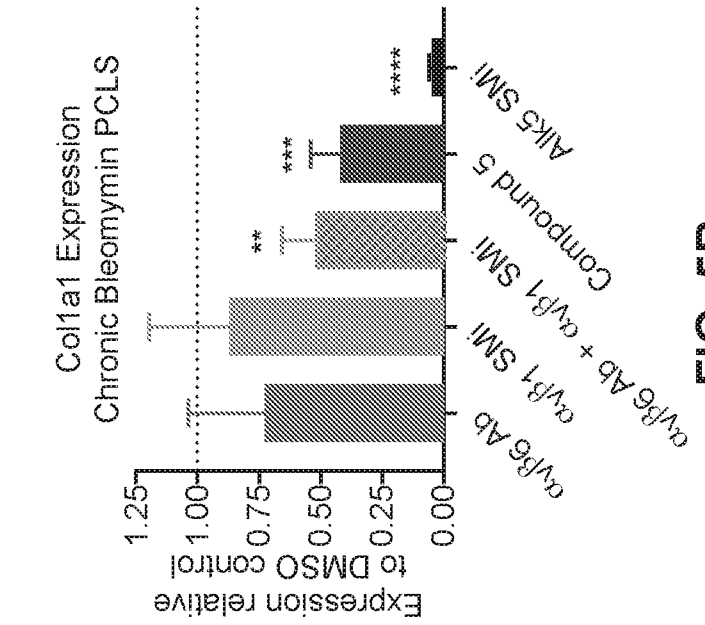

Col1a1 Expression
Chronic Bleomymin PCLS
Expression relative
to DMSO control
1.25
1.00
0.75
0.50
0.25
0.00
αvβ6 Ab
αvβ1 SMI
αvβ6 Ab + αvβ1 SMI
Compound 5
Alk5 SMI
**
***
****

FIG. 5B

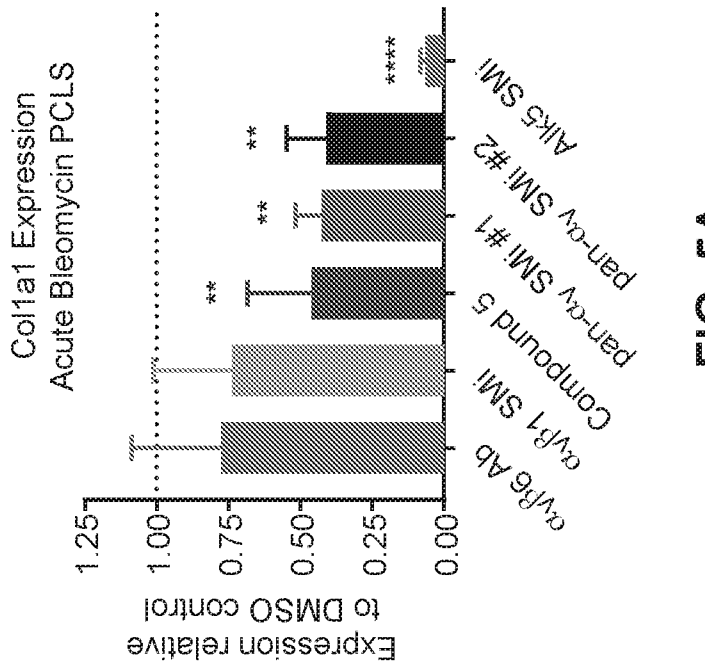

Col1a1 Expression
Acute Bleomycin PCLS
Expression relative
to DMSO control
1.25
1.00
0.75
0.50
0.25
0.00
αvβ6 Ab
αvβ1 SMI
Compound 5
pan-αv SMI #1
pan-αv SMI #2
Alk5 SMI
**
**
**
****

