(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 September 2016 (15.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/144958 A1

(51) International Patent Classification:
A61K 31/41 (2006.01) *A61K 31/4365* (2006.01)
A61K 31/426 (2006.01) *C07D 277/00* (2006.01)

(21) International Application Number:
PCT/US2016/021374

(22) International Filing Date:
8 March 2016 (08.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/129,885 8 March 2015 (08.03.2015) US

(71) Applicant: **CASE WESTERN RESERVE UNIVERSITY** [US/US]; 10900 Euclid Avenue, Cleveland, Ohio 44106 (US).

(72) Inventors: **MARKOWITZ, Sanford**; 10900 Euclid Avenu, Cleveland, Ohio 44106 (US). **GERSON, Stanton**; 10900 Euclid Avenue, Cleveland, Ohio 44106 (US). **DESAI, Amar**; 10900 Euclid Avenue, Cleveland, Ohio 44106 (US). **HO, Won Jin**; 10900 Euclid Avenue, Cleveland, Ohio 44106 (US).

(74) Agent: **SUTKUS, Richard A.**; 1300 E. 9th Street, Suite 1700, Cleveland, Ohio 44114 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2016/144958 A1

(54) Title: INHIBITORS OF SHORT-CHAIN DEHYDROGENASE ACTIVITY FOR TREATING FIBROSIS

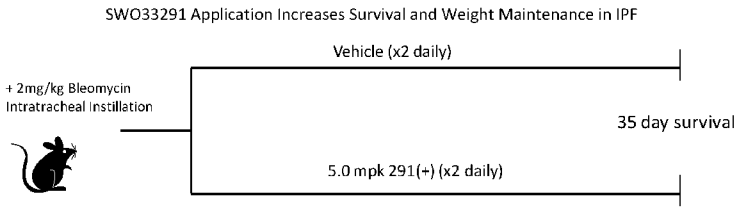


Fig. 1

(57) Abstract: A method of treating or preventing a fibrotic disease, disorder or condition includes administering to a subject in need of treatment a 15-PGDH inhibitor.

INHIBITORS OF SHORT-CHAIN DEHYDROGENASE ACTIVITY FOR TREATING FIBROSIS

RELATED APPLICATION

[0001] This application claims priority from U.S. Provisional Application No. 62/129,885, filed March 8, 2015, the subject matter of which is incorporated herein by reference in its entirety.

GOVERNMENT FUNDING

[0002] This invention was made with government support under Grant Nos. R01CA127306, R01CA127306-03S1, 1P01CA95471-10, AND 5P50CA150964, T32EB005583, F32DK107156, awarded by The National Institutes of Health. The United States government may have certain rights to the invention.

BACKGROUND

[0003] Fibrosis is a chronic and progressive process characterized by an excessive accumulation of extracellular matrix (ECM) leading to stiffening and/or scarring of the involved tissue. It develops through complex cell, extracellular matrix, cytokine and growth factor interactions. Distinct cell types are involved, such as resident mesenchymal cells (fibroblasts and myofibroblasts) and ECM-producing cells derived from epithelial and endothelial cells (through a process termed epithelial- and endothelial-mesenchymal transition), local or bone marrow-derived stem cells (fibrocytes). Myofibroblasts has long been regarded as a major cell type involved in normal wound healing, and as the key effector cell in fibrogenesis. They are highly synthetic for collagen and other ECM components, and are characterized by the de novo expression of α-smooth muscle actin α-SMA). The presence of myofibroblasts in fibrotic lesions in animal models of fibrosis correlates with the development of active fibrosis, and their persistence and localization to fibrotic foci in human disease is associated with disease progression. Myofibroblasts also exhibit an enhanced migratory phenotype and are capable of releasing numerous pro-fibrotic mediators.

[0004] Fibrotic diseases, including pulmonary fibrosis, systemic sclerosis, liver cirrhosis, and progressive kidney disease, are a leading cause of morbidity and mortality and can affect all tissues and organ systems. Fibrotic tissue remodeling can also influence cancer metastasis and accelerate chronic graft rejection in transplant recipients.

SUMMARY

[0005] Embodiments described herein relate to compositions and methods for treating and/or preventing fibrosis and various fibrotic diseases, disorders or conditions. As described in the Examples below, it was found that that inhibitors of short-chain dehydrogenase activity, such as 15-PGDH inhibitors, can be administered to a subject in need thereof to decrease fibrotic symptoms, such as collagen deposition, collagen accumulation, collagen fiber formation, inflammatory cytokine expression, and inflammatory cell infiltration, and treat and/or prevent various fibrotic diseases, disorders, and conditions characterized, in whole or in part, by the excess production of fibrous material, including excess production of fibrotic material within the extracellular matrix, or the replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components.

[0006] Fibrotic diseases, disorders and conditions characterized, in whole or in part, by excess production of fibrotic material can include systemic sclerosis, multifocal fibrosclerosis, nephrogenic systemic fibrosis, scleroderma(including morphea, generalized morphea, or linear scleroderma), sclerodermatous graft-vs-host-disease,, kidney fibrosis (including glomerular sclerosis, renal tubulointerstitial fibrosis, progressive renal disease or diabetic nephropathy), cardiac fibrosis (*e.g.,* myocardial fibrosis), pulmonary fibrosis (*e.g.* pulmonary fibrosis, glomerulosclerosis pulmonary fibrosis, idiopathic pulmonary fibrosis, silicosis, asbestosis, interstitial lung disease, interstitial fibrotic lung disease, and chemotherapy/radiation induced pulmonary fibrosis), oral fibrosis, endomyocardial fibrosis, deltoid fibrosis, pancreatitis, inflammatory bowel disease, Crohn's disease, nodular fascilitis, eosinophilic fasciitis, general fibrosis syndrome characterized by replacement of normal muscle tissue by fibrous tissue in varying degrees, retroperitoneal fibrosis, liver fibrosis, liver cirrhosis, chronic renal failure; myelofibrosis (bone marrow fibrosis), drug induced ergotism, myelodysplastic syndrome, myeloproferative syndrome, collagenous colitis, acute fibrosis, organ specific fibrosis, and the like.

[0007] In some embodiments, a method of treating or preventing a fibrotic disease, disorder or condition includes administering to a subject in need thereof a therapeutically effect amount of a 15-PGDH inhibitor.

[0008] In some embodiments, the 15-PGDH inhibitors can be used to treat or prevent lung fibrosis. Lung fibrosis, which can be treated, can be selected from the group consisting of pulmonary fibrosis, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, or pulmonary hypertension, and combinations thereof.

[0009] In other embodiments, the 15-PGDH inhibitors can be used to treat or prevent kidney fibrosis. The kidney fibrosis can result from dialysis following kidney failure, catheter placement, a nephropathy, glomerulosclerosis, glomerulonephritis, chronic renal insufficiency, acute kidney injury, end stage renal disease or renal failure, or combinations thereof.

[0010] In other embodiments, the 15-PGDH inhibitors can be used to treat or prevent liver fibrosis. The liver fibrosis can result from a chronic liver disease, viral induced hepatic cirrhosis, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, schistosomiasis, primary biliary cirrhosis, alcoholic liver disease or non-alcoholic steatohepatitis (NASH) , NASH associated cirrhosis obesity, diabetes, protein malnutrition, coronary artery disease, auto-immune hepatitis, cystic fibrosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, drug reaction and exposure to toxins, or combinations thereof.

[0011] In some embodiments, the 15-PGDH inhibitors can be used to treat or prevent heart fibrosis, for example, cardiac fibrosis and endomyocardial fibrosis.

[0012] In some embodiments, the 15-PGDH inhibitors can be used to treat or prevent systemic sclerosis.

[0013] In some embodiments, the 15-PGDH inhibitors can be used to treat or prevent fibrotic diseases, disorders or conditions caused by post-surgical adhesion formation.

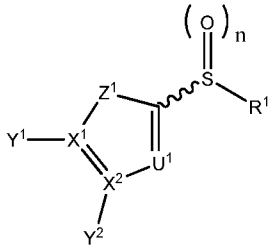
[0014] In some embodiments, the 15-PGDH inhibitors can used for reducing or preventing scar formation in a subject.

[0015] In other embodiments, the 15-PGDH inhibitors can be used to reduce or prevent scar formation on skin or scleroderma.

[0016] In various embodiments, the 15-PGDH inhibitors can be administered at a therapeutically effective amount such that at least one symptom or feature of a fibrotic disease, disorder or condition, or other related diseases, disorders or conditions, is reduced in intensity, severity, or frequency, or has delayed onset.

[0017] In other embodiments, the 15-PGDH inhibitors can be used in a method for decreasing or reducing collagen secretion, or collagen deposition, or collagen fiber accumulation, in a tissue or organ, such as the lung, the liver, the intestines, the colon, the skin or the heart, of a subject. The method can include administering a therapeutically effective amount of the 15-PGDH inhibitors to the subject in need thereof. The subject can have or be at risk of an excessive collagen secretion or collagen deposition in the tissue or organ, such as the kidney, the lung, the liver, the intestines, the colon, the skin or the heart. Usually, the excessive collagen secretion or collagen deposition in an organ results from an injury or an insult. Such injury and insult can be organ-specific. The 15-PGDH inhibitors can be administered over a sufficient period of time to decrease or reduce the level of collagen deposition in the tissue or organ, completely or partially. A sufficient period of time can be during one week, or between 1 week to 1 month, or between 1 to 2 months, or 2 months or more. For chronic condition, the15-PGDH inhibitors can be advantageously administered for life time period.

[0018] In some embodiments, the 15-PGDH inhibitor can be administered to a tissue of a subject at an amount effective to increase prostaglandin levels in the tissue. The 15-PGDH inhibitor can include formula (I):



(I)

wherein n is 0-2;

Y^1, Y^2, and R^1 are the same or different and are each selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)

(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein Y^1 and Y^2 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein

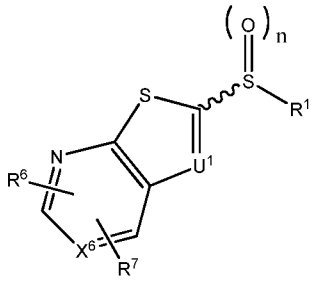
X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

X^1 and X^2 are independently N or C, and wherein when X^1 and/or X^2 are N, Y^1 and/or Y^2, respectively, are absent;

Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

[0019] In other embodiments, the 15-PGDH inhibitor can include a compound having the following (V):



(V)

wherein n is 0-2

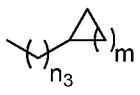
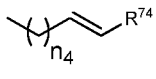
X^6 is independently is N or CR^c

R^1, R^6, R^7, and R^c are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido

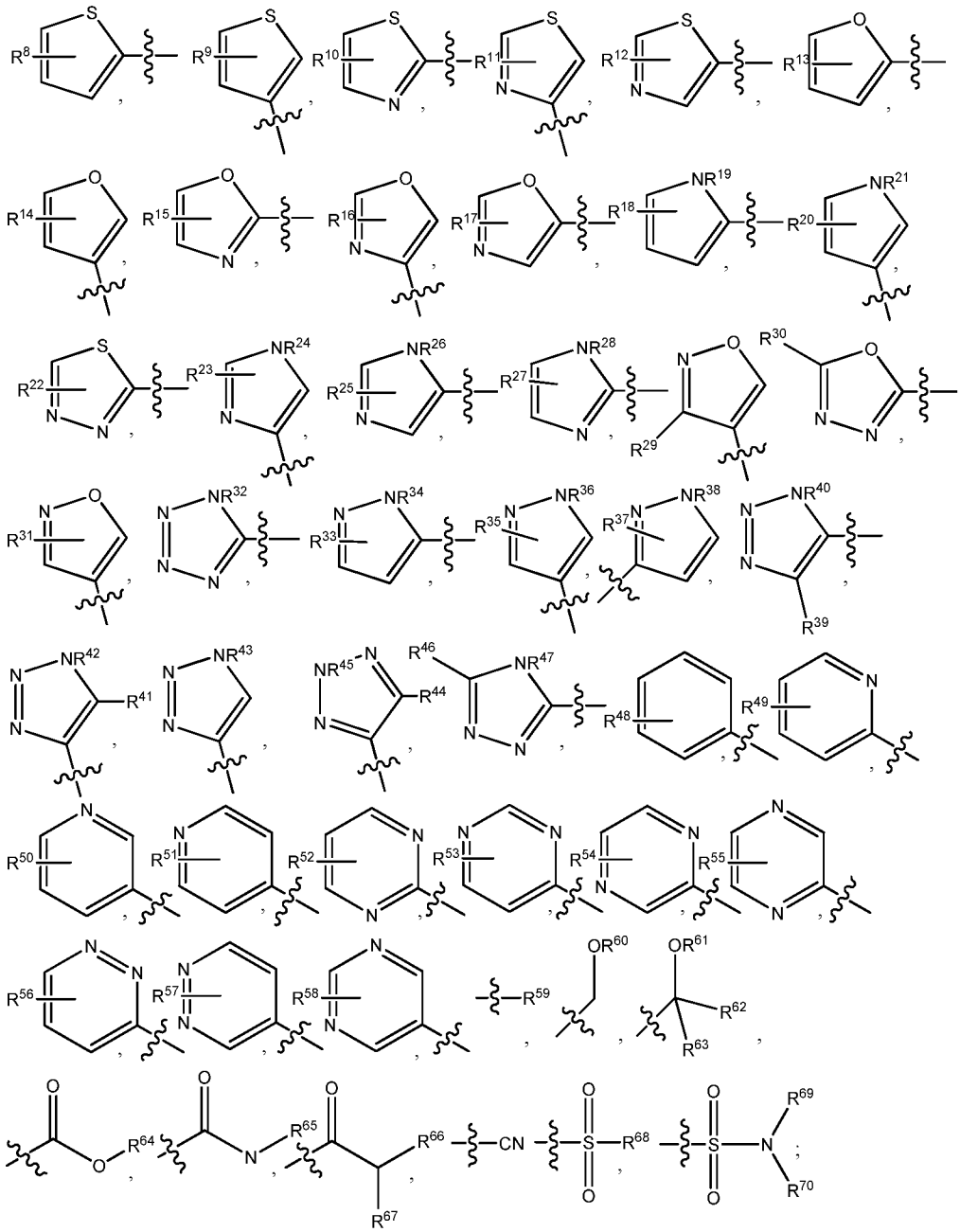
(-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)$N(R')_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)$N(R')_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

and pharmaceutically acceptable salts thereof.

[0020] In some embodiments, R^1 is selected from the group consisting of branched or linear alkyl including –$(CH_2)n_1CH_3$ (n_1=0-7),  wherein n_2=0-6 and X is any of the following: CF_yH_z (y + z = 3), CCl_yH_z (y + z = 3), OH, OAc, OMe, R^{71}, OR^{72}, CN, $N(R^{73})_2$,  (n_3=0-5, m=1-5), and  (n_4=0-5).

[0021] In other embodiments, R^6 and R^7 can each independently be one of the following:



each R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69},

R^{70}, R^{71}, R^{72}, R^{73}, and R^{74}, are the same or different and are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heterocycloalkenyl containing from 5-6 ring atoms, (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), heteroaryl or heterocyclyl containing from 5-14 ring atoms, (wherein from 1-6 of the ring atoms is independently selected from N, NH, N(C_1-C_3 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, silyl, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato ($-COO^-$), carbamoyl (-(CO)--NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano ($-N^+C^-$), cyanato (-O-CN), isocyanato ($-O-N^+=C^-$), isothiocyanato (-S-CN), azido ($-N=N^+=N^-$), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), sulfanamido ($-SO_2N(R)_2$ where R is independently H, alkyl, aryl or heteroaryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro ($-NO_2$), nitroso (-NO), sulfo ($-SO_2$-OH), sulfonato ($-SO_2-O^-$), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl ($-SO_2$-alkyl), C_5-C_{20} arylsulfonyl ($-SO_2$-aryl), sulfonamide ($-SO_2-NH_2$, $-SO_2NY_2$ (wherein Y is independently H, arlyl or alkyl), phosphono ($-P(O)(OH)_2$), phosphonato ($-P(O)(O^-)_2$), phosphinato ($-P(O)(O^-)$), phospho ($-PO_2$), phosphino (--PH_2), polyalkyl ethers ($-[(CH_2)_nO]_m$), phosphates, phosphate esters [$-OP(O)(OR)_2$ where R = H, methyl or other alkyl], groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, and combinations thereof, and pharmaceutically acceptable salts thereof.

[0022] In some embodiments, the 15-PGDH inhibitor can inhibit the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than 1 μM, or preferably at an IC_{50} of less than 250 nM, or more preferably at an IC_{50} of less than 50 nM, or more preferably at an IC_{50} of

less than 10 nM, or more preferably at an IC_{50} of less than 5 nM at a recombinant 15-PGDH concentration of about 5 nM to about 10 nM.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Fig. 1 illustrates a schematic diagram of an assay for measuring the effects of SW033291 on weight maintenance and survival in a mouse model of idiopathic pulmonary fibrosis.

[0024] Figs. 2(A-B) illustrate plots showing (A) weight change and (B) survival of vehicle and SW033291 treated mouse models of idiopathic pulmonary fibrosis.

[0025] Fig. 3 illustrates a schematic diagram of an assay for measuring the effects of SW033291 on collagen deposition in a mouse model of idiopathic pulmonary fibrosis.

[0026] Fig. 4 illustrates a graph showing collagen deposition in vehicle and SW033291 treated mouse models of idiopathic pulmonary fibrosis.

[0027] Fig. 5 illustrates a schematic diagram of an assay for measuring the effects of SW033291 on inflammatory cytokine expression in a mouse model of idiopathic pulmonary fibrosis.

[0028] Figs. 6(A-F) illustrate graphs showing inflammatory cytokine expression in vehicle and SW033291 treated mice models of idiopathic pulmonary fibrosis.

[0029] Figs. 7(A-D) illustrate images of vehicle and (+)SW033291 treated mouse models of intestinal fibrosis.

[0030] Fig. 8 illustrates a graph showing colonic fibrosis in vehicle and (+)SW033291 treated mouse models of intestinal fibrosis.

DETAILED DESCRIPTION

[0031] For convenience, certain terms employed in the specification, examples, and appended claims are collected here. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this application belongs.

[0032] The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.,* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0033] The terms "comprise," "comprising," "include," "including," "have," and "having" are used in the inclusive, open sense, meaning that additional elements may be

included. The terms "such as", "*e.g.*", as used herein are non-limiting and are for illustrative purposes only. "Including" and "including but not limited to" are used interchangeably.

[0034] The term "or" as used herein should be understood to mean "and/or", unless the context clearly indicates otherwise.

[0035] As used herein, the term "about" or "approximately" refers to a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by as much as 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length. In one embodiment, the term "about" or "approximately" refers a range of quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length ± 15%, ± 10%, ± 9%, ± 8%, ± 7%, ± 6%, ± 5%, ± 4%, ± 3%, ± 2%, or ± 1% about a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length.

[0036] It will be noted that the structure of some of the compounds of the application include asymmetric (chiral) carbon or sulfur atoms. It is to be understood accordingly that the isomers arising from such asymmetry are included herein, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. The compounds of this application may exist in stereoisomeric form, therefore can be produced as individual stereoisomers or as mixtures.

[0037] The term "isomerism" means compounds that have identical molecular formulae but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereoisomers", and stereoisomers that are non-superimposable mirror images are termed "enantiomers", or sometimes optical isomers. A carbon atom bonded to four nonidentical substituents is termed a "chiral center" whereas a sulfur bound to three or four different substitutents, e.g. sulfoxides or sulfinimides, is likewise termed a “chiral center”.

[0038] The term "chiral isomer" means a compound with at least one chiral center. It has two enantiomeric forms of opposite chirality and may exist either as an individual enantiomer or as a mixture of enantiomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2n-1 enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an

individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Alternatively, when one or more chiral centers are present, a stereoisomer may be characterized as (+) or (-). Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the Sequence Rule of Cahn, Ingold and Prelog. (Cahn et al, Angew. Chem. Inter. Edit. 1966, 5, 385; errata 511; Cahn et al., Angew. Chem. 1966, 78, 413; Cahn and Ingold, J Chem. Soc. 1951 (London), 612; Cahn et al., Experientia 1956, 12, 81; Cahn, J., Chem. Educ. 1964, 41, 116).

[0039] The term "disorder" refer to any disorder, disease, or condition that would benefit from an agent that reduces or retards fibrosis. For example, included are diseases, disorders and conditions characterized by excess production of fibrous material, including excess production of fibrous material within the extracellular matrix. Also included are diseases, disorders and conditions characterized by replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components.

[0040] The term "geometric Isomers" means the diastereomers that owe their existence to hindered rotation about double bonds. These configurations are differentiated in their names by the prefixes *cis* and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules. Further, the structures and other compounds discussed in this application include all atropic isomers thereof.

[0041] The term "atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[0042] The terms "crystal polymorphs" or "polymorphs" or "crystal forms" means crystal structures in which a compound (or salt or solvate thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density hardness, crystal shape, optical and electrical properties, stability and

solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Crystal polymorphs of the compounds can be prepared by crystallization under different conditions.

[0043] The term "derivative" refers to compounds that have a common core structure, and are substituted with various groups as described herein.

[0044] The term "bioisostere" refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include acyl sulfonimides, tetrazoles, sulfonates, and phosphonates. See, *e.g.,* Patani and LaVoie, Chem. Rev. 96, 3147-3176 (1996).

[0045] The phrases "parenteral administration" and "administered parenterally" are art-recognized terms, and include modes of administration other than enteral and topical administration, such as injections, and include, without limitation, intravenous, intramuscular, intrapleural, intravascular, intrapericardial, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal and intrastemal injection and infusion.

[0046] The term "treating" is art-recognized and includes inhibiting a disease, disorder or condition in a subject, *e.g.,* impeding its progress; and relieving the disease, disorder or condition, *e.g.,* causing regression of the disease, disorder and/or condition. Treating the disease or condition includes ameliorating at least one symptom of the particular disease or condition, even if the underlying pathophysiology is not affected.

[0047] The term "preventing" is art-recognized and includes stopping a disease, disorder or condition from occurring in a subject, which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it. Preventing a condition related to a disease includes stopping the condition from occurring after the disease has been diagnosed but before the condition has been diagnosed.

[0048] The term "pharmaceutical composition" refers to a formulation containing the disclosed compounds in a form suitable for administration to a subject. In a preferred embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit

dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler, or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salts thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, intranasal, inhalational, and the like. Dosage forms for the topical or transdermal administration of a compound described herein includes powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, nebulized compounds, and inhalants. In a preferred embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0049] The term "flash dose" refers to compound formulations that are rapidly dispersing dosage forms.

[0050] The term "immediate release" is defined as a release of compound from a dosage form in a relatively brief period of time, generally up to about 60 minutes. The term "modified release" is defined to include delayed release, extended release, and pulsed release. The term "pulsed release" is defined as a series of releases of drug from a dosage form. The term "sustained release" or "extended release" is defined as continuous release of a compound from a dosage form over a prolonged period.

[0051] The phrase "pharmaceutically acceptable" is art-recognized. In certain embodiments, the term includes compositions, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0052] The phrase "pharmaceutically acceptable carrier" is art-recognized, and includes, for example, pharmaceutically acceptable materials, compositions or vehicles, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being

compatible with the other ingredients of a subject composition and not injurious to the patient. In certain embodiments, a pharmaceutically acceptable carrier is non-pyrogenic. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0053] The compounds of the application are capable of further forming salts. All of these forms are also contemplated herein.

[0054] "Pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. For example, the salt can be an acid addition salt. One embodiment of an acid addition salt is a hydrochloride salt. The pharmaceutically acceptable salts can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile being preferred. Lists of salts are found in Remington's Pharmaceutical Sciences, 18th ed. (Mack Publishing Company, 1990).

[0055] The compounds described herein can also be prepared as esters, for example pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.,* a methyl, ethyl, or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.,* an acetate, propionate, or other ester.

[0056] The compounds described herein can also be prepared as prodrugs, for example pharmaceutically acceptable prodrugs. The terms "pro-drug" and "prodrug" are used interchangeably herein and refer to any compound, which releases an active parent drug *in vivo*. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.,* solubility, bioavailability, manufacturing, etc.) the compounds can be delivered in prodrug form. Thus, the compounds described herein are intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug *in vivo* when such prodrug is administered to a subject. Prodrugs are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds wherein a hydroxy, amino, sulfhydryl, carboxy, or carbonyl group is bonded to any group that may be cleaved *in vivo* to form a free hydroxyl, free amino, free sulfhydryl, free carboxy or free carbonyl group, respectively. Prodrugs can also include a precursor (forerunner) of a compound described herein that undergoes chemical conversion by metabolic processes before becoming an active or more active pharmacological agent or active compound described herein.

[0057] Examples of prodrugs include, but are not limited to, esters (*e.g.,* acetate, dialkylaminoacetates, formates, phosphates, sulfates, and benzoate derivatives) and carbamates (*e.g.,* N,N-dimethylaminocarbonyl) of hydroxy functional groups, ester groups (*e.g.,* ethyl esters, morpholinoethanol esters) of carboxyl functional groups, N-acyl derivatives (*e.g.,* N-acetyl) N-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in compounds, and the like, as well as sulfides that are oxidized to form sulfoxides or sulfones..

[0058] The term "protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in Green and Wuts, Protective Groups in Organic Chemistry, (Wiley, 2.sup.nd ed. 1991); Harrison and Harrison et al., Compendium of Synthetic Organic Methods, Vols. 1-8 (John Wiley and Sons, 1971-1996); and Kocienski, Protecting Groups, (Verlag, 3rd ed. 2003).

[0059] The term "amine protecting group" is intended to mean a functional group that converts an amine, amide, or other nitrogen-containing moiety into a different chemical group that is substantially inert to the conditions of a particular chemical reaction. Amine protecting groups are preferably removed easily and selectively in good yield under conditions that do not affect other functional groups of the molecule. Examples of amine protecting groups include, but are not limited to, formyl, acetyl, benzyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, t-butyloxycarbonyl (Boc), p-methoxybenzyl, methoxymethyl, tosyl, trifluoroacetyl, trimethylsilyl (TMS), fluorenyl-methyloxycarbonyl, 2-trimethylsilyl-ethyoxycarbonyl, 1-methyl-1-(4-biphenylyl) ethoxycarbonyl, allyloxycarbonyl, benzyloxycarbonyl (CBZ), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC), and the like. Those of skill in the art can identify other suitable amine protecting groups.

[0060] Representative hydroxy protecting groups include those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

[0061] Additionally, the salts of the compounds described herein, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Non-limiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0062] The term "solvates" means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H_2O, such combination being able to form one or more hydrate.

[0063] The compounds, salts and prodrugs described herein can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present application includes all tautomers of the present compounds. A tautomer is one of two or more structural isomers that exist in equilibrium and are readily

converted from one isomeric form to another. This reaction results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. The concept of tautomers that are interconvertable by tautomerizations is called tautomerism.

[0064] Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs.

[0065] Tautomerizations can be catalyzed by: Base: 1. deprotonation; 2. formation of a delocalized anion (*e.g.,* an enolate); 3. protonation at a different position of the anion; Acid: 1. protonation; 2. formation of a delocalized cation; 3. deprotonation at a different position adjacent to the cation.

[0066] The term "analogue" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analogue is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0067] A "patient," "subject," or "host" to be treated by the subject method may mean either a human or non-human animal, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder.

[0068] The terms "prophylactic" or "therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (*e.g.,* disease or other unwanted state of the host animal) then the treatment is prophylactic, *i.e.,* it protects the host against developing the unwanted condition, whereas if it is administered after manifestation

of the unwanted condition, the treatment is therapeutic (*i.e.,* it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

[0069] The terms "therapeutic agent", "drug", "medicament" and "bioactive substance" are art-recognized and include molecules and other agents that are biologically, physiologically, or pharmacologically active substances that act locally or systemically in a patient or subject to treat a disease or condition. The terms include without limitation pharmaceutically acceptable salts thereof and prodrugs. Such agents may be acidic, basic, or salts; they may be neutral molecules, polar molecules, or molecular complexes capable of hydrogen bonding; they may be prodrugs in the form of ethers, esters, amides and the like that are biologically activated when administered into a patient or subject.

[0070] The phrase "therapeutically effective amount" or "pharmaceutically effective amount" is an art-recognized term. In certain embodiments, the term refers to an amount of a therapeutic agent that produces some desired effect at a reasonable benefit/risk ratio applicable to any medical treatment. In certain embodiments, the term refers to that amount necessary or sufficient to eliminate, reduce or maintain a target of a particular therapeutic regimen. The effective amount may vary depending on such factors as the disease or condition being treated, the particular targeted constructs being administered, the size of the subject or the severity of the disease or condition. One of ordinary skill in the art may empirically determine the effective amount of a particular compound without necessitating undue experimentation. In certain embodiments, a therapeutically effective amount of a therapeutic agent for *in vivo* use will likely depend on a number of factors, including: the rate of release of an agent from a polymer matrix, which will depend in part on the chemical and physical characteristics of the polymer; the identity of the agent; the mode and method of administration; and any other materials incorporated in the polymer matrix in addition to the agent.

[0071] The term "ED50" is art-recognized. In certain embodiments, ED50 means the dose of a drug, which produces 50% of its maximum response or effect, or alternatively, the dose, which produces a pre-determined response in 50% of test subjects or preparations. The term "LD50" is art-recognized. In certain embodiments, LD50 means the dose of a drug, which is lethal in 50% of test subjects. The term "therapeutic index" is an art-recognized term, which refers to the therapeutic index of a drug, defined as LD50/ED50.

[0072] The terms "IC_{50}," or "half maximal inhibitory concentration" is intended to refer to the concentration of a substance (*e.g.,* a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc.

[0073] With respect to any chemical compounds, the present application is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

[0074] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent can be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent can be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0075] When an atom or a chemical moiety is followed by a subscripted numeric range (*e.g.,* C_{1-6}), it is meant to encompass each number within the range as well as all intermediate ranges. For example, "C_{1-6} alkyl" is meant to include alkyl groups with 1, 2, 3, 4, 5, 6, 1-6, 1-5, 1-4, 1-3, 1-2, 2-6, 2-5, 2-4, 2-3, 3-6, 3-5, 3-4, 4-6, 4-5, and 5-6 carbons.

[0076] The term "alkyl" is intended to include both branched (*e.g.,* isopropyl, tert-butyl, isobutyl), straight-chain *e.g.,* methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl), and cycloalkyl (*e.g.,* alicyclic) groups (*e.g.,* cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. Such aliphatic hydrocarbon groups have a specified number of carbon atoms. For example, C_{1-6} alkyl is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. As used herein, "lower alkyl" refers to alkyl groups having from 1 to 6 carbon atoms in the backbone of the carbon chain. "Alkyl" further includes alkyl groups that have oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more hydrocarbon backbone carbon atoms. In certain embodiments, a straight chain or branched chain alkyl has six or fewer carbon atoms in its backbone (*e.g.,* C_1-C_6 for straight chain, C_3-C_6 for branched chain), for example four or fewer. Likewise, certain cycloalkyls have from three to eight carbon atoms in their ring structure, such as five or six carbons in the ring structure.

[0077] The term "substituted alkyls" refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, *e.g.,* with the substituents described above. An "alkylaryl" or an "aralkyl" moiety is an alkyl substituted with an aryl (*e.g.,* phenylmethyl (benzyl)). If not otherwise indicated, the terms "alkyl" and "lower alkyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkyl or lower alkyl, respectively.

[0078] The term "alkenyl" refers to a linear, branched or cyclic hydrocarbon group of 2 to about 24 carbon atoms containing at least one double bond, such as ethenyl, n-propenyl, isopropenyl, n-butenyl, isobutenyl, octenyl, decenyl, tetradecenyl, hexadecenyl, eicosenyl, tetracosenyl, cyclopentenyl, cyclohexenyl, cyclooctenyl, and the like. Generally, although again not necessarily, alkenyl groups can contain 2 to about 18 carbon atoms, and more particularly 2 to 12 carbon atoms. The term "lower alkenyl" refers to an alkenyl group of 2 to 6 carbon atoms, and the specific term "cycloalkenyl" intends a cyclic alkenyl group, preferably having 5 to 8 carbon atoms. The term "substituted alkenyl" refers to alkenyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkenyl" and "heteroalkenyl" refer to alkenyl or heterocycloalkenyl (*e.g.,* heterocylcohexenyl) in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms "alkenyl" and "lower alkenyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkenyl and lower alkenyl, respectively.

[0079] The term "alkynyl" refers to a linear or branched hydrocarbon group of 2 to 24 carbon atoms containing at least one triple bond, such as ethynyl, n-propynyl, and the like. Generally, although again not necessarily, alkynyl groups can contain 2 to about 18 carbon atoms, and more particularly can contain 2 to 12 carbon atoms. The term "lower alkynyl"

intends an alkynyl group of 2 to 6 carbon atoms. The term "substituted alkynyl" refers to alkynyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkynyl" and "heteroalkynyl" refer to alkynyl in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms "alkynyl" and "lower alkynyl" include linear, branched, unsubstituted, substituted, and/or heteroatom-containing alkynyl and lower alkynyl, respectively.

[0080] The terms "alkyl", "alkenyl", and "alkynyl" are intended to include moieties which are diradicals, *i.e.,* having two points of attachment. A nonlimiting example of such an alkyl moiety that is a diradical is --CH_2CH_2--, *i.e.,* a C_2 alkyl group that is covalently bonded via each terminal carbon atom to the remainder of the molecule.

[0081] The term "alkoxy" refers to an alkyl group bound through a single, terminal ether linkage; that is, an "alkoxy" group may be represented as --O-alkyl where alkyl is as defined above. A "lower alkoxy" group intends an alkoxy group containing 1 to 6 carbon atoms, and includes, for example, methoxy, ethoxy, n-propoxy, isopropoxy, t-butyloxy, etc. Preferred substituents identified as "C_1-C_6 alkoxy" or "lower alkoxy" herein contain 1 to 3 carbon atoms, and particularly preferred such substituents contain 1 or 2 carbon atoms (*i.e.,* methoxy and ethoxy).

[0082] The term "aryl" refers to an aromatic substituent containing a single aromatic ring or multiple aromatic rings that are fused together, directly linked, or indirectly linked (such that the different aromatic rings are bound to a common group such as a methylene or ethylene moiety). Aryl groups can contain 5 to 20 carbon atoms, and particularly preferred aryl groups can contain 5 to 14 carbon atoms. Examples of aryl groups include benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, *e.g.,* tricyclic, bicyclic, *e.g.,* naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy,

aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkylamino, dialkylamino, arylamino, diaryl amino, and al kylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.,* tetralin, methylenedioxyphenyl). If not otherwise indicated, the term "aryl" includes unsubstituted, substituted, and/or heteroatom-containing aromatic substituents.

[0083] The term "alkaryl" refers to an aryl group with an alkyl substituent, and the term "aralkyl" refers to an alkyl group with an aryl substituent, wherein "aryl" and "alkyl" are as defined above. Exemplary aralkyl groups contain 6 to 24 carbon atoms, and particularly preferred aralkyl groups contain 6 to 16 carbon atoms. Examples of aralkyl groups include, without limitation, benzyl, 2-phenyl-ethyl, 3-phenyl-propyl, 4-phenyl-butyl, 5-phenyl-pentyl, 4-phenylcyclohexyl, 4-benzylcyclohexyl, 4-phenylcyclohexylmethyl, 4-benzylcyclohexylmethyl, and the like. Alkaryl groups include, for example, p-methylphenyl, 2,4-dimethylphenyl, p-cyclohexylphenyl, 2,7-dimethylnaphthyl, 7-cyclooctylnaphthyl, 3-ethyl-cyclopenta-1,4-diene, and the like.

[0084] The terms "heterocyclyl" or "heterocyclic group" include closed ring structures, *e.g.,* 3- to 10-, or 4- to 7-membered rings, which include one or more heteroatoms. "Heteroatom" includes atoms of any element other than carbon or hydrogen. Examples of heteroatoms include nitrogen, oxygen, sulfur and phosphorus.

[0085] Heterocyclyl groups can be saturated or unsaturated and include pyrrolidine, oxolane, thiolane, piperidine, piperazine, morpholine, lactones, lactams, such as azetidinones and pyrrolidinones, sultams, and sultones. Heterocyclic groups such as pyrrole and furan can have aromatic character. They include fused ring structures, such as quinoline and isoquinoline. Other examples of heterocyclic groups include pyridine and purine. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy,

alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety. Heterocyclic groups can also be substituted at one or more constituent atoms with, for example, a lower alkyl, a lower alkenyl, a lower alkoxy, a lower alkylthio, a lower alkylamino, a lower alkylcarboxyl, a nitro, a hydroxyl, --CF_3, or --CN, or the like.

[0086] The term "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo. "Counterion" is used to represent a small, negatively charged species such as fluoride, chloride, bromide, iodide, hydroxide, acetate, and sulfate. The term sulfoxide refers to a sulfur attached to 2 different carbon atoms and one oxygen and the S-O bond can be graphically represented with a double bond (S=O), a single bond without charges (S-O) or a single bond with charges [S(+)-O(-)].

[0087] The terms "substituted" as in "substituted alkyl," "substituted aryl," and the like, as alluded to in some of the aforementioned definitions, is meant that in the alkyl, aryl, or other moiety, at least one hydrogen atom bound to a carbon (or other) atom is replaced with one or more non-hydrogen substituents. Examples of such substituents include, without limitation: functional groups such as halo, hydroxyl, silyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (-CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO-), carbamoyl (-(CO)-NH_2), mono-(C_1-C_{24} alkyl)-substituted carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), di-(C_1-C_4 alkyl)-substituted carbamoyl (-(CO)--N(C_1-C_{24} alkyl)$_2$), mono-substituted arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O--CN), isocyanato (-ON^+C^-), isothiocyanato (-S-CN), azido (-$N=N^+=N^-$), formyl (-(CO)--H), thioformyl (-(CS)-H), amino (-NH_2), mono- and di-(C_1-C_{24} alkyl)-substituted amino, mono- and di-(C_5-C_{20} aryl)-substituted amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl),

imino (-CR=NH where R=hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (--CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2 -OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (--(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2 -aryl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), and phosphino (-PH_2); and the hydrocarbyl moieties C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, and C_6-C_{24} aralkyl.

[0088] In addition, the aforementioned functional groups may, if a particular group permits, be further substituted with one or more additional functional groups or with one or more hydrocarbyl moieties such as those specifically enumerated above. Analogously, the above-mentioned hydrocarbyl moieties may be further substituted with one or more functional groups or additional hydrocarbyl moieties such as those specifically enumerated.

[0089] When the term "substituted" appears prior to a list of possible substituted groups, it is intended that the term apply to every member of that group. For example, the phrase "substituted alkyl, alkenyl, and aryl" is to be interpreted as "substituted alkyl, substituted alkenyl, and substituted aryl." Analogously, when the term "heteroatom-containing" appears prior to a list of possible heteroatom-containing groups, it is intended that the term apply to every member of that group. For example, the phrase "heteroatom-containing alkyl, alkenyl, and aryl" is to be interpreted as "heteroatom-containing alkyl, substituted alkenyl, and substituted aryl.

[0090] "Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not. For example, the phrase "optionally substituted" means that a non-hydrogen substituent may or may not be present on a given atom, and, thus, the description includes structures wherein a non-hydrogen substituent is present and structures wherein a non-hydrogen substituent is not present.

[0091] The terms "stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation, and as appropriate, purification from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0092] The terms "free compound" is used herein to describe a compound in the unbound state.

[0093] Throughout the description, where compositions are described as having, including, or comprising, specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the compositions and methods described herein remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0094] The term "small molecule" is an art-recognized term. In certain embodiments, this term refers to a molecule, which has a molecular weight of less than about 2000 amu, or less than about 1000 amu, and even less than about 500 amu.

[0095] All percentages and ratios used herein, unless otherwise indicated, are by weight.

[0096] The terms "gene expression" or "protein expression" includes any information pertaining to the amount of gene transcript or protein present in a sample, as well as information about the rate at which genes or proteins are produced or are accumulating or being degraded (*e.g.,* reporter gene data, data from nuclear runoff experiments, pulse-chase data etc.). Certain kinds of data might be viewed as relating to both gene and protein expression. For example, protein levels in a cell are reflective of the level of protein as well as the level of transcription, and such data is intended to be included by the phrase "gene or protein expression information". Such information may be given in the form of amounts per cell, amounts relative to a control gene or protein, in unitless measures, etc.; the term "information" is not to be limited to any particular means of representation and is intended to mean any representation that provides relevant information. The term "expression levels" refers to a quantity reflected in or derivable from the gene or protein expression data, whether the data is directed to gene transcript accumulation or protein accumulation or protein synthesis rates, etc.

[0097] The terms "healthy" and "normal" are used interchangeably herein to refer to a subject or particular cell or tissue that is devoid (at least to the limit of detection) of a disease condition.

[0098] The term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include analogues of either RNA or DNA made from nucleotide analogues, and, as applicable to the embodiment being described, single-stranded (such as sense or antisense) and double-stranded polynucleotides. In some embodiments, "nucleic acid" refers to inhibitory nucleic acids. Some categories of inhibitory nucleic acid compounds include antisense nucleic acids, RNAi constructs, and catalytic nucleic acid constructs. Such categories of nucleic acids are well-known in the art.

[0099] Embodiments described herein relate to compositions and methods for treating and/or preventing fibrosis and various fibrotic diseases, disorders or conditions. As described in the Examples below, it was found that that inhibitors of short-chain dehydrogenase activity, such as 15-PGDH inhibitors, can be administered to a subject in need thereof to decrease fibrotic symptoms, such as collagen deposition, inflammatory cytokine expression, and inflammatory cell infiltration, and treat and/or prevent various fibrotic diseases, disorders, and conditions.

[00100] In some embodiments, a method of treating or preventing a fibrotic disease, disorder or condition includes administering to a subject in need thereof a therapeutically effect amount of a 15-PGDH inhibitor such that at least one symptom or feature of a fibrotic disease, disorder or condition, or other related diseases, disorders or conditions, is reduced in intensity, severity, or frequency, or has delayed onset.

[00101] 15-PGDH inhibitors are agents that, *e.g.,* inhibit expression of 15-PGDH or bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate the activity of 15-PGDH, *e.g.,* antagonists. 15-PGDH inhibitors described herein can provide a pharmacologic method for elevating prostaglandin levels in tissue.

[00102] As used herein, the term "fibrotic" diseases, disorders, or conditions include diseases, disorders, or conditions characterized, in whole or in part, by the excess production of fibrous material, including excess production of fibrotic material within the extracellular matrix, or the replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components. The fibriotic disesases, disorders, or conditions, can include acute and chronic, clinical or subclinical presentation, in which fibrogenic associated biology or pathology is evident.

[00103] Examples of fibrotic diseases, disorders and conditions include systemic sclerosis, multifocal fibrosclerosis, nephrogenic systemic fibrosis, scleroderma(including morphea, generalized morphea, or linear scleroderma), sclerodermatous graft-vs-host-disease, kidney fibrosis (including glomerular sclerosis, renal tubulointerstitial fibrosis, progressive renal disease or diabetic nephropathy), cardiac fibrosis (*e.g.,* myocardial fibrosis), pulmonary fibrosis (*e.g.,* pulmonary fibrosis, glomerulosclerosis pulmonary fibrosis, idiopathic pulmonary fibrosis, silicosis, asbestosis, interstitial lung disease, interstitial fibrotic lung disease, and chemotherapy/radiation induced pulmonary fibrosis), oral fibrosis, endomyocardial fibrosis, deltoid fibrosis, pancreatitis, inflammatory bowel disease, Crohn's disease, nodular fascilitis, eosinophilic fasciitis, general fibrosis syndrome characterized by replacement of normal muscle tissue by fibrous tissue in varying degrees, retroperitoneal fibrosis, liver fibrosis, liver cirrhosis, chronic renal failure; myelofibrosis (bone marrow fibrosis), drug induced ergotism, myelodysplastic syndrome, myeloproferative syndrome, gynecological cancer, Kaposi's sarcoma, Hansen's disease, collagenous colitis, acute fibrosis, organ specific fibrosis, and the like.

[00104] Illustrative organ specific fibrotic disorders include, but are not limited to, pulmonary fibrosis, pulmonary hypertension, cystic fibrosis, asthma, chronic obstructive pulmonary disease, liver fibrosis, kidney fibrosis, NASH, and the like. Many fibrotic diseases, disorders or conditions have disordered and/or exaggerated deposition of extracellular matrix in affected tissues. Fibrosis may be associated with inflammation, occur as a symptom of underlying disease, and/or caused by surgical procedure or wound healing process. Unchecked fibrosis can result in destruction of the architecture of the underlying organ or tissue, commonly referred to as scarring.

[00105] In some embodiments, the 15-PGDH inhibitors can be used to treat or prevent lung fibrosis. The lung fibrosis can be selected from the group consisting of pulmonary fibrosis, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, or pulmonary hypertension, and combinations thereof.

[00106] Pulmonary fibrosis is characterized by progressive scarring of lung tissue accompanied by fibroblast proliferation, excessive accumulation of extracellular matrix proteins, and abnormal alveolar structure. The thickened and stiff tissue makes it difficult for lungs to work properly, leading to breathing problems such as shortness of breath, and can ultimately be fatal. Pulmonary fibrosis may be caused by acute lung injury, viral infection, exposure to toxins, radiation, chronic disease, medications, or may be idiopathic (*i.e.,* an undiscovered underlying cause).

[00107] The classic findings in idiopathic pulmonary fibrosis show diffuse peripheral scarring of the lungs with small bubbles (known as bullae) adjacent to the outer lining of the surface of the lung, often at the bases of the lungs. Idiopathic pulmonary fibrosis often has a slow and relentless progression. Early on, patients often complain of a dry unexplained cough. Next, shortness of breath (dyspnea) sets in and worsens over time triggered by less and less activity. Eventually, the shortness of breath becomes disabling, limiting all activity and even occurring while sitting still. In rarer cases, the fibrosis can be rapidly progressive, with dyspnea and disability occurring in weeks to months of onset of the disease. This form of pulmonary fibrosis has been referred to as Hamman-Rich syndrome.

[00108] Pulmonary hypertension is marked by an increase in the blood pressure of the lung vasculature, including the pulmonary artery, pulmonary vein, and/or pulmonary capillaries. Abnormally high pressure strains the right ventricle of the heart, causing it to expand. Over time, the right ventricle can weaken and lose its ability to pump enough blood to the lungs, leading to the development of heart failure. Pulmonary hypertension can occur as a result of other medical conditions, such as chronic liver disease and liver cirrhosis; rheumatic disorders such as scleroderma or systemic lupus erythematosus (lupus); and lung conditions including tumors, emphysema, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. Pulmonary fibrosis may lead to narrowing of pulmonary vasculature resulting in pulmonary hypertension.

[00109] Chronic Obstructive Pulmonary Disease (COPD) is a common lung disease that is often associated with chronic bronchitis or emphysema. Symptoms can often include cough, mucus build up, fatigue, wheezing, and respiratory infection.

[00110] Chronic bronchitis and emphysema are diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs,

causing shortness of breath (dyspnea). In clinical practice, COPD is defined by its characteristically low airflow on lung function tests.

[00111] Lung damage and inflammation in the large airways results in chronic bronchitis. In the airways of the lung, the hallmark of chronic bronchitis is an increased number (hyperplasia) and increased size (hypertrophy) of the goblet cells and mucous glands of the airway. As a result, there is more mucus than usual in the airways, contributing to narrowing of the airways and causing a cough with sputum. Microscopically there is infiltration of the airway walls with inflammatory cells. Inflammation is followed by scarring and remodeling that thickens the walls and also results in narrowing of the airways. As chronic bronchitis progresses, there is squamous metaplasia (an abnormal change in the tissue lining the inside of the airway) and fibrosis (further thickening and scarring of the airway wall). The consequence of these changes is a limitation of airflow and difficulty breathing.

[00112] Asthma is a chronic lung disease characterized by inflammation and constriction of the airways. Asthma causes recurring periods of wheezing, tightness of the chest, shortness of breath, and coughing. Swelling and overproduction of mucus can cause further airway constriction and worsening of symptoms. There is evidence that increased matrix degradation may occur in asthma, and this may contribute to mechanical changes in the airways in asthma (Roberts et al (1995) Chest 107:111 S-117S, incorporated herein by reference in its entirety. Treatment of extracellular matrix degradation may ameliorate symptoms of asthma.

[00113] Cystic fibrosis is a recessive multi-system genetic disease characterized by abnormal transport of chloride and sodium across epithelium, leading to thick, viscous secretions in the lungs, pancreas, liver, intestine and reproductive tract. Cystic fibrosis is caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR). Lung disease results from clogging of the airways due to mucus build-up, decreased mucociliary clearance, and resulting inflammation, which can cause fibrotic injury and structural changes to the lungs. The fibrotic lung damage progresses over time leading some cystic fibrosis patients to require lung transplant.

[00114] Common symptoms of subjects suffering from cystic fibrosis include, but are not limited to, accumulation of thick mucus, copious phlegm production, frequent chest infections, frequent coughing, frequent shortness of breath, inflammation, decreased ability to exercise, opportunistic infections of the lung and sinus (including but not limited to

Staphylococcus aureus, Haemophilus influenzae, Mycobacterium aviium, and Pseudomonas aeruginosa), pneumonia, tuberculosis, bronchiectasis, hemoptysis, pulmonary hypertension (and resulting heart failure), hypoxia, respiratory failure, allergic bronchopulmonary aspergillosis, mucus in the paranasal sinuses, sinus infection, facial pain, fever, excessive nasal drainage, development of nasal polyps, cardiorespiratory complications, CF-related diabetes, rectal prolapse, pancreatitis, malabsorption, intestinal blockage, exocrine pancreatic insufficiency, bile duct blockage, and liver cirrhosis.

[00115] In other embodiments, the 15-PGDH inhibitors can be used to treat or prevent fibrotic diseases, disorders or conditions caused by post-surgical adhesion formation. Post-surgical adhesion formation is a common complication of surgery. The formation of adhesions, from mechanical damage, ischemia, and infections, can increase morbidity and mortality following surgery. Although refined surgical procedures can reduce the magnitude of adhesion formation, adhesions are rarely eviscerated and an effective adjunctive therapy is needed. Reducing the fibrosis associated with this process could reduce pain, obstruction and other complications of surgery and promote healing and recovery.

[00116] Wounds (*i.e.,* lacerations, openings) in mammalian tissue result in tissue disruption and coagulation of the microvasculature at the wound face. Repair of such tissue represents an orderly, controlled cellular response to injury. Soft tissue wounds, regardless of size, heal in a similar manner. Tissue growth and repair are biologic systems wherein cellular proliferation and angiogenesis occur in the presence of an oxygen gradient. The sequential morphological and structural changes which occur during tissue repair have been characterized in detail and have in some instances been quantified (see *e.g.,* Hunt, T. K., et al., "Coagulation and macrophage stimulation of angiogenesis and wound healing," in The Surgical Wound, pp. 1-18, ed. F. Dineen & G. Hildrick-Smith (Lea & Febiger, Philadelphia: 1981)). The cellular morphology consists of three distinct zones. The central avascular wound space is oxygen deficient, acidotic and hypercarbic, and has high lactate levels. Adjacent to the wound space is a gradient zone of local anemia (ischemia) which is populated by dividing fibroblasts. Behind the leading zone is an area of active collagen synthesis characterized by mature fibroblasts and numerous newly-formed capillaries (*i.e.,* neovascularization). U.S. Pat. Nos. 5,015,629 and 7,022,675 (each incorporated by reference herein) disclose methods and compositions for increasing the rate of wound repair.

[00117] In some embodiments, the 15-PGDH inhibitors can used for reducing or preventing scar formation in a subject by administering to a subject in need of treatment. Scar formation is a natural part of the healing process. Disorderly collagen synthesis and deposition in a wound can result in excessive, thick, or raised scar formation. Generally, the larger the wound, the longer it takes to heal and the greater the chance of a problematic scar.

[00118] In other embodiments, the 15-PGDH inhibitors can be used to reduce or prevent scar formation on skin or scleroderma. There are several types of scars on skin. Hypertropic scars are raised, pinkish-red areas located inside the borders of the original injury. They are often described as itchy. In some cases, hypertropic scars shrink and fade on their own. Keloids are raised, deep-red areas that tend to cover much more area than that of the original injury. Even when surgically removed, keloids tend to recur. Atrophic scars are skin depressions, like those that sometimes form from severe acne. They are caused by inflammation that destroys the collagen during the rebuilding process, leaving an area of indentation.

[00119] In some embodiments, the 15-PGDH inhibitors can be used to treat or prevent systemic sclerosis. Systemic sclerosis is a systemic connective tissue disease characterized by alterations of the microvasculature, disturbances of the immune system and by massive deposition of collagen and other matrix substances in the connective tissue. Systemic sclerosis is a clinically heterogeneous generalized disorder which affects the connective tissue of the skin and internal organs such as gastrointestinal tract, lungs, heart and kidneys. Reduction of fibrosis resulting from systemic sclerosis may ameliorate symptoms and/or prevent further complications in affected tissues.

[00120] In other embodiments, the 15-PGDH inhibitors can be used to treat or prevent liver fibrosis. Liver fibrosis can result from a chronic liver disease, viral induced hepatic cirrhosis, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, schistosomiasis, primary biliary cirrhosis, alcoholic liver disease or non-alcoholic steatohepatitis (NASH) , NASH associated cirrhosis obesity, diabetes, protein malnutrition, coronary artery disease, auto-immune hepatitis, cystic fibrosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, drug reaction and exposure to toxins.

[00121] Nonalcoholic steatohepatitis (NASH) is a common liver disease. It resembles alcoholic liver disease but occurs in people who drink little or no alcohol. The major feature in NASH is fat in the liver, along with inflammation and damage. Nevertheless, NASH can

be severe and can lead to cirrhosis, in which the liver is permanently damaged and scarred and no longer able to work properly.

[00122] NASH is usually a silent disease with few or no symptoms. Patients generally feel well in the early stages and only begin to have symptoms--such as fatigue, weight loss, and weakness--once the disease is more advanced or cirrhosis develops. The progression of NASH can take years, even decades. The process can stop and, in some cases may even begin to reverse on its own without specific therapy. Or NASH can slowly worsen, causing scarring or fibrosis to appear and accumulate in the liver. As fibrosis worsens, cirrhosis develops in which the liver becomes seriously scarred, hardened, and unable to function normally. Not every person with NASH develops cirrhosis, but once serious scarring or cirrhosis is present, few treatments can halt the progression. A person with cirrhosis experiences fluid retention, muscle wasting, bleeding from the intestines, and liver failure. Liver transplantation is the only treatment for advanced cirrhosis with liver failure, and transplantation is increasingly performed in people with NASH. NASH ranks as one of the major causes of cirrhosis in America, behind hepatitis C and alcoholic liver disease.

[00123] In some embodiments, the 15-PGDH inhibitors can be used to treat or prevent kidney fibrosis. Kidney fibrosis can result from dialysis following kidney failure, catheter placement, a nephropathy, glomerulosclerosis, glomerulonephritis, chronic renal insufficiency, acute kidney injury, end stage renal disease or renal failure.

[00124] Kidney (renal) fibrosis results from excessive formation of fibrous connective tissue in the kidney. Kidney fibrosis causes significant morbidity and mortality and leads to a need for dialysis or kidney transplantation. Fibrosis can occur in either the filtering or reabsorptive component of the nephron, the functional unit of the kidney. A number of factors may contribute to kidney scarring, particularly derangements of physiology involved in the autoregulation of glomerular filtration. This in turn leads to replacement of normal structures with accumulated extracellular matrix. A spectrum of changes in the physiology of individual cells leads to the production of numerous peptide and non-peptide fibrogens that stimulate alterations in the balance between extracellular matrix synthesis and degradation to favor scarring.

[00125] In some embodiments, the symptoms of fibrosis of a tissue organ can comprise inflammation. In these embodiments, a therapeutically effective amount of the 15-PGDH inhibitor administered to the subject in need thereof can be an amount effective to decrease or

reduce inflammatory cell count in the tissue or organ. A relevant sample can be obtained from the subject to determine the decrease or reduction in inflammatory cell count. In a non-limiting embodiment, the beneficial effect may be assessed by demonstrating a reduction in neutrophil count in BAL fluid from the subject with cystic fibrosis. The excessive recruitment of neutrophils into the airways of patients with CF is a significant predictor of lung disease severity in CF and therefore is an important therapeutic target. Methods for measuring such cell counts are well known in the art, including but not limited to FACS techniques. In some embodiments, the method may comprise reducing neutrophil cell count in BAL fluid from the subject compared to control. Any suitable control can be used for comparison, such as cystic fibrosis subjects not treated the 15-PGDH inhibitors. In some embodiments, a decrease in inflammatory cell count, such as neutrophil count, provides a clinical benefit to the subject. In various embodiments, the reduction in inflammatory cell count is at least 5%, 10%, 15%, 20%, 25%, 50%, or more compared to control.

[00126] In another embodiment, the beneficial effect of the 15-PGDH inhibitors may be assessed by a reduction in one or more inflammatory biomarkers in a relevant sample from the subject. In various non-limiting embodiments, the inflammatory biomarker may comprise or consist of one or more of cytokines or inflammatory cytokines associated with fibrosis. Such cytokines can include, for example, IL1β, MIP2 (*e.g.,* CCL3 or CCL4), IFNδ, TGFβ, TNFα, IL-6, MCP-1, IL2, and IL-10 in BAL fluid. Methods for measuring the amount of such biomarkers are well known in the art, including but not limited to ELISAs. Thus, in this embodiment, the methods may further comprise the reducing an amount of one or more inflammatory biomarkers in a sample from the subject compared to control.

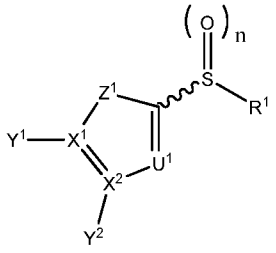
[00127] In other embodiments, the 15-PGDH inhibitors can be used in a method for decreasing or reducing collagen secretion or collagen deposition in a tissue or organ, such as the lung, the liver, the skin or the heart, of a subject. The method can include administering a therapeutically effective amount of the 15-PGDH inhibitors to the subject in need thereof. The subject can have or be at risk of an excessive collagen secretion or collagen deposition in the tissue or organ, such as the kidney, the lung, the liver, the intestines, the colon, the skin or the heart. Usually, the excessive collagen secretion or collagen deposition in an organ results from an injury or an insult. Such injury and insult are organ-specific. The 15-PGDH inhibitors can be administered over a sufficient period of time to decrease or reduce the level of collagen deposition in the tissue or organ, completely or partially. A sufficient period of

time can be during one week, or between 1 week to 1 month, or between 1 to 2 months, or 2 months or more. For chronic condition, the15-PGDH inhibitors can be advantageously administered for life time period.

[00128] 15-PGDH inhibitors used to treat the fibrotic disease, disorder or condition and/or reduce collagen deposition can be identified using assays in which putative inhibitor compounds are applied to cells expressing 15-PGDH and then the functional effects on 15-PGDH activity are determined. Samples or assays comprising 15-PGDH that are treated with a potential inhibitor are compared to control samples without the inhibitor to examine the extent of effect. Control samples (untreated with modulators) are assigned a relative 15-PGDH activity value of 100%. Inhibition of 15-PGDH is achieved when the 15-PGDH activity value relative to the control is about 80%, optionally 50% or 25%, 10%, 5% or 1%.

[00129] Agents tested as inhibitors of SCD (*e.g.,* 15-PGDH) can be any small chemical molecule or compound. Typically, test compounds will be small chemical molecules, natural products, or peptides. The assays are designed to screen large chemical libraries by automating the assay steps and providing compounds from any convenient source to assays, which are typically run in parallel (*e.g.,* in microtiter formats on microtiter plates in robotic assays).

[00130] In some embodiments, the 15-PGDH inhibitor can include a compound having the following formula (I):



(I)

wherein n is 0-2;

Y^1, Y^2, and R^1 are the same or different and are each selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl

(including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein Y^1 and Y^2 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

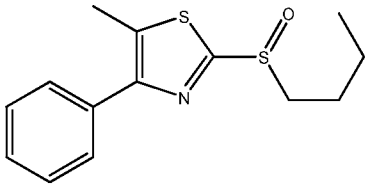
U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

X^1 and X^2 are independently N or C, and wherein when X^1 and/or X^2 are N, Y^1 and/or Y^2, respectively, are absent;

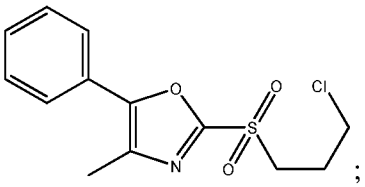
Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

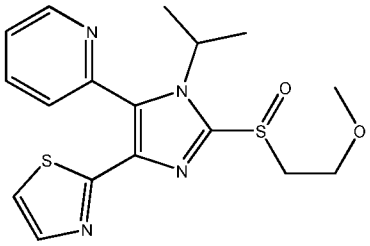
[00131] Examples of 15-PGDH inhibitors having formulas (I) include the following compounds:



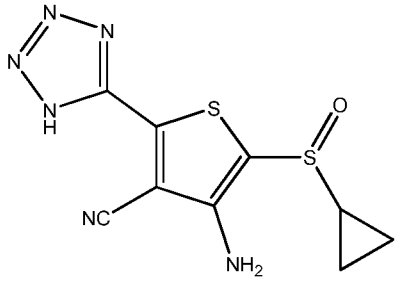
;



;

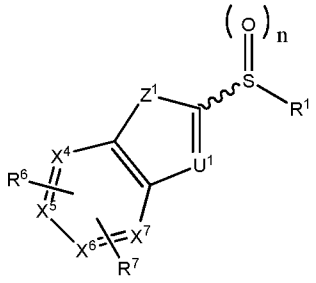


;



; and pharmaceutically acceptable salts thereof.

[00132] In other embodiments, the 15-PGDH inhibitor can include a compound having the following formula (II):



(II)

wherein n is 0-2

X^4, X^5, X^6, and X^7 are independently N or CR^c;

R^1, R^6, R^7, and R^c are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O,

and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incoporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

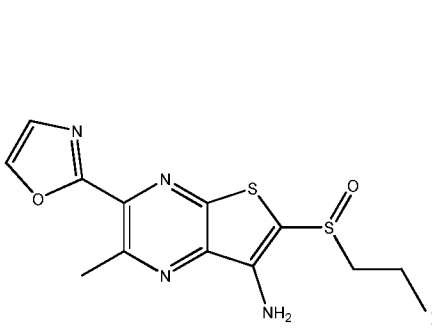
U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl,

Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

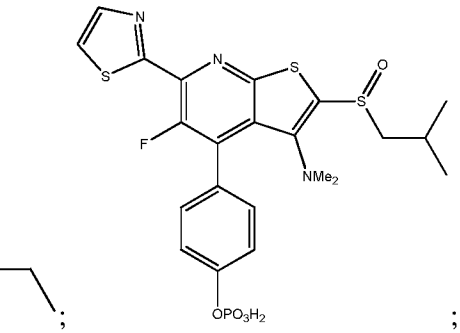
Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

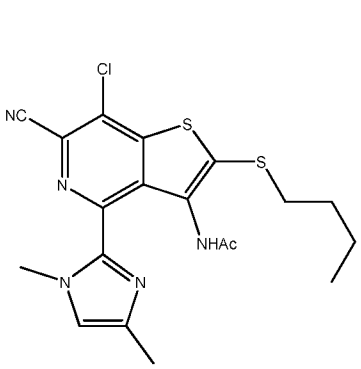
[00133] Examples of 15-PGDH inhibitors having formulas (II) include the following compounds:



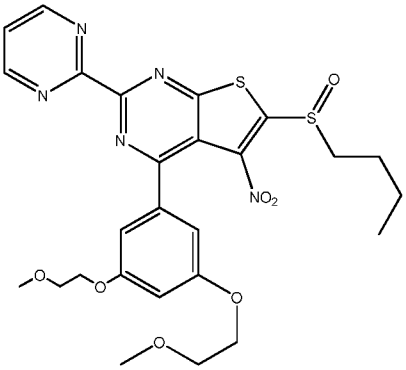
;



;

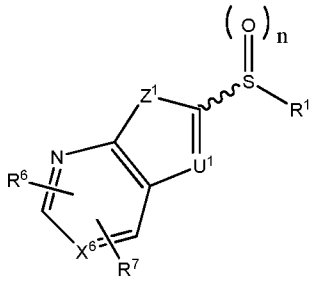


;

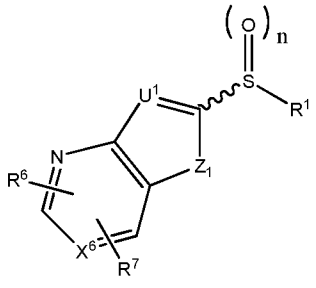


; and pharmaceutically acceptable salts thereof.

[00134] In yet other embodiments, the 15-PGDH inhibitor can include a compound having the following formula (III) or (IV):



(III), or



(IV)

wherein n is 0-2

X^6 is independently is N or CR^c;

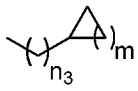
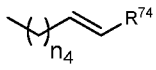
R^1, R^6, R^7, and R^c are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating

amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

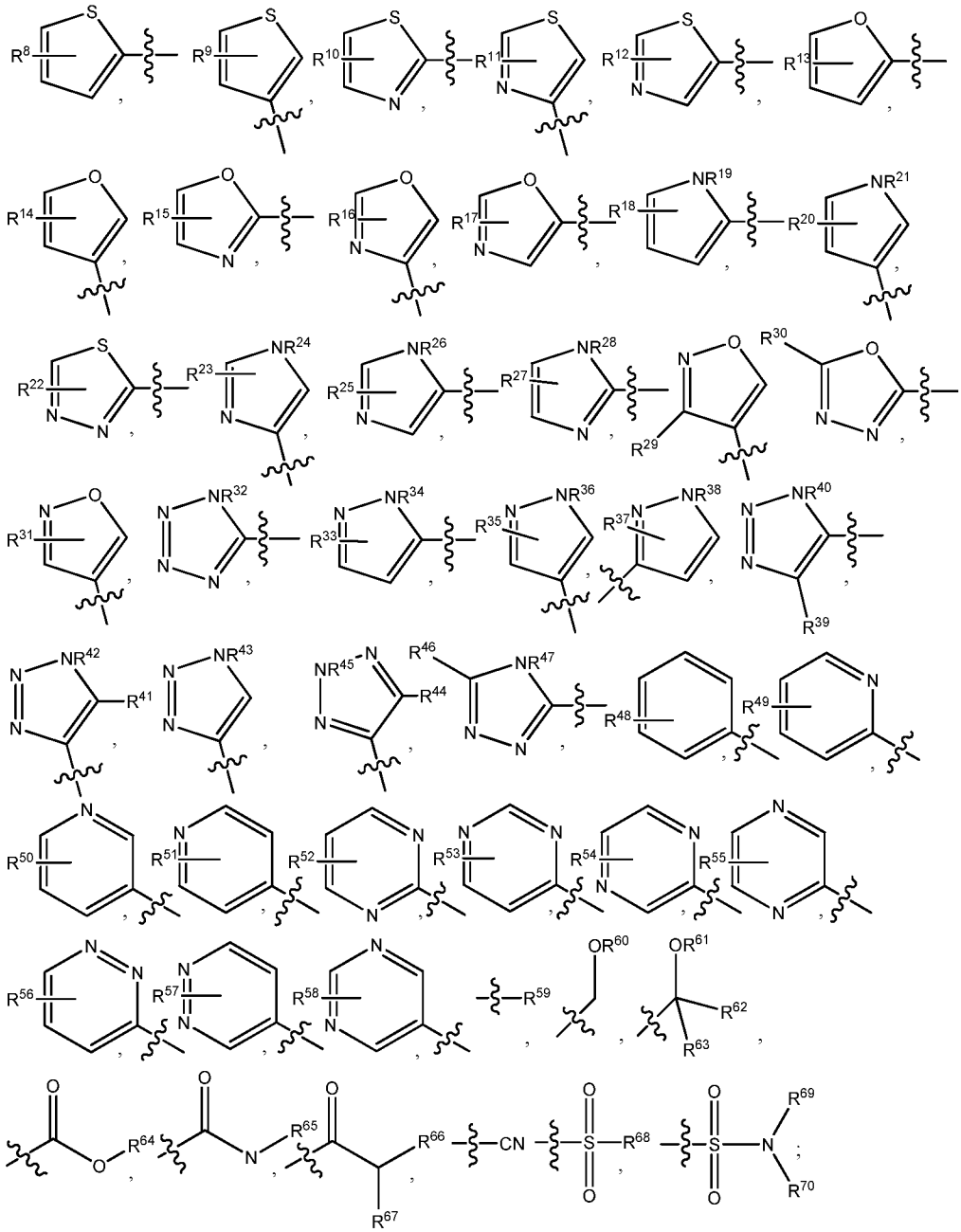
U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', $(C=O)N(R')_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', $(C=O)N(R')_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

[00135] In some embodiments, R^1 is selected from the group consisting of branched or linear alkyl including $-(CH_2)n_1CH_3$ (n_1=0-7),  wherein n_2=0-6 and X is any of the following: CF_yH_z (y + z = 3), CCl_yH_z (y + z = 3), OH, OAc, OMe, R^{71}, OR^{72}, CN, $N(R^{73})_2$,  (n_3=0-5, m=1-5), and  (n_4=0-5).

[00136] In other embodiments, R^6 and R^7 can each independently be one of the following:

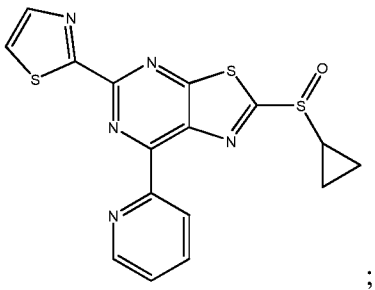
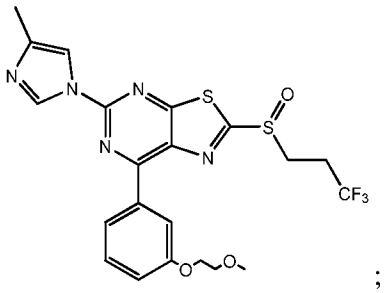
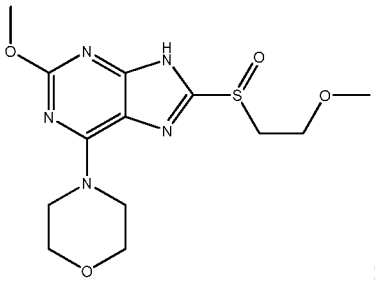
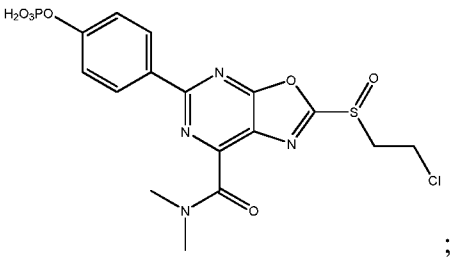
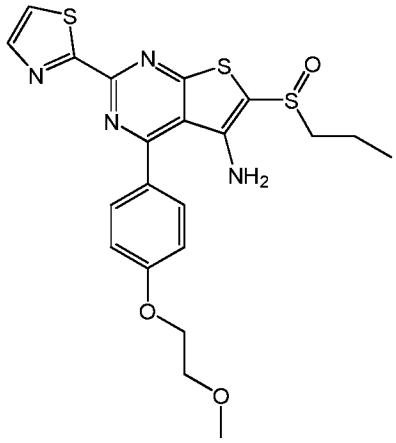
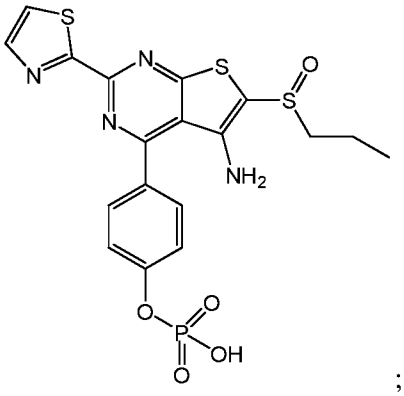
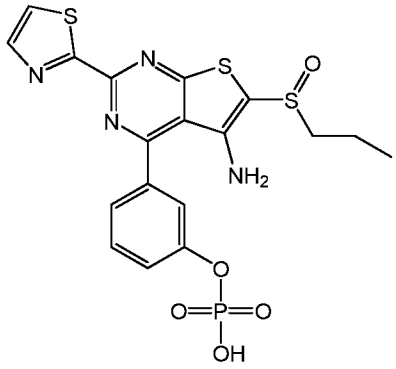
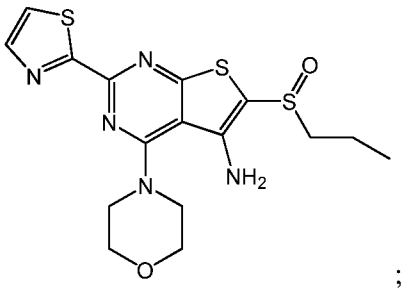


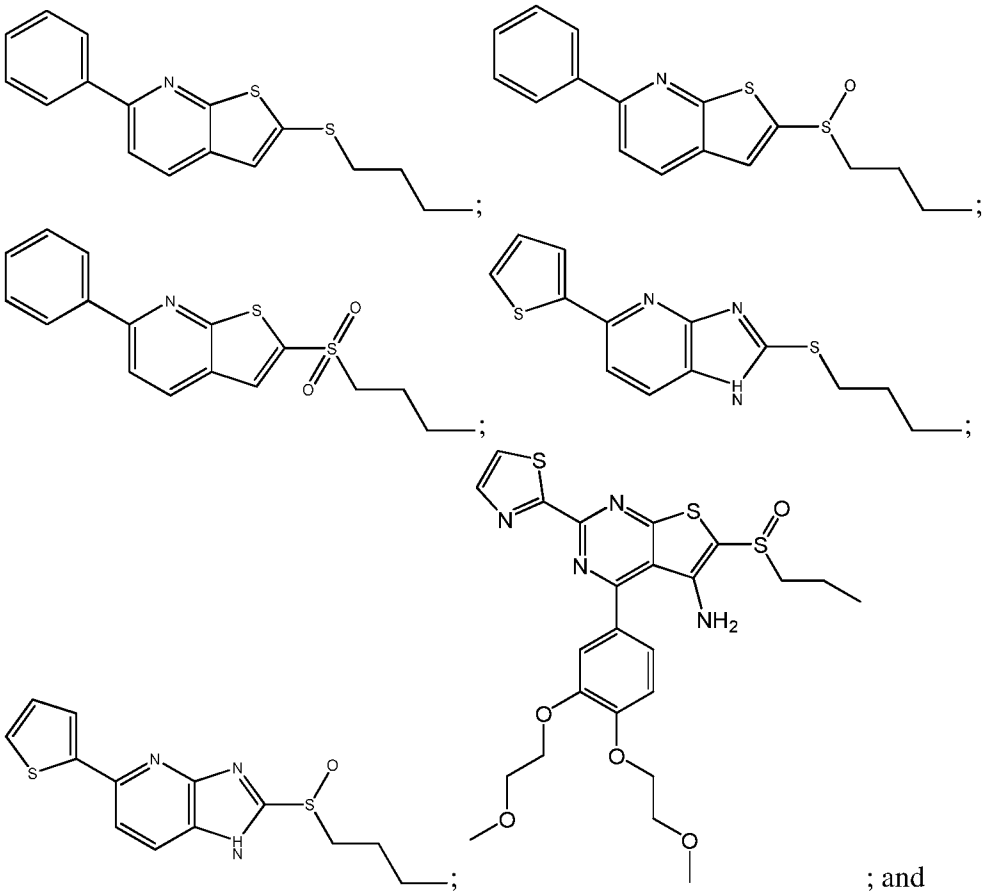
each R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, and R^{74} are the same or different and are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl,

C_2-C_{24} alkynyl, C_3-C_{20} aryl, heterocycloalkenyl containing from 5-6 ring atoms, (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O) (C_1-C_6 alkyl), O, and S), heteroaryl or heterocyclyl containing from 5-14 ring atoms, (wherein from 1-6 of the ring atoms is independently selected from N, NH, N(C_1-C_3 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, silyl, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)--NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), sulfanamido (-$SO_2N(R)_2$ where R is independently H, alkyl, aryl or heteroaryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH_2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkyl ethers (-[$(CH_2)_nO]_m$), phosphates, phosphate esters [-OP(O)$(OR)_2$ where R = H, methyl or other alkyl], groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, and combinations thereof, and pharmaceutically acceptable salts thereof.

[00137] In still other embodiments, R^6 and R^7 can independently be a group that improves aqueous solubility, for example, a phosphate ester (-OPO_3H_2), a phenyl ring linked to a phosphate ester (-OPO_3H_2), a phenyl ring substituted with one or more methoxyethoxy groups, or a morpholine, or an aryl or heteroaryl ring substituted with such a group.

[00138] Examples of 15-PGDH inhibitors having formulas (III) or (IV) include the following compounds:

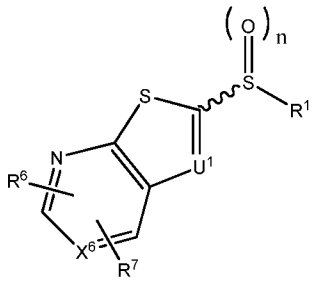

;

;

;

;

;

;

;

;



; and

pharmaceutically acceptable salts thereof.

[00139] In other embodiments, the 15-PGDH inhibitor can include a compound having the following formula (V):



(V)

wherein n is 0-2

X^6 is independently is N or CR^c

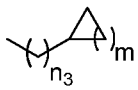
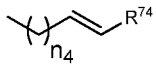
R^1, R^6, R^7, and R^c are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the

ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

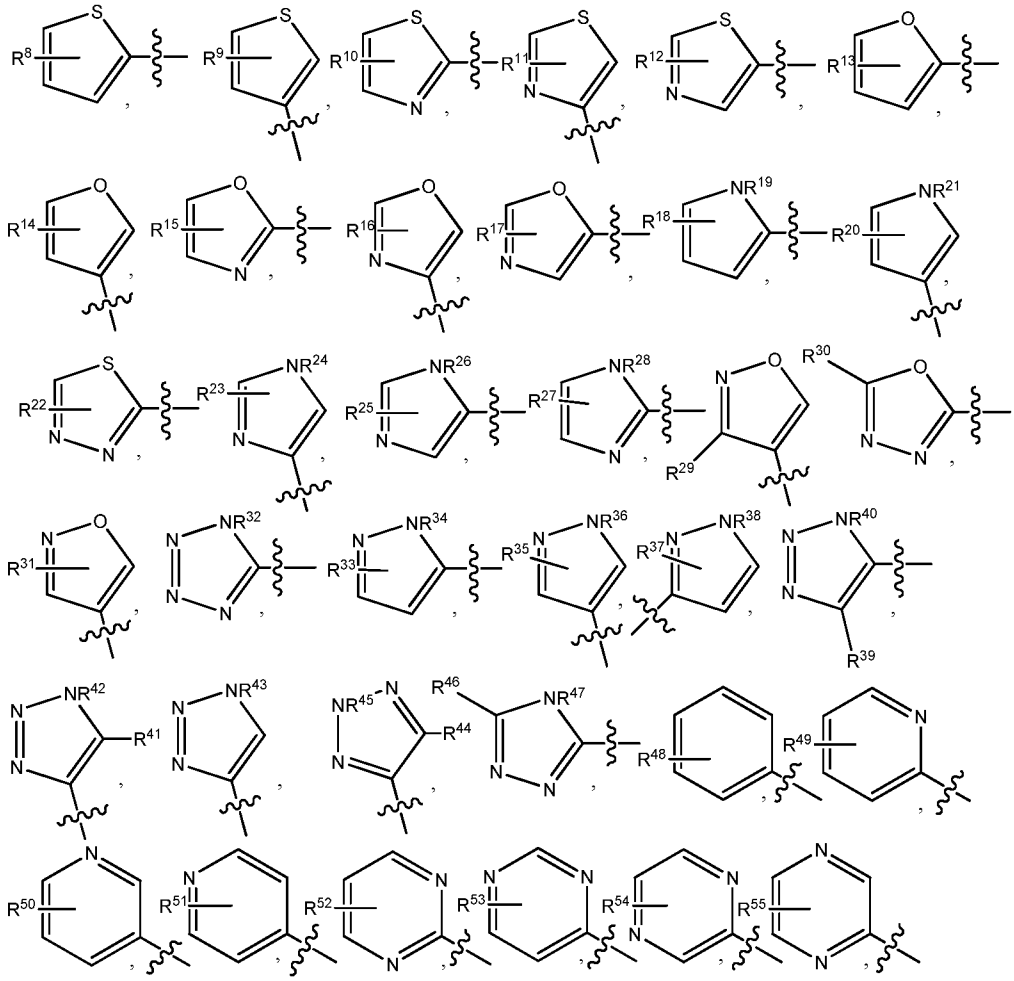
U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl

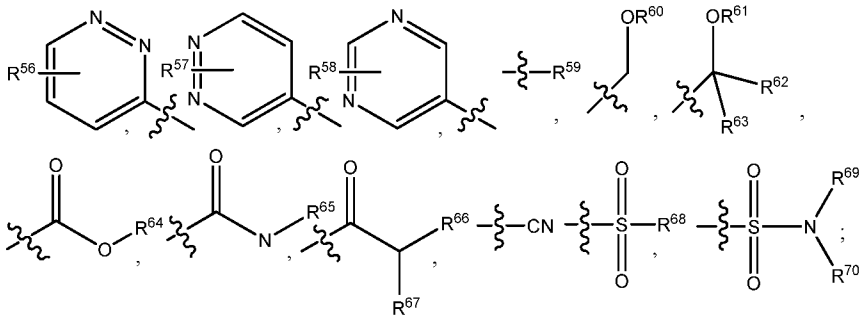
group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', $(C=O)N(R')_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

and pharmaceutically acceptable salts thereof.

[00140] In some embodiments, R^1 is selected from the group consisting of branched or linear alkyl including $-(CH_2)n_1CH_3$ (n_1=0-7),  wherein n_2=0-6 and X is any of the following: CF_yH_z (y + z = 3), CCl_yH_z (y + z = 3), OH, OAc, OMe, R^{71}, OR^{72}, CN, $N(R^{73})_2$,  (n_3=0-5, m=1-5), and  (n_4=0-5).

[00141] In other embodiments, R^6 and R^7 can each independently be one of the following:



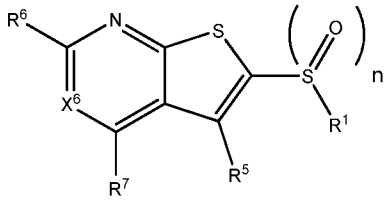


each each R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, and R^{74}, are the same or different and are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heterocycloalkenyl containing from 5-6 ring atoms, (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), heteroaryl or heterocyclyl containing from 5-14 ring atoms, (wherein from 1-6 of the ring atoms is independently selected from N, NH, N(C_1-C_3 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, silyl, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)--NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), sulfanamido (-$SO_2N(R)_2$ where R is independently H, alkyl, aryl or heteroaryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl

(-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH_2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkyl ethers (-$[(CH_2)_nO]_m$), phosphates, phosphate esters [-OP(O)$(OR)_2$ where R = H, methyl or other alkyl], groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, and combinations thereof, and pharmaceutically acceptable salts thereof.

[00142] In still other embodiments, R^6 and R^7 can independently be a group that improves aqueous solubility, for example, a phosphate ester (-OPO_3H_2), a phenyl ring linked to a phosphate ester (-OPO_3H_2), a phenyl ring substituted with one or more methoxyethoxy groups, or a morpholine, or an aryl or heteroaryl ring substituted with such a group.

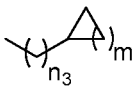
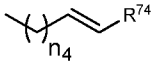
[00143] In other embodiments, the 15-PGDH inhibitor can include a compound having the following formula (VI):



(VI)

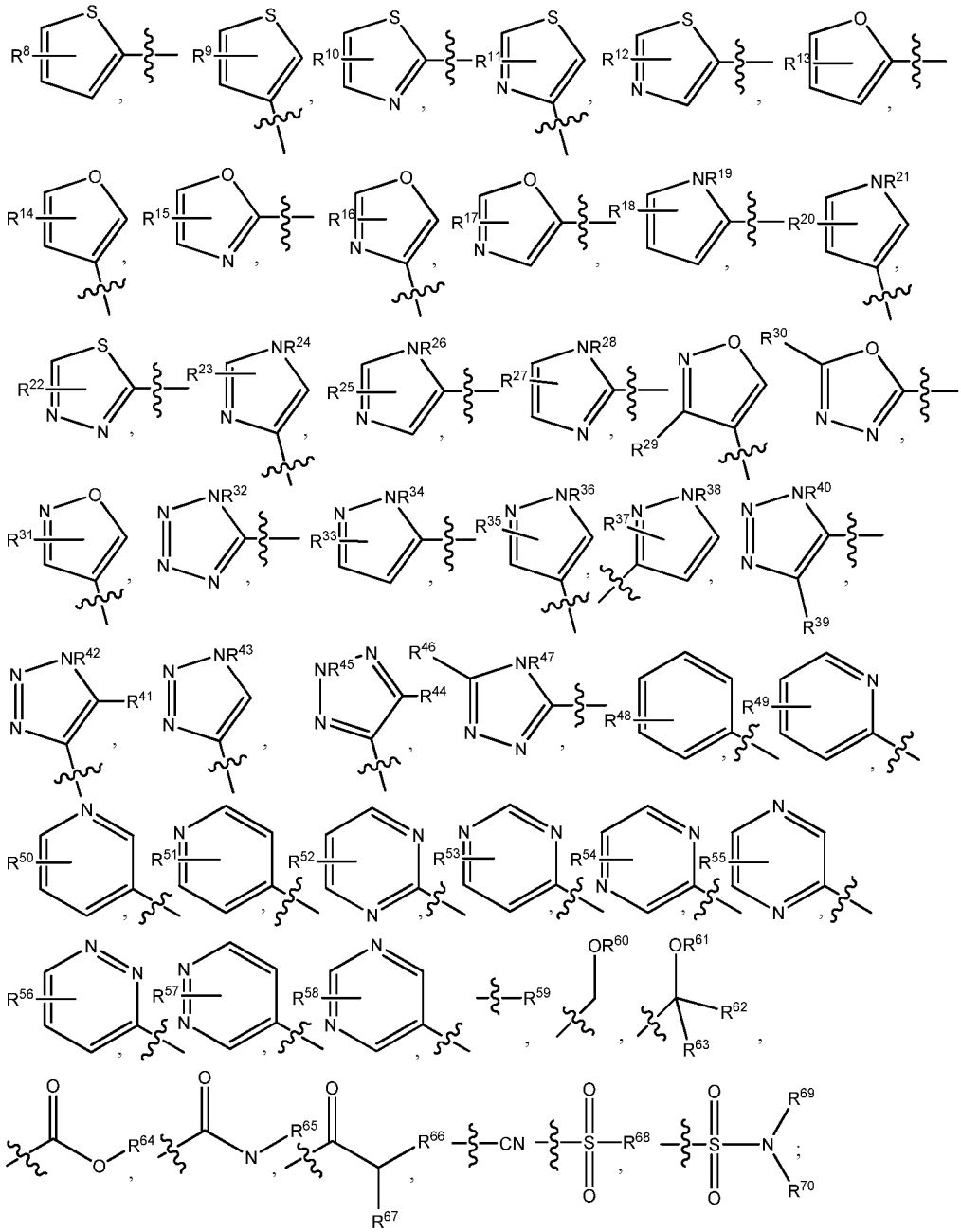
wherein n = 0-2;

X^6 is N or CR^c;

R^1 is selected from the group consisting of branched or linear alkyl including –$(CH_2)n_1CH_3$ (n_1=0-7),  wherein n_2=0-6 and X is any of the following: CF_yH_z (y + z = 3), CCl_yH_z (y + z = 3), OH, OAc, OMe, R^{71}, OR^{72}, CN, $N(R^{73})_2$,  (n_3=0-5, m=1-5), and  (n_4=0-5).

R^5 is selected from the group consisting of H, Cl, F, NH_2, and $N(R^{76})_2$;

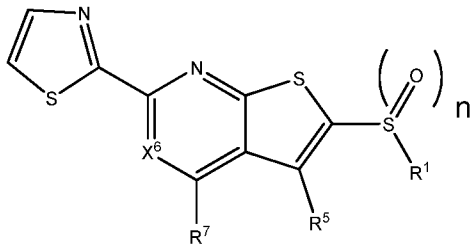
R^6 and R^7 can each independently be one of the following:



each R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{76}, and R^c are the same or different and are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl,

C_2-C_{24} alkynyl, C_3-C_{20} aryl, heterocycloalkenyl containing from 5-6 ring atoms, (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), heteroaryl or heterocyclyl containing from 5-14 ring atoms, (wherein from 1-6 of the ring atoms is independently selected from N, NH, N(C_1-C_3 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, silyl, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)--NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), sulfanamido (-$SO_2N(R)_2$ where R is independently H, alkyl, aryl or heteroaryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH_2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkyl ethers (-[$(CH_2)_nO]_m$), phosphates, phosphate esters [-OP(O)$(OR)_2$ where R = H, methyl or other alkyl], groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, and combinations thereof, and pharmaceutically acceptable salts thereof.

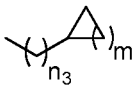
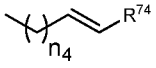
[00144] In other embodiments, the 15-PGDH inhibitor can include a compound having the following formula (VII):



(VII)

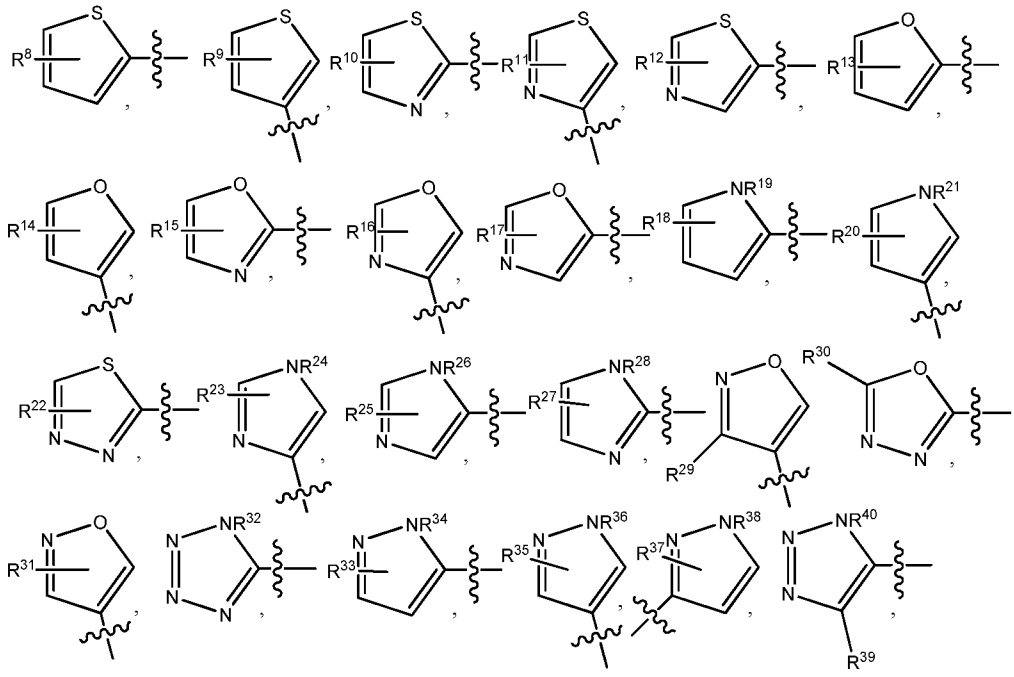
wherein n = 0-2;

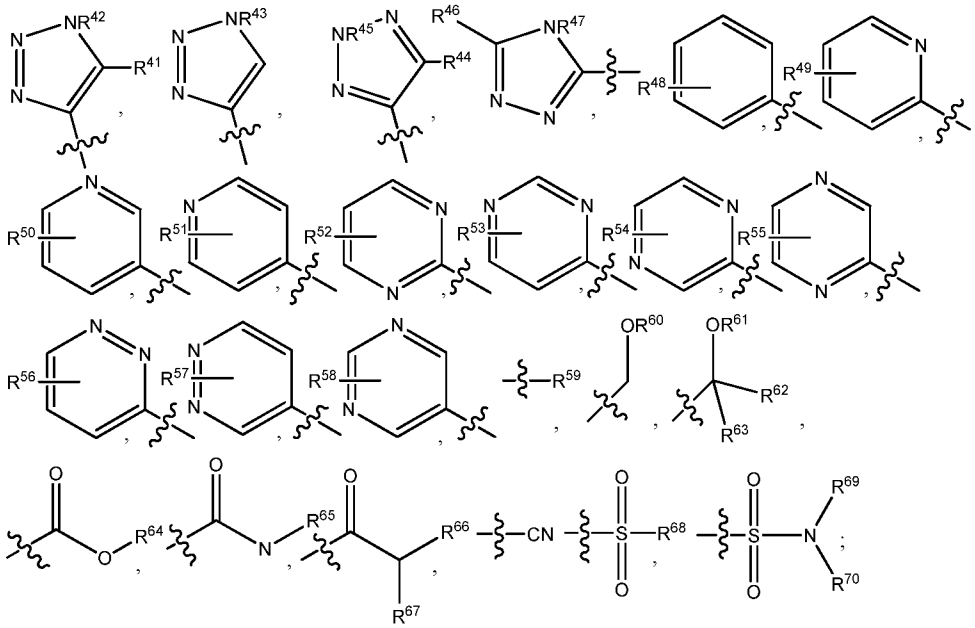
X^6 is N or CR^c;

R^1 is selected from the group consisting of branched or linear alkyl including –$(CH_2)n_1CH_3$ (n_1=0-7),  wherein n_2=0-6 and X is any of the following: CF_yH_z (y + z = 3), CCl_yH_z (y + z = 3), OH, OAc, OMe, R^{71}, OR^{72}, CN, $N(R^{73})_2$,  (n_3=0-5, m=1-5), and  (n_4=0-5).