FIG. 5A

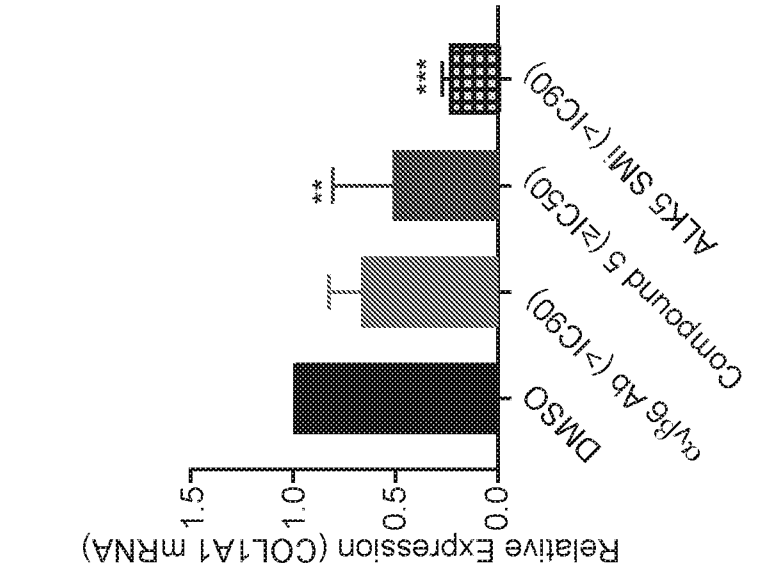


FIG. 6C

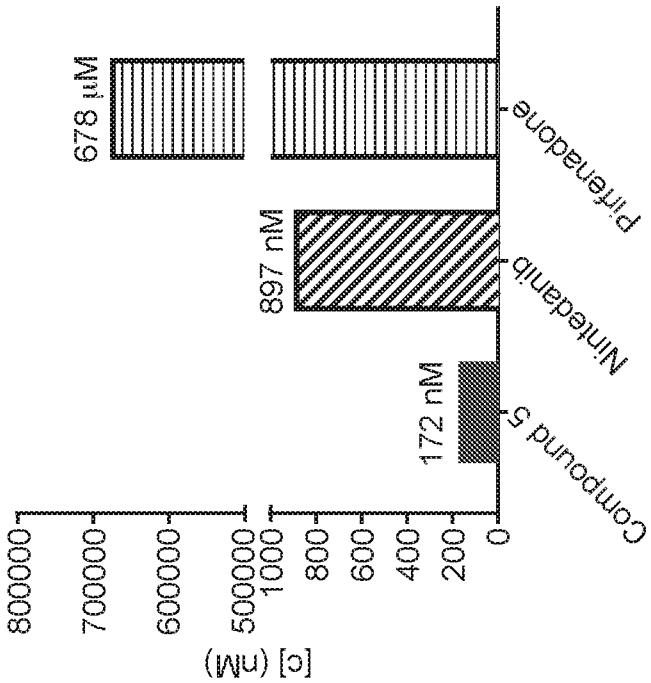


FIG. 6B

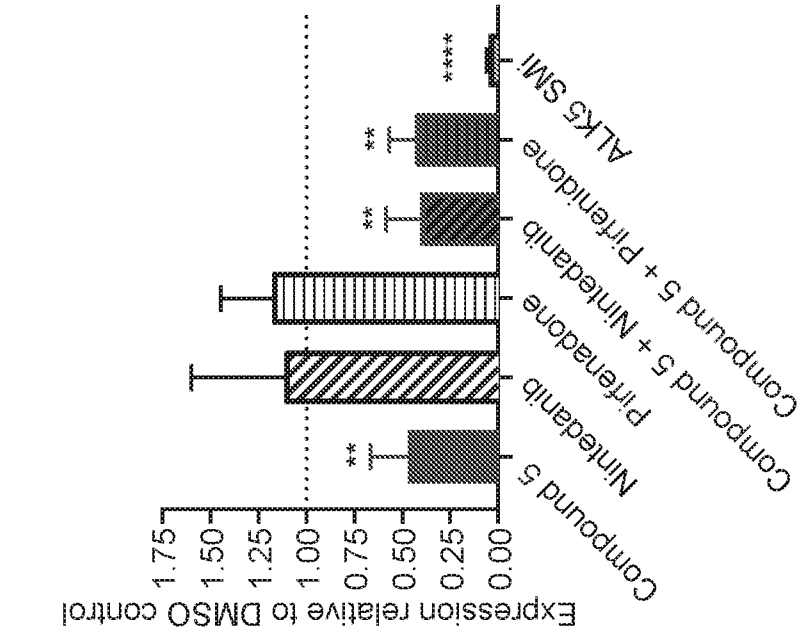


FIG. 6A

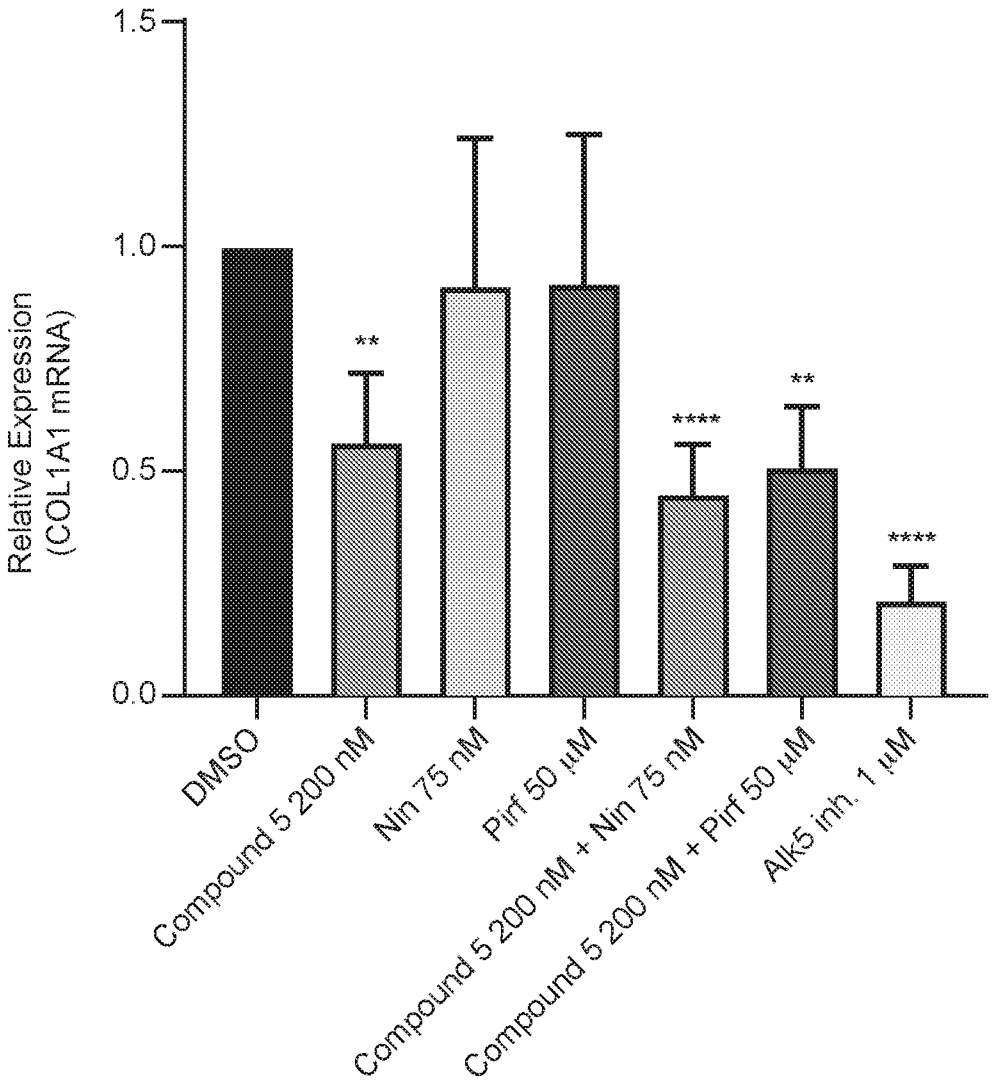

1.5
1.0
0.5
0.0
Relative Expression
(COL1A1 mRNA)
**
****
**
****
DMSO
Compound 5 200 nM
Nin 75 nM
Pirf 50 µM
Compound 5 200 nM + Nin 75 nM
Compound 5 200 nM + Pirf 50 µM
Alk5 inh. 1 µM

FIG. 6D

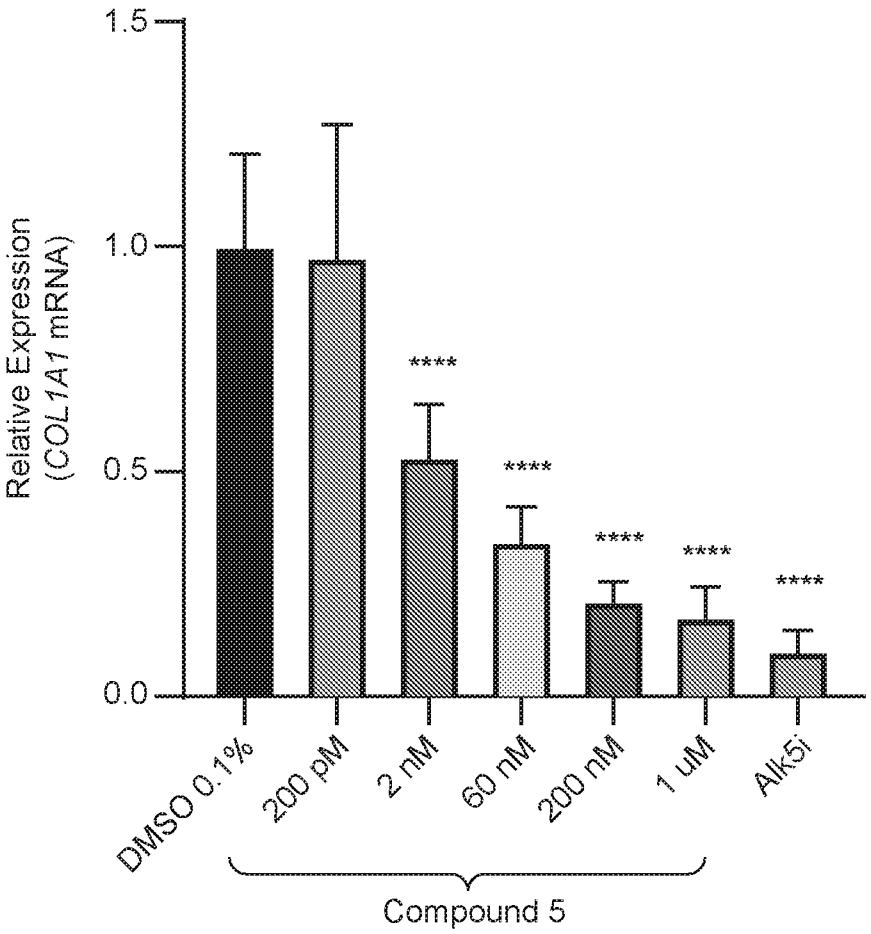

1.5
1.0
0.5
0.0
Relative Expression
(COL1A1 mRNA)
****
****
****
****
****
DMSO 0.1%
200 pM
2 nM
60 nM
200 nM
1 uM
Alk5i
Compound 5