R^5 is selected from the group consisting of H, Cl, F, NH_2, and $N(R^{76})_2$;

R^7 can each independently be one of the following:

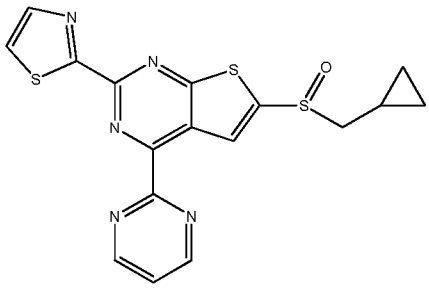
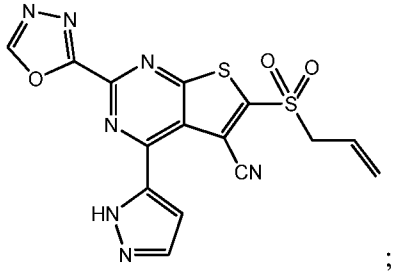
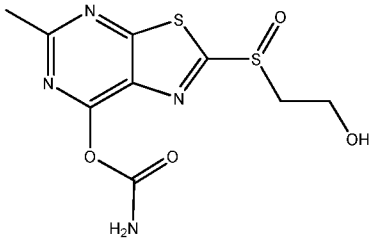
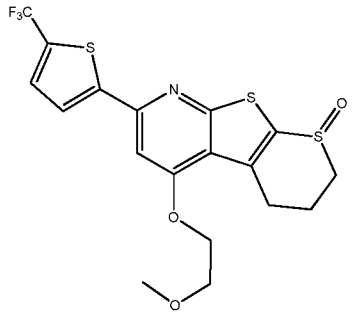
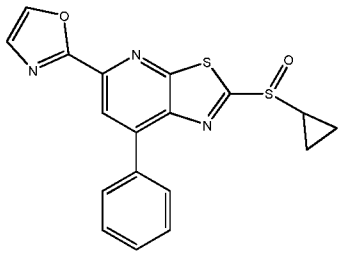
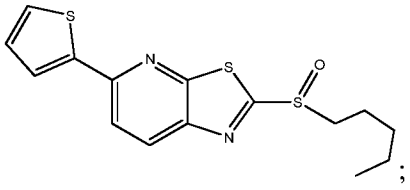


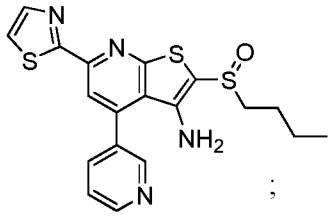


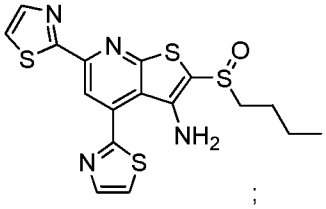
each R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{76}, and R^c are the same or different and are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heterocycloalkenyl containing from 5-6 ring atoms, (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), heteroaryl or heterocyclyl containing from 5-14 ring atoms, (wherein from 1-6 of the ring atoms is independently selected from N, NH, N(C_1-C_3 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, silyl, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato ($-COO^-$), carbamoyl (-(CO)--NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano ($-N^+C^-$), cyanato (-O-CN), isocyanato ($-O-N^+=C^-$), isothiocyanato (-S-CN), azido ($-N=N^+=N^-$), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20}

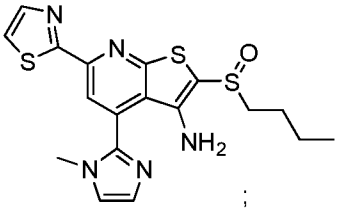
arylamido (-NH-(CO)-aryl), sulfanamido (-$SO_2N(R)_2$ where R is independently H, alkyl, aryl or heteroaryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH_2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkyl ethers (-$[(CH_2)_nO]_m$), phosphates, phosphate esters [-OP(O)$(OR)_2$ where R = H, methyl or other alkyl], groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, and combinations thereof, and pharmaceutically acceptable salts thereof.

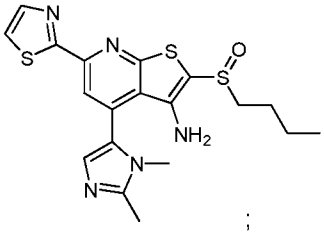
[00145] Examples of compounds having formulas (V), (VI), or (VIII) are selected from the group consisting of:

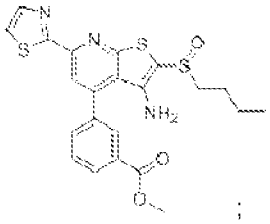

;

;

;

;

;

;

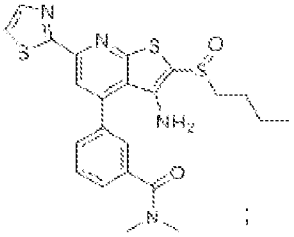

;

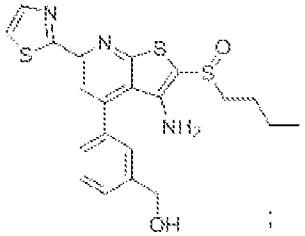

;

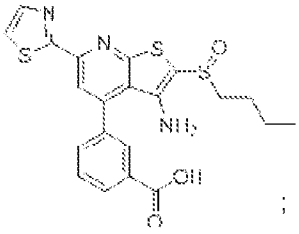

;

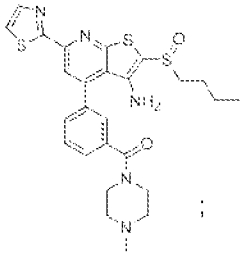

;

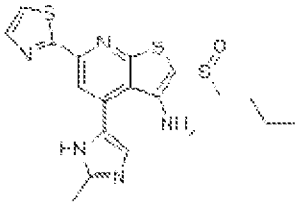

;

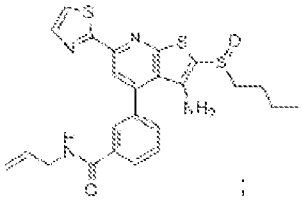

;

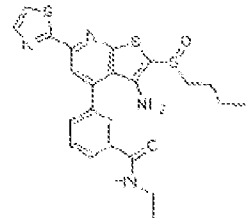

;


;


;


;

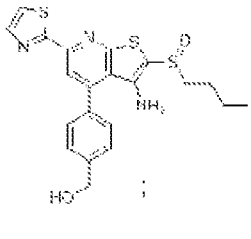

;

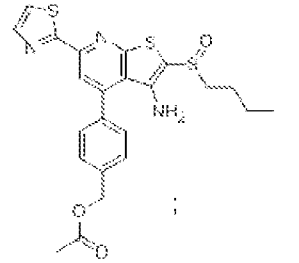

;

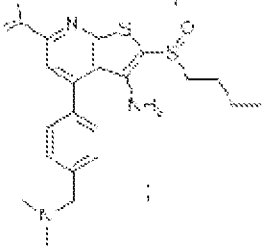
;

;

;


;


;


;

;

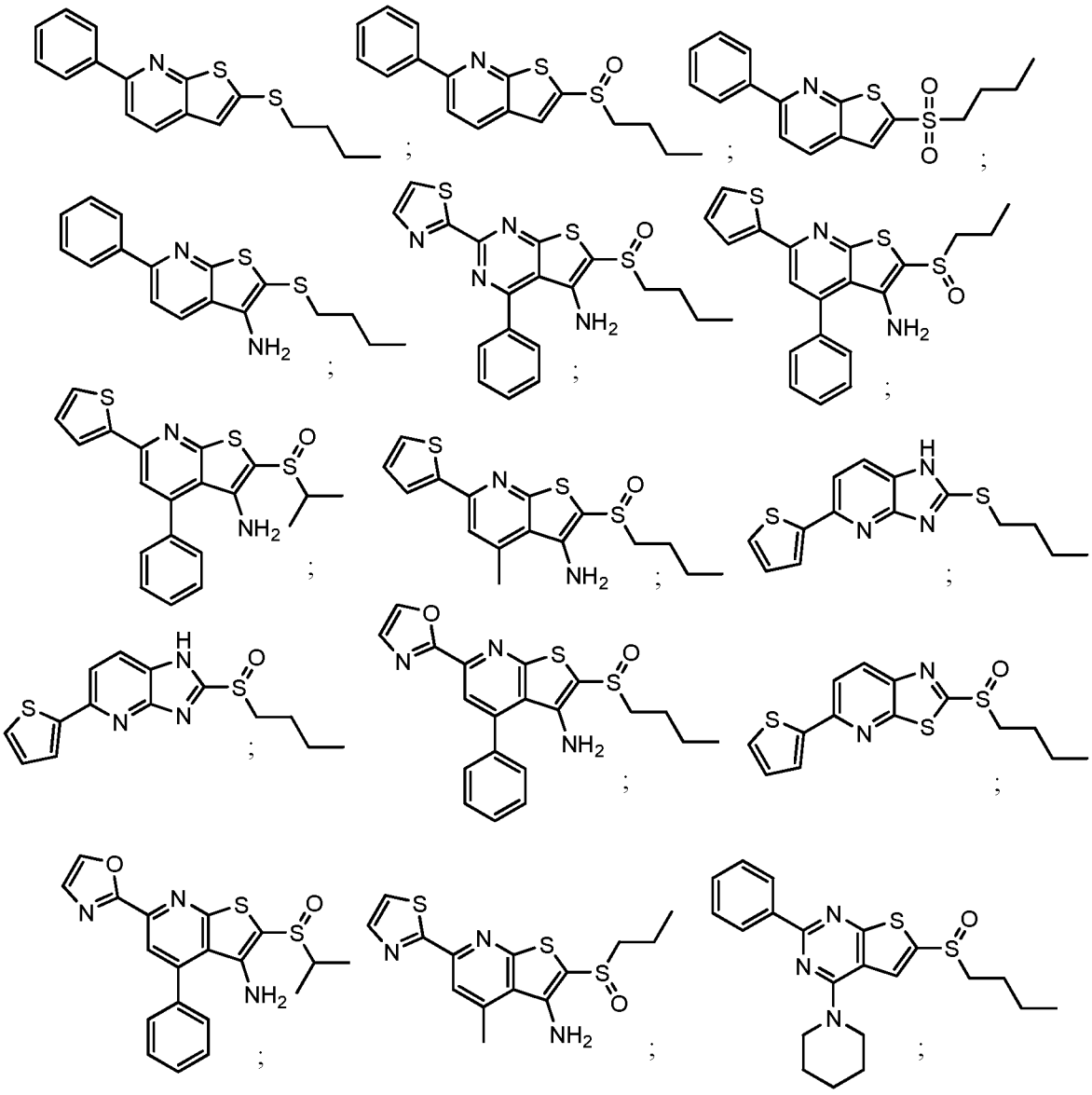
;

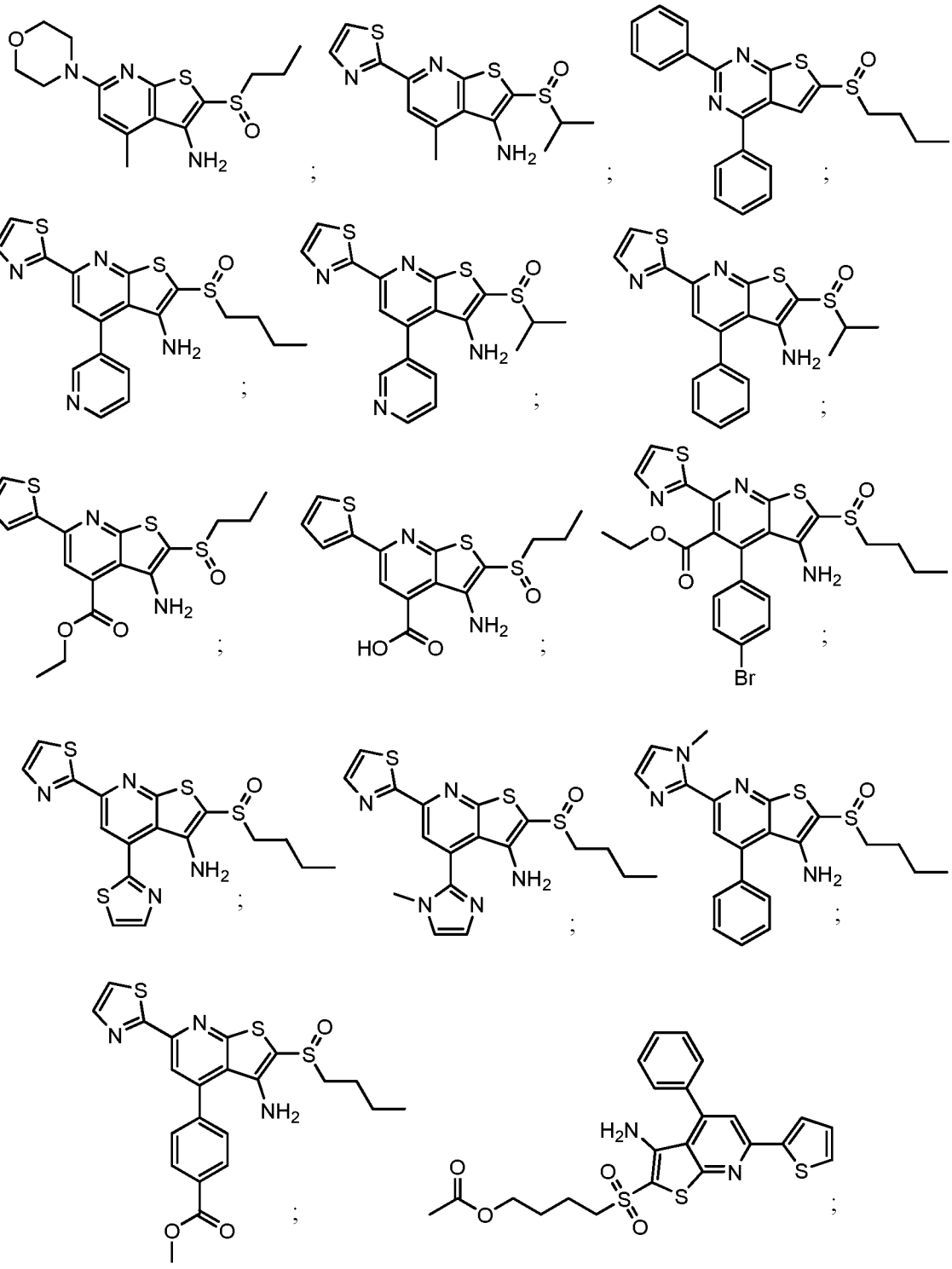
;

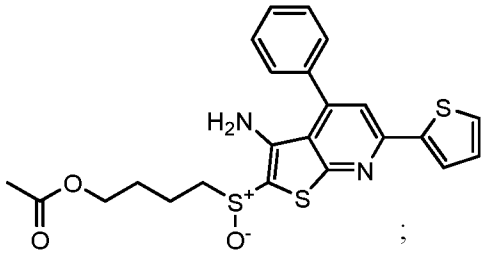
;

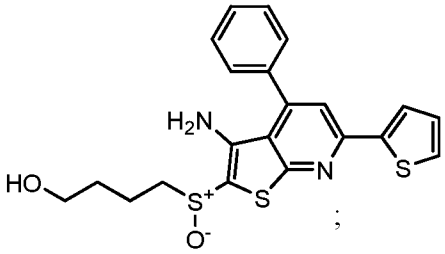
;

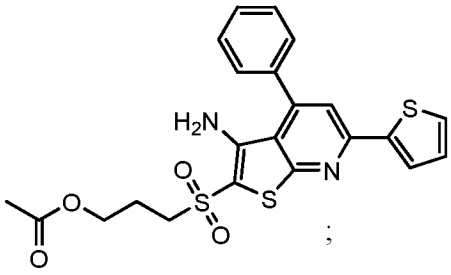
;

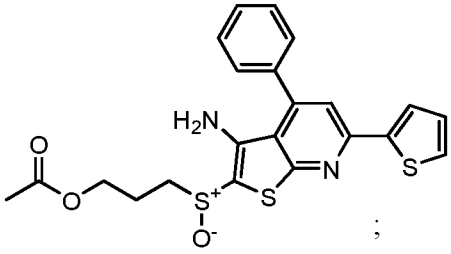


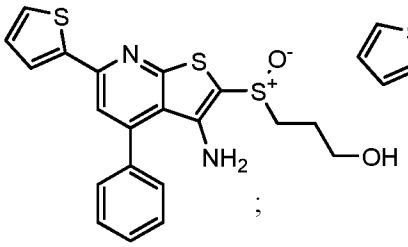


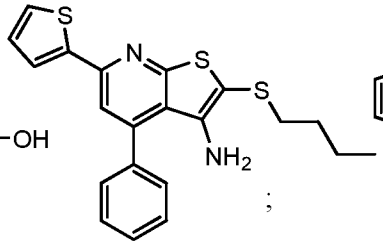

;

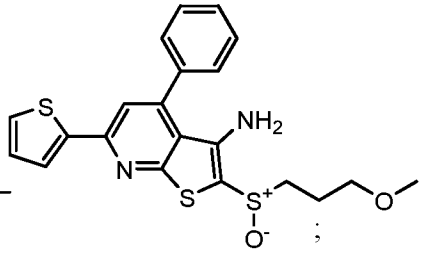

;

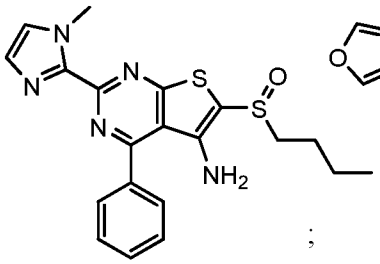

;

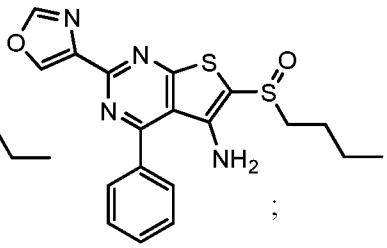

;

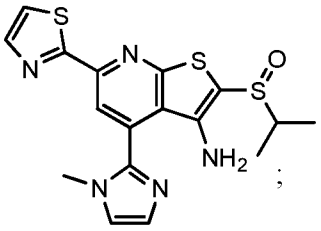

;

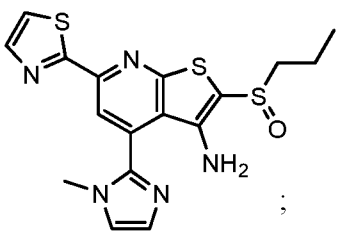

;

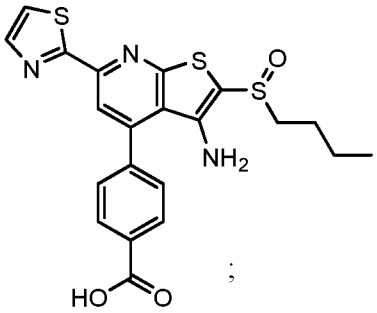

;

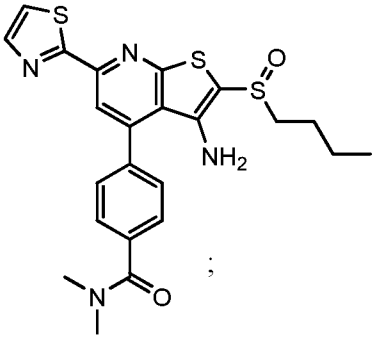

;

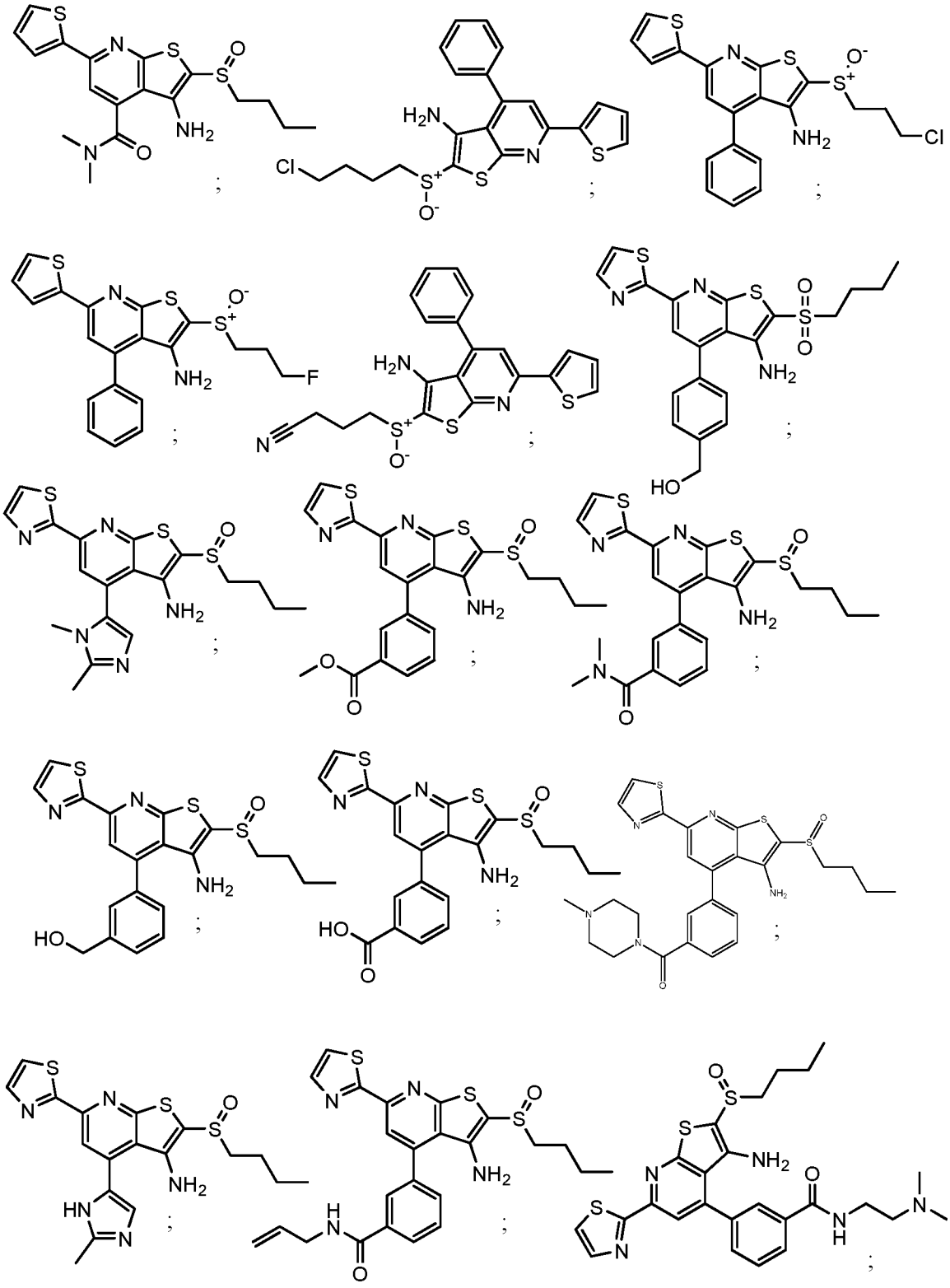

;

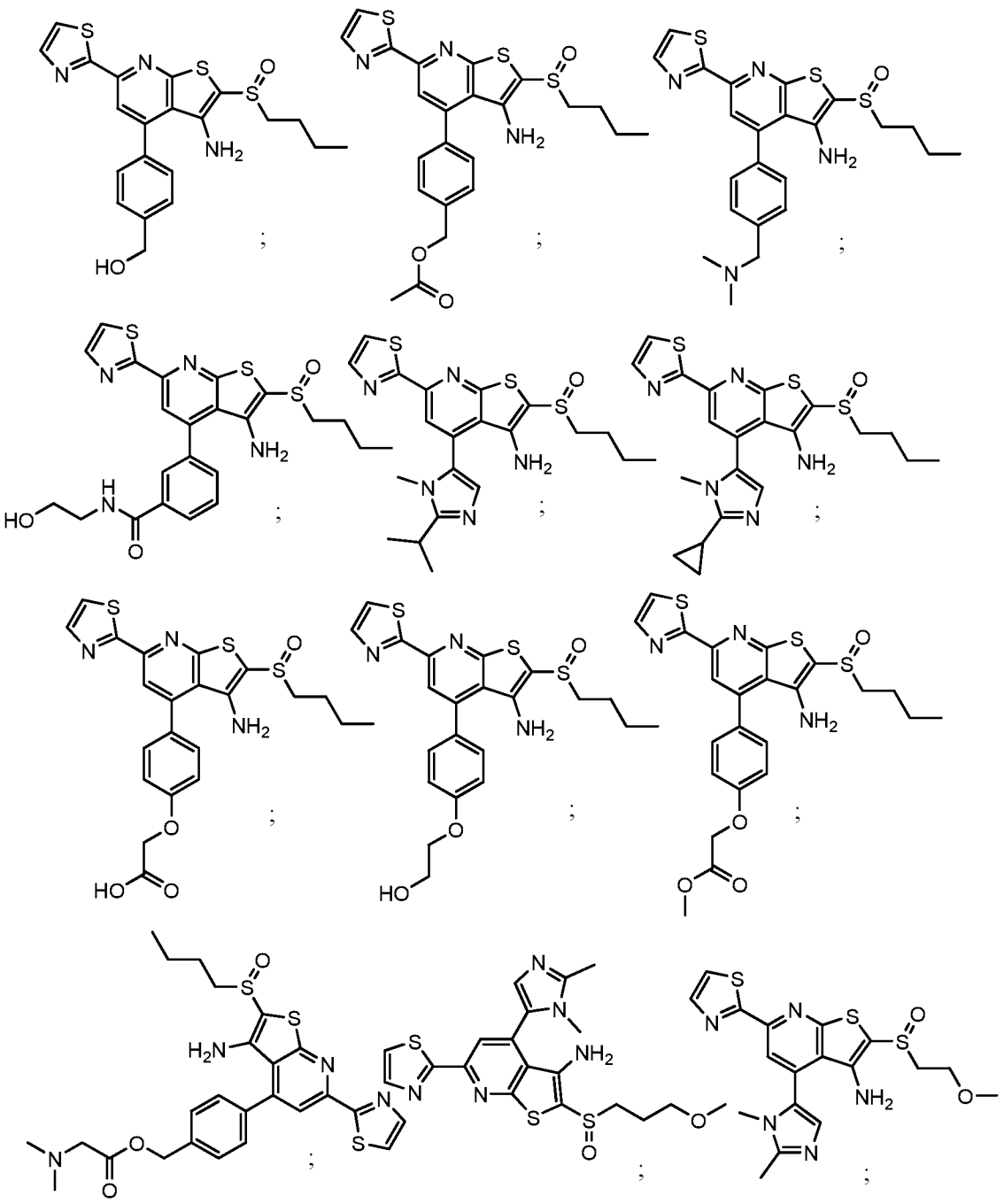

;

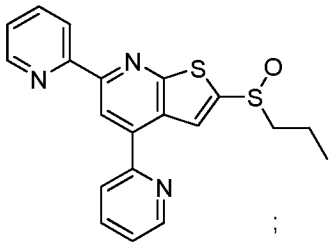
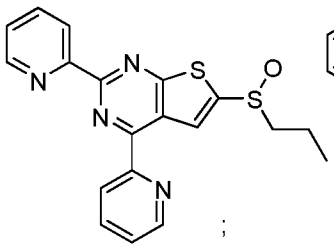
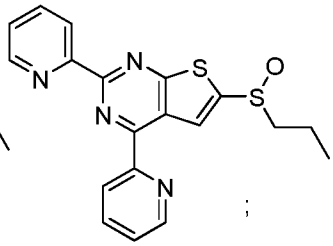
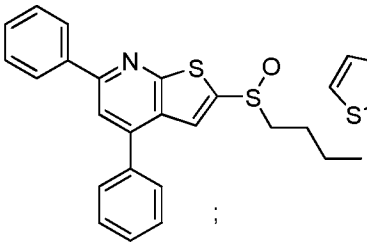
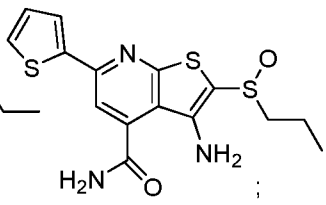
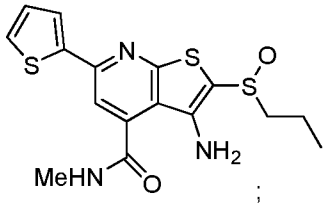
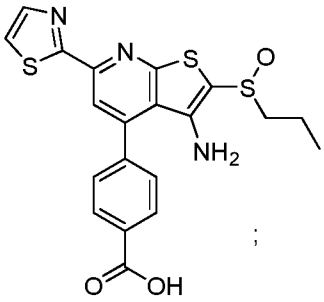
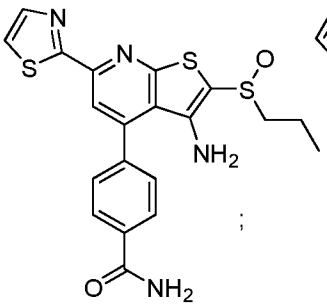
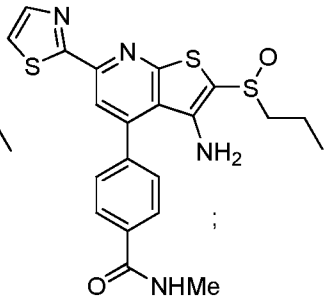
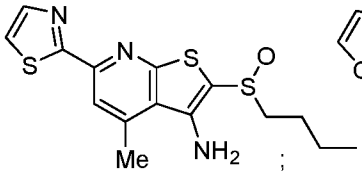
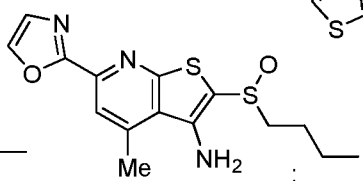
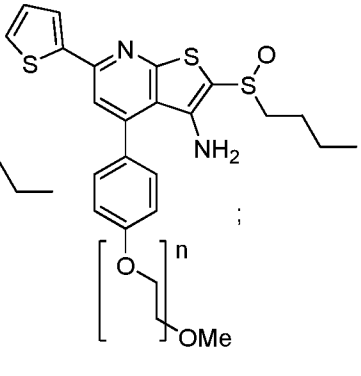

;

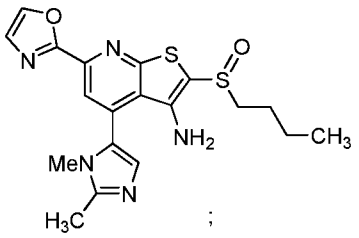

;

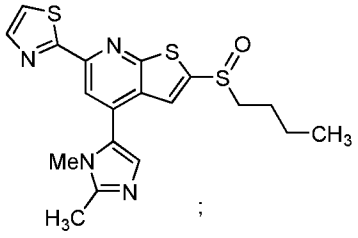

;

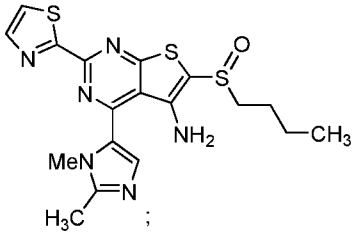


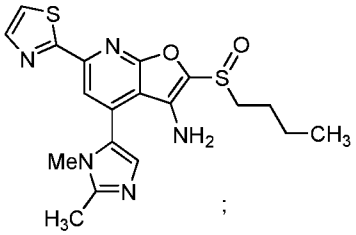


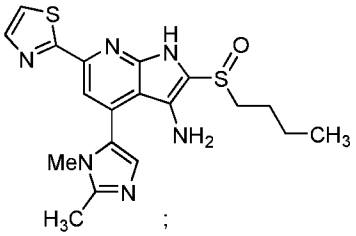

;

;

;

;

;

;

;

;

;

;

;


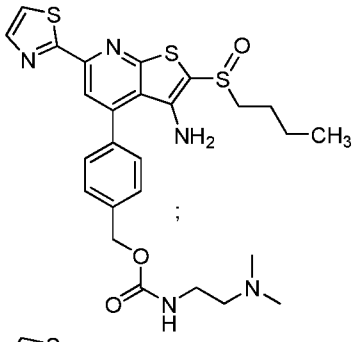

;

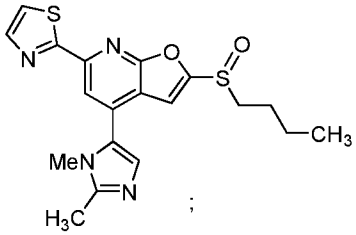

;

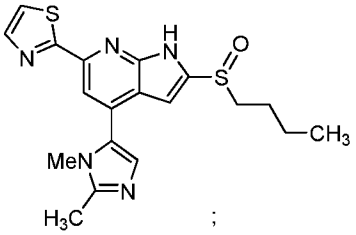

;

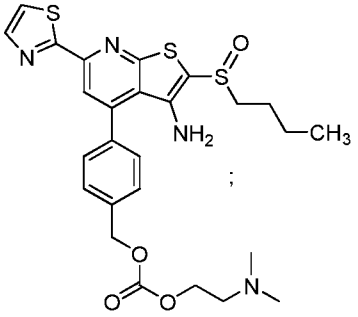

;

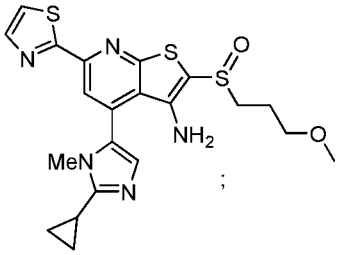

;

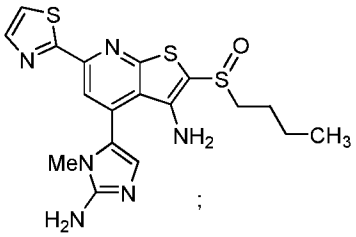

;

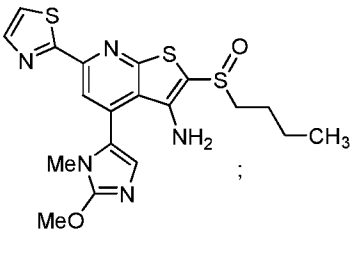

;

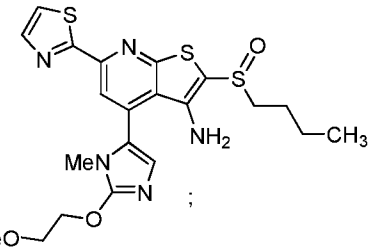

;

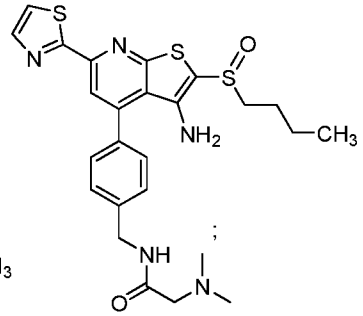

;


;


;


;


;


;

;

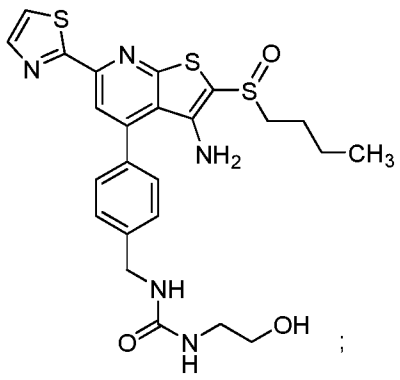
;

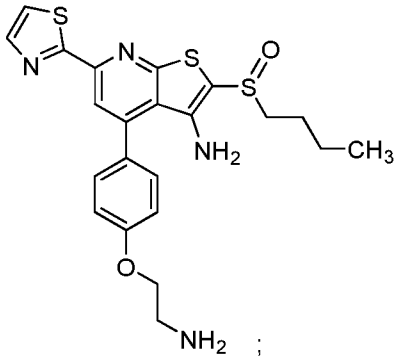
;

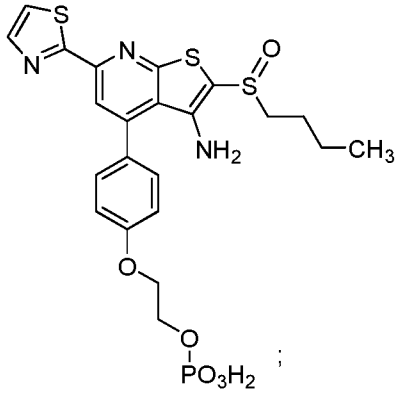
;

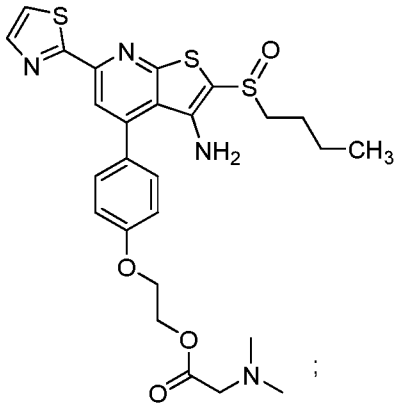
;

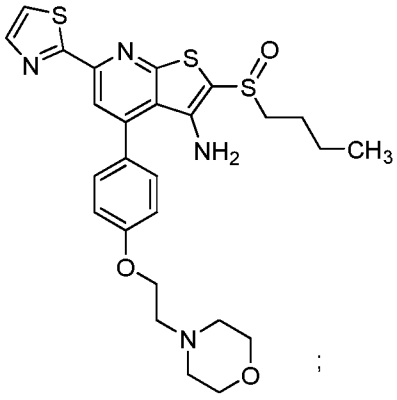
;

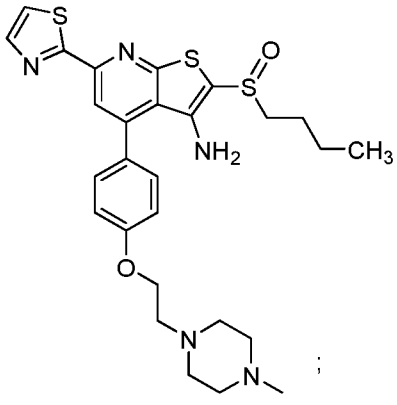

;

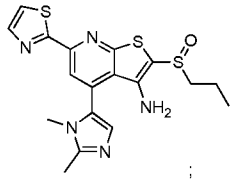

;

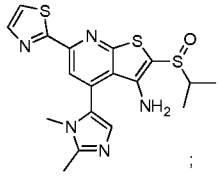

;

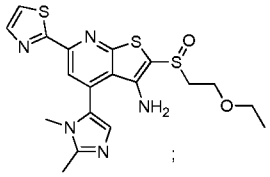

;

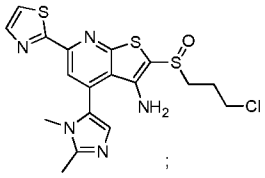

;

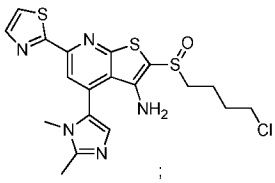

;

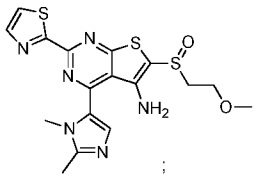

;

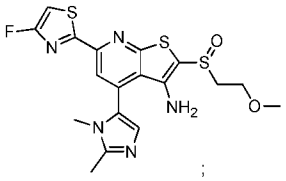

;

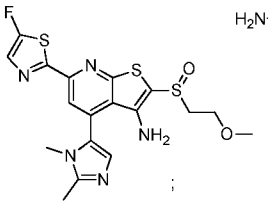

;

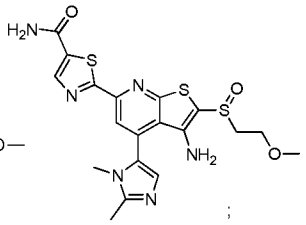

;

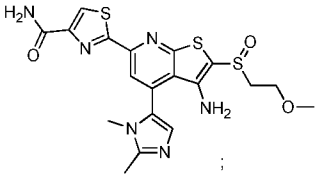

;

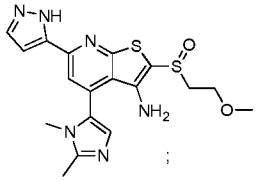

;

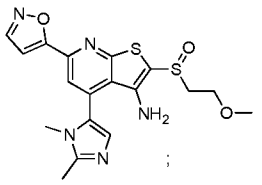

;

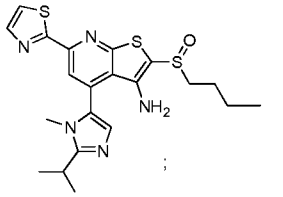

;

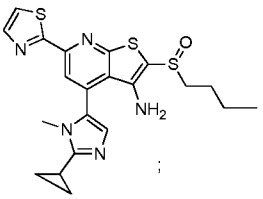

;

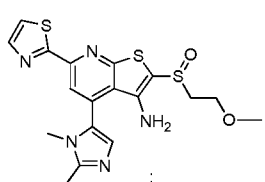

;


;


;

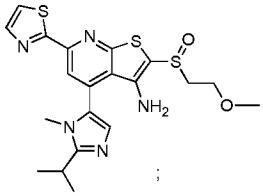

;


;

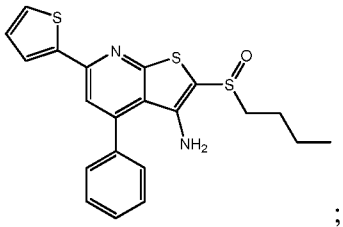
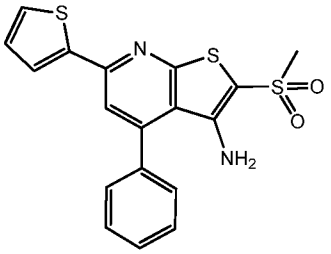
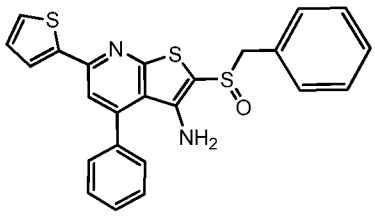
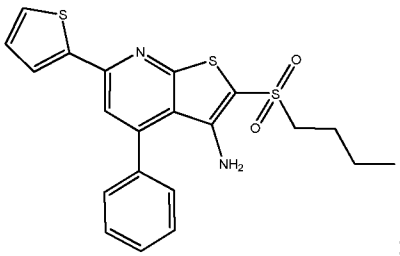
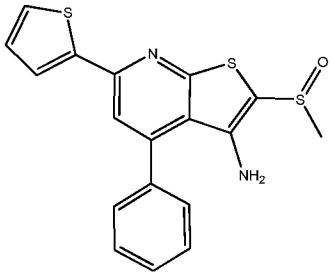
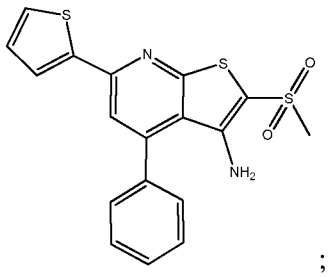
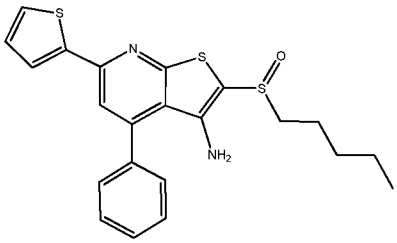
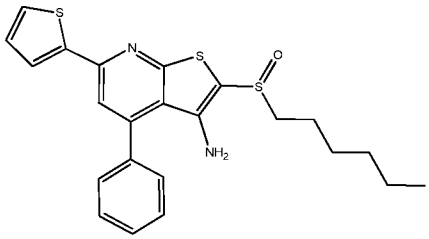
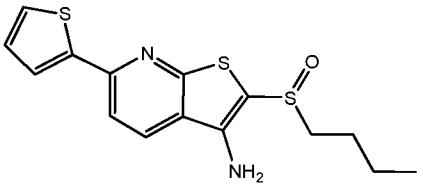
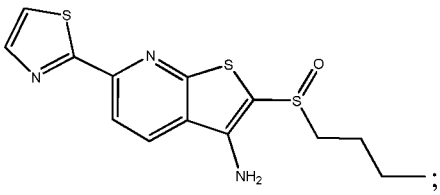
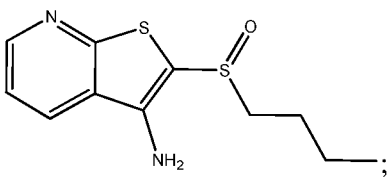
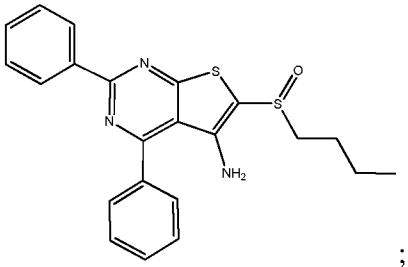
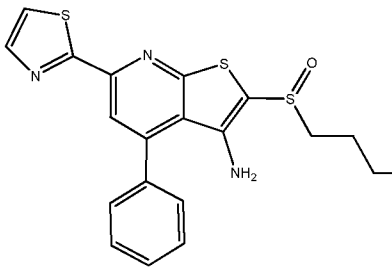
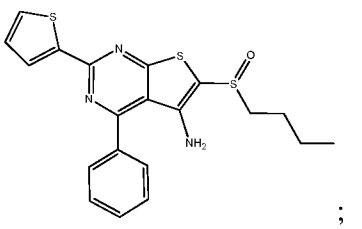

;

;

;

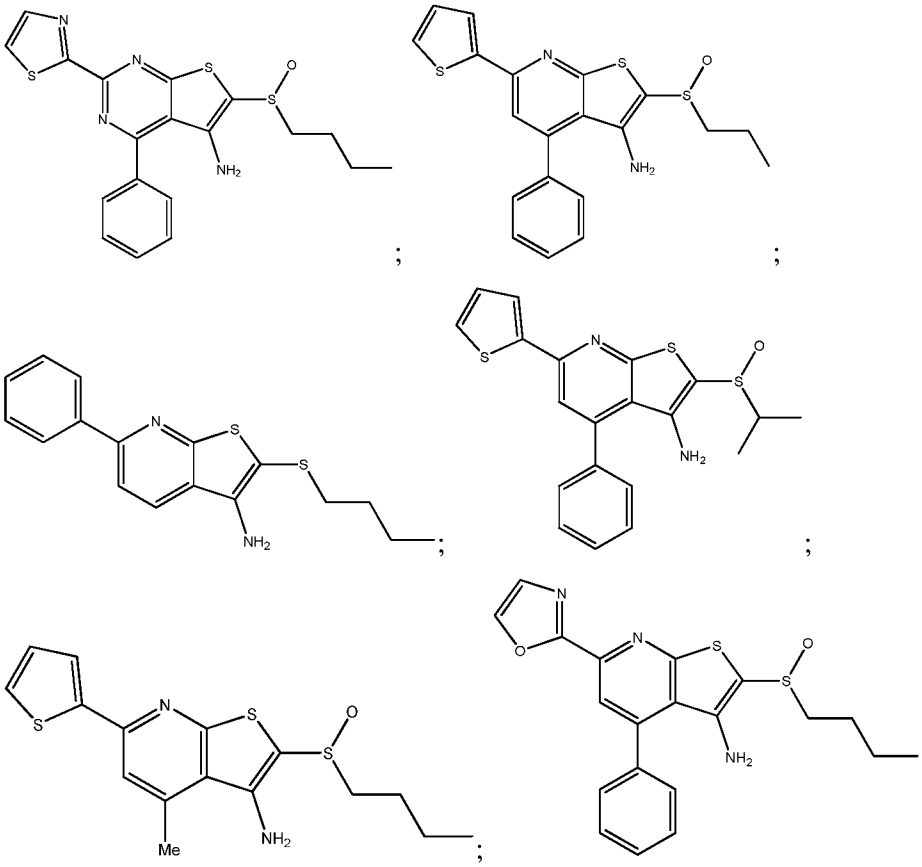

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;



and pharmaceutically acceptable salts thereof.

[00146] In certain embodiments, the 15-PGDH inhibitor having formula (I), (II), (IV), (V), (VI), and (VII) can be selected that can ia) at 2.5 μM concentration, stimulate a Vaco503 reporter cell line expressing a 15-PGDH luciferase fusion construct to a luciferase output level of greater than 70 (using a scale on which a value of 100 indicates a doubling of reporter output over baseline); iia) at 2.5 μM concentration stimulate a V9m reporter cell line expressing a 15-PGDH luciferase fusion construct to a luciferase output level of greater than 75; iiia) at 7.5 μM concentration stimulate a LS174T reporter cell line expressing a 15-PGDH luciferase fusion construct to a luciferase output level of greater than 70; and iva) at 7.5 μM concentration, does not activate a negative control V9m cell line expressing TK-renilla luciferase reporter to a level greater than 20; and va) inhibits the enzymatic activity of recombinant 15-PGDH protein at an IC_{50} of less than 1 μM.

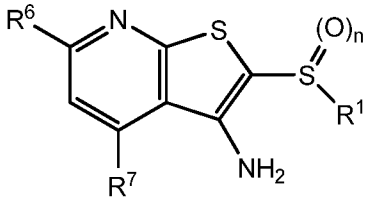
[00147] In other embodiments, the 15-PGDH inhibitor can ib) at 2.5 μM concentration, stimulate a Vaco503 reporter cell line expressing a 15-PGDH luciferase fusion construct to increase luciferase output; iib) at 2.5 μM concentration stimulate a V9m reporter cell line

expressing a 15-PGDH luciferase fusion construct to increase luciferase output; iiib) at 7.5 μM concentration stimulate a LS174T reporter cell line expressing a 15-PGDH luciferase fusion construct to increase luciferase output; ivb) at 7.5 μM concentration, does not activate a negative control V9m cell line expressing TK-renilla luciferase reporter to a luciferase level greater than 20% above background; and vb) inhibits the enzymatic activity of recombinant 15-PGDH protein at an IC_{50} of less than 1 μM.

[00148] In other embodiments, the 15-PGDH inhibitor can inhibit the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than 1 μM, or preferably at an IC_{50} of less than 250 nM, or more preferably at an IC_{50} of less than 50 nM, or more preferably at an IC_{50} of less than 10 nM, or more preferably at an IC_{50} of less than 5 nM at a recombinant 15-PGDH concentration of about 5 nM to about 10 nM.

[00149] In other embodiments, the 15-PGDH inhibitor can increase the cellular levels of PGE-2 following stimulation of an A459 cell with an appropriate agent, for example IL1-beta.

[00150] In some embodiments, a15-PGDH inhibitor can include a compound having the following formula (VIII):



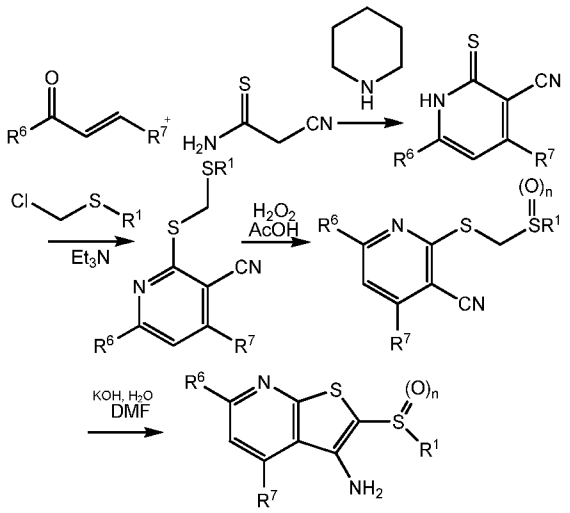
(VIII)

wherein n is 0-2;

R^1, R^6, and R^7 are the same or different and are each selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy

(-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl; and pharmaceutically acceptable salts thereof.

[00151] 15-PGDH inhibitors having formula (VIII) can be synthesized as shown:

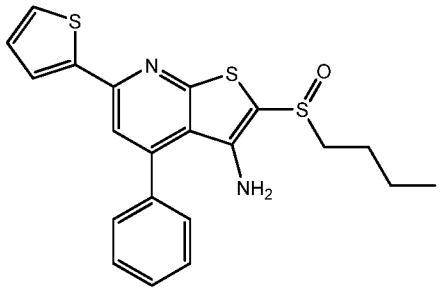


[00152] Any reaction solvent can be used in the above preparation process as long as it is not involved in the reaction. For example, the reaction solvent includes ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenized hydrocarbons, such as dichloromethane and chloroform; amines such as pyridine, piperidine and triethylamine; alkylketones, such as acetone, methylethylketone and methylisobutyl; alcohols, such as methanol, ethanol and propanol; non-protonic polar solvent, such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethylsulfoxide and hexamethyl phosphoric acid triamide. Among non-reactive organic solvents that are ordinarily used in the organic synthesis, preferable solvents are those from which water generated in the reaction can be removed by a Dean-Stark trap. The examples of such solvents include, but are not limited to benzene, toluene, xylene and the like. The reaction product thus obtained may be isolated and purified by condensation, extraction and the like, which is ordinarily conducted in the field of the organic synthesis, if desired, by silica gel column chromatography. The individual enantiomers of PGDH inhibitors having the formula III can be separated by a preparative HPLC using chromatography columns containing chiral stationary phases.

[00153] Further, embodiments of this application include any modifications for the preparation method of the 15-PGDH inhibitors described above. In this connection, any intermediate product obtainable from any step of the preparation method can be used as a starting material in the other steps. Such starting material can be formed in situ under certain reaction conditions. Reaction reagents can also be used in the form of their salts or optical isomers.

[00154] Depending on the kinds of the substituents to be used in the preparation of the 15-PGDH inhibitors, and the intermediate product and the preparation method selected, novel 15-PGDH inhibitors can be in the form of any possible isomers such as substantially pure geometrical (cis or trans) isomers, optical isomers (enantiomers) and racemates.

[00155] In some embodiments, a 15-PGDH inhibitor having formula (VIII) can include a compound with the following formula (IX):

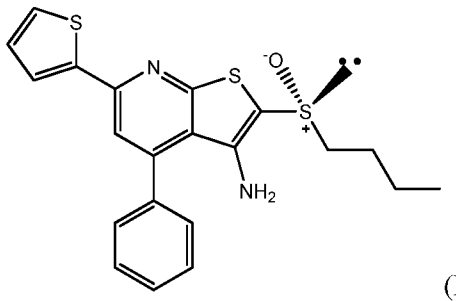


(IX),

and pharmaceutically acceptable salts thereof.

[00156] Advantageously, the 15-PDGH inhibitor having formula (IX) was found to: i) inhibit recombinant 15-PGDH at 1 nM concentration; ii) inhibit 15-PGDH in cell lines at 100 nM concentration, iii) increase PGE_2 production by cell lines; iv) is chemically stable in aqueous solutions over broad pH range; v) is chemically stable when incubated with hepatocyte extracts, vi) is chemically stable when incubated with hepatocyte cell lines; vii) shows 253 minutes plasma half-life when injected IP into mice; and viii) shows no immediate toxicity over 24 hours when injected IP into mice at 0.6 µmole/per mouse and at 1.2 µmole/per mouse and also no toxicity when injected IP into mice at 0.3 µmole/per mouse twice daily for 21 days.

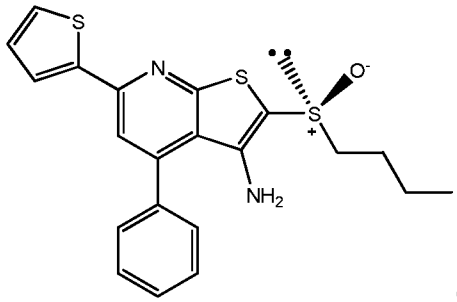
[00157] In other embodiments, a 15-PGDH inhibitor having formula (IX) can include a compound with the following formula (IXa):



(IXa)

and pharmaceutically acceptable salts thereof.

[00158] In still other embodiments, a 15-PGDH inhibitor having formula (IX) can include a compound with the following formula (IXb):



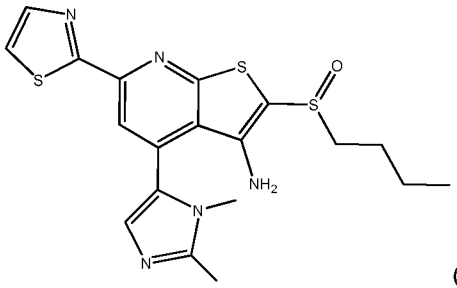
(Xb)

and pharmaceutically acceptable salts thereof.

[00159] In other embodiments, the 15-PDHG inhibitor can comprise a (+) or (-) optical isomer of a 15-PGDH inhibitor having formula (IX). In still other embodiments, the 15-PDHG inhibitor can comprise a mixture at least one of a (+) or (-) optical isomer of a 15-PGDH inhibitor having formula (IX). For example, the 15-PGDH inhibitor can comprise a mixture of: less than about 50% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX) and greater than about 50% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX), less than about 25% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX) and greater than about 75% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX), less than about 10% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX) and greater than about 90% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX), less than about 1% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX) and greater than about 99% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX), greater than about 50% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX) and less than about 50% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX), greater than about 75% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX) and less than about 25% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX), greater than about 90% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX) and less than about 10% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX), or greater than about 99% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX) and less than about 1% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX).

[00160] In a still further embodiment, the 15-PDGH inhibitor can consist essentially of or consist of the (+) optical isomer of a 15-PGDH inhibitor having formula (IX). In yet another embodiment, the PDGH inhibitor can consist essentially of or consist of the (-) optical isomer of a 15-PGDH inhibitor having formula (IX).

[00161] In other embodiments, a 15-PGDH inhibitor having formula (VIII) can include a compound with the following formula (X):

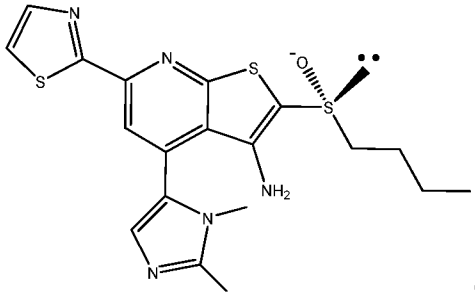


(X)

and pharmaceutically acceptable salts thereof.

[00162] Advantageously, the 15-PDGH inhibitor having formula (X) was found to: i) inhibit recombinant 15-PGDH at 3 nM concentration; ii) increase PGE_2 production by cell lines at 20nM; iii) is chemically stable in aqueous solutions over broad pH range; iv) is chemically stable when incubated with mouse, rat and human liver extracts, v) shows 33 minutes plasma half-life when injected IP into mice; viii) shows no immediate toxicity over 24 hours when injected IP into mice at 50 mg/kg body weight, and ix) is soluble in water (pH=3) at 1 mg/mL.

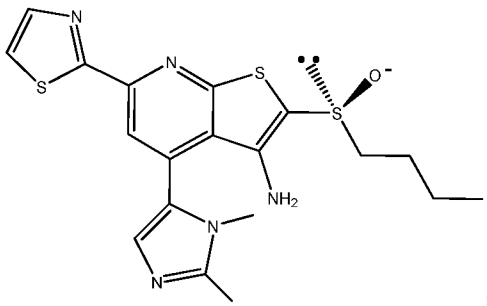
[00163] In other embodiments, a 15-PGDH inhibitor having formula (X) can include a compound with the following formula (Xa):



(Xa)

and pharmaceutically acceptable salts thereof.

[00164] In still other embodiments, a 15-PGDH inhibitor having formula (X) can include a compound with the following formula (Xb):



(Xb),

and pharmaceutically acceptable salts thereof.

[00165] In other embodiments, the 15-PDHG inhibitor can comprise a (+) or (-) optical isomer of a 15-PGDH inhibitor having formula (X). In still other embodiments, the 15-PDHG inhibitor can comprise a mixture at least one of a (+) or (-) optical isomer of a 15-PGDH inhibitor having formula (X). For example, the 15-PGDH inhibitor can comprise a mixture of: less than about 50% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (X) and greater than about 50% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (X), less than about 25% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (X) and greater than about 75% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (X), less than about 10% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (X) and greater than about 90% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (X), less than about 1% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (X) and greater than about 99% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (X), greater than about 50% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (X) and less than about 50% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (X), greater than about 75% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (X) and less than about 25% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (X), greater than about 90% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (X) and less than about 10% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (X), or greater than about 99% by weight of the (-) optical isomer of a 15-PGDH inhibitor having formula (X) and less than about 1% by weight of the (+) optical isomer of a 15-PGDH inhibitor having formula (X).

[00166] In a still further embodiment, the 15-PDGH inhibitor can consist essentially of or consist of the (+) optical isomer of a 15-PGDH inhibitor having formula (X). In yet another embodiment, the PDGH inhibitor can consist essentially of or consist of the (-) optical isomer of a 15-PGDH inhibitor having formula (X).

[00167] It will be appreciated that the other 15-PGDH inhibitors can be used in the methods described described herein. These other 15-PGDH inhibitors can include known 15-PGDH inhibitors including, for example, tetrazole compounds of formulas (I) and (II), 2-alkylideneaminooxyacetamidecompounds of formula (I), heterocyclic compounds of fourmulas (VI) and (VII), and pyrazole compounds of formula (III) described in U.S. Patent Application Publication No. 2006/0034786 and U.S. Patent No. 7,705,041; benzylidene-1,3-thiazolidine compounds of formula (I) described in U.S. Patent Application Publication No. 2007/0071699; phenylfurylmethylthiazolidine-2,4-dione and phenylthienylmethylthiazolidine-2,4-dione compounds described in U.S. Patent Application Publication No. 2007/0078175; thiazolidenedione derivatives described in U.S. Patent Application Publication No. 2011/0269954; phenylfuran, phenylthiophene, or phenylpyrrazole compounds described in U.S. Patent No. 7,294,641, 5-(3,5-disubstituted phenylazo)-2-hydroxybenzene-acetic acids and salts and lactones described in U.S. Patent No. 4,725,676, and azo compounds described in U.S. Patent No. 4,889,846.

[00168] The 15-PGDH inhibitors described herein can be provided in a pharmaceutical composition or cosmetic composition depending on the pathological or cosmetic condition or disorder being treated. A pharmaceutical composition containing the 15-PGDH inhibitors described herein as an active ingredient may be manufactured by mixing the derivative with a pharmaceutically acceptable carrier(s) or an excipient(s) or diluting the 15-PGDH inhibitors with a diluent in accordance with conventional methods. The pharmaceutical composition may further contain fillers, anti-cohesives, lubricants, wetting agents, flavoring agents, emulsifying agents, preservatives and the like. The pharmaceutical composition may be formulated into a suitable formulation in accordance with the methods known to those skilled in the art so that it can provide an immediate, controlled or sustained release of the 15-PGDH inhibitors after being administered into a mammal.

[00169] In some embodiments, the pharmaceutical composition may be formulated into a parenteral or oral dosage form. The solid dosage form for oral administration may be manufactured by adding excipient, if necessary, together with binder, disintegrants,

lubricants, coloring agents, and/or flavoring agents, to the 15-PGDH inhibitors and shaping the resulting mixture into the form of tablets, sugar-coated pills, granules, powder or capsules. The additives that can be added in the composition may be ordinary ones in the art. For example, examples of the excipient include lactose, sucrose, sodium chloride, glucose, starch, calcium carbonate, kaolin, microcrystalline cellulose, silicate and the like. Exemplary binders include water, ethanol, propanol, sweet syrup, sucrose solution, starch solution, gelatin solution, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropyl starch, methylcellulose, ethylcellulose, shellac, calcium phosphonate and polypyrrolidone. Examples of the disintegrant include dry starch, sodium arginate, agar powder, sodium bicarbonate, calcium carbonate, sodium lauryl sulfate, stearic monoglyceride and lactose. Further, purified talc, stearates, sodium borate, and polyethylene glycol may be used as a lubricant; and sucrose, bitter orange peel, citric acid, tartaric acid, may be used as a flavoring agent. In some embodiments, the pharmaceutical composition can be made into aerosol formulations (*e.g.,* they can be nebulized) to be administered via inhalation.

[00170] The 15-PGDH inhibitors described herein may be combined with flavoring agents, buffers, stabilizing agents, and the like and incorporated into oral liquid dosage forms such as solutions, syrups or elixirs in accordance with conventional methods. One example of the buffers may be sodium citrate. Examples of the stabilizing agents include tragacanth, acacia and gelatin.

[00171] In some embodiments, the 15-PGDH inhibitors described herein may be incorporated into an injection dosage form, for example, for a subcutaneous, intramuscular or intravenous route by adding thereto pH adjusters, buffers, stabilizing agents, relaxants, topical anesthetics. Examples of the pH adjusters and the buffers include sodium citrate, sodium acetate and sodium phosphate. Examples of the stabilizing agents include sodium pyrosulfite, EDTA, thioglycolic acid and thiolactic acid. The topical anesthetics may be procaine HCl, lidocaine HCl and the like. The relaxants may be sodium chloride, glucose and the like.

[00172] In other embodiments, the 15-PGDH inhibitors described herein may be incorporated into suppositories in accordance with conventional methods by adding thereto pharmaceutically acceptable carriers that are known in the art, for example, polyethylene glycol, lanolin, cacao butter or fatty acid triglycerides, if necessary, together with surfactants such as Tween.

[00173] The pharmaceutical composition may be formulated into various dosage forms as discussed above and then administered through various routes including an oral, inhalational, transdermal, subcutaneous, intravenous or intramuscular route. The dosage can be a pharmaceutically or therapeutically effective amount.

[00174] Therapeutically effective dosage amounts of the 15-PGDH inhibitor may be present in varying amounts in various embodiments. For example, in some embodiments, a therapeutically effective amount of the 15-PGDH inhibitor may be an amount ranging from about 10-1000 mg (*e.g.,* about 20 mg-1,000 mg, 30 mg-1,000 mg, 40 mg-1,000 mg, 50 mg-1,000 mg, 60 mg-1,000 mg, 70 mg-1,000 mg, 80 mg-1,000 mg, 90 mg-1,000 mg, about 10-900 mg, 10-800 mg, 10-700 mg, 10-600 mg, 10-500 mg, 100-1000 mg, 100-900 mg, 100-800 mg, 100-700 mg, 100-600 mg, 100-500 mg, 100-400 mg, 100-300 mg, 200-1000 mg, 200-900 mg, 200-800 mg, 200-700 mg, 200-600 mg, 200-500 mg, 200-400 mg, 300-1000 mg, 300-900 mg, 300-8*00 mg*, 300-700 mg, 300-600 mg, 300-500 mg, 400 mg-1,000 mg, 500 mg-1,000 mg, 100 mg-900 mg, 200 mg-800 mg, 300 mg-700 mg, 400 mg-700 mg, and 500 mg-600 mg). In some embodiments, the 15-PGDH inhibitor is present in an amount of or greater than about 10 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg. In some embodiments, the 15-PGDH inhibitor is present in an amount of or less than about 1000 mg, 950 mg, 900 mg, 850 mg, 800 mg, 750 mg, 700 mg, 650 mg, 600 mg, 550 mg, 500 mg, 450 mg, 400 mg, 350 mg, 300 mg, 250 mg, 200 mg, 150 mg, or 100 mg.

[00175] In other embodiments, a therapeutically effective dosage amount may be, for example, about 0.001 mg/kg weight to 500 mg/kg weight, *e.g.,* from about 0.001 mg/kg weight to 400 mg/kg weight, from about 0.001 mg/kg weight to 300 mg/kg weight, from about 0.001 mg/kg weight to 200 mg/kg weight, from about 0.001 mg/kg weight to 100 mg/kg weight, from about 0.001 mg/kg weight to 90 mg/kg weight, from about 0.001 mg/kg weight to 80 mg/kg weight, from about 0.001 mg/kg weight to 70 mg/kg weight, from about 0.001 mg/kg weight to 60 mg/kg weight, from about 0.001 mg/kg weight to 50 mg/kg weight, from about 0.001 mg/kg weight to 40 mg/kg weight, from about 0.001 mg/kg weight to 30 mg/kg weight, from about 0.001 mg/kg weight to 25 mg/kg weight, from about 0.001 mg/kg weight to 20 mg/kg weight, from about 0.001 mg/kg weight to 15 mg/kg weight, from about 0.001 mg/kg weight to 10 mg/kg weight.

[00176] In still other embodiments, a therapeutically effective dosage amount may be, for example, about 0.0001 mg/kg weight to 0.1 mg/kg weight, e.g. from about 0.0001 mg/kg weight to 0.09 mg/kg weight, from about 0.0001 mg/kg weight to 0.08 mg/kg weight, from about 0.0001 mg/kg weight to 0.07 mg/kg weight, from about 0.0001 mg/kg weight to 0.06 mg/kg weight, from about 0.0001 mg/kg weight to 0.05 mg/kg weight, from about 0.0001 mg/kg weight to about 0.04 mg/kg weight, from about 0.0001 mg/kg weight to 0.03 mg/kg weight, from about 0.0001 mg/kg weight to 0.02 mg/kg weight, from about 0.0001 mg/kg weight to 0.019 mg/kg weight, from about 0.0001 mg/kg weight to 0.018 mg/kg weight, from about 0.0001 mg/kg weight to 0.017 mg/kg weight, from about 0.0001 mg/kg weight to 0.016 mg/kg weight, from about 0.0001 mg/kg weight to 0.015 mg/kg weight, from about 0.0001 mg/kg weight to 0.014 mg/kg weight, from about 0.0001 mg/kg weight to 0.013 mg/kg weight, from about 0.0001 mg/kg weight to 0.012 mg/kg weight, from about 0.0001 mg/kg weight to 0.011 mg/kg weight, from about 0.0001 mg/kg weight to 0.01 mg/kg weight, from about 0.0001 mg/kg weight to 0.009 mg/kg weight, from about 0.0001 mg/kg weight to 0.008 mg/kg weight, from about 0.0001 mg/kg weight to 0.007 mg/kg weight, from about 0.0001 mg/kg weight to 0.006 mg/kg weight, from about 0.0001 mg/kg weight to 0.005 mg/kg weight, from about 0.0001 mg/kg weight to 0.004 mg/kg weight, from about 0.0001 mg/kg weight to 0.003 mg/kg weight, from about 0.0001 mg/kg weight to 0.002 mg/kg weight. In some embodiments, the therapeutically effective dose may be 0.0001 mg/kg weight, 0.0002 mg/kg weight, 0.0003 mg/kg weight, 0.0004 mg/kg weight, 0.0005 mg/kg weight, 0.0006 mg/kg weight, 0.0007 mg/kg weight, 0.0008 mg/kg weight, 0.0009 mg/kg weight, 0.001 mg/kg weight, 0.002 mg/kg weight, 0.003 mg/kg weight, 0.004 mg/kg weight, 0.005 mg/kg weight, 0.006 mg/kg weight, 0.007 mg/kg weight, 0.008 mg/kg weight, 0.009 mg/kg weight, 0.01 mg/kg weight, 0.02 mg/kg weight, 0.03 mg/kg weight, 0.04 mg/kg weight, 0.05 mg/kg weight, 0.06 mg/kg weight, 0.07 mg/kg weight, 0.08 mg/kg weight, 0.09 mg/kg weight, or 0.1 mg/kg weight. The effective dose for a particular individual can be varied (*e.g.,* increased or decreased) over time, depending on the needs of the individual.

[00177] In some embodiments, a therapeutically effective dosage may be a dosage of 10 μg/kg/day, 50 μg/kg/day, 100 μg/kg/day, 250 μg/kg/day, 500 μg/kg/day, 1000 μg/kg/day or more. In various embodiments, the amount of the 15-PGDH inhibitor or pharmaceutical salt thereof is sufficient to provide a dosage to a patient of between 0.01 μg/kg and 10 μg/kg;

0.1 μg/kg and 5 μg/kg; 0.1 μg/kg and 1000 μg/kg; 0.1 μg/kg and 900 μg/kg; 0.1 μg/kg and 900 μg/kg; 0.1 μg/kg and 800 μg/kg; 0.1 μg/kg and 700 μg/kg; 0.1 μg/kg and 600 μg/kg; 0.1 μg/kg and 500 μg/kg; or 0.1 μg/kg and 400 μg/kg.

[00178] Particular doses or amounts to be administered in accordance with the present invention may vary, for example, depending on the nature and/or extent of the desired outcome, on particulars of route and/or timing of administration, and/or on one or more characteristics (*e.g.,* weight, age, personal history, genetic characteristic, lifestyle parameter, severity of cardiac defect and/or level of risk of cardiac defect, etc., or combinations thereof). Such doses or amounts can be determined by those of ordinary skill. In some embodiments, an appropriate dose or amount is determined in accordance with standard clinical techniques. For example, in some embodiments, an appropriate dose or amount is a dose or amount sufficient to reduce a disease severity index score by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100% or more. For example, in some embodiments, an appropriate dose or amount is a dose or amount sufficient to reduce a disease severity index score by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100%. Alternatively or additionally, in some embodiments, an appropriate dose or amount is determined through use of one or more *in vitro* or *in vivo* assays to help identify desirable or optimal dosage ranges or amounts to be administered.

[00179] Various embodiments may include differing dosing regimen. In some embodiments, the 15-PGDH inhibitor can be administered via continuous infusion. In some embodiments, the continuous infusion is intravenous. In other embodiments, the continuous infusion is subcutaneous. Alternatively or additionally, in some embodiments, the 15-PGDH inhibitor can be administered bimonthly, monthly, twice monthly, triweekly, biweekly, weekly, twice weekly, thrice weekly, daily, twice daily, or on another clinically desirable dosing schedule. The dosing regimen for a single subject need not be at a fixed interval, but can be varied over time, depending on the needs of the subject.

[00180] For topical application, the composition can be administered in the form of aqueous, alcoholic, aqueous-alcoholic or oily solutions or suspensions, or of a dispersion of the lotion or serum type, of emulsions that have a liquid or semi-liquid consistency or are pasty, obtained by dispersion of a fatty phase in an aqueous phase (O/W) or vice versa (W/O) or multiple emulsions, of a free or compacted powder to be used as it is or to be incorporated

into a physiologically acceptable medium, or else of microcapsules or microparticles, or of vesicular dispersions of ionic and/or nonionic type. It may thus be in the form of a salve, a tincture, milks, a cream, an ointment, a powder, a patch, an impregnated pad, a solution, an emulsion or a vesicular dispersion, a lotion, aqueous or anhydrous gels, a spray, a suspension, a shampoo, an aerosol or a foam. It may be anhydrous or aqueous. It may also comprise solid preparations constituting soaps or cleansing cakes.

[00181] Pharmaceutical and/or cosmetic compositions including the 15-PGDH inhibitor described herein can additionally contain, for example, at least one compound chosen from prostaglandins, in particular prostaglandin PGE_1, PGE_2, their salts, their esters, their analogues and their derivatives, in particular those described in WO 98/33497, WO 95/11003, JP 97-100091, JP 96-134242, in particular agonists of the prostaglandin receptors. It may in particular contain at least one compound such as the agonists (in acid form or in the form of a precursor, in particular in ester form) of the prostaglandin $F_2\alpha$ receptor, such as for example latanoprost, fluprostenol, cloprostenol, bimatoprost, unoprostone, the agonists (and their precursors, in particular the esters such as travoprost) of the prostaglandin E_2 receptors such as 17-phenyl PGE_2, viprostol, butaprost, misoprostol, sulprostone, 16,16-dimethyl PGE_2, 11-deoxy PGE_1, 1-deoxy PGE_1, the agonists and their precursors, in particular esters, of the prostacycline (IP) receptor such as cicaprost, iloprost, isocarbacycline, beraprost, eprostenol, treprostinil, the agonists and their precursors, in particular the esters, of the prostaglandin D_2 receptor such as BW245C ((4S)-(3-[(3R,S)-3-cyclohexyl-3-isopropyl]-2,5-dioxo)-4-imidazolidinehept- anoic acid), BW246C ((4R)-(3-[(3R,S)-3-cyclohexyl-3-isopropyl]-2,5-dioxo)-4-imidazolidinehept- anoic acid), the agonists and their precursors, in particular the esters, of the receptor for the thromboxanes A2 (TP) such as I-BOP ([1S-[1a,2a(Z), 3b(1E,3S),4a]]-7-[3-[3-hydroxy-4-[4-(iodophenoxy)-1-butenyl]-7-oxabicyclo- [2.2.1]hept-2-yl]-5-heptenoic acid).

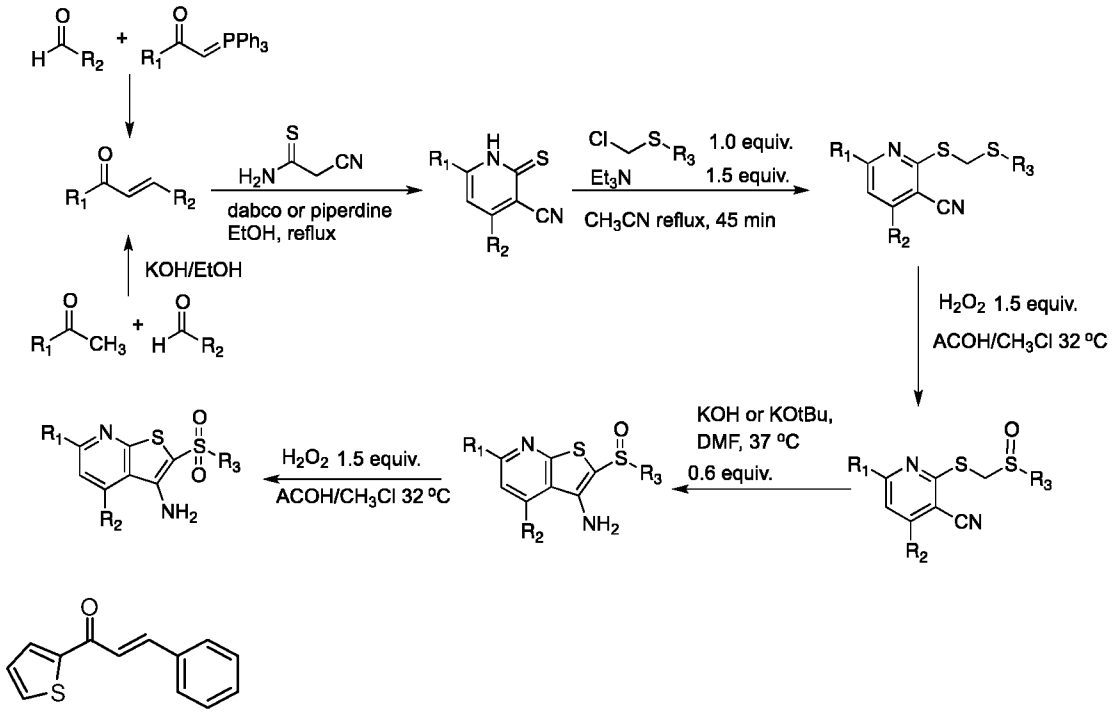
[00182] Advantageously, the composition can include at least one 15-PGDH inhibitor as defined above and at least one prostaglandin or one prostaglandin derivative such as for example the prostaglandins of series 2 including in particular $PGF_{2\alpha}$ and PGE_2 in saline form or in the form of precursors, in particular of the esters (example isopropyl esters), their derivatives such as 16,16-dimethyl PGE_2, 17-phenyl PGE_2 and 16,16-dimethyl $PGF_{2\alpha}$ 17-phenyl $PGF_{2\alpha}$, prostaglandins of series 1 such as 11-deoxyprostaglandin E1,

1-deoxyprostaglandin E1 in saline or ester form, is their analogues, in particular latanoprost, travoprost, fluprostenol, unoprostone, bimatoprost, cloprostenol, viprostol, butaprost, misoprostol, their salts or their esters.

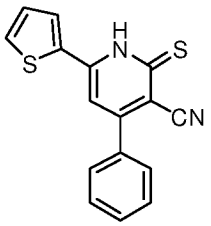
[00183] The invention is further illustrated by the following examples, which is not intended to limit the scope of the claims.

Example 1

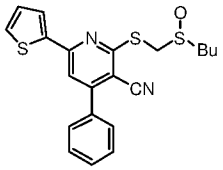
[00184] The following Example describes the synthesis of SW033291 and analogues thereof as well as provides mass spectrometry and NMR confirmation of the structures.



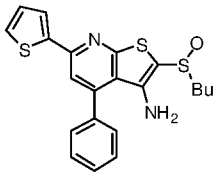
[00185] 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one was prepared from benzaldehyde and 1-(thiophen-2-yl)ethanone *via* aldol condensation using procedure described by Azam (Parveen, H.; Iqbal, P. F.; Azam, A. *Synth. Commu.*, 2008, *38*, 3973). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 2H), 7.67 (dd, J = 4.9, 1.1 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.47 – 7.34 (m, 4H), 7.18 (dd, J = 5.0, 3.8 Hz, 1H). ESI-MS (m/z): 215 $[M+H]^+$.



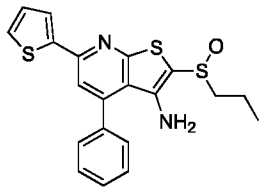
[00186] 4-phenyl-6-(thiophen-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile. To a solution of 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one (2.34 mmol, 500 mg) and cyanothioacetamide (7.0 mmol, 717 mg, 3.0 equiv.) in ethanol (7 mL), a few drops of piperidine were added. The reaction was refluxed for 3 h. The solid that formed was collected and recrystallized from acetic acid to give designed product in 46 % isolated yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 3.8 Hz, 1H), 7.96 (d, J = 5.0 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.54 (dd, J = 5.1, 2.0 Hz, 3H), 7.31 – 7.19 (m, 1H), 7.01 (s, 1H). ESI-MS (m/z): 295 $[M+H]^+$.



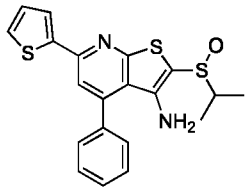
[00187] 2-(((butylthio)methyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Acetic Acid (900 µL) and hydrogen peroxide (0.57 mmol, 1.5 equiv., 30 % solution in water) were added to the solution of 2-(((butylthio)methyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile (0.38 mmol, 150 mg) in chloroform (900 µL). The reaction mixture was stirring at 32 °C for 45 min. The reaction was then diluted with EtOAc and washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 153 mg of designed product (98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 3.8, 1.1 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.58 – 7.51 (m, 4H), 7.47 (s, 1H), 7.16 (dd, J = 5.0, 3.8 Hz, 1H), 4.74 (d, J = 13.0 Hz, 1H), 4.41 (d, J = 13.0 Hz, 1H), 2.97 (dt, J = 13.0, 8.2 Hz, 1H), 2.81 (dt, J = 12.9, 7.3 Hz, 1H), 1.94 – 1.76 (m, 2H), 1.53 – 1.38 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ESI-MS (m/z): 413 $[M+H]^+$.



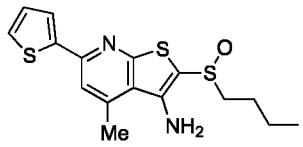
[00188] SW033291 2-(butylsulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine was prepared using procedure describe by Kalugin (Kalugin V.E. *Russian. Chem. Bull., Int. Ed.,* 2006, *55*, 529). To the solution of 4-(((butylthio)methyl)sulfinyl)-2,6-diphenylpyrimidine-5-carbonitrile (0.53 mmol, 220 mg) in DMF (0.25 M)/ EtOH (0.5 M) was added KOH (0.32 mmol, 18 mg, 0.6 equiv., 0.1 M in water). The reaction mixture was stirred at 35 °C for 40 min. Once complete, the reaction was diluted with EtOAc and washed with 10 % aq. solution of acidic acid, the organic phase was separated and aqueous layer was extracted twice with EtOAc, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 211 mg of SW033291 2-(butylsulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine (96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 1H), 7.57 – 7.35 (m, 7H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.54 (s, 2H), 3.26 (ddd, *J* = 12.8, 9.1, 6.0 Hz, 1H), 3.09 (ddd, *J* = 12.8, 9.1, 6.6 Hz, 1H), 1.83 – 1.61 (m, 2H), 1.53 – 1.38 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 413 $[M+H]^+$.



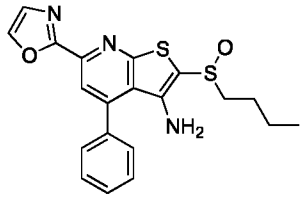
[00189] SW208437 4-phenyl-2-(propylsulfinyl)-6-(thiophen-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared in 56 % isolated yield using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.61 - 7.49 (m, 4H), 7.49 - 7.41 (m, 3H), 7.12 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.28 (ddd, *J* = 12.7, 8.4, 6.3 Hz, 1H), 3.07 (ddd, *J* = 12.7, 8.6, 7.0 Hz, 1H), 1.91 - 1.65 (m, 2H), 1.08 (t, *J* = 7.4 Hz, 3H). APCI-MS (m/z): 399 $[M+H]^+$.



[00190] SW208438 2-(isopropylsulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared in 48 % isolated yield using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, CDCl3) δ 7.64 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.58 - 7.47 (m, 5H), 7.47 -7.39 (m, 2H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.59 (s, 2H), 3.38 (p, *J* = 6.8 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H). ESI-MS (m/z): 399 $[M+H]^+$.

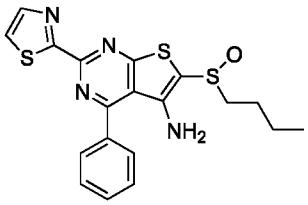


[00191] SW208488 2-(butylsulfinyl)-4-methyl-6-(thiophen-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.39 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.25 - 7.23 (m, 1H), 7.06 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.02 (s, 2H), 3.25 (ddd, *J* = 12.7, 9.1, 6.0 Hz, 1H), 3.08 (ddd, *J* = 12.8, 9.2, 6.4 Hz, 1H), 2.74 (s, 3H), 1.82 - 1.58 (m, 2H), 1.56 - 1.38 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 351 $[M+H]^+$.

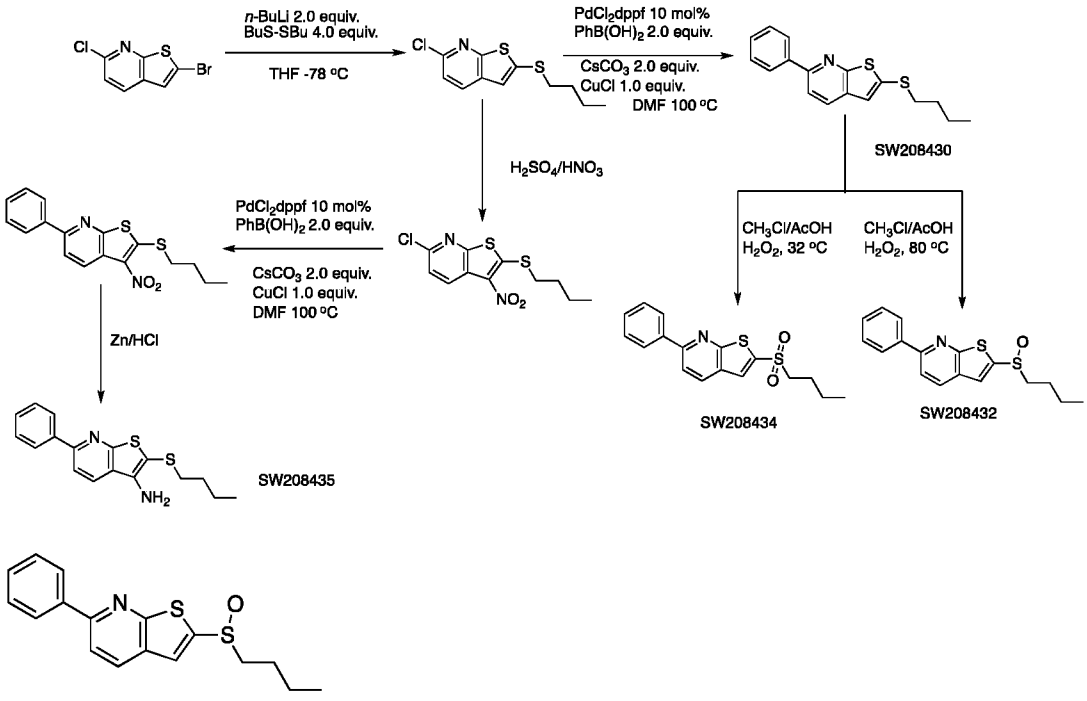


[00192] SW208496 2-(butylsulfinyl)-6-(oxazol-2-yl)-4-phenylthieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.84 (d, *J* = 0.8 Hz, 1H), 7.58 - 7.41 (m, 5H), 7.33 (d, *J* = 0.8 Hz, 1H), 4.65 (s, 2H), 3.30 (ddd, *J* = 12.9, 8.8, 6.2 Hz, 1H), 3.10

(ddd, J = 12.8, 8.9, 6.9 Hz, 1H), 1.86 - 1.64 (m, 2H), 1.42 – 1.54 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ESI-MS (m/z): 398.1 $[M+H]^+$.

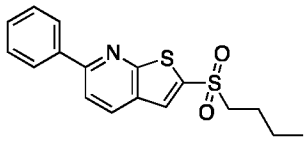


[00193] SW208436 6-(butylsulfinyl)-4-phenyl-2-(thiazol-2-yl)thieno[2,3-*d*]pyrimidin-5-amine was prepared by synthetic procedures described for the preparation of analog SW208065. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 3.1, 1H), 7.75 - 7.66 (m, 2H), 7.75 - 7.66 (m, 3H), 7.55 (dd, J = 3.1, 1H), 4.87 (s, 2H), 3.30 (ddd, J = 12.8, 8.4, 6.3 Hz, 1H), 3.12 (ddd, J = 12.8, 8.6, 6.9 Hz, 1H), 1.85 - 1.65 (m, 2H), 1.55 – 1.40 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 415.1 $[M+H]^+$.

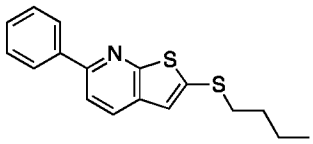


[00194] SW208432 2-(butylsulfinyl)-6-phenylthieno[2,3-*b*]pyridine. Acetic Acid (90 µL) and hydrogen peroxide (0.06 mmol, 1.5 equiv., 30 % solution in water) were added to the solution of 2-(butylthio)-6-phenylthieno[2,3-*b*]pyridine (0.04 mmol, 12 mg) in chloroform (90 µL). The reaction mixture was stirring at 32°C for 1 h. The reaction was

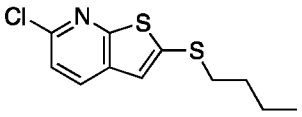
then diluted with EtOAc and washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give designed product in 76 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4, 1H), 8.08 (d, J = 8.2, 2H), 7.82 (d, J = 8.4, 1H), 7.58 – 7.36 (m, 4H), 3.30 - 2.73 (m, 2H), 1.90 - 1.62 (m, 2H), 1.55 - 1.41 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 316.1 $[M+H]^+$.



[00195] SW208434. Acetic Acid (200 µL) and hydrogen peroxide (0.15 mmol, 30 % solution in water) were added to the solution of 2-(butylthio)-6-phenylthieno[2,3-*b*]pyridine (0.09 mmol, 27 mg) in chloroform (200 µL). The reaction mixture was stirring at 100°C for 30 min. The reaction was then diluted with EtOAc and washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give designed product in 81 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.5 Hz, 1H), 8.09 (dd, J = 8.2, 1.6 Hz, 2H), 7.89 (d, J = 2.1 Hz, 1H), 7.59 - 7.39 (m, 4H), 3.39 - 3.10 (m, 2H), 1.92 - 1.68 (m, 2H), 1.54 - 1.27 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 332.1 $[M+H]^+$.

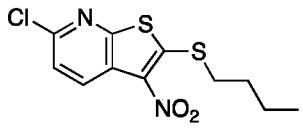


[00196] SW208430 2-(butylthio)-6-phenylthieno[2,3-*b*]pyridine. Phenylboronic acid (0.39 mmol, 2.0 equiv), 2-(butylthio)-6-chlorothieno[2,3-*b*]pyridine (50 mg, 0.195 mmol, 1.0 equiv), Cesium Carbonate (0.39 mmol, 2.0 equiv.), $PdCl_2$dppf (10 mol%), Copper Chloride (0.195 mmol, 1.0 equiv.) were heated in DMF at 100°C for 12 h. After cooling to r.t. the reaction mixture was diluted with EtOAc and washed with water and next brine. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (Hexanes/EtOAc: 8/2) to afford designed product in 32 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 - 8.00 (m, 2H), 7.93 (d, J = 8.3 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.52 - 7.34 (m, 4H), 2.99 (t, J = 7.9 Hz, 2H), 1.77 - 1.63 (m, 2H), 1.53 - 1.38 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 300.1 $[M+H]^+$.

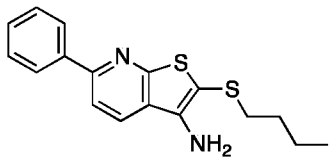


[00197] 2-(butylthio)-6-chlorothieno[2,3-*b*]pyridine. To the solution of 2-bromo-6-chlorothieno[2,3-*b*]pyridine (40 mg, 0.16 mmol) in THF (2 mL) at -78°C was added *n*-BuLi (0.32 mmol, 2.0 equiv.; 1.6 M solution in hexanes). The traction mixture was stirred for 5 min. and 1,2-dibutyldisulfane (0.48 mmol, 85.4 mg) was then added. The reaction mixture was stirred at -78°C for additional 1h, quenched with water and diluted with EtOAc. The organic layer was separated, dried over MgSO4, filtered and concentrated to give crude product, which was purified by flash column chromatography (95/5 Hexane/EtOAc) to give designed product in 91 % isolated yield.

[00198] ^{1}H NMR (400 MHz, CDCl3) δ 7.81 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.13 (s, 1H), 3.01 - 2.89 (m, 2H), 1.74 - 1.59 (m, 2H), 1.52 - 1.36 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 258.0 $[M+H]^+$.



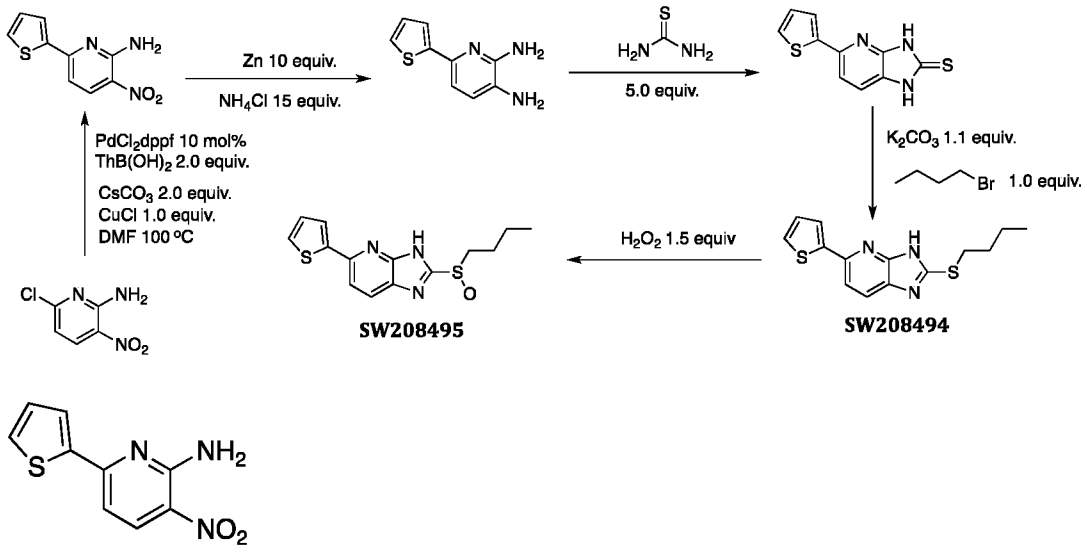
[00199] 2-(butylthio)-6-chloro-3-nitrothieno[2,3-*b*]pyridine was prepared in 53 % yield according procedure described by Nardine (Meth-Cohn, O.; Narine, B. *Tetrahedon Lett.*. 1978, *23*, 2045.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 3.15 (t, *J* = 7.4Hz, 2H), 1.95 - 1.73 (m, 2H), 1.68 - 1.41 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 303.0 $[M+H]^+$.