FIG. 6E

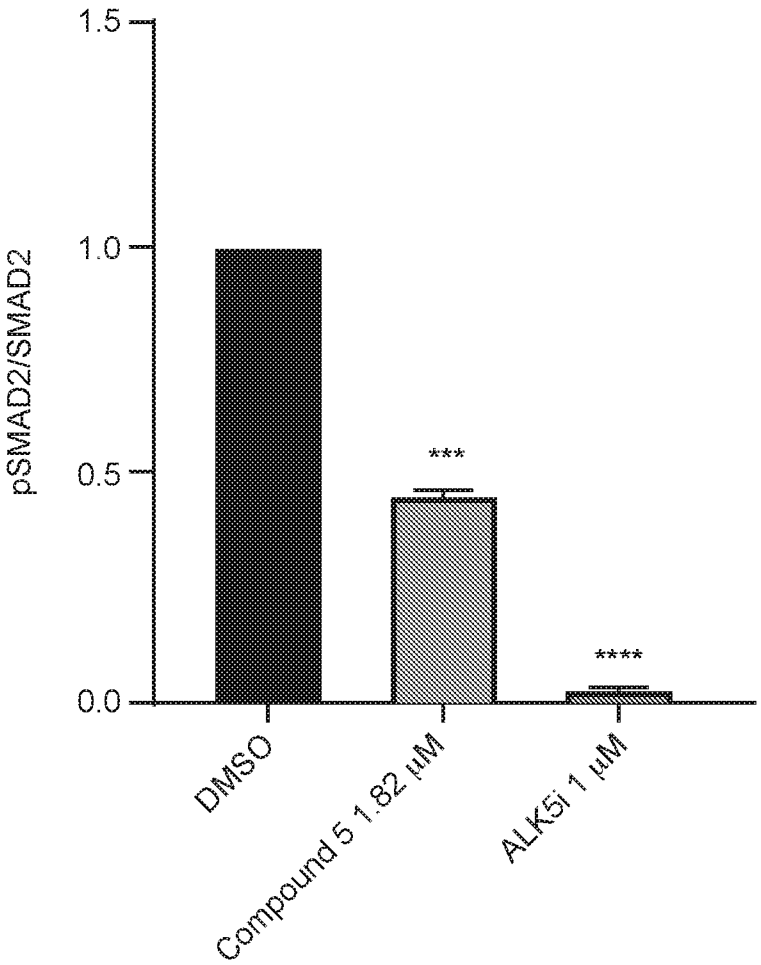


FIG. 6F

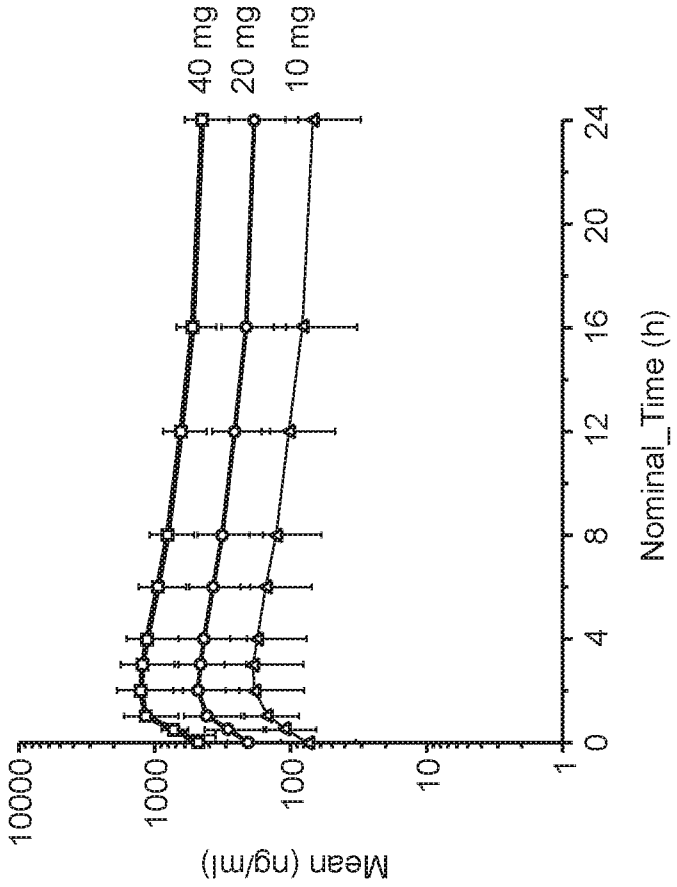
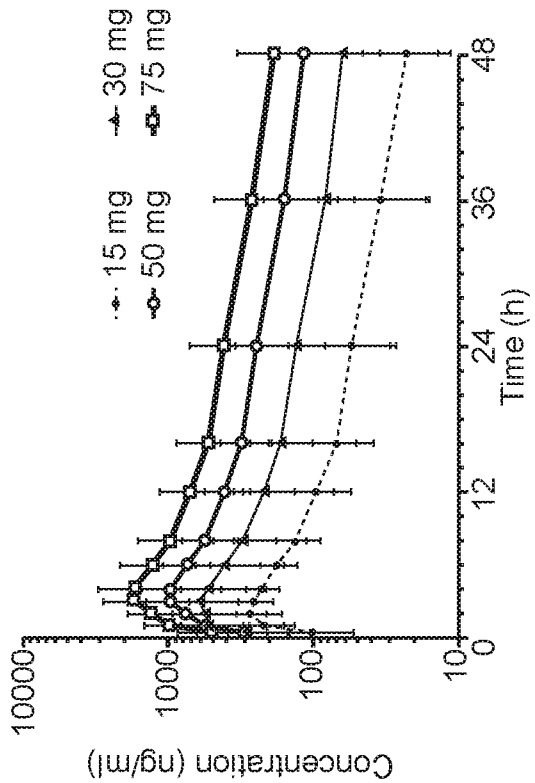


FIG. 7B



Parameter	75 mg
Tmax (h)	2.9±1.0 (34%)
Cmax(ng/mL)	1869±1241 (66%)
AUC0-24 (ng.h/mL)	19653±10860 (55%)
AUC0-48 (ng.h/mL)	22464±15679 (59%)
Thalf (h)	20.0±3.6 (18%)

FIG. 7A

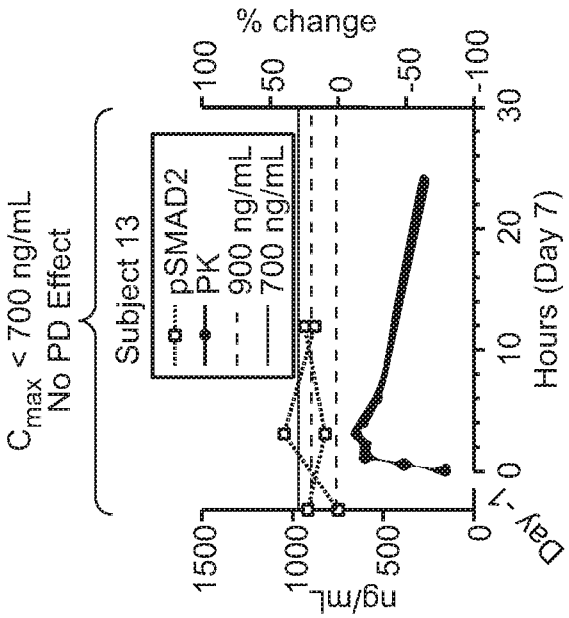


FIG. 8E

C_{max} < 700 ng/mL
No PD Effect

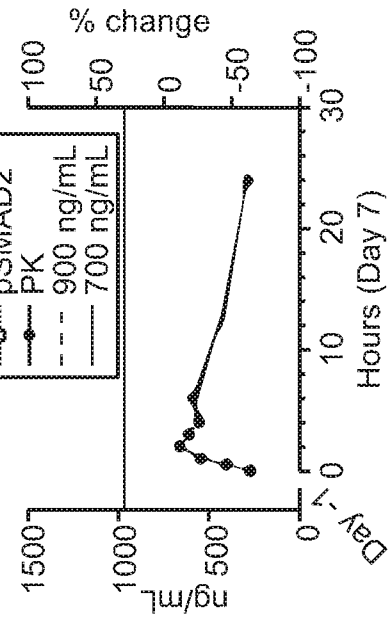


FIG. 8F

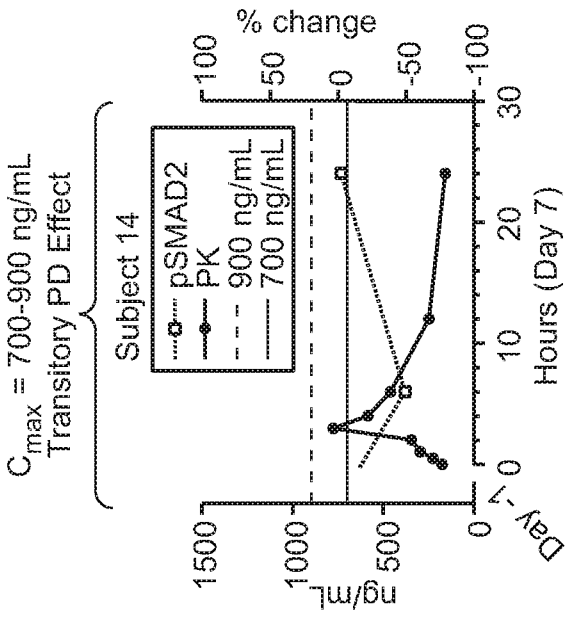


FIG. 8C

C_{max} = 700-900 ng/mL
Transitory PD Effect

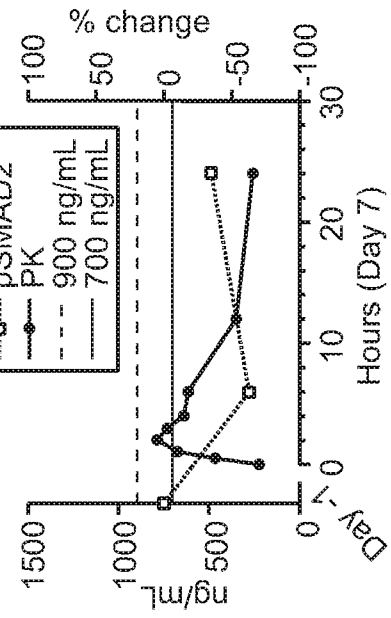


FIG. 8D

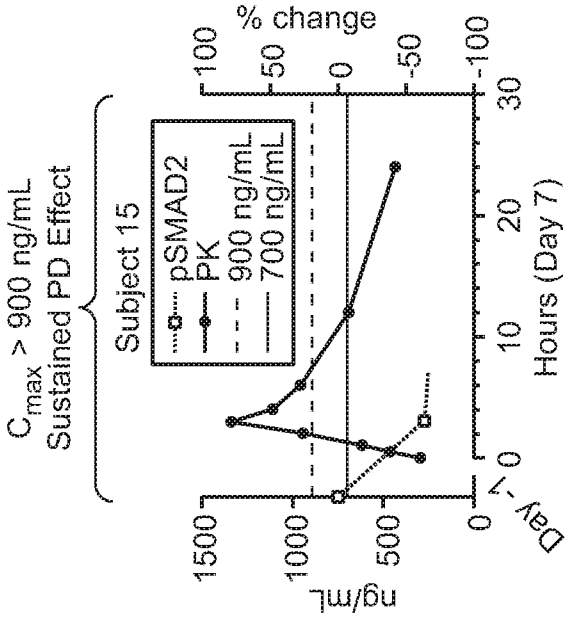


FIG. 8A