[00200] SW208435 2-(butylthio)-6-phenylthieno[2,3-*b*]pyridin-3-amine. Phenylboronic acid (37 mg, 0.30 mmol, 2.0 equiv), 2-(butylthio)-6-chloro-3-nitrothieno[2,3-*b*]pyridine (46 mg, 0.15 mmol, 1.0 equiv), Cesium Carbonate (0.30 mmol, 2.0 equiv.), $PdCl_2$dppf (10 mol%), Copper Chloride (0.15 mmol, 15 mg, 1.0 equiv.) were heated in DMF at 100°C for

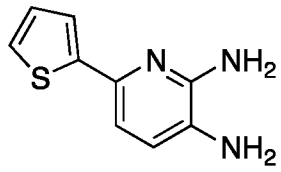
12 h. After cooling to r.t. the reaction mixture was diluted with EtOAc and washed with water and next brine. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by preparative TLC (AcOEt/Hexanes: 2/8) to afford 2-(butylthio)-3-nitro-6-phenylthieno[2,3-*b*]pyridine. ESI-MS (m/z): 345.1 $[M+H]^+$. 2-(butylthio)-3-nitro-6-phenylthieno[2,3-*b*]pyridine (0.017 mmol, 6 mg) was dissolved in a mixed solvent of acetic acid (0.12 mL) and conc. hydrochloric acid (one drop). Zinc (13 mg) was added at 0°C. After the mixture was stirred for 30 minutes, the reaction mixture was filtered, and the filtrate was neutralized with an aqueous solution of $NaHCO_3$, and extracted with DCM. The organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. Subsequently, the solvent was evaporated to obtain designed product. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 -7.54 (m, 3H), 7.50 - 7.40 (m, 2H), 7.35 -7.28 (m, 1H), 7.14 (d, J = 8.4 Hz, 1H), 3.35 - 3.18 (m, 2H), 1.80 - 1.65 (m, 2H), 1.54 -1.38 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 315.1 $[M+H]^+$.

[00201] 2-bromo-6-chlorothieno[2,3-*b*]pyridine was prepared according procedure described by Nardine. [1] ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H). ESI-MS (m/z): 249 $[M+H]^+$.

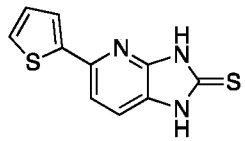


[00202] 3-nitro-6-(thiophen-2-yl)pyridin-2-amine. Thiophene boronic acid (742 mg, 5.8 mmol, 2.0 equiv), 6-chloro-3-nitropyridin-2-amine (500 mg, 2.9 mmol, 1.0 equiv), Cesium Carbonate (5.8 mmol, 2.0 equiv.), $PdCl_2$dppf (10 mol%), Copper Chloride

(2.9 mmol, 1.0 equiv.) in DMF were heated at 100°C for 12 h. After cooling to r.t. the reaction mixture was diluted with EtOAc and washed with water and next brine. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexanes/ EtOAc: 8/2) to afford 3-nitro-6-(thiophen-2-yl)pyridin-2-amine in 63 % yield. ^{1}H NMR (400 MHzCDCl$_3$) δ 8.42 (d, *J* = 8.7 Hz, 1H), 7.70 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.54 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H). ESI-MS (m/z): 222 [M+H]$^+$.

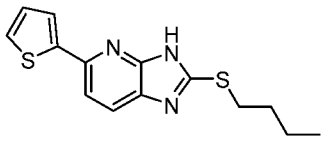


[00203] 6-(thiophen-2-yl)pyridine-2,3-diamine. The starting material, 3-nitro-6-(thiophen-2-yl)pyridin-2-amine (1.20 mmol, 265.4 mg), was dissolved in a 5:1 acetone/water mixture. Zinc (12.0 mmol, 784 mg, 10 eq) and ammonium chloride (18 mmol, 962.5 mg, 15 eq) were added to the solution, which was stirred at room temperature for 1 hour. The solution was then filtered through a celite pad and washed with ethyl acetate. The filtrate was extracted twice with brine then the aqueous layer was back extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Further purification by column chromatography gave 118.2 mg of 6-(thiophen-2-yl)pyridine-2,3-diamine (52 %). ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.34 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.25 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.96 – 6.86 (m, 2H), 4.85 (s, 4H). ESI-MS (m/z): 192 [M+H]$^+$.

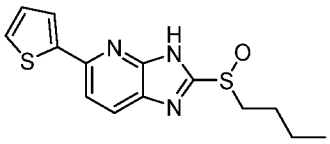


[00204] 5-(thiophen-2-yl)-1,3-dihydro-2H-imidazo[4,5-b]pyridine-2-thione. Thiourea (16.97 mmol, 223.0 mg, 5 eq) was added to 6-(thiophen-2-yl)pyridine-2,3-diamine. The solution was heated at 170°C for 2 hours. The addition of ethanol room temperature produced solid which was filtered to give 112.5 mg of 5-(thiophen-2-yl)-1,3-dihydro-2H-imidazo[4,5-b]pyridine-2-thione (82 %). ^{1}H NMR (400 MHz, (CD$_3$)$_2$SO) δ 7.69 (dd, *J* = 3.7,

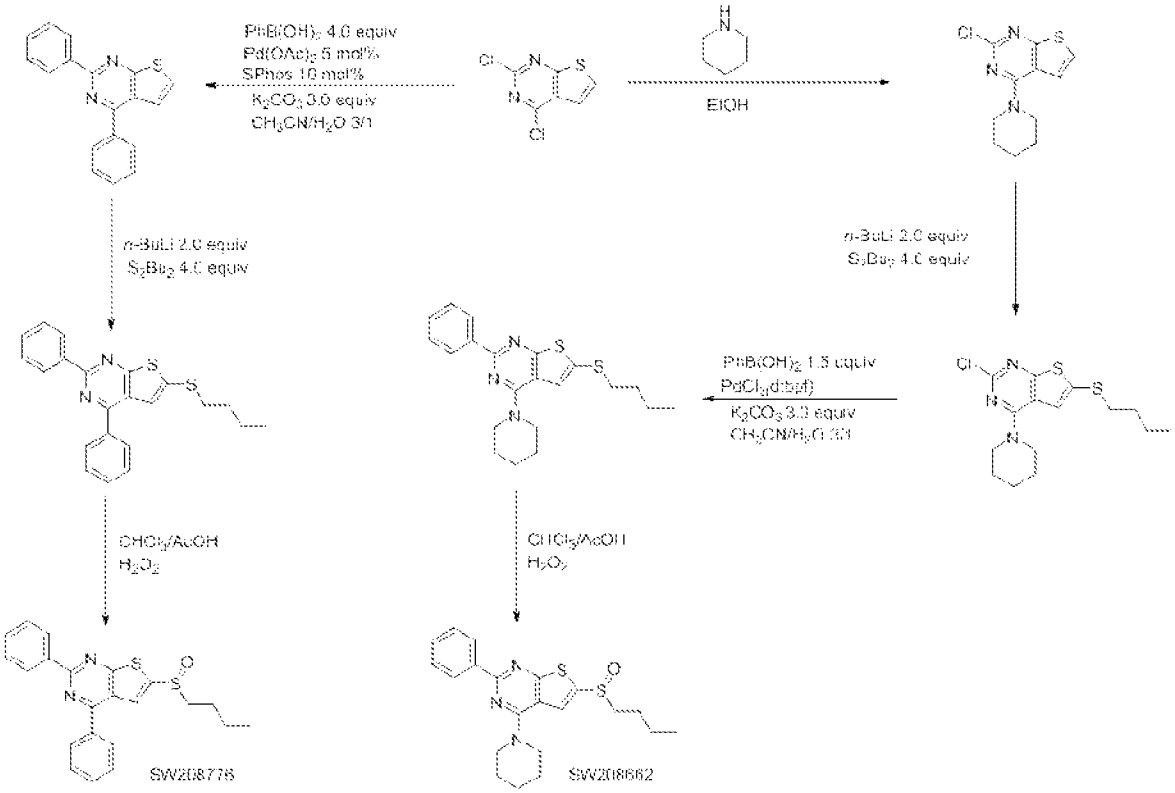
1.2 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.56 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.15 – 7.09 (m, 1H). ESI-MS (m/z): 235 $[M+2H]^+$.

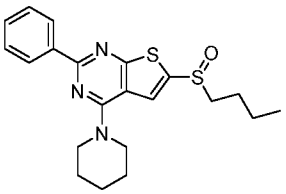


[00205] SW208494 2-(butylthio)-5-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine. A mixture of 5-(thiophen-2-yl)-1,3-dihydro-2H-imidazo[4,5-b]pyridine-2-thione (0.39 mmol, 92 mg), potassium carbonate (0.45 mmol, 61.9 mg, 1.1 eq), 1-bromobutane (0.39 mmol, 42.8 µL, 1 eq), 18-Crown-6 (0.039 mmol, 10.5 mg, 0.1 eq), and DMF (2.67 mL) was heated at 80 °C for 3 hours. This solution was then diluted with EtOAc and washed with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated under high pressure to give 74.4 mg of SW208494 2-(butylthio)-5-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine (65 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.83 (m, 1H), 7.61 – 7.53 (m, 2H), 7.36 (d, *J* = 5.1, 1H), 7.16 – 7.06 (m, 1H), 3.28 (t, *J* = 7.3 Hz, 2H), 1.76 – 1.62 (m, 2H), 1.48 – 1.32 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 290 $[M+H]^+$.

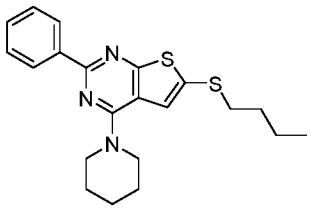


[00206] SW208495. 2-(butylsulfinyl)-5-(thiophen-2-yl)-3*H*-imidazo[4,5-*b*]pyridine. Chloroform (450 µL), acetic acid (450 µL), and hydrogen peroxide (0.376 mmol, 2.0 eq, 40 µL) were added to SW208494 2-(butylthio)-5-(thiophen-2-yl)-3H-imidazo[4,5-b]pyridine and heated at 45°C for 2.5 hours. The solution was then diluted with EtOAc and washed with 10 % acetic acid. The organic layer was separated, dried with magnesium sulfate, filtered, concentrated, and purified to give 16.8 mg of SW208495. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.5 Hz, 1H), 7.83 – 7.67 (m, 1H), 7.68 – 7.60 (m, 1H), 7.41 (d, *J* = 5.3Hz, 1H), 7.20 – 7.05 (m, 1H), 3.44 – 3.17 (m, 2H), 1.89 – 1.58 (m, 2H), 1.59 – 1.40 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 306 $[M+H]^+$.

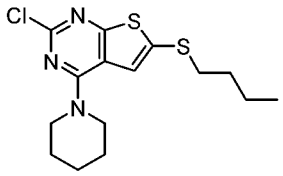




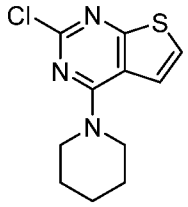
[00207] SW208662. 6-(butylsulfinyl)-2-phenyl-4-(piperidin-1-yl)thieno[2,3-d]pyrimidine. Acetic acid (50 µl) and hydrogen peroxide (5.0 µl, 30 % solution in water) were added to the solution of 2-(butylthio)-6-phenyl-4-(piperidin-1-yl)thieno[2,3-b]pyrimidine (10 mg, 0.026 mmol) in chloroform (50 µl). The reaction mixture was stirred at 32 °C for 45 min. Once complete, the reaction was diluted with EtOAc and was washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate, filtered and concentrated under reduce pressure to give designed product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.34 (m, 2H), 7.73 (s, 1H), 7.55 – 7.36 (m, 3H), 4.09 – 3.86 (m, 4H), 3.24 – 2.94 (m, 2H), 1.97 – 1.36 (m, 10H), 0.93 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 400.1 $[M+H]^+$.



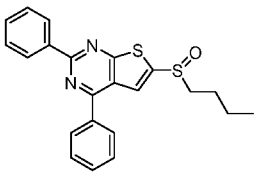
[00208] 2-(butylthio)-6-phenyl-4-(piperidin-1-yl)thieno[2,3-b]pyrimidine. 2-(butylthio)-6-chloro-4-(piperidin-1-yl)thieno[2,3-b]pyrimidine (52 mg, 0.15 mmol), phenylboronic acid (27 mg, 0.22 mmol, 1.5 equiv), Potassium Carbonate (0.3 mmol, 2.0 equiv.), PdCl2dtbpf (10 mol mol%), in CH3CN:H2O (2:1) were heated at 100°C overnight. After cooling to r.t. the reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to afford designed product. 1H NMR (400 MHz, CHCl3) δ 8.49 – 8.36 (m, 2H), 7.51 – 7.36 (m, 3H), 7.29 (s, 1H), 3.95-3.85 (m, 4H), 2.90 (t, J = 7.4 Hz, 2H), 1.76 – 1.73 (m, 6H), 1.70 – 1.59 (m, 2H), 1.48 – 1.39 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). ESI-MS (m/z): 384.0 [M+H]+.



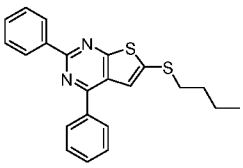
[00209] 2-(butylthio)-6-chloro-4-(piperidin-1-yl)thieno[2,3-b]pyrimidine. To the solution of 6-chloro-4-(piperidin-1-yl)thieno[2,3-b]pyrimidine (52 mg, 0.20 mmol) in THF was added *n*-BuLi (0.4 mmol, 2.0 equiv., 1.6 M solution in hexanes) at -78°C. The reaction mixture was stirred for 5 min and 1,2-dibutyldisulfane (0.80 mmol, 4.0 equiv.) in THF was added. The reaction mixture was stirred for additional 1h at -78 °C and then quenched. The crude product was purified by flash chromatography to afford designed product in 74 % yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.24 (s, 1 H), 3.93 – 3.74 (m, 4H), 2.83 (t, *J* = 7.3 Hz, 2H), 1.82 – 1.66 (m, 6H), 1.66 – 1.53 (m, 2H), 1.49 – 1.33 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 342.1 $[M+H]^+$.



[00210] 6-chloro-4-(piperidin-1-yl)thieno[2,3-b]pyrimidine. 4,6-dichlorothieno[2,3-b]pyrimidine (50 mg, 0.24 mmol) and piperidine (0.36 mmol, 1.5 equiv.) in EtOH were stirred at room temperature overnight. The solvent was evaporated and crude compound purified by flash chromatography to give designed product in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 6.1 Hz, 1H), 7.18 (d, J = 6.2 Hz, 1H), 4.01 – 3.67 (m, 4H), 1.92 – 1.63 (m, 6H). ESI-MS (m/z): 254.0 $[M+H]^+$.

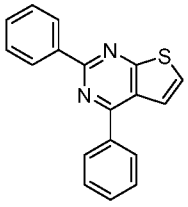


[00211] SW208776. 6-(butylsulfinyl)-2,4-diphenylthieno[2,3-d]pyrimidine. Acetic acid (250 µl) and hydrogen peroxide (20 µl, 30 % solution in water) were added to the solution of 6-(butylthio)-2,4-diphenylthieno[2,3-d]pyrimidine (35 mg, 0.1 mmol) in chloroform (250 µl). The reaction mixture was stirred at 32 °C for 45 min. Once complete, the reaction was diluted with EtOAc and was washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate, filtered and concentrated under reduce pressure to give designed product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 – 8.59 (m, 2H), 8.09 – 7.99 (m, 2H), 7.95 (s, 1H), 7.65 – 7.56 (m, 3H), 7.56 – 7.45 (m, 3H), 3.18 – 3.02 (m, 2H), 1.87 – 1.64 (m, 2H), 1.54 – 1.42 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 393.1 $[M+H]^+$.

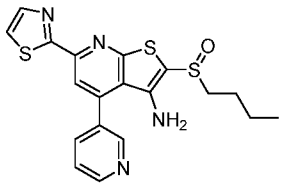


[00212] 6-(butylthio)-2,4-diphenylthieno[2,3-d]pyrimidine. To the solution of 2,4-diphenylthieno[2,3-d]pyrimidine (53 mg, 0.28 mmol) in THF was added *n*-BuLi (0.56 mmol,

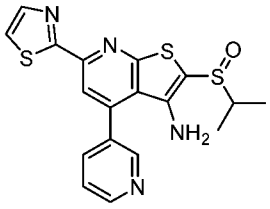
2.0 equiv., 225 µL, 2.5 M solution in hexanes) at -78°C. The reaction mixture was stirred for 5 min and 1,2-dibutyldisulfane (1.14 mmol, 4.0 equiv.) in THF was added. The reaction mixture was stirred for additional 1h at -78°C and then quenched. The crude product was purified by flash chromatography to afford designed product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.56 (m, 2H), 8.06 – 7.98 (m, 2H), 7.61 – 7.41 (m, 7H), 3.01 (t, *J* = 7.3, 2H), 1.76 – 1.62 (m, 2H), 1.55 – 1.38 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 377.1 $[M+H]^+$.



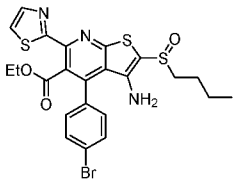
[00213] 2,4-diphenylthieno[2,3-d]pyrimidine. 2,4-dichlorothieno[2,3-*d*]pyrimidine (100 mg, 0.50 mmol), phenylboronic acid (242 mg, 2.0 mmmol, 4.0 equiv), Potassium Carbonate (1.5 mmol, 3.0 equiv.), $Pd(OAc)_2$ (5 mol mol%), SPhos (10 mol%) in CH_3CN:H_2O (1.5:1) were heated at 100 °C overnight. After cooling to r.t. the reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to afford designed product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.59 (m, 2H), 8.14 – 8.02 (m, 2H), 7.65 – 7.44 (m, 8H). ESI-MS (m/z): 289.0 $[M+H]^+$.



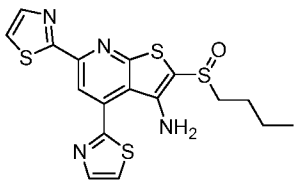
[00214] SW208777. 2-(butyl(λ^1-oxidanyl)-λ^3-sulfanyl)-4-(pyridin-3-yl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1 H), 8.78 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.04 (s, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.86 (d, *J* = 6.4 Hz, 1H), 7.51 (d, *J* = 3.1 Hz, 1H), 7.47 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.53 (s, 2H), 3.28 (ddd, *J* = 12.8, 8.8, 6.3 Hz, 1H), 3.11 (ddd, *J* = 12.8, 8.9, 6.9 Hz, 1H), 1.86 – 1.70 (m, 2H), 1.57 – 1.38 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 415.0 $[M+H]^+$.



[00215] SW208780. 2-(isopropyl(λ^1-oxidanyl)-λ^3-sulfanyl)-4-(pyridin-3-yl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 – 8.70 (m, 2H), 8.05 (s, 1H), 7.92 (d, *J* = 3.1 Hz, 1H), 7.85 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.51 (d, *J* = 3.2 Hz, 1H), 7.47 (dd, J = 7.9, 4.9 Hz, 1H), 4.57 (s, 2H), 3.38 (p, *J* = 6.8 Hz, 1H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.8 Hz, 3H). ESI-MS (m/z): 400.1 $[M+H]^+$.

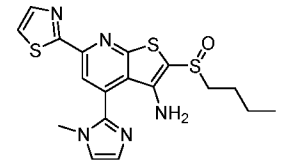


[00216] SW209123. Ethyl 3-amino-4-(4-bromophenyl)-2-(butylsulfinyl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridine-5-carboxylate was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.2 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.48 (d, *J* = 3.2 Hz, 1H), 7.36 – 7.27 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.26 (ddd, *J* = 12.9, 8.8, 6.3 Hz, 1H), 3.08 (ddd, *J* = 12.9, 8.8, 6.3 Hz, 1H), 1.80 – 1.63 (m, 2H), 1.58 – 1.37 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 564.0 $[M+H]^+$.

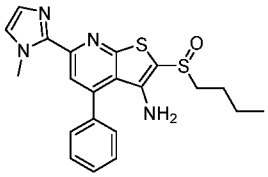


[00217] SW209124. 2-(butylsulfinyl)-4,6-di(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.01 (d, *J* = 3.1 Hz, 1H), 7.96 (d, *J* = 3.2 Hz, 1H),

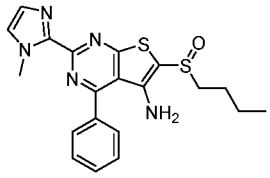
7.61 (d, *J* = 3.3 Hz, 1H), 7.52 (d, *J* = 3.1 Hz, 1H), 6.69 (s, 2H), 3.30 (ddd, *J* = 12.8, 9.2, 6.0 Hz, 1H), 3.14 (ddd, *J* = 12.8, 9.2, 6.4 Hz, 1H), 1.83 – 1.60 (m, 2H), 1.43 – 1.53 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 421.0 $[M+H]^+$.



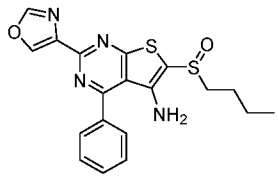
[00218] SW209125. 2-(butylsulfinyl)-4-(1-methyl-1H-imidazol-2-yl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.50 (d, *J* = 3.1 Hz, 1H), 7.24 (d, *J* = 1.2 Hz, 1H), 7.13 (d, *J* = 1.2 Hz, 1H), 5.78 (s, 2H), 3.80 (s, 3H), 3.26 (ddd, *J* = 12.8, 9.1, 6.0 Hz, 1H), 3.10 (ddd, *J* = 12.8, 9.2, 6.5 Hz, 1H), 1.82 – 1.57 (m, 2H), 1.56 – 1.35 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 418.1 $[M+H]^+$.



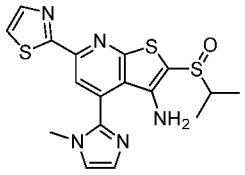
[00219] SW209126. 2-(butylsulfinyl)-6-(1-methyl-1H-imidazol-2-yl)-4-phenylthieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.58 – 7.32 (m, 5H), 7.11 (d, *J* = 1.1 Hz, 1H), 7.00 (d, *J* = 1.1 Hz, 1H), 4.58 (s, 2H), 4.19 (s, 3H), 3.27 (ddd, *J* = 12.7, 9.0, 6.0 Hz, 1H), 3.08 (ddd, *J* = 12.8, 9.1, 6.6 Hz, 1H), 1.79 – 1.60 (m, 2H), 1.56 – 1.37 (m, 2H), 0.92 (*t*, J = 7.3 Hz, 3H). ESI-MS (m/z): 411.1 $[M+H]^+$.



[00220] SW209277. 6-(butylsulfinyl)-2-(1-methyl-1H-imidazol-2-yl)-4-phenylthieno[2,3-*d*]pyrimidin-5-amine was prepared using synthetic procedures described for the preparation of analog SW208065. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 6.9, 2.8 Hz, 2H), 7.63 – 7.49 (m, 3H), 7.29 (s, 1H), 7.07 (s, 1H), 4.85 (s, 2H), 4.18 (s, 3H), 3.29 (ddd, *J* = 12.8, 8.6, 6.3 Hz, 1H), 3.11 (ddd, *J* = 12.8, 8.7, 6.9 Hz, 1H), 1.83 – 1.65 (m, 2H), 1.59 – 1.39 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 412.1 $[M+H]^+$.

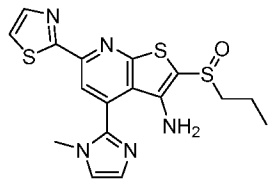


[00221] SW209278. 6-(butylsulfinyl)-2-(oxazol-4-yl)-4-phenylthieno[2,3-*d*]pyrimidin-5-amine was prepared using synthetic procedures described for the preparation of analog SW208065. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 1.1 Hz, 1H), 8.01 (d, *J* = 1.1 Hz, 1H), 7.75 – 7.61 (m, 2H), 7.62 – 7.48 (m, 3H), 4.56 (s, 2H), 3.29 (ddd, *J* = 12.9, 8.8, 6.3 Hz, 1H), 3.09 (ddd, *J* = 12.9, 8.9, 6.9 Hz, 1H), 1.81 – 1.64 (m, 2H), 1.56 – 1.39 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 399.1 $[M+H]^+$.

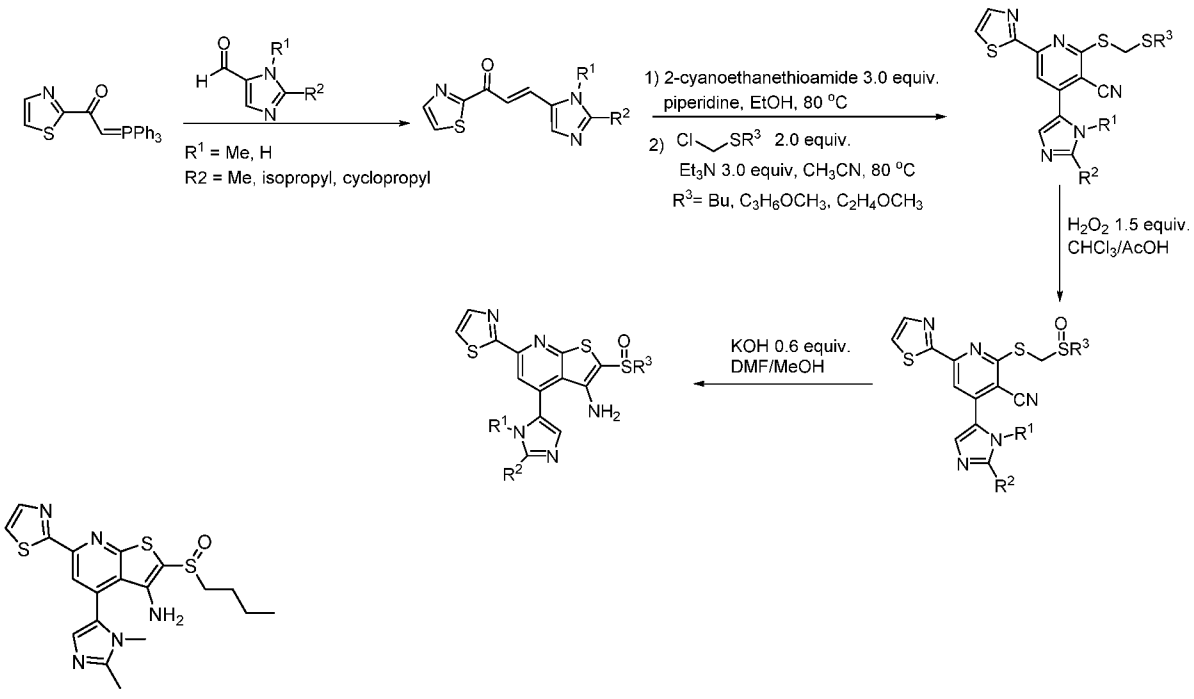


[00222] SW209279. 2-(isopropylsulfinyl)-4-(1-methyl-1H-imidazol-2-yl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.92 (d, *J* = 3.2 Hz, 1H), 7.51 (d, *J* = 3.2 Hz, 1H), 7.24 (s, 1H), 7.13 (d, *J* = 1.2 Hz, 1H), 5.92 (s, 2H),

3.80 (s, 3H), 3.38 (p, J = 6.8 Hz, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H). ESI-MS (m/z): 404.1 $[M+H]^+$.

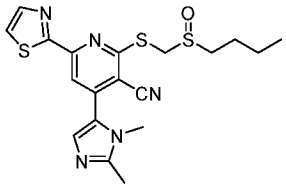


[00223] SW209280. 4-(1-methyl-1H-imidazol-2-yl)-2-(propylsulfinyl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW033291. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.92 (d, J = 3.2 Hz, 1H), 7.51 (d, J = 3.1, 1H), 7.25 (d, J = 1.3 Hz, 1H), 7.14 (d, J = 1.2 Hz, 1H), 5.97 (s, 2H), 3.80 (s, 3H), 3.27 (ddd, J = 12.7, 8.3, 6.5 Hz, 1H), 3.07 (ddd, J = 12.8, 8.4, 7.1 Hz, 1H), 1.85 – 1.69 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H). ESI-MS (m/z): 404.1 $[M+H]^+$.

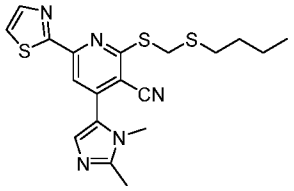


[00224] SW209415. 2-(butylsulfinyl)-4-(1,2-dimethyl-1H-imidazol-5-yl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine. To the solution of 2-(((butylsulfinyl)methyl)thio)-4-(1,2-dimethyl-1H-imidazol-5-yl)-6-(thiazol-2-yl)nicotinonitrile (0.14 mmol, 60 mg) in DMF (600 µl)/ MeOH (300 µl) was added KOH (0.084 mmol, 4.70 mg, 0.6 equiv., 2.0 M in water).

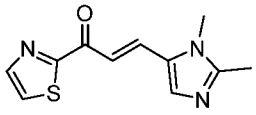
The reaction mixture was stirred at 32°C for 20 min. Once complete, the reaction was diluted with EtOAc and acidified to pH 7 with 5 % aq. solution of AcOH, the organic phase was separated and aqueous layer was extracted twice with EtOAc, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography to afford designed product in 97 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.90 (d, J = 3.1 Hz, 1H), 7.50 (d, J = 3.2 Hz, 1H), 7.11 (s, 1H), 4.76 (s, 2H), 3.39 (s, 3H), 3.27 (ddd, J = 12.9, 8.7, 6.4 Hz, 1H), 3.09 (ddd, J = 12.8, 8.8, 6.9 Hz, 1H), 2.47 (s, 3H), 1.83 – 1.62 (m, 2H), 1.57 – 1.38 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 432.1 $[M+H]^+$. Two enantiomers of SW209415 can be separated by chiral HPLC: Chiralpak AD-H, 10 X 250 mm, 5 μM, 100% MeOH.



[00225] 2-(((butylsulfinyl)methyl)thio)-4-(1,2-dimethyl-1H-imidazol-5-yl)-6-(thiazol-2-yl)nicotinonitrile. To the solution of 2-(((butylthio)methyl)thio)-4-(1,2-dimethyl-1H-imidazol-5-yl)-6-(thiazol-2-yl)nicotinonitrile (85 mg, 0.205 mmol) in $CHCl_3$/AcOH (1:1, 0.15 M) was added H_2O_2 (0.31 mmol, 1.5 equiv. 30% solution in water). The reaction mixture was stirred at 32 °C for 40 min. Once complete, the reaction was diluted with EtOAc and was washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate, filtered and concentrated under reduce pressure to give designed product in 92 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 3.1 Hz, 1H), 7.94 (s, 1H), 7.60 (d, J = 3.1 Hz, 1H), 7.43 (s, 1H), 4.72 (d, J = 13.1 Hz, 1H), 4.41 (d, J = 13.1 Hz, 1H), 3.63 (s, 3H), 2.96 (dt, J = 12.9, 8.2 Hz, 1H), 2.84 (dt, J = 12.9, 7.5 Hz, 1H), 2.51 (s, 3H), 1.94 – 1.74 (m, 2H), 1.63 – 1.38 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). ESI-MS (m/z): 432.1 $[M+H]^+$.

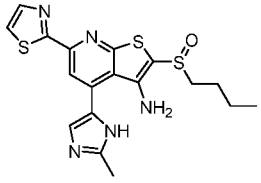


[00226] 2-(((butylthio)methyl)thio)-4-(1,2-dimethyl-1H-imidazol-5-yl)-6-(thiazol-2-yl)nicotinonitrile. To a suspension of 3-(1,2-dimethyl-1H-imidazol-5-yl)-1-(thiazol-2-yl)prop-2-en-1-one (0.31 mmol, 72 mg) and 2-cyanothioacetamide (0.93 mmol, 93 mg, 3.0 equiv.) in EtOH (1.5 mL), a few drops of piperidine were added. After being stirred at 80°C for 2 h, EtOH was evaporated and crude product was redissolved in CH_3CN. Butyl(chloromethyl)sulfane (0.62 mmol, 85.5 mg) and Et_3N (0.93 mmol, 94.1 mg, 130 μL) were then added and the reaction mixture was stirred at 80°C for 20 min. Once complete, the reaction was diluted with EtOAc and water. The organic phase was separated and aqueous layer was extracted twice with EtOAc. The combined extractions were washed with saturated NaCl solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give 99 mg of designed product (77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 3.1 Hz, 1H), 7.85 (s, 1H), 7.56 (d, J = 3.1 Hz, 1H), 7.37 (s, 1H), 4.49 (s, 2H), 3.60 (s, 3H), 2.72 (t, J = 7.4 Hz, 2H), 2.48 (s, 3H), 1.62 (p, J = 7.3 Hz, 2H), 1.40 (h, J = 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 416.6 $[M+H]^+$.

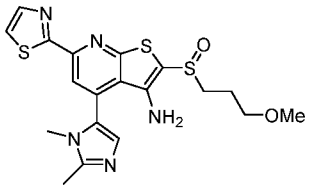


[00227] (E)-3-(1,2-dimethyl-1H-imidazol-5-yl)-1-(thiazol-2-yl)prop-2-en-1-one. To a solution of 1,5-dimethyl-1H-imidazole-2-carbaldehyde (2.0 mmol, 250 mg) in 6 ml of CH_3CN was added 1-(thiazol-2-yl)-2-(triphenyl-l5-phosphanylidene)ethan-1-one (4.0 mmol, 1.55 g, 2.0 equiv.). The reaction mixture was stirred at 90°C for 48 h. Once complete, solvent was evaporated and residue was purified by flash chromatography to give 331 mg of designed product (71%). ^{1}H NMR (400 MHz, Methanol-d4) δ 8.08 (d, J = 3.0 Hz, 1H), 7.97

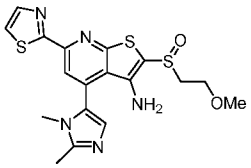
(d, J = 3.0 Hz, 1H), 7.90 (d, J = 15.9 Hz, 1H), 7.76 (d, J = 15.9 Hz, 1H), 7.60 (s, 1H), 3.72 (s, 3H), 2.43 (s, 3H).ESI-MS (m/z): 234.3 $[M+H]^+$.



[00228] SW209428. 2-(butylsulfinyl)-4-(2-methyl-1*H*-imidazol-5-yl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW209415. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.10 (s, 1H), 7.89 (d, J = 3.2 Hz, 1H), 7.46 (d, J = 3.2 Hz, 1H), 7.40 (s, 1H), 3.31 (ddd, J = 12.8, 9.3, 5.8 Hz, 1H), 3.15 (ddd, J = 12.8, 9.3, 6.2 Hz, 1H), 2.42 (s, 3H), 1.79 – 1.58 (m, 2H), 1.57 – 1.38 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 418.1 $[M+H]^+$.

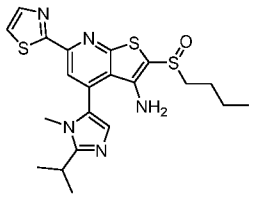


[00229] SW211688. 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-2-((3-methoxypropyl) sulfinyl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW209415. ^{1}H NMR (400 MHz, Acetone-d6) δ 8.03 (s, 1H), 7.99 (d, J = 3.2 Hz, 1H), 7.82 (d, J = 3.2 Hz, 1H), 7.09 (s, 1H), 5.06 (s, 2H), 3.51 (s, 3H), 3.48 (t, J = 6.1 Hz, 2H), 3.26 (s, 3H), 3.26 – 3.18 (m, 1H), 3.18 – 3.12 (m, 1H), 2.43 (s, 3H), 2.00 – 1.89 (m, 2H). ESI-MS (m/z): 448.1 $[M+H]^+$.

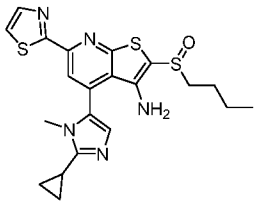


[00230] SW211689. 4-(1,2-dimethyl-1*H*-imidazol-5-yl)-2-((2-methoxyethyl) sulfinyl)-6-(thiazol-2-yl)thieno[2,3-*b*]pyridin-3-amine was prepared using synthetic procedures

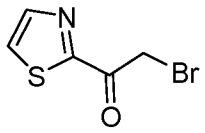
described for the preparation of analog SW209415. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.92 (d, J = 3.2 Hz, 1H), 7.51 (d, J = 3.2 Hz, 1H), 7.11 (s, 1H), 4.73 (s, 2H), 3.88 – 3.82 (m, 1H), 3.75 – 3.62 (m, 1H), 3.57 (ddd, J = 13.1, 6.0, 3.9 Hz, 1H), 3.40 (s, 3H), 3.37 (s, 3H), 3.25 (ddd, J = 12.8, 8.0, 4.4 Hz, 1H), 2.48 (s, 3H). ESI-MS (m/z): 434.1 $[M+H]^+$.



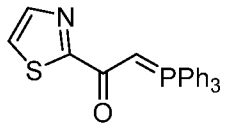
[00231] SW212344. 2-(butylsulfinyl)-4-(2-isopropyl-1-methyl-1H-imidazol-5-yl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW209415. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.92 (d, J = 3.1 Hz, 1H), 7.51 (d, J = 3.2 Hz, 1H), 7.15 (s, 1H), 4.71 (s, 2H), 3.41 (s, 3H), 3.27 (ddd, J = 13.0, 8.5, 6.5 Hz, 1H), 3.19 – 2.98 (m, 2H), 1.83 – 1.59 (m, 2H), 1.58 – 1.41 (m, 2H), 1.39 (d, J = 6.7 Hz, 6H), 0.94 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 460.1 $[M+H]^+$.



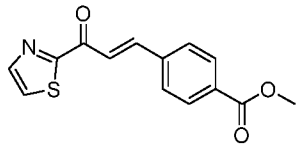
[00232] SW212345. 2-(butylsulfinyl)-4-(2-cyclopropyl-1-methyl-1H-imidazol-5-yl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-3-amine was prepared using synthetic procedures described for the preparation of analog SW209415. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.91 (d, J = 3.1 Hz, 1H), 7.50 (d, J = 3.1 Hz, 1H), 7.07 (s, 1H), 4.77 (s, 2H), 3.51 (s, 3H), 3.27 (ddd, J = 12.9, 8.7, 6.4 Hz, 1H), 3.10 (ddd, J = 12.9, 8.8, 6.9 Hz, 1H), 1.95 – 1.78 (m, 1H), 1.81 – 1.62 (m, 2H), 1.58 – 1.37 (m, 2H), 1.17 – 0.98 (m, 4H), 0.93 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 458.1 $[M+H]^+$.



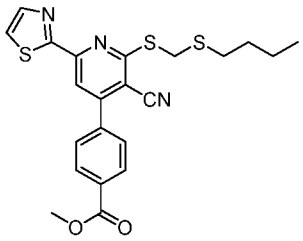
[00233] 2-bromo-1-(thiazol-2-yl)ethan-1-one. n-Butyllithium (24.7 mL, 0.0617 mol, 2.5M in Hexane) was added dropwise to a solution of 2-thiazole (5.0 g, 0.059 mol) in anhydrous diethyl ether (48.8 mL) at -78°C. After 15 minutes, ethylbromoacetate (6.84 mL, 0.0617 mol) was added, the cold bath was removed and the solution was allowed to warm to room temperature. The reaction mixture was diluted with ether and water. The organic layer was separated, dried over Na2SO4, filtered and concetrated under reduced pressure. The crude product was suspended in hexanes and heated to reflux for 15 minutes then the product was decanted off leaving the impure oil. This was repeated 5 times to give a white solid with 88 % yield. ^{1}H NMR (400 MHz, CDCl3) δ 8.05 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 3.0 Hz, 1H), 4.71 (s, 2H). ESI-MS (m/z): 207.8 [M+H]+.



[00234] 1-(thiazol-2-yl)-2-(triphenyl-l5-phosphanylidene)ethan-1-one. To a solution of 2-bromo-1-(thiazol-2-yl)ethan-1-one (10.7 g, 0.0517 mol) in toluene (337.7 mL), triphenylphosphine (14.1 g, 0.0539 mol) was added portion wise. The mixture was stirred at room temperature for 3 hours. The yellowish precipitate was removed by filtration, and was washed several times with toluene and then petroleum ether. Water was added to the precipitate and was treated dropwise with 1N NaOH to pH 10 (at pH 7 there was a color change from yellow to orange). The mixture was stirred for 30 minutes at room temperature. The precipitate was removed by filtration and washed several times with water. The resulting orange solid, was heated at 50°C under vacuum to remove any water, giving a 96 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 3.1 Hz, 1H), 7.72 (ddd, J = 12.8, 8.3, 1.4 Hz, 6H), 7.61 – 7.54 (m, 3H), 7.51 – 7.45 (m, 6H), 7.38 (dd, J = 3.1, 1.3 Hz, 1H), 5.00 (d, J = 23.3 Hz, 1H). ESI-MS (m/z): 387.9 $[M+H]^+$.

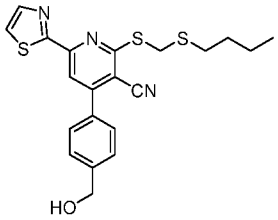


[00235] Methyl (E)-4-(3-oxo-3-(thiazol-2-yl)prop-1-en-1-yl)benzoate. In a dried flask, 1-(thiazol-2-yl)-2-(triphenyl-l5-phosphanylidene)ethan-1-one (1.5 g, 3.9 mmol) and methyl 4-formyl benzoate (634 mg, 3.86 mmol) were dissolved in anhydrous chloroform (19.3 mL) and the solution stirred at 71°C overnight. The solvent was evaporated under reduced pressure and the solid precipitate was purified using automated flash chromatography (100 % DCM) to give a white solid in 76 % yield. ^{1}H NMR (400 MHz, CDC3) δ 8.10 – 8.05 (m, 3H), 8.01 (d, J = 1.3 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 3.0 Hz, 1H), 3.93 (s, 3H). ESI-MS (m/z): 274.0 [M+H]+.

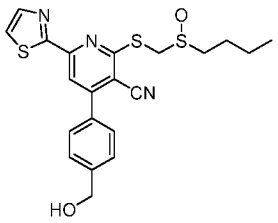


[00236] Methyl 4-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate. 2-cyanothioacetamide (274.8 mg, 2.744 mmol) and methyl (E)-4-(3-oxo-3-(thiazol-2-yl)prop-1-en-1-yl)benzoate (250.0 mg, 0.9147 mmol) were combined in a vial that was evacuated and backfilled with O2 then ethanol (2.75 mL) and piperdine (2 drops) were added. The solution was sparged for a few minutes then stirred at 80°C for 4 hours. Once cooled, the solution was filtered, and the precipitate was rinsed with ethanol, and then washed in minimal amounts of acetic acid by heating at 80°C for 45 minutes. When cooled, the washed solution was filtered leaving the crude brown/red solid product, which was carried forward to the next step. Standard alkylation procedure: Butyl(chloromethyl)sulfane (111.2 mg, 0.8059 mmol) in acetonitrile (1.32 mL), was added to the product from the first step, and Et3N (168.6 μL, 1.209 mmol) was added last. The solution was stirred at 80°C for 20 minutes. The reaction mixture was diluted with EtOAc and washed with H2O, dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude solid was purified using automated flash chromatography (80 % hexane, 20% EtOAc). This produced a solid in 24 % yield. ^{1}H NMR (400 MHz, CDCl3) δ 8.18 (d, J = 8.4 Hz, 2H), 8.02 (s, 1H), 7.98 (d, J =

3.1 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 3.2 Hz, 1H), 4.52 (s, 2H), 3.95 (s, 3H), 2.76 (t, J = 7.3 Hz, 2H), 1.64 (tt, J = 7.7, 6.3 Hz, 2H), 1.42 (h, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 456.1 [M+H]+.

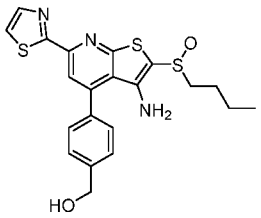


[00237] 2-(((butylthio)methyl)thio)-4-(4-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile. To the solution of methyl 4-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate (336 mg, 0.737 mmol) in THF (8.41 mL) $LiBH_4$ (96.3 mg, 4.42 mmol) was added at 0°C. The reaction was stirred at room temperature for 36 hours, and the reaction was monitored by LC/MS. The reaction mixture was diluted with EtOAc and H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure, to give product in 96 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.98 (d, *J* = 3.1 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.56 (d, *J* = 3.1 Hz, 1H), 7.56 – 7.49 (m, 2H), 4.79 (d, *J* = 4.3 Hz, 2H), 4.52 (s, 2H), 2.82 – 2.60 (m, 2H), 1.71 – 1.58 (m, 2H), 1.49 – 1.33 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 428.1 $[M+H]^+$.

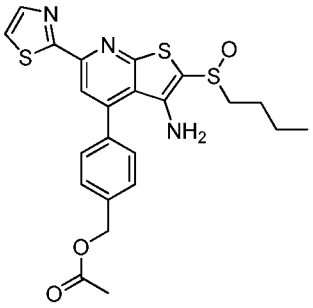


[00238] Standard oxidation procedure: 2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-4-(4-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile. Chloroform (2.53 mL), acetic acid (1.39 mL), and hydrogen peroxide (108.0 µL, 1.057 mmol, 30 % solution in water) were added to 2-(((butylthio)methyl)thio)-4-(4-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile. The solution was stirred at 32°C for 45 minutes. The reaction mixture was then diluted with EtOAc and washed with saturated $NaHCO_3$, and the organic layer was dried over Na2SO4, filtered, and concentrated under reduced pressure to give the desired product in 94 % yield. ^{1}H NMR (400 MHz, CDCl3) δ 8.03 (s, 1H), 7.93 (d, J = 3.1 Hz, 1H), 7.59

(d, J = 8.2 Hz, 2H), 7.55 (d, J = 3.1 Hz, 1H), 7.48 (d, J = 7.9 Hz, 2H), 4.73 (s, 2H), 4.66 (d, J = 13.1 Hz, 1H), 4.38 (d, J = 13.1 Hz, 1H), 2.93 (dt, J = 13.0, 8.1 Hz, 1H), 2.79 (dt, J = 13.0, 7.2 Hz, 1H), 1.84 – 1.72 (m, 2H), 1.55 – 1.33 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H).). ESI-MS (m/z): 444.1 [M+H]+.

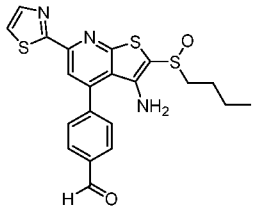


[00239] SW209510 (4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)phenyl)methanol. *t*-BuOK (22.78 mg, 0.2028 mmol) was added to 2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-4-(4-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile (150 mg, 0.338 mmol) and the vial was evacuated backfilled with N_2 three times before adding DMF (1.3 mL). The solution was sparged with N_2 for a few minutes before heating at 32°C. The reaction mixture was monitored every five minutes by TLC (80 % EtOAc. 20 % hexanes) and upon completion was diluted with EtOAc and washed with 10 % AcOH. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified using automated flash chromatography to give an isolated green solid/oil in 16 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.90 (d, *J* = 3.2 Hz, 1H), 7.59 – 7.40 (m, 5H), 4.80 (s, 2H), 4.63 (s, 2H), 3.27 (ddd, *J* = 12.8, 9.0, 6.1 Hz, 1H), 3.10 (ddd, *J* = 12.8, 9.1, 6.6 Hz, 1H), 1.78 – 1.61 (m, 2H), 1.55 – 1.40 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 444.1 $[M+H]^+$.

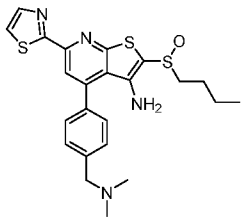


[00240] SW209511 4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzyl acetate. This compound was formed during the workup

of SW209510 in EtOAc (47 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.87 (d, *J* = 3.2 Hz, 1H), 7.56 – 7.40 (m, 5H), 5.18 (s, 2H), 4.62 (s, 2H), 3.26 (ddd, *J* = 12.8, 9.0, 6.1 Hz, 1H), 3.08 (ddd, *J* = 12.8, 9.1, 6.6 Hz, 1H), 2.14 (s, 3H), 1.77 – 1.59 (m, 2H), 1.53 – 1.37 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 486.1 $[M+H]^+$.

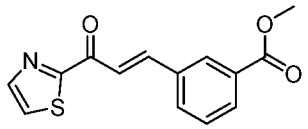


[00241] 4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzaldehyde. MnO_2 (111.3 mg, 1.28 mmol) was added to a solution of SW209510 (56.8 mg, 0.128 mmol) in DCM (2.3 mL) and stirred at room temperature overnight. LC/MS indicated that the reaction was incomplete. The reaction was filtered over celite, washed with DCM and the filtrate was concentrated under reduced pressure. The crude mixture was redissolved in DCM (2.3 mL) and MnO_2 (5 eq) was added. The solution was left to stir 24 hours at room temperature, was filtered over celite and washed with DCM. The filtrate was concentrated under reduced pressure and the resulting crude product was purified using automated flash chromatography (55 % EtOAc, 45 % hexanes) resulting in 24 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.11 – 7.99 (m, 3H), 7.92 (d, *J* = 3.1 Hz, 1H), 7.75 – 7.62 (m, 2H), 7.51 (d, *J* = 3.2 Hz, 1H), 4.56 (s, 2H), 3.29 (ddd, *J* = 12.8, 8.8, 6.3 Hz, 1H), 3.11 (ddd, *J* = 12.8, 8.9, 6.9 Hz, 1H), 1.82 – 1.66 (m, 2H), 1.54 – 1.41 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 442.1 $[M+H]^+$.

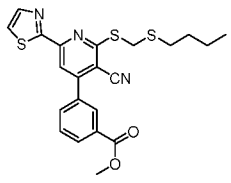


[00242] SW209513. 2-(butyl(l1-oxidanyl)-l3-sulfanyl)-4-(4-((dimethylamino)methyl)phenyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-3-amine. To a solution of 4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzaldehyde (13.3 mg, 0.0301) in methanol (802.7 µL), dimethylamine (174 µL,

0.301 mmol, 2.0M in THF) and acetic acid (1.72 μL, 0.0301 mmol) were added and the reaction was stirred at room temperature for 90 minutes. The reaction was then cooled down to 0°C and sodium cyanoborohydride (3.7 mg, 0.060 mmol) was added and the reaction stirred for 2 hours at this temperature before allowing to warm up to room temperature. After 24 hours, more sodium cyanoborohydride (2 eq) was added at 0°C and left to stir at room temperature another 24 hours. Nitrogen was used to evaporate the solvent, giving a solid that was diluted with EtOAc and washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using flash chromatography (7 % MeOH, 93 % DCM) isolating the product in 13 % yield. ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.07 (s, 1H), 7.93 (d, J = 3.2 Hz, 1H), 7.51 (d, J = 3.2 Hz, 1H), 7.49 – 7.41 (m, 4H), 4.67 (s, 2H), 3.55 (s, 2H), 3.36 – 3.25 (m, 1H), 3.13 (ddd, J = 12.8, 9.0, 6.7 Hz, 1H), 2.30 (s, 6H), 1.78 – 1.68 (m, 2H), 1.55 – 1.44 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 471.2 $[M+H]^+$.

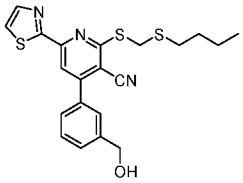


[00243] Methyl (E)-3-(3-oxo-3-(thiazol-2-yl)prop-1-en-1-yl)benzoate. Followed procedure for methyl (E)-4-(3-oxo-3-(thiazol-2-yl)prop-1-en-1-yl)benzoate using methyl 3-formyl benzoate as the starting material. Purified the crude product using automated flash chromatography (50 % EtOAc, 50 % hexanes) isolating the product in 51 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.35 (m, 1H), 8.11 – 8.05 (m, 2H), 8.02 (d, J = 1.3 Hz, 2H), 7.89 – 7.83 (m, 1H), 7.72 (d, J = 3.0 Hz, 1*H*), 7.50 (t, J = 7.8 Hz, 1H), 3.95 (s, 3H). ESI-MS (m/z): 274.1

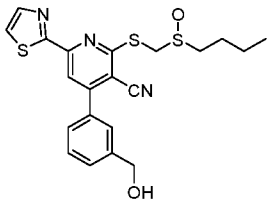


[00244] Methyl 3-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate. Followed the procedure for methyl 4-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate using methyl (E)-3-(3-oxo-3-(thiazol-2-yl)prop-1-en-1-yl)benzoate as the starting material. Isolated product in 87 % yield. ^{1}H NMR (400 MHz,

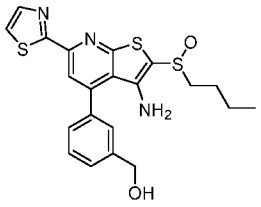
$CDCl_3$) δ 8.32 – 8.26 (m, 1H), 8.20 (dt, *J* = 7.9, 1.3 Hz, 1H), 8.04 (s, 1H), 7.99 (d, *J* = 3.1 Hz, 1H), 7.85 (ddd, *J* = 7.7, 2.0, 1.1 Hz, 1H), 7.62 (td, *J* = 7.8, 0.6 Hz, 1H), 7.58 (d, *J* = 3.1 Hz, 1H), 4.53 (s, 2H), 3.95 (s, 3H), 2.76 (t, *J* = 7.3 Hz, 2H), 1.71 – 1.59 (m, 2H), 1.49 – 1.36 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 456.1 $[M+Z]^+$.



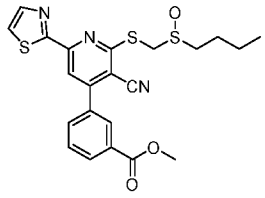
[00245] 2-(((butylthio)methyl)thio)-4-(3-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile. Followed procedure for 2-(((butylthio)methyl)thio)-4-(4-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile using methyl 3-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate as the starting material. Isolated product in 84 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.95 (d, *J* = 3.1 Hz, 1H), 7.64 – 7.61 (m, 1H), 7.58 – 7.52 (m, 2H), 7.52 – 7.46 (m, 2H), 4.76 (s, 2H), 4.50 (s, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 1.69 – 1.54 (m, 2H), 1.46-1.37 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 428.1 $[M+H]^+$



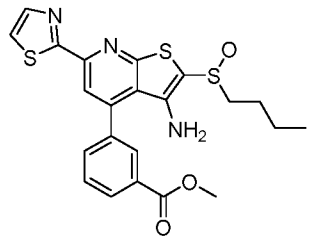
[00246] 2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-4-(3-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile. Followed standard oxidation procedure using 2-(((butylthio)methyl)thio)-4-(3-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile as the starting material. Isolated product in 88 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.96 (d, *J* = 3.1 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.58 – 7.53 (m, 2H), 7.53 – 7.48 (m, 2H), 4.77 (s, 2H), 4.71 (d, *J* = 13.1 Hz, 1H), 4.36 (d, *J* = 13.1 Hz, 1H), 2.96 (dt, *J* = 13.0, 8.2 Hz, 1H), 2.81 (dt, *J* = 13.0, 7.3 Hz, 1H), 1.82 (p, *J* = 7.7 Hz, 2H), 1.58 – 1.40 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 444.1 $[M+H]^+$.



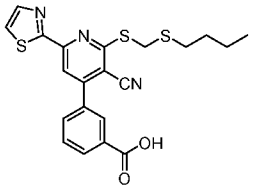
[00247] SW209418 (3-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)phenyl)methanol. Followed procedure for SW209510 using 2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-4-(3-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile as the starting material to give an isolated product in 68 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.88 (d, *J* = 3.1 Hz, 1H), 7.55 – 7.30 (m, 5H), 4.75 (s, 2H), 4.62 (s, 2H), 3.26 (ddd, *J* = 12.8, 9.1, 6.0 Hz, 1H), 3.09 (ddd, *J* = 12.8, 9.2, 6.5 Hz, 1H), 1.76 – 1.61 (m, 2H), 1.51 – 1.38 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 444.1 $[M+H]^+$.



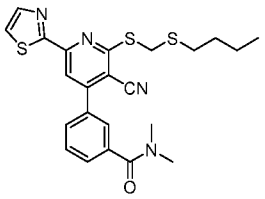
[00248] Methyl 3-(2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate. Followed standard oxidation procedure, using methyl 3-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate as the starting material. This gave an isolated product in 86 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (t, *J* = 1.6 Hz, 1H), 8.17 (dt, *J* = 7.9, 1.4 Hz, 1H), 8.09 (s, 1H), 7.97 (d, *J* = 3.1 Hz, 1H), 7.82 (ddd, *J* = 7.7, 1.9, 1.1 Hz, 1H), 7.61 (m, 1H), 7.58 (d, *J* = 3.1 Hz, 1H), 4.72 (d, *J* = 13.1 Hz, 1H), 4.42 (d, *J* = 13.1 Hz, 1H), 3.92 (s, 3H), 2.95 (dt, *J* = 13.0, 8.1 Hz, 1H), 2.83 (dt, *J* = 13.0, 7.3 Hz, 1H), 1.81 (p, *J* = 7.7 Hz, 2H), 1.57 – 1.36 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 472.1 $[M+H]^+$.



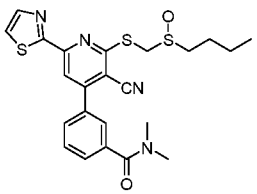
[00249] SW209416. Methyl 3-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzoate. Followed procedure for SW209510 using methyl 3-(2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate as the starting material to give an isolated product in 68 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.11 (m, 2H), 8.02 (s, 1H), 7.89 (d, *J* = 3.2 Hz, 1H), 7.76 – 7.56 (m, 2H), 7.49 (d, *J* = 3.1 Hz, 1H), 4.54 (s, 2H), 3.93 (s, 3H), 3.27 (ddd, *J* = 12.8, 9.0, 6.2 Hz, 1H), 3.09 (ddd, *J* = 12.8, 9.0, 6.7 Hz, 1H), 1.79 – 1.61 (m, 2H), 1.55 – 1.39 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 472.1 $[M+H]^+$.



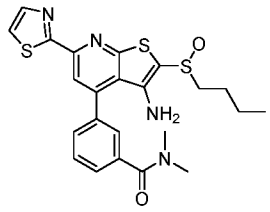
[00250] Standard Hydrolysis Procedure of Ester to Carboxylic Acid: 3-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoic acid. THF (214.3 μL), MeOH (214.3 μL), and H_2O (71.4 μL) were added to methyl 3-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate (50 mg, 0.110 mmol), and last LiOH (7.9 mg, 0.329 mmol) was added. The solution was stirred at room temperature for 3 hours. The reaction mixture was diluted with EtOAc and washed with 1M HCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting product gave a 94 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (t, *J* = 1.7 Hz, 1H), 8.26 (dt, *J* = 8.0, 1.3 Hz, 1H), 8.13 (s, *1*H), 8.02 (d, *J* = 3.1 Hz, 1*H*), 7.94 – 7.89 (m, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 3.1 Hz, 1H), 4.53 (s, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 1.64 (p, *J* = 7.5 Hz, 2H), 1.43 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). E*S*I-MS (m/z): 442.1 $[M+Z]^+$.



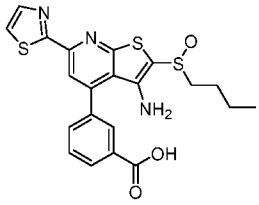
[00251] Standard amide bond coupling procedure: 3-(2-(((butylt^{hi}o)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)-N,N-dimethylbenzamide. Dimethylamine hydrochloride (9.25 mg, 0.114 mmol) was added to a solution of 3-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoic acid (45.6 mg, 0.103 mmol), HATU (43.2 mg, 0.114 mmol), and DMF (266 μL) followed by DIPEA (36 μL, 0.21 mmol). The solution was stirred at room temperature for 3 hours, then diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The isolated solid gave an 86 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.97 (d, *J* = 3.1 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.58 – 7.51 (m, 3H), 4.50 (s, 2H), 3.11 (s, 3H), 3.03 (s, 3H), 2.73 (t, *J* = 7.3 Hz, 2H), 1.62 (p, *J* = 7.4 Hz, 2H), 1.40 (h, *J* = 7.3 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 469.1 $[M+H]^+$.



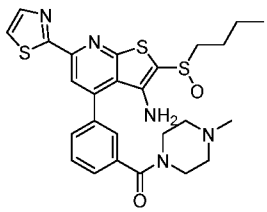
[00252] 3-(2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)-N,N-dimethylbenzamide. Followed standard oxidation procedure, using 3-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)-N,N-dimethylbenzamide as the starting material to give the isolated product in 96 % yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.98 (d, *J* = 3.1 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.61 – 7.54 (m, 3H), 4.70 (d, *J* = 13.1 Hz, 1H), 4.42 (d, *J* = 13.1 Hz, 1H), 3.11 (s, 3H), 3.03 (s, 3H), 2.95 (dt, *J* = 12.9, 8.2 Hz, 1H), 2.81 (dt, *J* = 12.9, 7.2 Hz, 1H), 1.82 (p, *J* = 7.7 Hz, 2H), 1.56 – 1.36 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 485.1 $[M+H]^+$.



[00253] SW209417. 3-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)-N,N-dimethylbenzamide. Followed procedure for SW209510 using 3-(2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)-N,N-dimethylbenzamide as the starting material to give the isolated product in 63 % yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.90 (d, *J* = 3.1 Hz, 1H), 7.62 – 7.51 (m, 4H), 7.49 (d, *J* = 3.1 Hz, 1H), 4.59 (s, 2H), 3.27 (ddd, *J* = 12.8, 9.0, 6.1 Hz, 1H), 3.15 – 2.97 (m, 7H), 1.78 – 1.64 (m, 2H), 1.55 – 1.39 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

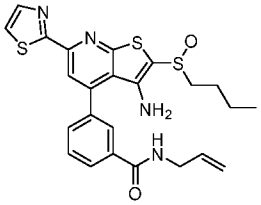


[00254] SW209419. 3-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzoic acid. Using SW209416 as the starting material, follow the standard hydrolysis procedure of ester to carboxylic acid. This gave an isolated yield of 98 %. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.28 – 8.18 (m, 2H), 8.07 (s, 1H), 7.98 (d, *J* = 3.2 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 3.2 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 4.82 (s, 2H), 3.20 (ddd, *J* = 12.8, 8.8, 6.3 Hz, 1H), 3.09 (ddd, *J* = 12.9, 8.8, 6.8 Hz, 1H), 1.76 – 1.66 (m, 2H), 1.54 – 1.43 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 458.1 $[M+H]^+$.

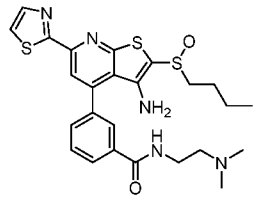


[00255] SW209420. (3-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)phenyl)(4-methylpiperazin-1-yl)methanone. Followed the

standard amide bond coupling procedure, using SW209419 as the starting material and 1-methylpiperazine as the substrate. The product was purified using automated flash chromatography, recovering 38 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.65 – 7.42 (m, 5H), 4.56 (s, 2H), 3.79 (m, 2H), 3.46 (m, 2H), 3.28 (ddd, *J* = 12.9, 8.9, 6.1 Hz, 1H), 3.10 (ddd, *J* = 12.9, 9.2, 7.0 Hz, 1H), 2.48 (m, 2H), 2.35 (m, 2H), 2.31 (s, 3H), 1.77 – 1.58 (m, 2H), 1.54 – 1.38 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 540.2 $[M+H]^+$.

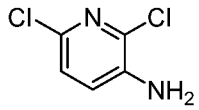


[00256] SW209508. N-allyl-3-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzamide. Followed the standard amide bond coupling procedure using SW209419 as the starting material and allylamine as the substrate. The isolated product gave a 92 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.91 (m, 3H), 7.88 (d, *J* = 3.2 Hz, 1H), 7.68 – 7.53 (m, 2H), 7.48 (d, *J* = 3.1 Hz, 1H), 6.01 – 5.82 (m, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.16 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.52 (s, 2H), 4.19 – 3.98 (m, 2H), 3.24 (ddd, *J* = 12.8, 9.0, 5.9 Hz, 1H), 3.16 – 2.98 (m, 1H), 1.78 – 1.56 (m, 2H), 1.57 – 1.38 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 497.1 $[M+H]^+$.

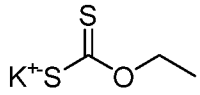


[00257] SW209509. 3-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)-N-(2-(dimethylamino)ethyl)benzamide. Followed the standard amide bond coupling procedure, using SW209419 as the starting material and N,n-dimethyl-ethane-1,2-diamine as the substrate. The reaction mixture was diluted with EtOAc and washed with water and NaOH was added to neutralize the pH. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was

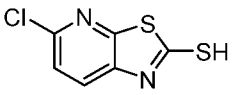
purified using automated flash chromatography (93 % DCM, 2 % Et_3N, 5 % MeOH) to give product in 70 % isolated yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 8.00 – 7.95 (m, 2H), 7.88 (d, *J* = 3.2 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.48 (d, *J* = 3.2 Hz, 1H), 4.55 (s, 2H), 3.59 – 3.50 (m, 2H), 3.25 (ddd, *J* = 12.8, 9.0, 6.0 Hz, 1H), 3.08 (ddd, *J* = 12.8, 9.1, 6.6 Hz, 1H), 2.58 (t, *J* = 5.9 Hz, 2H), 2.28 (s, 6H), 1.77 – 1.61 (m, 2H), 1.53 – 1.43 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 528.2 $[M+H]^+$.



[00258] 2,6-dichloropyridin-3-amine. The acetone/water mixture (297 mL, 5:1) was added to 2,6-dichloro-3-nitropyridine (3.0 g, 0.016 mol) followed by Zn (10.17 g, 0.1550 mol) and NH_4Cl (12.44 g, 0.2325 mol). The solution stirred at room temperature overnight. The reaction mixture was then filtered through celite and the filtrate was extracted with EtOAc. With the help of brine, the organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 4.11 (s, 2H). ESI-MS (m/z): 163.0.

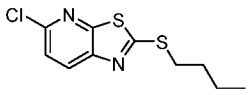


[00259] Potassium Ethyl Xanthate. A potassium ethoxide solution was prepared by dissolving KOH (6.5 g, 0.12 mol) in EtOH (63.4 mL). Carbon disulfide (7.14 mL, 0.118 mol) was added to the solution slowly with continuous stirring. The reaction mixture was cooled down to 5 °C, filtered, and the precipitate was recrystallized twice from warm ethanol.

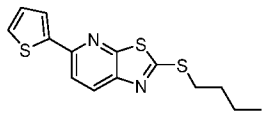


[00260] 5-Chlorothiazolo[5,4-b]pyridine-2-thiol. Potassium ethyl xanthate (1.9 g, 0.012 mol) and anhydrous N-methyl-2-pyrrolidone (14.1 mL) were added to 2,6-dichloropyridin-3-amine (1.0 g, 0.0061 mol) under N_2. The solution was refluxed (170°C) for 3.5 hours. The reaction mixture was cooled down to room temperature, acidified to pH 5 using AcOH, diluted in EtOAc, and washed several times with H_2O. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. This gave a red solid in 18 %

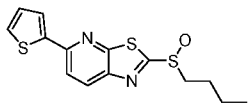
yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H). ESI-MS (m/z): 202.9.



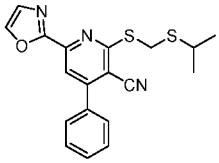
[00261] 2-(Butylthio)-5-chlorothiazolo[5,4-b]pyridine. K_2CO_3 (75 mg, 0.54 mmol), 1-bromobutane (53.3 μL, 0.493 mmol), 18-Crown-6 (13.2 mg, 0.0493 mmol), and DMF (3.4 mL) were added to 5-chlorothiazolo[5,4-b]pyridine-2-thiol and the solution was heated at 80°C for 3 hours. The solution was diluted with EtOAc, washed with H_2O, and the organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified using flash chromatography to give 76 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 3.31 (t, *J* = 7.3 Hz, 2H), 1.76 (p, *J* = 7.5 Hz, 2H), 1.52 – 1.39 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 259.0 $[M+H]^+$.



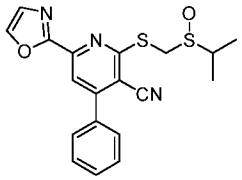
[00262] 2-(Butylthio)-5-(thiophen-2-yl)thiazolo[5,4-b]pyridine. 2-Thienylboronic acid (49.4 mg, 0.386 mmol), $CsCO_3$ (126 mg, 0.386 mmol), $Pd(dppf)Cl_2$ (15.8 mg, 0.0193 mmol), CuCl (19.1 mg, 0.193 mmol) and DMF (1 mL) were added to 2-(butylthio)-5-chlorothiazolo[5,4-b]pyridine (50 mg, 0.19 mmol) under N_2. The reaction mixture was heated to 100°C for 30 minutes. Then the N_2 was disconnected and the vial was capped and sealed with teflon tape and allowed to stir overnight. The reaction mixture was diluted in EtOAc, washed with H_2O, and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the product in 31 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.6 Hz, 1H), 7.63 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.51 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.24 (t, *J* = 7.3 Hz, 2H), 1.78 – 1.66 (m, 2H), 1.57 – 1.41 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 307.0 $[M+H]^+$.



[00263] SW208599. 2-(butyl(l1-oxidanyl)-l3-sulfanyl)-5-(thiophen-2-yl)thiazolo[5,4-b]pyridine. $CHCl_3$ (142 μL), AcOH (142 μL), and H_2O_2 (12.0 μL, 0.118 mmol, 30 % solution in H_2O) were added to 2-(butylthio)-5-(thiophen-2-yl)thiazolo[5,4-b]pyridine (18 mg. 0.059 mmol) and heated at 35ºC for 2.5 hours. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give product in 60 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.61 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.19 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.15 (ddd, *J* = 13.3, 9.8, 6.0 Hz, 1H), 2.96 (ddd, *J* = 13.3, 9.9, 4.9 Hz, 1H), 1.98 – 1.80 (m, 1H), 1.60 – 1.52 (m, 1H), 1.52 – 1.37 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ESI-MS (m/z): 323.0 $[M+H]^+$.

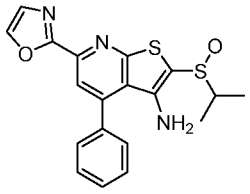


[00264] 2-(((Isopropylthio)methyl)thio)-6-(oxazol-2-yl)-4-phenylnicotinonitrile. Follow the standard alkylation procedure, using (chloromethyl)(isopropyl)sulfane as the alkylating substrate, and 6-(oxazol-2-yl)-4-phenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile as the starting material. The crude product was purified using flash chromatography to give a solid in 62 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.88 (d, *J* = 0.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.56 – 7.50 (m, 3H), 7.37 (d, *J* = 0.8 Hz, 1H), 4.63 (s, 2H), 3.24 (hept, *J* = 6.7 Hz, 1H), 1.35 (d, *J* = 6.7 Hz, 6H). ESI-MS (m/z): 368.0 $[M+H]^+$.

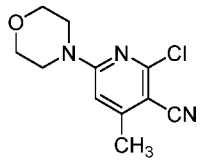


[00265] 2-(((Isopropyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-6-(oxazol-2-yl)-4-phenylnicotinonitrile. Follow the standard oxidation procedure using 2-(((isopropylthio)methyl)thio)-6-(oxazol-2-yl)-4-phenylnicotinonitrile as the starting material.

Recovered quatitative isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.88 (d, *J* = 0.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.58 – 7.50 (m, 3H), 7.39 (d, *J* = 0.7 Hz, 1H), 4.79 (d, *J* = 13.3 Hz, 1H), 4.55 (d, *J* = 13.3 Hz, 1H), 3.18 (hept, *J* = 6.9 Hz, 1H), 1.42 (d, *J* = 1.5 Hz, 3H), 1.40 (d, *J* = 1.3 Hz, 3H). ESI-MS (m/z): 384.1 $[M+H]^+$.

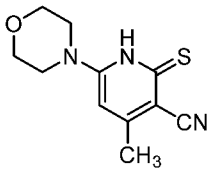


[00266] Standard Final Cyclization Procedure: SW208660. 2-(Isopropyl(l1-oxidanyl)-l3-sulfanyl)-6-(oxazol-2-yl)-4-phenylthieno[2,3-b]pyridin-3-amine. DMF (485 μL) and MeOH (244 μL) were added to 2-(((isopropyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-6-(oxazol-2-yl)-4-phenylnicotinonitrile (47.2 mg, 0.123 mmol) dissolving it completely before KOH (4.1 mg in 100 μL of H_2O) was added to the solution. The reaction mixture was stirred at 35°C for 40 minutes. The reaction mixture was diluted with EtOAc, washed with 10 % AcOH and then washed with H_2O multiple times. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified using flash chromatography to give product in 40 % isolated yield^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.85 (d, J = 0.7 Hz, 1H), 7.56 – 7.44 (m, 5H), 7.34 (d, J = 0.8 Hz, 1H), 4.69 (s, 2H), 3.41 (hept, J = 6.8 Hz, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H). ESI-MS (m/z): 384.1 $[M+H]^+$.

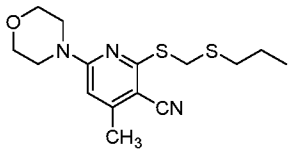


[00267] 2-Chloro-4-methyl-6-morpholinonicotinonitrile. Anhydrous MeOH (3.97 mL) was added to 2,6-dichloro-4-methylnicotinonitrile (500 mg, 2.67 mmol) under N_2 and the mixture was cooled down to 0°C. Morpholine (473.7 μL, 5.493 mmol) was added dropwise to the solution and the solution stirred at room temperature overnight. The reaction mixture was filtered, washing the precipitate with MeOH (500 μL) and H_2O (3-4 mL). DCM was added to the precipitate, followed by $MgSO_4$, and the solution was filtered, then concentrated under reduced pressure. The crude producte was purified using automated flash chromatography to

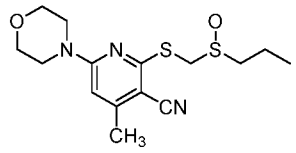
give product in 85 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 3.81 – 3.73 (m, 4H), 3.68 – 3.58 (m, 4H), 2.42 (d, J = 0.8 Hz, 3H). ESI-MS (m/z): 238.1 $[M+H]^+$.



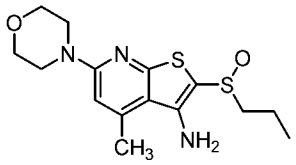
[00268] 4-Methyl-6-morpholino-2-thioxo-1,2-dihydropyridine-3-carbonitrile. NaOME (73.6 mg, 1.36 mmol) and methyl 3-mercapiopropionate (151 µL, 1.363 mmol) were added to a solution of 2-chloro-4-methyl-6morpholinonicotinonitrile (324 mg, 1.36 mmol) in DMF (4.10 mL) and the reaction mixture was stirred at 80°C for 1 hour. Once cooled down, the reaction mixture was diluted with EtOAc and washed with H_2O. The organic layer was separated, dried over MgSO4, filtered, and concentrated under reduced pressure to give a crude mixture of 1:1 starting material to product, which was carried forward to the next step. ESI (m/z): 322.1 [M+H]+. NaH (150.8 mg, 3.769 mmol, 60 % in mineral oil) and THF (10 mL) were added to a flame dried flask under N2, followed by the crude product from the previous step dissolved in THF (10 mL). The reaction mixture was refluxed for 6 hours and addition NaH (2 eq) was and left refluxing overnight. EtOH (1.5 mL) was added then the reaction mixture was concentrated down under reduced pressure. H_2O (8 mL) was added and the solution was adjusted to pH 6 with concentrated HCl before filtering to leave a crude solid that was carried forward. ESI (m/z): 236.1 [M+H]+.



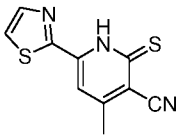
[00269] 4-Methyl-6-morpholino-2-(((propylthio)methyl)thio)nicotinonitrile. Followed the standard alkylating procedure, using 4-methyl-6-morpholino-2-thioxo-1,2-dihydropyridine-3-carbonitrile as the starting material and (chloromethyl)(propyl)sulfane as the alkylating substrate. The crude product was carried forward. ESI (m/z): 324.1 [M+H]+.



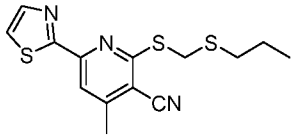
[00270] 2-((((l1-oxidanyl)(propyl)-l3-sulfanyl)methyl)thio)-4-methyl-6-morpholinonicotinonitrile. Followed the standard oxidation procedure using 4-methyl-6-morpholino-2-(((propylthio)methyl)thio)nicotinonitrile as the starting material. The crude product was carried forward. ESI (m/z): 340.1 $[M+H]^+$.



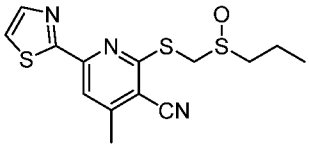
[00271] SW208663. 2-((l1-oxidanyl)(propyl)-l3-sulfanyl)-4-methyl-6-morpholinothieno[2,3-b]pyridin-3-amine. Followed the standard final cyclization procedure using 2-((((l1-oxidanyl)(propyl)-l3-sulfanyl)methyl)thio)-4-methyl-6-morpholinonicotinonitrile as the starting material. The crude product was purified by flash chromatography, and PTLC to give isolated product in 10 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 4.91 (s, 2H), 3.85 – 3.76 (m, 4H), 3.63 – 3.58 (m, 4H), 3.32 – 3.18 (m, 1H), 3.09 – 2.99 (m, 1H), 2.65 (s, 3H), 1.81 – 1.66 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H). ESI (m/z): 340.1 $[M+H]^+$.



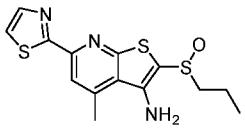
[00272] 4-Methyl-6-(thiazol-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile. Followed same procedure as 4-Methyl-6-morpholino-2-thioxo-1,2-dihydropyridine-3-carbonitrile, using methyl 3-((3-cyano-4-methyl-6-(thiazol-2-yl)pyridin-2-yl)thio)propanoate as the starting material. The crude product was carried forward. ESI-MS (m/z): 234.0 $[M+H]^+$.



[00273] 4-Methyl-2-(((propylthio)methyl)thio)-6-(thiazol-2-yl)nicotinonitrile. Followed the standard alkylation procedure using 4-Methyl-6-(thiazol-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile as the starting material, and (chloromethyl)(propyl)sulfane as the alkylating substrate. The crude product was purified using automated flash chromatography to give product in 23 % isolated yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 3.1 Hz, 1H), 7.83 (s, 1H), 7.54 (d, *J* = 3.1 Hz, 1H), 4.47 (s, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.55 (s, 3H), 1.67 (h, *J* = 7.3 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 322.0 {M+H]$^+$.

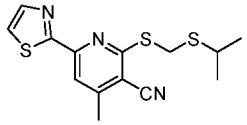


[00274] 2-((((l1-oxidanyl)(propyl)-l3-sulfanyl)methyl)thio)-4-methyl-6-(thiazol-2-yl)nicotinonitrile. Followed the standard oxidation procedure using 4-methyl-2-(((propylthio)methyl)thio)-6-(thiazol-2-yl)nicotinonitrile as the starting material to give white solid in 91 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 3.1 Hz, 1H), 7.92 (s, 1H), 7.56 (d, *J* = 3.2 Hz, 1H), 4.74 (d, *J* = 13.2 Hz, 1H), 4.44 (d, *J* = 13.1 Hz, 1H), 2.89 (m, 2H), 2.57 (s, 3H), 1.93 – 1.79 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 338.0 [M+H]$^+$.

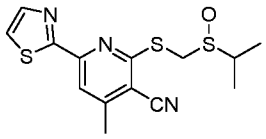


[00275] SW208661. 2-((l1-oxidanyl)(propyl)-l3-sulfanyl)-4-methyl-6-(thiazol-2-yl)thieno[2,3-b]pyridin-3-amine. Followed standard final cyclization procedure using 2-((((l1-oxidanyl)(propyl)-l3-sulfanyl)methyl)thio)-4-methyl-6-(thiazol-2-yl)nicotinonitrile as the starting material. Purified the crude product using flash chromatography to give 61 % bright green isolated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.93 (d, *J* = 3.2

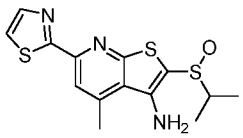
Hz, 1H), 7.48 (d, *J* = 3.2 Hz, 1H), 5.16 (s, 2H), 3.37 – 3.23 (m, 1H), 3.16 – 3.05 (m, 1H), 2.85 (s, 3H), 1.83 (h, *J* = 7.5 Hz, 2H), 1.11 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 338.0 $[M+H]^+$.



[00276] 2-(((isopropylthio)methyl)thio)-4-methyl-6-(thiazol-2-yl)nicotinonitrile. Followed standard alkylating procedure using (chloromethyl)(isopropyl)sulfane as the alkylating substrate and 4-methyl-6-(thiazol-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile as the starting material. Purified using automated flash chromatography to give product in 32 % isolated yield. ^{1}H NMR (400 MHz, CDCl3) δ 7.94 (d, J = 3.2 Hz, 1H), 7.82 (s, 1H), 7.52 (d, J = 3.2 Hz, 1H), 4.48 (s, 2H), 3.18 (hept, J = 6.6 Hz, 1H), 2.54 (s, 3H), 1.31 (d, J = 6.7 Hz, 6H). ESI-MS (m/z): 322.0 [M+H]+.

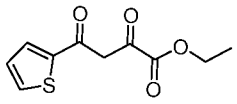


[00277] 2-(((isopropyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-4-methyl-6-(thiazol-2-yl)nicotinonitrile. Followed standard oxidation procedure using 2-(((isopropylthio)methyl)thio)-4-methyl-6-(thiazol-2-yl)nicotinonitrile as the starting material to give a solid product in 84 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 3.1 Hz, 1H), 7.91 (s, 1H), 7.56 (d, *J* = 3.1 Hz, 1H), 4.57 (d, *J* = 13.3 Hz, 1H), 4.46 (d, *J* = 13.3 Hz, 1H), 3.05 (hept, *J* = 6.9 Hz, 1H), 2.57 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.36 (d, *J* = 6.7 Hz, 3H). ESI-MS (m/z): 338.0 $[M+H]^+$.

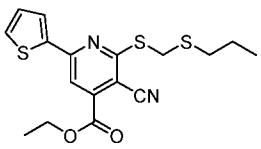


[00278] SW208664. 2-(Isopropyl(l1-oxidanyl)-l3-sulfanyl)-4-methyl-6-(thiazol-2-yl)thieno[2,3-b]pyridin-3-amine. Followed standard final cyclization procedure using 2-(((isopropyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-4-methyl-6-(thiazol-2-yl)nicotinonitrile as

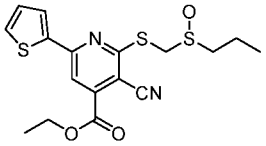
the starting material. The crude product was purified using flash chromatography to give bright green oil/solid in 48 % isolated yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (s, 1H), 7.92 (d, *J* = 3.2 Hz, 1H), 7.46 (d, *J* = 3.2 Hz, 1H), 3.38 (hept, *J* = 6.9 Hz, 1H), 2.84 (s, 3H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.8 Hz, 3H). ESI-MS (m/z): 338.0 $[M+H]^+$.



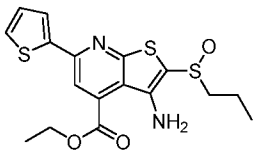
[00279] Ethyl 2,4-dioxo-4-(thiophen-2-yl)butanoate. 2-Acetylthiophene (1.71 mL, 0.0159 mol) was added to a solution of NaOEt (730 mg Na cubes in 50 mL of EtOH) and the solution was cooled to 0°C for 1-2 hours then diethyl oxylate (3.2 ^{m}L) was added to the solution. This was left to stir at room temperature overnight. The reaction mixture was diluted with EtOAc and H_2O with a little brine to assist the separation. The organic layer was collected, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified using automated flash chromatography giving an oil product with 23 % yield. ESI-MS (m/z): 227.0 $[M+H]^+$.



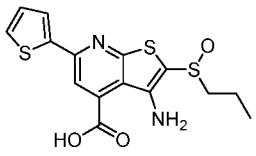
[00280] Ethyl 3-cyano-2-(((propylthio)methyl)thio)-6-(thiophen-2-yl)isonicotinate. 2-Cyanothioacetamide (250.6 mg, 2.503 mmol) and ethyl 2,4-dioxo-4-(thiophen-2-yl)butanoate (565.7 mg, 2.503 mmol) were dissolved in EtOH (7.46 mL) under gentle heating (40°C), then Et_3N (174.5 μL, 1.251 mmol) was added drop wise to the stirring solution. The reaction mixture was heated at 60°C and after 3 hours was concentrated down under reduced pressure and the crude product was carried forward to the next step. Followed standard alkylating procedure using ethyl 3-cyano-6-(thiophen-2-yl)-2-thioxo-1,2-dihydropyridine-4-carboxylate as the starting material and (chloromethyl)(propyl)sulfane as the alkylating reagent. The crude product was purified twice using automated flash chromatography (20 % EtOAc, 80 % hexanes) to give 34 % isolated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.60 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.44 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.04 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.32 (s, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 1.57 (h, *J* = 7.4 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 378.9 $[M+H]^+$.



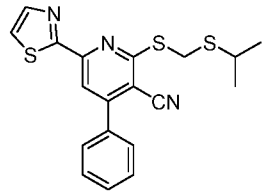
[00281] Ethyl 2-((((l1-oxidanyl)(propyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiophen-2-yl)isonicotinate. Followed standard oxidation procedure using ethyl 3-cyano-2-(((propylthio)methyl)thio)-6-(thiophen-2-yl)isonicotinate as the starting material to give a solid with quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.72 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.53 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.11 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.68 (d, *J* = 13.2 Hz, 1H), 4.49 (d, *J* = 13.2 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.96 – 2.82 (m, 2H), 1.87 – 1.75 (m, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 394.9 $[M+H]^+$.



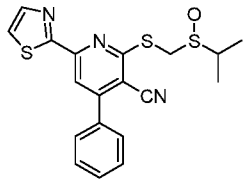
[00282] SW208781. Ethyl 2-((l1-oxidanyl)(propyl)-l3-sulfanyl)-3-amino-6-(thiophen-2-yl)thieno[2,3-b]pyridine-4-carboxylate. t-BuOK (74.1 mg, 0.661 mmol) was added to a solution of ethyl 2-((((l1-oxidanyl)(propyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiophen-2-yl)isonicotinate (433.7 mg, 1.101 mmol) in DMF (4.3 mL) and the solution stirred for 40 minutes at 35°C. More t-BuOK (74.1 mg, 0.661 mmol) was added and allowed to stir at 35°C for an hour. The reaction mixture was diluted with EtOAc and washed with 10 % AcOH, and then multiple times with H_2O. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified using flash chromatography to give product in 30 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.69 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.46 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.11 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.09 (s, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.36 – 3.22 (m, 1H), 3.15 – 3.00 (m, 1H), 1.87 – 1.68 (m, 2H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.4 Hz, 3H).ESI-MS (m/z): 394.9 $[M+H]^+$.



[00283] SW208782. 2-((11-oxidanyl)(propyl)-13-sulfanyl)-3-amino-6-(thiophen-2-yl)thieno[2,3-b]pyridine-4-carboxylic acid. Followed the standard hydrolysis procedure using SW208781 as the starting material which gave product in 40 % isolated yield. ^{1}H NMR (400 MHz, C_3D_7NO) δ 8.56 (s, 1H), 8.29 (d, *J* = 3.7 Hz, 1H), 8.19 (s, 1H), 7.99 (d, *J* = 5.0 Hz, 1H), 7.47 – 7.41 (m, 1H), 3.36 (ddd, *J* = 12.8, 8.4, 6.1 Hz, 1H), 3.24 (ddd, *J* = 12.8, 8.6, 6.8 Hz, 1H), 1.98 – 1.85 (m, 2H), 1.23 (t, *J* = 7.4 Hz, 3H). ESI-MS (m/z): 366.8.

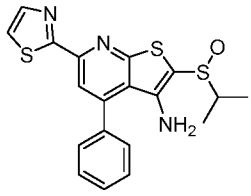


[00284] 2-(((isopropylthio)methyl)thio)-4-phenyl-6-(thiazol-2-yl)nicotinonitrile. Followed the standard alkylation procedure using 4-phenyl-6-(thiazol-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile as the starting material and (chloromethyl)(isopropyl)sulfane as the alkylating reagent. This was purified using automated flash chromatography to give product in 72 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.98 (d, *J* = 3.1 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.57 (d, *J* = 3.1 Hz, 1H), 7.56 – 7.48 (m, 3H), 4.56 (s, 2H), 3.24 (hept, *J* = 6.7 Hz, 1H), 1.36 (d, *J* = 6.7 Hz, 6H). ESI-MS (m/z): 383.9.

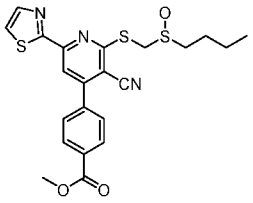


[00285] 2-(((isopropyl(11-oxidanyl)-13-sulfanyl)methyl)thio)-4-phenyl-6-(thiazol-2-yl)nicotinonitrile. Followed the standard oxidation procedure using 2-(((isopropylthio)methyl)thio)-4-phenyl-6-(thiazol-2-yl)nicotinonitrile as the starting material. This gave white solid product in 91 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.00 (d, *J* = 3.1 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.60 (d, *J* = 3.1 Hz, 1H), 7.58 – 7.51 (m, 3H),

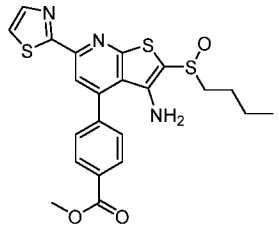
4.63 (d, *J* = 13.2 Hz, 1H), 4.48 (d, *J* = 13.2 Hz, 1H), 3.09 (hept, *J* = 6.9 Hz, 1H), 1.42 (d, *J* = 10.5 Hz, 3H), 1.39 (d, *J* = 10.5 Hz, 3H). ESI-MS (m/z): 399.9.



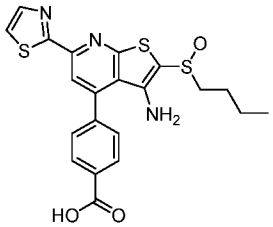
[00286] SW208780. 2-(isopropyl(11-oxidanyl)-13-sulfanyl)-4-phenyl-6-(thiazol-2-yl)thieno[2,3-b]pyridin-3-amine. t-BuOK (2.5 mg, 0.023 mmol) was added to a solution of 2-(((isopropyl(11-oxidanyl)-13-sulfanyl)methyl)thio)-4-phenyl-6-(thiazol-2-yl)nicotinonitrile (15 mg, 0.038 mmol) in DMF (148 μL), and stirred at 35°C for 40 minutes. The reaction mixture was diluted with EtOAc and washed with 10 % AcOH, then several times with H_2O. The organic layer was dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified using flash chromatography to give product` in 75 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.57 – 7.42 (m, 6H), 4.68 (s, 2H), 3.47 – 3.33 (m, 1H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 3H). ESI-MS (m/z): 399.9.



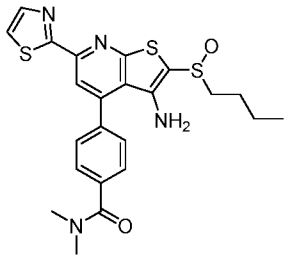
[00287] Methyl 4-(2-(((butyl(11-oxidanyl)-13-sulfanyl)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate. Followed standard oxidation procedure using methyl 4-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate as the starting material to give white solid in 98 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 2H), 8.05 (s, 1H), 7.95 (d, *J* = 3.1 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 3.1 Hz, 1H), 4.68 (d, *J* = 13.1 Hz, 1H), 4.42 (d, *J* = 13.1 Hz, 1H), 3.91 (s, 3H), 3.01 – 2.86 (m, 1H), 2.87 – 2.74 (m, 1H), 1.88 – 1.72 (m, 2H), 1.55 – 1.35 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 472.1 $[M+H]^+$.



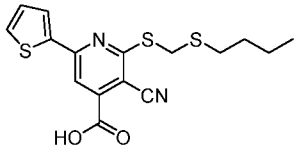
[00288] SW209127. Methyl 4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzoate. t-BuOK (21.8 mg, 0.194 mmol) was added to methyl 4-(2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)benzoate (152.8 mg, 0.3239 mmol) in DMF (1.30 mL) and the solution stirred at 35°C for 40 minutes. The reaction mixture was diluted with EtOAc and washed with 10 % AcOH, and several times with H_2O. The o^{r}ganic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude produc$_t$ was purified using automated flash chromatograph$_y$ t$_o$ give the bright green product in 66 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.5 Hz, 2H), 8.04 (s, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.67 – 7.54 (m, 2H), 7.50 (d, *J* = 3.2 Hz, 1H), 3.9$_7$ (s, 3H), 3.27 (ddd, *J* = 12.8, 8.9, 6.2 Hz, 1H), 3.10 (*d*dd, *J* = 12.8, 9.0, 6.8 Hz, 1H), 1.81 – 1.63 (m, 2H), 1.54 – 1.39 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 472.1 $[M+H]^+$.



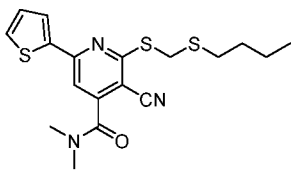
[00289] SW209281. 4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzoic acid. Followed standard hydrolysis procedure using SW209127 as the starting material to give bright green solid in 84 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 2H), 8.05 (s, 1H), 7.95 (d, *J* = 3.2 Hz, 1H), 7.68 – 7.55 (m, 2H), 7.52 (d, *J* = 3.2 Hz, 1H), 3.40 – 3.24 (m, 1H), 3.24 – 3.04 (m, 1H), 1.83 – 1.65 (m, 2H), 1.55 – 1.37 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 458.1 $[M+H]^+$.