C_{max} > 900 ng/mL
Sustained PD Effect

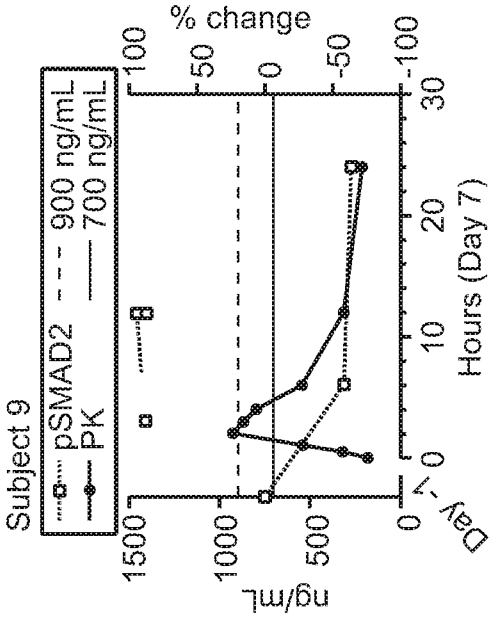


FIG. 8B

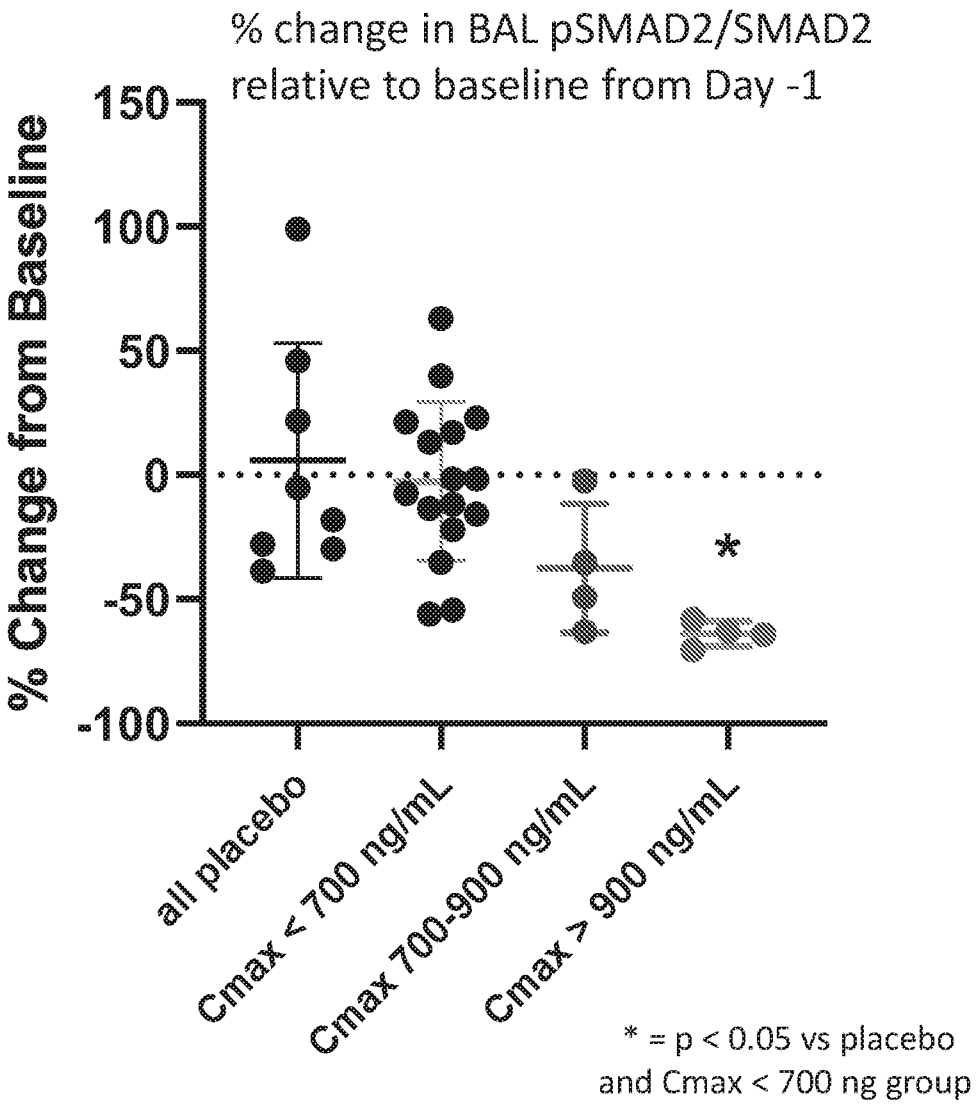

% change in BAL pSMAD2/SMAD2
relative to baseline from Day -1
% Change from Baseline
150
100
50
0
-50
-100
*
all placebo
Cmax < 700 ng/mL
Cmax 700-900 ng/mL
Cmax > 900 ng/mL
* = p < 0.05 vs placebo
and Cmax < 700 ng group