[00290] SW209282. 4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)-N,N-dimethylbenzamide. Followed standard amide bond coupling procedure using SW209281 as the starting material and dimethylamine hydrochloride as the coupling reagent. The product was purified using automated flash chromatography (20 % hexane, 80 % EtOAc) to give bright green solid in 59 % isolated yield ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.66 – 7.44 (m, 5H), 3.36 – 3.21 (m, 1H), 3.14 (s, 3H), 3.13 – 3.06 (m, 1H), 3.02 (s, 3H), 1.81 – 1.64 (m, 2H), 1.55 – 1.41 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 485.1 $[M+H]^+$.

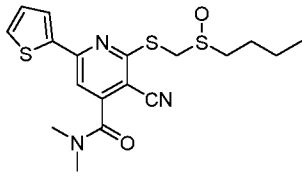


[00291] 2-(((butylthio)methyl)thio)-3-cyano-6-(thiophen-2-yl)isonicotinic acid. Followed standard hydrolysis procedure using ethyl 2-(((butylthio)methyl)thio)-3-cyano-6-(thiophen-2-yl)isonicotinate as the starting material to give isolated product in 94 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.95 (s, 1H), 7.76 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.57 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.17 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.46 (s, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 1.67 – 1.55 (m, 2H), 1.40 (h, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 365.0 $[M+H]^+$.

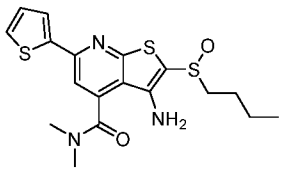


[00292] 2-(((butylthio)methyl)thio)-3-cyano-N,N-dimethyl-6-(thiophen-2-yl)isonicotinamide. Followed standard amide bond coupling procedure using 2-(((butylthio)methyl)thio)-3-cyano-6-(thiophen-2-yl)isonicotinic acid as the starting material and dimethylamine as the coupling reagent. The crude material was purified using automated

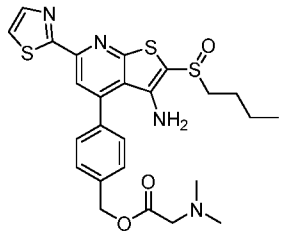
flash chromatography (20 % EtOAc, 80 % hexanes) to give product in 53 % isolated yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (d, *J* = 3.8 Hz, 1H), 7.54 (d, *J* = 5.0 Hz, 1H), 7.34 (s, 1H), 7.15 (t, *J* = 4.8, 3.9, 0.7 Hz, 1H), 4.49 (s, 2H), 3.16 (s, 3H), 2.98 (s, 3H), 2.72 (t, 2H), 1.62 (p, *J* = 7.7 Hz, 2H), 1.41 (h, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.7, 7.0 Hz, 3H). ESI-MS (m/z): 392.1 $[M+H]^+$.



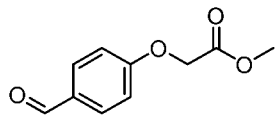
[00293] 2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-N,N-dimethyl-6-(thiophen-2-yl)isonicotinamide. Followed standard oxidation procedure using 2-(((butylthio)methyl)thio)-3-cyano-N,N-dimethyl-6-(thiophen-2-yl)isonicotinamide as the starting material to give solid product in 85 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 3.8 Hz, 1H), 7.54 (d, *J* = 5.0 Hz, 1H), 7.34 (s, 1H), 7.20-7.06 (m, 1H), 4.49 (s, 2H), 3.16 (s, 3H), 2.98 (s, 3H), 2.72 (t, 2H), 1.62 (p, *J* = 7.7 Hz, 2H), 1.41 (h, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.7, 7.0 Hz, 3H). ESI-MS (m/z): 408.1 $[M+H]^+$.



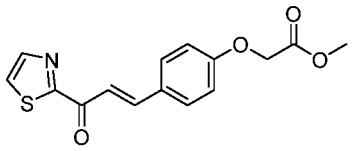
[00294] SW209283. 3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-N,N-dimethyl-6-(thiophen-2-yl)thieno[2,3-b]pyridine-4-carboxamide. t-BuOK (6.5 mg, 0.058 mmol) was added to a solution of 2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-N,N-dimethyl-6-(thiophen-2-yl)isonicotinamide (39.2 mg, 0.962 mmol) in DMF (380 μL) and the solution was heated at 35°C for 40 minutes. The reaction mixture was diluted with EtOAc and washed with 10 % AcOH, then several times with H_2O. The organic layer was separated and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was isolated using automated flash chromatography (20 % hexanes, 80 % EtOAc) to give the final product in 20 % isolated yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.13 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.34 – 3.23 (m, 1H), 3.21 (s, 3H), 3.15 – 3.02 (m, 1H), 2.96 (s, 3H), 1.79 – 1.62 (m, 2H), 1.55 – 1.36 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 408.1 $[M+H]^+$.



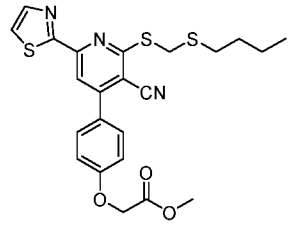
[00295] SW212366. 4-(3-amino-2-(butylsulfinyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)benzyl dimethylglycinate. N,N-Dimethylglycine (3.5 mg, 0.034 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (6.5 mg, 0.034 mmol), and DMAP (4.1 mg, 0.0334 mmol) were added to SW209510 (10 mg, 0.023 mmol) and dissolved in DMF (270 μL). The reaction mixture stirred at room temperature overnight, then neutralized with 1M NaOH, washed with H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography (7 % MeOH, 93 % DCM) to give a quantitative yield of green solid product ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.56 – 7.43 (m, 5H), 5.25 (s, 2H), 4.61 (s, 2H), 3.35 – 3.27 (m, 1H), 3.26 (s, 2H), 3.16 – 3.04 (m, 1H), 2.37 (s, 6H), 1.78 – 1.63 (m, 2H), 1.55 – 1.39 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ESI-MS (m/z): 529.1 $[M+H]^+$.



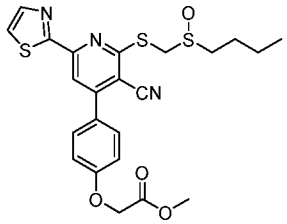
[00296] Methyl 2-(4-formylphenoxy)acetate. To a solution of 4-hydroxybenzaldehyde (3.0 g, 25 mmol) in acetone (61.4 mL), K_2CO_3 (5.43 g, 39.3 mmol) was added and the mixture was stirred vigorously. Methylbromoacetate (2.8 mL, 29 mmol) was added and the mixture was stirred for 3.5 hrs at room temperature. The reaction mixture was concentrated down under reduced pressure then washed with H_2O and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to give a colorless oil that solidified under vacuum in 82 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.82 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 4.70 (s, 2H), 3.79 (s, 3H). ESI-MS (m/z): 195.1 $[M+H]^+$.



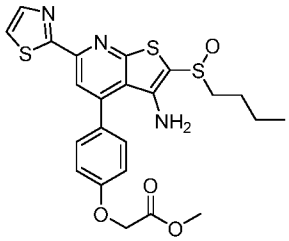
[00297] Methyl (E)-2-(4-(3-oxo-3-(thiazol-2-yl)prop-1-en-1-yl) phenoxy)acetate. 2-acetylthiazole (534 µL, 5.15 mmol) was added to a solution of methyl 2-(4-formylphenoxy)acetate (1.0 g, 5.2 mmol) in MeOH (11mL) under N_2. NaOMe (279 mg, 5.15 mmol) was added last and the reaction mixture stirred at room temperature overnight. The reaction mixture was filtered, and the precipitate was washed with small amount of MeOH then diluted with DCM and washed with H_2O. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This gave solid product in 21 % isolated yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (d, *J* = 3.0 Hz, 1H), 7.95 (d, *J* = 15.9 Hz, 1H), 7.82 (d, *J* = 16.0 Hz, 1H), 7.70 – 7.61 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.67 (s, 2H), 3.80 (s, 3H). ESI-MS (m/z): 304.1 $[M+H]^+$.



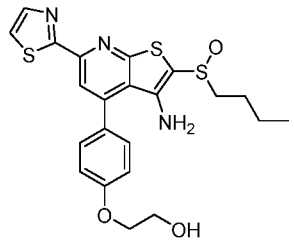
[00298] Methyl 2-(4-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)phenoxy)acetate. EtOH (495 µL) was added to 2-cyanothioacetamide (49.5 mg, 0.494 mmol) and methyl(E)-2-(4-(3-oxo-3-(thiazol-2-yl)prop-1-en-1-yl)phenoxy)acetate (50 mg, 0.16 mmol), followed by 1 drop of piperidine. The reaction mixture stirred at 80°C for 4 hours then was concentrated under reduced pressure and the crude was carried forward to the next step. Followed the standard alkylation procedure, using methyl 2-(4-(3-cyano-6-(thiazol-2-yl)-2-thioxo-1,2-dihydropyridin-4-yl)phenoxy)acetate as the starting material and butyl(chloromethyl)sulfane as the alkylating reagent. The crude product was purified using automated flash chromatography (20 % EtOAc, 80 % hexanes) to give solid product in 70 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.95 (d, *J* = 3.1 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 3.1 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.69 (s, 2H), 4.49 (s, 2H), 3.81 (s, 3H), 2.73 (t, *J* = 7.3 Hz, 2H), 1.68 – 1.56 (m, 2H), 1.46 – 1.34 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 486.1 $[M+H]^+$.



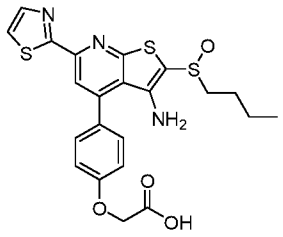
[00299] Methyl 2-(4-(2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)phenoxy)acetate. Followed the standard oxidation procedure using methyl 2-(4-(2-(((butylthio)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)phenoxy)acetate as the starting material. The crude product was purified using automated flash chromatography (50 % EtOAc, 50 % hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.90 (d, *J* = 3.1 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 3.1 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.65 (s, 2H), 4.62 (d, *J* = 13.1 Hz, 1H), 4.37 (d, *J* = 13.1 Hz, 1H), 3.75 (s, 3H), 2.96 – 2.84 (m, 1H), 2.81 – 2.71 (m, 1H), 1.76 (p, *J* = 7.6 Hz, 2H), 1.51 – 1.33 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 502.1 $[M+H]^+$.



[00300] SW212365. Methyl 2-(4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)phenoxy)acetate. Methyl 2-(4-(2-(((butyl(l1-oxidanyl)-l3-sulfanyl)methyl)thio)-3-cyano-6-(thiazol-2-yl)pyridin-4-yl)phenoxy)acetate (80 mg, 0.16 mmol) and t-BuOK (10.7 mg, 0.0954 mmol) were combined in a vial that was evacuated and backfilled with N_2 three times, then DMF (627 µL) was added and N_2 was bubbled through the solution. The reaction mixture was stirred at room temperature for about 10 minutes and then was diluted with EtOAc and washed with 10 % AcOH. The organic layer was washed several times with water, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified using automated flash chromatography (30 % EtOAc, 70 % hexanes) to give green solid with 56 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.89 – 7.86 (m, 1H), 7.47 (d, *J* = 3.1 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 4.70 (s, 2H), 4.66 (s, 2H), 3.82 (s, 3H), 3.34 – 3.18 (m, 1H), 3.16 – 3.01 (m, 1H), 1.77 – 1.64 (m, 2H), 1.51 – 1.38 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 502.1 $[M+H]^+$

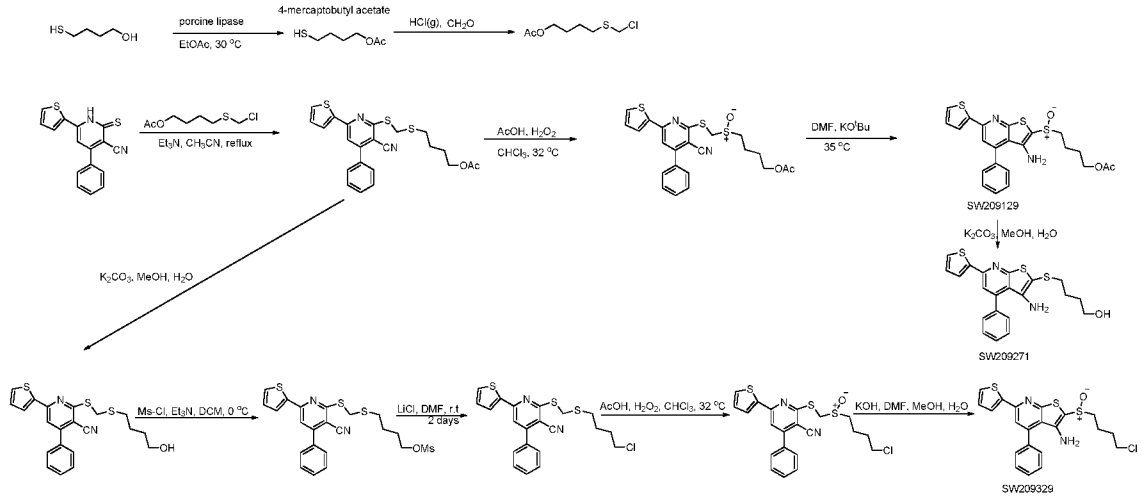


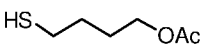
[00301] SW212364. 2-(4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)phenoxy)ethan-1-ol. Followed the same procedure as for 2-(((butylthio)methyl)thio)-4-(4-(hydroxymethyl)phenyl)-6-(thiazol-2-yl)nicotinonitrile using SW212365 as the starting material to give a quantitative yield of desired product ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.90 (d, *J* = 3.2 Hz, 1H), 7.48 (d, *J* = 3.1 Hz, 1H), 7.46 – 7.35 (m, 2H), 7.07 – 6.99 (m, 2H), 4.69 (s, 2H), 4.18 – 4.11 (m, 2H), 4.04 – 3.96 (m, 2H), 3.34 – 3.23 (m, 1H), 3.17 – 3.04 (m, 1H), 1.80 – 1.61 (m, 2H), 1.53 – 1.40 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 474.1 $[M+H]^+$.



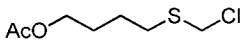
[00302] SW212363. 2-(4-(3-amino-2-(butyl(l1-oxidanyl)-l3-sulfanyl)-6-(thiazol-2-yl)thieno[2,3-b]pyridin-4-yl)phenoxy)acetic acid. Followed the standard hydrolysis procedure using SW212365 as the starting material to give a quantitative yield. ^{1}H NMR (400 MHz, MeOD) δ 7.98 (s, 1H), 7.94 (d, *J* = 3.2 Hz, 1H), 7.74 (d, *J* = 3.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.9 Hz, 2H), 4.67 (s, 2H), 3.35 – 3.24 (m, 1H), 3.16 – 3.04 (m, 1H), 1.78 – 1.57 (m, 2H), 1.55 – 1.43 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ESI-MS (m/z): 488.1 $[M+H]^+$.

Synthesis of chloromethyl thio ethers

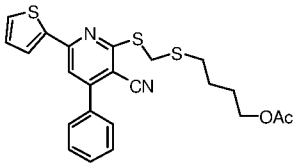




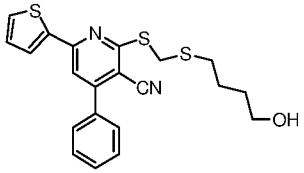
[00303] 4-mercaptobutyl acetate. Porcine lipase (2.35 g) was added to a solution of 4-mercapto-1-butanol (2.45 g, 23.10 mmol) in ethyl acetate (42.0 ml). The reaction was heated at 30ºC for 6 days. Despite incomplete conversion the mixture was filtered and condensed. Purification was carried out on an automated flash chromatography system in 100% DCM to give oil in 84% yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.08 (t, J = 6.2 Hz, 2H), 2.57 (q, J = 7.1 Hz, 2H), 2.05 (s, 3H), 1.85 – 1.59 (m, 4H), 1.36 (t, J = 7.9 Hz, 1H).



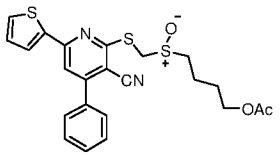
[00304] 4-((chloromethyl)thio)butyl acetate. Hydrogen chloride gas was bubbled for 40 minutes into 4-mercaptobutyl acetate (2.84 g, 19.2 mmol) which had been cooled in a dry ice/acetone bath and until the internal temperature stabilized before paraformaldehyde (0.815 g, 27.17 mmol) was slowly added using a solid addition funnel. The reaction was stirred cold for 3 hours during which hydrogen chloride bubbling was continued and then ceased as the reaction was warmed gently to ambient temperature and stirred overnight. The crude mixture was diluted with minimal DCM. The aqueous phase was removed and the organic layer was washed with brine and dried over Na_2SO_4, filtered and condensed to give an oil in 62% yield. ^{1}H NMR (400 MHz, $CHCl_3$) 4.75 (s, 2H), 4.10 (t, J = 6.0 Hz, 2H), 2.95 – 2.66 (m, 2H), 2.06 (s, 3H), 1.85 – 1.67 (m, 4H).



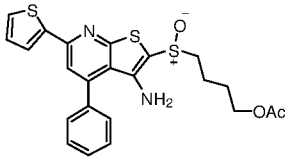
[00305] 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)butyl acetate. A mixture of 4-((chloromethyl)thio)butyl acetate (602.3 mg, 3.1 mmol), 4-phenyl-6-(thiophen-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (352.2 mg, 1.2 mmol) and triethylamine (250 ml, 1.8 mmol) in acetonitrile (1.2 ml) was refluxed for three hours. The crude mixture was then condensed and purified on an automated flash chromatography system in 0-40% EtOAc/hexanes. Fractions containing the desired product were further purified on an automated flash chromatography in 0-30% EtOAc/hexanes to give a clear oil in 41 % yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.72 (dd, J = 3.7, 1.1 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.55 (dt, J = 5.6, 2.3 Hz, 4H), 7.44 (s, 1H), 7.17 (dd, J = 5.0, 3.8 Hz, 1H), 4.55 (s, 2H), 4.11 – 4.02 (m, 2H), 2.86 – 2.63 (m, 2H), 2.05 (s, 3H), 1.77 (t, J = 3.4 Hz, 4H). ESI-MS (m/z): 455.1 $[M+H]^+$.



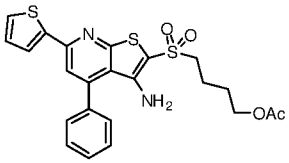
[00306] 2-((((4-hydroxybutyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. K_2CO_3 (157.7 mg, 1.14 mmol) was added to a solution of 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)butyl acetate. (245.4 mg, 0.54 mmol) in methanol (8.0 ml) and water (2.0 ml) and the reaction was stirred for 2 hours. The mixture was dried then diluted with EtOAc and washed twice with water and then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduce pressure to give desired product in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 3.7, 1.1 Hz, 1H), 7.61 (dd, J = 6.6, 3.0 Hz, 2H), 7.54 (dd, J = 5.1, 2.2 Hz, 4H), 7.43 (s, 1H), 7.16 (dd, J = 5.0, 3.8 Hz, 1H), 4.55 (s, 2H), 3.67 (t, J = 6.2 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H), 1.84 – 1.63 (m, 4H). ESI-MS (m/z): 413.1 $[M+H]^+$.



[00307] 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)sulfinyl)butyl acetate. Acetic acid (370 µl) and hydrogen peroxide (29 µl, 30 % solution in water) were added to the solution of 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)butyl acetate (85.2 mg, 0.19 mmol) in chloroform (370 µl). The reaction mixture was stirred at 32 °C for 90 min. Once complete, the reaction was diluted with chloroform and washed with saturated $NaHCO_3$ solution, and extracted three times with chloroform. The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduce pressure to give designed product in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 3.8 Hz, 1H), 7.62 (dd, *J* = 4.1, 2.3 Hz, 2H), 7.60 – 7.54 (m, 4H), 7.51 (s, 1H), 7.19 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.78 (d, *J* = 13.0 Hz, 1H), 4.44 (d, *J* = 13.0 Hz, 1H), 4.11 (t, *J* = 6.4 Hz, 2H), 3.03 (dt, *J* = 12.9, 8.0 Hz, 1H), 2.87 (dt, *J* = 12.8, 7.3 Hz, 1H), 2.05 (s, 3H), 2.03 – 1.77 (m, 4H). ESI-MS (m/z): 471.1 $[M+H]^+$.

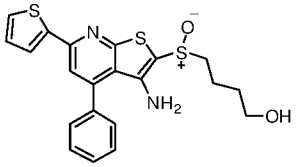


[00308] SW209129. 4-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)butyl acetate. Potassium tert-butoxide (9.7 mg, 0.086 mmol) was added to a solution of 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)sulfinyl)butyl acetate (58.2 mg, 0.12 mmol) in DMF (490 µl). The reaction mixture was stirred at 35°C for 45 minutes, then diluted with EtOAc and washed several times with water. The aqueous layer was also back-extracted. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduce pressure. Purification was carried out using automated flash chromatography in 0-90% EtOAc/hexanes to give the desired product in 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.49 (m, 5H), 7.45 (dd, *J* = 4.9, 1.1 Hz, 2H), 7.41 (s, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.59 (bs, 2H), 4.08 (t, *J* = 5.8 Hz, 2H), 3.39 – 3.23 (m, 1H), 3.10 (ddd, *J* = 12.8, 8.4, 6.2 Hz, 1H), 2.03 (s, 3H), 1.96 – 1.72 (m, 4H). ESI-MS (m/z): 471.1 $[M+H]^+$.

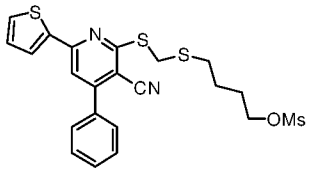


[00309] SW209128. 4-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfonyl)butyl acetate. Isolated as the over oxidation product from 4-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)butyl acetate in 13.5 % yield.

[00310] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.61 – 7.55 (m, 3H), 7.53 – 7.44 (m, 4H), 7.15 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.10 (s, 2H), 4.06 (t, *J* = 6.3 Hz, 2H), 3.32 – 3.18 (m, 2H), 2.02 (s, 3H), 1.98 – 1.87 (m, 2H), 1.77 (dt, *J* = 8.6, 6.4 Hz, 2H). ESI-MS (m/z): 487.1 $[M+H]^+$.

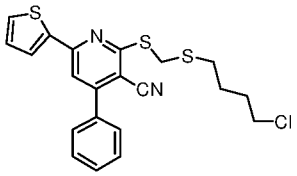


[00311] SW209271. 4-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)butan-1-ol. K_2CO_3 (12.5 mg, 0.09 mmol) was added to a solution of SW209129 (18.7 mg, 0.04 mmol) in methanol (470 µl) and water (100 µl) and the reaction was stirred for 2.5 hours. The mixture was dried then diluted with EtOAc and washed twice with water and then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduce pressure to give desired product in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 1.1 Hz, 1H), 7.60 – 7.50 (m, 4H), 7.49 – 7.41 (m, 3H), 7.11 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.68 – 4.44 (s, 2H), 3.67 (t, *J* = 6.1 Hz, 2H), 3.42 – 3.27 (m, 1H), 3.13 (ddd, *J* = 12.9, 8.4, 6.9 Hz, 1H), 1.93 – 1.65 (m, 4H). ESI-MS (m/z): 429.0 $[M+H]^+$.

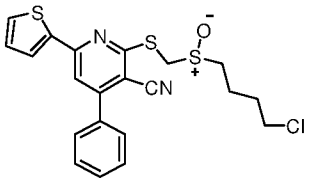


[00312] 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)butyl methanesulfonate. A solution of triethylamine (38 µl, 0.28 mmol) in anhydrous DCM (1.0 ml) is cooled in an ice bath before the addition of 2-((((4-hydroxybutyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile (40.6 mg, 0.098 mmol) followed by dropwise

addition of methanesulfonyl chloride (17.5 µl, 0.23 mmol). After 30 minutes the crude mixture was washed with brine and dried over Na_2SO_4, filtered and condensed to give desired product in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.64 – 7.50 (m, 7H), 7.17 (dd, *J* = 5.1, 3.8 Hz, 1H), 5.46 (s, 2H), 4.01 – 3.78 (m, 2H), 2.65 (ddd, *J* = 10.1, 5.3, 1.9 Hz, 2H), 2.52 – 2.37 (m, 4H). ESI-MS (m/z): 491.1 $[M+H]^+$.

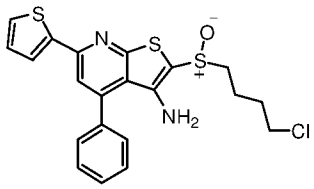


[00313] 2-((((4-chlorobutyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Lithium chloride (32.0 mg, 0.75 mmol) was added to a solution of 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)butyl methanesulfonate (21.8 mg, 0.044 mmol) in DMF (0.4 ml). The reaction went to completion within two days. The mixture was diluted with EtOAc and washed several times with water and then brine. The organic layer was dried over Na_2SO_4, filtered and condensed. Purification was performed on an automated chromatography system in 0-40% EtOAc/hexanes and gave the desired product in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.62 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.59 – 7.52 (m, 4H), 7.44 (s, 1H), 7.17 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.56 (s, 2H), 3.56 (t, *J* = 6.3 Hz, 2H), 2.80 (t, *J* = 7.0 Hz, 2H), 1.95 – 1.79 (m, 4H). ESI-MS (m/z): 431.0 $[M+H]^+$.

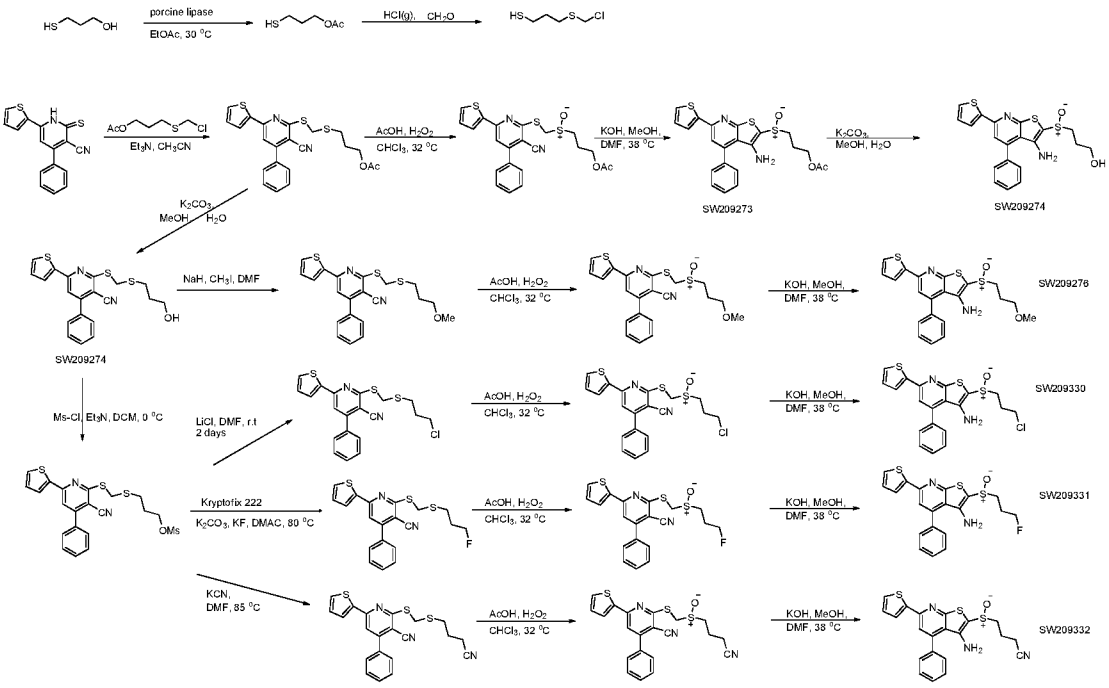


[00314] 2-((((4-chlorobutyl)sulfinyl)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Acetic acid (70 µl) and hydrogen peroxide (5.2 µl, 30 % solution in water) were added to the solution of 2-((((4-chlorobutyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile (14.6 mg, 0.034 mmol) in chloroform (70 µl). The reaction mixture was stirred at 32°C for 40 min and then diluted with chloroform and was washed with saturated $NaHCO_3$ solution and extracted three times with chloroform. The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduce pressure to give designed product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 3.8 Hz, 1H), 7.62 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.57 (q, *J* = 4.5, 3.1 Hz, 4H), 7.51 (s, 1H), 7.19 (t, *J* = 4.4 Hz, 1H), 4.77 (d, *J* = 13.0 Hz,

1H), 4.47 (d, *J* = 13.0 Hz, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.03 (dt, *J* = 13.2, 7.7 Hz, 1H), 2.87 (dt, *J* = 13.4, 7.0 Hz, 1H), 2.16 – 1.87 (m, 4H). ESI-MS (m/z): 447.1 $[M+H]^+$.

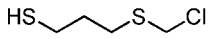


[00315] SW209329. 2-((4-chlorobutyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine. A basic methanolic solution (1.0 mg, 0.018 mmol of potassium hydroxide in 12.0 µl water and 57.5 µl methanol) was transferred to a vial containing a solution of 2-((((4-chlorobutyl)sulfinyl)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile (12.4 mg, 0.028 mmol) in dimethylformamide (91.5 µl). The reaction was heated at 38 °C for 30 minutes, before being cooled, diluted with EtOAc and washed several times with water, then brine. The organic layer was dried over Na_2SO_4, filtered and condensed. The crude mixture was purified using an automated chromatography system in 0-60% EtOAc/hexanes. Isolated yield = 65 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 3.7 Hz, 1H), 7.61 – 7.50 (m, 4H), 7.50 – 7.43 (m, 3H), 7.12 (t, *J* = 4.4 Hz, 1H), 4.59 (s, 2H), 3.66 – 3.47 (m, 2H), 3.40 – 3.24 (m, 1H), 3.20 – 3.06 (m, 1H), 1.95 (q, *J* = 5.6 Hz, 4H). ESI-MS (m/z): 447.0 $[M+H]^+$.

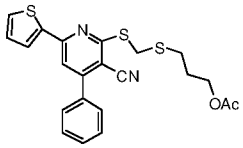




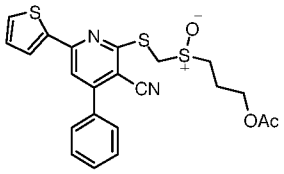
[00316] 3-mercaptopropyl acetate. Porcine lipase (5.52 g) was added to a solution of 3-mercapto-1-propanol (5.03 g, 54.6 mmol) in ethyl acetate (70 ml). The reaction was heated at 28 °C for 12 days. Despite incomplete conversion the mixture was filtered and condensed. Purification was carried out on an automated flash chromatography system in 100% DCM to give oil in 66% yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.17 (t, *J* = 6.2 Hz, 2H), 2.60 (q, *J* = 7.4 Hz, 2H), 2.05 (s, 3H), 1.93 (p, *J* = 6.6 Hz, 2H), 1.39 (t, *J* = 8.1 Hz, 2H).



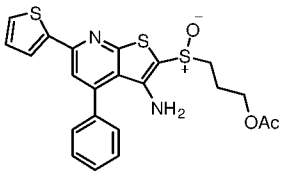
[00317] 3-((chloromethyl)thio)propane-1-thiol. Hydrogen chloride gas was bubbled for 60 minutes into 3-((chloromethyl)thio)propane-1-thiol (4.80 g, 35.7 mmol) which had been cooled in a dry ice/acetone bath and until the internal temperature stabilized before paraformaldehyde (1.59 g, 53.3 mmol) was slowly added using a solid addition funnel. The reaction was stirred cold for 1.5 hours during which hydrogen chloride bubbling was continued and then ceased as the reaction was warmed gently to ambient temperature and stirred overnight. The crude mixture was diluted with minimal DCM. The aqueous phase was removed and the organic layer was washed with brine and dried over Na_2SO_4, filtered and condensed to give an oil in 80% yield of a mixture of 2.4:1 desired monomer chloride to diacetate dimer. ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.74 (s, 2H), 4.17 (t, *J* = 6.4 Hz, 2H), 2.91 – 2.77 (m, 2H), 2.06 (d, *J* = 1.0 Hz, 3H), 2.03 – 1.94 (m, 2H).



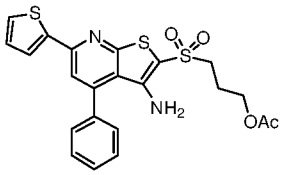
[00318] 3-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)propyl acetate. Prepared analogously to 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)butyl acetate in 26% yield(isolated). ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.72 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.54 (dd, *J* = 4.2, 2.9 Hz, 4H), 7.44 (d, *J* = 1.3 Hz, 1H), 7.17 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.55 (s, 2H), 4.18 (t, *J* = 6.3 Hz, 2H), 2.84 (t, *J* = 7.3 Hz, 2H), 2.05 (s, 3H), 2.05 – 1.97 (m, 2H). ESI-MS (m/z): 441.0 $[M+H]^+$.



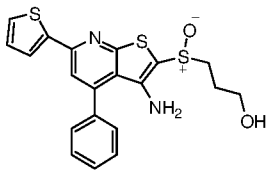
[00319] 3-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)sulfinyl)propyl acetate. Prepared analogously to 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)sulfinyl)butyl acetate in 90% yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.77 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.57 (ddd, *J* = 6.9, 4.5, 2.0 Hz, 4H), 7.51 (s, 1H), 7.19 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.81 (d, *J* = 13.1 Hz, 1H), 4.44 (d, *J* = 13.1 Hz, 1H), 4.22 (td, *J* = 6.3, 1.3 Hz, 2H), 3.09 (dt, *J* = 13.0, 8.1 Hz, 1H), 2.89 (dt, *J* = 13.1, 7.1 Hz, 1H), 2.28 – 2.17 (m, 2H), 2.04 (s, 3H). ESI-MS (m/z): 457.1 $[M+H]^+$.



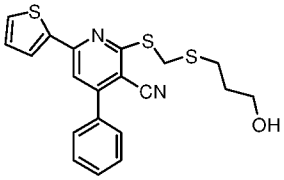
[00320] SW209273. 3-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)propyl acetate. Prepared analogously to 4-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)butyl acetate in 37% yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.62 – 7.52 (m, 5H), 7.45 (dd, *J* = 5.0, 1.1 Hz, 2H), 7.41 (s, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.65 – 4.56 (s, 2H), 4.27 – 4.14 (m, 2H), 3.42 – 3.25 (m, 1H), 3.15 (dt, *J* = 12.9, 7.7 Hz, 1H), 2.09 (ddd, *J* = 7.5, 6.2, 1.3 Hz, 2H), 2.05 (s, 3H). ESI-MS (m/z): 457.1 $[M+H]^+$.



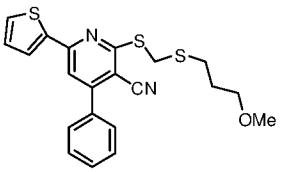
[00321] SW209272. 3-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfonyl)propyl acetate. Isolated as the over oxidation product from 3-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)propyl acetate in 7 % yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.72 (d, *J* = 3.8 Hz, 1H), 7.62 – 7.53 (m, 3H), 7.54 – 7.45 (m, 4H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H), 5.12 (s, 2H), 4.15 (t, *J* = 6.2 Hz, 2H), 3.39 – 3.19 (m, 2H), 2.25 – 2.12 (m, 2H), 2.03 (s, 3H). ESI-MS (m/z): 457.1 $[M+H]^+$.



[00322] SW209274. 3-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)propan-1-ol. Was prepared analogously to SW209271. 4-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)butan-1-ol in 84% yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.63 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.55 (p, *J* = 4.6, 3.2 Hz, 4H), 7.46 (dd, *J* = 5.0, 1.1 Hz, 2H), 7.43 (s, 1H), 7.11 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.60 (s, 2H), 3.77 (t, *J* = 5.8 Hz, 2H), 3.49 – 3.33 (m, 1H), 3.21 (dt, *J* = 13.5, 6.9 Hz, 1H), 2.13 – 1.98 (m, 2H). ESI-MS (m/z): 415.1 $[M+H]^+$.

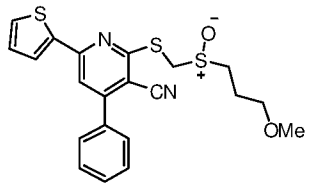


[00323] 2-((((3-hydroxypropyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Prepared analogously to 2-((((4-hydroxybutyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile in 98% yield. ^{1}H NMR (400 MHz, $CHCl_3$) 7.71 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.55 – 7.50 (m, 4H), 7.41 (s, 1H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.54 (s, 2H), 3.76 (t, *J* = 6.1 Hz, 2H), 2.88 (t, *J* = 7.1 Hz, 2H), 1.93 (ddd, *J* = 13.2, 7.1, 6.1 Hz, 2H), 1.88 – 1.80 (m, 1H). ESI-MS (m/z): 399.1 $[M+H]^+$.

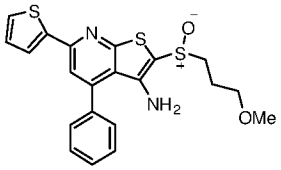


[00324] 2-((((3-methoxypropyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Sodium hydride (micro spatula tipful) was added to an ice-cooled solution of 2-((((3-hydroxypropyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile(41.6 mg, 0.10 mmol) in DMF(1.0 ml). The mixture was stirred cold for 15 minutes before the addition of methyl iodide (34 ml, 0.55 mmol). The mixture was stirred cold in the melting ice-bath for 2 hours, then diluted with EtOAc and washed several times

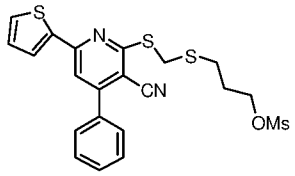
with water and then brine. The organic layer was dried over Na_2SO_4, filtered and condensed. Purification was carried out on an automated flash chromatography system in 0-40% EtOAc/hexanes with an isolated yield of 56%. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.72 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.61 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.57 – 7.51 (m, 4H), 7.43 (s, 1H), 7.17 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.55 (s, 2H), 3.49 (t, *J* = 6.1 Hz, 2H), 3.34 (s, 3H), 2.85 (t, *J* = 7.3 Hz, 2H), 1.95 (ddd, *J* = 13.4, 7.3, 6.1 Hz, 2H). ESI-MS (m/z): 413.1 $[M+H]^+$.



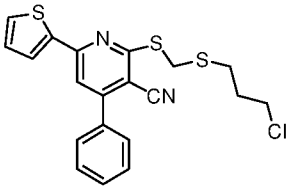
[00325] 2-((((3-methoxypropyl)sulfinyl)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Prepared analogously to 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)sulfinyl)butyl acetate in 71% yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.76 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.56 (td, *J* = 4.6, 2.0 Hz, 4H), 7.49 (s, 1H), 7.18 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.73 (d, *J* = 13.1 Hz, 1H), 4.47 (d, *J* = 13.0 Hz, 1H), 3.54 (qt, *J* = 9.5, 5.8 Hz, 2H), 3.34 (s, 3H), 3.14 (dt, *J* = 13.1, 7.9 Hz, 1H), 2.89 (ddd, *J* = 13.1, 8.0, 6.4 Hz, 1H), 2.20 – 2.08 (m, 2H). ESI-MS (m/z): 429.1 $[M+H]^+$.



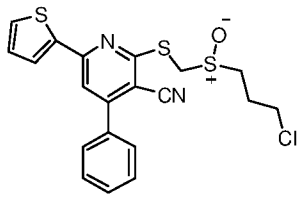
[00326] SW209276. 2-((3-methoxypropyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine. Was prepared analogously to SW209329. 2-((4-chlorobutyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine. Isolated yield = 48%. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.64 (ddd, *J* = 7.2, 3.8, 1.7 Hz, 2H), 7.58 – 7.52 (m, 4H), 7.48 – 7.42 (m, 2H), 7.12 (qd, *J* = 3.7, 1.8 Hz, 1H), 4.57 (s, 2H), 3.50 (td, *J* = 6.1, 1.6 Hz, 2H), 3.40 – 3.29 (m, 4H), 3.26 – 3.13 (m, 1H), 2.09 – 1.95 (m, 2H). ESI-MS (m/z): 429.1 $[M+H]^+$.



[00327] 3-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)propyl methanesulfonate. Prepared analogously to 4-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)butyl methanesulfonate in quantitative yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.69 (t, *J* = 3.3 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.52 (p, *J* = 3.6, 3.0 Hz, 4H), 7.41 (q, *J* = 2.6, 2.2 Hz, 1H), 7.14 (p, *J* = 3.4, 2.5 Hz, 1H), 4.52 (q, *J* = 2.2 Hz, 2H), 4.40 – 4.22 (m, 2H), 2.99 (s, 3H), 2.86 (td, *J* = 7.2, 4.8 Hz, 2H), 2.10 (qt, *J* = 6.4, 2.3 Hz, 2H). ESI-MS (m/z): 477.0 $[M+H]^+$.

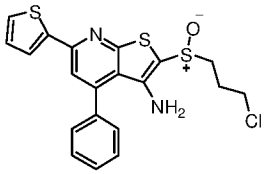


[00328] 2-((((3-chloropropyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Prepared analogously to 2-((((4-chlorobutyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Purification was performed using an automated flash chromatography system in 0-50% EtOAc/hexanes with an isolated yield of 69%. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.72 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.57 – 7.53 (m, 4H), 7.44 (s, 1H), 7.17 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.56 (s, 2H), 3.68 (t, *J* = 6.3 Hz, 2H), 2.93 (t, *J* = 7.0 Hz, 2H), 2.15 (p, *J* = 6.7 Hz, 2H). ESI-MS (m/z): 417.0 $[M+H]^+$.

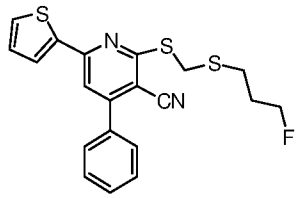


[00329] 2-((((3-chloropropyl)sulfinyl)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Prepared analogously to 2-((((4-chlorobutyl)sulfinyl)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile in 90% yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.76 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.62 (dq, *J* = 7.1, 2.6, 2.2 Hz, 2H), 7.59 – 7.53 (m, 4H), 7.51 (s,

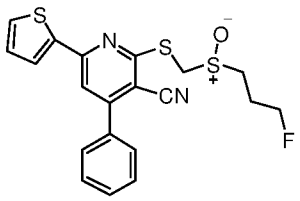
1H), 7.18 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.74 (d, *J* = 13.1 Hz, 1H), 4.51 (d, *J* = 13.1 Hz, 1H), 3.79 – 3.63 (m, 2H), 3.28 – 3.16 (m, 1H), 3.04 – 2.88 (m, 1H), 2.43 – 2.31 (m, 2H). ESI-MS (m/z): 433.0 $[M+H]^+$.



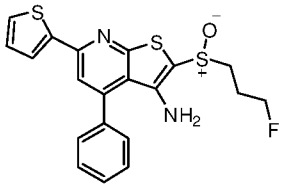
[00330] SW209330. 2-((3-chloropropyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine.Prepared analogously to SW209329. 2-((4-chlorobutyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine. Purification on an automated chromatography system in 0-60% EtOAc/hexanes gave the desired in 88% yield. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.57 (h, *J* = 5.7, 5.3 Hz, 1H), 7.45 (t, *J* = 6.0 Hz, 0H), 7.40 (s, 0H), 7.09 (t, *J* = 4.4 Hz, 0H), 4.61 (s, 0H), 3.67 (td, *J* = 6.4, 3.2 Hz, 0H), 3.40 (dt, *J* = 14.1, 7.3 Hz, 0H), 3.24 (dt, *J* = 13.1, 7.6 Hz, 0H), 2.25 (p, *J* = 7.0 Hz, 0H).
ESI-MS (m/z): 433.0 $[M+H]^+$.



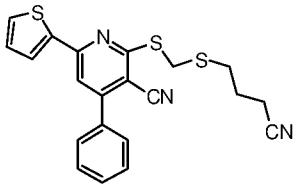
[00331] 2-((((3-fluoropropyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Kryptofix 222 (44.4 mg, 0.012 mmol), KF (6.1 mg, 0.10 mmol) and K_2CO_3 (3.0 mg, 0.022 mmol) were charged to a vial containing 3-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)propyl methanesulfonate (54.2 mg, 0.11 mmol). DMF (1.1 ml) was added and the reaction was heated at 85ºC for 65 minutes. The cooled mixture was diluted with EtOAc and washed several times with water and then brine. The organic layer was dried over Na_2SO_4, filtered and condensed. Yield = 96%. Crude product was carried forward. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.72 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.54 (dd, *J* = 4.9, 2.2 Hz, 4H), 7.43 (s, 1H), 7.17 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.63 (t, *J* = 5.7 Hz, 1H), 4.55 (s, 2H), 4.51 (t, *J* = 5.8 Hz, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.91 (dt, *J* = 11.2, 7.1 Hz, 1H), 2.14 (p, *J* = 6.7 Hz, 1H). ESI-MS (m/z): 401.1 $[M+H]^+$.



[00332] 2-((((3-fluoropropyl)sulfinyl)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Acetic acid (215 µl) and hydrogen peroxide (16.75 µl, 30 % solution in water) were added to the solution of 2-((((3-fluoropropyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile (43.3 mg, 0.034 mmol) in chloroform (215 µl). The reaction mixture was stirred at 32°C for 50 min and then diluted with chloroform and was washed with saturated $NaHCO_3$ solution and extracted three times with chloroform. The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduce pressure in 94 % yield. ESI-MS (m/z): 417.1 $[M+H]^+$.

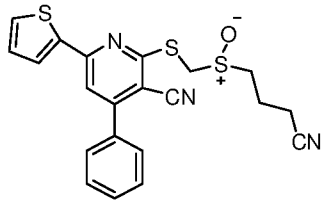


[00333] SW209331. 2-((3-fluoropropyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine. Prepared analogously to SW209329. 2-((4-chlorobutyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine. The crude mixture was purified preparatively in 4% MeOH/DCM. Isolated yield = 32 %. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.68 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.56 (q, *J* = 2.7 Hz, 4H), 7.53 – 7.44 (m, 3H), 7.14 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.65 (td, *J* = 5.8, 3.2 Hz, 1H), 4.60 (s, 2H), 4.53 (td, *J* = 5.8, 3.1 Hz, 1H), 3.40 (dt, *J* = 13.0, 7.3 Hz, 1H), 3.24 (dt, *J* = 13.1, 7.6 Hz, 1H), 2.19 (dtt, *J* = 26.4, 7.5, 5.7 Hz, 2H). ESI-MS (m/z): 417.1 $[M+H]^+$.

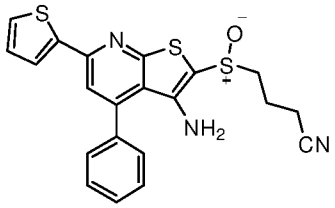


[00334] 2-((((3-cyanopropyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. A solution of 3-((((3-cyano-4-phenyl-6-(thiophen-2-yl)pyridin-2-yl)thio)methyl)thio)propyl methanesulfonate (54.6 mg, 0.11 mmol) and KCN (76.9 mg, 1.18 mmol) in DMF (1.14 ml)

was heated at 85 °C for 4 hours. The cooled mixture was diluted with EtOAc and washed several times with water and then brine. The organic phase was dried over Na_2SO_4, filtered and condensed. Yield = 89 %. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.71 (d, *J* = 3.5 Hz, 1H), 7.60 (dt, *J* = 6.4, 2.0 Hz, 3H), 7.54 (qt, *J* = 5.6, 2.5 Hz, 4H), 7.44 (d, *J* = 1.4 Hz, 1H), 7.16 (ddd, *J* = 5.2, 3.8, 1.5 Hz, 1H), 4.53 (d, *J* = 1.7 Hz, 2H), 2.93 – 2.82 (m, 2H), 2.52 (td, *J* = 7.1, 1.4 Hz, 2H), 2.09 – 1.92 (m, 2H). ESI-MS (m/z): 408.1 $[M+H]^+$.



[00335] 2-((((3-cyanopropyl)sulfinyl)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile. Acetic acid (205 µl) and hydrogen peroxide (15.6 µl, 30 % solution in water) were added to the solution of 2-((((3-cyanopropyl)thio)methyl)thio)-4-phenyl-6-(thiophen-2-yl)nicotinonitrile (41.1 mg, 0.10 mmol) in chloroform (205 µl). The reaction mixture was stirred at 32 °C for 70 min and then diluted with chloroform and was washed with saturated $NaHCO_3$ solution and extracted three times with chloroform. The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduce pressure in 91 % yield. ESI-MS (m/z): 424.1 $[M+H]^+$.



[00336] SW209332. 4-((3-amino-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-2-yl)sulfinyl)butanenitrile. Prepared analogously to SW209329. 2-((4-chlorobutyl)sulfinyl)-4-phenyl-6-(thiophen-2-yl)thieno[2,3-b]pyridin-3-amine. The crude mixture was purified preparatively in 4% MeOH/DCM. Isolated yield = 45 %. ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.65 (d, *J* = 3.7 Hz, 1H), 7.60 – 7.51 (m, 4H), 7.51 – 7.44 (m, 3H), 7.13 (t, *J* = 4.4 Hz, 1H), 4.64 (s, 2H), 3.41 (dt, *J* = 14.0, 7.3 Hz, 1H), 3.19 (dt, *J* = 13.3, 7.5 Hz, 1H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.20 (p, *J* = 7.3 Hz, 2H). ESI-MS (m/z): 424.0 $[M+H]^+$.

Example 2

Methods

Mice

[00337] 8 week old female C57/BL6J mice were purchased from Jackson Labs (stock # 000664). All mouse studies were approved by the institutional animal care and use committee at Case Western Reserve University.

Bleomycin Instillation

[00338] To induce disease onset, mice were anesthetized with ketamine/xylazine and the trachea exposed by cervical excision. Bleomycin sulfate (Enzo- BML-AP302-0010) was dissolved in H_2O and administered intratracheally as a single dose of 2 mg/kg in 50 μl solution per animal.

IP Injections

[00339] Following bleomycin instillation, mice were injected in the intraperitoneal cavity with either Vehicle (10% EtOH, 5% Cremaphor, D5 H2O), or 5.0 mg/kg SW033291 (+) 2x daily for 35 days.

Animal Mortality and Body Weight

[00340] Mortality was observed daily over the duration of the study. Body weights were measured prior to instillation and twice weekly post-bleomycin instillation.

Hydroxyproline Assay

[00341] Hydroxyproline was used to measure collagen content in mouse lungs (Sigma-MAK008-1KT). Briefly, mice were sacrificed and the right lung dissected for collagen quantitation. Experiments were performed according to the manufacturer's protocol. 10mg of total lung was weighed, homogenized in sterile water and hydrolyzed in 12N HCl on 120°C heat block for 3 h. The hydrolyzed samples were incubated with 4-(Dimethylamino) benzaldehyde (DMAB) for 90 min at 60°C, and the absorbance of oxidized hydroxyproline was measured at 560 nm.

Gene Expression Studies

[00342] To measure expression of inflammatory cytokines at Day 35 post bleomycin instillation, mice were sacrificed and the left lung dissected for RNA isolation. Tissue samples were homogenized on ice and the RNAqueous kit (Ambion- AM1912) was used to isolate total RNA. cDNA was synthesized (Invitrogen Superscript III- 18080044) and real-time PCR performed using the following Taqman primers (Applied Biosystems):

Mouse B2M (endogenous control)- Mm00437762_m1

Mouse CCL4- Mm00443111_m1

Mouse TNF-Mm00443258_m1

Mouse TGFB-Mm01178820_m1

Mouse IFNG-Mm01168134_m1

Mouse IL2-Mm99999222_m1

Mouse CCL3-Mm00441259_g1.

[00343] Fig. 1 illustrates a schematic diagram of an assay for measuring the effects of SW033291 on weight maintenance and survival in a mouse model of idiopathic pulmonary fibrosis.

[00344] Figs. 2(A-B) illustrate plots showing (A) weight change and (B) survival of vehicle and SW033291 treated mouse models of idiopathic pulmonary fibrosis. SW033291 treated mice exhibited enhanced maintenance of weight and improved survival compared to vehicle treated mice.

[00345] Fig. 3 illustrates a schematic diagram of an assay for measuring the effects of SW033291 on collagen deposition in a mouse model of idiopathic pulmonary fibrosis.

[00346] Fig. 4 illustrates a graph showing collagen deposition in vehicle and SW033291 treated mouse models of idiopathic pulmonary fibrosis. SW033291 treated mice exhibited reduced collagen deposition compared to vehicle treated mice, as assayed by tissue hydroxyproline content.

[00347] Fig. 5 illustrates a schematic diagram of an assay for measuring the effects of SW033291 on inflammatory cytokine expression in a mouse model of idiopathic pulmonary fibrosis.

[00348] Figs. 6(A-F) illustrate graphs showing inflammatory cytokine expression in vehicle and SW033291 treated mice models of idiopathic pulmonary fibrosis.

Example 3

[00349] To establish a model of intestinal fibrosis due to chronic colitis, 8-week male FVB/N mice were subjected to three cycles of dextran sodium sulfate (DSS; 2% w/v) in sterile drinking water. Each cycle consisted of 7 days of DSS followed by 10 days of recovery without DSS. To explore the effects of 15-PGDH inhibition on intestinal fibrosis, mice were administered either (+)SW033291 5mg/kg IP injections twice a day or vehicle injections from the end of the third DSS exposure (day 41) for a total of 28 days. On day 69, colons were harvested from mice, longitudinally open, and embedded in agar for orientation, and fixed in formalin overnight. Slides were prepared from paraffin-embedded formalin-fixed samples according to standard procedures. The degree of fibrosis in the mouse colon in the two groups were compared by Masson's Trichrome staining. The intensity of positive trichrome staining was quantified using ImageJ software in the following manner. 10 evenly spaced images were captured at 20X from each third of the colon from each mouse. (Figs.7(A-D)) Significant lymphovascular compartments or extracolonic connective tissue attachments seen on slides were excluded during the image capture. RGB channels were split from the images, and the blue channel from each image was divided by the red channel. After generating an intensity histogram of all pixels in the resultant image, the area under the curve (AUC) was calculated for intensities above 1.3 (blue/red) cutoff. The sum of AUC (total trichrome intensity) was normalized by the colon length. Fig. 8 shows colonic fibrosis (+)SW033291 treated mice was substantially reduced compared to vehicle treated mice.

[00350] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims. All patents, publications and references cited in the foregoing specification are herein incorporated by reference in their entirety.

The following is claimed:

1. A method of treating or preventing a fibrotic disease, disorder or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a 15-PGDH inhibitor.

2. The method of claim 1, wherein the fibrotic disease, disorder or condition is characterized, in whole or in part, by the excess production of fibrous material, including excess production of fibrotic material within the extracellular matrix, or the replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components.

3. The method of claim 1, wherein the fibrotic disease, disorder, or condition is selected from the group consistin of systemic sclerosis, multifocal fibrosclerosis, nephrogenic systemic fibrosis, scleroderma, sclerodermatous graft-vs-host-disease, kidney fibrosis, glomerular sclerosis, renal tubulointerstitial fibrosis, progressive renal disease or diabetic nephropathy, cardiac fibrosis, pulmonary fibrosis, glomerulosclerosis pulmonary fibrosis, idiopathic pulmonary fibrosis, silicosis, asbestosis, interstitial lung disease, interstitial fibrotic lung disease, chemotherapy/radiation induced pulmonary fibrosis, oral fibrosis, endomyocardial fibrosis, deltoid fibrosis, pancreatitis, inflammatory bowel disease, Crohn's disease, nodular fascilitis, eosinophilic fasciitis, general fibrosis syndrome characterized by replacement of normal muscle tissue by fibrous tissue in varying degrees, retroperitoneal fibrosis, liver fibrosis, liver cirrhosis, chronic renal failure; myelofibrosis, bone marrow fibrosis, drug induced ergotism, myelodysplastic syndrome,, collagenous colitis, acute fibrosis, and organ specific fibrosis.

4. The method of claim 1, wherein the fibrotic disease, disorder, or condition comprises lung fibrosis.

5. The method of claim 3, wherein the lung fibrosis is selected from the group consisting of pulmonary fibrosis, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, or pulmonary hypertension, and combinations there.

6. The method of claim 5, wherein the lung fibrosis is cystic fibrosis.

7. The method of claim 1, wherein the fibrotic disease, disorder or condition comprises kidney fibrosis.

8. The method of claim 1, wherein the fibrotic disease, disorder or condition comprises liver fibrosis.

9. The method of claim 8, wherein the liver fibrosis results from a chronic liver disease, viral induced hepatic cirrhosis, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, schistosomiasis, primary biliary cirrhosis, alcoholic liver disease or non-alcoholic steatohepatitis (NASH) , NASH associated cirrhosis obesity, diabetes, protein malnutrition, coronary artery disease, auto-immune hepatitis, cystic fibrosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, drug reaction and exposure to toxins, or combinations thereof.

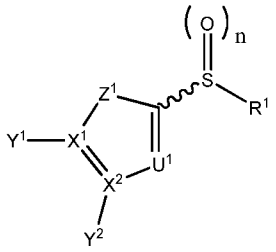
10. The method of claim 1, wherein the fibrotic disease, disorder or condition comprises heart fibrosis.

11. The method of claim 1, wherein the fibrotic disease, disorder or condition is systemic sclerosis.

12. The method of claim 1, wherein the fibrotic disease, disorder or condition is caused by post-surgical adhesion formation.

13. The method of claim 1, wherein the 15-PGDH inhibitor is admninistered at amount effective to reduce or inhibit any of collagen deposition, collagen accumulation, collagen fiber accumulation, inflammatory cytokine expression, and/or inflammatory cell infiltration in a tissue or organ of the subject being treated.

14. The method of claim 1, wherein the 15-PGDH inhibitor includes a compound having formula (I):



(I)

wherein n is 0-2;

Y^1, Y^2, and R^1 are the same or different and are each selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido

(-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), combinations thereof, and wherein Y^1 and Y^2 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

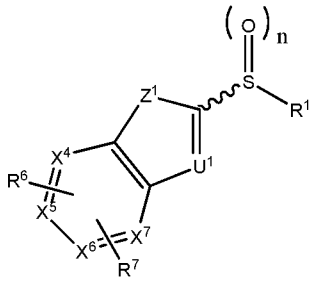
U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)$N(R')_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)$N(R')_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

X^1 and X^2 are independently N or C, and wherein when X^1 and/or X^2 are N, Y^1 and/or Y^2, respectively, are absent;

Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

15. The method of claim 14, wherein the compound has the following formula (II):



(II)

wherein n is 0-2

X^4, X^5, X^6, and X^7 are independently N or CR^c;

R^1, R^6, R^7, and R^c are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono

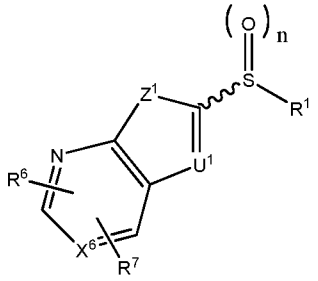
(-P(O)(OH)$_2$), phosphonato (-P(O)(O$^-$)$_2$), phosphinato (-P(O)(O$^-$)), phospho (-PO$_2$), phosphino (--PH$_2$), polyalkylethers, phosphates, phosphate esters, groups incoporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

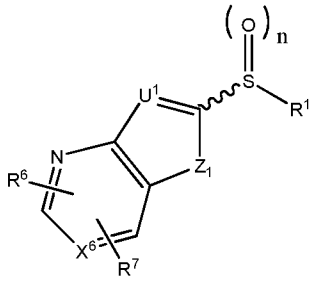
Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

16. The method of claim 14, wherein the compound has the following formula (III) or (IV):



(III), or



(IV)

wherein n is 0-2

X^6 is independently is N or CR^c;

R^1, R^6, R^7, and R^c are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating

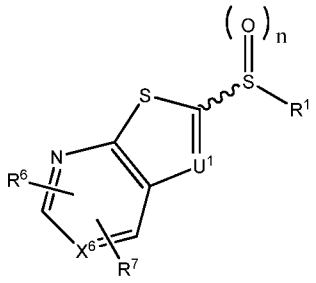
amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', $(C=O)N(R')_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', $(C=O)N(R')_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

17. The method of claim 14, wherein the compound has the following formula (V):



(V)

wherein n is 0-2

X^6 is independently is N or CR^c

R^1, R^6, R^7, and R^c are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O,

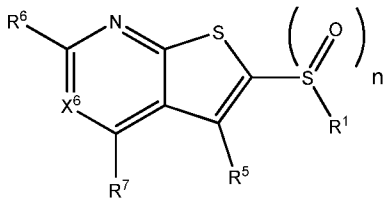
and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein

X=H, F, Cl, Br, or I), CN, (C=O)-R', $(C=O)N(R')_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

and pharmaceutically acceptable salts thereof.

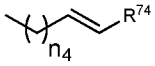
18. The method of claim 14, wherein the compound has the following formula (VI):



(VI)

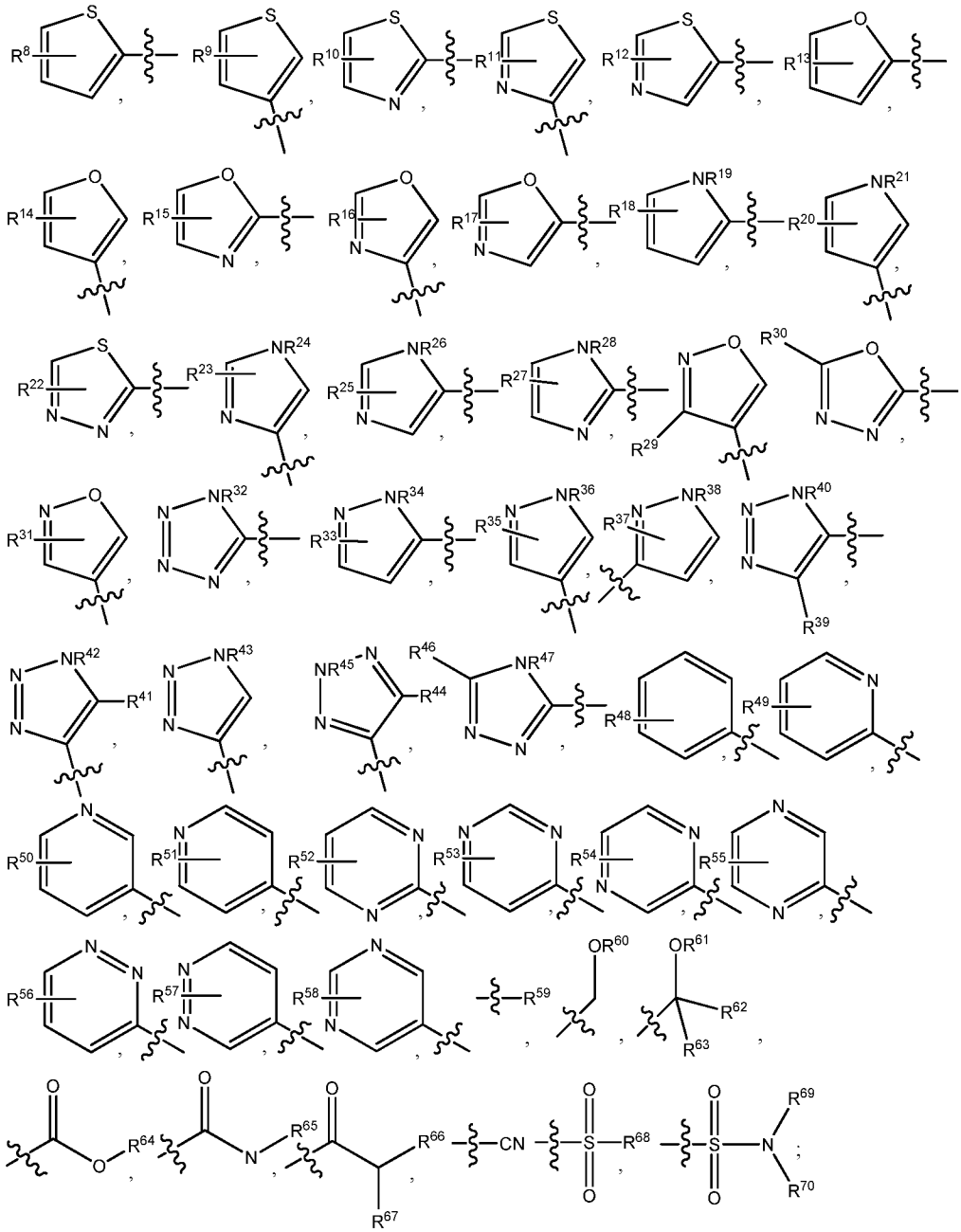
wherein n = 0-2;

X^6 is N or CR^c;

R^1 is selected from the group consisting of branched or linear alkyl including $-(CH_2)n_1CH_3$ (n_1=0-7),  wherein n_2=0-6 and X is any of the following: CF_yH_z (y + z = 3), CCl_yH_z (y + z = 3), OH, OAc, OMe, R^{71}, OR^{72}, CN, $N(R^{73})_2$,  (n_3=0-5, m=1-5), and  (n_4=0-5).

R^5 is selected from the group consisting of H, Cl, F, NH_2, and $N(R^{76})_2$;

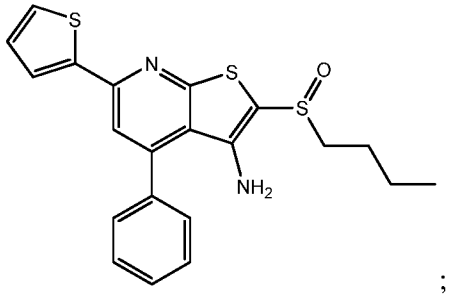
R^6 and R^7 can each independently be one of the following:



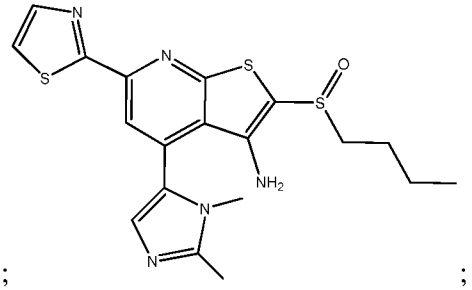
each R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{76}, and R^c are the same or different and are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl,

C_2-C_{24} alkynyl, C_3-C_{20} aryl, heterocycloalkenyl containing from 5-6 ring atoms, (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), heteroaryl or heterocyclyl containing from 5-14 ring atoms, (wherein from 1-6 of the ring atoms is independently selected from N, NH, N(C_1-C_3 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, silyl, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)--NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), sulfanamido (-$SO_2N(R)_2$ where R is independently H, alkyl, aryl or heteroaryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH_2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkyl ethers (-[$(CH_2)_nO]_m$), phosphates, phosphate esters [-OP(O)$(OR)_2$ where R = H, methyl or other alkyl], groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, and combinations thereof, and pharmaceutically acceptable salts thereof.

19. The method of claim 14, wherein the compound is selected from the group consisting of:



;



;

and pharmaceutically acceptable salts thereof.

20. The method of claim 14, wherein the inhibitor i) at 2.5μM concentration, stimulates a Vaco503 reporter cell line expressing a 15-PGDH luciferase fusion construct to a luciferase output level of greater than 70 (using a scale on which a value of 100 indicates a doubling of reporter output over baseline); ii) at 2.5μM concentration stimulates a V9m reporter cell line expressing a 15-PGDH luciferase fusion construct to a luciferase output level of greater than 75; iii) at 7.5μM concentration stimulates a LS174T reporter cell line expressing a 15-PGDH luciferase fusion construct to a luciferase output level of greater than 70; iv) 7.5μM concentration, does not activate a negative control V9m cell line expressing TK-renilla luciferase reporter to a level greater than 20; and v) inhibits the enzymatic activity of recombinant 15-PGDH protein at an IC_{50} of less than 1μM.

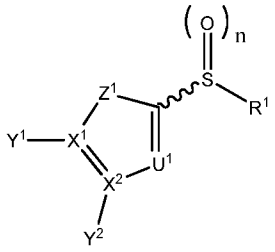
21. The methof claim 14, wherein the inhibitor i) at 2.5 μM concentration stimulates a Vaco503 reporter cell line expressing a 15-PGDH luciferase fusion construct to increase luciferase output; ii) at 2.5 μM concentration stimulates a V9m reporter cell line expressing a 15-PGDH luciferase fusion construct to increase luciferase output; iii) at 7.5 μM concentration stimulates a LS174T reporter cell line expressing a 15-PGDH luciferase fusion construct to increase luciferase output; iv) at 7.5 μM concentration, does not activate a negative control V9m cell line expressing TK-renilla luciferase reporter to a luciferase level greater than 20% above background; and v) inhibits the enzymatic activity of recombinant 15-PGDH protein at an IC50 of less than 1 μM.

22. The method of claim 14, wherein the inhibitor inhibits the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than 1uM, or preferably at an IC_{50} of less than 250 nM, or more preferably at an IC_{50} of less than 50 nM, or more preferably at an IC_{50} of less than 10 nM, or more preferably at an IC_{50} of less than 5 nM at a recombinant 15-PGDH concentration of about 5 nM to about 10 nM.

23. A method of a method for decreasing or reducing collagen secretion and/or collagen deposition and/or collagen accumulation and/or collagen fiber accumulation in a tissue or organ of a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the 15-PGDH inhibitor.

24. The method of claim 23, wherein the organ or tissue comprises at least one of kidney, lung, liver, intestine, colon, skin, or heart.

25. The method of claim 23, wherein the 15-PGDH inhibitor includes a compound having formula (I):



(I)

wherein n is 0-2;

Y^1, Y^2, and R^1 are the same or different and are each selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O) (C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy

(-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), combinations thereof, and wherein Y^1 and Y^2 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

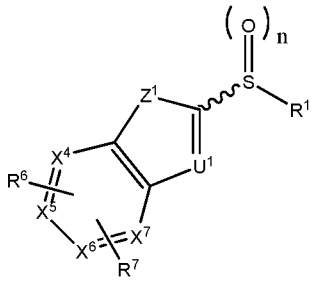
U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

X^1 and X^2 are independently N or C, and wherein when X^1 and/or X^2 are N, Y^1 and/or Y^2, respectively, are absent;

Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

26. The method of claim 25, wherein the compound has the following formula (II):



(II)

wherein n is 0-2

X^4, X^5, X^6, and X^7 are independently N or CR^c;

R^1, R^6, R^7, and R^c are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono

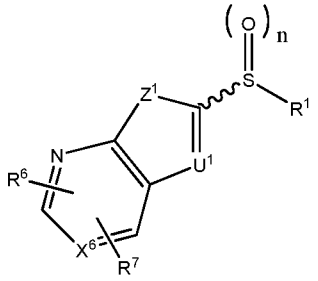
(-P(O)(OH)$_2$), phosphonato (-P(O)(O$^-$)$_2$), phosphinato (-P(O)(O$^-$)), phospho (-PO$_2$), phosphino (--PH$_2$), polyalkylethers, phosphates, phosphate esters, groups incoporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

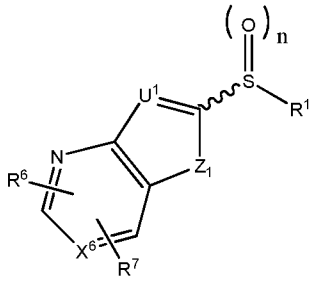
Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

27. The method of claim 25, wherein the compound has the following formula (III) or (IV):



(III), or



(IV)

wherein n is 0-2

X^6 is independently is N or CR^c;

R^1, R^6, R^7, and R^c are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating

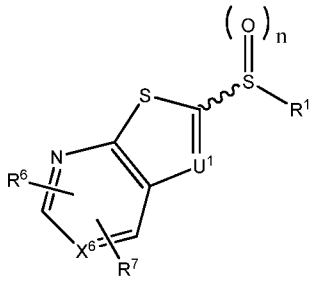
amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)$N(R')_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}OR'$ (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)$N(R')_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

Z^1 is O, S, CR^aR^b or NR^a, wherein R^a and R^b are independently H or a C_{1-8} alkyl, which is linear, branched, or cyclic, and which is unsubstituted or substituted;

and pharmaceutically acceptable salts thereof.

28. The method of claim 25, wherein the compound has the following formula (V):



(V)

wherein n is 0-2

X^6 is independently is N or CR^c

R^1, R^6, R^7, and R^c are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl, C_2-C_{24} alkynyl, C_3-C_{20} aryl, heteroaryl, heterocycloalkenyl containing from 5-6 ring atoms (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O,

and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, -Si(C_1-C_3 alkyl)$_3$, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)-NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)$(OH)_2$), phosphonato (-P(O)$(O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkylethers, phosphates, phosphate esters, groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, combinations thereof, and wherein R^6 and R^7 may be linked to form a cyclic or polycyclic ring, wherein the ring is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, and a substituted or unsubstituted heterocyclyl;

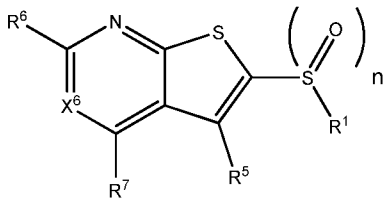
U^1 is N, C-R^2, or C-NR^3R^4, wherein R^2 is selected from the group consisting of a H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X,

O-CH_2-CH_2X, CH_2-CH_2-CH_2X, O-CH_2-CH_2X, X, (wherein X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, O(CO)R', COOR' (wherein R' is H or a lower alkyl group), and wherein R^1 and R^2 may be linked to form a cyclic or polycyclic ring, wherein R^3 and R^4 are the same or different and are each selected from the group consisting of H, a lower alkyl group, O, $(CH_2)_{n1}$OR' (wherein n1=1, 2, or 3), CF_3, CH_2-CH_2X, CH_2-CH_2-CH_2X, (wherein

X=H, F, Cl, Br, or I), CN, (C=O)-R', (C=O)N(R')$_2$, COOR' (wherein R' is H or a lower alkyl group), and R^3 or R^4 may be absent;

and pharmaceutically acceptable salts thereof.

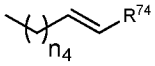
29. The method of claim 25, wherein the compound has the following formula (VI):



(VI)

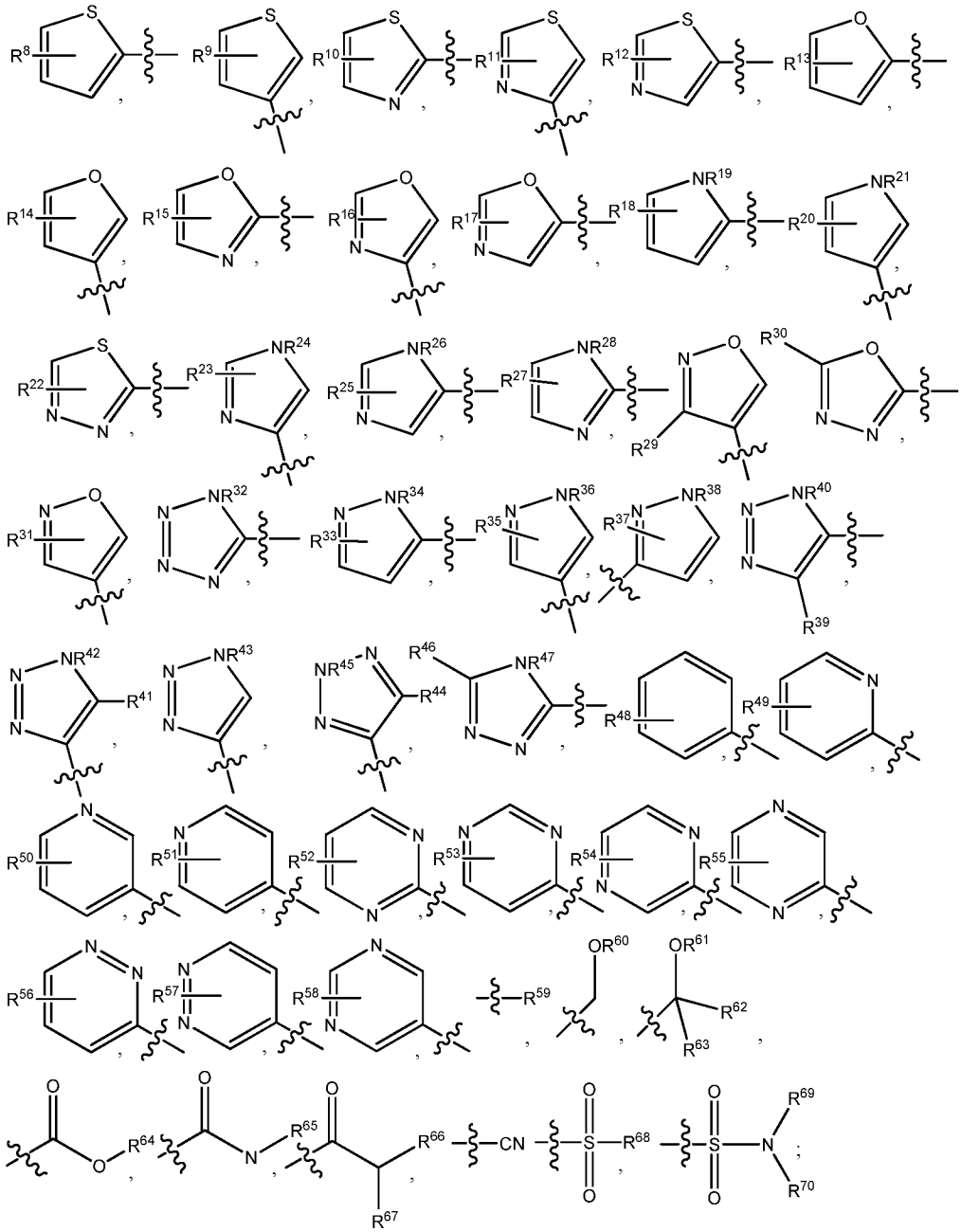
wherein n = 0-2;

X^6 is N or CR^c;

R^1 is selected from the group consisting of branched or linear alkyl including –$(CH_2)n_1CH_3$ (n_1=0-7),  wherein n_2=0-6 and X is any of the following: CF_yH_z (y + z = 3), CCl_yH_z (y + z = 3), OH, OAc, OMe, R^{71}, OR^{72}, CN, $N(R^{73})_2$,  (n_3=0-5, m=1-5), and  (n_4=0-5).

R^5 is selected from the group consisting of H, Cl, F, NH_2, and $N(R^{76})_2$;

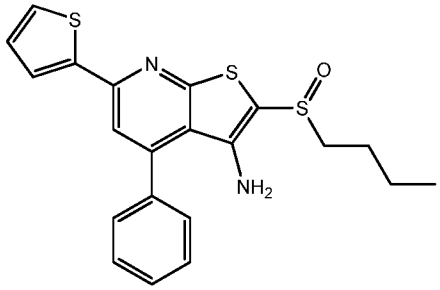
R^6 and R^7 can each independently be one of the following:



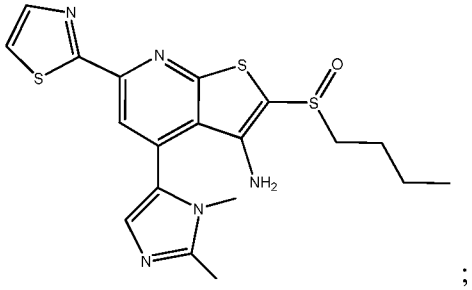
each R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{76}, and R^c are the same or different and are independently selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{24} alkyl, C_2-C_{24} alkenyl,

C_2-C_{24} alkynyl, C_3-C_{20} aryl, heterocycloalkenyl containing from 5-6 ring atoms, (wherein from 1-3 of the ring atoms is independently selected from N, NH, N(C_1-C_6 alkyl), NC(O)(C_1-C_6 alkyl), O, and S), heteroaryl or heterocyclyl containing from 5-14 ring atoms, (wherein from 1-6 of the ring atoms is independently selected from N, NH, N(C_1-C_3 alkyl), O, and S), C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, halo, silyl, hydroxyl, sulfhydryl, C_1-C_{24} alkoxy, C_2-C_{24} alkenyloxy, C_2-C_{24} alkynyloxy, C_5-C_{20} aryloxy, acyl (including C_2-C_{24} alkylcarbonyl (--CO-alkyl) and C_6-C_{20} arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C_2-C_{24} alkoxycarbonyl (-(CO)-O-alkyl), C_6-C_{20} aryloxycarbonyl (-(CO)-O-aryl), C_2-C_{24} alkylcarbonato (-O-(CO)-O-alkyl), C_6-C_{20} arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO^-), carbamoyl (-(CO)--NH_2), C_1-C_{24} alkyl-carbamoyl (-(CO)-NH(C_1-C_{24} alkyl)), arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH_2), carbamido (-NH-(CO)-NH_2), cyano(-CN), isocyano (-N^+C^-), cyanato (-O-CN), isocyanato (-O-N^+=C^-), isothiocyanato (-S-CN), azido (-N=N^+=N^-), formyl (--(CO)--H), thioformyl (--(CS)--H), amino (--NH_2), C_1-C_{24} alkyl amino, C_5-C_{20} aryl amino, C_2-C_{24} alkylamido (-NH-(CO)-alkyl), C_6-C_{20} arylamido (-NH-(CO)-aryl), sulfanamido (-$SO_2N(R)_2$ where R is independently H, alkyl, aryl or heteroaryl), imino (-CR=NH where R is hydrogen, C_1-C_{24} alkyl, C_5-C_{20} aryl, C_6-C_{24} alkaryl, C_6-C_{24} aralkyl, etc.), alkylimino (-CR=N(alkyl), where R=hydrogen, alkyl, aryl, alkaryl, aralkyl, etc.), arylimino (-CR=N(aryl), where R=hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO_2), nitroso (-NO), sulfo (-SO_2-OH), sulfonato (-SO_2-O^-), C_1-C_{24} alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C_1-C_{24} alkylsulfinyl (-(SO)-alkyl), C_5-C_{20} arylsulfinyl (-(SO)-aryl), C_1-C_{24} alkylsulfonyl (-SO_2-alkyl), C_5-C_{20} arylsulfonyl (-SO_2-aryl), sulfonamide (-SO_2-NH_2, -SO_2NY_2 (wherein Y is independently H, arlyl or alkyl), phosphono (-P(O)($OH)_2$), phosphonato (-P(O)($O^-)_2$), phosphinato (-P(O)(O^-)), phospho (-PO_2), phosphino (--PH_2), polyalkyl ethers (-[$(CH_2)_nO]_m$), phosphates, phosphate esters [-OP(O)($OR)_2$ where R = H, methyl or other alkyl], groups incorporating amino acids or other moieties expected to bear positive or negative charge at physiological pH, and combinations thereof, and pharmaceutically acceptable salts thereof.

30. The method of claim 25, wherein the compound is selected from the group consisting of:



;



;

and pharmaceutically acceptable salts thereof.

SWO33291 Application Increases Survival and Weight Maintenance in IPF

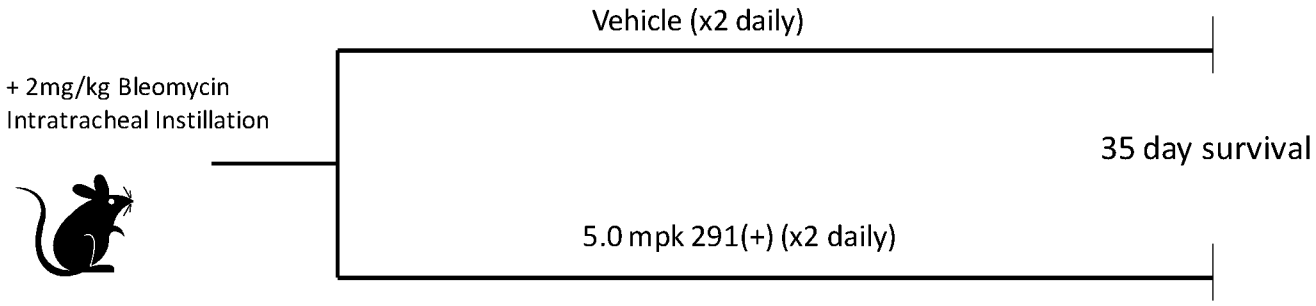
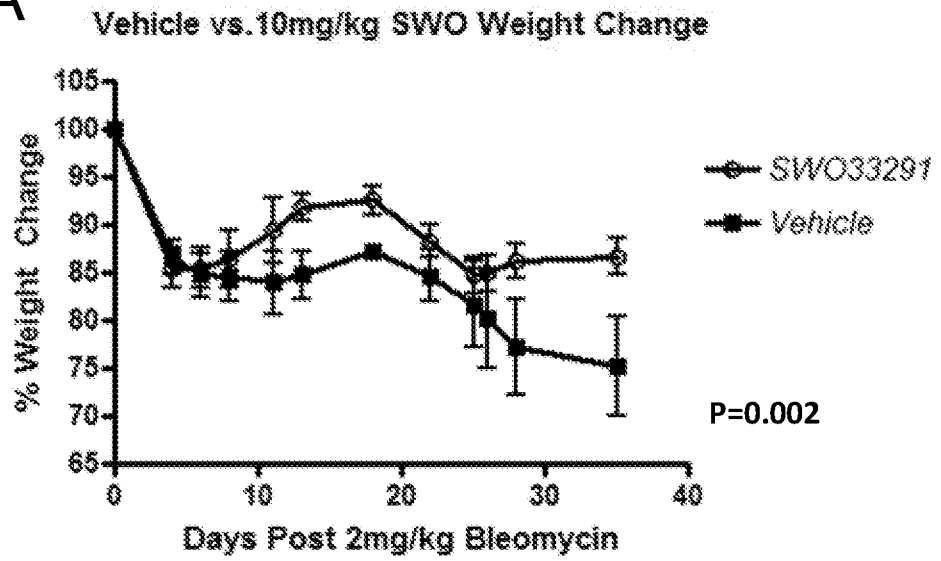


Fig. 1

A



N= 10 mice/group

Fig. 2A

B

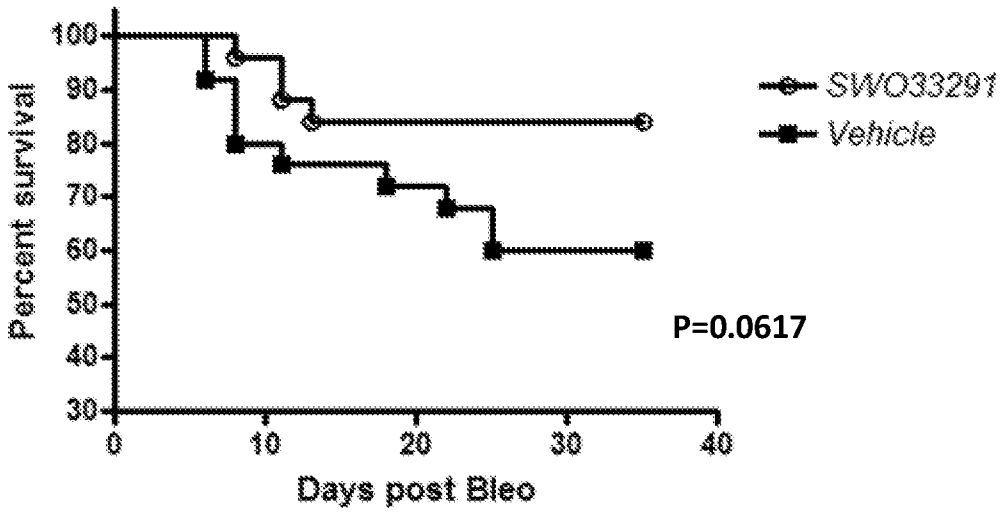


Fig. 2B

N= 25 mice/group

SWO33291 Treatment Decreases Collagen Deposition in IPF

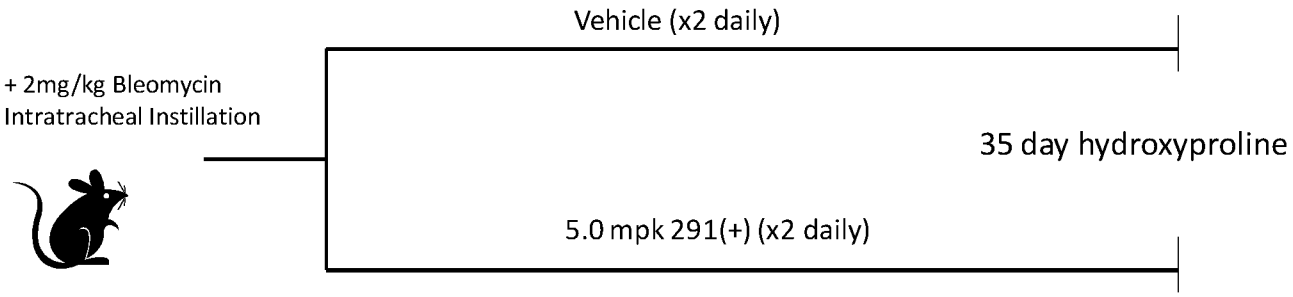
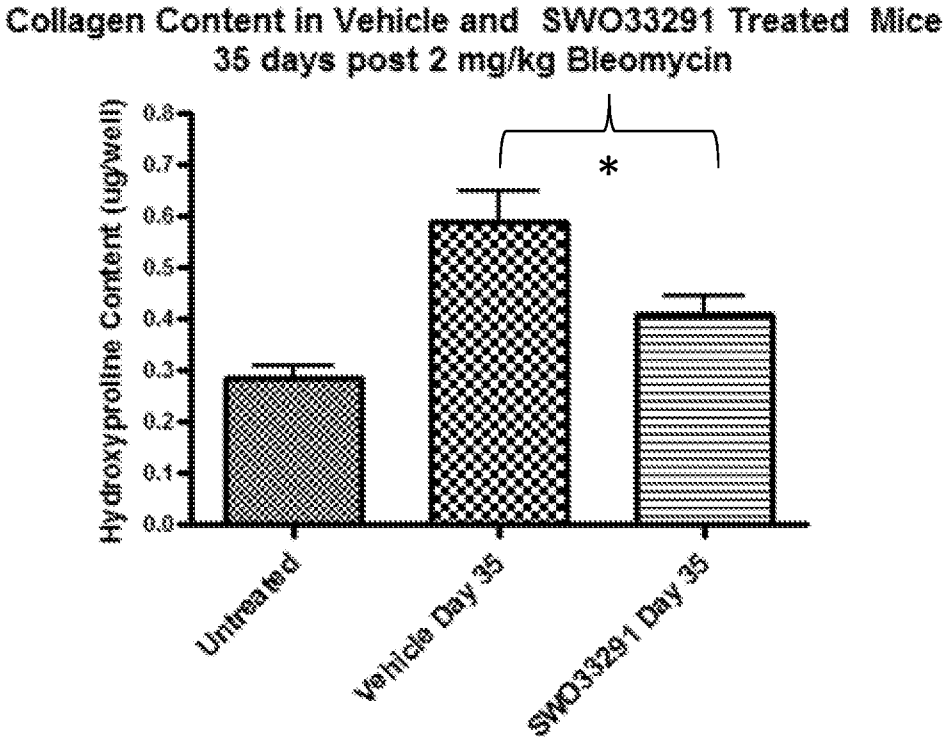


Fig. 3



N= 9 untreated
N= 15 Vehicle
N= 20 SWO33291

Fig. 4

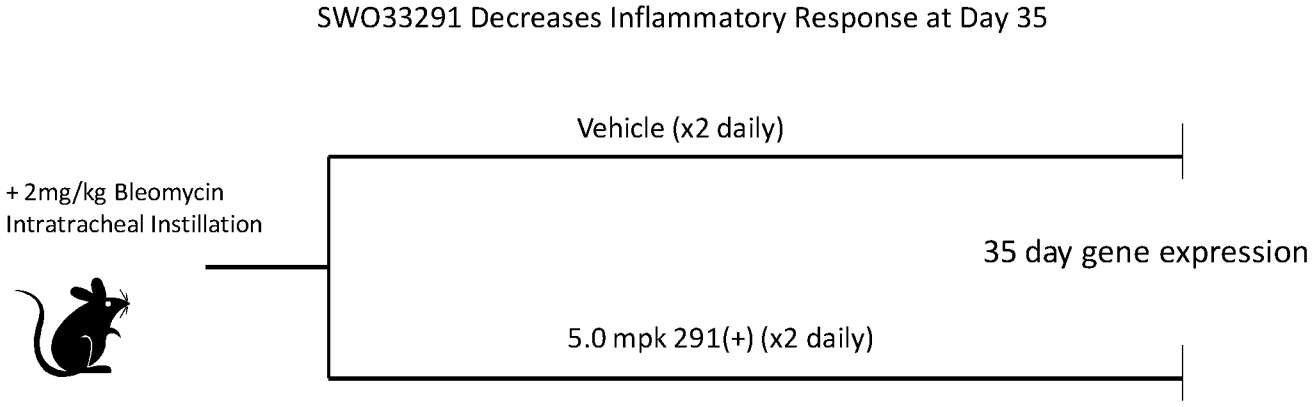


Fig. 5

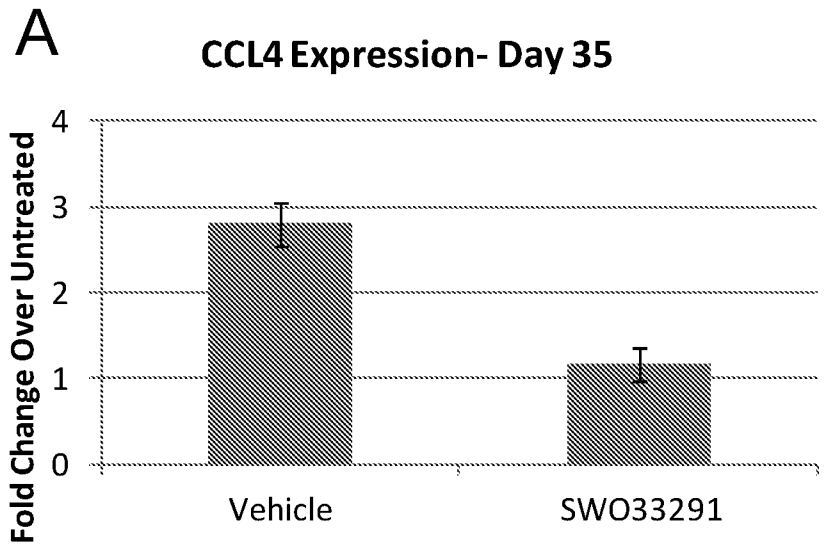


Fig. 6A

N= 2 untreated
N= 3 Vehicle
N= 5 SWO33291

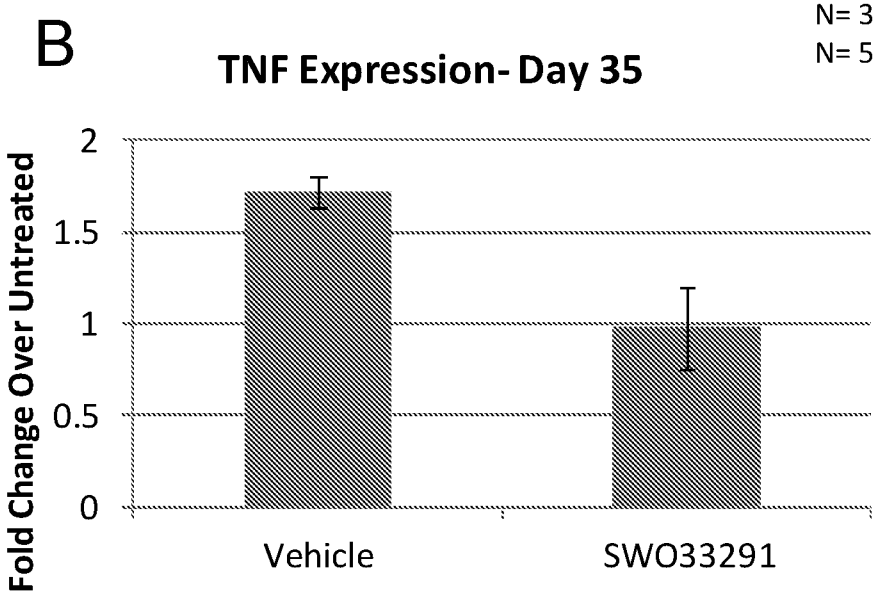


Fig. 6B

SWO33291 Decreases Inflammatory Response at Day 35

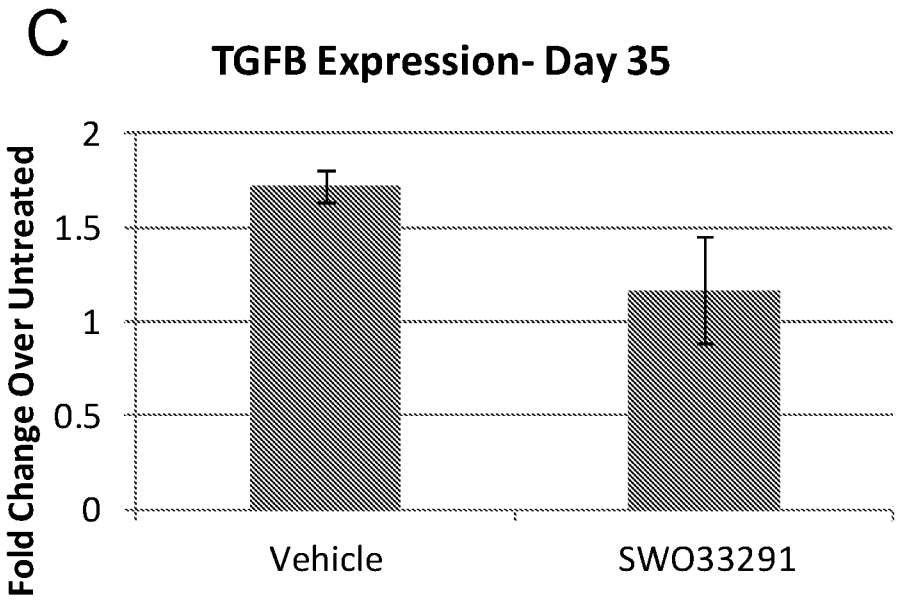


Fig. 6C

N= 2 untreated
N= 3 Vehicle
N= 5 SWO33291

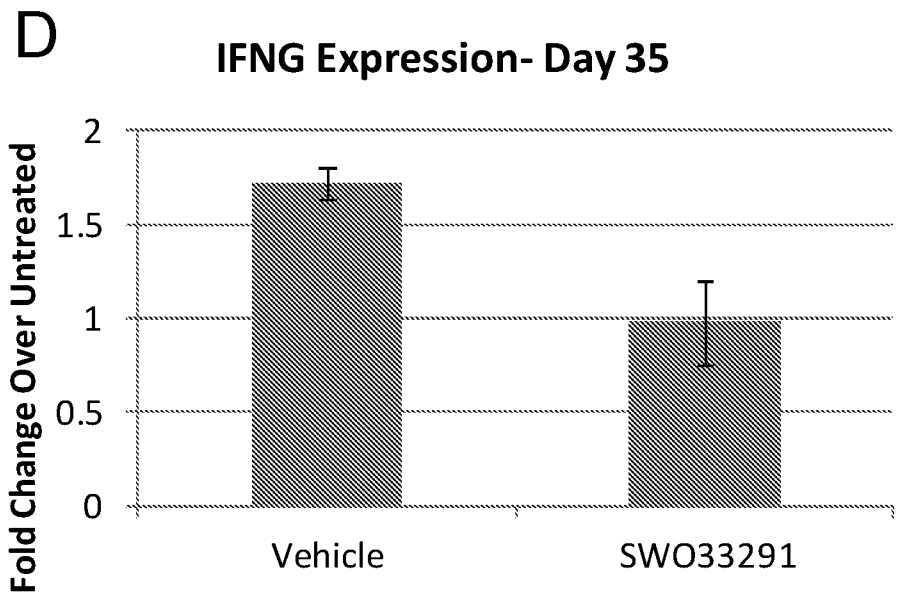


Fig. 6D

SWO33291 Decreases Inflammatory Response at Day 35

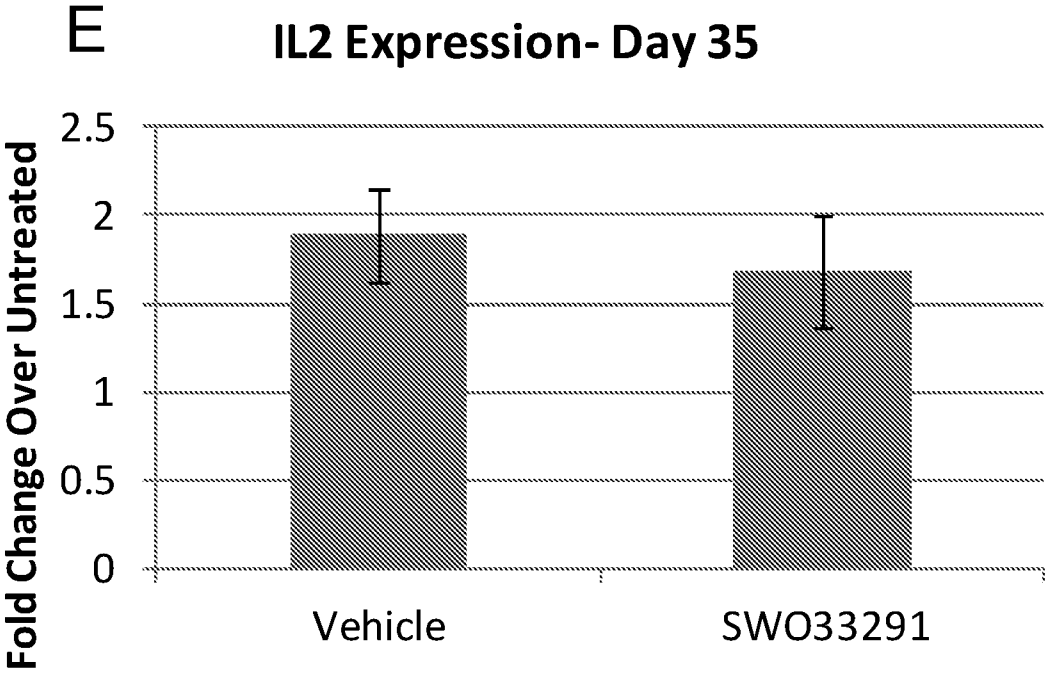


Fig. 6E

N= 2 untreated
N= 3 Vehicle
N= 5 SWO33291

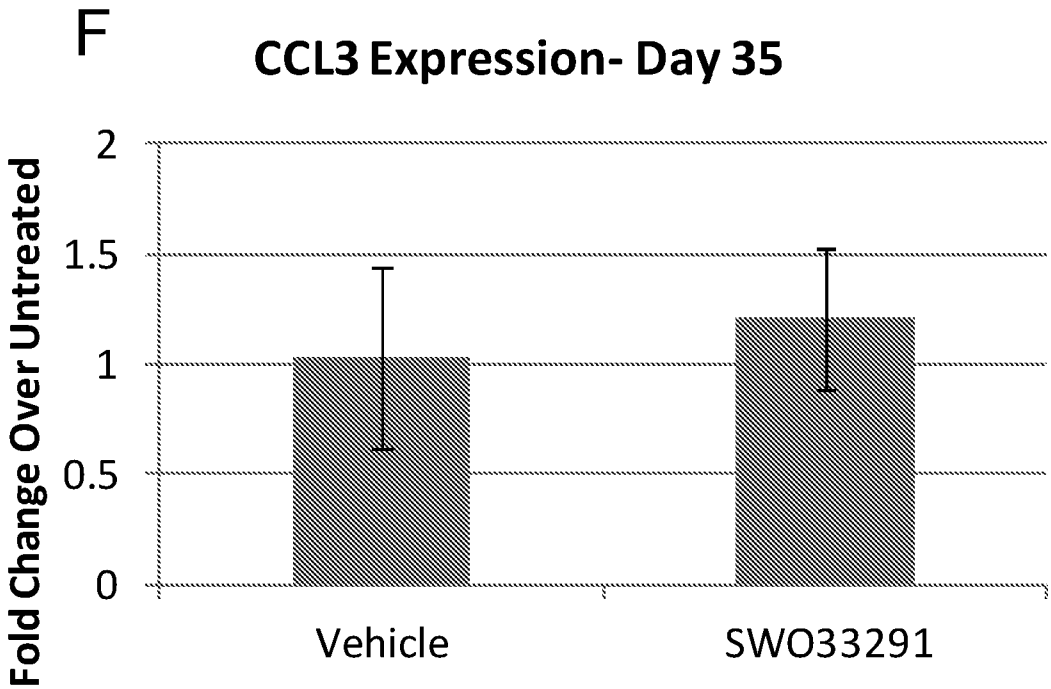


Fig. 6F

Comparing fibrosis at Day 69 by Masson's Trichrome:
Two representative images of distal colon from each group

A

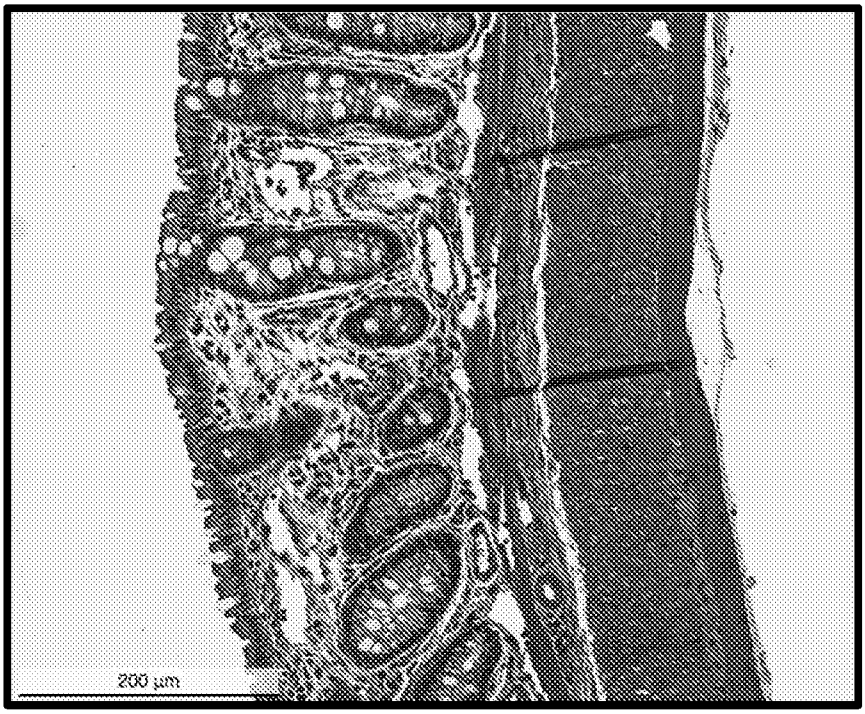


Fig. 7A

B

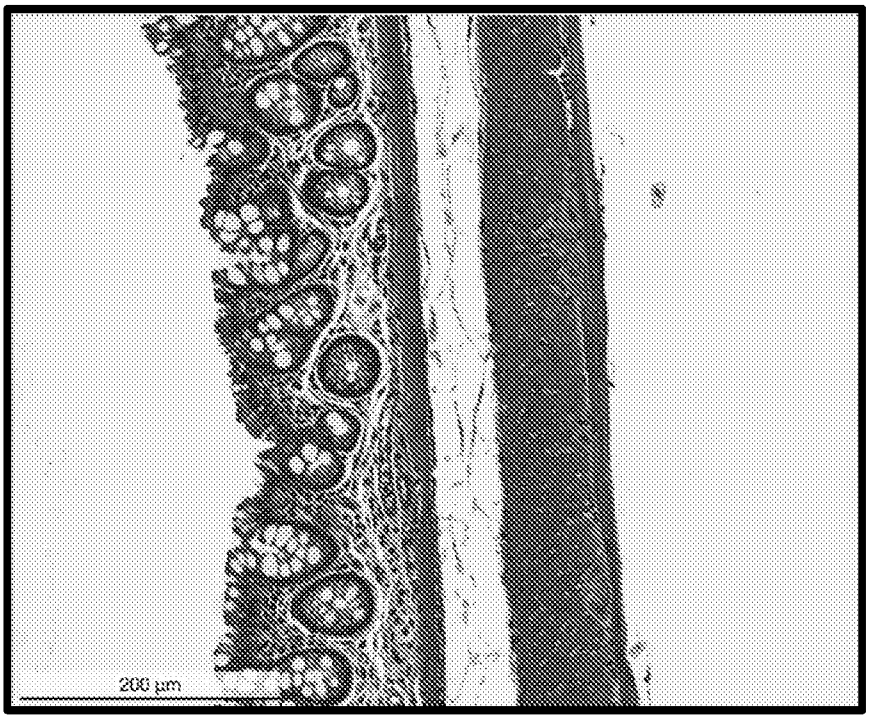


Fig. 7B

Comparing fibrosis at Day 69 by Masson's Trichrome:
Two representative images of distal colon from each group

C

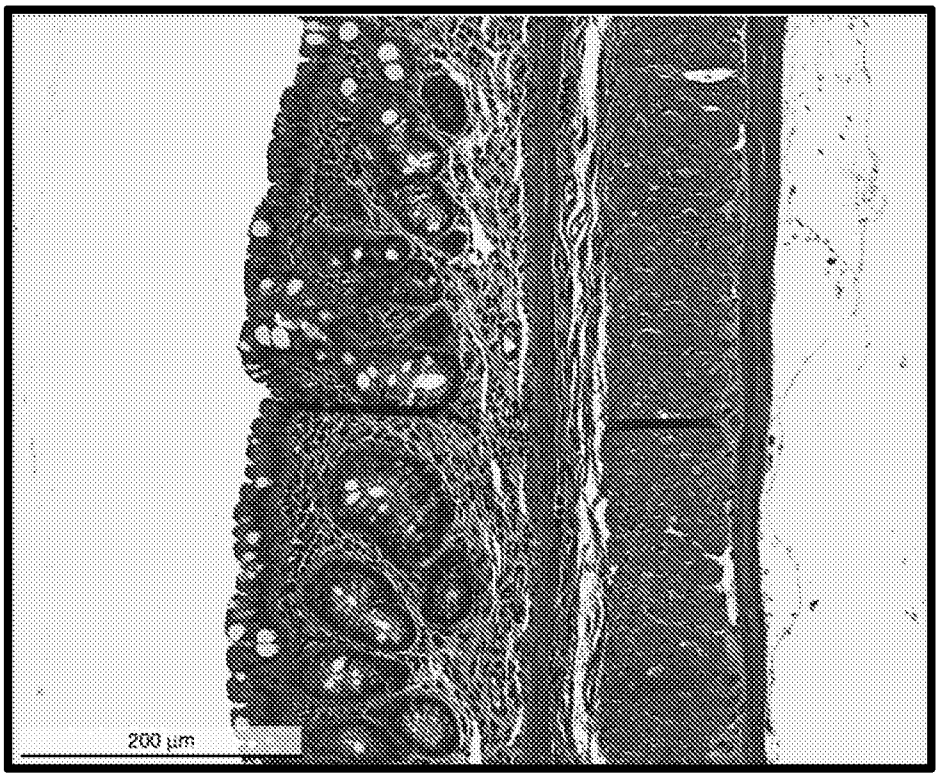


Fig. 7C

D

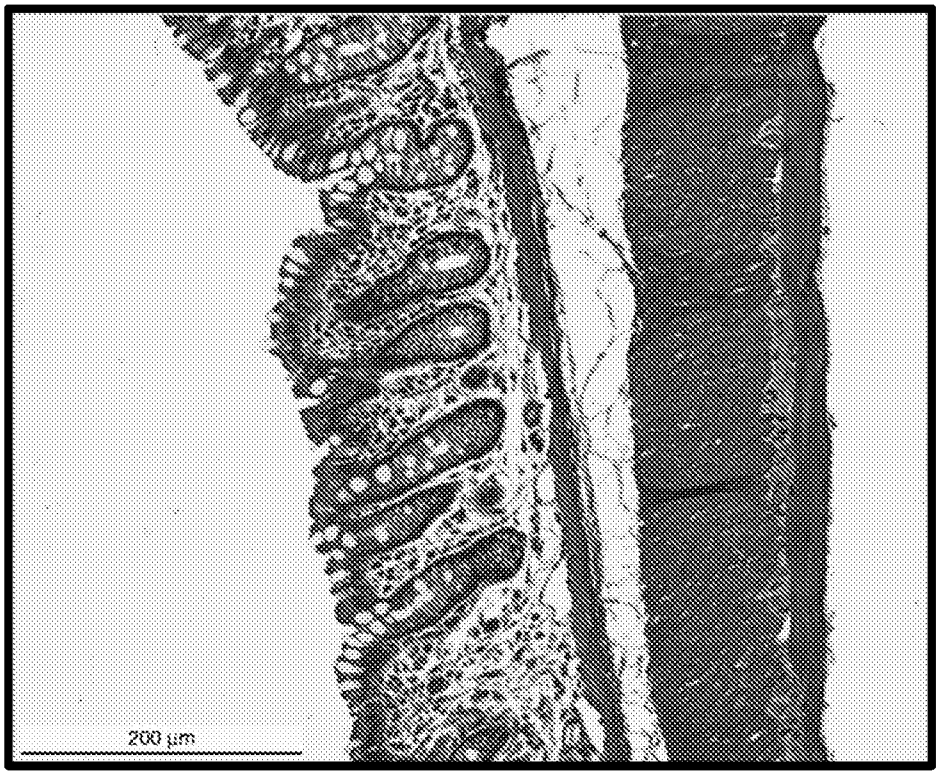


Fig. 7D

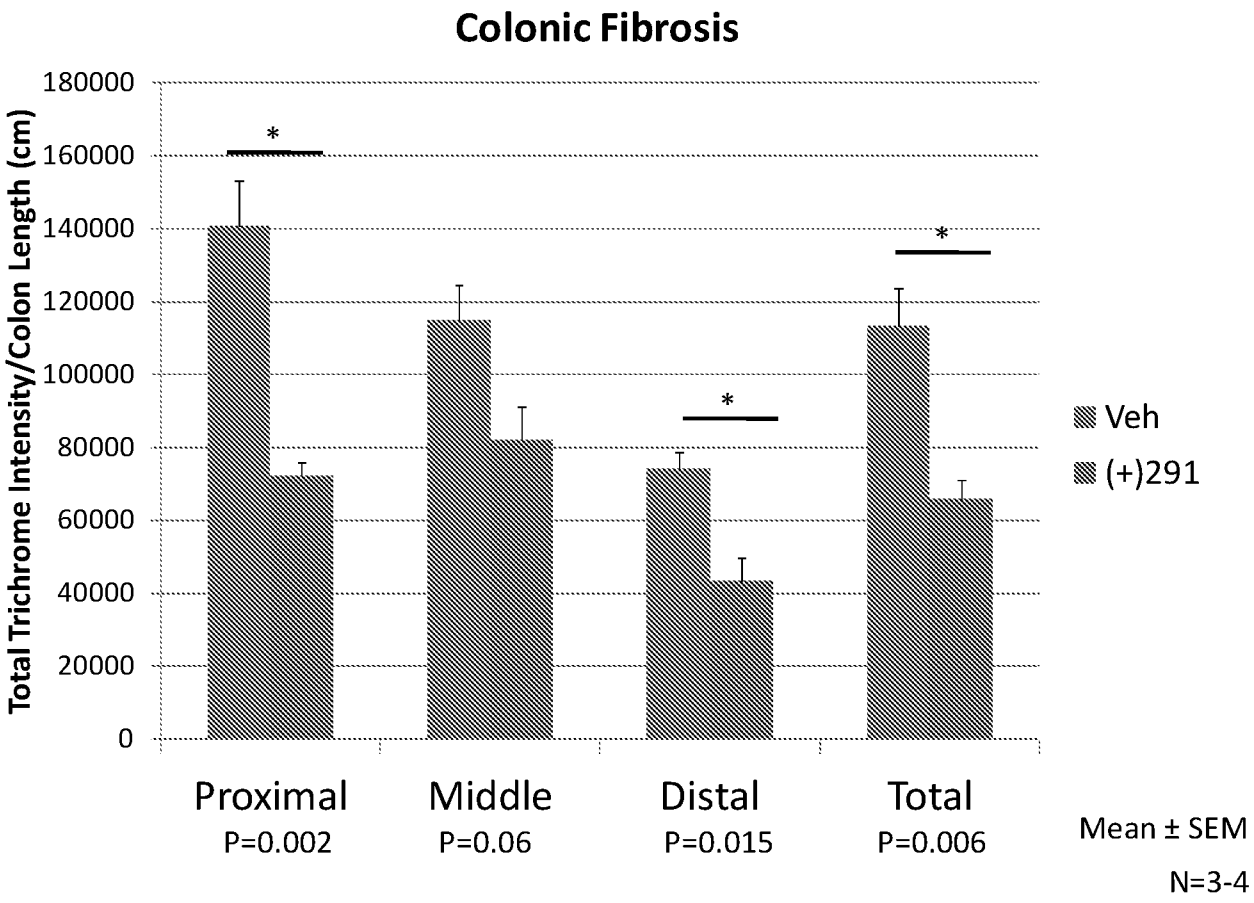

Colonic Fibrosis
Total Trichrome Intensity/Colon Length (cm)
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
*
*
*
Proximal
P=0.002
Middle
P=0.06
Distal
P=0.015
Total
P=0.006
Veh
(+)291
Mean ± SEM
N=3-4

Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/021374

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/41; A61K 31/426; A61K 31/4365; C07D 277/00 (2016.01)
CPC - C12Y 101/01141; A61K 31/41; A61K 31/426; A61K 31/4365; C07D 277/00 (2016.05)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/41; A61K 31/426; A61K 31/4365; C07D 277/00 (2016.01)
CPC - A61K 31/41; A61K 31/426; A61K 31/4365; C07D 277/00; C12Y 101/01141 (2016.05)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/301; 514/361; 514/365 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, STN, Google Scholar
Search terms used: 15-PGDH inhibitor, fibrosis, fibrotic disease, systemic sclerosis, collagen, thienopyridine, pyrazole, sw033291, oxatriaazole, sulfanyloxatriazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2001/017480 A2 (ANDROSOLUTIONS INC) 15 March 2001 (15.03.2001) entire document	1-3, 11, 13, 14, 20-25
A	WO 2013/158649 A1 (CASE WESTERN RESERVE UNIVERSITY et al) 24 October 2013 (24.10.2013) entire document	1-3, 11, 13, 14, 20-25
A	US 6,214,533 B1 (HÓ et al) 10 April 2001 (10.04.2001) entire document	1-3, 11, 13, 14, 20-25
A	EP 1 080 728 A1 (TORAY INDUSTRIES, INC) 07 March 2001 (07.03.2001) entire document	1-3, 11, 13, 14, 20-25
A	US 7,629,112 B1 (ZENGERLE et al) 08 December 2009 (08.12.2009) entire document	1-3, 11, 13, 14, 20-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2016	05 AUG 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-30 are drawn to methods.

The first invention of Group I+ is restricted to a method of treating or preventing a fibrotic disease, disorder or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a 15-PGDH inhibitor, wherein the fibrotic disease, disorder or condition is systemic sclerosis; wherein the 15-PGDH inhibitor includes a compound having formula (I): as shown in claim 14 of the instant invention, wherein n is 0; Y1, Y2, and R1 are each hydrogen; U1 is N; X1 and X2 are independently N; Z1 is O; and methods thereof. It is believed that claims 1-3, 11, 13, 14, and 20-25 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would a method of treating or preventing a fibrotic disease, disorder or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a 15-PGDH inhibitor, wherein the fibrotic disease, disorder or condition is chronic renal failure; wherein the 15-PGDH inhibitor includes a compound having formula (I): as shown in claim 14 of the instant invention, wherein n is 0; Y1, Y2, and R1 are each C24 alkyl; U1 is C-R2, wherein R2 is CF3; X1 and X2 are independently N; Z1 is S; and methods thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the fibrotic disease, disorder or condition and 15-PGDH inhibitor.

The Groups I+ share the technical features of a method of treating or preventing a fibrotic disease, disorder or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a 15-PGDH inhibitor; and a method for decreasing or reducing collagen secretion and/or collagen deposition and/or collagen accumulation and/or collagen fiber accumulation in a tissue or organ of a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the 15-PGDH inhibitor. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 01/17480 A2 to Androsolutions Inc. teaches a method of treating or preventing a fibrotic disease, disorder or condition in a subject in need thereof (Abstract), the method comprising administering (Claims 1, 2, and 7; Pg. 9, Lns. 17-34; Pg. 13, Ln. 31 through Pg. 14, Ln. 2) to the subject a therapeutically effective amount of a 15-PGDH inhibitor (Claims 1, 2, and 7; Pg. 9, Lns. 17-34; Pg. 13, Ln. 31 through Pg. 14, Ln. 2).

Additionally, EP 1 080 728 A1 to Toray Industries Inc. teaches a method for decreasing or reducing collagen secretion and/or collagen deposition and/or collagen accumulation and/or collagen fiber accumulation in a tissue or organ of a subject in need thereof (Claims 5 and 6; Abstract; Para. [0009]), comprising administering to the subject a therapeutically effective amount of a compound for elevating prostaglandins in the tissue (Para. [0006], The present invention provides a prostaglandin EP4 receptor ligand comprising prostaglandin I2 derivatives as effective ingredients, and a method for treating prostaglandin EP4 receptor-mediated diseases.; Para. [0009], For example, since it is made clear that the compound according to the present invention has a suppressive property of collagen production in Example 2, it may be effective for prevention or therapy of the diseases caused by collagen production.; Para. [0017]; See Para. [0101] of the applicants specification which describes 15-PGDH inhibitors for elevating prostaglandins in the tissue).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/021374

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1-3, 11, 13, 14, and 20-25 have been analyzed subject to the restriction that the claims read on the formula (I) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a method of treating or preventing a fibrotic disease, disorder or condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a 15-PGDH inhibitor, wherein the fibrotic disease, disorder or condition is systemic sclerosis; wherein the 15-PGDH inhibitor includes a compound having formula (I): as shown in claim 14 of the instant invention, wherein n is 0; Y1, Y2, and R1 are each hydrogen; U1 is N; X1 and X2 are Independently N; Z1 is O; and methods thereof.

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 11, 13, 14, 20-25

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 107921025 A
(43)申请公布日 2018.04.17

(21)申请号 201680026631.8

(22)申请日 2016.03.08

(30)优先权数据
62/129,885 2015.03.08 US

(85)PCT国际申请进入国家阶段日
2017.11.07

(86)PCT国际申请的申请数据
PCT/US2016/021374 2016.03.08

(87)PCT国际申请的公布数据
WO2016/144958 EN 2016.09.15

(71)申请人 卡斯西部储备大学
地址 美国俄亥俄州

(72)发明人 S·马科维茨 S·格尔森
A·德赛 W·J·浩

(74)专利代理机构 余姚德盛专利代理事务所（普通合伙）33239
代理人 郑洪成

(51)Int.Cl.
A61K 31/41(2006.01)
A61K 31/426(2006.01)
A61K 31/4365(2006.01)
C07D 277/00(2006.01)

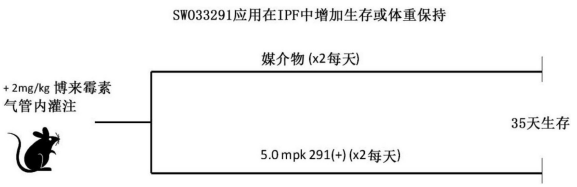
权利要求书15页 说明书105页 附图7页

(54)发明名称

用于治疗纤维症的短链脱氢酶活性的抑制剂

(57)摘要

本发明提供了一种用于治疗或预防纤维化疾病、紊乱或状况的方法，其包括向有需要治疗的受试对象给予15-PGDH抑制剂。



CN 107921025 A

1.一种在有需要的受试对象中治疗或预防纤维化疾病、紊乱或状况的方法,该方法包括向所述的受试对象给予治疗有效量的15-PGDH抑制剂。

2.权利要求1所述的方法,其中所述的纤维化疾病、紊乱或状况全部或部分表征为纤维物质的过量产生,包括纤维化物质在细胞外基质中的过量产生;或者正常组织元素被异常的、非功能性的和/或过量累积的基质相关成分替代。

3.权利要求1所述的方法,其中所述的纤维化疾病、紊乱或状况选自系统性硬化病,多灶性纤维硬化,肾性系统纤维症,硬皮病,硬皮病的移植物抗宿主病,肾纤维症,肾小球硬化,肾小管间质纤维症,进行性肾病或糖尿病肾病,心脏纤维症,肺纤维症,肾小球硬化症肺纤维症,特发性肺纤维症,硅肺病,石棉沉滞症,间质性肺病,间质性肺病,化疗/放疗诱导的肺纤维症,口腔纤维症,心肌心内膜纤维症,三角肌纤维症,胰腺炎,炎性肠病,Crohn病,坏死性筋膜炎,嗜酸性筋膜炎,表征为正常肌肉组织不同程度地被纤维组织替代的一般的纤维化综合征,腹膜内纤维症,肝纤维症,慢性间质性肝炎,慢性肾功能衰竭;骨髓纤维症,骨髓纤维症,药物诱发的麦角中毒,骨髓增生异常综合征,胶原性结肠炎,急性纤维症,特定器官纤维症。

4.权利要求1所述的方法,其中所述的纤维化疾病、紊乱或状况包括肺纤维症。

5.权利要求3所述的方法,其中所述的肺纤维症选自肺纤维症,肺动脉高压,肺慢性阻塞性疾病(COPD),哮喘,特发性肺纤维症,结节病,囊性纤维症,家族性肺纤维症,硅肺病,石棉沉滞症,煤矿工人尘肺,炭尘肺,过敏性肺炎,由吸入无机粉尘导致的肺纤维症,由感染性试剂导致的肺纤维症,由吸入有毒气体、气溶胶、化学粉尘、烟或蒸汽导致的肺纤维症,药物诱发的间质性肺病,或肺动脉高压,以及它们的组合。

6.权利要求5所述的方法,其中所述的肺纤维症为囊性纤维症。

7.权利要求1所述的方法,其中所述的纤维症疾病、紊乱或状况包括肾纤维症。

8.权利要求1所述的方法,其中所述的纤维化疾病、紊乱或状况包括肝纤维症。

9.权利要求8所述的方法,其中所述的肝纤维症是由慢性肝病,肝炎后肝硬化,乙型肝炎病毒感染,丙型肝炎病毒感染,丁型肝炎病毒感染,血吸虫病,原发性胆汁性肝硬化,酒精性肝病或非酒精性脂肪性肝炎(NASH),NASH相关肝硬化肥胖,糖尿病,蛋白质营养不良,冠心病,自身免疫性肝炎,囊性纤维症,α-1-抗胰蛋白酶缺乏,原发性胆汁性肝硬化,药物反应和暴露于毒素,或它们的组合引起的。

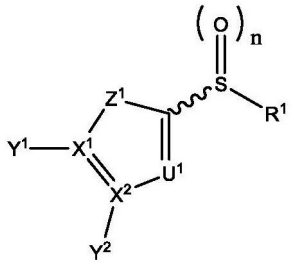
10.权利要求1所述的方法,其中所述的纤维化疾病、紊乱或状况包括心脏纤维症。

11.权利要求1所述的方法,其中所述的纤维化疾病、紊乱或状况为系统性硬化病。

12.权利要求1所述的方法,其中所述的纤维化疾病、紊乱或状况是由手术后粘连形成造成的。

13.权利要求1所述的方法,其中所述的15-PGDH抑制剂是以有效减少或抑制代治疗受试对象的组织或器官中胶原蛋白沉积、胶原蛋白累积、胶原纤维累积、炎性细胞因子表达和/或炎性细胞浸润的量而给予的。

14.权利要求1所述的方法,其中所述的15-PGDH抑制剂包括具有下式(I)所示的化合物及其药物可接受的盐:



(I)

其中n为0-2；

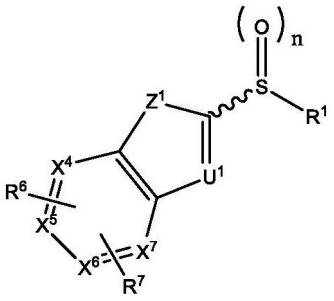
Y^1,Y^2和R^1是相同的或不同的,并且均选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2$-OH),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2$-NH2,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中Y^1和Y^2可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基；

U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省；

X^1和X^2独立地为N或C,并且其中当X^1和/或X^2为N时,Y^1和/或Y^2各自是缺省的；

Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线状的、支化的或环状的,并且其是非取代的或取代的。

15.权利要求14所述的方法,其中所述的化合物具有下式(II)及其药物可接受的盐:



(II)

其中n为0-2;

X^4,X^5,X^6和X^7独立地为N或CR^c;

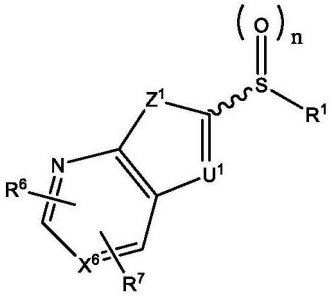
R^1,R^6,R^7和R^c均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省;

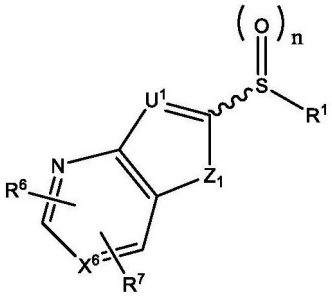
Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线状的、支化的或环状的,

并且其是非取代的或取代的。

16.权利要求14所述的方法，其中所述的化合物具有下式(III)或(IV)及其药物可接受的盐：



(III)，或



(IV)

其中n为0-2；

X^6独立地为N或CR^c；

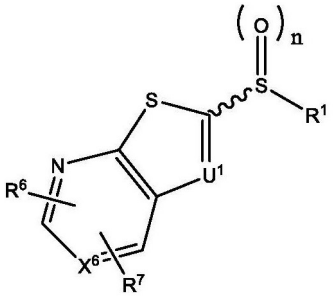
R^1,R^6,R^7和R^c均独立地选自氢，取代的或非取代的C_1-C_{24}烷基，C_2-C_{24}烯基，C_2-C_{24}炔基，C_3-C_{20}芳基，杂芳基，包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基)，NC(O)(C_1-C_6烷基)，O和S)，C_6-C_{24}烷芳基，C_6-C_{24}芳烷基，卤素，-Si(C_1-C_3烷基)$_3$，羟基，硫氢基，C_1-C_{24}烷氧基，C_2-C_{24}烯氧基，C_2-C_{24}炔氧基C_5-C_{20}芳氧基，酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基))，酰氧基(-O-酰基)，C_2-C_{24}烷氧基羰基(-(CO)-O-烷基)，C_6-C_{20}芳氧基羰基(-(CO)-O-芳基)，C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基)，C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基)，羧基(-COOH)，羧酸($-COO^-$)，氨基甲酰(-(CO)-NH_2)，C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基))，芳基氨基甲酰(-(CO)-NH-芳基)，硫代氨基甲酰(-(CS)-NH_2)，脲基(-NH-(CO)-NH_2)，氰基(-CN)，异氰基($-N^+C^-$)，氰氧基(-O-CN)，异氰氧基($-O-N^+=C^-$)，异硫代氰氧基(-S-CN)，叠氮基($-N=N^+=N^-$)，甲酰基(--(CO)--H)，硫代甲酰基(--(CS)--H)，氨基(--NH_2)，C_1-C_{24}烷基氨基，C_5-C_{20}芳基氨基，C_2-C_{24}烷基氨基(-NH-(CO)-烷基)，C_6-C_{20}芳基氨基(-NH-(CO)-芳基)，亚氨基(-CR=NH，其中R为氢，C_1-C_{24}烷基，C_5-C_{20}芳基，C_6-C_{24}烷芳基，C_6-C_{24}芳烷基等)，烷基亚氨基(-CR=N(烷基)，其中R=氢，烷基，芳基，烷芳基，芳烷基等)，芳基亚氨基(-CR=N(芳基)，其中R=氢，烷基，芳基，烷芳基等)，硝基(-NO_2)，亚硝基(-NO)，磺基(-SO_2-OH)，磺酸($-SO_2-O^-$)，C_1-C_{24}烷基硫基(-S-烷基；还称为"烷基硫代")，芳基硫基(-S-芳基；还称为"芳基硫代")，C_1-C_{24}烷基亚磺酰基(-(SO)-烷基)，C_5-C_{20}芳基亚磺酰基(-(SO)-芳基)，C_1-C_{24}烷基亚磺酰基(-SO_2-烷基)，C_5-C_{20}芳基亚磺酰基(-SO_2-芳基)，磺胺(-SO_2-NH2，-SO_2NY_2(其中Y独立地为H,arlyl或烷基)，膦酰基(-P(O)($OH)_2$)，磷酰基(-P(O)($O^-)_2$)，次膦酸基(-P(O)(O^-))，亚磷酸(-PO_2)，膦基(--PH_2)，聚烷基醚，磷酸盐，磷酸酯，引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团，它们的组合，并且其中R^6和R^7可以连接而形成环或多环，其中所述的环为取代的或非取代的芳基，

取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省;

Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线性的、支化的或环状的,并且其是非取代的或取代的。

17.权利要求14所述的方法,其中所述的化合物具有下式(V)及其药物可接受的盐:



(V)

其中n为0-2;

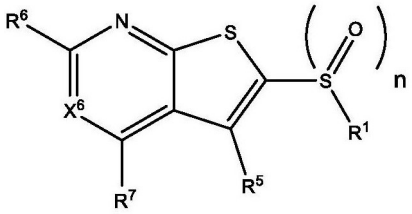
X^6独立地为N或CR^c;

R^1,R^6,R^7和R^c均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸(-SO_2-O^-),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的

基团,它们的组合,并且其中R^6和R^7可以连接从而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省。

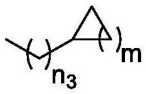
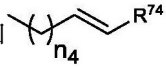
18.权利要求14所述的方法,其中所述的化合物具有下式(VI)及其药物可接受的盐:



(VI)

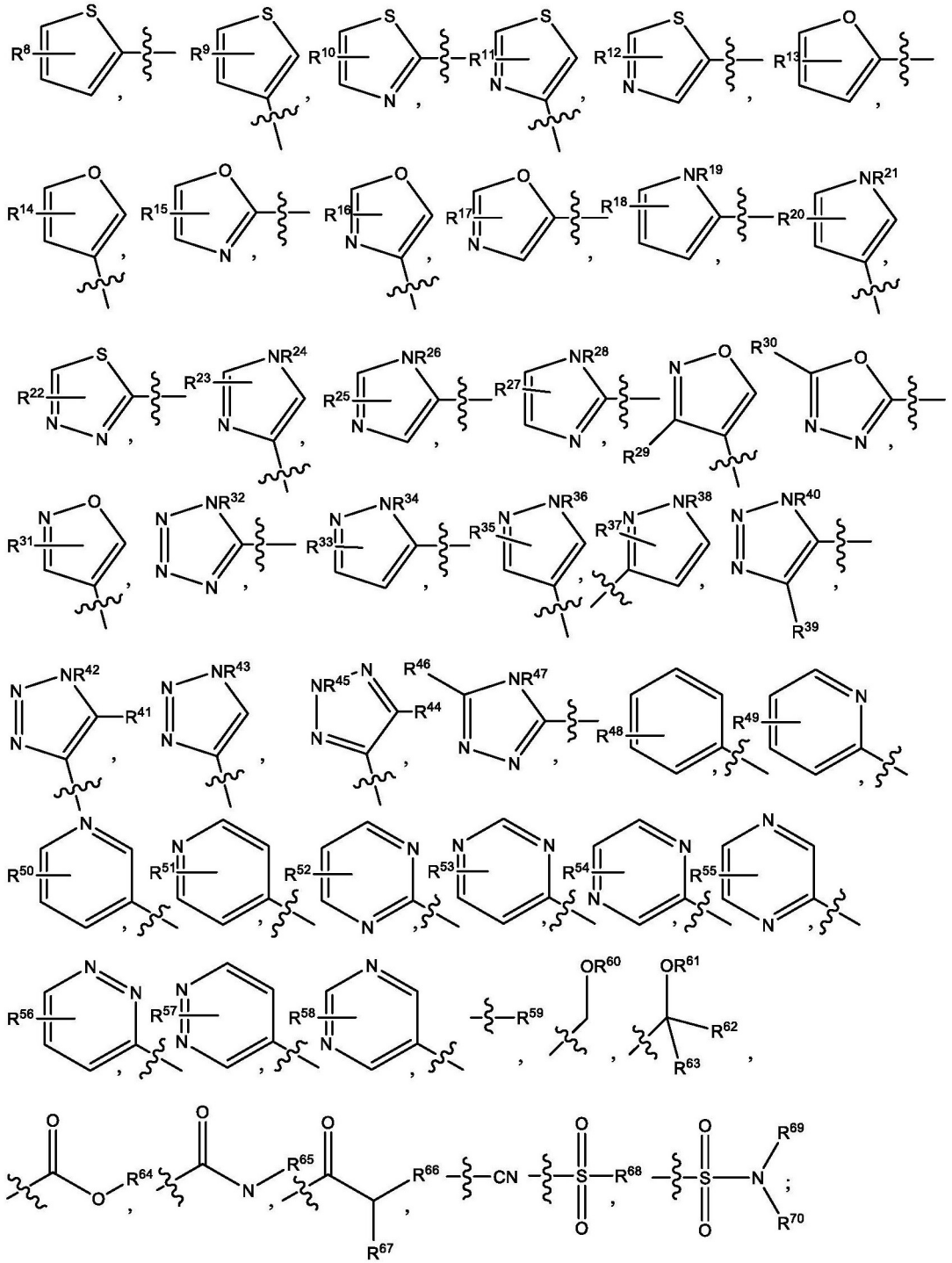
其中n=0-2;

X^6为N或CR^c;

R^1选自支化的或线性的芳烷基,包括-$(CH_2)_{n1}CH_3$(n_1=0-7),  ,其中n_2=0-6,并且X为以下一者:CF_yH_z(y+z=3),CCl_yH_z(y+z=3),OH,OAc,OMe,R^{71},OR^{72},CN,$N(R^{73})_2$,  (n_3=0-5,m=1-5),和  (n_4=0-5);

R^5选自H,Cl,F,NH_2和$N(R^{76})_2$;

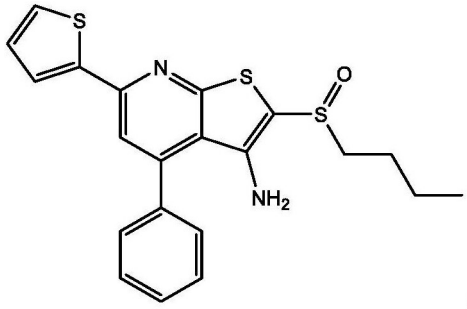
R^6和R^7均可以独立地为以下的一者:

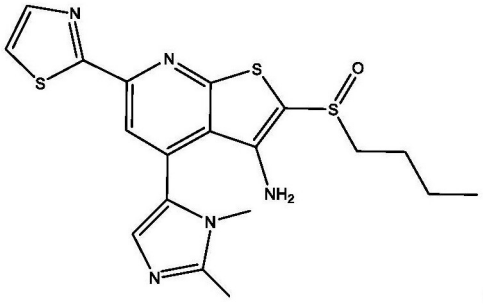


R^8,R^9,R^{10},R^{11},R^{12},R^{13},R^{14},R^{15},R^{16},R^{17},R^{18},R^{19},R^{20},R^{21},R^{22},R^{23},R^{24},R^{25},R^{26},R^{27},R^{28},R^{29},R^{30},R^{31},R^{32},R^{33},R^{34},R^{35},R^{36},R^{37},R^{38},R^{39},R^{40},R^{41},R^{42},R^{43},R^{44},R^{45},R^{46},R^{47},R^{48},R^{49},R^{50},R^{51},R^{52},R^{53},R^{54},R^{55},R^{56},R^{57},R^{58},R^{59},R^{60},R^{61},R^{62},R^{63},R^{64},R^{65},R^{66},R^{67},R^{68},R^{69},R^{70},R^{71},R^{72},R^{73},R^{74},R^{76}和R^c均是相同的或不同的,并且独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),包含5-14环原子的杂芳基或杂环基(其中1-6个环原子独立地选自N,NH,N(C_1-C_3烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,甲硅烷基,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰

基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)--NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),二氧化硫氨基($-SO_2N(R)_2$,其中R独立地为H,烷基,芳基或杂芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2-OH$),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2-NH_2$,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)$(OH)_2$),磷酰基(-P(O)$(O^-)_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯[-OP(O)$(OR)_2$,其中R=H,甲基或其他烷基],引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合。

19.权利要求14所述的方法,其中所述的化合物以下及其药物可接受的盐:



;


。

20.权利要求14所述的方法,其中所述的抑制剂:i)在2.5μM浓度下,刺激表达15-PGDH荧光素酶融合物构建体的Vaco503报告细胞系,达到超过70的荧光素酶生产水平(使用一定的规模,在该规模上,值100表示报告生产水平超过基线的2倍);ii)在2.5μM浓度下,刺激表达15-PGDH荧光素酶融合物构建体的V9m报告细胞系,达到超过75的荧光素酶生产水平;iii)在7.5μM浓度下,刺激表达15-PGDH荧光素酶融合物构建体的LS174T报告细胞系,达到超过70的荧光素酶生产水平;以及iv)在7.5μM浓度下,不能激活表达TK-海肾荧光素酶报告物的阴性对照V9m细胞系达到超过20的水平;以及v)在IC_{50}低于1μM下抑制重组15-PGDH蛋白质的酶活性。

21.权利要求14所述的方法,其中所述的抑制剂:i)在2.5μM浓度下,刺激表达15-PGDH荧光素酶融合物构建体的Vaco503报告细胞系,从而增加荧光素酶的生产;ii)在2.5μM浓度下,刺激表达15-PGDH荧光素酶融合物构建体的V9m报告细胞系,从而增加荧光素酶的生产;iii)在7.5μM浓度下,刺激表达15-PGDH荧光素酶融合物构建体的LS174T报告细胞系,从而增加荧光素酶的生产;iv)在7.5μM浓度下,不能刺激表达TK-海肾荧光素酶报告物的阴性对

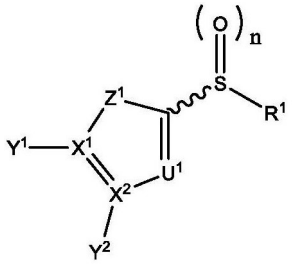
照V9m细胞系，达到荧光素酶水平超过背景20％以上；以及v)在IC_{50}低于1μM下抑制重组15-PGDH蛋白质的酶活性。

22.权利要求14所述的方法，其中在重组15-PGDH浓度为大约5nM至大约10nM下，在IC_{50}低于1μM下，或者优选地在IC_{50}低于250nM下，或者更优选地在IC_{50}低于50nM下，或者更优选地在IC_{50}低于10nM下，或者更优选地在IC_{50}低于5nM下，所述的抑制剂可以抑制所述的重组15-PGDH的酶活性。

23.一种用于在有需要的受试对象的组织或器官中降低或减少胶原蛋白分泌和/或胶原蛋白沉积和/或胶原蛋白累积和/或胶原纤维累积的方法，其包括向所述的受试对象给予治疗有效量的所述的15-PGDH抑制剂。

24.权利要求23所述的方法，其中所述的器官或组织包括肾脏、肺、肝脏、肠、结肠、皮肤或心脏的至少一种。

25.权利要求23所述的方法，其中所述的15-PGDH抑制剂包括具有下式(I)的化合物及其药物可接受的盐：



(I)

其中n为0-2；

Y^1，Y^2和R^1是相同的或不同的，并且均选自氢，取代的或非取代的C_1-C_{24}烷基，C_2-C_{24}烯基，C_2-C_{24}炔基，C_3-C_{20}芳基，杂芳基，包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N，NH，N(C_1-C_6烷基)，NC(O)(C_1-C_6烷基)，O和S)，C_6-C_{24}烷芳基，C_6-C_{24}芳烷基，卤素，-Si(C_1-C_3烷基)$_3$，羟基，硫氢基，C_1-C_{24}烷氧基，C_2-C_{24}烯氧基，C_2-C_{24}炔氧基C_5-C_{20}芳氧基，酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基))，酰氧基(-O-酰基)，C_2-C_{24}烷氧基羰基(-(CO)-O-烷基)，C_6-C_{20}芳氧基羰基(-(CO)-O-芳基)，C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基)，C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基)，羧基(-COOH)，羧酸($-COO^-$)，氨基甲酰(-(CO)-NH_2)，C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基))，芳基氨基甲酰(-(CO)-NH-芳基)，硫代氨基甲酰(-(CS)-NH_2)，脲基(-NH-(CO)-NH_2)，氰基(-CN)，异氰基($-N^+C^-$)，氰氧基(-O-CN)，异氰氧基($-O-N^+=C^-$)，异硫代氰氧基(-S-CN)，叠氮基($-N=N^+=N^-$)，甲酰基(--(CO)--H)，硫代甲酰基(--(CS)--H)，氨基(--NH_2)，C_1-C_{24}烷基氨基，C_5-C_{20}芳基氨基，C_2-C_{24}烷基氨基(-NH-(CO)-烷基)，C_6-C_{20}芳基氨基(-NH-(CO)-芳基)，亚氨基(-CR＝NH，其中R为氢，C_1-C_{24}烷基，C_5-C_{20}芳基，C_6-C_{24}烷芳基，C_6-C_{24}芳烷基等)，烷基亚氨基(-CR＝N(烷基)，其中R＝氢，烷基，芳基，烷芳基，芳烷基等)，芳基亚氨基(-CR＝N(芳基)，其中R＝氢，烷基，芳基，烷芳基等)，硝基($-NO_2$)，亚硝基(-NO)，磺基($-SO_2$-OH)，磺酸($-SO_2-O^-$)，C_1-C_{24}烷基硫基(-S-烷基；还称为"烷基硫代")，芳基硫基(-S-芳基；还称为"芳基硫代")，C_1-C_{24}烷基亚磺酰基(-(SO)-烷基)，C_5-C_{20}芳基亚磺酰基(-(SO)-芳基)，C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基)，C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基)，磺胺($-SO_2$-NH2，$-SO_2NY_2$(其中Y独立地为H，arlyl或烷基)，膦酰基(-P(O)(OH)$_2$)，磷酰基(-P(O)(O^-)$_2$)，次膦酸基(-P(O)(O^-))，亚磷酸($-PO_2$)，膦基(--PH_2)，聚烷

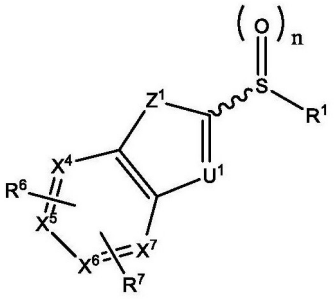
基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中Y^1和Y^2可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省;

X^1和X^2独立地为N或C,并且其中当X^1和/或X^2为N时,Y^1和/或Y^2各自是缺省的;

Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线状的、支化的或环状的,并且其是非取代的或取代的。

26.权利要求25述的方法,其中所述的化合物包括具有下式(II)及其药物可接受的盐:



(II)

其中n为0-2;

X^4,X^5,X^6和X^7独立地为N或CR^c;

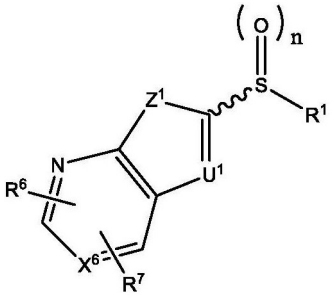
R^1,R^6,R^7和R^c均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}

芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

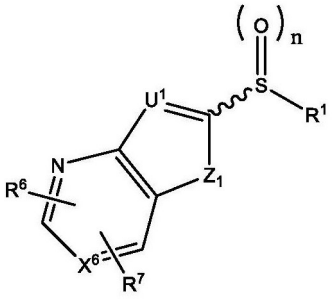
U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省;

Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线状的、支化的或环状的,并且其是非取代的或取代的。

27.权利要求25述的方法,其中所述的化合物包括具有下式(III)或(IV)及其药物可接受的盐:



(III),或



(IV)

其中n为0-2;

X^6独立地为N或CR^c;

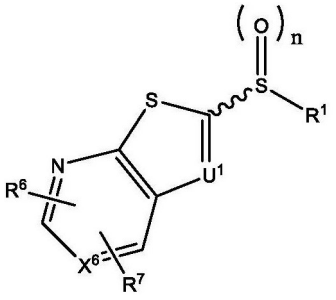
R^1,R^6,R^7和R^c均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-

C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基(-N^+C^-),氰氧基(-O-CN),异氰氧基(-O-N^+=C^-),异硫代氰氧基(-S-CN),叠氮基(-N=N^+=N^-),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸(-SO_2-O^-),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}$OR'(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}$OR'(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省;

Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线性的、支化的或环状的,并且其是非取代的或取代的。

28.权利要求25述的方法,其中所述的化合物包括具有下式(V)及其药物可接受的盐:



(V)

其中n为0-2;

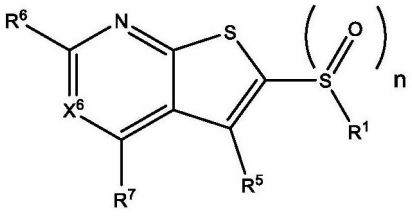
X^6独立地为N或CR^c;

R^1,R^6,R^7和R^c均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),

C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2-OH$),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2-NH2$,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)$(OH)_2$),磷酰基(-P(O)$(O^-)_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接从而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,$O-CH_2-CH_2X$,$CH_2-CH_2-CH_2X$,$O-CH_2-CH_2X$,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,$CH_2-CH_2-CH_2X$,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省。

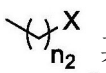
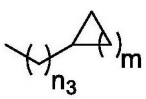
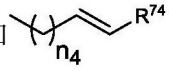
29.权利要求25述的方法,其中所述的化合物包括具有下式(VI)及其药物可接受的盐:



(VI)

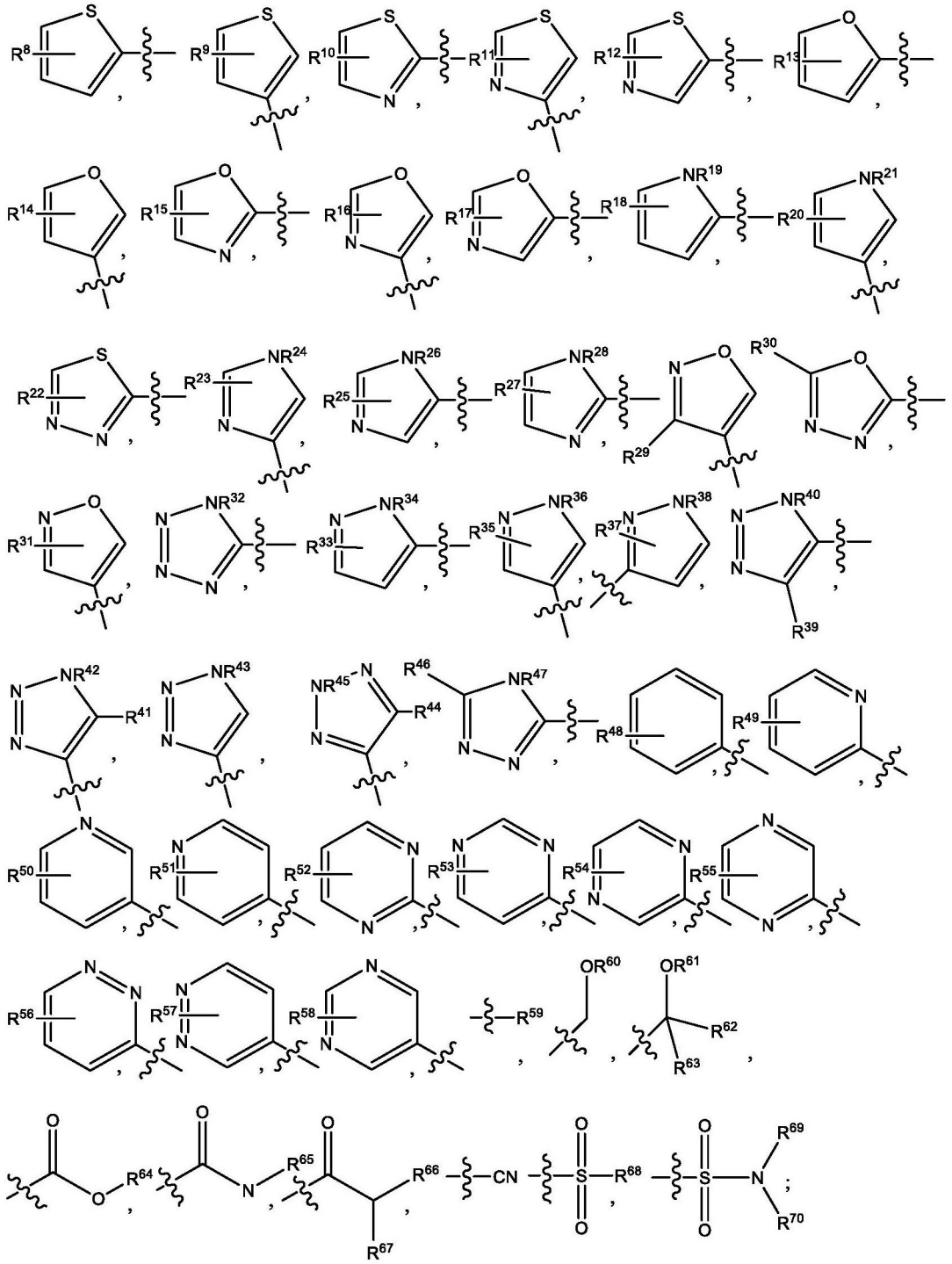
其中n=0-2;

X^6为N或CR^c;

R^1选自支化的或线性的芳烷基,包括-$(CH_2)_{n1}CH_3$(n_1=0-7),  ,其中n_2=0-6,并且X为以下一者:CF_yH_z(y+z=3),CCl_yH_z(y+z=3),OH,OAc,OMe,R^{71},OR^{72},CN,$N(R^{73})_2$,  (n_3=0-5,m=1-5),和  (n_4=0-5);

R^5选自H,Cl,F,NH_2和$N(R^{76})_2$;

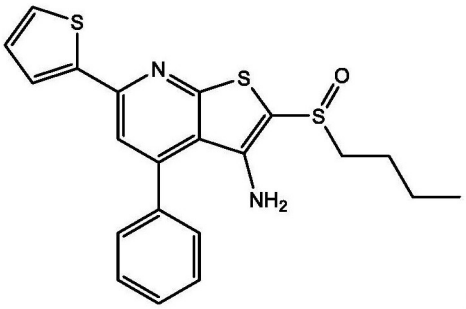
R^6和R^7均可以独立地为以下的一者:

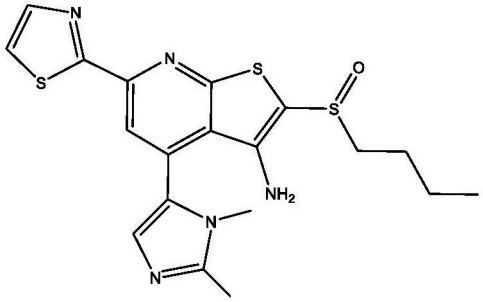


R^8,R^9,R^{10},R^{11},R^{12},R^{13},R^{14},R^{15},R^{16},R^{17},R^{18},R^{19},R^{20},R^{21},R^{22},R^{23},R^{24},R^{25},R^{26},R^{27},R^{28},R^{29},R^{30},R^{31},R^{32},R^{33},R^{34},R^{35},R^{36},R^{37},R^{38},R^{39},R^{40},R^{41},R^{42},R^{43},R^{44},R^{45},R^{46},R^{47},R^{48},R^{49},R^{50},R^{51},R^{52},R^{53},R^{54},R^{55},R^{56},R^{57},R^{58},R^{59},R^{60},R^{61},R^{62},R^{63},R^{64},R^{65},R^{66},R^{67},R^{68},R^{69},R^{70},R^{71},R^{72},R^{73},R^{74},R^{76}和R^c均是相同的或不同的,并且独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),包含5-14环原子的杂芳基或杂环基(其中1-6个环原子独立地选自N,NH,N(C_1-C_3烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,甲硅烷基,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰

基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)--NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),二氧化硫氨基($-SO_2N(R)_2$,其中R独立地为H,烷基,芳基或杂芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2-OH$),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2-NH_2$,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯[-OP(O)(OR)$_2$,其中R=H,甲基或其他烷基],引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合。

30.权利要求25所述的方法,其中所述的化合物以下及其药物可接受的盐:



;


。

用于治疗纤维症的短链脱氢酶活性的抑制剂

[0001] 相关申请

[0002] 本申请要求2015年3月8日提交的美国临时申请No.62/129,885的优先权,该申请的主题以引用方式全文并入本文。

[0003] 政府资助

[0004] 本发明是由The National Institutes of Health授予的,在Grant No.R01CA127306,R01CA127306-03S1,1P01CA95471-10,和5P50CA150964,T32EB005583,F32DK107156的政府支持下进行的。美国政府可以具有本发明的某些权利。

背景技术

[0005] 纤维症是一种慢性的并且进行性的过程,其表征为细胞外基质(ECM)的过量累积,从而导致所涉及组织的变硬和/或瘢痕形成。其通过复杂细胞、细胞外基质、细胞因子和生长因子相互作用而发展。其中涉及不同的细胞类型,例如衍生自上皮和内皮细胞的(通过称为上皮和内皮-间叶细胞过渡的过程)残留的间质细胞(成纤维细胞和成肌纤维细胞)和产ECM的细胞,局部或骨髓衍生的干细胞(纤维细胞)。成肌纤维细胞长期被认为是与正常的伤口愈合有关的主要细胞类型,并且作为纤维发生的重要效应器细胞。它们高度合成用于胶原蛋白和其他ECM成分,并且表征为α-平滑肌肌动蛋白(α-SMA)的从头表达。在纤维症的动物模型中,纤维化病变中成肌纤维细胞的存在与活性纤维症的发展有关,并且它们在人类疾病中在纤维化病灶的存留和定位与疾病进展有关。成肌纤维细胞还展现出增强的迁移表现型,并且能够释放大量的促纤维化中间物。

[0006] 纤维化疾病(包括肺纤维症、系统性硬化病、慢性间质性肝炎和进行性肾病)是发病率和死亡率的主要原因,并且可以影响所有的组织和器官系统。纤维化组织重塑还可以影响癌症转移并且在移植受体中加速慢性移植物排斥。

[0007] 发明概述

[0008] 本发明所述的实施方案涉及用于治疗和/或预防纤维症以及多种纤维化疾病、紊乱或状况的组合物和方法。如以下实施例中所述,发现短链脱氢酶活性的抑制剂,例如15-PGDH抑制剂,可以给予有需要的受试对象,从而降低纤维化症状,例如胶原沉积、胶原累积、胶原纤维形成、炎性细胞因子表达和炎性细胞浸润,并且治疗和/或预防纤维化疾病、紊乱和状况,其全部或部分表征为纤维物质的过量产生,包括纤维化物质在细胞外基质中的过量产生;或者正常组织元素被异常的、非功能性的和/或过量累积的基质相关成分替代。

[0009] 整体或部分表征为纤维化物质的过量产生的纤维化疾病、紊乱和状况可以包括系统性硬化病,多灶性纤维硬化,肾性系统纤维症,硬皮病(包括硬斑病,泛发性硬斑病或线状硬皮病),硬皮病的移植物抗宿主病,,肾纤维症(包括肾小球硬化,肾小管间质纤维症,进行性肾病或糖尿病肾病),心脏纤维症(例如心肌纤维症),肺纤维症(例如肺纤维症,肾小球硬化症肺纤维症,特发性肺纤维症,硅肺病,石棉沉滞症,间质性肺病,间质性肺病,和化疗/放疗诱导的肺纤维症),口腔纤维症,心肌心内膜纤维症,三角肌纤维症,胰腺炎,炎性肠病,Crohn病,坏死性筋膜炎,嗜酸性筋膜炎,一般的纤维化综合征(表征为正常肌肉组织不同程

度地被纤维组织替代),肺纤维症,慢性间质性肝炎,慢性肾功能衰竭;骨髓纤维症(骨髓纤维症),药物诱发的麦角中毒,骨髓增生异常综合征,骨髓增殖性综合征,胶原性结肠炎,急性纤维症,特定器官纤维症等。

[0010] 在一些实施方案中,治疗或预防纤维化疾病、紊乱或状况的方法包括向有需要的受试对象给予治疗有效量的15-PGDH抑制剂。

[0011] 在一些实施方案中,15-PGDH抑制剂可以用于治疗或预防肺纤维症。可以治疗的肺纤维症可以选自肺纤维症,肺动脉高压,肺慢性阻塞性疾病(COPD),哮喘,特发性肺纤维症,结节病,囊性纤维症,家族性肺纤维症,硅肺病,石棉沉滞症,煤矿工人尘肺,炭尘肺,过敏性肺炎,由吸入无机粉尘导致的肺纤维症,由感染性试剂导致的肺纤维症,由吸入有毒气体、气溶胶、化学粉尘、烟或蒸汽导致的肺纤维症,药物诱发的间质性肺病,或肺动脉高压,以及它们的组合。

[0012] 在其他的实施方案中,15-PGDH抑制剂可以用于治疗或预防肾纤维症。肾纤维症可以在肾衰竭,导管放置,肾病,肾小球硬化症,血管球性肾炎,慢性肾功能不全,急性肾损伤,终末期肾病或肾衰竭,或者它们的组合之后由透析导致。

[0013] 在其他的实施方案中,15-PGDH抑制剂可以用于治疗或预防肝纤维症。肝纤维症可以由慢性肝病,肝炎后肝硬化,乙型肝炎病毒感染,丙型肝炎病毒感染,丁型肝炎病毒感染,血吸虫病,原发性胆汁性肝硬化,酒精性肝病或非酒精性脂肪性肝炎(NASH),NASH相关肝硬化肥胖,糖尿病,蛋白质营养不良,冠心病,自身免疫性肝炎,囊性纤维症,α-1-抗胰蛋白酶缺乏,原发性胆汁性肝硬化,药物反应和暴露于毒素或它们的组合导致。

[0014] 在一些实施方案中,15-PGDH抑制剂可以用于治疗或预防心脏纤维症,例如心脏纤维症和心肌心内膜纤维症。

[0015] 在一些实施方案中,15-PGDH抑制剂可以用于治疗或预防系统性硬化病。

[0016] 在一些实施方案中,15-PGDH抑制剂可以用于治疗或预防由手术后粘连形成导致的纤维化疾病、紊乱或状况。

[0017] 在一些实施方案中,15-PGDH抑制剂可以用于减少或防止受试对象中的瘢痕的形成。

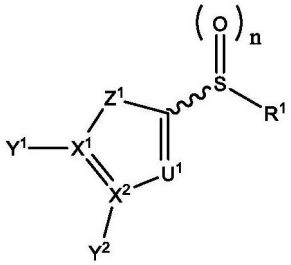
[0018] 在一些实施方案中,15-PGDH抑制剂可以用于减少或防止皮肤上瘢痕的形成或硬皮病。

[0019] 在多种实施方案中,可以给予治疗有效量的15-PGDH抑制剂,使得纤维化疾病、紊乱或状况、或者其他相关的疾病、紊乱或状况的至少一个症状或特征在强度、严重性或频率方面降低,或者具有延迟的发作。

[0020] 在其他的实施方案中,15-PGDH抑制剂可以用于降低或减少在受试对象的组织或器官(例如肺、肝脏、肠、结肠、皮肤或心脏)中胶原蛋白分泌、或胶原蛋白沉积、或胶原纤维累积的方法中。所述的方法可以包括向有需要的受试对象给予治疗有效量的15-PGDH抑制剂。所述的受试对象可以具有或者处于在组织或器官(例如肾、肺、肝脏、肠、结肠、皮肤或心脏)中过量胶原蛋白分泌的风险之下。通常,器官中过量的胶原蛋白分泌或胶原蛋白沉积是由损伤或损害导致的。这种损伤或损害可以是器官特异性的。可以在足够的时间内给予15-PGDH抑制剂,从而完全或部分降低或减少组织或器官中胶原蛋白沉积的水平。足够的时间可以为1周、或者1周至1个月、或者1个月至2个月、或者2个月或更长。对于慢性状况而言,可

以终生有利地给予15-PGDH抑制剂。

[0021] 在一些实施方案中，15-PGDH抑制剂可以以有效增加组织中前列腺素水平的量给予受试对象的组织。15-PGDH抑制剂可以包括式(I)、以及它们的药物可接受的盐：

[0022]  (I)，

[0023] 其中n为0-2；

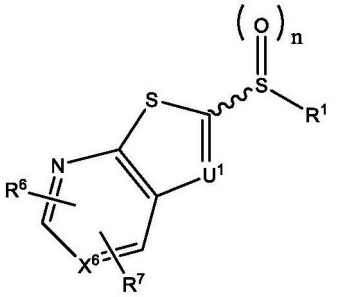
[0024] Y^1，Y^2和R^1是相同的或不同的，并且均选自氢，取代的或非取代的C_1-C_{24}烷基，C_2-C_{24}烯基，C_2-C_{24}炔基，C_3-C_{20}芳基，杂芳基，包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N，NH，N(C_1-C_6烷基)，NC(O)(C_1-C_6烷基)，O和S)，C_6-C_{24}烷芳基，C_6-C_{24}芳烷基，卤素，-Si(C_1-C_3烷基)$_3$，羟基，硫氢基，C_1-C_{24}烷氧基，C_2-C_{24}烯氧基，C_2-C_{24}炔氧基C_5-C_{20}芳氧基，酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基))，酰氧基(-O-酰基)，C_2-C_{24}烷氧基羰基(-(CO)-O-烷基)，C_6-C_{20}芳氧基羰基(-(CO)-O-芳基)，C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基)，C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基)，羧基(-COOH)，羧酸($-COO^-$)，氨基甲酰(-(CO)-NH_2)，C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基))，芳基氨基甲酰(-(CO)-NH-芳基)，硫代氨基甲酰(-(CS)-NH_2)，脲基(-NH-(CO)-NH_2)，氰基(-CN)，异氰基($-N^+C^-$)，氰氧基(-O-CN)，异氰氧基($-O-N^+=C^-$)，异硫代氰氧基(-S-CN)，叠氮基($-N=N^+=N^-$)，甲酰基(--(CO)--H)，硫代甲酰基(--(CS)--H)，氨基(--NH_2)，C_1-C_{24}烷基氨基，C_5-C_{20}芳基氨基，C_2-C_{24}烷基氨基(-NH-(CO)-烷基)，C_6-C_{20}芳基氨基(-NH-(CO)-芳基)，亚氨基(-CR=NH，其中R为氢，C_1-C_{24}烷基，C_5-C_{20}芳基，C_6-C_{24}烷芳基，C_6-C_{24}芳烷基等)，烷基亚氨基(-CR=N(烷基)，其中R=氢，烷基，芳基，烷芳基，芳烷基等)，芳基亚氨基(-CR=N(芳基)，其中R=氢，烷基，芳基，烷芳基等)，硝基($-NO_2$)，亚硝基(-NO)，磺基($-SO_2$-OH)，磺酸($-SO_2-O^-$)，C_1-C_{24}烷基硫基(-S-烷基；还称为"烷基硫代")，芳基硫基(-S-芳基；还称为"芳基硫代")，C_1-C_{24}烷基亚磺酰基(-(SO)-烷基)，C_5-C_{20}芳基亚磺酰基(-(SO)-芳基)，C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基)，C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基)，磺胺($-SO_2$-NH2，$-SO_2NY_2$(其中Y独立地为H，arlyl或烷基)，膦酰基(-P(O)(OH)$_2$)，磷酰基(-P(O)(O^-)$_2$)，次膦酸基(-P(O)(O^-))，亚磷酸($-PO_2$)，膦基(--PH_2)，聚烷基醚，磷酸盐，磷酸酯，引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团，它们的组合，并且其中Y^1和Y^2可以连接而形成环或多环，其中所述的环为取代的或非取代的芳基，取代的或非取代的杂芳基，取代的或非取代的环烷基，和取代的或非取代的杂环基；

[0025] U^1为N，C-R^2或C-NR^3R^4，其中R^2选自H，低级烷基基团，O，$(CH_2)_{n1}OR'$(其中n1=1，2或3)，CF_3，CH_2-CH_2X，O-CH_2-CH_2X，CH_2-CH_2-CH_2X，O-CH_2-CH_2X，X，(其中X=H，F，Cl，Br或I)，CN，(C=O)-R'，(C=O)N(R')$_2$，O(CO)R'，COOR'(其中R'为H或低级烷基基团)，并且其中R^1和R^2可以连接而形成环或多环，其中R^3和R^4是相同的或不同的，并且均选自H，低级烷基基团，O，$(CH_2)_{n1}OR'$(其中n1=1，2或3)，CF_3，CH_2-CH_2X，CH_2-CH_2-CH_2X，(其中X=H，F，Cl，Br或I)，CN，(C=O)-R'，(C=O)N(R')$_2$，COOR'(其中R'为H或低级烷基基团)，并且R^3或R^4可以缺省；

[0026] X^1和X^2独立地为N或C，并且其中当X^1和/或X^2为N时，Y^1和/或Y^2各自是缺省的；

[0027] Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线状的、支化的或环状的,并且其是非取代的或取代的。

[0028] 在其他的实施方案中,15-PGDH抑制剂可以包括具有式(V)的化合物、以及它们的药物可接受的盐:

[0029] 

(V),

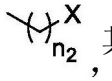
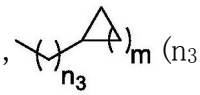
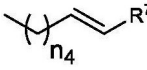
[0030] 其中n为0-2;

[0031] X^6独立地为N或CR^c;

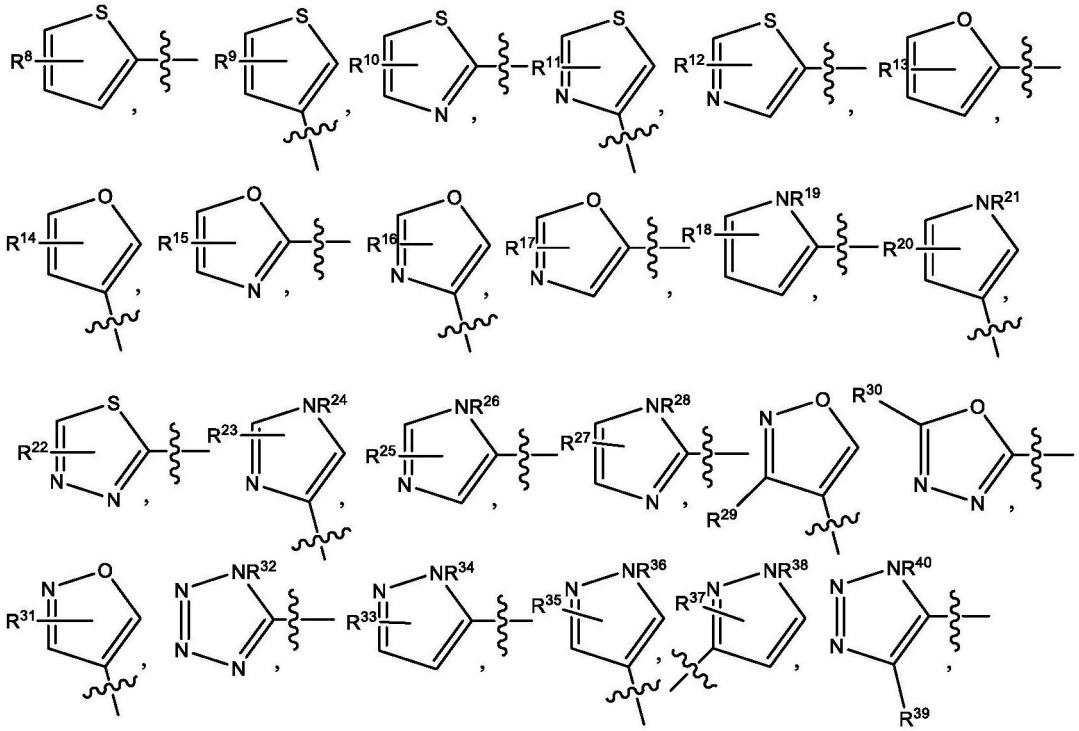
[0032] R^1,R^6,R^7和R^c均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

[0033] 低级烷基基团,O,$(CH_2)_{n1}$OR'(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}$OR'(其中n1=1,2或3),CF_3,CH_2-

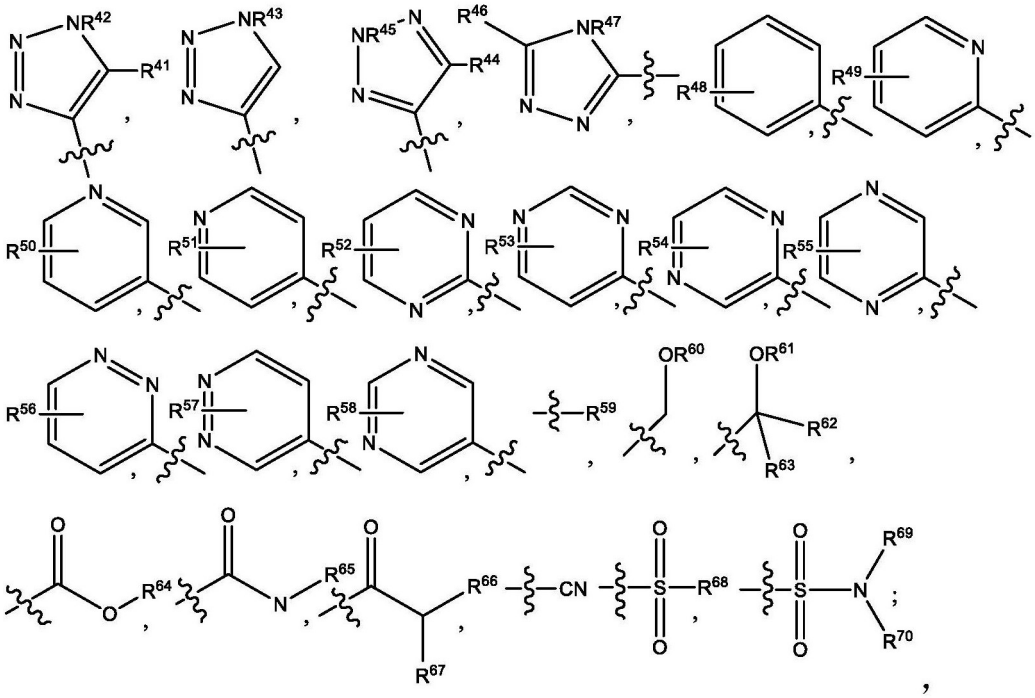
CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省。

[0034] 在一些实施方案中,R^1选自支化的或线性的烷基,包括,-$(CH_2)n_1CH_3$(n_1=0-7);  ,其中n_2=0-6,并且X为以下任意一者:CF_yH_z(y+z=3),CCl_yH_z(y+z=3),OH,OAc,OMe,R^{71},OR^{72},CN,$N(R^{73})_2$,  (n_3=0-5,m=1-5),和  (n_4=0-5)。

[0035] 在其他的实施方案中,R^6和R^7均可以独立地为以下的一者及其药物可接受的盐:



[0036]



[0037] R^8,R^9,R^{10},R^{11},R^{12},R^{13},R^{14},R^{15},R^{16},R^{17},R^{18},R^{19},R^{20},R^{21},R^{22},R^{23},R^{24},R^{25},R^{26},R^{27},R^{28},R^{29},R^{30},R^{31},R^{32},R^{33},R^{34},R^{35},R^{36},R^{37},R^{38},R^{39},R^{40},R^{41},R^{42},R^{43},R^{44},R^{45},R^{46},R^{47},R^{48},R^{49},R^{50},R^{51},R^{52},R^{53},R^{54},R^{55},R^{56},R^{57},R^{58},R^{59},R^{60},R^{61},R^{62},R^{63},R^{64},R^{65},R^{66},R^{67},R^{68},R^{69},R^{70},R^{71},R^{72},R^{73}和R^{74}均是相同的或不同的,并且独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),包含5-14环原子的杂芳基或杂环基(其中1-6个环原子独立地选自N,NH,N(C_1-C_3烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,甲硅烷基,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)--NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),二氧化硫氨基($-SO_2N(R)_2$,其中R独立地为H,烷基,芳基或杂芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2-OH$),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2-NH_2$,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚($-[(CH_2)_nO]_m$),磷酸盐,磷酸酯[-OP(O)(OR)$_2$,其中R=H,甲基或其他烷基],引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合。

[0038] 在一些实施方案中,15-PGDH抑制剂可以在重组15-PGDH浓度为大约5nM至大约10nM下以IC_{50}低于1μM、或者优选地IC_{50}低于250nM、或者更优选地IC_{50}低于50nM、或者更优选地IC_{50}低于10nM、或者更优选地IC_{50}低于5nM抑制重组15-PGDH的酶活性。

[0039] 附图简述

[0040] 图1示出在特发性肺纤维症的小鼠模型中,用于测量SW033291对体重保持和生存的影响的测试的示意图。

[0041] 图2(A-B)示出显示媒介物和SW033291处理的特发性肺纤维症的小鼠模型的(A)体重变化和(B)生存的图。

[0042] 图3示出在特发性肺纤维症的小鼠模型中,用于测量SW033291对胶原蛋白沉积的影响的测试的示意图。

[0043] 图4示出显示在媒介物和SW033291处理的特发性肺纤维症的小鼠模型中胶原蛋白沉积的图。

[0044] 图5示出在特发性肺纤维症的小鼠模型中,用于测量SW033291对炎性细胞因子表

达的影响的测试的示意图。

[0045] 图6(A-F)示出显示在媒介物和SW033291处理的特发性肺纤维症的小鼠模型中炎性细胞因子表达的图。

[0046] 图7(A-D)示出显示在媒介物和SW033291处理的特发性肺纤维症的小鼠模型中炎性细胞因子表达的图。

[0047] 图8示出显示在媒介物和(+)SW033291处理的肠纤维症的小鼠模型中结肠纤维症的图。

[0048] 发明详述

[0049] 为了方便,在说明书、实施例和所附的权利要求书中使用的某些术语均收集如此。除非另外定义,否则在本文中使用的所有技术和科学术语均具有本申请所属技术领域中任一普通技术人员通常理解的相同的含义。

[0050] 冠词“一个”和“一种”在本文中用于指一个或多于一个(即,指至少一个)的冠词的语法对象。例如,“一种元素”是指一种元素或多于一种元素。

[0051] 术语动词形式的“包含”、分词形式的“包含”、动词形式的“包括”、分词形式的“包括”、动词形式的“具有”和分词形式的“具有”以包含一切的、开放式的含义使用,是指其他的元素可以包含在内。如本文所用,术语“诸如”、“例如”是非限定性的,并且仅是为了说明的目的。“包括”和“包括但不限于”可交换使用。

[0052] 如本文所用,术语“或”应该理解为是指“和/或”,除非内容中另外清楚地指出。

[0053] 如本文所用,术语“大约”或“大致”是指相对于参照定量、水平、值、数量、频率、百分率、维度、尺寸、量、重量或长度可以改变差不多15%,10%,9%,8%,7%,6%,5%,4%,3%,2%或1%的定量、水平、值、数量、频率、百分率、维度、尺寸、量、重量或长度。在一个实施方案中,术语“大约”或“大致”是指关于参照定量、水平、值、数量、频率、百分率、维度、尺寸、量、重量或长度而言,定量、水平、值、数量、频率、百分率、维度、尺寸、量、重量或长度±15%,±10%,±9%,±8%,±7%,±6%,±5%,±4%,±3%,±2%或±1%的范围。

[0054] 应该注意,本申请的一些化合物的结构包括不对称的(手性的)碳或硫原子。因此,应该理解的是,由这种不对称形成的异构体包含在本发明中,除非另外指出。此类异构体可以通过传统的分离技术并且通过立体化学可控的合成方法以基本纯的形式获得。本申请的化合物可以以立体异构体的形式存在,因此可以作为单一的立体异构体或作为混合物生产。

[0055] 术语“异构”是指具有相同的分子式、但是本性不同或者原子的结合顺序或者原子的空间排列不同的化合物。原子的空间排列不同的异构体称为“立体异构体”。彼此不为镜像的立体异构体称为“非对映异构体”,而不重叠镜像的立体异构体称为“对映异构体”,或者有时称为光学异构体。与4个不一致的取代基键合的碳原子称为“手性中心”,而与3个或4个不同的取代基键合的硫(例如亚砜或亚磺酰胺)同样称为“手性中心”。

[0056] 术语“手性异构体”是指具有至少一个手性中心的化合物。其具有2种相反的手性的对映异构体形式,并且可以以单一的对映异构体或作为对映异构体的混合物的形式存在。包含等量的相反手性的单一对映异构体形式的混合物称为“外消旋混合物”。具有多于一个手性中心的化合物具有2n-1个对映异构体对,其中n为手性中心的数量。具有对于一个手性中心的化合物可以以单一的非对映异构体或者作为非对映异构体的混合物的形式存

在,称为“非对映异构体混合物”。当存在一个手性中心时,立体异构体可以表征为该手性中心的绝对构型(R或S)。备选地,当存在一个或多个手性中心时,立体异构体可以表征为(+)或(-)。绝对构型是指与手性中心连接的取代基的空间排列。根据the Sequence Rule of Cahn,Ingold and Prelog,对所考虑的与手性中心连接的取代基进行排序(Cahn et al,Angew.Chem.Inter.Edit.1966,5,385;errata 511;Cahn et al.,Angew.Chem.1966,78,413;Cahn and Ingold,J Chem.Soc.1951(London),612;Cahn et al.,Experientia 1956,12,81;Cahn,J.,Chem.Educ.1964,41,116)。

[0057] 术语“紊乱”是指能够受益于减少或延迟纤维症的试剂的任何紊乱、疾病或状况。例如包括表征为过量产生纤维物质的疾病、紊乱和状况,包括在细胞外基质中过量产生纤维物质。还包括表征为正常组织元素被异常的、非功能的和/或过量累积的基质相关成分替代的疾病、紊乱和状况。

[0058] 术语“几何异构体”是指由于它们的存在而阻碍关于双键的旋转的非对映异构体。这些构型通过名字中的前缀cis和trans、或者Z和E而区分,其表明根据Cahn-Ingold-Prelog规则,所述的基团在分子中在双键的相同的一侧或相对的一侧。此外,本申请中所讨论的结构和其他化合物包含它们所有的反转异构体。

[0059] 术语“反转异构体”是一种立体异构体的类型,其中2个异构体的原子的空间排列不同。由于反转异构体的存在,使得通过较大基团关于中心键的旋转受阻而导致受限的旋转。此类反转异构体通常以混合物形式存在,但是由于近来层析技术的发展,已经可以在所选的情况下分离2种反转异构体的混合物。

[0060] 术语“晶型”或“多晶型物”或“晶形”是指晶体结构,其中化合物(或其盐或溶剂化物)在不同的晶体堆积排列中可以结晶,其中所有的排列都具有相同的元素组成。不同的晶形通常具有不同的X线衍射图谱、红外光谱、熔点、密度硬度、晶体形式、光学和电学性质、稳定性和溶解性。重结晶溶剂、结晶速率、储存温度和其他因素可以导致一种晶形占据优势。化合物的晶型可以通过在不同条件下结晶来制备。

[0061] 术语“衍生物”是指具有共同的核心结构,并且被多种基团取代的化合物,如本文所述。

[0062] 术语“生物电子等排体”是指一个原子或一组原子被另一个广义相似的原子或一组原子互换而得到的化合物。生物电子等排替代(生物电子等排替代)的目的是创建与亲代化合物具有相似的生物学性质的新的化合物。生物电子等排替代可以是以物理化学为基础的或者以拓扑学为基础的。羧酸生物电子等排体的实例包括酰基磺酰亚胺,四唑,磺酸酯和膦酸酯。例如参见Patani and LaVoie,Chem.Rev.96,3147-3176(1996)。

[0063] 短语“肠胃外给予”和“以肠胃外方式给予”是本领域公认的术语,并且包括除了肠内和局部给予以外的给予模式,例如注射,并且包括但不限于静脉内,肌肉内,胸膜内,血管内,心包内,动脉内,鞘内,囊内,眶内,心脏内,皮内,腹膜内,经气管内,皮下,表皮下,关节内,囊下,蛛网膜下,脊柱内和胸骨内注射和输注。

[0064] 术语“治疗”是本领域公认的,并且包括抑制受试对象的基本、紊乱或状况,例如阻止其进程;以及减轻疾病、紊乱或状况,例如疾病、紊乱和/或状况的回撤。治疗疾病或状况包括减缓特定疾病或状况的至少一种症状,即使潜在的病理生理学未受影响。

[0065] 术语“预防”是本领域公认的,并且包括终止疾病、紊乱或状况在受试对象中发生,

其中所述的受试对象可能倾向于疾病、紊乱和/或状况，但是尚未诊断为患有疾病、紊乱和/或状况。预防与疾病有关的状况包括在疾病被诊断之后但是在状况被诊断之前终止状况的发生。

[0066] 术语“药物组合物”是指包含其形式适用于给予受试对象的所公开的化合物的配制物。在优选的实施方案中，药物组合物是散装的或者单位剂型。单位剂型是多种形式的任意一种，例如包括胶囊、IV袋、片剂、气雾剂上的单向流向泵、或者小瓶。在单位剂量的组合物中，活性组分的定量(例如所公开的化合物或其盐的配制物)是有效量，并且根据所涉及的特定的治疗而改变。本领域的任一技术人员将理解的是有时必须根据患者的年龄和状况而对剂量进行常规的改变。剂量还可以根据给予途径。可以考虑多种途径，包括口服、肺内、直肠、肠胃外、经皮、皮下、静脉内、肌肉内、腹膜内、鼻内、吸入等。用于本发明所述的化合物的局部或经皮给予的剂型包括粉末、喷雾、软膏、糊、乳霜、洗剂、凝胶、溶液、贴剂、雾化化合物和吸入剂。在优选的实施方案中，活性化合物在无菌条件下与药物可接受的载体以及与所需的任何防腐剂、缓冲剂或推进剂混合。

[0067] 术语“闪式剂量(flash dose)”是指快速分散剂型的化合物配制物。

[0068] 术语“立即释放”定义为化合物在相对短的时间内由剂型中释放，通常至多大约60分钟。术语“修饰释放”定义为包括延时释放、延长释放和脉冲释放。术语“脉冲释放”定义为药品由剂型的系列释放。术语“持续释放”或“延长释放”定义为化合物经过延长的时间由剂型中连续释放。

[0069] 短语“药物可接受的”是本领域公认的。在某些实施方案中，该术语包括组合物、聚合物和其他物质和/或剂型，在合理的医学判断范围内，其适用于与人类和动物的组织接触使用，而不具有过量的毒性、刺激、过敏反应或者其他的问题或并发症，相当于合理的收益/风险比。

[0070] 短语“药物可接受的载体”是本领域公认的，并且包括例如药物可接受的物质、组合物或媒介物(例如液体或固体填料、稀释剂、赋形剂、溶剂或囊封物质)，其涉及将任何题述组合物由肌体的一个器官或部分携带或转运至肌体的另一个器官或部分。就与题述组合物的其他组分相容并且不会损伤患者的意义而言，各种载体必须是“可接受的”。在某些实施方案中，药物可接受的载体是无热原的。可以作为药物可接受的载体的物质的一些实例包括：(1)糖，例如乳糖、葡萄糖和蔗糖；(2)淀粉，例如玉米淀粉和马铃薯淀粉；(3)纤维素及其衍生物，例如羧甲基纤维素钠、乙基纤维素和醋酸纤维素；(4)西黄蓍胶粉；(5)麦芽；(6)凝胶；(7)滑石；(8)赋形剂，例如可可油和栓蜡；(9)油，例如花生油、棉油、向日葵油、麻油、橄榄油、玉米油和大豆油；(10)乙二醇，例如丙二醇；(11)多元醇，例如甘油、山梨醇、甘露醇和聚乙二醇；(12)酯，例如油酸乙酯和月桂酸乙酯；(13)琼脂；(14)缓冲剂，例如氢氧化镁和氢氧化铝；(15)褐藻酸；(16)无热原水；(17)生理盐水；(18)Ringer溶液；(19)乙醇；(20)磷酸盐缓冲溶液；以及(21)在药物配制物中使用的其他无毒性相容的物质。

[0071] 本申请的化合物能够进一步形成盐。所有的这些形式也在本发明的考虑范围内。

[0072] 化合物的“药物可接受的盐”是指是药物可接受的并且具有亲代化合物的所需的药物活性的盐。。例如所述的盐可以是酸加成盐。酸加成盐的一个实施方案为盐酸盐。药物可接受的盐可以是通过传统的化学方法由亲代化合物合成的，所述的亲代化合物包含碱和酸的部分。通常，此类盐可以通过使游离酸或碱形式的这些化合物与化学计量的合适的碱

或酸在水或有机溶剂中、或者在二者的混合物(通常无水性介质,例如醚、乙酸乙酯、乙醇、异丙醇或乙腈是优选的)中反应而制备。盐的列表可以在Remington's Pharmaceutical Sciences,18th ed.(Mack Publishing Company,1990)找到。

[0073] 本发明所述的化合物还可以制备成酯,例如药物可接受的酯。例如化合物中的羧酸官能团可以转化成其相应的酯,例如甲基、乙基或其他的酯。此外,化合物中的醇基团可以转化成其相应的酯,例如乙酸酯、丙酸酯或其他的酯。