FIG. 8G

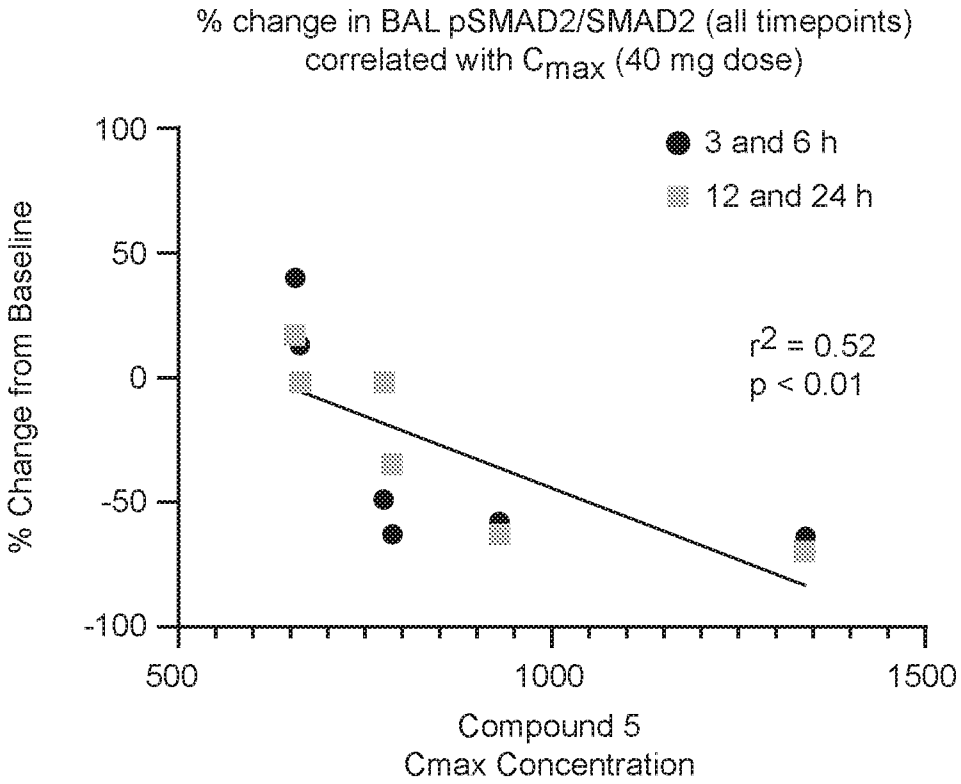
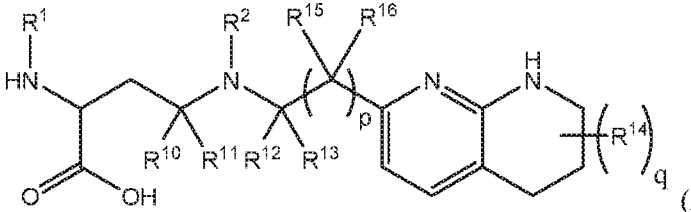
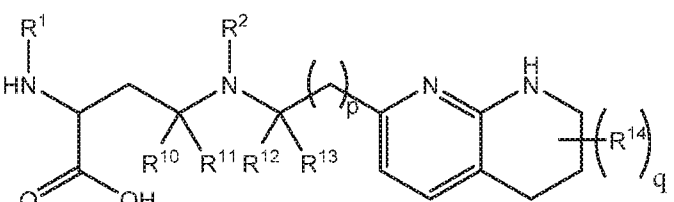

% change in BAL pSMAD2/SMAD2 (all timepoints)
correlated with Cmax (40 mg dose)
3 and 6 h
12 and 24 h
r2 = 0.52
p < 0.01
% Change from Baseline
100
50
0
-50
-100
500
1000
1500
Compound 5
Cmax Concentration

FIG. 8H



(A)



(I).