[0074] 本发明所述的化合物还可以制备成前药,例如药物可接受的前药。术语"潜药"和"前药"在本发明中可交换使用,并且是指在体内释放活性亲代药品的任何化合物。由于已知前药会增强药物的多种所需的性质(例如溶解性、生物利用性、制造性等),所以该化合物可以以前药形式传递。因此,本发明所述的化合物意图涵盖本发明要求权利的化合物的前药、传递该前药的方法以及包含该前药的组合物。"前药"意图包括当将该前药给予受试对象时,在体内释放活性亲代药品的任何共价键合的载体。前药可以通过改性化合物中存在的官能团来制备,其方式使得所述的修饰物以常规操作或者在体内与亲代化合物裂解。前药包括其中羟基、氨基、硫氢基、羧基或羰基基团与任何基团键合的化合物,其中所述的任何基团可以在体内裂解从而分别形成游离的羟基、游离的氨基、游离的硫氢基、游离的羧基或游离的羰基基团。前药还可以包括本发明所述的化合物的前体(先行者),其在成为本发明所述的活性或更加活性的药物试剂或者活性化合物之前通过代谢工艺发生化学转化。

[0075] 前药的实例包括但不限于羟基官能团的酯(例如乙酸酯、二烷基氨基乙酸酯、甲酸酯、磷酸酯、硫酸酯和苯甲酸酯衍生物)和氨基甲酸酯(例如N,N-二甲基氨基羰基);羧基官能团的酯基团(例如乙基酯、吗啉乙醇酯);氨基官能团的N-酰基衍生物(例如N-乙酰基)N-Mannich碱、Schiff碱和烯胺酮;化合物中酮和醛官能团的肟、乙缩醛、缩酮和烯醇酯等,乙基氧化形成亚砜或砜的硫化物。

[0076] 术语"保护性基团"是指当与分子中的反应性基团连接时会掩饰、降低或阻止其反应性的一组原子。保护性基团的实例可以在Green and Wuts,Protective Groups in Organic Chemistry,(Wiley,2.sup.nd ed.1991);Harrison and Harrison et al.,Compendium of Synthetic Organic Methods,Vols.1-8(John Wiley and Sons,1971-1996);and Kocienski,Protecting Groups,(Verlag,3rd ed.2003)中找到。

[0077] 术语"胺保护性基团"意图是指胺、酰胺或其他含氮部分转化成不同的化学基团的官能团,其中所述的化学基团对于特定的化学反应条件而言基本上是惰性的。胺保护性基团优选为在不影响分子的其他官能团的条件下以良好的产率容易地且可选择地除去的。胺保护性基团的实例包括但不限于甲酰基,乙酰基,苄基,叔丁基二甲基甲硅烷基,叔丁基二苯基甲硅烷基,叔丁氧基羰基(Boc),对甲氧基苄基,甲氧基甲基,甲苯磺酰基,三氟乙酰基,三甲基甲硅烷基(TMS),芴基-甲氧基羰基,2-三甲基甲硅烷基-乙氧基羰基,1-甲基-1-(4-二苯基)乙氧基羰基,烯丙氧基羰基,苄氧基羰基(CBZ),2-三甲基甲硅烷基-乙烷亚磺酰基(SES),三苯基和取代的三苯基基团,9-芴基甲氧基羰基(FMOC),硝基-藜芦氧基羰基(NVOC)等。本领域的那些技术人员可以鉴定其他的合适的胺保护性基团。

[0078] 代表性的羟基保护性基团包括其中羟基基团被酰基化或烷基化的那些,例如苄基和三苯基醚,以及烷基醚、四氢吡喃醚、三烷基甲硅烷基醚和烯丙基醚。

[0079] 此外,本发明所述的化合物的盐可以以水合的或非水合的(无水)形式存在,或者

与其他的溶剂分子形成溶剂化物存在。水合物的非限定性实例包括一水合物、二水合物等。溶剂化物的非限定性实例包括乙醇溶剂化物、丙酮溶剂化物等。

[0080] 术语“溶剂化物”是指包含化学计量的或非化学计量的溶剂的溶剂加成形式。一些化合物趋向于在结晶固体状态下捕集固定摩尔比的溶剂分子，由此形成溶剂化物。如果溶剂是水，则所形成的溶剂化合物为水合物，当溶剂为醇时，则所形成的溶剂为醇化物。水合物是通过将一个或多个分子的水与一种物质结合而形成的，其中水保持其H_2O的分子状态，这种结合能够形成一个或多个水合物。

[0081] 本发明所述的化合物、盐和前药可以以多种互变异构形式存在，包括烯醇和亚胺形式，酮类和烯胺形式，以及几何异构体和它们的混合物。互变异构体在溶液中以互变异构集的混合物形式存在。在固体形式下，通常一种互变异构体占优势。即使可以描述一种互变异构体，但是本申请包括本发明化合物的所有互变异构体。互变异构体是2种或多种结构异构体之一，所述的结构异构体以平衡状态存在，并且容易地由一种异构形式转化成另一种异构形式。这种反应导致氢原子的形式迁移，并伴有相邻的共轭双键的开关。在其中互变异构可行的溶液中，将达到互变异构体的化学平衡状态。互变异构体的确切比例取决于多种因素，包括温度、溶剂和pH。通过互变异构而相互转化的互变异构体的概念称为互变现象。

[0082] 在多种类型的可行的互变现象中，通常观察到2中。在酮-烯醇互变现象中，电子和氢原子发生同时位移。

[0083] 互变异构可以通过以下过程催化：碱：1.去质子化；2.形成离域阴离子(例如烯醇化物)；3.在阴离子的不同位置质子化；酸：1.质子化；2.形成离域阳离子；3.在与阳离子相邻的不同位置去质子化。

[0084] 术语“类似物”是指结构上与另一种物质相似、但是组成稍微不同的化合物化合物(由于一个原子被不同元素的原子替代或者存在特定的官能团，或者一个官能团被另一个官能团替代)。因此，类似物是在功能和表观上相似或相当的化合物，但是类似物在结构或来源上与参照化合物不同。

[0085] 有待通过题述方法治疗的“患者”、“受试对象”或“宿主”可以是指人类或非人类动物，例如哺乳动物、鱼、鸟、爬行动物或两栖动物。因此，本发明公开的方法的受试对象可以是人类、非人类灵长动物、马、猪、兔、狗、绵羊、山羊、牛、猫、天竺鼠或啮齿动物。该术语未指示特定的年龄或性别。因此，成年的和新生的受试对象以及胎儿(无论雄性或雌性)都将涵盖在内。在一个方面中，受试对象为哺乳动物。患者是指患有疾病或紊乱的受试对象。

[0086] 术语“预防性”或“治疗性”治疗是本领域公认的，并且包括向宿主给予一种或多种题述的组合物。如果在不需要的状况(例如宿主动物的疾病或其他不需要的状态)的临床表现之前给予，则所述的治疗是预防性的，即，其保护宿主免于发展成不需要的状况，而如果在不需要的状况的表现之后给予，则所述的治疗是治疗性的(即，其意图消除、减缓或稳定现存的不需要的状况或其副作用)。

[0087] 术语“治疗试剂”、“药品”、“药剂”和“生物活性物质”是本领域公认的，并且包括生物学、生理学或药理学活性物质的分子和其他试剂，其中所述的活性物质在患者或受试对象中局部或系统性地发挥作用从而治疗疾病或状况。所述的术语包括但不限于药物可接受的盐和前药。此类试剂可以是酸性、碱性或盐；它们可以是中性分子、极性分子或与氢键合的分子复合物；它们可以是醚、酯、酰胺等的前药，当将它们给予患者或受试对象时，其是被

生物激活。

[0088] 短语“治疗有效量”或“药物有效量”是本领域公认的术语。在某些实施方案中，该术语是指在可应用于任何医疗的合理的收益/风险比下，产生某种所需的作用的治疗试剂的量。在某些实施方案中，该术语是指必须或足以消除、减少或保持特定治疗方案的目标的量。有效量可以根据诸如待治疗的疾病或状况、待给予的特定的靶向构建体、受试对象的尺寸或者疾病或状况的严重性之类的因素而改变。本领域的任一普通技术人员可以凭经验确定特定化合物的有效量而无需过度的试验。在某些实施方案中，体内用途的治疗试剂的治疗有效量可能取决于多种因素，包括试剂由聚合物基质的释放速率，其将部分取决于聚合物的化学和物理特征；试剂的特性；给予的模式和方法；以及引入到聚合物基质中的除了所述的试剂以外的任何其他的物质。

[0089] 术语“ED50”是本领域公认的。在某些实施方案中，ED50是指药品产生其最大应答或作用的50％的剂量，或者备选地，药品在50％测试受试对象或制备物中产生预定应答的剂量。术语“LD50”是本领域公认的。在某些实施方案中，LD50是指药品使50％测试受试对象致死的剂量。术语“治疗指数”是本领域公认的术语，其是指药品的治疗指数，定义为LD50/ED50。

[0090] 术语“IC_{50}”或“半抑制浓度”意图50％抑制生物过程或过程的成分(包括蛋白质、亚基、细胞器、核蛋白等)所需的物质(例如化合物或药品)的浓度。

[0091] 对于任何化学化合物，本申请意图包括在本发明化合物中形成的所有原子的同位素。同位素包括具有相同的原子序数但不同的质量数的那些原子。一般实例但不限于氢的同位素包括氚和氘，碳的同位素包括C-13和C-14。

[0092] 当与取代基形成的键显示跨越了连接环上的2个原子的键时，则此类取代基可以与环上的任何原子键合。当列出的取代基未表明具有以下原子(通过该原子，此类取代基与给定通式的化合物的其余部分键合)时，则此类取代基可以通过此类取代基中的任何原子键合。取代基和/或变体的组合是可行的，但是只要此类组合得到稳定的化合物即可。

[0093] 当原子或化学部分跟有下标数字范围(例如C_{1-6})时，其是指涵盖该范围内的各个数字以及所有中间范围。例如“C_{1-6}烷基”是指包括具有1,2,3,4,5,6,1-6,1-5,1-4,1-3,1-2,2-6,2-5,2-4,2-3,3-6,3-5,3-4,4-6,4-5,和5-6个碳的烷基基团。

[0094] 术语“烷基”意图包括支化的(例如异丙基、叔丁基、异丁基)，直链的(例如甲基，乙基，丙基，丁基，戊基，己基，庚基，辛基，壬基，癸基)，以及环烷基(例如脂环族)基团(例如环丙基，环戊基，环己基，环庚基，环辛基)，烷基取代的环烷基基团，以及环烷基取代的烷基基团。此类脂肪族烃基基团具有特定数量的碳原子。例如C_{1-6}烷基意图包括C_1，C_2，C_3，C_4，C_5，和C_6烷基基团。如本文所用，“低级烷基”是指在碳链的主链中具有1至6个碳原子的烷基基团。“烷基”进一步包括具有氧、氮、硫或磷原子的烷基基团，所述的氧、氮、硫或磷原子替代了一个或多个烃基主链的碳原子。在某些实施方案中，支链或支链烷基在其主链中具有6个或更少的碳原子(例如直链为C_1-C_6，支链为C_3-C_6)，例如4个或更少。类似地，某些环烷基在其环结构中具有3至8个碳原子，例如环结构中具有5或6个碳。

[0095] 术语“取代的烷基”是指其中取代基替代烃主链的一个或多个碳上的氢的烷基部分。此类取代基可以包括例如烷基，烯基，炔基，卤素，羟基，烷基羰氧基，芳基羰氧基，烷氧基羰氧基，芳氧基羰氧基，羧酸基，烷基羰基，芳基羰基，烷氧基羰基，氨基羰基，烷基氨基羰

基,二烷基氨基羰基,烷基硫代羰基,烷氧基,磷酸基,膦酸基,次膦酸基,氰基,氨基(包括烷基氨基,二烷基氨基,芳基氨基,二芳基氨基和烷基芳基氨基),酰基氨基(包括烷基羰基氨基,芳基羰基氨基,氨基甲酰和脲基),脒基,亚氨基,硫氢基,烷基硫,芳基硫,硫代羧酸基,硫酸基,烷基亚磺酰基,磺酸,氨磺酰,磺酰氨基,硝基,三氟甲基,氰基,叠氮基,杂环基,烷基芳基,或者芳香族或杂芳香族部分。环烷基可以进一步被例如上文所述的取代基取代。“烷基芳基”或“芳烷基”部分为芳基取代的烷基(例如苯基甲基(苄基))。如果未另外指出,术语“烷基”和“低级烷基”分别包括线性的、支化的、环状、未取代的、取代的和/或含杂原子的烷基或低级烷基。

[0096] 术语“烯基”是指包含至少一个双键的2至大约24个碳原子的线性的、支化的或环状烃基基团,例如乙烯基,正丙烯基,异丙烯基,正丁烯基,异丁烯基,辛烯基,癸烯基,四癸烯基,六癸烯基,十六碳烯基,tetracoseny l,环戊烯基,环己烯,环辛烯基等。通常,尽管也是不必要的,但是烯基基团可以包含2至大约18个碳原子,更具体为2至12个碳原子。术语“低级烯基”是指2至6个碳原子的烯基基团,特定术语“环烯基”是指环状烯基基团,优选具有5至8个碳原子。术语“取代的烯基”是指被一个或多个取代基基团取代的烯基,术语“含杂原子的烯基”和“杂烯基”是指其中至少一个碳原子被杂原子替代的烯基或杂环烯基(例如杂环己烯)。如果未另外指出,术语“烯基”和“低级烯基”分别包括线性的、支化的、环状的、未取代的、取代的和/或含杂原子的烯基和低级烯基。

[0097] 术语“炔基”是指包含至少一个三键的2至24个碳原子的线性的或支化的烃基基团,例如乙炔基、正丙炔基等。通常,尽管也是不必要的,但是炔基基团可以包含2至大约18个碳原子,更具体为可以包含2至12个碳原子。术语“低级炔基”是指2至6个碳原子的炔基基团。术语“取代的炔基”是指被一个或多个取代基基团取代的炔基,术语“含杂原子的炔基”和“杂炔基”是指其中至少一个碳原子被杂原子替代的炔基。如果未另外指出,术语“炔基”和“低级炔基”分别包括线性的、支化的、未取代的、取代的和/或含杂原子的炔基或低级炔基。

[0098] 术语“烷基”、“烯基”和“炔基”意图包括其为双自由基的部分,即,具有2个连接点。此类双自由基的烷基部分的非限定性实例为--CH_2CH_2--,即,通过各个末端碳原子与分子的其余部分共价键合的C_2烷基基团。

[0099] 术语“烷氧基”是指通过单一的末端醚键键合的烷基基团;即,“烷氧基”基团可以表示为--O-烷基,其中烷基如上文定义。“低级烷氧基”基团是指包含1至6个碳原子的烷氧基基团,并且包括例如甲氧基、乙氧基、正丙氧基、异丙氧基、叔丁氧基等。本发明鉴定为“C_1-C_6烷氧基”或“低级烷氧基”的优选的取代基包含1至3个碳原子,并且特别优选的此类取代基包含1或2个碳原子(即,甲氧基和乙氧基)。

[0100] 术语“芳基”是指包含单一芳香族环或多个稠合在一起的(通过直接连接或间接连接)(使得不同的芳香族环与共同的基团键合,例如亚甲基或亚乙基部分)芳香族环的芳香族取代基。芳基基团可以包含5至20个碳原子,并且特别优选的芳基基团可以包含5至14个碳原子。芳基基团的实例包括苯,苯基,吡咯,呋喃,噻吩,噻唑,异噻唑,咪唑,三唑,四唑,吡唑,恶唑,异恶唑,吡啶,吡嗪,哒嗪和嘧啶等。此外,术语“芳基”包括多环芳基基团,例如三环,双环,例如萘,苯并恶唑,苯并二恶唑,苯并噻唑,苯并咪唑,苯并噻吩,亚甲二氧基苯基,喹啉,异喹啉,萘啶,吲哚,苯并呋喃,嘌呤,苯并呋喃,去氮杂嘌呤或吲嗪。在环结构中具有

杂原子的那些芳基基团还可以称为“芳基杂环”、“杂环”、“杂芳基”或“杂芳香族”。芳香族环可以在一个或多个环位置处被上文所述的此类取代基取代，例如卤素，羟基，烷氧基，烷基羰氧基，芳基羰氧基，烷氧基羰氧基，芳氧基羰氧基，羧酸基，烷基羰基，烷基氨基羰基，芳烷基氨基羰基，烯基氨基羰基，烷基羰基，芳基羰基，芳烷基羰基，烯基羰基，烷氧基羰基，氨基羰基，烷基硫代羰基，磷酸基，膦酸基，次膦酸基，氰基，氨基(包括烷基氨基，二烷基氨基，芳基氨基，二芳基氨基和烷基芳基氨基)，酰基氨基(包括烷基羰基氨基，芳基羰基氨基，氨基甲酰和脲基)，脒基，亚氨基，硫氢基，烷基硫，芳基硫，硫代羧酸基，硫酸基，烷基亚磺酰基，磺酸，氨磺酰，磺酰氨基，硝基，三氟甲基，氰基，叠氮基，杂环基，烷基芳基，或者芳香族或杂芳香族部分。芳基基团还可以与脂环族或杂环稠合，它们不是芳香族的，从而形成多环系统(例如萘满，亚甲二氧基苯基)。如果未另外指出，术语“芳基”包括未取代的、取代的和/或含杂原子的芳香族取代基。

[0101] 术语“烷芳基”是指具有烷基取代基的芳基基团，并且术语“芳烷基”是指具有芳基取代基的烷基基团，其中“芳基”和“烷基”如上文定义。示例性的芳烷基基团包含6至24个碳原子，并且特别优选的芳烷基基团包含6至16个碳原子。芳烷基基团的实例包括但不限于苄基，2-苯基-乙基，3-苯基-丙基，4-苯基-丁基，5-苯基-戊基，4-苯基环己基，4-苄基环己基，4-苯基环己基甲基，4-苄基环己基甲基等。烷芳基基团包括例如对甲基苯基，2,4-二甲基苯基，对环己基苯基，2,7-二甲基萘基，7-环辛基萘基，3-乙基-环戊-1,4-二烯等。

[0102] 术语“杂环基”或“杂环基团”包括闭合环结构，例如3-至10-，或4-至7-元环，其包含一个或多个杂原子。“杂原子”包括除了碳或氢以外的任何元素的原子。杂原子的实例包括氮、氧、硫和磷。

[0103] 杂环基基团可以是饱和的或不饱和的，并且包括吡咯烷，氧杂戊环，四氢噻吩，哌啶，哌嗪，吗啉，内酯，内酰胺(例如氮杂环丁酮和吡咯酮)，磺内酰胺和磺内酯。杂环基团(例如吡咯和呋喃)可以具有芳香族特征。它们包括稠合环结构，例如喹啉和异喹啉。杂环基团的其他实例包括吡啶和噁唑。杂环可以在一个或多个位置被诸如上文所述的取代基取代，例如卤素，羟基，烷基羰氧基，芳基羰氧基，烷氧基羰氧基，芳氧基羰氧基，羧酸基，烷基羰基，烷氧基羰基，氨基羰基，烷基硫代羰基，烷氧基，磷酸基，膦酸基，次膦酸基，氰基，氨基(包括烷基氨基，二烷基氨基，芳基氨基，二芳基氨基和烷基芳基氨基)，酰基氨基(包括烷基羰基氨基，芳基羰基氨基，氨基甲酰和脲基)，脒基，亚氨基，硫氢基，烷基硫，芳基硫，硫代羧酸基，硫酸基，磺酸，氨磺酰，磺酰氨基，硝基，三氟甲基，氰基，叠氮基，杂环基，或者芳香族或杂芳香族部分。杂环基团在一个或多个取代基原子上被例如低级烷基、低级烯基、低级烷氧基、低级烷基硫、低级烷基氨基、低级烷基羧基、硝基、羟基、--CF_3或--CN等取代。

[0104] 术语“卤代”或“卤素”是指氟代、氯代、溴代和碘代。“抗衡离子”用于代表小的负电荷的种类，例如氟化物、氯化物、溴化物、碘化物、氢氧化物、乙酸酯和硫酸酯。术语亚砜是指与2个不同的碳原子和1个氧连接的硫，并且S-O键可以以绘图表示为双键(S=O)，不具有电荷的单键(S-O)，或者具有电荷的单键[S(+)-O(-)]。

[0105] 在一些上述定义中提及的，在“取代的烷基”、“取代的芳基”等中使用的术语“取代的”是指在烷基、芳基或其他部分中，与碳(或其他)原子键合的至少一个氢原子被一个或多个非氢取代基替代。此类取代基的实例包括但不限于官能团，例如卤素，羟基，甲硅烷基，硫氢基，C_1-C_{24}烷氧基，C_2-C_{24}烯氧基，C_2-C_{24}炔氧基C_5-C_{20}芳氧基，酰基(包括C_2-C_{24}烷基羰基(-

CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸(-COO-),氨基甲酰(-(CO)-NH_2),一-(C_1-C_{24}烷基)-取代的氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),二-(C_1-C_4烷基)-取代的氨基甲酰(-(CO)--N(C_1-C_{24}烷基)$_2$),一-取代的芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基(-N^+C^-),氰氧基(-O--CN),异氰氧基(-ON^+C^-),异硫代氰氧基(-S-CN),叠氮基(-N=N^+=N^-),甲酰基(-(CO)--H),硫代甲酰基(-(CS)-H),氨基(-NH_2),一-和二-(C_1-C_{24}烷基)-取代的氨基,一-和二-(C_5-C_{20}芳基)-取代的氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R=氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(--CR=N(烷基),其中R=氢,烷基,芳基,烷芳基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸(-SO_2-O^-),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(--(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷基(-PO_2),和膦基(-PH_2);以及烃基部分C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,和C_6-C_{24}芳烷基。

[0106] 此外,如果特定基团允许的话,上述提及的官能团进一步被一个或多个其他的官能团或者一个或多个烃基部分取代,例如上文具体列举的那些。类似地,上文提及的烃基部分可以进一步被一个或多个官能团或其他的烃基部分取代,例如具体列举的那些。

[0107] 当术语"取代的"出现在可能被取代的基团的列表之前时,其是指该术语适用于该列表的每一个成员。例如短语"取代的烷基、烯基和芳基"将解释为"取代的烷基、取代的烯基和取代的芳基"。类似地,当术语"含杂原子"出现在可能的含杂原子基团的列表之前时,其是指该术语适用于该列表的每一个成员。例如短语"含杂原子烷基、烯基和芳基"解释为"含杂原子的烷基、取代的烯基和取代的芳基"。

[0108] "可任选的"或"可任选地"是指随后描述的环境可能发生或者可能不发生,使得所述的描述包括其中所述的环境发生的情况以及其中所述的环境不发生的情况。例如短语"可任选地取代的"是指非氢取代基可能存在于或可能不存在于给定的原子上,因此所述的描述包括其中非氢取代基存在的结构以及其中非氢取代基不存在的结构。

[0109] 术语"稳定的化合物"和"稳定的结构"是指足够稳健地(robust)存在于分离、以及由反应混合物的纯化(合适地)、以及形成有效的治疗试剂的化合物。

[0110] 术语"游离的化合物"在本发明中用于描述未键合状态的化合物。

[0111] 在整个描述中,其中组合物被描述为具有、包含或包括特定的成分,应该考虑的是组合物还基本上由或者由所述的成分组成。类似地,其中方法或工艺被描述为具有、包含或包括特定的工艺步骤,则该工艺还基本上由或者由所述的处理步骤组成。此外,应该理解的是步骤的次序或者用于实施某些行动的次序是不重要的,只要本发明所述的组合物和方法保持可操作即可。此外,可以同时实施2个或多个步骤或行动。

[0112] 术语"小分子"是本领域公认的术语。在某些实施方案中,该术语是指其分子量低于大约2000amu、或者低于大约1000amu、以及甚至低于大约500amu的分子。

[0113] 除非另外指出，否则本发明使用的所有百分率和比例均以重量计。

[0114] 术语“基因表达”或“蛋白质表达”包括关于在样品中存在的基因转录物或蛋白质的量的任何信息，以及关于基因或蛋白质产生的、或累积的、或降解的速率的信息(例如报告基因数据、得自核径流试验的数据、脉冲追踪数据等)。某种数据可以视为与基因和蛋白质表达有关。例如细胞中的蛋白质水平反映了蛋白质的水平以及转录的水平，并且此类术语意图被包含在短语“基因或蛋白质表达信息”中。此类信息可以以量/细胞、相对于对照基因或蛋白质的量、无单位量度等形式给出；术语“信息”不局限于任何特定的表示手段，并且意图指提供相关信息的任何表示。术语“表达水平”是指基因或蛋白质表达数据所反映的或衍生的定量，无论数据是否涉及基因转录物累积或蛋白质累积或蛋白质合成速率等。

[0115] 术语“健康的”和“正常的”在本发明中可交换使用，是指缺乏(至少限于检测)疾病状况的受试对象或特定细胞或组织。

[0116] 术语“核酸”是指多核苷酸，例如脱氧核糖核酸(DNA)，和核糖核酸(RNA)(如果合适)。该术语还应该理解为包含由核苷酸类似物制得的RNA或DNA的类似物，以及单链(例如正义或反义)和双链多核苷酸(在应用所述的实施方案时)。在一些实施方案中，“核酸”是指抑制核酸。一些类别的抑制核酸化合物包括反义核酸、RNAi构建体和催化核酸构建体。此类别的核酸是本领域公知的。

[0117] 本发明所述的实施方案涉及用于治疗和/或预防纤维症和多种纤维化疾病、紊乱或症状的组合物和方法。如以下实施例中所述，发现短链脱氢酶活性抑制剂(例如15-PGDH抑制剂)可以给予有需要的受试对象，从而减少纤维化症状，例如胶原蛋白沉积、炎性细胞因子表达和炎性细胞浸润；以及治疗和/或预防多种纤维化疾病、紊乱和状况。

[0118] 在一些实施方案中，治疗或预防纤维化疾病、紊乱或状况的方法包括向有需要的患者给予治疗有效量的15-PGDH抑制剂，从而得以在强度、严重性或频率方面减少纤维化疾病、紊乱或状况、或者其他相关疾病、紊乱或状况的至少一种症状或特征，或者延迟发作。

[0119] 15-PGDH抑制剂是例如展现15-PGDH表达或者结合15-PGDH，部分或完全阻断刺激，降低，预防，延迟作用，灭活，脱敏或下调节15-PGDH活性(例如拮抗剂)的试剂。本发明所述的15-PGDH抑制剂可以提供用于升高组织中前列腺素水平的药理学方法。

[0120] 如本发明所用，术语“纤维化”疾病、紊乱或状况包括全部或部分表征为纤维物质的过量产生(包括细胞外基质中纤维化物质的过量产生)、或者正常组织元素被异常的非功能的和/或过量累积的机制相关成分替代的疾病、紊乱或状况。纤维化疾病、紊乱或状况可以包括急性和慢性的临床或亚临床表现，其中纤维发生相关的生物学或病理学是明显的。

[0121] 纤维化疾病、紊乱和状况的实例包括系统性硬化病，多灶性纤维硬化，肾性系统纤维症，硬皮病(包括硬斑病，泛发性硬斑病或线状硬皮病)，硬皮病的移植物抗宿主病，肾纤维症(包括肾小球硬化，肾小管间质纤维症，进行性肾病或糖尿病肾病)，心脏纤维症(例如心肌纤维症)，肺纤维症(例如肺纤维症，肾小球硬化症肺纤维症，特发性肺纤维症，硅肺病，石棉沉滞症，间质性肺病，间质性肺病和化疗/放疗诱导的肺纤维症)，口腔纤维症，心肌心内膜纤维症，三角肌纤维症，胰腺炎，炎性肠病，Crohn病，坏死性筋膜炎，嗜酸性筋膜炎，一般的纤维化综合征(表征为正常肌肉组织不同程度地被纤维组织替代)，腹膜后纤维症，肝纤维症，慢性间质性肝炎，慢性肾功能衰竭；骨髓纤维症(骨髓纤维症)，药物诱发的麦角中毒，骨髓增生异常综合征，骨髓增殖性综合征，妇科肿瘤，卡波济肉瘤，Hansen病，胶原性结

肠炎,急性纤维症,特定器官纤维症等。

[0122] 示意性的器官特异性纤维化紊乱包括但不限于肺纤维症,肺动脉高压,囊性纤维症,哮喘,肺慢性阻塞性疾病,肝纤维症,肾纤维症,NASH等。许多纤维化疾病、紊乱或状况在受影响的组织中具有紊乱的和/或过多的细胞外基质沉积。纤维症可以与炎症有关,作为潜在的疾病症状发生,和/或由手术过程或伤口愈合过程导致。未检查的纤维症可以导致潜在的器官或组织结构体系的破坏,通常称为瘢痕。

[0123] 在一些实施方案中,15-PGDH抑制剂可以用于治疗或预防肺纤维症。肺纤维症可以选自肺纤维症,肺动脉高压,肺慢性阻塞性疾病(COPD),哮喘,特发性肺纤维症,结节病,囊性纤维症,家族性肺纤维症,硅肺病,石棉沉滞症,煤矿工人尘肺,炭尘肺,过敏性肺炎,由吸入无机粉尘导致的肺纤维症,由感染性试剂导致的肺纤维症,由吸入有毒气体、气溶胶、化学粉尘、烟或蒸汽导致的肺纤维症,药物诱发的间质性肺病,或肺动脉高压,以及它们的组合。

[0124] 肺纤维症表征为肺组织的进程性瘢痕,伴有纤维细胞增生、细胞外基质蛋白质的过量累积和异常肺泡结构。增厚的和僵硬的组织难以使肺正常的工作,导致呼吸问题,例如呼吸浅短,并且最终可以致命。肺纤维症可以由急性肺损伤、病毒感染、暴露于毒素、辐射、慢性疾病、药物导致,或者可以是特发性的(即,未发现的潜在的原因)。

[0125] 特发性肺纤维症的经典发现显示肺的弥漫周边的瘢痕,并且在肺表面的外衬相邻处(通常在肺的基底处)具有小泡(称为肺大泡)。特发性肺纤维症通常具有缓慢的且不间断的进展。早期,患者通常抱怨不明原因的干咳。接着,开始呼吸浅短(呼吸困难)并且经过一段时间,由于越来越低的活性而引发恶化。最终,呼吸浅短变成残疾、限制所有的活性、甚至在座位时仍然发生。在更罕见的情况下,纤维症可以快速进展,并且在疾病发作的几周至几个月内发生呼吸困难和残疾。这种形式的肺纤维症称为Hamman-Rich综合征。

[0126] 肺动脉高压标记为肺血管血压升高,包括肺动脉、肺静脉和/或肺毛细血管。异常的高压拉紧了心脏的右心室,导致其扩张。经过一段时间,右心室可以变弱并失去其泵送足够的血液至肺的能力,导致心脏衰竭的发展。其他医学状况的发展可以导致肺动脉高压,例如慢性肝病和慢性间质性肝炎;风湿病紊乱,例如硬皮病或系统性红斑狼疮(狼疮);肺状况,包括肿瘤、肺气肿、肺慢性阻塞性疾病(COPD)和肺纤维症。肺纤维症可以导致肺血管变窄,导致肺动脉高压。

[0127] 肺慢性阻塞性疾病(COPD)是一种普通的肺病,其通常与慢性支气管炎或肺气肿有关。症状通常可以包括咳嗽、粘液形成、疲劳、喘鸣和呼吸道感染。

[0128] 慢性支气管炎和肺气肿是其中气道变窄的肺病。这导致空气流入和流出肺受到限制,导致呼吸浅短(呼吸困难)。在临床实践中,COPD定义为在肺功能测试中特征性的低气流。

[0129] 肺损伤和大气道炎症导致慢性支气管炎。在肺的气道中,慢性支气管炎的标志是气道杯状细胞和粘液腺的数量增加(增生)和尺寸增大(肥大)。结果,气道中比平时更粘,造成气道变窄并导致咳嗽和痰。在显微镜下,气道壁被炎性细胞浸润。炎症后发生瘢痕形成和重塑,其增厚了气道壁还导致气道变窄。随着慢性支气管炎的进展,具有鳞状上皮化生(气道内侧衬里的组织中发生异常变化)和纤维症(气道壁进一步增厚并形成瘢痕)。这些变化的结果是气流受限和难以呼吸。

[0130] 哮喘是表征为气道炎症和收缩的慢性肺病。哮喘导致喘鸣、胸闷、呼吸浅短和咳嗽的复发时期。肿胀和粘液过度产生可以进一步导致气道收缩和症状恶化。其证据为哮喘中可以发生基质降解增加，并且可以可能有助于哮喘中气道的机械变化(Roberts et al (1995)Chest 107:111S-117S,该文献以引用方式全文并入本文)。细胞外基质降解的治疗可以减缓哮喘症状。

[0131] 囊性纤维症是隐性多系统遗传疾病，其表征为穿越上皮细胞的氯和钠的异常转运，导致肺、胰腺、肝脏、肠和生殖道的增厚、粘性分泌物。囊性纤维症是囊性纤维症跨膜传导调节蛋白质(CFTR)基因突变导致的。肺病是由于粘液形成、粘膜纤毛清除率降低以及所产生的炎症导致气道堵塞造成的，其可以导致纤维化损伤和肺的结构改变。纤维化肺损伤在一段时间内发展，导致一些囊性纤维症患者需要肺移植。

[0132] 患有囊性纤维症的受试对象的一般症状包括但不限于稠粘液的累积、痰多产生、频繁的胸腔感染、频繁的咳嗽、频繁的呼吸短浅、炎症、活动能力降低、肺和窦道机会性感染(包括但不限于金黄色酿脓葡萄球菌(Staphylococcus aureus)，流感嗜血杆菌(Haemophilus influenzae)，Mycobacterium aviium和绿浓杆菌(Pseudomonas aeruginosa))、肺炎、肺结核、支气管扩张、咳血、肺动脉高压(及所产生的心脏衰竭)、组织缺氧，呼吸衰竭，变应性支气管肺曲菌病，鼻旁窦中的粘液，鼻窦感染，面神经痛，发烧，过度的鼻引流，鼻息肉的发展，心肺并发症，CF-相关糖尿病，直肠脱垂，胰腺炎，吸收障碍，肠道阻塞，胰腺外分泌机能不全，胆管堵塞和慢性间质性肝炎。

[0133] 在其他的实施方案中，15-PGDH抑制剂可以用于治疗或预防由手术后粘连形成造成的纤维化疾病、紊乱或状况。手术后粘连形成是手术的常见并发症。由机械损伤、缺血和感染形成的粘连可以增加术后发病率和死亡率。尽管精细的手术过程可以降低粘连形成的程度，但是粘连很少被切除并且需要有效的辅助治疗。减少与该过程有关的纤维症可以减少手术的疼痛、阻塞和其他并发症，并促进治愈和恢复。

[0134] 哺乳动物组织中的伤口(即，撕裂、开口)导致组织破坏以及伤口表面的微血管凝血。此类组织的修复表明对损伤的有序的受控的细胞应答。软组织伤口不管尺寸如何，都以相似的方式治愈。组织生长和修复是生物系统，其中在氧梯度存在下发生细胞增殖和血管生成。在组织修复过程中发生的相继的形态学和结构变化已经详细表征，并且在一些情况下进行了定量(例如参见Hunt,T.K.,et al.,"Coagulation and macrophage stimulation of angiogenesis and wound healing,"in The Surgical Wound,pp.1-18,ed.F.Dineen& G.Hildrick-Smith(Lea&Febiger,Philadelphia:1981))。细胞形态学由3个不同的区域组成。中央缺血伤口空间是氧缺乏的、酸中毒的和hypercarbic，并且具有高的乳酸盐水平。与伤口空间相邻的是局部贫血(缺血)的梯度区域，其占据了分裂的成纤维细胞。在前导区域之后是活性胶原蛋白合成区，其表征为成熟的成纤维细胞和大量新形成的毛细血管(即，新血管形成)。美国专利No.5,015,629和7,022,675(均以引用方式并入本文)公开了用于增加伤口修复速率的方法和组合物。

[0135] 在一些实施方案中，15-PGDH抑制剂可以通过给予需要治疗的受试对象而用于减少或预防受试对象的瘢痕形成。瘢痕形成是治愈过程的自然部分。伤口处混乱的胶原蛋白合成和沉积可以导致过量的、增厚的或增加的瘢痕形成。通常，伤口越大，其需要治愈的时间越长，形成问题性瘢痕的机会就更高。

[0136] 在其他的实施方案中，15-PGDH抑制剂可以用于减少或预防皮肤或硬皮病的瘢痕形成。皮肤上有多种类型的瘢痕。在位于原始损伤的边界内部的肉红色区域，肥厚型瘢痕增多。它们通常描述为发痒的。在一些情况下，肥厚型瘢痕收缩并自行退去。在趋向于覆盖比原始损伤更大区域的深红色区域，瘢痕瘤增多。即使在手术去除时，瘢痕瘤往往复发。萎缩性瘢痕是皮肤凹陷，类似于通常由严重的痤疮形成的那些。它们是由炎症导致，炎症在重塑过程中破坏胶原蛋白，导致凹进的区域。

[0137] 在一些实施方案中，15-PGDH抑制剂可以用于治疗或预防系统性硬化病。系统性硬化病是系统性结缔组织疾病，其表征为微血管改变、免疫系统紊乱、以及胶原蛋白和其他基质物质在结缔组织中大量沉积。系统性硬化病为临床异质广义紊乱，其影响皮肤和内部器官的结缔组织，例如胃肠道、肺、心脏和肾脏。减少由系统性硬化病导致的纤维症可以减缓症状和/或预防受影响组织的其他并发症。

[0138] 在其他的实施方案中，15-PGDH抑制剂可以用于治疗或预防肝纤维症。肝纤维症可以由慢性肝病，肝炎后肝硬化，乙型肝炎病毒感染，丙型肝炎病毒感染，丁型肝炎病毒感染，血吸虫病，原发性胆汁性肝硬化，酒精性肝病或非酒精性脂肪性肝炎(NASH)，NASH相关肝硬化肥胖，糖尿病，蛋白质营养不良，冠心病，自身免疫性肝炎，囊性纤维症，α-1-抗胰蛋白酶缺乏，原发性胆汁性肝硬化，药物反应和暴露于毒素导致。

[0139] 非酒精性脂肪性肝炎(NASH)是普通的肝脏疾病。其类似于酒精性肝病，但是在饮酒较少或不饮酒的人中发生。NASH的主要特征是肝脏中的脂肪，连通炎症和损伤。然而，NASH可以是严重的，并且可以导致肝硬化，其中肝脏永久损伤和形成瘢痕，并且不能再正常工作。

[0140] NASH通常为具有较少或不具有症状的沉默的疾病。患者通常在早期感觉良好，并且仅开始时具有诸如疲劳、体重减轻或虚弱之类的症状，但是疾病进一步发展或者肝硬化形成。NASH的过程可以几年，甚至几十年。该过程可以停止，在一些情况下，甚至可以在未进行特定治疗的情况下自身开始逆转。或者NASH可以缓慢恶化，导致在肝脏中出现或累积瘢痕或纤维症。随着纤维症恶化，肝硬化发展，其中肝脏形成严重的瘢痕、变硬并且不能正常的发挥功能。并非每一位患有NASH的人都发展成肝硬化，但是一旦严重的瘢痕形成或肝硬化存在，则很少有治疗可以阻止该过程。患有肝硬化的人经历液体潴留、肌肉萎缩、肠出血和肝脏衰竭。肝脏移植是患有肝脏衰竭的晚期肝硬化的唯一治疗方法，并且越来越多地在患有NASH的人中实施移植。在美洲，NASH排名为在丙型肝炎和酒精性肝病之后的肝硬化的主要原因之一。

[0141] 在一些实施方案中，15-PGDH抑制剂可以用于治疗或预防肾纤维症。肾纤维症可以由肾衰竭，导管放置，肾病，肾小球硬化症，血管球性肾炎，慢性肾功能不全，急性肾损伤，终末期肾病或肾衰竭之后的透析所导致。

[0142] 肾脏(肾)纤维症由肾脏中纤维结缔组织过量形成导致。肾纤维症造成显著的发病率和死亡率，并且导致需要透析或肾脏移植。纤维症可以在肾元(肾脏的功能单位)的过滤或重吸收部分中形成。多种因素可以有助于肾脏瘢痕形成，特别是与肾小球过滤的自身调节有关的生理学紊乱。这会相应地导致正常结构被累积的细胞外基质替代。单个细胞的生理学的变化谱导致多种肽和非肽纤维原(fibrogen)产生，它们刺激了细胞外基质合成和降解之间的平衡的改变，从而有利于瘢痕形成。

[0143] 在一些实施方案中，组织器官的纤维症的症状可以包括炎症。在这些实施方案中，向有需要的受试对象给予治疗有效量的15-PGDH抑制剂可以是有效降低或减少组织或器官中炎性细胞计数的量。相关样品可以得自受试对象，从而测定炎性细胞计数的降低或减少。在非限定性实施方案中，可以通过证明在得自囊性纤维症受试对象的BAL流体中嗜中性粒细胞计数的减少来评估有利的作用。嗜中性粒细胞过量募集于CF患者的气道中是CF的肺病严重性的明显预报器，因此是重要的治疗靶物。用于测量此类细胞计数的方法是本领域公知的，包括但不限于FACS计数。在一些实施方案中，所述的方法可以包括与对照相比，减少得自受试对象的BAL流体中嗜中性粒细胞的计数。任何合适的对照都可以用于比较，例如未使用15-PGDH抑制剂治疗的囊性纤维症受试对象。在一些实施方案中，炎性细胞计数的减少(例如嗜中性粒细胞计数)为受试对象提供了临床益处。在多种实施方案中，与对照相比，炎性细胞计数减少至少5％，10％，15％，20％，25％，50％或更多。

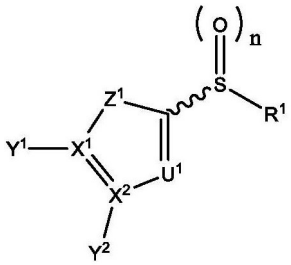
[0144] 在另一个实施方案中，15-PGDH抑制剂的有利作用可以通过在得自受试对象的相关样品中的一种或多种炎性生物标志物的减少来评估。在多个非限定性实施方案中，炎性生物标志物可以包括或者由与纤维症有关的一种或多种细胞因子或炎性细胞因子组成。此类细胞因子可以包括例如BAL流体中的IL1β，MIP2(例如CCL3或CCL4)，IFNδ，TGFβ，TNFα，IL-6，MCP-1，IL2和IL-10。用于测量此类生物标志物的量的方法是本领域公知的，包括但不限于ELISA。因此，在这种实施方案中，所述的方法可以进一步包括与对照相比，减少在得自受试对象的样品中的一种或多种炎性生物标志物的量。

[0145] 在其他的实施方案中，15-PGDH抑制剂可以用于降低或减少受试对象组织或器官中胶原蛋白分泌或胶原蛋白沉积的方法中，例如肺、肝脏、皮肤或心脏。所述的方法可以包括向有需要的受试对象给予治疗有效量的15-PGDH抑制剂。所述的受试对象可以具有或者处于组织或器官中过量胶原蛋白分泌或胶原蛋白沉积的风险之下，例如肾脏、肺、肝脏、肠、结肠、皮肤或心脏。通常，器官中过量胶原蛋白分泌或胶原蛋白沉积是由损伤或损害导致的。这种损伤和损害是器官特异性的。可以在足够的时间内给予15-PGDH抑制剂，从而完全或部分降低或减少组织或器官中的胶原蛋白沉积的水平。足够的时间可以为1周、1周至1个月、1个月至2个月、2个月或更多。对于慢性状况而言，可以终生有利地给予15-PGDH抑制剂。

[0146] 可以使用测试方法来鉴定用于治疗纤维化疾病、紊乱或状况和/或减少胶原蛋白沉积的15-PGDH抑制剂，在所述的测试中，将推定的抑制剂化合物施加于表达15-PGDH的细胞上，然后测定对15-PGDH活性的功能作用。将包含使用潜在抑制剂处理的包含15-PGDH的样品或测试与不具有所述的抑制剂的对照样品比较，从而检查作用的程度。将对照样品(未使用调控剂处理)分配为100％的相对15-PGDH活性值。当相对于对照的15-PGDH活性值为大约80％，可任选地为50％or 25％，10％，5％或1％时，得到15-PGDH的抑制。

[0147] 作为SCD的抑制剂(例如15-PGDH)测试的试剂可以为任何小的化学分子或化合物。通常，测试化合物为小的化学分子、天然产物或肽。通过自动操作测试步骤并将得自任何方便来源的化合物提供给测试(它们通常平行运行)(在机器测试中在微量滴定板上的微量滴定形式)，设计所述的测试从而筛选大的化学文库。

[0148] 在一些实施方案中，15-PGDH抑制剂可以包括具有下式(I)所示的化合物以及它们药物可接受的盐：

[0149] 

(I)

[0150] 其中n为0-2；

[0151] Y^1,Y^2和R^1是相同的或不同的,并且均选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2$-OH),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2$-NH2,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中Y^1和Y^2可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基；

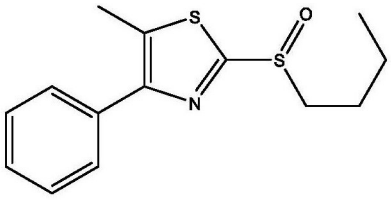
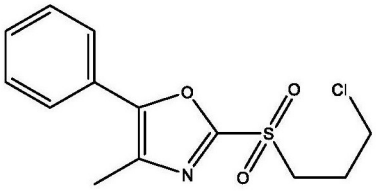
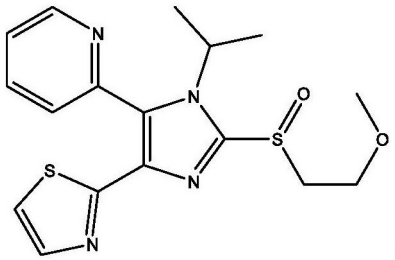
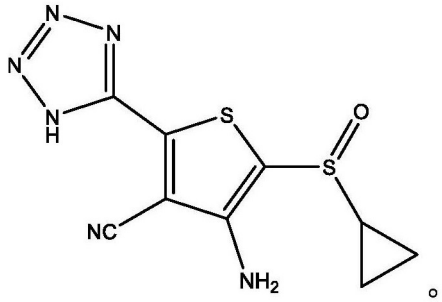
[0152] U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省；

[0153] X^1和X^2独立地为N或C,并且其中当X^1和/或X^2为N时,Y^1和/或Y^2各自是缺省的；

[0154] Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线状的、支化的或环状的,并且其是非取代的或取代的。

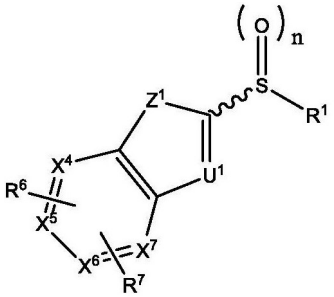
[0155] 具有式(I)的15-PGDH抑制剂的实例包括以下化合物及其药物可接受的盐：

[0156]

[0157] 在其他的实施方案中，15-PGDH抑制剂可以包括具有下式(II)的化合物及其药物可接受的盐：

[0158]



(II)

[0159] 其中n为0-2；

[0160] X^4，X^5，X^6和X^7独立地为N或CR^c；

[0161] R^1，R^6，R^7和R^c均独立地选自氢，取代的或非取代的C_1-C_{24}烷基，C_2-C_{24}烯基，C_2-C_{24}炔基，C_3-C_{20}芳基，杂芳基，包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N，NH，N(C_1-C_6烷基)，NC(O)(C_1-C_6烷基)，O和S)，C_6-C_{24}烷芳基，C_6-C_{24}芳烷基，卤素，-Si(C_1-C_3烷基)$_3$，羟基，硫氢基，C_1-C_{24}烷氧基，C_2-C_{24}烯氧基，C_2-C_{24}炔氧基C_5-C_{20}芳氧基，酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基))，酰氧基(-O-酰基)，C_2-C_{24}烷氧基羰基(-(CO)-O-烷基)，C_6-C_{20}芳氧基羰基(-(CO)-O-芳基)，C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基)，C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基)，羧基(-COOH)，羧酸($-COO^-$)，氨基甲酰(-(CO)-NH_2)，C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基))，芳基氨基甲酰(-(CO)-NH-芳基)，硫代氨基甲酰(-(CS)-NH_2)，脲基(-NH-(CO)-NH_2)，氰基(-CN)，异氰基($-N^+C^-$)，氰氧基(-O-CN)，异氰氧基($-O-N^+=C^-$)，异硫代氰氧基(-S-CN)，叠氮基($-N=N^+=N^-$)，甲酰基(--(CO)--H)，硫代甲酰基(--(CS)--H)，氨基(--NH_2)，C_1-C_{24}烷基氨基，C_5-C_{20}芳基氨基，C_2-C_{24}烷基氨基(-NH-(CO)-烷基)，C_6-C_{20}芳基氨基(-NH-(CO)-芳基)，亚氨基(-CR=NH，其中R为氢，C_1-C_{24}烷基，C_5-C_{20}芳基，C_6-C_{24}烷芳基，C_6-C_{24}芳烷基等)，烷基亚氨基(-CR=N(烷基)，其中R=氢，烷基，芳基，烷芳基，芳烷基等)，芳基亚氨基(-CR=N(芳基)，其中R=氢，烷基，芳基，烷芳基等)，硝基(-NO_2)，亚硝基(-NO)，磺基(-SO_2-OH)，磺酸($-SO_2-O^-$)，C_1-C_{24}烷基硫基(-S-烷基；还称为"烷基

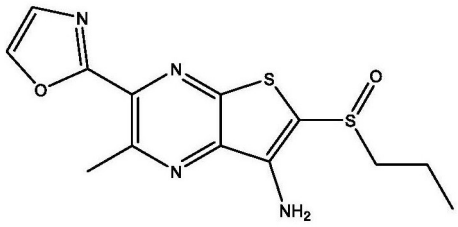
硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

[0162] U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}$OR'(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}$OR'(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省;

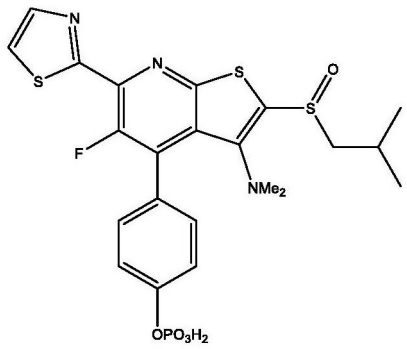
[0163] Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线性的、支化的或环状的,并且其是非取代的或取代的。

[0164] 具有式(II)的15-PGDH抑制剂的实例包括以下化合物及其药物可接受的盐:

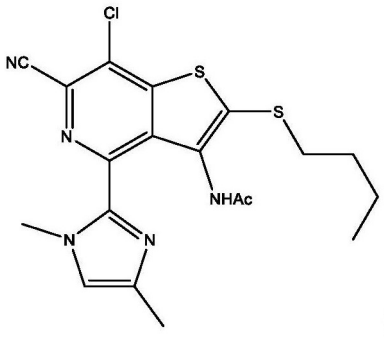
[0165]



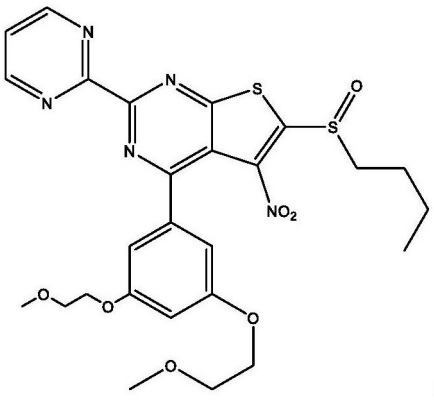
;



;

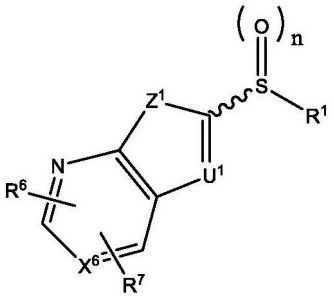


;



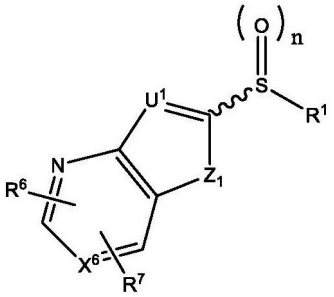
。

[0166] 在其他的实施方案中,15-PGDH抑制剂可以包括具有下式(III)或(IV)的化合物及其药物可接受的盐:



(III)，或

[0167]



(IV)

[0168] 其中n为0-2；

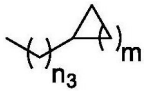
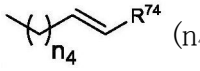
[0169] X^6独立地为N或CR^c；

[0170] R^1,R^6,R^7和R^c均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基；

[0171] U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或

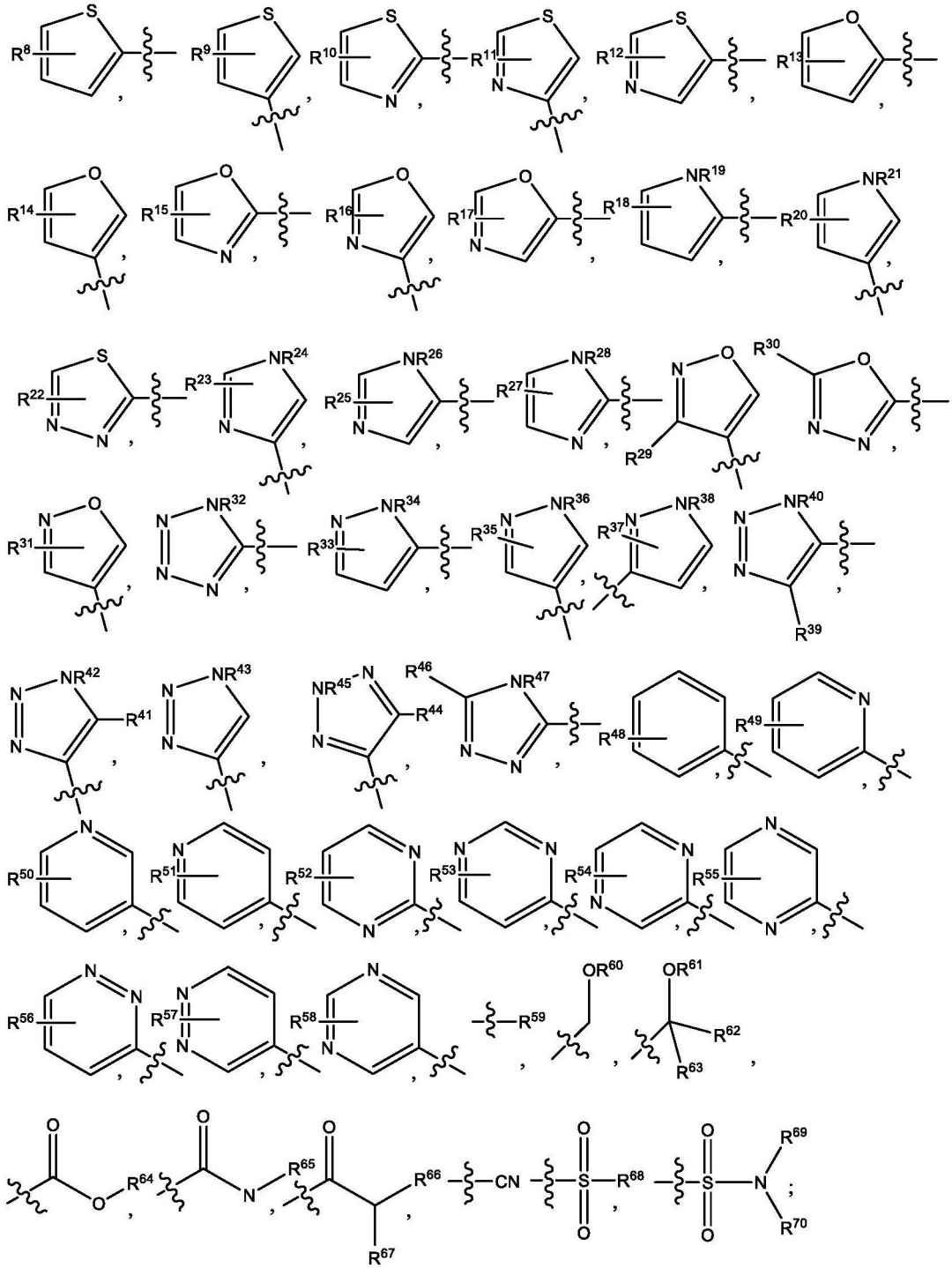
3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}OR'$(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省;

[0172] Z^1为O,S,CR^aR^b或NR^a,其中R^a和R^b独立地为H或C_{1-8}烷基,其为线性的、支化的或环状的,并且其是非取代的或取代的。

[0173] 在一些实施方案中,R^1选自支化的或线性的芳烷基,包括-$(CH_2)_{n1}CH_3$(n_1=0-7),  ,其中n_2=0-6,并且X为以下一者:CF_yH_z(y+z=3),CCl_yH_z(y+z=3),OH,OAc,OMe,R^{71},OR^{72},CN,N(R^{73})$_2$,  (n_3=0-5,m=1-5),和  (n_4=0-5)。

[0174] 在其他的实施方案中,R^6和R^7均可以独立地为以下的一者:

[0175]

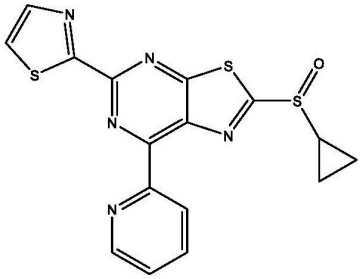
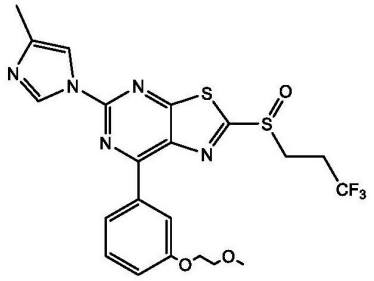


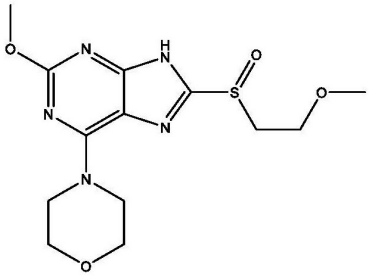
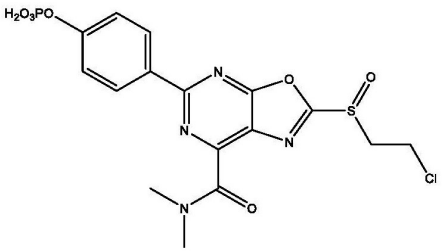
[0176] R^8,R^9,R^{10},R^{11},R^{12},R^{13},R^{14},R^{15},R^{16},R^{17},R^{18},R^{19},R^{20},R^{21},R^{22},R^{23},R^{24},R^{25},R^{26},R^{27},R^{28},R^{29},R^{30},R^{31},R^{32},R^{33},R^{34},R^{35},R^{36},R^{37},R^{38},R^{39},R^{40},R^{41},R^{42},R^{43},R^{44},R^{45},R^{46},R^{47},R^{48},R^{49},R^{50},R^{51},R^{52},R^{53},R^{54},R^{55},R^{56},R^{57},R^{58},R^{59},R^{60},R^{61},R^{62},R^{63},R^{64},R^{65},R^{66},R^{67},R^{68},R^{69},R^{70},R^{71},R^{72},R^{73}和R^{74}均是相同的或不同的,并且独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),包含5-14环原子的杂芳基或杂环基(其中1-6个环原子独立地选自N,NH,N(C_1-C_3烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,甲硅烷基,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--

CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)--NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),二氧化硫氨基($-SO_2N(R)_2$,其中R独立地为H,烷基,芳基或杂芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2-OH$),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2-NH_2$,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基($-P(O)(OH)_2$),磷酰基($-P(O)(O^-)_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯[$-OP(O)(OR)_2$,其中R=H,甲基或其他烷基],引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合。

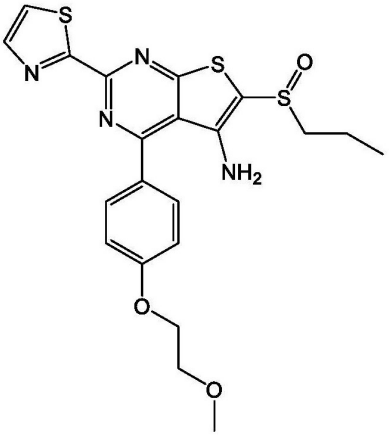
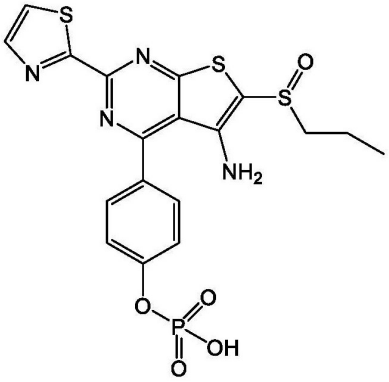
[0177] 在其他的实施方案中,R^6和R^7可以独立地为改善水溶性的基团,例如磷酸酯($-OPO_3H_2$),与磷酸酯连接的苯环($-OPO_3H_2$),被一个或多个甲氧基乙氧基基团或吗啉取代的苯环,或者被此类基团取代的芳基或杂芳基。

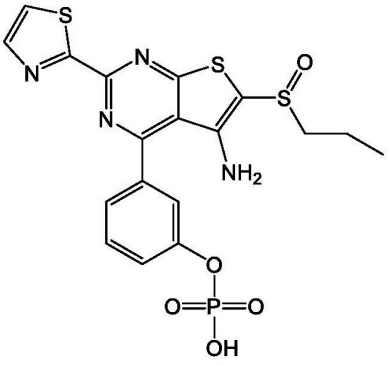
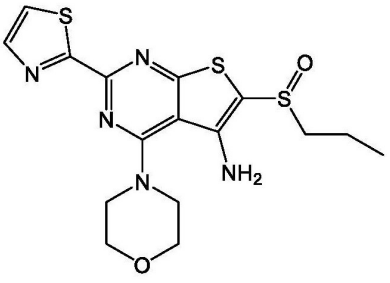
[0178] 具有式(III)或(IV)的15-PGDH抑制剂的实例包括以下化合物及其药物可接受的盐:

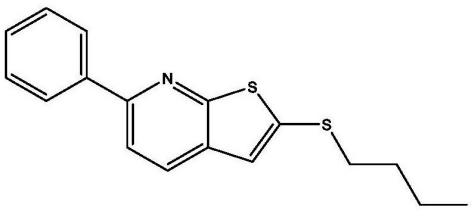
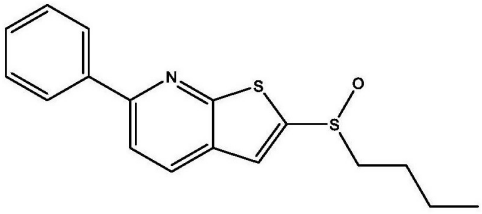
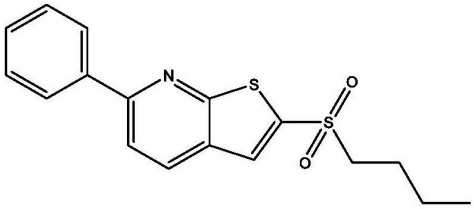
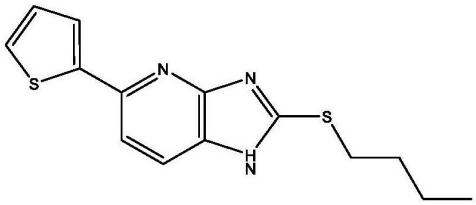

;

;


;

;

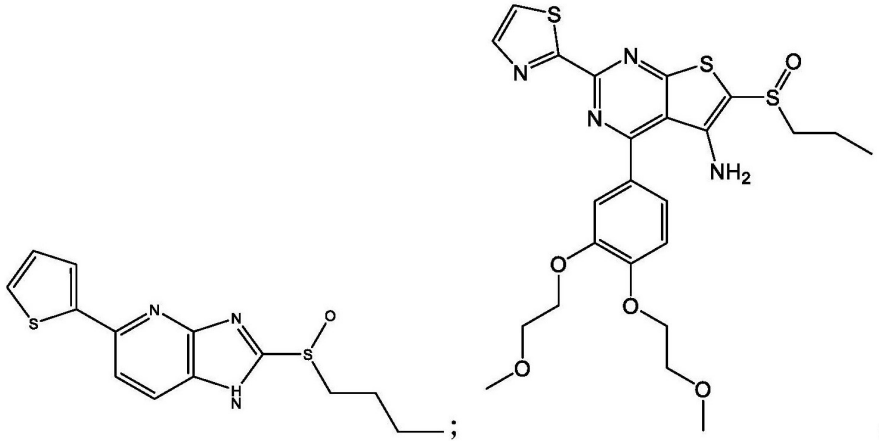
[0179]


;

;


;

;

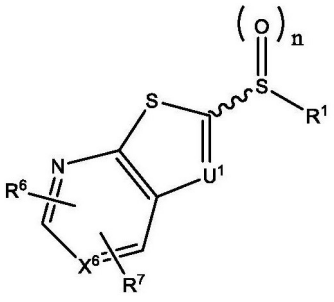

;

;

;

;

[0180]


;
。

[0181] 在其他的实施方案中,15-PGDH抑制剂可以包括具有下式(V)的化合物及其药物可接受的盐:

[0182]


(V)

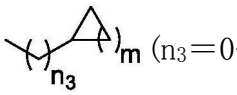
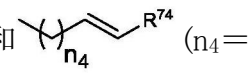
[0183] 其中n为0-2;

[0184] X^6独立地为N或CR^c;

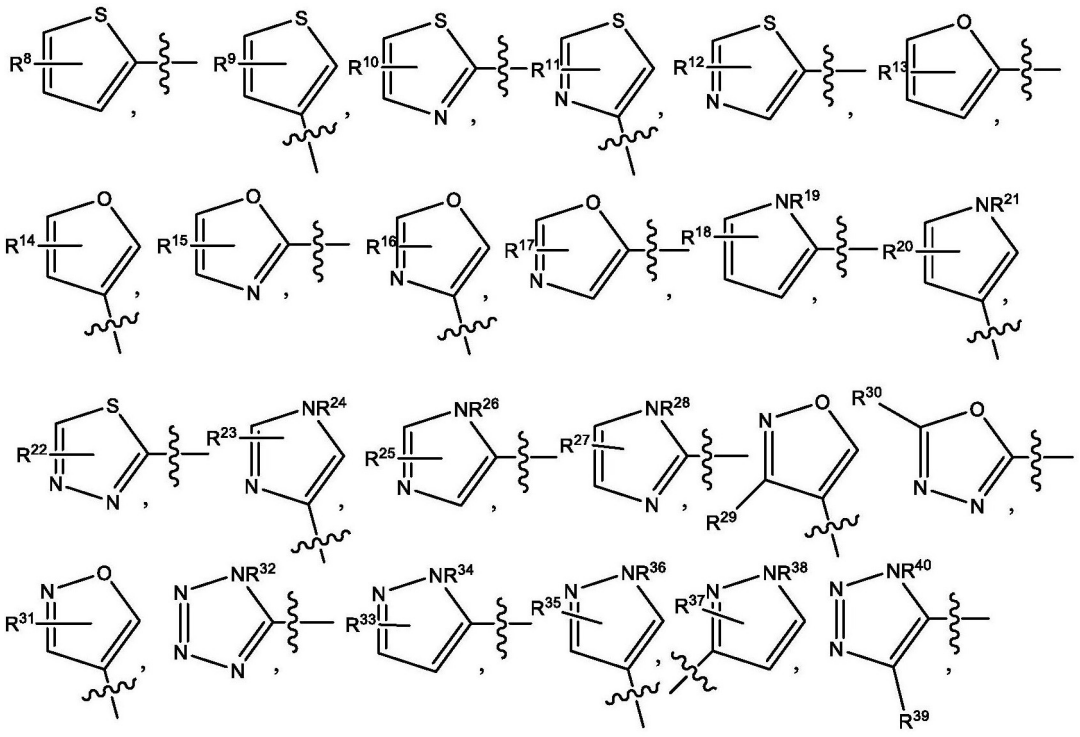
[0185] R^1,R^6,R^7和R^c均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基

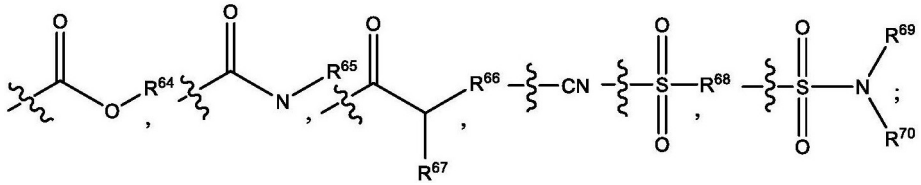
(-O-N^+=C^-),异硫代氰氧基(-S-CN),叠氮基(-N=N^+=N^-),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸(-SO_2-O^-),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接从而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基;

[0186] U^1为N,C-R^2或C-NR^3R^4,其中R^2选自H,低级烷基基团,O,$(CH_2)_{n1}$OR'(其中n1=1,2或3),CF_3,CH_2-CH_2X,O-CH_2-CH_2X,CH_2-CH_2-CH_2X,O-CH_2-CH_2X,X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,O(CO)R',COOR'(其中R'为H或低级烷基基团),并且其中R^1和R^2可以连接而形成环或多环,其中R^3和R^4是相同的或不同的,并且均选自H,低级烷基基团,O,$(CH_2)_{n1}$OR'(其中n1=1,2或3),CF_3,CH_2-CH_2X,CH_2-CH_2-CH_2X,(其中X=H,F,Cl,Br或I),CN,(C=O)-R',(C=O)N(R')$_2$,COOR'(其中R'为H或低级烷基基团),并且R^3或R^4可以缺省。

[0187] 在一些实施方案中,R^1选自支化的或线性的芳烷基,包括-$(CH_2)_{n1}CH_3$(n_1=0-7),  ,其中n_2=0-6,并且X为以下一者:CF_yH_z(y+z=3),CCl_yH_z(y+z=3),OH,OAc,OMe,R^{71},OR^{72},CN,N(R^{73})$_2$,  (n_3=0-5,m=1-5),和  (n_4=0-5)。

[0188] 在其他的实施方案中,R^6和R^7均可以独立地为以下一者及其药物可接受的盐:

[0189] 

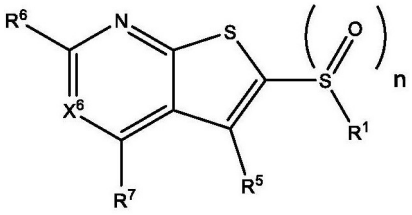
[0190] 

[0191] R^8,R^9,R^{10},R^{11},R^{12},R^{13},R^{14},R^{15},R^{16},R^{17},R^{18},R^{19},R^{20},R^{21},R^{22},R^{23},R^{24},R^{25},R^{26},R^{27},R^{28},R^{29},R^{30},R^{31},R^{32},R^{33},R^{34},R^{35},R^{36},R^{37},R^{38},R^{39},R^{40},R^{41},R^{42},R^{43},R^{44},R^{45},R^{46},R^{47},R^{48},R^{49},R^{50},R^{51},R^{52},R^{53},R^{54},R^{55},R^{56},R^{57},R^{58},R^{59},R^{60},R^{61},R^{62},R^{63},R^{64},R^{65},R^{66},R^{67},R^{68},R^{69},R^{70},R^{71},R^{72},R^{73}和R^{74}均是相同的或不同的,并且独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),包含5-14环原子的杂芳基或杂环基(其中1-6个环原子独立地选自N,NH,N(C_1-C_3烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,甲硅烷基,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--

CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸(-COO^-),氨基甲酰(-(CO)--NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基(-N^+C^-),氰氧基(-O-CN),异氰氧基(-O-N^+=C^-),异硫代氰氧基(-S-CN),叠氮基(-N=N^+=N^-),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),二氧化硫氨基(-$SO_2N(R)_2$,其中R独立地为H,烷基,芳基或杂芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基(-NO_2),亚硝基(-NO),磺基(-SO_2-OH),磺酸(-SO_2-O^-),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基(-SO_2-烷基),C_5-C_{20}芳基亚磺酰基(-SO_2-芳基),磺胺(-SO_2-NH_2,-SO_2NY_2(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸(-PO_2),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯[-OP(O)(OR)$_2$,其中R=H,甲基或其他烷基],引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合。

[0192] 在其他的实施方案中,R^6和R^7可以独立地为改善水溶性的基团,例如磷酸酯(-OPO_3H_2),与磷酸酯连接的苯环(-OPO_3H_2),被一个或多个甲氧基乙氧基基团或吗啉取代的苯环,或者被此类基团取代的芳基或杂芳基。

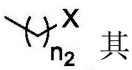
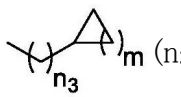
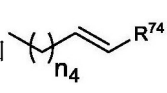
[0193] 在其他的实施方案中,15-PGDH抑制剂可以包括具有下式(VI)的化合物及其药物可接受的盐:

[0194] 

(VI)

[0195] 其中n=0-2;

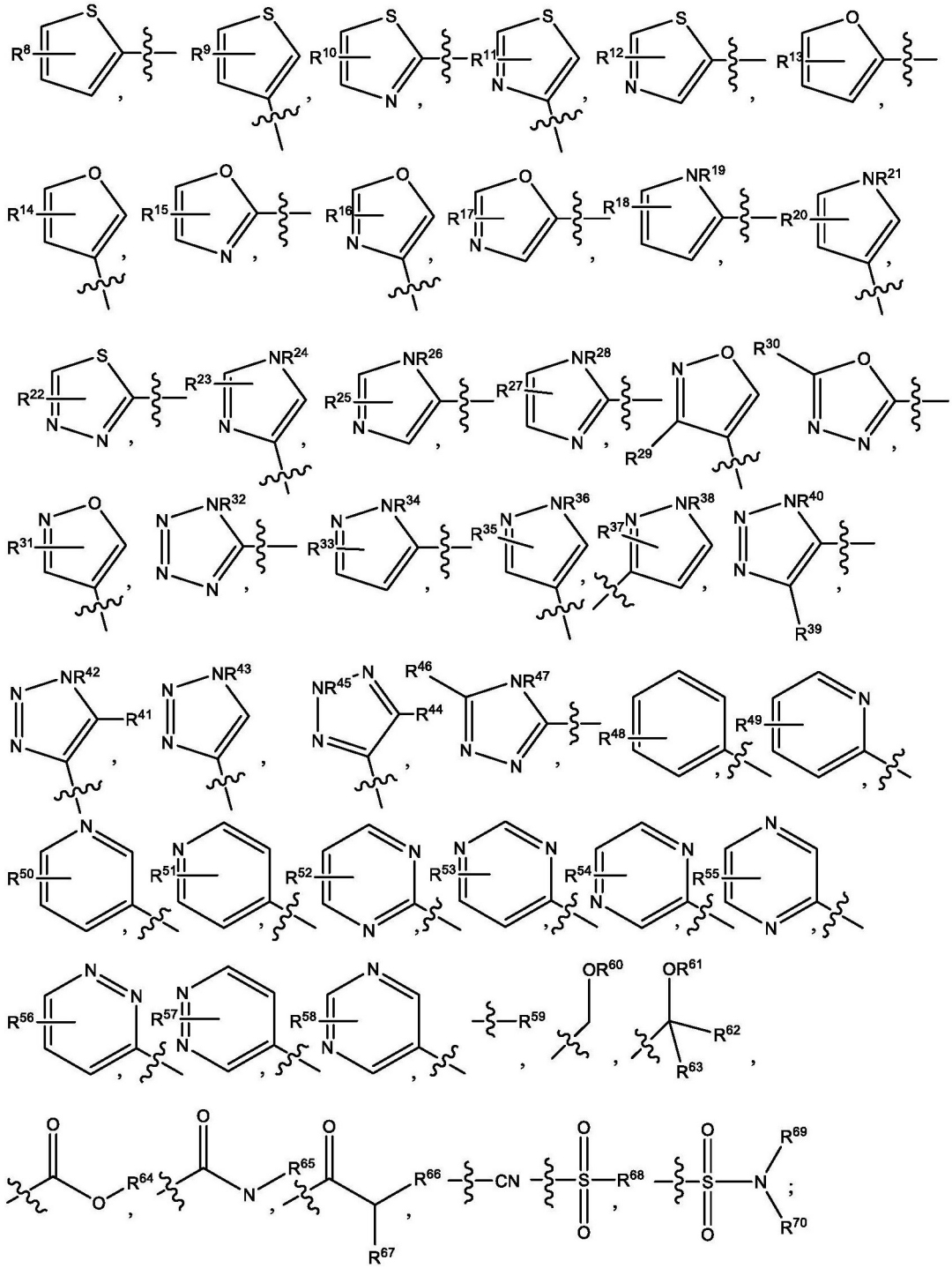
[0196] X^6为N或CR^c;

[0197] R^1选自支化的或线性的芳烷基,包括-$(CH_2)_{n_1}CH_3$(n_1=0-7),  ,其中n_2=0-6,并且X为以下一者:CF_yH_z(y+z=3),CCl_yH_z(y+z=3),OH,OAc,OMe,R^{71},OR^{72},CN,$N(R^{73})_2$,  (n_3=0-5,m=1-5),和  (n_4=0-5);

[0198] R^5选自H,Cl,F,NH_2和$N(R^{76})_2$;

[0199] R^6和R^7均可以独立地为以下的一者:

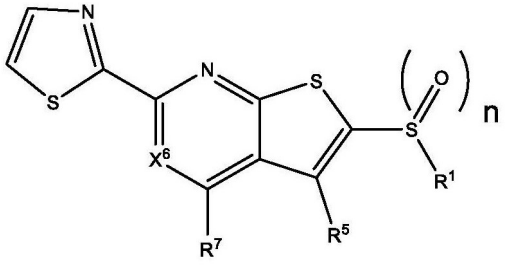
[0200]



[0201] R^8,R^9,R^{10},R^{11},R^{12},R^{13},R^{14},R^{15},R^{16},R^{17},R^{18},R^{19},R^{20},R^{21},R^{22},R^{23},R^{24},R^{25},R^{26},R^{27},R^{28},R^{29},R^{30},R^{31},R^{32},R^{33},R^{34},R^{35},R^{36},R^{37},R^{38},R^{39},R^{40},R^{41},R^{42},R^{43},R^{44},R^{45},R^{46},R^{47},R^{48},R^{49},R^{50},R^{51},R^{52},R^{53},R^{54},R^{55},R^{56},R^{57},R^{58},R^{59},R^{60},R^{61},R^{62},R^{63},R^{64},R^{65},R^{66},R^{67},R^{68},R^{69},R^{70},R^{71},R^{72},R^{73},R^{74},R^{76}和R^c均是相同的或不同的,并且独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),包含5-14环原子的杂芳基或杂环基(其中1-6个环原子独立地选自N,NH,N(C_1-C_3烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,甲硅烷基,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}

烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)--NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),二氧化硫氨基($-SO_2N(R)_2$,其中R独立地为H,烷基,芳基或杂芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2-OH$),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2-NH_2$,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯[-OP(O)(OR)$_2$,其中R=H,甲基或其他烷基],引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合。

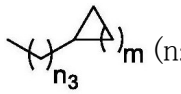
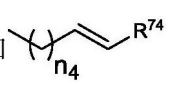
[0202] 在其他的实施方案中,15-PGDH抑制剂可以包括具有下式(VII)的化合物及其药物可接受的盐:

[0203] 

(VII)

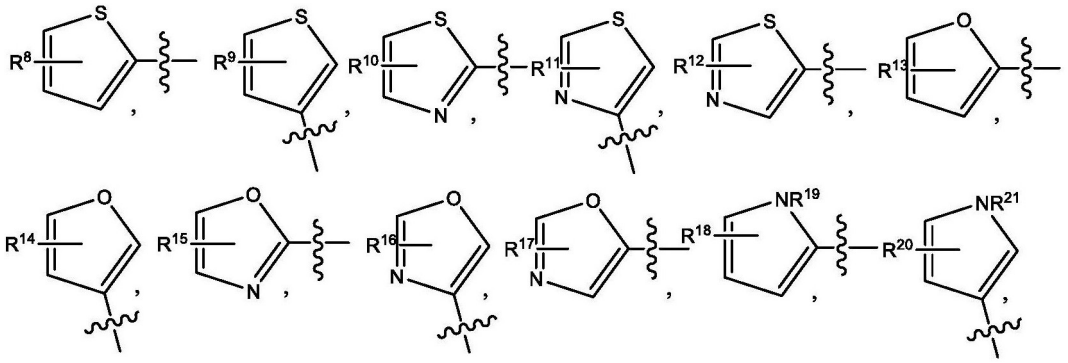
[0204] 其中n=0-2;

[0205] X^6为N或CR^c;

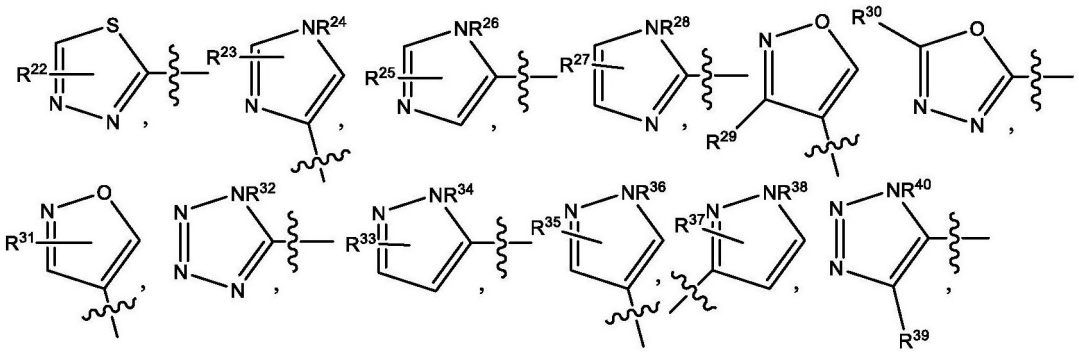
[0206] R^1选自支化的或线性的芳烷基,包括-$(CH_2)_{n1}CH_3$(n_1=0-7),  ,其中n_2=0-6,并且X为以下一者:CF_yH_z(y+z=3),CCl_yH_z(y+z=3),OH,OAc,OMe,R^{71},OR^{72},CN,$N(R^{73})_2$,  (n_3=0-5,m=1-5),和  (n_4=0-5);

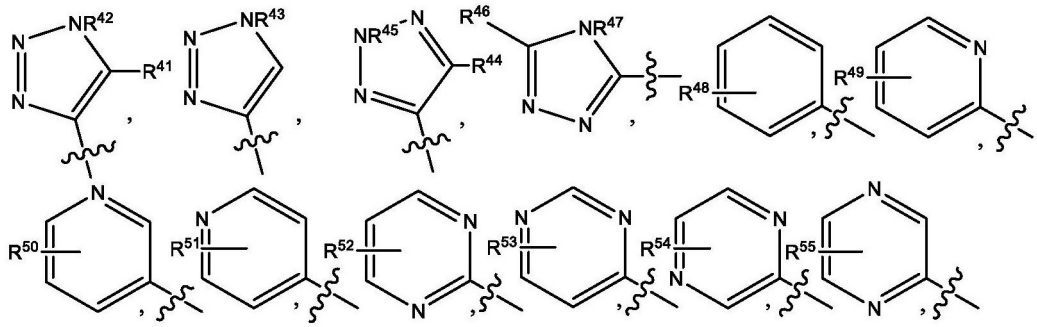
[0207] R^5选自H,Cl,F,NH_2和$N(R^{76})_2$;

[0208] R^7均可以独立地为以下的一者:

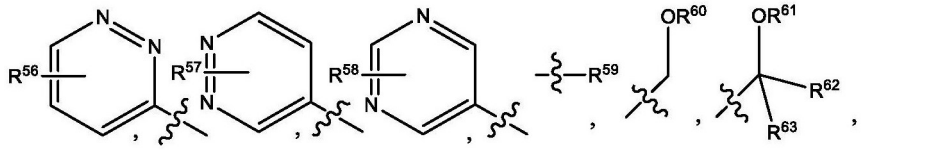


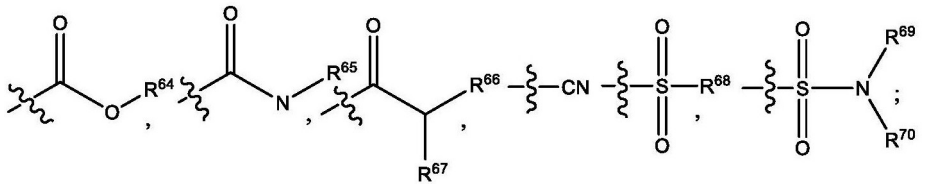
[0209]





[0210]

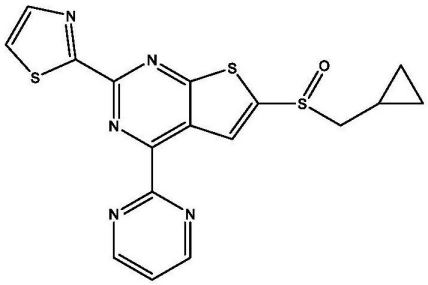




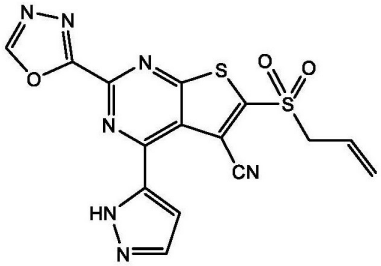
[0211] R^8,R^9,R^{10},R^{11},R^{12},R^{13},R^{14},R^{15},R^{16},R^{17},R^{18},R^{19},R^{20},R^{21},R^{22},R^{23},R^{24},R^{25},R^{26},R^{27},R^{28},R^{29},R^{30},R^{31},R^{32},R^{33},R^{34},R^{35},R^{36},R^{37},R^{38},R^{39},R^{40},R^{41},R^{42},R^{43},R^{44},R^{45},R^{46},R^{47},R^{48},R^{49},R^{50},R^{51},R^{52},R^{53},R^{54},R^{55},R^{56},R^{57},R^{58},R^{59},R^{60},R^{61},R^{62},R^{63},R^{64},R^{65},R^{66},R^{67},R^{68},R^{69},R^{70},R^{71},R^{72},R^{73},R^{74},R^{76}和R^c均是相同的或不同的,并且独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),包含5-14环原子的杂芳基或杂环基(其中1-6个环原子独立地选自N,NH,N(C_1-C_3烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,甲硅烷基,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}

烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)--NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),二氧化硫氨基($-SO_2N(R)_2$,其中R独立地为H,烷基,芳基或杂芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2-OH$),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2-NH_2$,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)(OH)$_2$),磷酰基(-P(O)(O^-)$_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚(-[$(CH_2)_nO]_m$),磷酸盐,磷酸酯[-OP(O)(OR)$_2$,其中R=H,甲基或其他烷基],引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合。

[0212] 具有式(V)、(VI)或(VIII)的化合物的实例选自:

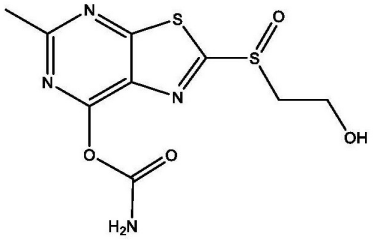


;

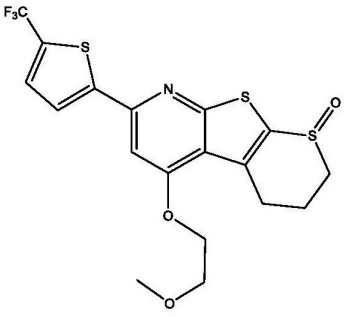


;

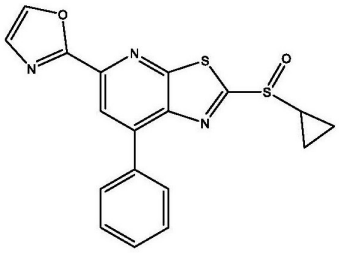
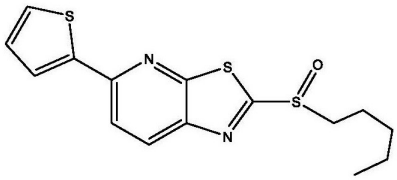
[0213]

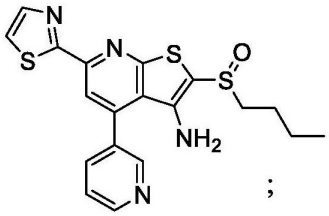
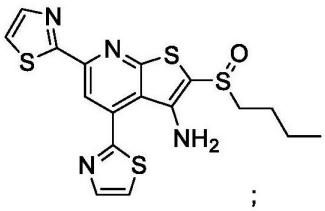
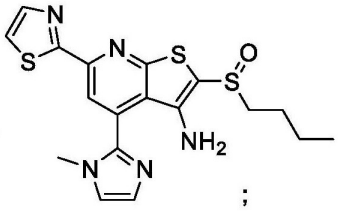


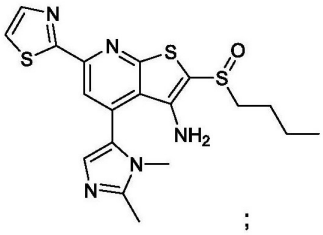
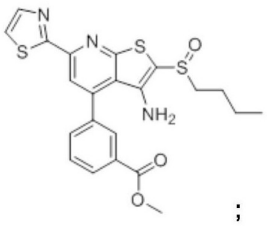
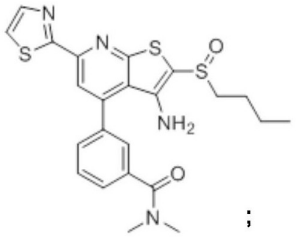
;



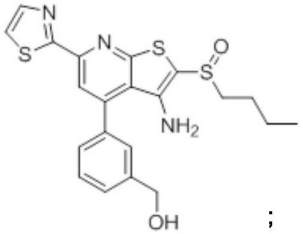
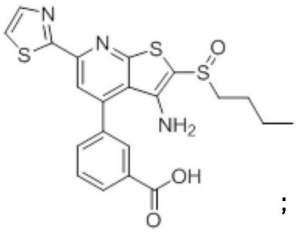
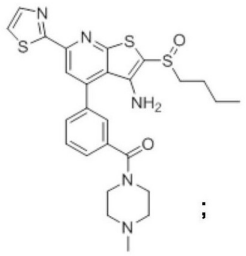
;

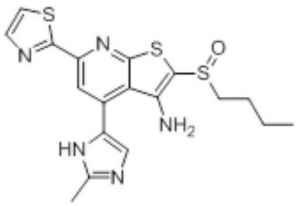
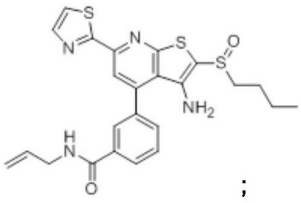
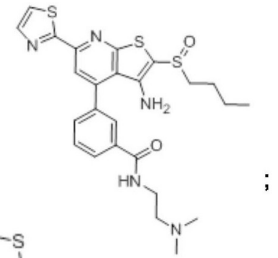

;

;

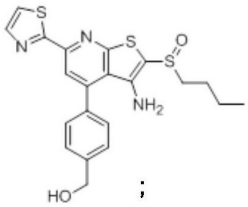
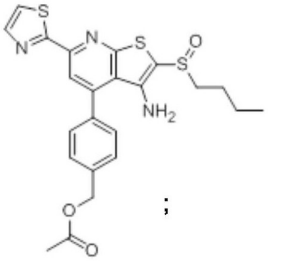
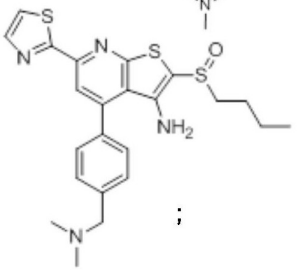

;

;

;


;

;

;

[0214]


;

;

;

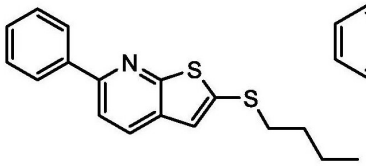
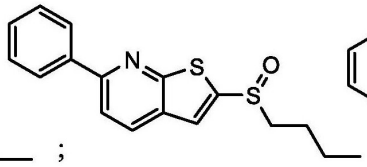
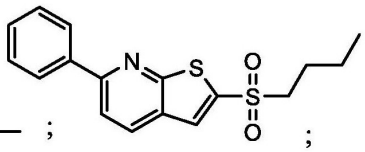
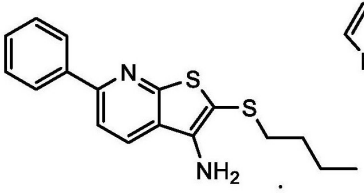
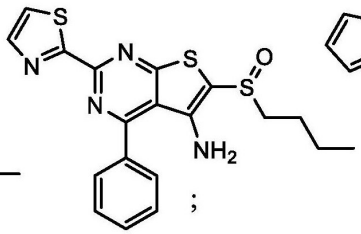
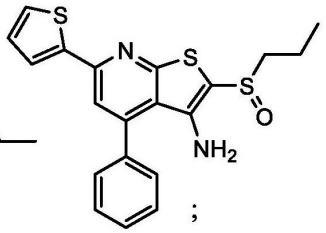
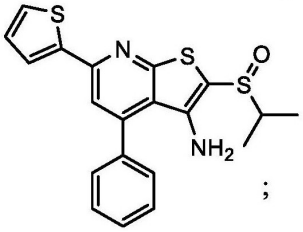
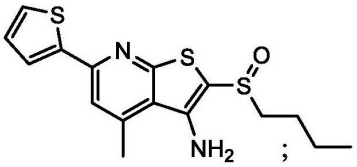
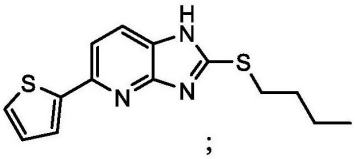
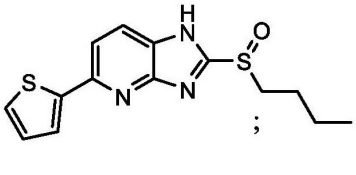
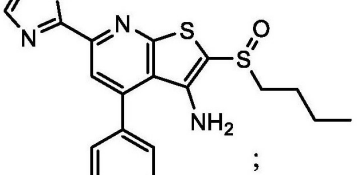
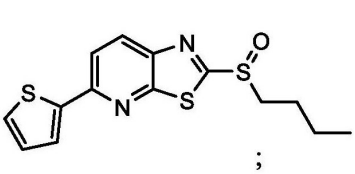
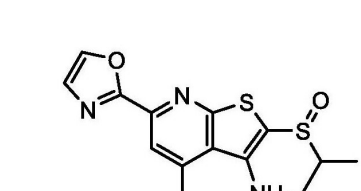
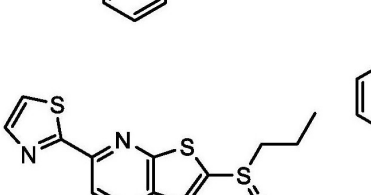
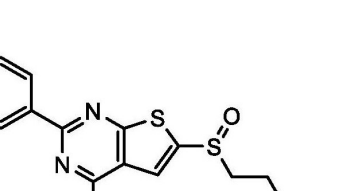

;

;

;

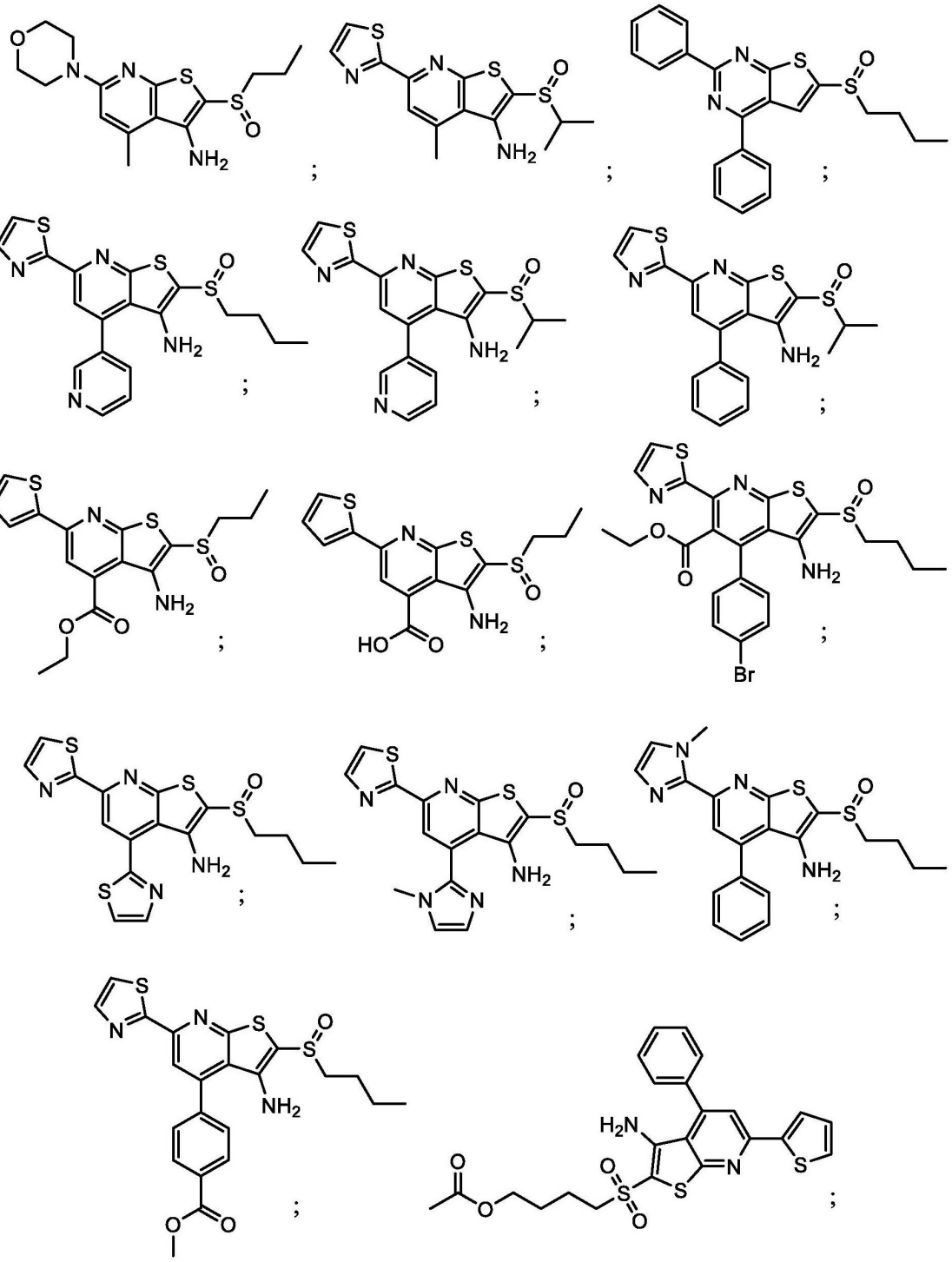

;

;

;

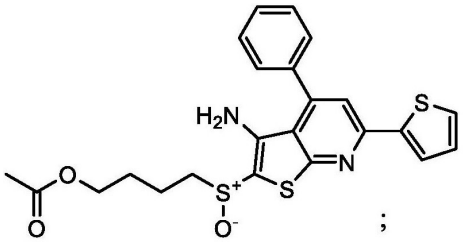
;

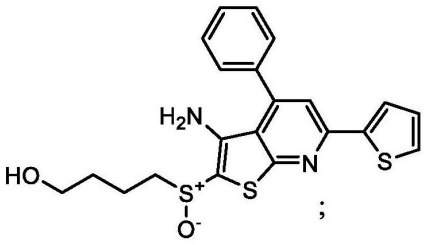
;

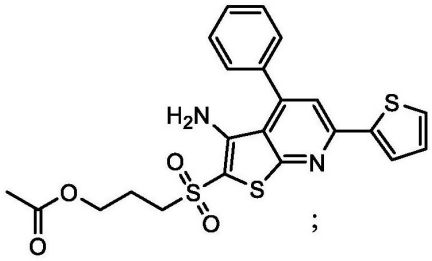
;

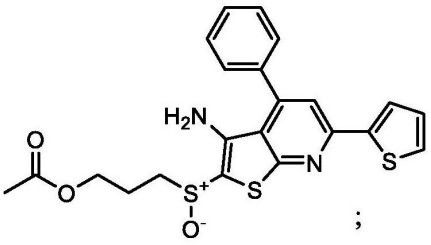
[0215]  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; ; ; ;

[0216] 

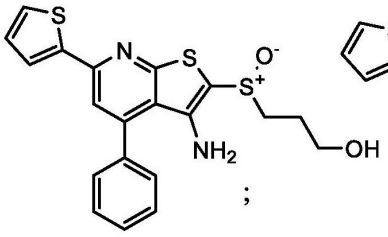

;

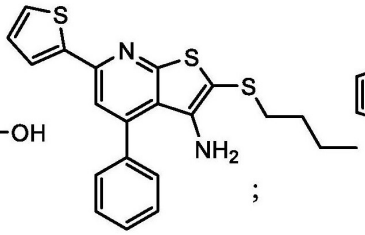

;

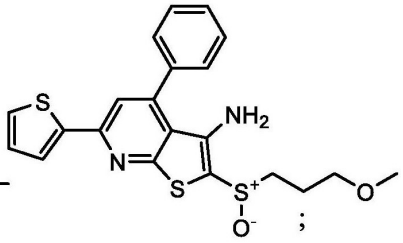

;

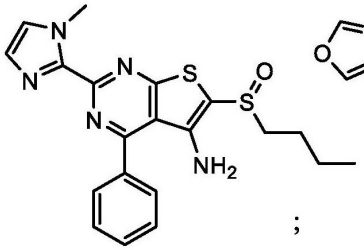

;

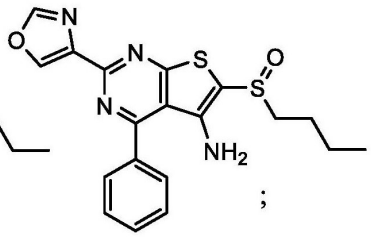
[0217]

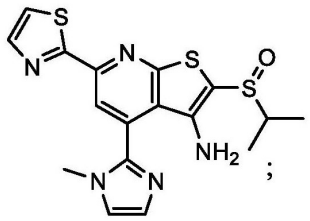

;

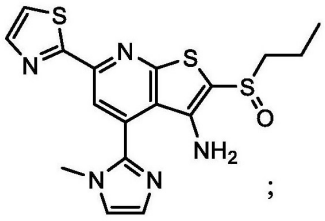

;

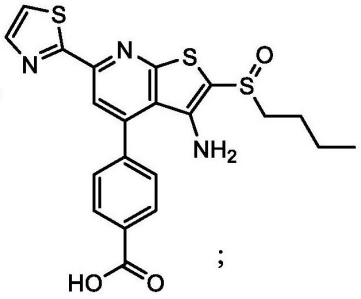

;

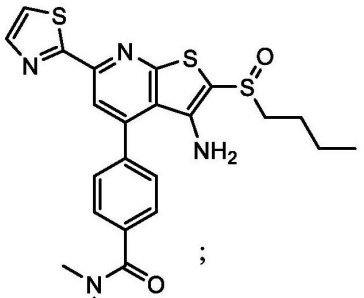

;

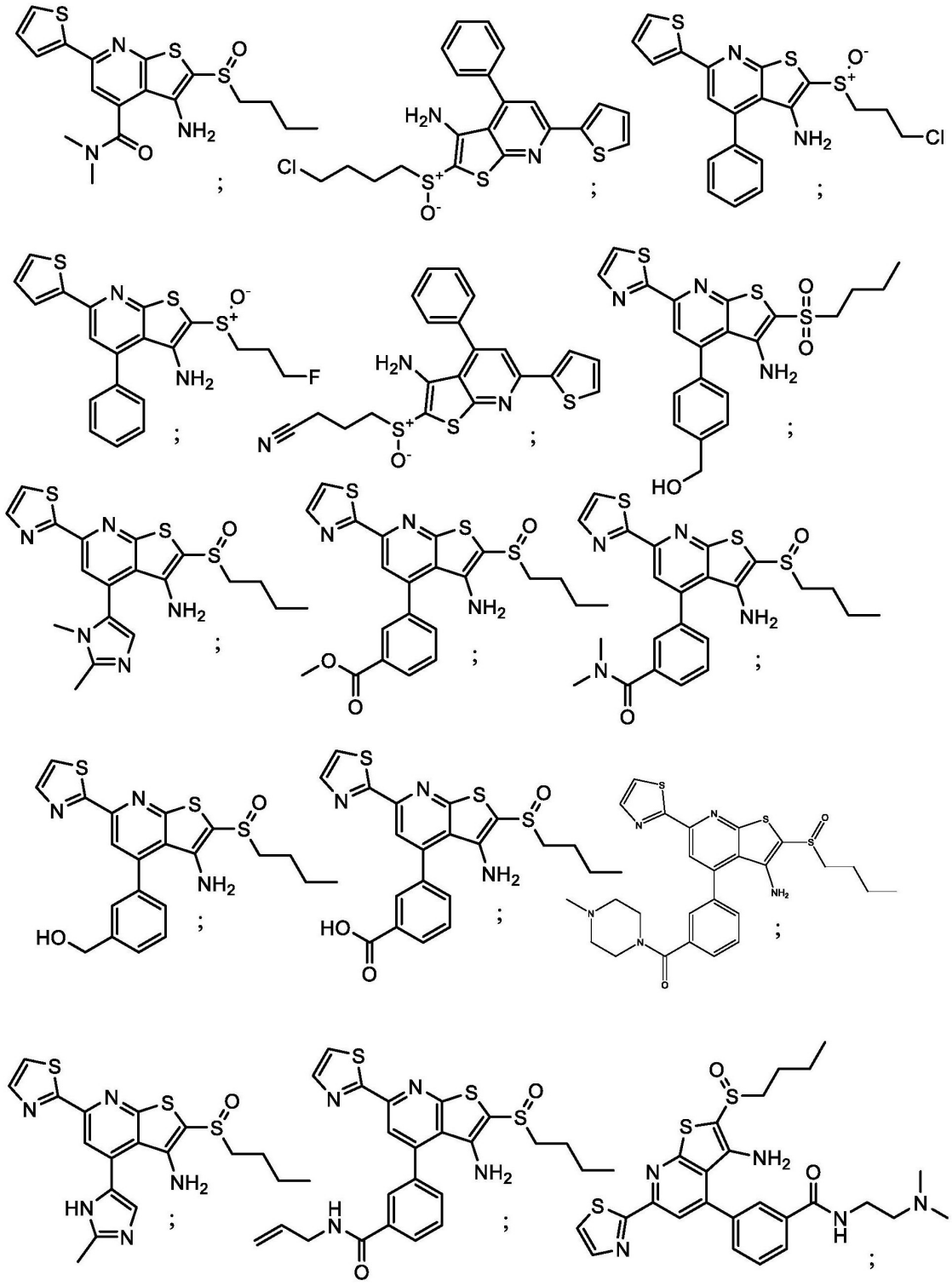

;

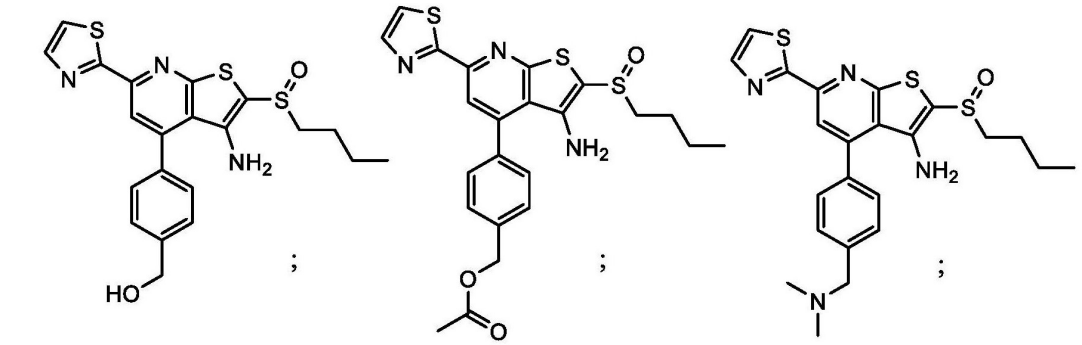

;

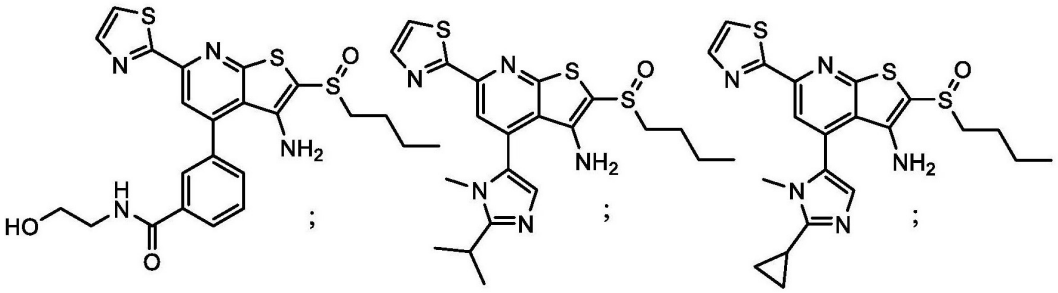

;


;

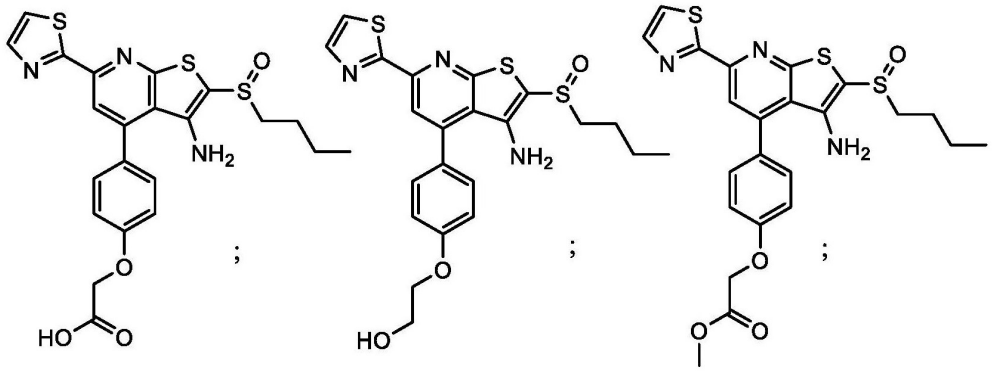

;

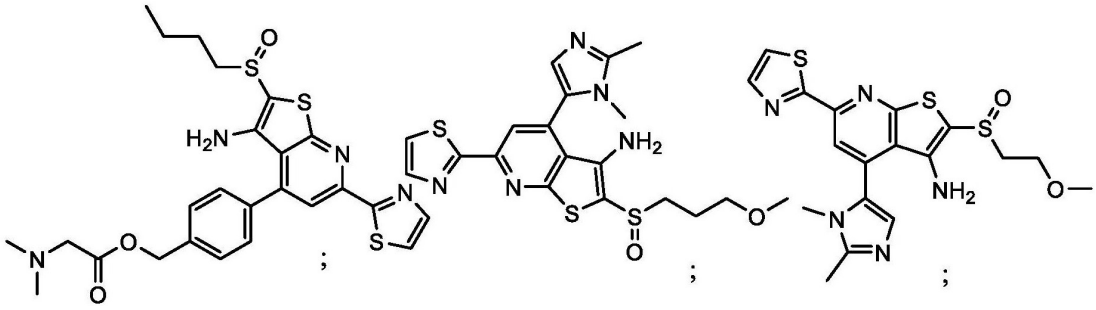
[0218] 

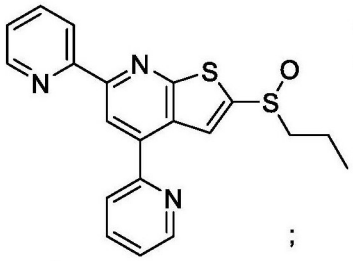
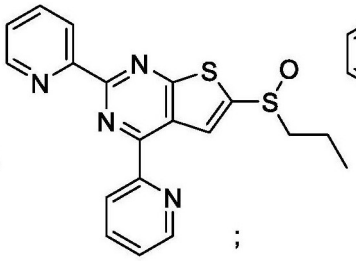
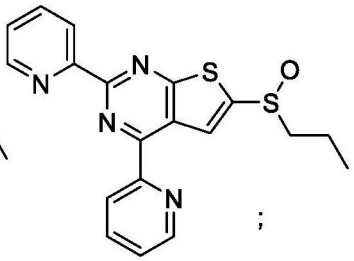
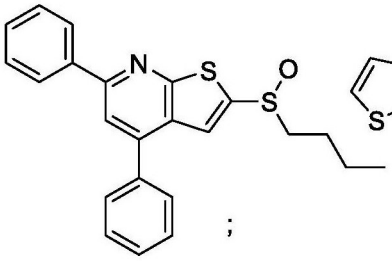
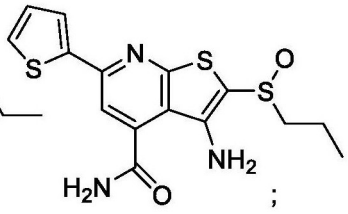
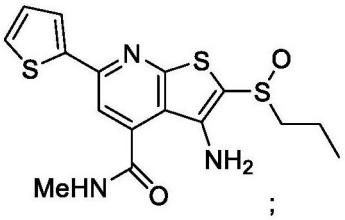


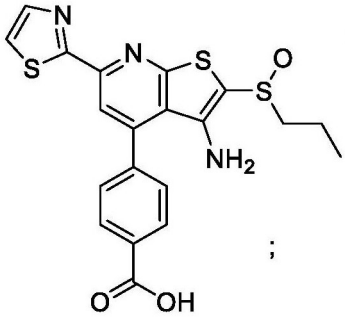
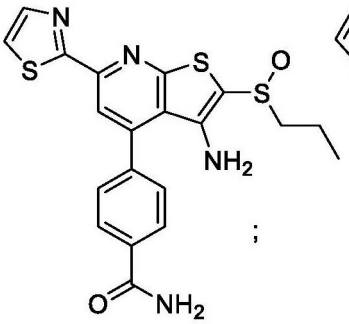
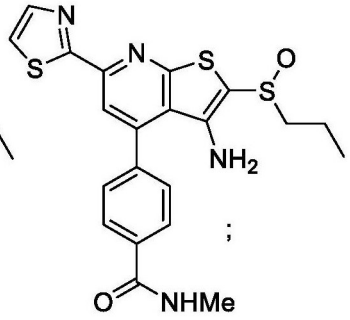
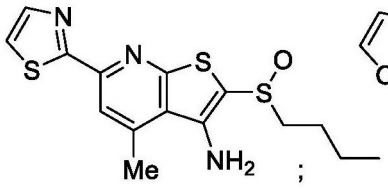
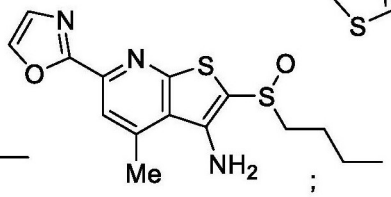
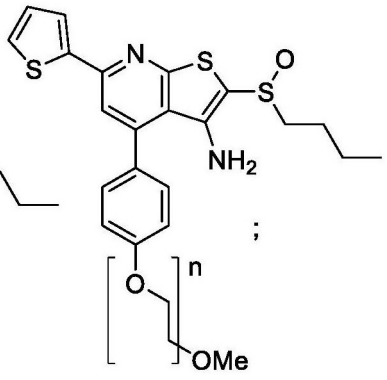


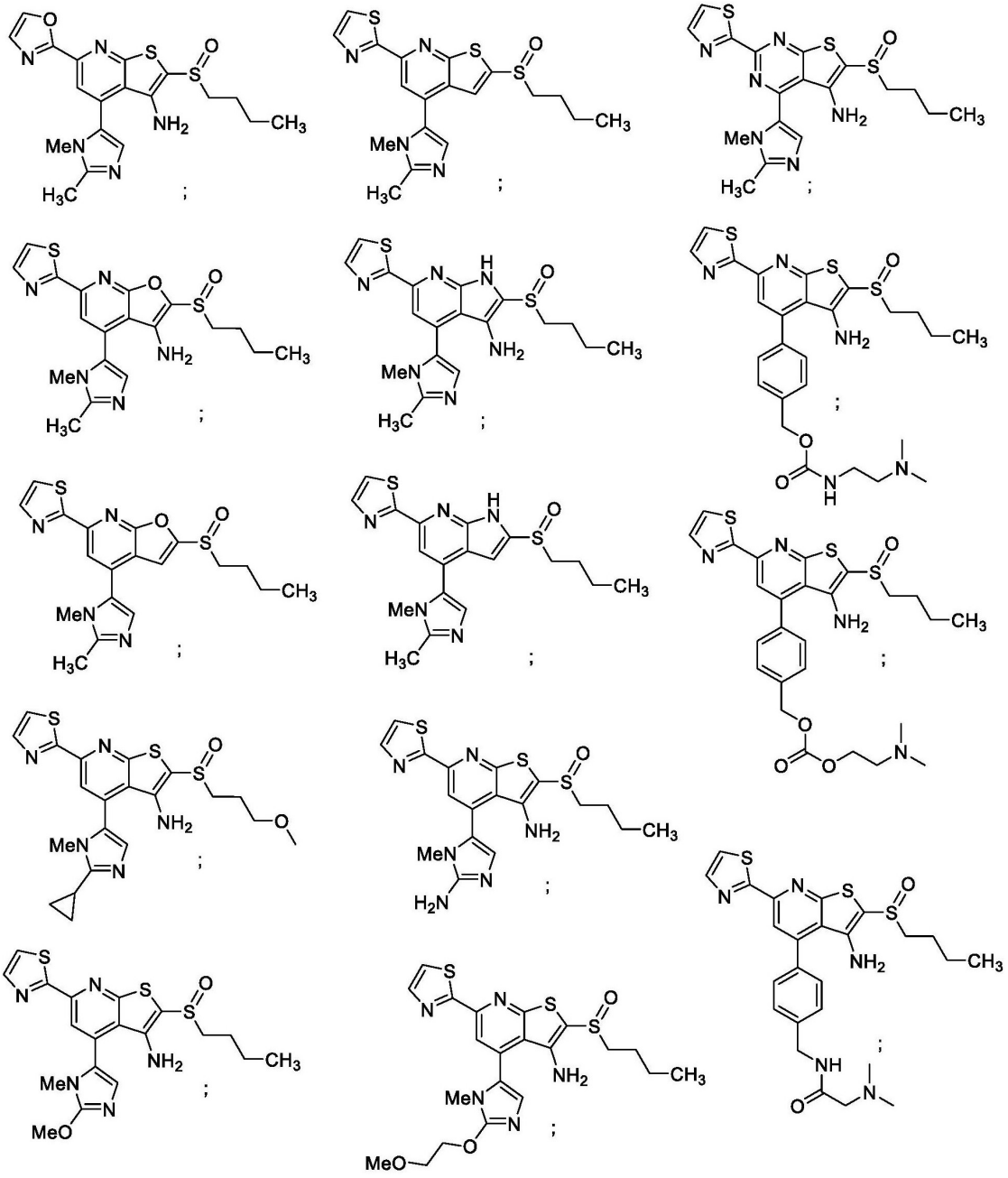
[0219]

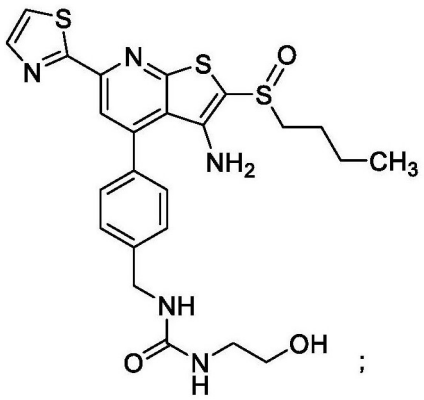


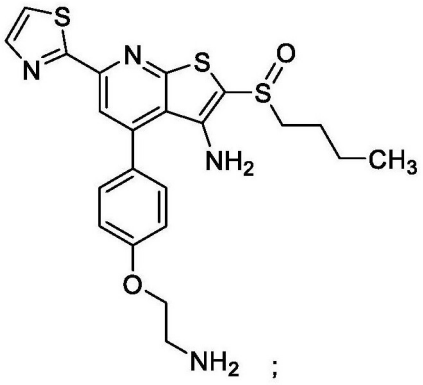



;

;

;

;

;

;

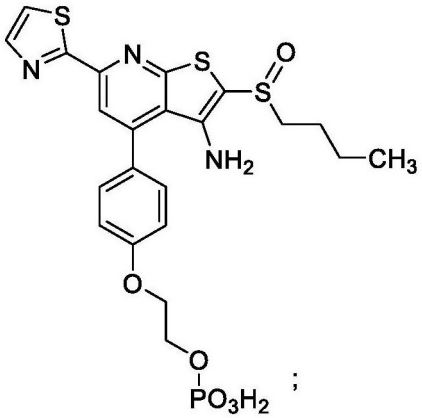
[0220]

;

;

;

;

;

;

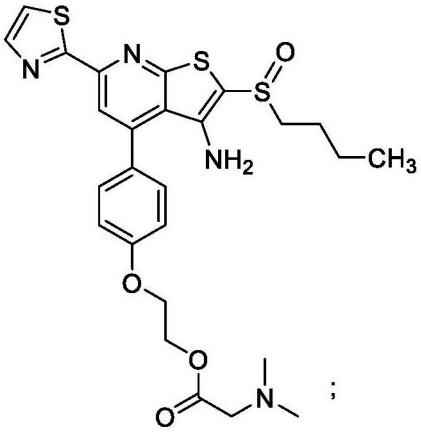
[0221] 

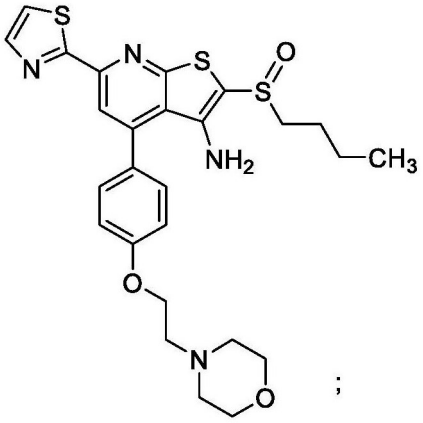

;

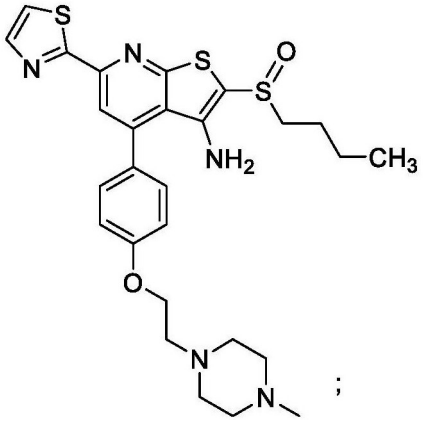

;

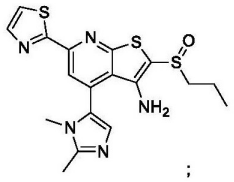
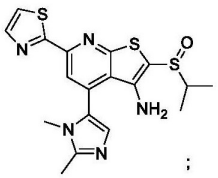
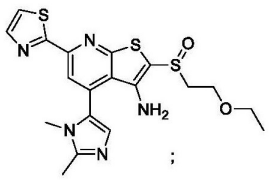
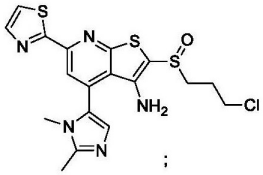
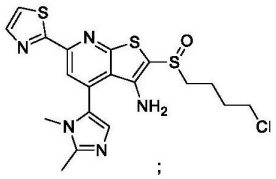
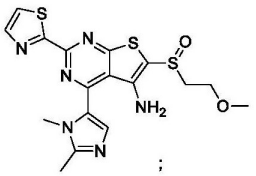
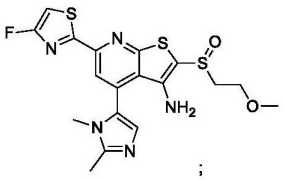
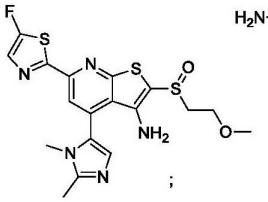
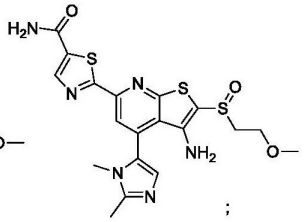
[0222]


;

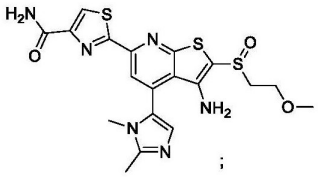
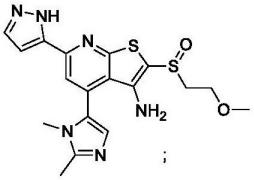
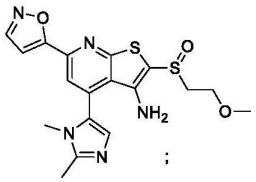
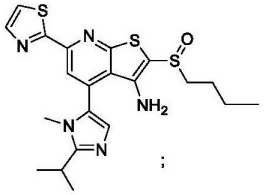
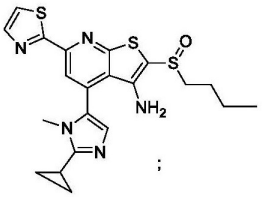
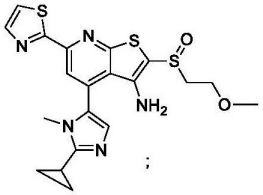
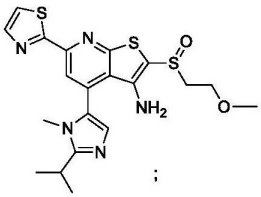

;

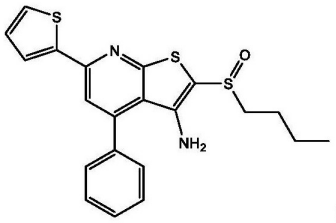
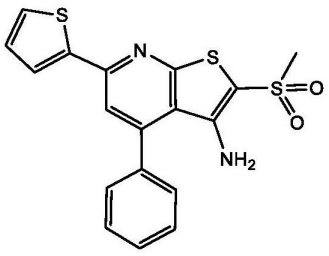
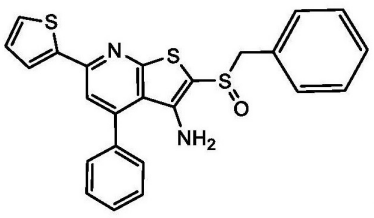

;

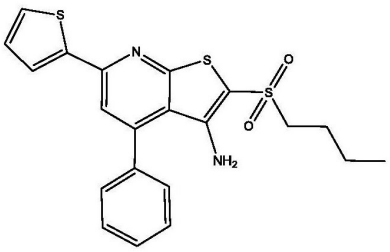
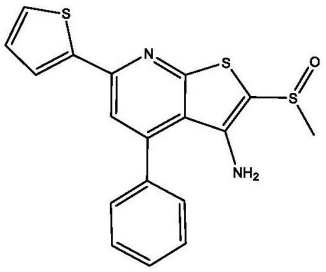
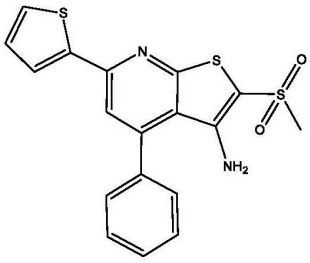

;

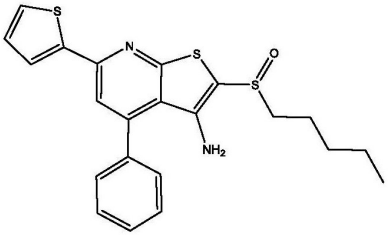
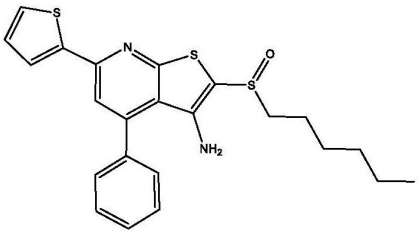

;

;

;

;

;

;

;

;

;

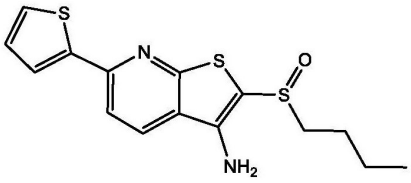
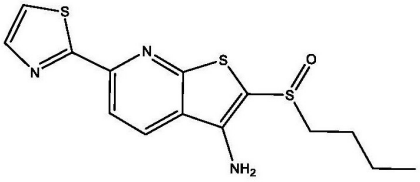
[0223]


;

;

;

;

;

;

;

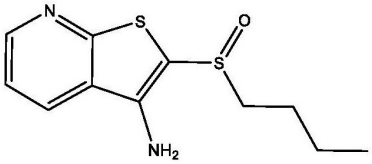
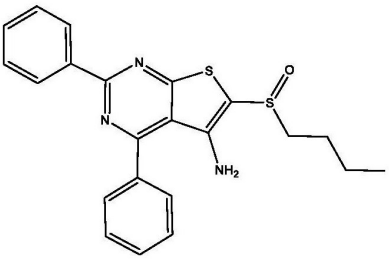
;

;

;

;

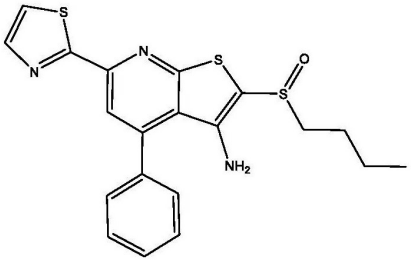
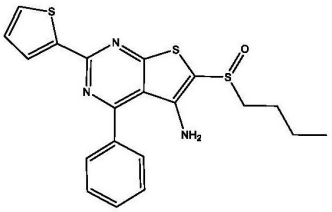

;

;

;

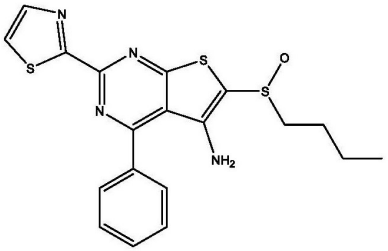
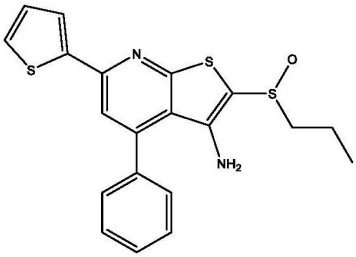

;

;

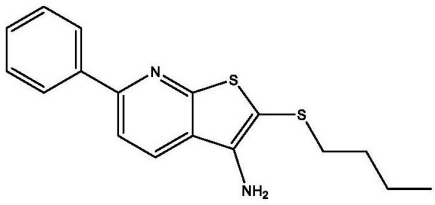

;

;

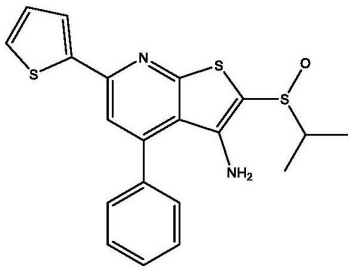
[0224]

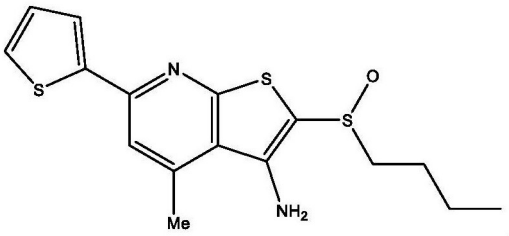

;

;

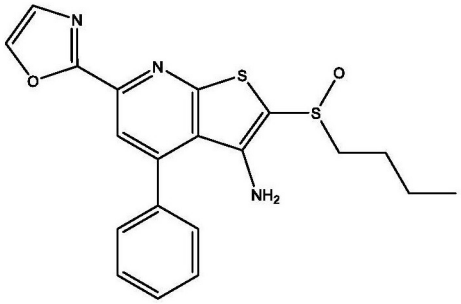

;

;


;

;

[0225] 

； 

； 

； 

；及其药物可接受的盐。

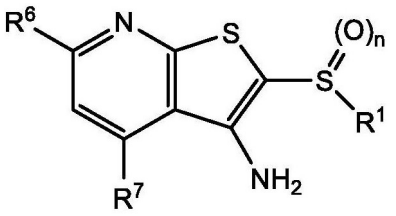
[0226] 在某些实施方案中，可以选择具有式(I)，(II)，(IV)，(V)，(VI)，和(VII)的15-PGDH抑制剂，其可以：ia)在2.5μM浓度下，刺激表达15-PGDH荧光素酶融合物构建体的Vaco503报告细胞系，达到超过70的荧光素酶生产水平(使用一定的规模，在该规模上，值100表示报告生产水平超过基线的2倍)；iia)在2.5μM浓度下，刺激表达15-PGDH荧光素酶融合物构建体的V9m报告细胞系，达到超过75的荧光素酶生产水平；iiia)在7.5μM浓度下，刺激表达15-PGDH荧光素酶融合物构建体的LS174T报告细胞系，达到超过70的荧光素酶生产水平；以及iva)在7.5μM浓度下，不能激活表达TK-海肾荧光素酶报告物的阴性对照V9m细胞系达到超过20的水平；以及va)在IC_{50}低于1μM下抑制重组15-PGDH蛋白质的酶活性。

[0227] 在其他的实施方案中，15-PGDH抑制剂可以：ib)在2.5μM浓度下，刺激表达15-PGDH荧光素酶融合物构建体的Vaco503报告细胞系，从而增加荧光素酶的生产；iib)在2.5μM浓度下，刺激表达15-PGDH荧光素酶融合物构建体的V9m报告细胞系，从而增加荧光素酶的生产；iiib)在7.5μM浓度下，刺激表达15-PGDH荧光素酶融合物构建体的LS174T报告细胞系，从而增加荧光素酶的生产；ivb)在7.5μM浓度下，不能刺激表达TK-海肾荧光素酶报告物的阴性对照V9m细胞系，达到荧光素酶水平超过背景20％以上；以及vb)在IC_{50}低于1μM下抑制重组15-PGDH蛋白质的酶活性。

[0228] 在其他的实施方案中，在重组15-PGDH浓度为大约5nM至大约10nM下，在IC_{50}低于1μM下，或者优选地在IC_{50}低于250nM下，或者更优选地在IC_{50}低于50nM下，或者更优选地在IC_{50}低于10nM下，或者更优选地在IC_{50}低于5nM下，15-PGDH抑制剂可以抑制重组15-PGDH的酶活性。

[0229] 在其他的实施方案中，在使用合适的试剂(例如IL1-β)刺激A459细胞后，15-PGDH抑制剂可以增加PGE-2的细胞水平。

[0230] 在一些实施方案中，15-PGDH抑制剂可以包括具有下式(VIII)的化合物及其药物可接受的盐：

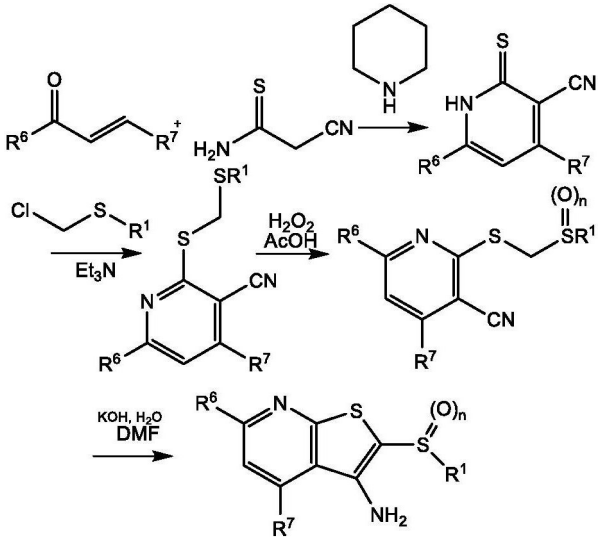
[0231] 

(VIII)

[0232] 其中n为0-2；

[0233] R^1,R^6和R^7是相同的或不同的,并且均独立地选自氢,取代的或非取代的C_1-C_{24}烷基,C_2-C_{24}烯基,C_2-C_{24}炔基,C_3-C_{20}芳基,杂芳基,包含5-6个环原子的杂环烯基(其中1-3个环原子独立地选自N,NH,N(C_1-C_6烷基),NC(O)(C_1-C_6烷基),O和S),C_6-C_{24}烷芳基,C_6-C_{24}芳烷基,卤素,-Si(C_1-C_3烷基)$_3$,羟基,硫氢基,C_1-C_{24}烷氧基,C_2-C_{24}烯氧基,C_2-C_{24}炔氧基C_5-C_{20}芳氧基,酰基(包括C_2-C_{24}烷基羰基(--CO-烷基)和C_6-C_{20}芳基羰基(-CO-芳基)),酰氧基(-O-酰基),C_2-C_{24}烷氧基羰基(-(CO)-O-烷基),C_6-C_{20}芳氧基羰基(-(CO)-O-芳基),C_2-C_{24}烷基碳酸(-O-(CO)-O-烷基),C_6-C_{20}芳基碳酸(-O-(CO)-O-芳基),羧基(-COOH),羧酸($-COO^-$),氨基甲酰(-(CO)-NH_2),C_1-C_{24}烷基-氨基甲酰(-(CO)-NH(C_1-C_{24}烷基)),芳基氨基甲酰(-(CO)-NH-芳基),硫代氨基甲酰(-(CS)-NH_2),脲基(-NH-(CO)-NH_2),氰基(-CN),异氰基($-N^+C^-$),氰氧基(-O-CN),异氰氧基($-O-N^+=C^-$),异硫代氰氧基(-S-CN),叠氮基($-N=N^+=N^-$),甲酰基(--(CO)--H),硫代甲酰基(--(CS)--H),氨基(--NH_2),C_1-C_{24}烷基氨基,C_5-C_{20}芳基氨基,C_2-C_{24}烷基氨基(-NH-(CO)-烷基),C_6-C_{20}芳基氨基(-NH-(CO)-芳基),亚氨基(-CR=NH,其中R为氢,C_1-C_{24}烷基,C_5-C_{20}芳基,C_6-C_{24}烷芳基,C_6-C_{24}芳烷基等),烷基亚氨基(-CR=N(烷基),其中R=氢,烷基,芳基,烷芳基,芳烷基等),芳基亚氨基(-CR=N(芳基),其中R=氢,烷基,芳基,烷芳基等),硝基($-NO_2$),亚硝基(-NO),磺基($-SO_2-OH$),磺酸($-SO_2-O^-$),C_1-C_{24}烷基硫基(-S-烷基;还称为"烷基硫代"),芳基硫基(-S-芳基;还称为"芳基硫代"),C_1-C_{24}烷基亚磺酰基(-(SO)-烷基),C_5-C_{20}芳基亚磺酰基(-(SO)-芳基),C_1-C_{24}烷基亚磺酰基($-SO_2$-烷基),C_5-C_{20}芳基亚磺酰基($-SO_2$-芳基),磺胺($-SO_2$-NH2,$-SO_2NY_2$(其中Y独立地为H,arlyl或烷基),膦酰基(-P(O)$(OH)_2$),磷酰基(-P(O)$(O^-)_2$),次膦酸基(-P(O)(O^-)),亚磷酸($-PO_2$),膦基(--PH_2),聚烷基醚,磷酸盐,磷酸酯,引入氨基酸或其他部分(预计在生理学pH下携带正电荷或负电荷)的基团,它们的组合,并且其中R^6和R^7可以连接从而形成环或多环,其中所述的环为取代的或非取代的芳基,取代的或非取代的杂芳基,取代的或非取代的环烷基,和取代的或非取代的杂环基。

[0234] 具有式(VIII)的15-PGDH抑制剂可以如下所示合成：

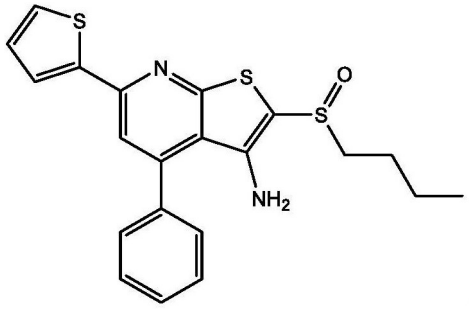
[0235] 

[0236] 在上述制备工艺中可以使用任何反应溶剂，只要其不涉及反应即可。例如反应溶剂包括醚，例如二乙醚、四氢呋喃和二氧六环；卤化烃，例如二氯甲烷和氯仿；胺，例如吡啶、哌啶和三乙胺；烷基酮，例如丙酮、甲基乙基酮和甲基异丁基；醇，例如甲醇、乙醇和丙醇；非质子极性溶剂，例如N,N-二甲基甲酰胺,N,N-二甲基乙酰胺,乙腈,二甲基亚砜and六甲基磷酰三胺。在有机合成中常用的非反应性有机溶剂中，优选的溶剂是其中反应中产生的水可以通过Dean-Stark分水器除去的那些。此类溶剂的实例包括但不限于苯、甲苯、二甲苯等。由此获得的反应产物可以分离，并通过冷凝、提取等纯化，其通常是在有机合成领域中通过硅胶柱层析(如果需要)来实施的。具有式III的PGDH抑制剂的单个对映异构体可以使用包含手性固定相的色谱柱通过制备型HPLC分离的。

[0237] 此外，本申请的实施方案包括上述15-PGDH抑制剂的制备方法的任何修改。在这种关联中，由制备方法的任何步骤中获得的任何中间产物都可以用作其他步骤中的起始材料。此类起始材料可以在某些反应条件下原位形成。反应试剂还可以以它们的盐或光学异构体的形式使用。

[0238] 根据在15-PGDH抑制剂的制备中使用的取代基的类型以及中间产物和所选的制备方法，新型15-PGDH抑制剂可以为任何可行的异构体形式，例如基本纯的几何(cis或trans)异构体、光学异构体(对映异构体)和外消旋物。

[0239] 在一些实施方案中，具有式(VIII)的15-PGDH抑制剂可以包括具有下式(IX)的化合物及其药物可接受的盐：

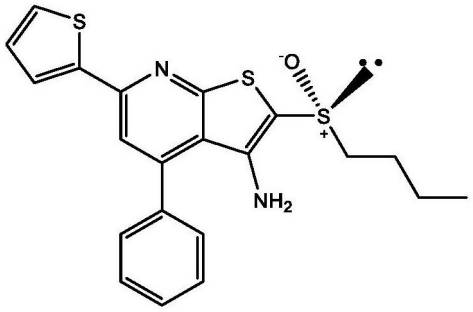
[0240] 

(IX)。

[0241] 发现具有式(IX)的15-PDGH抑制剂：i)在1nM浓度下，抑制重组15-PGDH；ii)在100nM浓度下，抑制细胞系中的15-PGDH；iii)增加细胞系的PGE_2生产；iv)在广泛pH范围的水性溶液中是化学稳定的；v)当与肝细胞提取物温育时是化学稳定的；vi)当与肝细胞系温

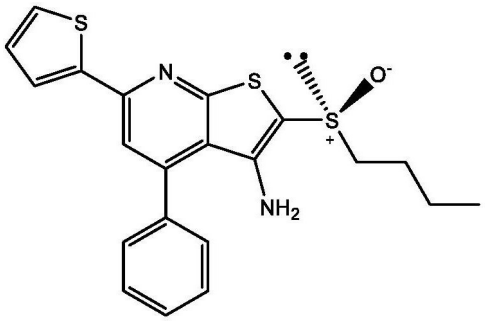
育时是化学稳定的;vii)当IP注射至小鼠中时,显示253分钟的血浆半衰期;以及viii)当以0.6μmole/每只小鼠和1.2μmole/每只小鼠IP注射小鼠中时,经过24小时显示无即时毒性,并且当以0.3μmole/每只小鼠每日2次在21天内IP注射至小鼠中时,还显示无毒性。

[0242] 在其他的实施方案中,具有式(IX)的15-PGDH抑制剂可以包括下式(Ixa)的化合物及其药物可接受的盐:

[0243] 

(IXa)。

[0244] 在其他的实施方案中,具有式(IX)的15-PGDH抑制剂可以包括具有下式(Ixb)的化合物及其药物可接受的盐:

[0245] 

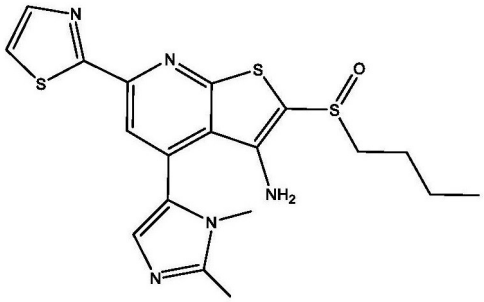
(Xb)。

[0246] 在其他的实施方案中,15-PDHG抑制剂可以包括具有式(IX)的15-PDHG抑制剂的(+)或(-)光学异构体。在其他的实施方案中,15-PDHG抑制剂可以包括具有式(IX)的15-PDHG抑制剂的至少一种(+)或(-)光学异构体的混合物。例如15-PGDH抑制剂可以包含以下物质的混合物:低于大约50重量%的具有式(IX)的15-PGDH抑制剂的(-)光学异构体和超过大约50重量%的具有式(IX)的15-PGDH抑制剂的(+)光学异构体,低于大约25重量的具有式(IX)的15-PGDH抑制剂的(-)光学异构体和超过大约75重量%的具有式(IX)的15-PGDH抑制剂的(+)光学异构体,低于大约10重量的具有式(IX)的15-PGDH抑制剂的(-)光学异构体和超过大约90重量%的具有式(IX)的15-PGDH抑制剂的(+)光学异构体,低于大约1重量的具有式(IX)的15-PGDH抑制剂的(-)光学异构体和超过大约99重量%的具有式(IX)的15-PGDH抑制剂的(+)光学异构体,超过大约50重量%的具有式(IX)的15-PGDH抑制剂的(-)光学异构体和低于大约50重量%的具有式(IX)的15-PGDH抑制剂的(+)光学异构体,超过大约75重量%的具有式(IX)的15-PGDH抑制剂的(-)光学异构体和低于大约25重量%的具有式(IX)的15-PGDH抑制剂的(+)光学异构体,超过大约90重量%的具有式(IX)的15-PGDH抑制剂的(-)光学异构体和低于大约10重量%的具有式(IX)的15-PGDH抑制剂的(+)光学异构体,或者超过大约99重量%的具有式(IX)的15-PGDH抑制剂的(-)光学异构体和低于大约1重量%的具有式(IX)的15-PGDH抑制剂的(+)光学异构体。

[0247] 在另一个实施方案中,15-PDGH抑制剂基本上可以由或者由具有式(IX)的15-PGDH抑制剂的(+)光学异构体组成。在另一个实施方案中,PDGH抑制剂可以基本上由或者由具有

式(IX)的15-PGDH抑制剂的(-)光学异构体组成。

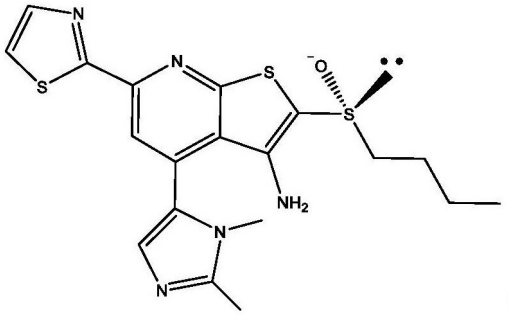
[0248] 在其他的实施方案中,具有式(VIII)的15-PGDH抑制剂可以包括具有下式(X)的化合物及其药物可接受的盐:

[0249] 

(X)

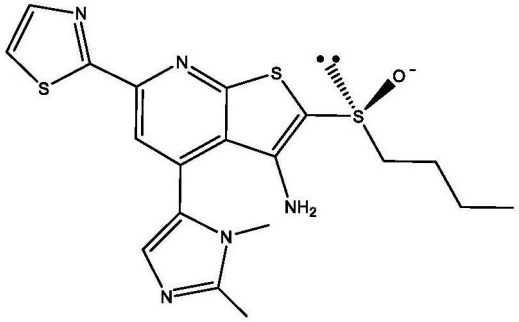
[0250] 有利地,发现具有式(X)的15-PDGH抑制剂:i)在3nM浓度下,抑制重组15-PGDH;ii)在20nM下,增加细胞系的PGE_2生产;iii)在广泛pH范围的水性溶液中是化学稳定的;iv)当与小鼠、大鼠和人类肝脏提取物温育时是化学稳定的;v)当IP注射至小鼠中时,显示33分钟的血浆半衰期;viii)当以50mg/kg体重IP注射小鼠中时,经过24小时显示无即时毒性;以及ix)在1mg/mL下在水中可溶解(pH=3)。

[0251] 在其他的实施方案中,具有式(X)的15-PGDH抑制剂可以包括具有下式(Xa)的化合物及其药物可接受的盐:

[0252] 

(Xa)

[0253] 在其他的实施方案中,具有式(X)的15-PGDH抑制剂可以包括具有下式(Xb)的化合物及其药物可接受的盐:

[0254] 

(Xb)

[0255] 在其他的实施方案中,15-PDHG抑制剂可以包括具有式(X)的15-PDHG抑制剂的(+)或(-)光学异构体。在其他的实施方案中,15-PDHG抑制剂可以包括具有式(X)的15-PDHG抑制剂的至少一种(+)或(-)光学异构体的混合物。例如15-PGDH抑制剂可以包含以下物质的混合物:低于大约50重量%的具有式(X)的15-PGDH抑制剂的(-)光学异构体和超过大约50重量%的具有式(X)的15-PGDH抑制剂的(+)光学异构体,低于大约25重量的具有式(X)的15-PGDH抑制剂的(-)光学异构体和超过大约75重量%的具有式(X)的15-PGDH抑制剂的(+)

光学异构体，低于大约10重量的具有式(X)的15-PGDH抑制剂的(-)光学异构体和超过大约90重量％的具有式(X)的15-PGDH抑制剂的(+)光学异构体，低于大约1重量的具有式(X)的15-PGDH抑制剂的(-)光学异构体和超过大约99重量％的具有式(X)的15-PGDH抑制剂的(+)光学异构体，超过大约50重量％的具有式(X)的15-PGDH抑制剂的(-)光学异构体和低于大约50重量％的具有式(X)的15-PGDH抑制剂的(+)光学异构体，超过大约75重量％的具有式(X)的15-PGDH抑制剂的(-)光学异构体和低于大约25重量％的具有式(X)的15-PGDH抑制剂的(+)光学异构体，超过大约90重量％的具有式(X)的15-PGDH抑制剂的(-)光学异构体和低于大约10重量％的具有式(X)的15-PGDH抑制剂的(+)光学异构体，或者超过大约99重量％的具有式(X)的15-PGDH抑制剂的(-)光学异构体和低于大约1重量％的具有式(X)的15-PGDH抑制剂的(+)光学异构体。

[0256] 在另一个实施方案中，15-PDGH抑制剂基本上可以由或者由具有式(X)的15-PGDH抑制剂的(+)光学异构体组成。在另一个实施方案中，PDGH抑制剂可以基本上由或者由具有式(X)的15-PGDH抑制剂的(-)光学异构体组成。

[0257] 应该理解的是其他的15-PGDH抑制剂可以用于本发明所述的方法中。这些其他的15-PGDH抑制剂可以包括已知的15-PGDH抑制剂，例如包括式(I)和(II)所示的四唑化合物，式(I)所示的2-亚烷基氨基阳极乙酰胺化合物，式(VI)和(VII)所示的杂环化合物，以及在美国专利申请公开No.2006/0034786和美国专利No.7,705,041中所述的式(III)所示的吡唑化合物；在美国专利申请公开No.2007/0071699中所述的式(I)所示的苄亚甲基-1,3-噻唑烷化合物；在美国专利申请公开No.2007/0078175中所述的苯基呋喃基甲基噻唑烷-2,4-二酮和苯基噻吩基甲基噻唑烷-2,4-二酮化合物；在美国专利申请公开No.2011/0269954中所述的噻唑烷二酮衍生物；在美国专利No.7,294,641中所述的苯基呋喃，苯基噻吩，或苯基吡咯化合物；在美国专利No.4,725,676中所述的5-(3,5-二取代的苯基偶氮)-2-羟基苯-乙酸及其盐和内酯，和在美国专利No.4,889,846中所述的偶氮化合物。

[0258] 本发明所述的15-PGDH抑制剂可以根据待治疗的病理学或美容状况或紊乱而在药物组合物或美容组合物中提供。包含本发明所述的15-PGDH抑制剂作为活性组分的药物组合物可以通过将衍生物与药物可接受的载体(多种)或赋形剂(多种)混合，或者根据传统方法使用稀释剂稀释15-PGDH抑制剂来制造。药物组合物可以进一步包含填料、抗粘合剂、润滑剂、润湿剂、风味剂、乳化剂、防腐剂等。药物组合物可以根据本领域那些技术人员已知的方法配制成合适的配制物，使得其可以在给予哺乳动物之后提供即刻的、受控的或持续释放的15-PGDH抑制剂。

[0259] 在一些实施方案中，药物组合物可以配制成肠胃外或口服形式。用于口服给予的固体剂型可以通过将赋形剂(如果需要)连同粘结剂、崩解剂、润滑剂、着色剂和/或风味剂一同加入15-PGDH抑制剂中并将所得的混合物形成片剂、糖包衣丸剂、颗粒、粉末或胶囊形式来制造。可以加入组合物中的添加剂可以为本领域普通的添加剂。例如赋形剂的实例包括乳糖，蔗糖，氯化钠，葡萄糖，淀粉，碳酸钙，高岭土，微晶纤维素，硅酸盐等。示例性粘结剂包括水，乙醇，丙醇，甜的糖浆，蔗糖溶液，淀粉溶液，凝胶溶液，羧甲基纤维素，羟丙基纤维素，羟丙基淀粉，甲基纤维素，乙基纤维素，虫漆，膦酸钙和吡咯烷酮。崩解剂的实例包括干淀粉，海藻酸钠，琼脂粉，碳酸氢钠，碳酸钙，月桂基硫酸钠，硬脂酸单甘酯和乳糖。此外，纯的滑石，硬脂酸盐，硼酸钠和聚乙二醇可以用作润滑剂；并且蔗糖，苦橙皮，柠檬酸，酒石酸

可以用作风味剂。在一些实施方案中，药物组合物可以制成通过吸入给予的喷雾剂配制物(例如它们可以为雾状)。

[0260] 本发明所述的15-PGDH抑制剂可以与风味剂、缓冲剂、稳定剂等结合，并根据传统方法引入至口服液体剂型中，例如溶液、糖浆或酏剂。缓冲剂的一个实例可以为柠檬酸钠。稳定剂的实例包括黄芪胶，阿拉伯树胶和凝胶。

[0261] 在一些实施方案中，本发明所述的15-PGDH抑制剂可以通过向其中加入pH调节剂、缓冲剂、稳定剂、弛缓药、局部麻醉剂而被引入至注射剂型中，例如用于皮下、肌肉内或静脉内途径。pH调节剂和缓冲剂的实例包括柠檬酸钠、乙酸钠和磷酸钠。稳定剂的实例包括焦亚硫酸钠、EDTA、巯基乙酸和硫代乳酸。局部麻醉剂可以为普鲁卡因HCl、利多卡因HCl等。弛缓药可以为氯化钠、葡萄糖等。

[0262] 在其他的实施方案中，本文所述的15-PGDH抑制剂可以根据传统方法通过向其中加入本领域已知的药物可接受的载体(如果需要)(例如聚乙二醇，羊毛脂，可可油脂或脂肪酸甘油酯)连同表面活性剂(例如Tween)一起引入至栓剂中。

[0263] 药物组合物可以配制成上文所讨论的多种剂型，然后通过多种途径给予，包括口服、吸入、经皮、皮下、静脉内或肌肉内途径。剂量可以为药物或治疗有效量。

[0264] 在不同的实施方案中，15-PGDH抑制剂的治疗有效量可以以变化量存在。例如在一些实施方案中，15-PGDH抑制剂的治疗有效量可以为大约10-1000mg范围的量(例如大约20mg-1,000mg,30mg-1,000mg,40mg-1,000mg,50mg-1,000mg,60mg-1,000mg,70mg-1,000mg,80mg-1,000mg,90mg-1,000mg,大约10-900mg,10-800mg,10-700mg,10-600mg,10-500mg,100-1000mg,100-900mg,100-800mg,100-700mg,100-600mg,100-500mg,100-400mg,100-300mg,200-1000mg,200-900mg,200-800mg,200-700mg,200-600mg,200-500mg,200-400mg,300-1000mg,300-900mg,300-800mg,300-700mg,300-600mg,300-500mg,400mg-1,000mg,500mg-1,000mg,100mg-900mg,200mg-800mg,300mg-700mg,400mg-700mg和500mg-600mg)。在一些实施方案中，15-PGDH抑制剂以或者超过大约10mg,50mg,100mg,150mg,200mg,250mg,300mg,350mg,400mg,450mg,500mg,550mg,600mg,650mg,700mg,750mg,800mg的量存在。在一些实施方案中，15-PGDH抑制剂以或者低于大约1000mg,950mg,900mg,850mg,800mg,750mg,700mg,650mg,600mg,550mg,500mg,450mg,400mg,350mg,300mg,250mg,200mg,150mg或100mg的量存在。

[0265] 在其他的实施方案中，治疗有效剂量可以为例如大约0.001mg/kg重量至500mg/kg重量，例如大约0.001mg/kg重量至400mg/kg重量，大约0.001mg/kg重量至300mg/kg重量，大约0.001mg/kg重量至200mg/kg重量，大约0.001mg/kg重量至100mg/kg重量，大约0.001mg/kg重量至90mg/kg重量，大约0.001mg/kg重量至80mg/kg重量，大约0.001mg/kg重量至70mg/kg重量，大约0.001mg/kg重量至60mg/kg重量，大约0.001mg/kg重量至50mg/kg重量，大约0.001mg/kg重量至40mg/kg重量，大约0.001mg/kg重量至30mg/kg重量，大约0.001mg/kg重量至25mg/kg重量，大约0.001mg/kg重量至20mg/kg重量，大约0.001mg/kg重量至15mg/kg重量，大约0.001mg/kg重量至10mg/kg重量。

[0266] 在其他的实施方案中，治疗有效剂量可以为例如大约0.0001mg/kg重量至0.1mg/kg重量，例如大约0.0001mg/kg重量至0.09mg/kg重量，大约0.0001mg/kg重量至0.08mg/kg重量，大约0.0001mg/kg重量至0.07mg/kg重量，大约0.0001mg/kg重量至0.06mg/kg重量，大

约0.0001mg/kg重量至0.05mg/kg重量,大约0.0001mg/kg重量至大约0.04mg/kg重量,大约0.0001mg/kg重量至0.03mg/kg重量,大约0.0001mg/kg重量至0.02mg/kg重量,大约0.0001mg/kg重量至0.019mg/kg重量,大约0.0001mg/kg重量至0.018mg/kg重量,大约0.0001mg/kg重量至0.017mg/kg重量,大约0.0001mg/kg重量至0.016mg/kg重量,大约0.0001mg/kg重量至0.015mg/kg重量,大约0.0001mg/kg重量至0.014mg/kg重量,大约0.0001mg/kg重量至0.013mg/kg重量,大约0.0001mg/kg重量至0.012mg/kg重量,大约0.0001mg/kg重量至0.011mg/kg重量,大约0.0001mg/kg重量至0.01mg/kg重量,大约0.0001mg/kg重量至0.009mg/kg重量,大约0.0001mg/kg重量至0.008mg/kg重量,大约0.0001mg/kg重量至0.007mg/kg重量,大约0.0001mg/kg重量至0.006mg/kg重量,大约0.0001mg/kg重量至0.005mg/kg重量,大约0.0001mg/kg重量至0.004mg/kg重量,大约0.0001mg/kg重量至0.003mg/kg重量,大约0.0001mg/kg重量至0.002mg/kg重量。在一些实施方案中,治疗有效剂量可以为0.0001mg/kg重量,0.0002mg/kg重量,0.0003mg/kg重量,0.0004mg/kg重量,0.0005mg/kg重量,0.0006mg/kg重量,0.0007mg/kg重量,0.0008mg/kg重量,0.0009mg/kg重量,0.001mg/kg重量,0.002mg/kg重量,0.003mg/kg重量,0.004mg/kg重量,0.005mg/kg重量,0.006mg/kg重量,0.007mg/kg重量,0.008mg/kg重量,0.009mg/kg重量,0.01mg/kg重量,0.02mg/kg重量,0.03mg/kg重量,0.04mg/kg重量,0.05mg/kg重量,0.06mg/kg重量,0.07mg/kg重量,0.08mg/kg重量,0.09mg/kg重量或0.1mg/kg重量。用于特定个体的有效剂量可以根据个体需要在一段时间内改变(例如增加或减少)。

[0267] 在一些实施方案中,治疗有效剂量可以为10μg/kg/天,50μg/kg/天,100μg/kg/天,250μg/kg/天,500μg/kg/天,1000μg/kg/天或更高的剂量。在多种实施方案中,15-PGDH抑制剂或其药用盐的量足以提供给患者0.01μg/kg至10μg/kg;0.1μg/kg至5μg/kg;0.1μg/kg至1000μg/kg;0.1μg/kg至900μg/kg;0.1μg/kg至900μg/kg;0.1μg/kg至800μg/kg;0.1μg/kg至700μg/kg;0.1μg/kg至600μg/kg;0.1μg/kg至500μg/kg;or 0.1μg/kg至400μg/kg的剂量。

[0268] 根据本发明给予的特定剂量或量可以根据例如所需结果的本性和/或程度、给予途径和/或定时的具体情况、和/或一种或多种特征(例如体重、年龄、个人经历、遗传特征、生活方式参数、心脏缺陷严重性和/或心脏缺陷风险的水平等、或它们的组合)而给予。该剂量或量可以通过本领域那些普通技术人员测定。在一些实施方案中,根据标准的临床技术测定合适的剂量或量。例如在一些实施方案中,合适的剂量或量为足以将疾病严重性指数得分降低1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,25,30,35,40,45,50,55,60,65,70,75,80,85,90,95,100%或更高的剂量或量。例如在一些实施方案中,合适的剂量或量为足以将疾病严重性指数得分降低1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,25,30,35,40,45,50,55,60,65,70,75,80,85,90,95,100%的剂量或量。备选地或此外,在一些实施方案中,通过使用一种或多种体外或体内测试来测定合适的剂量或量,从而帮助鉴定待给予的合适的或最佳的剂量范围或量。

[0269] 多种实施方案可以包括不同的服药方案。在一些实施方案中,15-PGDH抑制剂可以通过连续输注的方式给予。在一些实施方案中,连续输注为静脉内输注。在其他的实施方案中,连续的输注为皮下输注。备选地或此外,在一些实施方案中,15-PGDH抑制剂可以两个月一次、每月、每月两次、每三周一次、每两周一次、每周、每周两次、每周三次、每天、每天两次或另外临床需要的服药时间表给予。用于单一受试对象的服药方案不必为固定的间隔,但

是可以根据受试对象的需要在一段时间内改变。

[0270] 对于局部应用而言，组合物可以以水性、醇、含醇水溶液或油性溶液或悬液形式、或者以洗剂或血清型分散剂、乳液(其具有液体或半液体一致性，或者是膏体，是通过将脂肪相分散于水相(O/W)中、反之亦然(W/O)或者分散于多种乳液中而获得的)、待原样使用的或被引入至生理学可接受的介质中的自由粉末或压实粉末、其他的微囊或微颗粒、或者离子和/或阴离子类型的囊泡分散液形式给予。因此，其可以为药膏，酊剂，乳液，乳霜，油膏，粉末，贴剂，浸垫，溶液，乳液或囊泡分散液，洗剂，水性或非水性凝胶，喷雾，悬液，洗剂，喷雾剂或泡沫形式。其可以是无水的或水性的。其还可以包括构成肥皂或清洁块的固体配制物。

[0271] 包含本发明所述的15-PGDH抑制剂的药物和/或美容组合物可以额外含有例如选自以下的至少一种化合物：前列腺素，特别是前列腺素PGE_1，PGE_2，它们的盐，它们的酯，它们的类似物和它们的衍生物，尤其是在WO 98/33497，WO 95/11003，JP 97-100091，JP 96-134242中描述的那些，特别是前列腺素受体激动剂。其可以特别包含至少一种化合物，例如前列腺素$F_{2\alpha}$受体的激动剂(酸性水或前体形式，特别是酯形式)，例如拉坦前列素，氟前列醇，氯前列醇，比马前列素，乌诺前列酮；前列腺素E_2受体的激动剂(以及它们的前体，特别是酯，例如曲伏前列素)，例如17-苯基PGE_2，维前列醇，布他前列素，迷索前列醇，硫前列酮，16，16-二甲基PGE_2，11-脱氧PGE_1，1-脱氧PGE_1；前列腺环素(IP)受体的激动剂及其前体，特别是酯，例如西卡前列素，伊洛前列素，isocarbacycline，贝前列素合成制剂，eprostenol，曲前列环素；前列腺素D_2受体的激动剂及其前体，特别是酯，例如BW245C((4S)-(3-[(3R,S)-3-环己基-3-异丙基]-2,5-二氧)-4-咪唑烷庚-酸)，BW246C((4R)-(3-[(3R,S)-3-环己基-3-异丙基]-2,5-二氧)-4-咪唑烷庚-酸)；凝血恶烷A2(TP)受体的激动剂及其前体，特别是酯，例如I-BOP([1S-[1a,2a(Z),3b(1E,3S),4a]]-7-[3-[3-羟基-4-[4-(碘代苯氧基)-1-丁烯基]-7-氧杂双环-[2.2.1]庚-2-基]-5-庚烯酸)。

[0272] 有利地，组合物可以包含至少一种上文定义的15-PGDH抑制剂，以及至少一种前列腺素或一种前列腺素衍生物，例如系列2的前列腺素，特别包括生理盐水形式的或前体形式的$PGF_{2\alpha}$和PGE_2，特别是酯(例如异丙基酯)，它们的衍生物，例如16，16-二甲基PGE_2，17-苯基PGE_2和16，16-二甲基$PGF_{2\alpha}$17-苯基$PGF_{2\alpha}$；系列1的前列腺素，例如生理盐水形式的或酯形式的11-脱氧前列腺素E1，1-脱氧前列腺素E1，它们的类似物，特别是拉坦前列素，曲伏前列素，氟前列醇，乌诺前列酮，比马前列素，氯前列醇，维前列醇，布他前列素，迷索前列醇，它们的盐或它们的酯。

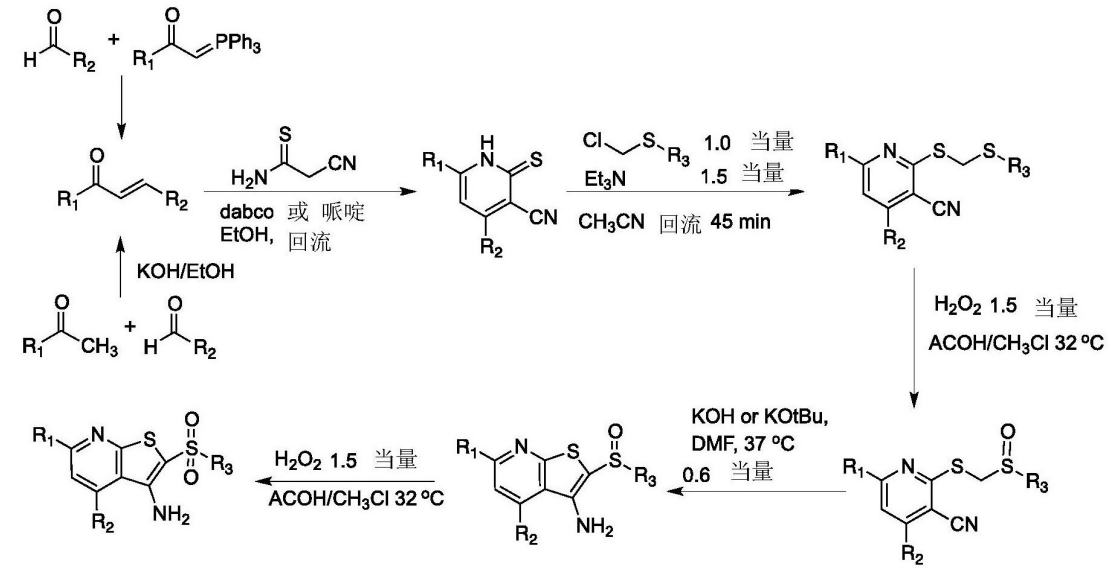
[0273] 本发明进一步通过以下实施例来说明，这些实施例无意于限定权利要求书的范围。

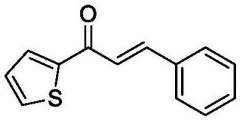
实施例

[0274] 实施例1

[0275] 以下实施例描述了SW033291及其类似物的合成，并提供了所述的结构的质谱和NMR构造。

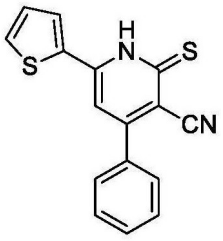
[0276]





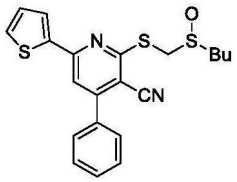
[0277] 使用Azam所述的过程,通过醇醛缩合,由安息香醛和1-(苯硫-2-基)乙酮制备3-苯基-1-(苯硫-2-基)丙-2-烯-1-酮(Parveen,H.;Iqbal,P.F.;Azam,A.Synth.Commu.,2008,38,3973)。^{1}H NMR(400MHz,$CDCl_3$)δ7.88-7.80(m,2H),7.67(dd,J=4.9,1.1Hz,1H),7.66-7.59(m,2H),7.47-7.34(m,4H),7.18(dd,J=5.0,3.8Hz,1H).ESI-MS(m/z):215$[M+H]^+$。

[0278]



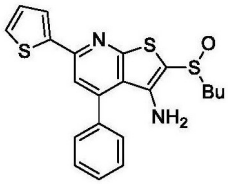
[0279] 4-苯基-6-(苯硫-2-基)-2-硫代-1,2-二氢吡啶-3-腈。向3-苯基-1-(苯硫-2-基)丙-2-烯-1-酮(2.34mmol,500mg)和氰基硫代乙酰胺(7.0mmol,717mg,3.0当量)在乙醇(7mL)中形成的溶液中,加入几滴哌啶。使反应物回流3h。收集形成的固体,并由乙酸再结晶,从而以46%分离的产率给予所设计的产物。^{1}H NMR(400MHz,DMSO-d_6)δ8.17(d,J=3.8Hz,1H),7.96(d,J=5.0Hz,1H),7.74-7.62(m,2H),7.54(dd,J=5.1,2.0Hz,3H),7.31-7.19(m,1H),7.01(s,1H).ESI-MS(m/z):295$[M+H]^+$。

[0280]

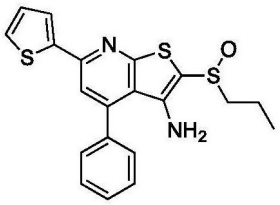


[0281] 将2-(((丁基硫代)甲基)亚磺酰基)-4-苯基-6-(苯硫-2-基)烟腈。乙酸(900μL)和过氧化氢(0.57mmol,1.5当量,在水中形成30%溶液)加入至2-(((丁基硫代)甲基)亚磺酰基)-4-苯基-6-(苯硫-2-基)烟腈(0.38mmol,150mg)在氯仿(900μL)中形成的溶液中。将反

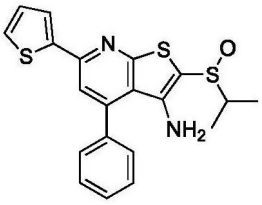
应混合物在32℃下搅拌45min。然后，使用EtOAc稀释反应物，并使用饱和的$NaHCO_3$溶液洗涤，在硫酸镁上干燥，过滤并在减压下浓缩，从而给出153mg所设计的产物(98％)。^1H NMR(400MHz,$CDCl_3$)δ7.75(dd,J＝3.8,1.1Hz,1H),7.66-7.57(m,2H),7.58-7.51(m,4H),7.47(s,1H),7.16(dd,J＝5.0,3.8Hz,1H),4.74(d,J＝13.0Hz,1H),4.41(d,J＝13.0Hz,1H),2.97(dt,J＝13.0,8.2Hz,1H),2.81(dt,J＝12.9,7.3Hz,1H),1.94-1.76(m,2H),1.53-1.38(m,2H),0.94(t,J＝7.4Hz,3H).ESI-MS(m/z):413$[M+H]^+$。

[0282] 

[0283] 使用Kalugin所述的过程制备SW0332912-(丁基亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺(Kalugin V.E.Russian.Chem.Bull.,Int.Ed.,2006,55,529)。向4-(((丁基硫代)甲基)亚磺酰基)-2,6-二苯基嘧啶-5-腈(0.53mmol,220mg)在DMF(0.25M)/EtOH(0.5M)中形成的溶液中加入KOH(0.32mmol,18mg,0.6当量，在水中0.1M)。将反应混合物在35℃下搅拌40min。一旦完成，便使用EtOAc稀释反应物，并使用10％当量的乙酸溶液洗涤，分离有机相，使用EtOAc将水性层洗涤2次，在硫酸镁上干燥，过滤并在减压下浓缩，从而给出211mg SW0332912-(丁基亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺(96％)。^1H NMR(400MHz,$CDCl_3$)δ7.67-7.60(m,1H),7.57-7.35(m,7H),7.10(dd,J＝5.0,3.7Hz,1H),4.54(s,2H),3.26(ddd,J＝12.8,9.1,6.0Hz,1H),3.09(ddd,J＝12.8,9.1,6.6Hz,1H),1.83-1.61(m,2H),1.53-1.38(m,2H),0.93(t,J＝7.3Hz,3H).ESI-MS(m/z):413$[M+H]^+$。

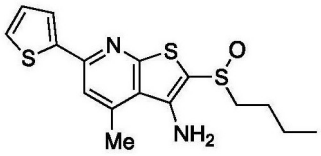
[0284] 

[0285] 使用类似物SW033291的制备中所述的合成过程，以56％分离产率制备SW2084374-苯基-2-(丙基亚磺酰基)-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺。^1H NMR(400MHz,$CDCl_3$)δ7.65(dd,J＝3.8,1.1Hz,1H),7.61-7.49(m,4H),7.49-7.41(m,3H),7.12(dd,J＝5.0,3.7Hz,1H),3.28(ddd,J＝12.7,8.4,6.3Hz,1H),3.07(ddd,J＝12.7,8.6,7.0Hz,1H),1.91-1.65(m,2H),1.08(t,J＝7.4Hz,3H).APCI-MS(m/z):399$[M+H]^+$。

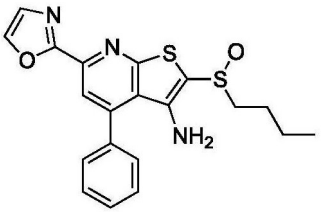
[0286] 

[0287] 使用类似物SW033291的制备所述的合成过程，以48％分离产率制备SW2084382-(异丙基亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺。^1H NMR(400MHz,CDCl3)δ7.64(dd,J＝3.7,1.1Hz,1H),7.58-7.47(m,5H),7.47-7.39(m,2H),7.10(dd,J＝5.0,3.7Hz,1H),4.59(s,2H),3.38(p,J＝6.8Hz,1H),1.43(d,J＝6.9Hz,3H),1.25(d,J＝

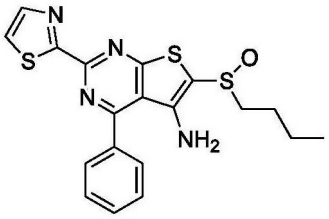
6.8Hz,3H).ESI-MS(m/z):399[M+H]$^+$。

[0288] 

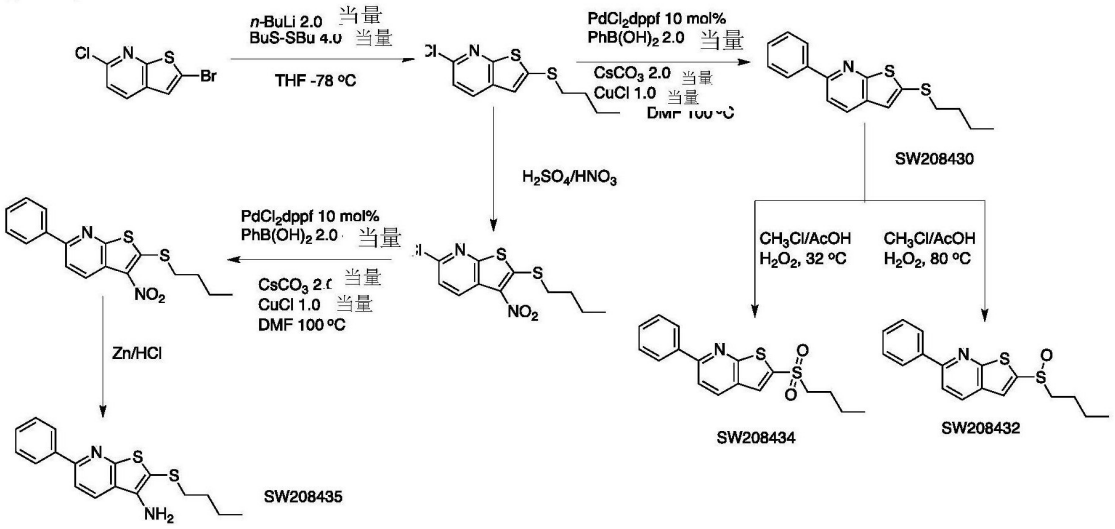
[0289] 使用类似物SW033291的制备所述的合成过程制备SW2084882-(丁基亚磺酰基)-4-甲基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ7.55(dd,J=3.7,1.2Hz,1H),7.39(dd,J=5.0,1.1Hz,1H),7.25-7.23(m,1H),7.06(dd,J=5.0,3.7Hz,1H),5.02(s,2H),3.25(ddd,J=12.7,9.1,6.0Hz,1H),3.08(ddd,J=12.8,9.2,6.4Hz,1H),2.74(s,3H),1.82-1.58(m,2H),1.56-1.38(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):351[M+H]$^+$。

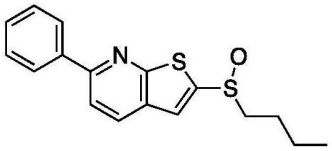
[0290] 

[0291] 使用类似物SW033291的制备所述的合成过程制备SW2084962-(丁基亚磺酰基)-6-(恶唑-2-基)-4-苯基噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ7.99(s,1H),7.84(d,J=0.8Hz,1H),7.58-7.41(m,5H),7.33(d,J=0.8Hz,1H),4.65(s,2H),3.30(ddd,J=12.9,8.8,6.2Hz,1H),3.10(ddd,J=12.8,8.9,6.9Hz,1H),1.86-1.64(m,2H),1.42-1.54(m,2H),0.93(t,J=7.4Hz,3H).ESI-MS(m/z):398.1[M+H]$^+$。

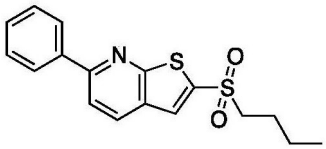
[0292] 

[0293] 使用类似物SW208065的制备所述的合成过程制备SW208436 6-(丁基亚磺酰基)-4-苯基-2-(噻唑-2-基)噻吩并[2,3-d]嘧啶-5-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.06(dd,J=3.1,1H),7.75-7.66(m,2H),7.75-7.66(m,3H),7.55(dd,J=3.1,1H),4.87(s,2H),3.30(ddd,J=12.8,8.4,6.3Hz,1H),3.12(ddd,J=12.8,8.6,6.9Hz,1H),1.85-1.65(m,2H),1.55-1.40(m,2H),0.95(t,J=7.3Hz,3H).ESI-MS(m/z):415.1[M+H]$^+$。

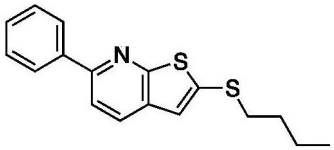
[0294] 



[0295] SW2084322-(丁基亚磺酰基)-6-苯基噻吩并[2,3-b]吡啶。将乙酸(90μL)和过氧化氢(0.06mmol,1.5当量,在水中的30%溶液)加入2-(丁基硫代)-6-苯基噻吩并[2,3-b]吡啶(0.04mmol,12mg)在氯仿(90μL)中形成的溶液中。将反应混合物在32℃下搅拌1h。然后使用EtOAc稀释反应物,并使用饱和的$NaHCO_3$溶液洗涤,在硫酸镁上干燥,并在减压下浓缩,从而以76%分离产率给出所设计的产物。^1H NMR(400MHz,$CDCl_3$)δ8.14(d,J=8.4,1H),8.08(d,J=8.2,2H),7.82(d,J=8.4,1H),7.58-7.36(m,4H),3.30-2.73(m,2H),1.90-1.62(m,2H),1.55-1.41(m,2H),0.94(t,J=7.3Hz,3H).ESI-MS(m/z):316.1$[M+H]^+$。

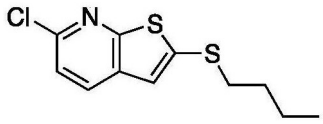
[0296] 

[0297] SW208434。将乙酸(200μL)和过氧化氢(0.15mmol,在水中的30%溶液)加入2-(丁基硫代)-6-苯基噻吩并[2,3-b]吡啶(0.09mmol,27mg)在氯仿(200μL)中形成的溶液中。将反应混合物在100℃下搅拌30min。然后使用EtOAc稀释反应物,并使用饱和的$NaHCO_3$溶液洗涤,在硫酸镁上干燥,过滤并在减压下浓缩,从而以81%分离产率给出所设计的产物。^1H NMR(400MHz,$CDCl_3$)δ8.23(d,J=8.5Hz,1H),8.09(dd,J=8.2,1.6Hz,2H),7.89(d,J=2.1Hz,1H),7.59-7.39(m,4H),3.39-3.10(m,2H),1.92-1.68(m,2H),1.54-1.27(m,2H),0.91(t,J=7.3Hz,3H).ESI-MS(m/z):332.1$[M+H]^+$。

[0298] 

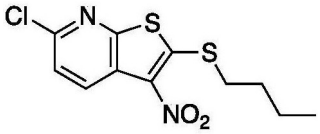
[0299] SW2084302-(丁基硫代)-6-苯基噻吩并[2,3-b]吡啶。将苯基硼酸(0.39mmol,2.0当量),2-(丁基硫代)-6-氯代噻吩并[2,3-b]吡啶(50mg,0.195mmol,1.0当量),碳酸铯

(0.39mmol,2.0当量),$PdCl_2$dppf(10mol%),氯化铜(0.195mmol,1.0当量)在DMF中在100℃下加热12h。在冷却至r.t.后,使用EtOAc稀释反应混合物并使用水、接着使用生理盐水洗涤。将有机层在硫酸镁上干燥,并在减压下除去溶剂。通过快速色谱法(己烷/EtOAc:8/2)纯化粗产物,从而以32%产率提供所设计的产物。^{1}HNMR(400MHz,$CDCl_3$)δ8.09-8.00(m,2H),7.93(d,J=8.3Hz,1H),7.69(d,J=8.3Hz,1H),7.52-7.34(m,4H),2.99(t,J=7.9Hz,2H),1.77-1.63(m,2H),1.53-1.38(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):300.1$[M+H]^+$。

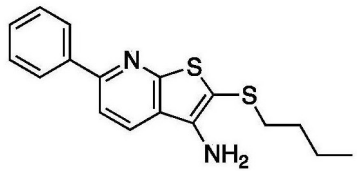
[0300] 

[0301] 2-(丁基硫代)-6-氯代噻吩并[2,3-b]吡啶。在-78℃下,向2-溴代-6-氯代噻吩并[2,3-b]吡啶(40mg,0.16mmol)在THF(2mL)中形成的溶液中加入n-BuLi(0.32mmol,2.0当量;在己烷中的1.6M溶液)。将萃取的混合物搅拌5min,然后加入1,2-二丁基二硫烷(0.48mmol,85.4mg)。将反应混合物在-78℃再搅拌1h,使用水猝灭并使用EtOAc稀释。分离有机层,在MgSO4上干燥,并浓缩,从而给出粗产物,通过快速柱色谱法(95/5己烷/EtOAc)纯化该粗产物,从而以91%分离产率给出所设计的产物。

[0302] ^{1}H NMR(400MHz,CDCl3)δ7.81(d,J=8.3Hz,1H),7.24(d,J=8.3Hz,1H),7.13(s,1H),3.01-2.89(m,2H),1.74-1.59(m,2H),1.52-1.36(m,2H),0.91(t,J=7.4Hz,3H).ESI-MS(m/z):258.0$[M+H]^+$。

[0303] 

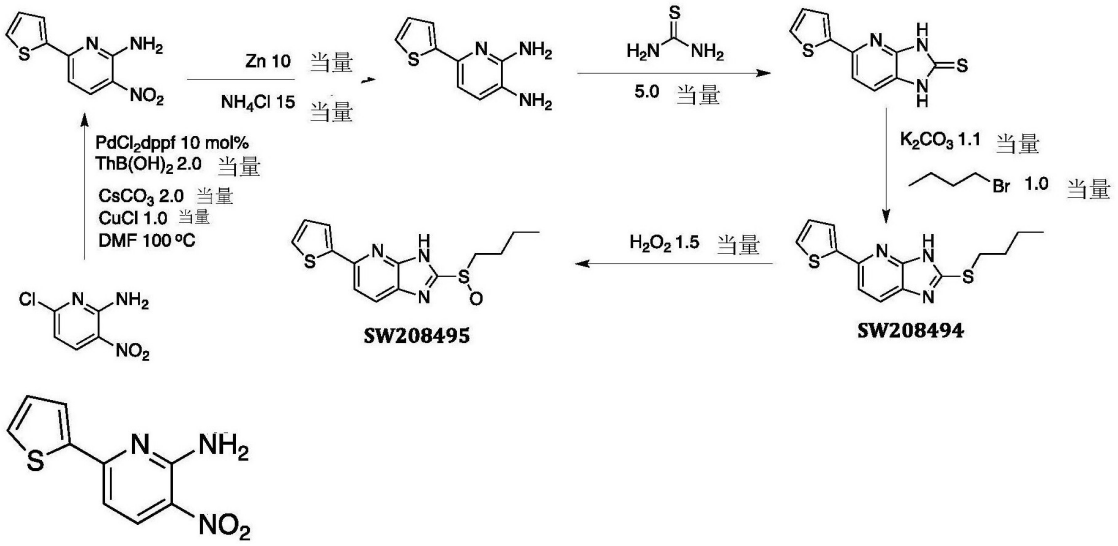
[0304] 根据Nardine所述的过程以53%产率制备2-(丁基硫代)-6-氯代-3-硝基噻吩并[2,3-b]吡啶(Meth-Cohn,O.;Narine,B.Tetrahedon Lett..1978,23,2045.)。^{1}H NMR(400MHz,$CDCl_3$)δ8.68(d,J=8.6Hz,1H),7.45(d,J=8.6Hz,1H),3.15(t,J=7.4Hz,2H),1.95-1.73(m,2H),1.68-1.41(m,2H),0.99(t,J=7.4Hz,3H).ESI-MS(m/z):303.0$[M+H]^+$。

[0305] 

[0306] SW2084352-(丁基硫代)-6-苯基噻吩并[2,3-b]吡啶-3-胺。将苯基硼酸(37mg,0.30mmol,2.0当量),2-(丁基硫代)-6-氯代-3-硝基噻吩并[2,3-b]吡啶(46mg,0.15mmol,1.0当量),碳酸铯(0.30mmol,2.0当量),$PdCl_2$dppf(10mol%),氯化铜(0.15mmol,15mg,1.0当量)在DMF中在100℃下加热12h。在冷却至r.t.后,使用EtOAc稀释反应混合物,并使用水、接着使用生理盐水洗涤。将有机层在硫酸镁上干燥,并在减压下除去溶剂。通过制备型TLC(AcOEt/己烷:2/8)纯化粗产物,从而提供2-(丁基硫代)-3-硝基-6-苯基噻吩并[2,3-b]吡啶。ESI-MS(m/z):345.1$[M+H]^+$。将2-(丁基硫代)-3-硝基-6-苯基噻吩并[2,3-b]吡啶(0.017mmol,6mg)溶解于乙酸(0.12mL)和浓盐酸(1滴)的混合溶剂中。在0℃下加入锌(13mg)。在将混合物搅拌30分钟后,过滤反应混合物,并使用$NaHCO_3$水性溶液中和滤液,再使用DCM萃取。使用水、接着使用饱和的氯化钠水性溶液洗涤有机层,并在硫酸钠上干燥。随

后，蒸发溶剂从而获得所设计的产物。^{1}HNMR(400MHz,$CDCl_3$)δ7.65-7.54(m,3H),7.50-7.40(m,2H),7.35-7.28(m,1H),7.14(d,J＝8.4Hz,1H),3.35-3.18(m,2H),1.80-1.65(m,2H),1.54-1.38(m,2H),0.95(t,J＝7.3Hz,3H).ESI-MS(m/z):315.1$[M+H]^+$。

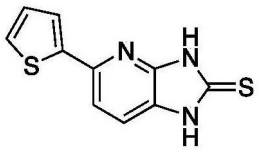
[0307] 根据Nardine所述的过程制备2-溴代-6-氯代噻吩并[2,3-b]吡啶。^{11}H NMR(400MHz,$CDCl_3$)δ7.87(d,J＝8.4Hz,1H),7.28(s,1H),7.27(d,J＝8.4Hz,1H).ESI-MS(m/z):249$[M+H]^+$。

[0308] 

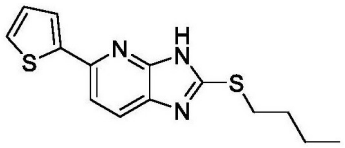
[0309] 3-硝基-6-(苯硫-2-基)吡啶-2-胺。将处于DMF中的噻吩硼酸(742mg,5.8mmol,2.0当量),6-氯代-3-硝基吡啶-2-胺(500mg,2.9mmol,1.0当量),碳酸铯(5.8mmol,2.0当量),$PdCl_2$dppf(10mol％),氯化铜(2.9mmol,1.0当量)在100℃下加热12h。在冷却至r.t.后，使用EtOAc稀释反应混合物，并使用水、接着使用生理盐水洗涤。将有机层在硫酸镁上干燥，并在减压下除去溶剂。通过柱色谱法(己烷/EtOAc:8/2)纯化粗产物，从而以64％产率提供3-硝基-6-(苯硫-2-基)吡啶-2-胺。^{1}H NMR(400MHz$CDCl_3$)δ8.42(d,J＝8.7Hz,1H),7.70(dd,J＝3.8,1.1Hz,1H),7.54(dd,J＝5.0,1.1Hz,1H),7.15(dd,J＝5.0,3.8Hz,1H),7.09(d,J＝8.7Hz,1H).ESI-MS(m/z):222$[M+H]^+$。

[0310] 

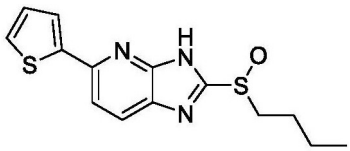
[0311] 6-(苯硫-2-基)吡啶-2,3-二胺。将起始材料3-硝基-6-(苯硫-2-基)吡啶-2-胺(1.20mmol,265.4mg)溶解于5:1丙酮/水混合物中。将锌(12.0mmol,784mg,10eq)和氯化铵(18mmol,962.5mg,15eq)加入至溶液中，将其在室温下搅拌1小时。然后，通过硅藻土垫过滤溶液，并使用乙酸乙酯洗涤。使用生理盐水将滤液洗涤2次，然后使用EtOAc反萃取水层。将合并的有机层在硫酸镁上干燥，过滤并在减压下浓缩。通过柱色谱法进一步纯化，给出118.2mg 6-(苯硫-2-基)吡啶-2,3-二胺(52％)。^{1}H NMR(400MHz,CD_3OD)δ7.34(dd,J＝3.6,1.1Hz,1H),7.25(dd,J＝5.1,1.1Hz,1H),7.00(dd,J＝5.1,3.6Hz,1H),6.96-6.86(m,2H),4.85(s,4H).ESI-MS(m/z):192$[M+H]^+$。

[0312] 

[0313] 5-(苯硫-2-基)-1,3-二氢-2H-咪唑并[4,5-b]吡啶-2-硫酮。将硫脲(16.97mmol,223.0mg,5eq)加入至6-(苯硫-2-基)吡啶-2,3-二胺中。将溶液在170℃下加热2小时。在室温下加入乙醇,产生固体,经过滤得到112.5mg 5-(苯硫-2-基)-1,3-二氢-2H-咪唑并[4,5-b]吡啶-2-硫酮(82%)。^{1}H NMR(400MHz,$(CD_3)_2SO$)δ7.69(dd,J=3.7,1.2Hz,1H),7.66(d,J=8.3Hz,1H),7.56(dd,J=5.1,1.1Hz,1H),7.47(d,J=8.2Hz,1H),7.15-7.09(m,1H).ESI-MS(m/z):235$[M+2H]^+$。

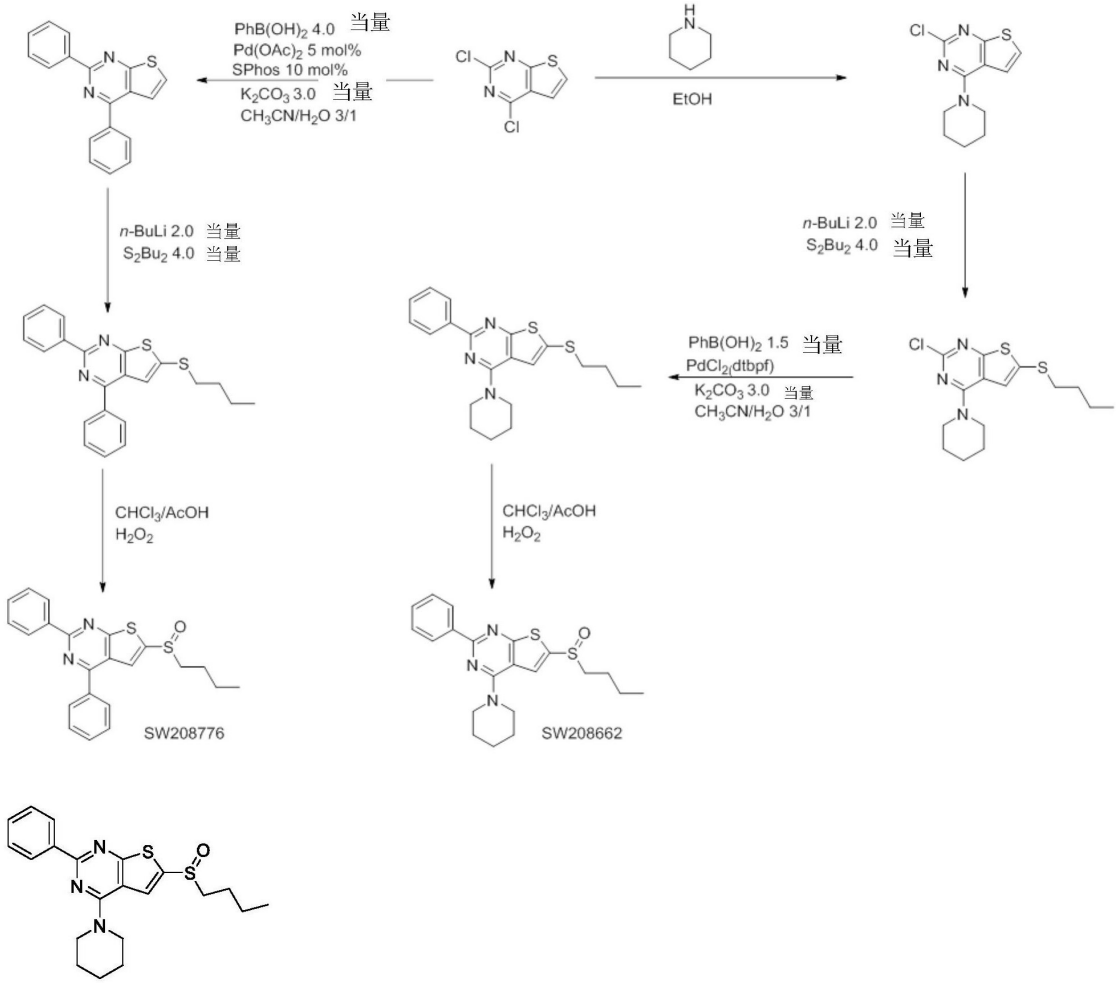
[0314] 

[0315] SW2084942-(丁基硫代)-5-(苯硫-2-基)-3H-咪唑并[4,5-b]吡啶。将5-(苯硫-2-基)-1,3-二氢-2H-咪唑并[4,5-b]吡啶-2-硫酮(0.39mmol,92mg),碳酸钾(0.45mmol,61.9mg,1.1eq),1-溴丁烷(0.39mmol,42.8μL,1eq),18-Crown-6(0.039mmol,10.5mg,0.1eq)和DMF(2.67mL)的混合物在80℃下加热3小时。然后使用EtOAc稀释该溶液,并用水洗涤。将有机层在硫酸镁上干燥,过滤并在减压下浓缩,得到74.4mgSW2084942-(丁基硫代)-5-(苯硫-2-基)-3H-咪唑并[4,5-b]吡啶(65%)。^{1}H NMR(400MHz,$CDCl_3$)δ7.95-7.83(m,1H),7.61-7.53(m,2H),7.36(d,J=5.1,1H),7.16-7.06(m,1H),3.28(t,J=7.3Hz,2H),1.76-1.62(m,2H),1.48-1.32(m,2H),0.90(t,J=7.4Hz,3H).ESI-MS(m/z):290$[M+H]^+$。

[0316] 

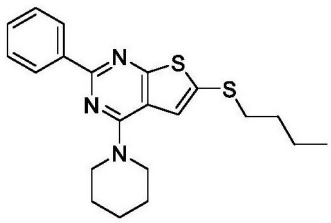
[0317] SW208495.2-(丁基亚磺酰基)-5-(苯硫-2-基)-3H-咪唑并[4,5-b]吡啶。将氯仿(450μL),乙酸(450μL)和过氧化氢(0.376mmol,2.0eq,40μL)加入至SW2084942-(丁基硫代)-5-(苯硫-2-基)-3H-咪唑并[4,5-b]吡啶中,并在45℃下加热2.5小时。然后使用EtOAc稀释溶液,并使用10%乙酸洗涤。分离有机层,在硫酸镁上干燥,过滤、浓缩并纯化,得到16.8mg SW208495。^{1}H NMR(400MHz,$CDCl_3$)δ8.06(d,J=8.5Hz,1H),7.83-7.67(m,1H),7.68-7.60(m,1H),7.41(d,J=5.3Hz,1H),7.20-7.05(m,1H),3.44-3.17(m,2H),1.89-1.58(m,2H),1.59-1.40(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):306$[M+H]^+$。

[0318]



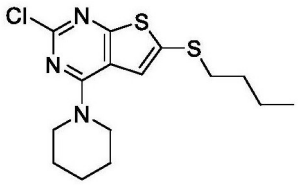
[0319] SW208662.6-(丁基亚磺酰基)-2-苯基-4-(哌啶-1-基)噻吩并[2,3-d]嘧啶。将乙酸(50μl)和过氧化氢(5.0μl,在水中的30％溶液)加入至2-(丁基硫代)-6-苯基-4-(哌啶-1-基)噻吩并[2,3-b]嘧啶(10mg,0.026mmol)在氯仿(50μl)中形成的溶液中。将反应混合物在32℃下搅拌45min。一旦完成,便使用EtOAc稀释反应物,并使用饱和的$NaHCO_3$溶液洗涤,在硫酸镁上干燥,过滤并在减压下浓缩,得到所设计的产物。^1H NMR(400MHz,$CDCl_3$)δ8.54-8.34(m,2H),7.73(s,1H),7.55-7.36(m,3H),4.09-3.86(m,4H),3.24-2.94(m,2H),1.97-1.36(m,10H),0.93(t,J＝7.3Hz,3H).ESI-MS(m/z):400.1$[M+H]^+$。

[0320]

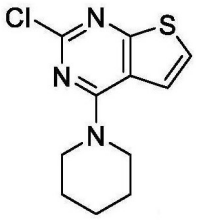


[0321] 2-(丁基硫代)-6-苯基-4-(哌啶-1-基)噻吩并[2,3-b]嘧啶。将2-(丁基硫代)-6-氯代-4-(哌啶-1-基)噻吩并[2,3-b]嘧啶(52mg,0.15mmol),苯基硼酸(27mg,0.22mmol,1.5当量),碳酸钾(0.3mmol,2.0当量),PdCl2dtbpf(10mol mol％)在CH3CN:H2O(2:1)中在100℃下过夜加热。在冷却至r.t.后,使用EtOAc稀释反应混合物,并使用水洗涤。将有机层在硫酸镁上干燥,并在减压下除去溶剂。通过快速色谱法纯化粗产物,从而提供所设计的产物。1H NMR(400MHz,CHCl3)δ8.49-8.36(m,2H),7.51-7.36(m,3H),7.29(s,1H),3.95-3.85(m,

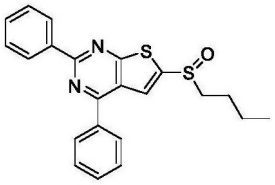
4H),2.90(t,J＝7.4Hz,2H),1.76-1.73(m,6H),1.70-1.59(m,2H),1.48-1.39(m,2H),0.91(t,J＝7.4Hz,3H).ESI-MS(m/z):384.0[M+H]+。

[0322] 

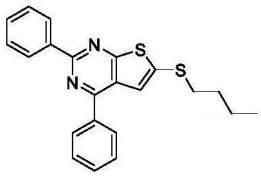
[0323] 2-(丁基硫代)-6-氯代-4-(哌啶-1-基)噻吩并[2,3-b]嘧啶。在-78℃下,向6-氯代-4-(哌啶-1-基)噻吩并[2,3-b]嘧啶(52mg,0.20mmol)在THF中形成的溶液中加入n-BuLi(0.4mmol,2.0当量,在己烷中的1.6M溶液)。将反应混合物搅拌5min,并加入处于THF中的1,2-二丁基二硫烷(0.80mmol,4.0当量)。将反应混合物在-78℃下再搅拌1h,然后猝灭。通过快速色谱法纯化粗产物,从而以74%产率提供所设计的产物。^{1}H NMR(400MHz,$CHCl_3$)δ7.24(s,1H),3.93-3.74(m,4H),2.83(t,J＝7.3Hz,2H),1.82-1.66(m,6H),1.66-1.53(m,2H),1.49-1.33(m,2H),0.89(t,J＝7.3Hz,3H).ESI-MS(m/z):342.1$[M+H]^+$。

[0324] 

[0325] 6-氯代-4-(哌啶-1-基)噻吩并[2,3-b]嘧啶。在室温下过夜搅拌处于EtOH中的4,6-二氯噻吩并[2,3-b]嘧啶(50mg,0.24mmol)和哌啶(0.36mmol,1.5当量)。蒸发溶剂,并通过快速色谱法纯化化合物粗品,从而以定量的产率给出所设计的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.28(d,J＝6.1Hz,1H),7.18(d,J＝6.2Hz,1H),4.01-3.67(m,4H),1.92-1.63(m,6H).ESI-MS(m/z):254.0$[M+H]^+$。

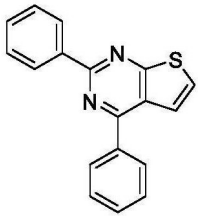
[0326] 

[0327] SW208776.6-(丁基亚磺酰基)-2,4-二苯基噻吩并[2,3-d]嘧啶。将乙酸(250μl)和过氧化氢(20μl,在水中的30%溶液)加入6-(丁基硫代)-2,4-二苯基噻吩并[2,3-d]嘧啶(35mg,0.1mmol)在氯仿(250μl)中形成的溶液中。将反应混合物在32℃下搅拌45min。一旦完成,便使用EtOAc稀释反应物,并使用饱和的$NaHCO_3$溶液洗涤,在硫酸镁上干燥,过滤并在减压下浓缩,得到所设计的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.69-8.59(m,2H),8.09-7.99(m,2H),7.95(s,1H),7.65-7.56(m,3H),7.56-7.45(m,3H),3.18-3.02(m,2H),1.87-1.64(m,2H),1.54-1.42(m,2H),0.94(t,J＝7.3Hz,3H).ESI-MS(m/z):393.1$[M+H]^+$。

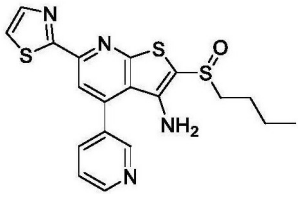
[0328] 

[0329] 6-(丁基硫代)-2,4-二苯基噻吩并[2,3-d]嘧啶。在-78℃下,向2,4-二苯基噻吩并

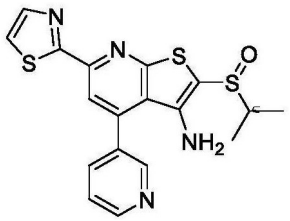
[2,3-d]嘧啶(53mg,0.28mmol)在THF中形成的溶液中加入n-BuLi(0.56mmol,2.0当量,225μL,在己烷中的2.5M溶液)。将反应混合物搅拌5min,并加入处于THF中的1,2-二丁基二硫烷(1.14mmol,4.0当量)。将反应混合物在-78℃下再搅拌1h,然后猝灭。通过快速色谱法纯化粗产物,从而提供所设计的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.62-8.56(m,2H),8.06-7.98(m,2H),7.61-7.41(m,7H),3.01(t,J=7.3,2H),1.76-1.62(m,2H),1.55-1.38(m,2H),0.92(t,J=7.4Hz,3H).ESI-MS(m/z):377.1$[M+H]^+$。

[0330] 

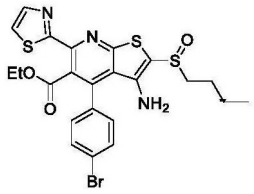
[0331] 2,4-二苯基噻吩并[2,3-d]嘧啶。在100℃下过夜加热处于CH_3CN:H_2O(1.5:1)中的2,4-二氯噻吩并[2,3-d]嘧啶(100mg,0.50mmol),苯基硼酸(242mg,2.0mmmol,4.0当量),碳酸钾(1.5mmol,3.0当量),$Pd(OAc)_2$(5mol mol%),SPhos(10mol%)。在冷却至r.t.后,使用EtOAc稀释反应混合物,并使用水洗涤。将有机层在硫酸镁上干燥,并在减压下除去溶剂。通过快速色谱法纯化粗产物,从而提供所设计的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.70-8.59(m,2H),8.14-8.02(m,2H),7.65-7.44(m,8H).ESI-MS(m/z):289.0$[M+H]^+$。

[0332] 

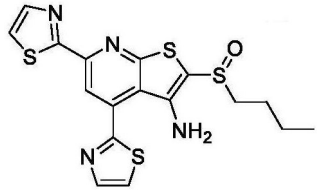
[0333] SW208777.使用类似物SW033291的制备中所述的合成过程制备2-(丁基(λ^1-氧基)-λ^3-巯基)-4-(吡啶-3-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.80(s,1H),8.78(dd,J=4.9,1.7Hz,1H),8.04(s,1H),7.91(d,J=3.2Hz,1H),7.86(d,J=6.4Hz,1H),7.51(d,J=3.1Hz,1H),7.47(dd,J=7.8,4.8Hz,1H),4.53(s,2H),3.28(ddd,J=12.8,8.8,6.3Hz,1H),3.11(ddd,J=12.8,8.9,6.9Hz,1H),1.86-1.70(m,2H),1.57-1.38(m,2H),0.94(t,J=7.3Hz,3H).ESI-MS(m/z):415.0$[M+H]^+$。

[0334] 

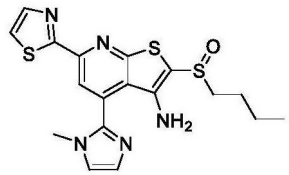
[0335] SW208780.使用类似物SW033291的制备中所述的合成过程制备2-(异丙基(λ^1-氧基)-λ^3-巯基)-4-(吡啶-3-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.87-8.70(m,2H),8.05(s,1H),7.92(d,J=3.1Hz,1H),7.85(dd,J=7.8,2.4Hz,1H),7.51(d,J=3.2Hz,1H),7.47(dd,J=7.9,4.9Hz,1H),4.57(s,2H),3.38(p,J=6.8Hz,1H),1.43(d,J=6.8Hz,3H),1.29(d,J=6.8Hz,3H).ESI-MS(m/z):400.1$[M+H]^+$。

[0336] 

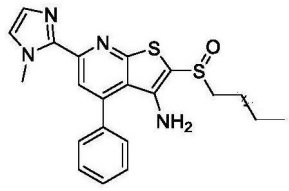
[0337] SW209123.使用类似物SW033291的制备中所述的合成过程制备乙基3-氨基-4-(4-溴代苯基)-2-(丁基亚磺酰基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-5-羧酸酯。^{1}H NMR(400MHz,$CDCl_3$)δ7.86(d,J=3.2Hz,1H),7.69-7.60(m,2H),7.48(d,J=3.2Hz,1H),7.36-7.27(m,2H),4.12(q,J=7.2Hz,2H),3.26(ddd,J=12.9,8.8,6.3Hz,1H),3.08(ddd,J=12.9,8.8,6.3Hz,1H),1.80-1.63(m,2H),1.58-1.37(m,2H),1.06(t,J=7.2Hz,3H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):564.0$[M+H]^+$。

[0338] 

[0339] SW209124.使用类似物SW033291的制备中所述的合成过程制备乙基2-(丁基亚磺酰基)-4,6-二(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.48(s,1H),8.01(d,J=3.1Hz,1H),7.96(d,J=3.2Hz,1H),7.61(d,J=3.3Hz,1H),7.52(d,J=3.1Hz,1H),6.69(s,2H),3.30(ddd,J=12.8,9.2,6.0Hz,1H),3.14(ddd,J=12.8,9.2,6.4Hz,1H),1.83-1.60(m,2H),1.43-1.53(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):421.0$[M+H]^+$。

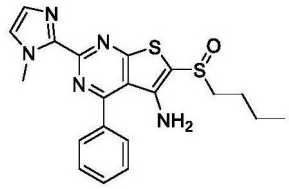
[0340] 

[0341] SW209125.使用类似物SW033291的制备中所述的合成过程制备2-(丁基亚磺酰基)-4-(1-甲基-1H-咪唑并1-2-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.13(s,1H),7.91(d,J=3.2Hz,1H),7.50(d,J=3.1Hz,1H),7.24(d,J=1.2Hz,1H),7.13(d,J=1.2Hz,1H),5.78(s,2H),3.80(s,3H),3.26(ddd,J=12.8,9.1,6.0Hz,1H),3.10(ddd,J=12.8,9.2,6.5Hz,1H),1.82-1.57(m,2H),1.56-1.35(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):418.1$[M+H]^+$。

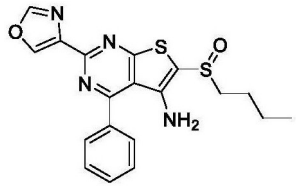
[0342] 

[0343] SW209126.使用类似物SW033291的制备中所述的合成过程制备2-(丁基亚磺酰基)-4-(1-甲基-1H-咪唑并1-2-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.08(s,1H),7.58-7.32(m,5H),7.11(d,J=1.1Hz,1H),7.00(d,J=1.1Hz,1H),4.58(s,2H),4.19(s,3H),3.27(ddd,J=12.7,9.0,6.0Hz,1H),3.08(ddd,J=12.8,9.1,6.6Hz,1H),1.79-1.60(m,2H),1.56-1.37(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS

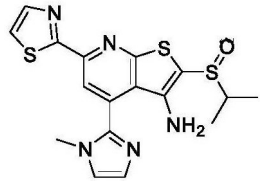
(m/z):411.1[M+H]$^+$。

[0344] 

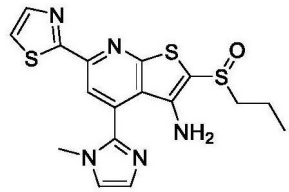
[0345] SW209277.使用类似物SW208065的制备中所述的合成过程制备6-(丁基亚磺酰基)-2-(1-甲基-1H-咪唑并1-2-基)-4-苯基噻吩并[2,3-d]嘧啶-5-胺。^{1}H NMR(400MHz,$CDCl_3$)δ7.71(dd,J=6.9,2.8Hz,2H),7.63-7.49(m,3H),7.29(s,1H),7.07(s,1H),4.85(s,2H),4.18(s,3H),3.29(ddd,J=12.8,8.6,6.3Hz,1H),3.11(ddd,J=12.8,8.7,6.9Hz,1H),1.83-1.65(m,2H),1.59-1.39(m,2H),0.94(t,J=7.3Hz,3H).ESI-MS(m/z):412.1[M+H]$^+$。

[0346] 

[0347] SW209278.使用类似物SW208065的制备中所述的合成过程制备6-(丁基亚磺酰基)-2-(恶唑-4-基)-4-苯基噻吩并[2,3-d]嘧啶-5-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.51(d,J=1.1Hz,1H),8.01(d,J=1.1Hz,1H),7.75-7.61(m,2H),7.62-7.48(m,3H),4.56(s,2H),3.29(ddd,J=12.9,8.8,6.3Hz,1H),3.09(ddd,J=12.9,8.9,6.9Hz,1H),1.81-1.64(m,2H),1.56-1.39(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):399.1[M+H]$^+$。

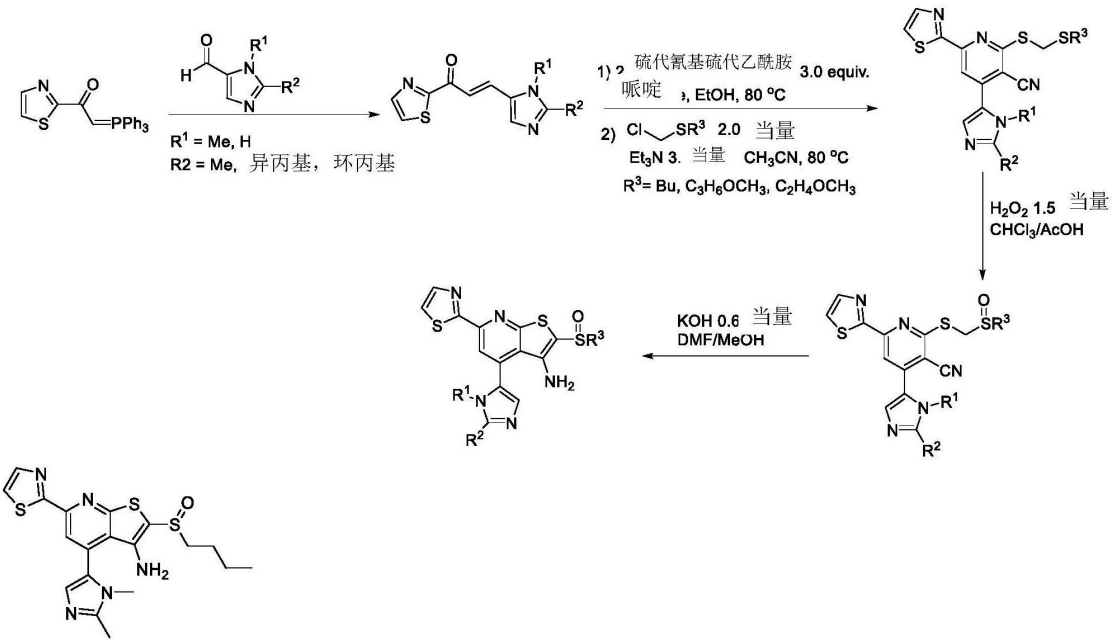
[0348] 

[0349] SW209279.使用类似物SW033291的制备中所述的合成过程制备2-(异丙基亚磺酰基)-4-(1-甲基-1H-咪唑并1-2-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.14(s,1H),7.92(d,J=3.2Hz,1H),7.51(d,J=3.2Hz,1H),7.24(s,1H),7.13(d,J=1.2Hz,1H),5.92(s,2H),3.80(s,3H),3.38(p,J=6.8Hz,1H),1.44(d,J=6.8Hz,3H),1.25(d,J=6.8Hz,3H).ESI-MS(m/z):404.1[M+H]$^+$。

[0350] 

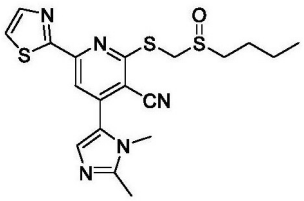
[0351] SW209280.使用类似物SW033291的制备中所述的合成过程制备4-(1-甲基-1H-咪唑并1-2-基)-2-(丙基亚磺酰基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.14(s,1H),7.92(d,J=3.2Hz,1H),7.51(d,J=3.1,1H),7.25(d,J=1.3Hz,1H),7.14(d,J=1.2Hz,1H),5.97(s,2H),3.80(s,3H),3.27(ddd,J=12.7,8.3,6.5Hz,1H),3.07(ddd,J=12.8,8.4,7.1Hz,1H),1.85-1.69(m,2H),1.07(t,J=7.4Hz,3H).ESI-MS(m/z):404.1[M+H]$^+$。

[0352]

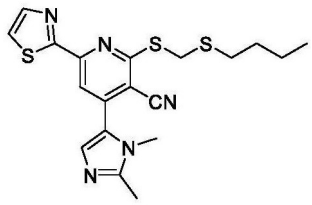


[0353] SW209415.2-(丁基亚磺酰基)-4-(1,2-二甲基-1H-咪唑并1-5-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。向2-(((丁基亚磺酰基)甲基)硫代)-4-(1,2-二甲基-1H-咪唑并1-5-基)-6-(噻唑-2-基)烟腈(0.14mmol,60mg)在DMF(600μl)/MeOH(300μl)中形成的溶液中加入KOH(0.084mmol,4.70mg,0.6当量,在水中2.0M)。将反应混合物在32℃下搅拌20min。一旦完成,便使用EtOAc稀释反应物,并使用5当量%的AcOH溶液酸化至pH 7,在硫酸镁上干燥,过滤并在减压下浓缩。通过快速色谱法纯化粗产物,从而以97%分离产率提供所设计的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.03(s,1H),7.90(d,J=3.1Hz,1H),7.50(d,J=3.2Hz,1H),7.11(s,1H),4.76(s,2H),3.39(s,3H),3.27(ddd,J=12.9,8.7,6.4Hz,1H),3.09(ddd,J=12.8,8.8,6.9Hz,1H),2.47(s,3H),1.83-1.62(m,2H),1.57-1.38(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):432.1$[M+H]^+$。可以通过手性HPLC:Chiralpak AD-H,10X250mm,5μM,100%MeOH分离SW209415的2种对映异构体。

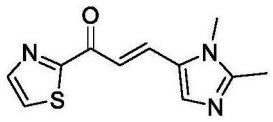
[0354]



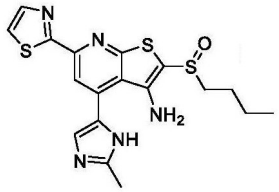
[0355] 2-(((丁基亚磺酰基)甲基)硫代)-4-(1,2-二甲基-1H-咪唑并1-5-基)-6-(噻唑-2-基)烟腈。向2-(((丁基硫代)甲基)硫代)-4-(1,2-二甲基-1H-咪唑并1-5-基)-6-(噻唑-2-基)烟腈(85mg,0.205mmol)在$CHCl_3$/AcOH(1:1,0.15M)中形成的溶液中加入H_2O_2(0.31mmol,在水中1.5当量30%溶液)。将反应混合物在32℃下搅拌40min。一旦完成,便使用EtOAc稀释反应物,并使用饱和的$NaHCO_3$溶液洗涤,在硫酸镁上干燥,过滤并在减压下浓缩,从而以92%产率给出所设计的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.98(d,J=3.1Hz,1H),7.94(s,1H),7.60(d,J=3.1Hz,1H),7.43(s,1H),4.72(d,J=13.1Hz,1H),4.41(d,J=13.1Hz,1H),3.63(s,3H),2.96(dt,J=12.9,8.2Hz,1H),2.84(dt,J=12.9,7.5Hz,1H),2.51(s,3H),1.94-1.74(m,2H),1.63-1.38(m,2H),0.95(t,J=7.4Hz,3H).ESI-MS(m/z):432.1$[M+H]^+$。

[0356] 

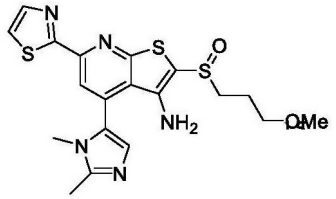
[0357] 2-(((丁基硫代)甲基)硫代)-4-(1,2-二甲基-1H-咪唑并1-5-基)-6-(噻唑-2-基)烟腈。向3-(1,2-二甲基-1H-咪唑并1-5-基)-1-(噻唑-2-基)丙-2-烯-1-酮(0.31mmol,72mg)和2-氰基硫代乙酰胺(0.93mmol,93mg,3.0当量)在EtOH(1.5mL)中形成的悬液中,加入几滴哌啶。在80℃下搅拌2h后,EtOH蒸发,并将粗产物再次溶解于CH_3CN中。然后加入丁基(氯代甲基)硫烷(0.62mmol,85.5mg)和Et_3N(0.93mmol,94.1mg,130μL),并将反应混合物在80℃下搅拌20min。一旦完成,便使用EtOAc和水稀释反应物。分离有机相,并使用EtOAc萃取水层2次。使用饱和的NaCl溶液洗涤合并的萃取物,在硫酸镁上干燥,过滤并在减压下浓缩。通过快速色谱法纯化残余物,从而给出99mg所设计的产物(77%)。^1H NMR(400MHz,$CDCl_3$)δ7.96(d,J=3.1Hz,1H),7.85(s,1H),7.56(d,J=3.1Hz,1H),7.37(s,1H),4.49(s,2H),3.60(s,3H),2.72(t,J=7.4Hz,2H),2.48(s,3H),1.62(p,J=7.3Hz,2H),1.40(h,J=7.3Hz,2H),0.90(t,J=7.3Hz,3H).ESI-MS(m/z):416.6$[M+H]^+$。

[0358] 

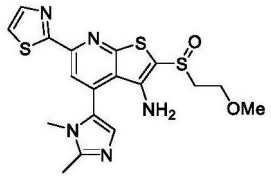
[0359] (E)-3-(1,2-二甲基-1H-咪唑并1-5-基)-1-(噻唑-2-基)丙-2-烯-1-酮。向1,5-二甲基-1H-咪唑-2-甲醛(2.0mmol,250mg)在6ml CH_3CN中形成的溶液中加入1-(噻唑-2-基)-2-(三苯基-l5-phosphanylidene)乙-1-酮(4.0mmol,1.55g,2.0当量)。将反应混合物在90℃下搅拌48h。一旦完成,便蒸发溶剂,并通过快速色谱法纯化残余物,从而给出331mg所设计的产物(71%)。^1H NMR(400MHz,甲醇-d4)δ8.08(d,J=3.0Hz,1H),7.97(d,J=3.0Hz,1H),7.90(d,J=15.9Hz,1H),7.76(d,J=15.9Hz,1H),7.60(s,1H),3.72(s,3H),2.43(s,3H).ESI-MS(m/z):234.3$[M+H]^+$。

[0360] 

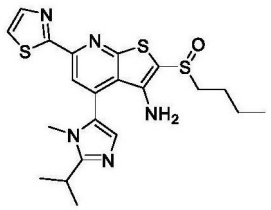
[0361] SW209428.使用类似物SW209415的制备中所述的合成过程制备2-(丁基亚磺酰基)-4-(2-甲基-1H-咪唑并1-5-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^1H NMR(400MHz,$CDCl_3$)δ10.51(s,1H),8.10(s,1H),7.89(d,J=3.2Hz,1H),7.46(d,J=3.2Hz,1H),7.40(s,1H),3.31(ddd,J=12.8,9.3,5.8Hz,1H),3.15(ddd,J=12.8,9.3,6.2Hz,1H),2.42(s,3H),1.79-1.58(m,2H),1.57-1.38(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):418.1$[M+H]^+$。

[0362] 

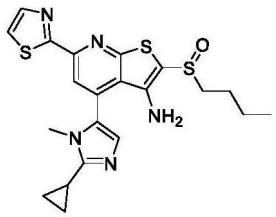
[0363] SW211688.使用类似物SW209415的制备中所述的合成过程制备4-(1,2-二甲基-1H-咪唑并1-5-基)-2-((3-甲氧基丙基)亚磺酰基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,丙酮-d6)δ8.03(s,1H),7.99(d,J=3.2Hz,1H),7.82(d,J=3.2Hz,1H),7.09(s,1H),5.06(s,2H),3.51(s,3H),3.48(t,J=6.1Hz,2H),3.26(s,3H),3.26-3.18(m,1H),3.18-3.12(m,1H),2.43(s,3H),2.00-1.89(m,2H).ESI-MS(m/z):448.1[M+H]$^+$。

[0364] 

[0365] SW211689.使用类似物SW209415的制备中所述的合成过程制备4-(1,2-二甲基-1H-咪唑并1-5-基)-2-((2-甲氧基乙基)亚磺酰基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.05(s,1H),7.92(d,J=3.2Hz,1H),7.51(d,J=3.2Hz,1H),7.11(s,1H),4.73(s,2H),3.88-3.82(m,1H),3.75-3.62(m,1H),3.57(ddd,J=13.1,6.0,3.9Hz,1H),3.40(s,3H),3.37(s,3H),3.25(ddd,J=12.8,8.0,4.4Hz,1H),2.48(s,3H).ESI-MS(m/z):434.1[M+H]$^+$。

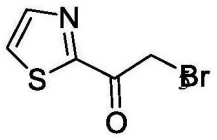
[0366] 

[0367] SW212344.使用类似物SW209415的制备中所述的合成过程制备2-(丁基亚磺酰基)-4-(2-异丙基-1-甲基-1H-咪唑并1-5-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.06(s,1H),7.92(d,J=3.1Hz,1H),7.51(d,J=3.2Hz,1H),7.15(s,1H),4.71(s,2H),3.41(s,3H),3.27(ddd,J=13.0,8.5,6.5Hz,1H),3.19-2.98(m,2H),1.83-1.59(m,2H),1.58-1.41(m,2H),1.39(d,J=6.7Hz,6H),0.94(t,J=7.3Hz,3H).ESI-MS(m/z):460.1[M+H]$^+$。

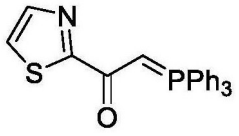
[0368] 

[0369] SW212345.使用类似物SW209415的制备中所述的合成过程制备2-(丁基亚磺酰基)-4-(2-环丙基-1-甲基-1H-咪唑并1-5-基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。^{1}H NMR(400MHz,$CDCl_3$)δ8.04(s,1H),7.91(d,J=3.1Hz,1H),7.50(d,J=3.1Hz,1H),7.07(s,1H),4.77(s,2H),3.51(s,3H),3.27(ddd,J=12.9,8.7,6.4Hz,1H),3.10(ddd,J=12.9,

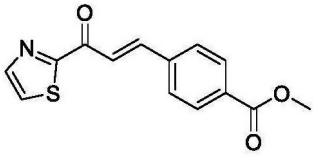
8.8,6.9Hz,1H),1.95-1.78(m,1H),1.81-1.62(m,2H),1.58-1.37(m,2H),1.17-0.98(m,4H),0.93(t,J＝7.3Hz,3H).ESI-MS(m/z):458.1[M+H]$^+$。

[0370] 

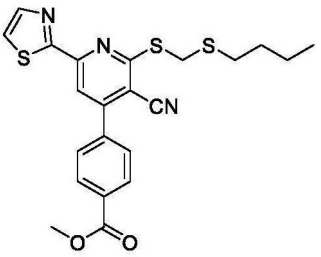
[0371] 2-溴代-1-(噻唑-2-基)乙-1-酮.在-78℃下,将n-丁基锂(24.7mL,0.0617mol,在己烷中2.5M)滴加至2-噻唑(5.0g,0.059mol)在无水二乙醚(48.8mL)中形成的溶液中。在15分钟后,加入溴乙酸乙酯(6.84mL,0.0617mol),除去冷水浴,并使溶液温暖至室温。使用乙醚和水稀释反应混合物。分离有机层,在Na2SO4上干燥,过滤并在减压下浓缩。将粗产物悬浮于己烷中,并加热回流15分钟,然后倒出产物,得到不纯的油。将该过程重复5次,给出88％产率的白色固体。^{1}H NMR(400MHz,CDCl3)δ8.05(d,J＝3.0Hz,1H),7.77(d,J＝3.0Hz,1H),4.71(s,2H).ESI-MS(m/z):207.8[M+H]+。

[0372] 

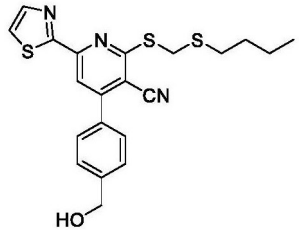
[0373] 1-(噻唑-2-基)-2-(三苯基-15-phosphanylidene)乙-1-酮。向2-溴代-1-(噻唑-2-基)乙-1-酮(10.7g,0.0517mol)在甲苯(337.7mL)中形成的溶液中,逐步加入三苯基膦(14.1g,0.0539mol)。将混合物在室温下搅拌3小时。通过过滤除去浅黄色的沉淀,并使用甲苯、然后使用石油醚多次洗涤。将水加入至沉淀物中,并使用pH 10的1N NaOH逐滴处理(在pH 7时,颜色由黄色变成橘色)。将混合物在室温下搅拌30分钟。通过过滤除去沉淀物,并使用水多次洗涤。将所得的橘色固体在真空下在50℃下加热,从而除去任何水,给出96％产率。^{1}H NMR(400MHz,$CDCl_3$)δ7.82(d,J＝3.1Hz,1H),7.72(ddd,J＝12.8,8.3,1.4Hz,6H),7.61-7.54(m,3H),7.51-7.45(m,6H),7.38(dd,J＝3.1,1.3Hz,1H),5.00(d,J＝23.3Hz,1H).ESI-MS(m/z):387.9[M+H]$^+$。

[0374] 

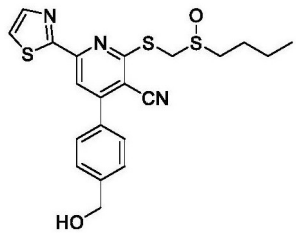
[0375] 甲基(E)-4-(3-氧代-3-(噻唑-2-基)丙-1-烯-1-基)安息香酸酯。在干燥的烧瓶中,将1-(噻唑-2-基)-2-(三苯基-15-phosphanylidene)乙-1-酮(1.5g,3.9mmol)和甲基4-甲酰基安息香酸酯(634mg,3.86mmol)溶解于无水氯仿(19.3mL)中,并将溶液在71℃过夜搅拌。在减压下蒸发溶剂,并使用自动化快速色谱法(100％DCM)纯化固体沉淀物,从而以76％产率给出白色固体。^{1}H NMR(400MHz,CDC3)δ8.10-8.05(m,3H),8.01(d,J＝1.3Hz,2H),7.76(d,J＝8.4Hz,2H),7.72(d,J＝3.0Hz,1H),3.93(s,3H).ESI-MS(m/z):274.0[M+H]+。

[0376] 

[0377] 甲基4-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯。将2-氰基硫代乙酰胺(274.8mg,2.744mmol)和甲基(E)-4-(3-氧代-3-(噻唑-2-基)丙-1-烯-1-基)安息香酸酯(250.0mg,0.9147mmol)合并于小瓶中,该小瓶被排空气体,并使用02回充,然后加入乙醇(2.75mL)和哌啶(2滴)。将溶液喷射几分钟,然后在80℃下搅拌4小时。一旦冷却,便过滤溶液,并使用乙醇漂洗沉淀物,然后通过在80℃加热45分钟在少量乙酸中洗涤。当冷却时,过滤洗涤的溶液,得到棕色/红色的固体粗产物,将该产物进入下一步骤。标准的烷基化过程:在第一步骤中,将处于乙腈(1.32mL)中的丁基(氯代甲基)硫烷(111.2mg,0.8059mmol)加入产物中,最后加入Et3N(168.6μL,1.209mmol)。将该溶液在80℃下搅拌20分钟。使用EtOAc稀释反应混合物,并使用H2O洗涤,在Na2SO4上干燥,过滤并在减压下浓缩。使用自动化快速色谱法(80%己烷,20%EtOAc)纯化固体粗品。这产生24%产率的固体。^{1}H NMR(400MHz,CDCl3)δ8.18(d,J=8.4Hz,2H),8.02(s,1H),7.98(d,J=3.1Hz,1H),7.71(d,J=8.4Hz,2H),7.58(d,J=3.2Hz,1H),4.52(s,2H),3.95(s,3H),2.76(t,J=7.3Hz,2H),1.64(tt,J=7.7,6.3Hz,2H),1.42(h,J=7.3Hz,2H),0.91(t,J=7.3Hz,3H).ESI-MS(m/z):456.1[M+H]+。

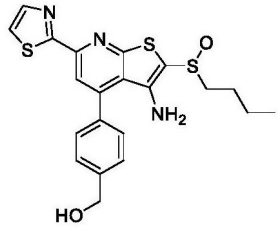
[0378] 

[0379] 2-(((丁基硫代)甲基)硫代)-4-(4-(羟甲基)苯基)-6-(噻唑-2-基)烟腈。在0℃下加入甲基4-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯(336mg,0.737mmol)在THF(8.41mL)$LiBH_4$(96.3mg,4.42mmol)中形成的溶液。将反应物在室温下搅拌36小时,并通过LC/MS监测反应物。使用EtOAc和H_2O稀释反应混合物。将有机层在Na_2SO_4上干燥,过滤并在减压下浓缩,从而以96%产率给出产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.02(s,1H),7.98(d,J=3.1Hz,1H),7.69-7.62(m,2H),7.56(d,J=3.1Hz,1H),7.56-7.49(m,2H),4.79(d,J=4.3Hz,2H),4.52(s,2H),2.82-2.60(m,2H),1.71-1.58(m,2H),1.49-1.33(m,2H),0.91(t,J=7.4Hz,3H).ESI-MS(m/z):428.1$[M+H]^+$。

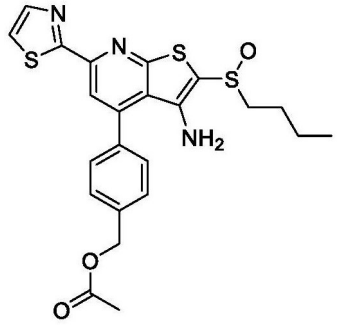
[0380] 

[0381] 标准的氧化过程:2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-4-(4-(羟甲基)苯基)-6-(噻唑-2-基)烟腈。将氯仿(2.53mL),乙酸(1.39mL)和过氧化氢(108.0μL,1.057mmol,水中的30%溶液)加入2-(((丁基硫代)甲基)硫代)-4-(4-(羟甲基)苯基)-6-(噻唑-2-基)烟腈中。将溶液在32℃下搅拌45分钟。然后使用EtOAc稀释反应混合物,并使用饱和$NaHCO_3$洗涤,然后将有机层在Na2SO4上干燥,过滤并在减压下浓缩,从而以94%产率给出所需的产物。^{1}H NMR(400MHz,CDCl3)δ8.03(s,1H),7.93(d,J=3.1Hz,1H),7.59(d,J=8.2Hz,2H),7.55(d,J=3.1Hz,1H),7.48(d,J=7.9Hz,2H),4.73(s,2H),4.66(d,J=

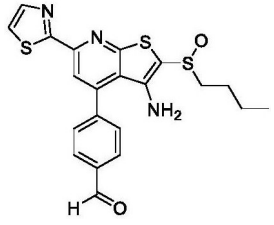
13.1Hz,1H),4.38(d,J＝13.1Hz,1H),2.93(dt,J＝13.0,8.1Hz,1H),2.79(dt,J＝13.0,7.2Hz,1H),1.84-1.72(m,2H),1.55-1.33(m,2H),0.91(t,J＝7.3Hz,3H).).ESI-MS(m/z):444.1[M+H]+。

[0382] 

[0383] SW209510(4-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯基)甲醇。将t-BuOK(22.78mg,0.2028mmol)加入2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-4-(4-(羟甲基)苯基)-6-(噻唑-2-基)烟腈(150mg,0.338mmol)中,并3次排空小瓶气体,再回充N_2,然后加入DMF(1.3mL)。使用N_2喷射溶液几分钟,然后在32℃下加热。通过TLC(80％EtOAc.20％己烷)每5分钟监测一次反应混合物,在结束时,使用EtOAc稀释并使用10％AcOH洗涤。然后将有机层在Na_2SO_4上干燥,过滤并在减压下浓缩。使用自动化快速色谱法纯化产物,从而以16％产率给出分离的绿色固体/油。^{1}H NMR(400MHz,$CDCl_3$)δ8.02(s,1H),7.90(d,J＝3.2Hz,1H),7.59-7.40(m,5H),4.80(s,2H),4.63(s,2H),3.27(ddd,J＝12.8,9.0,6.1Hz,1H),3.10(ddd,J＝12.8,9.1,6.6Hz,1H),1.78-1.61(m,2H),1.55-1.40(m,2H),0.93(t,J＝7.3Hz,3H).ESI-MS(m/z):444.1$[M+H]^+$。

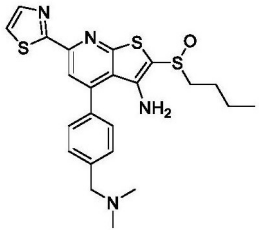
[0384] 

[0385] SW2095114-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苄基乙酸酯。在EtOAc中在SW209510的处理(workup)过程中,形成上述化合物(47％产率)。^{1}H NMR(400MHz,$CDCl_3$)δ7.99(s,1H),7.87(d,J＝3.2Hz,1H),7.56-7.40(m,5H),5.18(s,2H),4.62(s,2H),3.26(ddd,J＝12.8,9.0,6.1Hz,1H),3.08(ddd,J＝12.8,9.1,6.6Hz,1H),2.14(s,3H),1.77-1.59(m,2H),1.53-1.37(m,2H),0.92(t,J＝7.3Hz,3H).ESI-MS(m/z):486.1$[M+H]^+$。

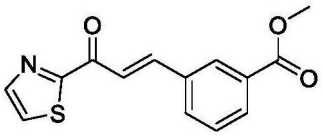
[0386] 

[0387] 4-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)安息香醛。将MnO_2(111.3mg,1.28mmol)加入SW209510(56.8mg,0.128mmol)在DCM(2.3mL)中形成的溶液中,并在室温下过夜搅拌。LC/MS表明反应不完全。在硅藻土上过滤反

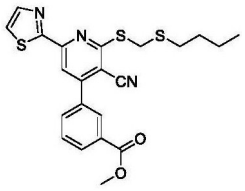
应物，使用DCM洗涤，并将滤液在减压下浓缩。在混合物粗品再次溶解于DCM(2.3mL)中并加入MnO_2(5eq)。将溶液在室温下搅拌24小时，在硅藻土上过滤并使用DCM洗涤。将滤液在减压下浓缩，并使用自动化快速色谱法(55％EtOAc,45％己烷)纯化所得的粗产物，得到24％分离产率。^{1}H NMR(400MHz,$CDCl_3$)δ10.13(s,1H),8.11-7.99(m,3H),7.92(d,J＝3.1Hz,1H),7.75-7.62(m,2H),7.51(d,J＝3.2Hz,1H),4.56(s,2H),3.29(ddd,J＝12.8,8.8,6.3Hz,1H),3.11(ddd,J＝12.8,8.9,6.9Hz,1H),1.82-1.66(m,2H),1.54-1.41(m,2H),0.94(t,J＝7.3Hz,3H).ESI-MS(m/z):442.1$[M+H]^+$。

[0388] 

[0389] SW209513.2-(丁基(11-氧基)-13-巯基)-4-(4-((二甲基氨基)甲基)苯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。加入4-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)安息香醛(13.3mg,0.0301)在甲醇(802.7μL),二甲基胺(174μL,0.301mmol,2.0M in THF)和乙酸(1.72μL,0.0301mmol)中形成的溶液，并将反应物在室温下搅拌90分钟。然后将反应物冷却至0℃，加入氰基硼氢化钠(3.7mg,0.060mmol)并将反应物在该温度下搅拌2小时，然后温暖至室温。在24小时后，在0℃下加入更多的氰基硼氢化钠(2eq)，并在室温下再搅拌24小时。氮用于使溶剂蒸发，得到固体，使用EtOAc稀释该固体，并使用饱和的$NaHCO_3$洗涤。将有机层在Na_2SO_4上干燥，过滤并在减压下浓缩。使用快速色谱法纯化粗产物(7％MeOH,93％DCM)，分离13％产率的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.07(s,1H),7.93(d,J＝3.2Hz,1H),7.51(d,J＝3.2Hz,1H),7.49-7.41(m,4H),4.67(s,2H),3.55(s,2H),3.36-3.25(m,1H),3.13(ddd,J＝12.8,9.0,6.7Hz,1H),2.30(s,6H),1.78-1.68(m,2H),1.55-1.44(m,2H),0.95(t,J＝7.3Hz,3H).ESI-MS(m/z):471.2$[M+H]^+$。

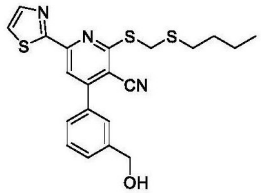
[0390] 

[0391] 甲基(E)-3-(3-氧代-3-(噻唑-2-基)丙-1-烯-1-基)安息香酸酯。用于甲基(E)-4-(3-氧代-3-(噻唑-2-基)丙-1-烯-1-基)安息香酸酯的随后的过程中，使用甲基3-甲酰基安息香酸酯作为起始材料。使用自动化快速色谱法(50％EtOAc,50％己烷)纯化粗产物，分离51％产率的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.41-8.35(m,1H),8.11-8.05(m,2H),8.02(d,J＝1.3Hz,2H),7.89-7.83(m,1H),7.72(d,J＝3.0Hz,1H),7.50(t,J＝7.8Hz,1H),3.95(s,3H).ESI-MS(m/z):274.1。

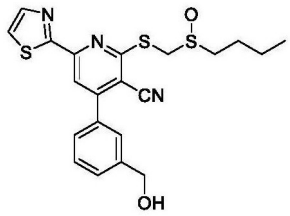
[0392] 

[0393] 甲基3-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香

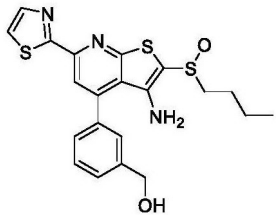
酸酯。用于甲基4-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯的随后的过程中,使用甲基(E)-3-(3-氧代-3-(噻唑-2-基)丙-1-烯-1-基)安息香酸酯作为起始材料。分离87%产率的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.32-8.26(m,1H),8.20(dt,J=7.9,1.3Hz,1H),8.04(s,1H),7.99(d,J=3.1Hz,1H),7.85(ddd,J=7.7,2.0,1.1Hz,1H),7.62(td,J=7.8,0.6Hz,1H),7.58(d,J=3.1Hz,1H),4.53(s,2H),3.95(s,3H),2.76(t,J=7.3Hz,2H),1.71-1.59(m,2H),1.49-1.36(m,2H),0.91(t,J=7.3Hz,3H).ESI-MS(m/z):456.1[M+Z]$^+$。

[0394] 

[0395] 2-(((丁基硫代)甲基)硫代)-4-(3-(羟甲基)苯基)-6-(噻唑-2-基)烟腈。用于2-(((丁基硫代)甲基)硫代)-4-(4-(羟甲基)苯基)-6-(噻唑-2-基)烟腈的随后的过程中,使用甲基3-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯作为起始材料。分离84%产率的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.00(s,1H),7.95(d,J=3.1Hz,1H),7.64-7.61(m,1H),7.58-7.52(m,2H),7.52-7.46(m,2H),4.76(s,2H),4.50(s,2H),2.74(t,J=7.3Hz,2H),1.69-1.54(m,2H),1.46-1.37(m,2H),0.90(t,J=7.3Hz,3H).ESI-MS(m/z):428.1[M+H]$^+$。

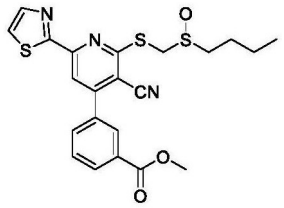
[0396] 

[0397] 2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-4-(3-(羟甲基)苯基)-6-(噻唑-2-基)烟腈。根据标准的氧化过程,使用2-(((丁基硫代)甲基)硫代)-4-(3-(羟甲基)苯基)-6-(噻唑-2-基)烟腈作为起始材料。分离88%产率的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.08(s,1H),7.96(d,J=3.1Hz,1H),7.68-7.64(m,1H),7.58-7.53(m,2H),7.53-7.48(m,2H),4.77(s,2H),4.71(d,J=13.1Hz,1H),4.36(d,J=13.1Hz,1H),2.96(dt,J=13.0,8.2Hz,1H),2.81(dt,J=13.0,7.3Hz,1H),1.82(p,J=7.7Hz,2H),1.58-1.40(m,2H),0.94(t,J=7.3Hz,3H).ESI-MS(m/z):444.1[M+H]$^+$。

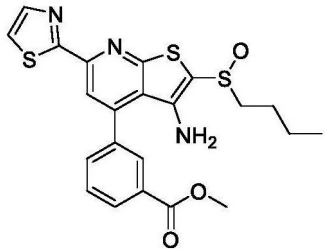
[0398] 

[0399] SW209418(3-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯基)甲醇。用于SW209510的随后的过程中,使用2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-4-(3-(羟甲基)苯基)-6-(噻唑-2-基)烟腈作为起始材料,从而以68%产率给出分离的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.01(s,1H),7.88(d,J=3.1Hz,1H),7.55-7.30

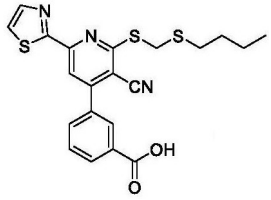
(m,5H),4.75(s,2H),4.62(s,2H),3.26(ddd,J=12.8,9.1,6.0Hz,1H),3.09(ddd,J=12.8,9.2,6.5Hz,1H),1.76-1.61(m,2H),1.51-1.38(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):444.1[M+H]$^+$。

[0400] 

[0401] 甲基3-(2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯。根据标准的氧化过程,使用甲基3-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯作为起始材料。这以86%产率给出分离的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.27(t,J=1.6Hz,1H),8.17(dt,J=7.9,1.4Hz,1H),8.09(s,1H),7.97(d,J=3.1Hz,1H),7.82(ddd,J=7.7,1.9,1.1Hz,1H),7.61(m,1H),7.58(d,J=3.1Hz,1H),4.72(d,J=13.1Hz,1H),4.42(d,J=13.1Hz,1H),3.92(s,3H),2.95(dt,J=13.0,8.1Hz,1H),2.83(dt,J=13.0,7.3Hz,1H),1.81(p,J=7.7Hz,2H),1.57-1.36(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):472.1[M+H]$^+$。

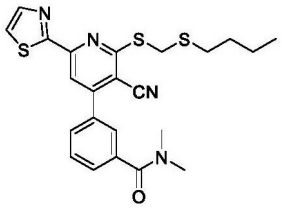
[0402] 

[0403] SW209416.甲基3-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)安息香酸酯。用于SW209510的随后的过程中,使用甲基3-(2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯作为起始材料,从而以68%产率给出分离的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.26-8.11(m,2H),8.02(s,1H),7.89(d,J=3.2Hz,1H),7.76-7.56(m,2H),7.49(d,J=3.1Hz,1H),4.54(s,2H),3.93(s,3H),3.27(ddd,J=12.8,9.0,6.2Hz,1H),3.09(ddd,J=12.8,9.0,6.7Hz,1H),1.79-1.61(m,2H),1.55-1.39(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):472.1[M+H]$^+$。

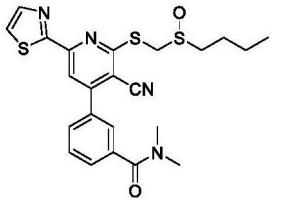
[0404] 

[0405] 酯形成羧酸的标准的水解过程:3-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)苯甲酸。将THF(214.3μL),MeOH(214.3μL),和H_2O(71.4μL)加入甲基3-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯(50mg,0.110mmol)中,最后加入LiOH(7.9mg,0.329mmol)。将溶液在室温下搅拌3小时。使用EtOAc稀释反应混合物,并使用1M HCl洗涤。将有机层在Na_2SO_4上干燥,过滤并在减压下浓缩。所得的产物给出94%产率。^{1}H NMR(400MHz,$CDCl_3$)δ8.41(t,J=1.7Hz,1H),8.26(dt,J=8.0,

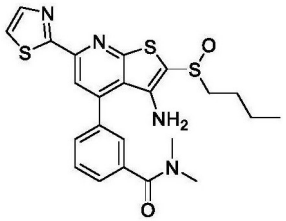
1.3Hz,1H),8.13(s,1H),8.02(d,J=3.1Hz,1H),7.94-7.89(m,1H),7.65(t,J=7.8Hz,1H),7.59(d,J=3.1Hz,1H),4.53(s,2H),2.75(t,J=7.3Hz,2H),1.64(p,J=7.5Hz,2H),1.43(m,2H),0.91(t,J=7.3Hz,3H).ESI-MS(m/z):442.1[M+Z]$^+$。

[0406] 

[0407] 标准的酰胺键偶联过程:3-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)-N,N-二甲基苯甲酰胺。将二甲基胺盐酸盐(9.25mg,0.114mmol)加入3-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)苯甲酸(45.6mg,0.103mmol),HATU(43.2mg,0.114mmol),和DMF(266μL)的溶液中,然后加入DIPEA(36μL,0.21mmol)。将溶液在室温下搅拌3小时,然后使用EtOAc稀释,并使用水洗涤。将有机层在Na_2SO_4上干燥,过滤并减压浓缩。分离固体给出86%产率。^{1}H NMR(400MHz,$CDCl_3$)δ7.99(s,1H),7.97(d,J=3.1Hz,1H),7.69-7.61(m,2H),7.58-7.51(m,3H),4.50(s,2H),3.11(s,3H),3.03(s,3H),2.73(t,J=7.3Hz,2H),1.62(p,J=7.4Hz,2H),1.40(h,J=7.3Hz,2H),0.89(t,J=7.3Hz,3H).ESI-MS(m/z):469.1[M+H]$^+$。

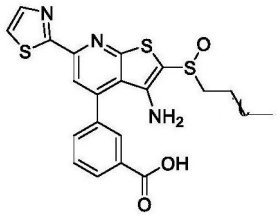
[0408] 

[0409] 3-(2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)-N,N-二甲基苯甲酰胺。根据标准的氧化过程,使用3-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)-N,N-二甲基苯甲酰胺作为起始材料,从而给出96%产率的分离产物。^{1}H NMR(400MHz,氯仿-d)δ8.08(s,1H),7.98(d,J=3.1Hz,1H),7.70-7.64(m,2H),7.61-7.54(m,3H),4.70(d,J=13.1Hz,1H),4.42(d,J=13.1Hz,1H),3.11(s,3H),3.03(s,3H),2.95(dt,J=12.9,8.2Hz,1H),2.81(dt,J=12.9,7.2Hz,1H),1.82(p,J=7.7Hz,2H),1.56-1.36(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):485.1[M+H]$^+$。

[0410] 

[0411] SW209417.3-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)-N,N-二甲基苯甲酰胺。随后的用于SW209510的过程中,使用3-(2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)-N,N-二甲基苯甲酰胺作为起始材料,从而给出63%产率的分离产物。^{1}H NMR(400MHz,氯仿-d)δ8.02(s,1H),7.90(d,J=3.1Hz,1H),7.62-7.51(m,4H),7.49(d,J=3.1Hz,1H),4.59(s,2H),3.27(ddd,J=12.8,9.0,6.1Hz,1H),3.15-2.97(m,7H),1.78-1.64(m,2H),1.55-1.39(m,2H),0.93(t,J

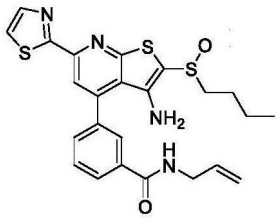
=7.3Hz,3H)。

[0412] 

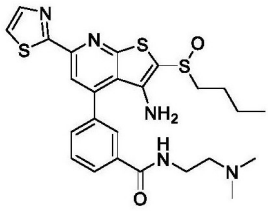
[0413] SW209419.3-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯甲酸。根据酯形成羧酸的标准的水解过程,使用SW209416作为起始材料。这给出98%分离产率。^{1}H NMR(400MHz,$(CD_3)_2CO$))δ8.28-8.18(m,2H),8.07(s,1H),7.98(d,J=3.2Hz,1H),7.90(d,J=7.6Hz,1H),7.82(d,J=3.2Hz,1H),7.76(t,J=7.6Hz,1H),4.82(s,2H),3.20(ddd,J=12.8,8.8,6.3Hz,1H),3.09(ddd,J=12.9,8.8,6.8Hz,1H),1.76-1.66(m,2H),1.54-1.43(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):458.1$[M+H]^+$。

[0414] 

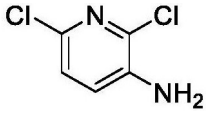
[0415] SW209420.(3-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯基)(4-甲基哌嗪-1-基)甲酮。根据标准的酰胺键偶联过程,使用SW209419作为起始材料,并使用1-甲基哌嗪作为底物。使用自动化快速色谱法纯化产物,回收38%分离产率。^{1}H NMR(400MHz,$CDCl_3$)δ8.04(s,1H),7.91(d,J=3.2Hz,1H),7.65-7.42(m,5H),4.56(s,2H),3.79(m,2H),3.46(m,2H),3.28(ddd,J=12.9,8.9,6.1Hz,1H),3.10(ddd,J=12.9,9.2,7.0Hz,1H),2.48(m,2H),2.35(m,2H),2.31(s,3H),1.77-1.58(m,2H),1.54-1.38(m,2H),0.94(t,J=7.3Hz,3H).ESI-MS(m/z):540.2$[M+H]^+$。

[0416] 

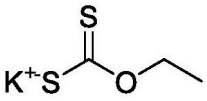
[0417] SW209508.N-allyl-3-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯甲酰胺。根据标准的酰胺键偶联过程,使用SW209419作为起始材料,并使用丙烯胺作为底物。分离产物给出92%产率。^{1}H NMR(400MHz,$CDCl_3$)δ8.05-7.91(m,3H),7.88(d,J=3.2Hz,1H),7.68-7.53(m,2H),7.48(d,J=3.1Hz,1H),6.01-5.82(m,1H),5.25(d,J=17.2Hz,1H),5.16(dd,J=10.2,1.4Hz,1H),4.52(s,2H),4.19-3.98(m,2H),3.24(ddd,J=12.8,9.0,5.9Hz,1H),3.16-2.98(m,1H),1.78-1.56(m,2H),1.57-1.38(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):497.1$[M+H]^+$。

[0418] 

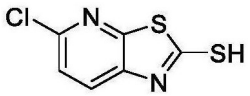
[0419] SW209509.3-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)-N-(2-(二甲基氨基)乙基)苯甲酰胺。根据标准的酰胺键偶联过程,使用SW209419作为起始材料,并使用N,n-二甲基-乙-1,2-二胺作为底物。使用EtOAc稀释反应混合物,并使用水洗涤,然后加入NaOH以中和pH。接着,将有机层在Na_2SO_4上干燥,过滤并在减压下浓缩。使用自动化快速色谱法纯化粗产物(93%DCM,2%Et_3N,5%MeOH),从而给出70%分离产率的产物。^1H NMR(400MHz,$CDCl_3$)δ8.02(s,1H),8.00-7.95(m,2H),7.88(d,J=3.2Hz,1H),7.63-7.54(m,2H),7.48(d,J=3.2Hz,1H),4.55(s,2H),3.59-3.50(m,2H),3.25(ddd,J=12.8,9.0,6.0Hz,1H),3.08(ddd,J=12.8,9.1,6.6Hz,1H),2.58(t,J=5.9Hz,2H),2.28(s,6H),1.77-1.61(m,2H),1.53-1.43(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):528.2$[M+H]^+$。

[0420] 

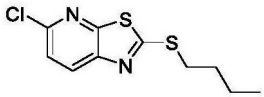
[0421] 2,6-二氯吡啶-3-胺。将丙酮/水混合物(297mL,5:1)加入2,6-二氯-3-硝基吡啶(3.0g,0.016mol)中,然后加入Zn(10.17g,0.1550mol)和NH_4Cl(12.44g,0.2325mol)。将溶液在室温下过夜搅拌。接着通过硅藻土过滤反应混合物,并使用EtOAc萃取滤液。在生理盐水的帮助下,分离有机层,在$MgSO_4$上干燥,并减压浓缩。^1H NMR(400MHz,$CDCl_3$)δ7.07(d,J=8.2Hz,1H),7.02(d,J=8.3Hz,1H),4.11(s,2H).ESI-MS(m/z):163.0。

[0422] 

[0423] 乙基黄原酸钾。通过将KOH(6.5g,0.12mol)溶解于EtOH(63.4mL)中制备乙醇钾溶液。在缓慢的连续的搅拌下,将二硫化碳(7.14mL,0.118mol)加入溶液中。将反应混合物冷却至5℃,过滤并由温暖的乙醇2次重结晶沉淀物。

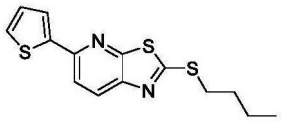
[0424] 

[0425] 5-氯代噻唑并[5,4-b]吡啶-2-硫醇。在N_2下,将乙基黄原酸钾(1.9g,0.012mol)和无水N-甲基-2-吡咯烷酮(14.1mL)加入2,6-二氯吡啶-3-胺(1.0g,0.0061mol)中。将溶液回流(170ºC)3.5小时。将反应混合物冷却至室温,使用AcOH酸化至pH 5,在EtOAc中稀释,并使用H_2O多次洗涤。分离有机层,在$MgSO_4$上干燥,并在减压下浓缩。这给出18%产率的红色固体。^1H NMR(400MHz,氯仿-d)δ7.41(d,J=8.4Hz,1H),7.30(d,J=8.4Hz,1H).ESI-MS(m/z):202.9。

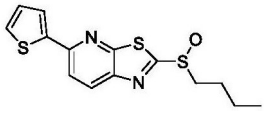
[0426] 

[0427] 2-(丁基硫代)-5-氯代噻唑并[5,4-b]吡啶。将K_2CO_3(75mg,0.54mmol),1-溴丁烷

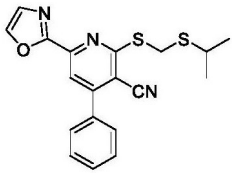
(53.3μL,0.493mmol),18-Crown-6(13.2mg,0.0493mmol),和DMF(3.4mL)加入5-氯代噻唑并[5,4-b]吡啶-2-硫醇中,并将溶液在80℃下加热3小时。使用EtOAc稀释溶液,使用H_2O洗涤,并分离有机层,在$MgSO_4$上干燥,再在减压下浓缩。使用快速色谱法纯化粗产物,从而给出76%分离产率。^1H NMR(400MHz,$CDCl_3$)δ7.93(d,J=8.5Hz,1H),7.30(d,J=8.5Hz,1H),3.31(t,J=7.3Hz,2H),1.76(p,J=7.5Hz,2H),1.52-1.39(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):259.0$[M+H]^+$。

[0428] 

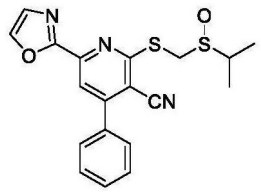
[0429] 2-(丁基硫代)-5-(苯硫-2-基)噻唑并[5,4-b]吡啶。在N_2下,将2-噻吩基硼酸(49.4mg,0.386mmol),$CsCO_3$(126mg,0.386mmol),Pd(dppf)Cl_2(15.8mg,0.0193mmol),CuCl(19.1mg,0.193mmol)和DMF(1mL)加入2-(丁基硫代)-5-氯代噻唑并[5,4-b]吡啶(50mg,0.19mmol)中。将反应混合物在100℃下加热30分钟。然后,中断N_2,将小瓶盖上盖子,并使用铁氟龙胶带密封,再将其过夜搅拌。将反应混合物在EtOAc中稀释,使用H_2O洗涤,并分离有机层,在$MgSO_4$上干燥,过滤并在减压下浓缩,从而给出31%分离产率的产物。^1H NMR(400MHz,$CDCl_3$)δ7.98(d,J=8.6Hz,1H),7.63(dd,J=3.8,1.1Hz,1H),7.51(dd,J=5.1,1.1Hz,1H),7.23(d,J=8.6Hz,1H),7.14(dd,J=5.0,3.8Hz,1H),3.24(t,J=7.3Hz,2H),1.78-1.66(m,2H),1.57-1.41(m,2H),0.96(t,J=7.4Hz,3H).ESI-MS(m/z):307.0$[M+H]^+$。

[0430] 

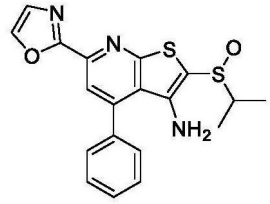
[0431] SW208599.2-(丁基(11-氧基)-13-巯基)-5-(苯硫-2-基)噻唑并[5,4-b]吡啶。将$CHCl_3$(142μL),AcOH(142μL),和H_2O_2(12.0μL,0.118mmol,在H_2O中30%溶液)加入2-(丁基硫代)-5-(苯硫-2-基)噻唑并[5,4-b]吡啶(18mg.0.059mmol)中,并在35℃下加热2.5小时。使用EtOAc稀释溶液,并使用饱和的$NaHCO_3$洗涤。分离有机层,在$MgSO_4$上干燥,过滤并在减压下浓缩,从而给出60%分离产率的产物。^1H NMR(400MHz,$CDCl_3$)δ8.39(d,J=8.4Hz,1H),8.06(d,J=8.4Hz,1H),7.74(dd,J=3.8,1.1Hz,1H),7.61(dd,J=5.0,1.1Hz,1H),7.19(dd,J=5.0,3.8Hz,1H),3.15(ddd,J=13.3,9.8,6.0Hz,1H),2.96(ddd,J=13.3,9.9,4.9Hz,1H),1.98-1.80(m,1H),1.60-1.52(m,1H),1.52-1.37(m,2H),0.93(t,J=7.2Hz,3H).ESI-MS(m/z):323.0$[M+H]^+$。

[0432] 

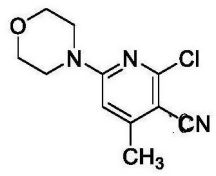
[0433] 2-(((异丙基硫代)甲基)硫代)-6-(恶唑-2-基)-4-苯基烟腈。根据标准的烷基化过程,使用(氯代甲基)(异丙基)硫烷作为烷基化底物,并使用6-(恶唑-2-基)-4-苯基-2-硫代-1,2-二氢吡啶-3-腈作为起始材料。使用快速色谱法纯化粗产物,从而给出62%分离产率的固体。^1H NMR(400MHz,$CDCl_3$)δ7.97(s,1H),7.88(d,J=0.7Hz,1H),7.67-7.61(m,2H),7.56-7.50(m,3H),7.37(d,J=0.8Hz,1H),4.63(s,2H),3.24(hept,J=6.7Hz,1H),1.35(d,J=6.7Hz,6H).ESI-MS(m/z):368.0$[M+H]^+$。

[0434] 

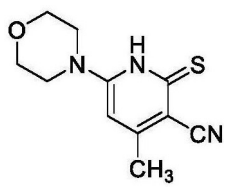
[0435] 2-(((异丙基(11-氧基)-13-巯基)甲基)硫代)-6-(恶唑-2-基)-4-苯基烟腈。根据标准的氧化过程,使用2-(((异丙基硫代)甲基)硫代)-6-(恶唑-2-基)-4-苯基烟腈作为起始材料。回收定量的分离产率。^{1}H NMR(400MHz,$CDCl_3$)δ8.03(s,1H),7.88(d,J=0.7Hz,1H),7.67-7.61(m,2H),7.58-7.50(m,3H),7.39(d,J=0.7Hz,1H),4.79(d,J=13.3Hz,1H),4.55(d,J=13.3Hz,1H),3.18(hept,J=6.9Hz,1H),1.42(d,J=1.5Hz,3H),1.40(d,J=1.3Hz,3H).ESI-MS(m/z):384.1$[M+H]^+$。

[0436] 

[0437] 标准的最后的环化过程:SW208660.2-(异丙基(11-氧基)-13-巯基)-6-(恶唑-2-基)-4-苯基噻吩并[2,3-b]吡啶-3-胺。将DMF(485μL)和MeOH(244μL)加入2-(((异丙基(11-氧基)-13-巯基)甲基)硫代)-6-(恶唑-2-基)-4-苯基烟腈(47.2mg,0.123mmol)中,使其完全溶解,然后将KOH(4.1mg,处于100μL H_2O中)加入溶液中。将反应混合物在35℃下搅拌40分钟。使用EtOAc稀释反应混合物,使用10%AcOH洗涤,然后使用H_2O多次洗涤。分离有机层,在$MgSO_4$上干燥,过滤并在减压下浓缩。使用快速色谱法纯化粗产物,从而给出40%分离产率的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.99(s,1H),7.85(d,J=0.7Hz,1H),7.56-7.44(m,5H),7.34(d,J=0.8Hz,1H),4.69(s,2H),3.41(hept,J=6.8Hz,1H),1.44(d,J=6.8Hz,3H),1.28(d,J=6.9Hz,3H).ESI-MS(m/z):384.1$[M+H]^+$。

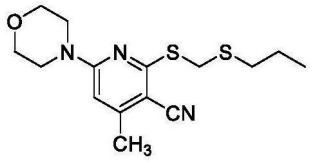
[0438] 

[0439] 2-氯代-4-甲基-6-吗啉烟腈。在N_2下,将无水MeOH(3.97mL)加入2,6-二氯-4-甲基烟腈(500mg,2.67mmol)中,并将混合物冷却至0℃。将吗啉(473.7μL,5.493mmol)滴加至溶液中,并将溶液在室温下过夜搅拌。过滤反应混合物,使用MeOH(500μL)和H_2O(3-4mL)洗涤沉淀物。将DCM加入沉淀物中,然后加入$MgSO_4$,过滤溶液,然后在减压下浓缩。使用自动化快速色谱法纯化粗产物,从而给出85%分离产率的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.26(s,1H),3.81-3.73(m,4H),3.68-3.58(m,4H),2.42(d,J=0.8Hz,3H).ESI-MS(m/z):238.1$[M+H]^+$。

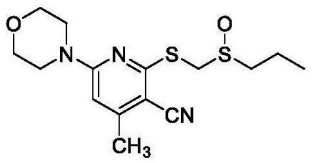
[0440] 

[0441] 4-甲基-6-吗啉-2-硫代-1,2-二氢吡啶-3-腈。将NaOME(73.6mg,1.36mmol)和3-巯

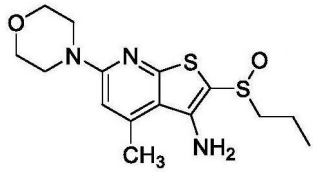
基丙酸甲酯(151μL,1.363mmol)加入2-氯代-4-甲基-6吗啉烟腈(324mg,1.36mmol)在DMF(4.10mL)中形成的溶液中,并将反应混合物在80℃下搅拌1小时。一旦冷却,便使用EtOAc稀释反应混合物,并使用H_2O洗涤。分离有机层,在MgSO4上干燥,过滤并在减压下浓缩,从而给出起始材料与产物为1:1的混合物粗品,使该粗品进入下一步骤中。ESI(m/z):322.1[M+H]+。在N2下,将NaH(150.8mg,3.769mmol,在矿物油中60%)和THF(10mL)加入火焰干燥瓶中,然后将得自之前的步骤的粗产物溶解于THF(10mL)中。使反应混合物回流6小时,加入NaH(2eq),并使其过夜回流。然后加入EtOH(1.5mL),并在减压下将反应混合物浓缩。加入H_2O(8mL),并使用浓HCl将溶液调节至pH 6,然后过滤,从而得到进入下一步骤的固体粗品。ESI(m/z):236.1[M+H]+。

[0442] 

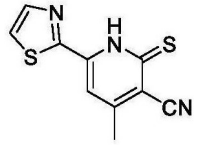
[0443] 4-甲基-6-吗啉-2-(((丙基硫代)甲基)硫代)烟腈。根据标准的烷基化过程,使用4-甲基-6-吗啉-2-硫代-1,2-二氢吡啶-3-腈作为起始材料,并使用(氯代甲基)(丙基)硫烷作为烷基化底物。使粗产物进入下一步骤。ESI(m/z):324.1[M+H]+。

[0444] 

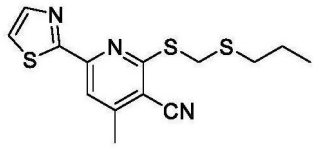
[0445] 2-((((11-氧基)(丙基)-13-巯基)甲基)硫代)-4-甲基-6-吗啉烟腈。根据标准的氧化过程,使用4-甲基-6-吗啉-2-(((丙基硫代)甲基)硫代)烟腈作为起始材料。使粗产物进入下一步骤。ESI(m/z):340.1$[M+H]^+$。

[0446] 

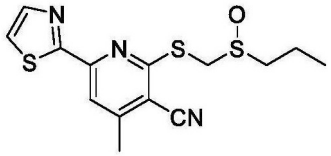
[0447] SW208663.2-((11-氧基)(丙基)-13-巯基)-4-甲基-6-吗啉噻吩并[2,3-b]吡啶-3-胺。根据标准的最后的环化过程,使用2-((((11-氧基)(丙基)-13-巯基)甲基)硫代)-4-甲基-6-吗啉烟腈作为起始材料。通过快速色谱法和PTLC纯化粗产物,从而给出10%产率的分离产物。^1H NMR(400MHz,$CDCl_3$)δ6.36(s,1H),4.91(s,2H),3.85-3.76(m,4H),3.63-3.58(m,4H),3.32-3.18(m,1H),3.09-2.99(m,1H),2.65(s,3H),1.81-1.66(m,2H),1.07(t,J=7.4Hz,3H).ESI(m/z):340.1$[M+H]^+$。

[0448] 

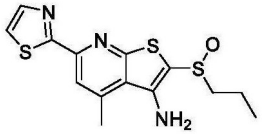
[0449] 4-甲基-6-(噻唑-2-基)-2-硫代-1,2-二氢吡啶-3-腈。在与4-甲基-6-吗啉-2-硫代-1,2-二氢吡啶-3-腈相同的过程后,使用甲基3-((3-氰基-4-甲基-6-(噻唑-2-基)吡啶-2-基)硫代)丙酸酯作为起始材料。使粗产物进入下一步骤。ESI-MS(m/z):234.0$[M+H]^+$。

[0450] 

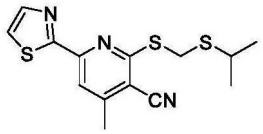
[0451] 4-甲基-2-(((丙基硫代)甲基)硫代)-6-(噻唑-2-基)烟腈。根据标准的烷基化过程,使用4-甲基-6-(噻唑-2-基)-2-硫代-1,2-二氢吡啶-3-腈作为起始材料,并使用(氯代甲基)(丙基)硫烷作为烷基化底物。使用自动化快速色谱法纯化粗产物,从而给出23%分离产率的产物。^{1}H NMR(400MHz,氯仿-d)δ7.96(d,J=3.1Hz,1H),7.83(s,1H),7.54(d,J=3.1Hz,1H),4.47(s,2H),2.70(t,J=7.2Hz,2H),2.55(s,3H),1.67(h,J=7.3Hz,2H),0.99(t,J=7.3Hz,3H).ESI-MS(m/z):322.0{M+H]$^+$。

[0452] 

[0453] 2-((((11-氧基)(丙基)-13-巯基)甲基)硫代)-4-甲基-6-(噻唑-2-基)烟腈。根据标准的氧化过程,使用4-甲基-2-(((丙基硫代)甲基)硫代)-6-(噻唑-2-基)烟腈作为起始材料,从而给出91%分离产率的白色固体。^{1}H NMR(400MHz,$CDCl_3$)δ7.97(d,J=3.1Hz,1H),7.92(s,1H),7.56(d,J=3.2Hz,1H),4.74(d,J=13.2Hz,1H),4.44(d,J=13.1Hz,1H),2.89(m,2H),2.57(s,3H),1.93-1.79(m,2H),1.06(t,J=7.4Hz,3H).ESI-MS(m/z):338.0[M+H]$^+$。

[0454] 

[0455] SW208661.2-((11-氧基)(丙基)-13-巯基)-4-甲基-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。根据标准的最后的环化过程,使用2-((((11-氧基)(丙基)-13-巯基)甲基)硫代)-4-甲基-6-(噻唑-2-基)烟腈作为起始材料。使用快速色谱法纯化粗产物,从而给出61%亮绿色分离产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.95(s,1H),7.93(d,J=3.2Hz,1H),7.48(d,J=3.2Hz,1H),5.16(s,2H),3.37-3.23(m,1H),3.16-3.05(m,1H),2.85(s,3H),1.83(h,J=7.5Hz,2H),1.11(t,J=7.4Hz,3H).ESI-MS(m/z):338.0[M+H]$^+$。

[0456] 

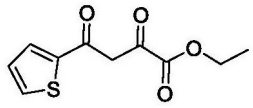
[0457] 2-(((异丙基硫代)甲基)硫代)-4-甲基-6-(噻唑-2-基)烟腈。根据标准的烷基化过程,使用(氯代甲基)(异丙基)硫烷作为烷基化底物,并使用4-甲基-6-(噻唑-2-基)-2-硫代-1,2-二氢吡啶-3-腈作为起始材料。使用自动化快速色谱法纯化,从而给出32%分离产率的产物。^{1}H NMR(400MHz,CDCl3)δ7.94(d,J=3.2Hz,1H),7.82(s,1H),7.52(d,J=3.2Hz,1H),4.48(s,2H),3.18(hept,J=6.6Hz,1H),2.54(s,3H),1.31(d,J=6.7Hz,6H).ESI-MS(m/z):322.0[M+H]+。

[0458] 

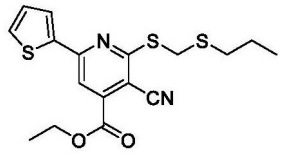
[0459] 2-(((异丙基(11-氧基)-13-巯基)甲基)硫代)-4-甲基-6-(噻唑-2-基)烟腈。根据标准的氧化过程,使用2-(((异丙基硫代)甲基)硫代)-4-甲基-6-(噻唑-2-基)烟腈作为起始材料,从而给出84%固体产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.97(d,J=3.1Hz,1H),7.91(s,1H),7.56(d,J=3.1Hz,1H),4.57(d,J=13.3Hz,1H),4.46(d,J=13.3Hz,1H),3.05(hept,J=6.9Hz,1H),2.57(s,3H),1.38(d,J=7.1Hz,3H),1.36(d,J=6.7Hz,3H).ESI-MS(m/z):338.0$[M+H]^+$。

[0460] 

[0461] SW208664.2-(异丙基(11-氧基)-13-巯基)-4-甲基-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。根据标准的最后的环化过程,使用2-(((异丙基(11-氧基)-13-巯基)甲基)硫代)-4-甲基-6-(噻唑-2-基)烟腈作为起始材料。使用快速色谱法纯化粗产物,从而以48%分离产率给出亮绿色油/固体。^{1}H NMR(400MHz,氯仿-d)δ7.93(s,1H),7.92(d,J=3.2Hz,1H),7.46(d,J=3.2Hz,1H),3.38(hept,J=6.9Hz,1H),2.84(s,3H),1.46(d,J=6.8Hz,3H),1.29(d,J=6.8Hz,3H).ESI-MS(m/z):338.0$[M+H]^+$。

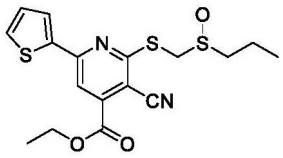
[0462] 

[0463] 乙基2,4-二氧-4-(苯硫-2-基)丁酸酯。将2-乙酰基噻吩(1.71mL,0.0159mol)加入NaOEt(730mg Na立方体,处于50mL EtOH中)的溶液中,并将溶液在0℃冷却1-2小时,然后将二乙氧基化物(3.2mL)加入溶液中。使该溶液在室温下过夜搅拌。使用EtOAc和H_2O、以及少量生理盐水稀释反应混合物。以有助于分离。收集有机层,使用$MgSO_4$干燥,过滤并在减压下浓缩。使用自动化快速色谱法纯化粗产物,从而给出23%产率的油状产物。ESI-MS(m/z):227.0$[M+H]^+$。

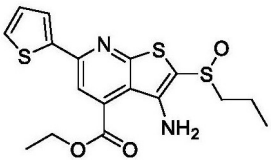
[0464] 

[0465] 乙基3-氰基-2-(((丙基硫代)甲基)硫代)-6-(苯硫-2-基)异烟酸酯。在温和加热(40℃)下,将2-氰基硫代乙酰胺(250.6mg,2.503mmol)和乙基2,4-二氧-4-(苯硫-2-基)丁酸酯(565.7mg,2.503mmol)溶解于EtOH(7.46mL)中,然后将Et_3N(174.5μL,1.251mmol)滴加至搅拌溶液中。将反应混合物在60℃下加热,并在3小时后在减压下浓缩,并使粗产物进入下一步骤中。根据标准的烷基化过程,使用乙基3-氰基-6-(苯硫-2-基)-2-硫代-1,2-二氢吡啶-4-羧酸酯作为起始材料,并使用(氯代甲基)(丙基)硫烷作为烷基化试剂。使用自动化快速色谱法(20%EtOAc,80%己烷)2次纯化粗产物,从而给出34%分离产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.70(s,1H),7.60(dd,J=3.8,1.1Hz,1H),7.44(dd,J=5.1,1.1Hz,1H),

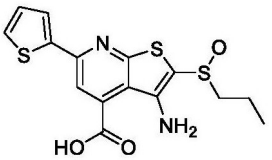
7.04(dd,J＝5.0,3.8Hz,1H),4.38(q,J＝7.2Hz,2H),4.32(s,2H),2.59(t,J＝7.2Hz,2H),1.57(h,J＝7.4Hz,2H),1.36(t,J＝7.1Hz,3H),0.89(t,J＝7.3Hz,3H).ESI-MS(m/z):378.9[M+H]$^+$。

[0466] 

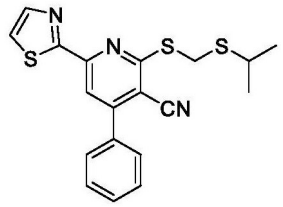
[0467] 乙基2-((((11-氧基)(丙基)-13-巯基)甲基)硫代)-3-氰基-6-(苯硫-2-基)异烟酸酯。根据标准的氧化过程,使用乙基3-氰基-2-(((丙基硫代)甲基)硫代)-6-(苯硫-2-基)异烟酸酯作为起始材料,从而给出具有定量产率的固体。^{1}H NMR(400MHz,$CDCl_3$)δ7.86(s,1H),7.72(dd,J＝3.8,1.1Hz,1H),7.53(dd,J＝5.0,1.1Hz,1H),7.11(dd,J＝5.0,3.8Hz,1H),4.68(d,J＝13.2Hz,1H),4.49(d,J＝13.2Hz,1H),4.43(q,J＝7.1Hz,2H),2.96-2.82(m,2H),1.87-1.75(m,2H),1.40(t,J＝7.2Hz,3H),1.02(t,J＝7.4Hz,3H).ESI-MS(m/z):394.9[M+H]$^+$。

[0468] 

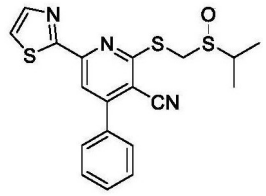
[0469] SW208781.乙基2-((11-氧基)(丙基)-13-巯基)-3-氨基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-4-羧酸酯。将t-BuOK(74.1mg,0.661mmol)加入乙基2-((((11-氧基)(丙基)-13-巯基)甲基)硫代)-3-氰基-6-(苯硫-2-基)异烟酸酯(433.7mg,1.101mmol)在DMF(4.3mL)中形成的溶液中,并将该溶液在35℃下搅拌40分钟。加入更多的t-BuOK(74.1mg,0.661mmol),并使其在35℃下搅拌1小时。使用EtOAc稀释反应混合物,并使用10％AcOH洗涤,然后使用H_2O多次洗涤。分离有机层,在$MgSO_4$上干燥,过滤并在减压下浓缩。使用快速色谱法纯化粗产物,从而以30％分离产率给出产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.01(s,1H),7.69(dd,J＝3.8,1.1Hz,1H),7.46(dd,J＝5.0,1.1Hz,1H),7.11(dd,J＝5.0,3.8Hz,1H),6.09(s,2H),4.49(q,J＝7.1Hz,2H),3.36-3.22(m,1H),3.15-3.00(m,1H),1.87-1.68(m,2H),1.47(t,J＝7.1Hz,3H),1.07(t,J＝7.4Hz,3H).ESI-MS(m/z):394.9[M+H]$^+$。

[0470] 

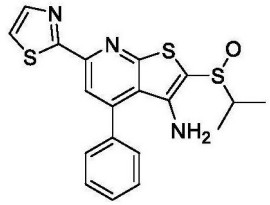
[0471] SW208782.2-((11-氧基)(丙基)-13-巯基)-3-氨基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-4-羧酸。根据标准的水解过程,使用SW208781作为起始材料,其以40％分离产率给出产物。^{1}H NMR(400MHz,C_3D_7NO)δ8.56(s,1H),8.29(d,J＝3.7Hz,1H),8.19(s,1H),7.99(d,J＝5.0Hz,1H),7.47-7.41(m,1H),3.36(ddd,J＝12.8,8.4,6.1Hz,1H),3.24(ddd,J＝12.8,8.6,6.8Hz,1H),1.98-1.85(m,2H),1.23(t,J＝7.4Hz,3H).ESI-MS(m/z):366.8。

[0472] 

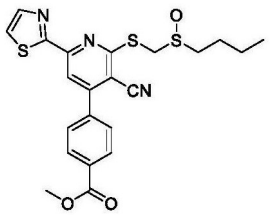
[0473] 2-(((异丙基硫代)甲基)硫代)-4-苯基-6-(噻唑-2-基)烟腈。根据标准的烷基化过程,使用4-苯基-6-(噻唑-2-基)-2-硫代-1,2-二氢吡啶-3-腈作为起始材料,并使用(氯代甲基)(异丙基)硫烷作为烷基化试剂。使用自动化快速色谱法纯化所述的物质,从而以72%分离产率给出产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.03(s,1H),7.98(d,J=3.1Hz,1H),7.70-7.62(m,2H),7.57(d,J=3.1Hz,1H),7.56-7.48(m,3H),4.56(s,2H),3.24(hept,J=6.7Hz,1H),1.36(d,J=6.7Hz,6H).ESI-MS(m/z):383.9。

[0474] 

[0475] 2-(((异丙基(11-氧基)-13-巯基)甲基)硫代)-4-苯基-6-(噻唑-2-基)烟腈。根据标准的氧化过程,使用2-(((异丙基硫代)甲基)硫代)-4-苯基-6-(噻唑-2-基)烟腈作为起始材料。其以91%产率给出白色固体产物。^{1}HNMR(400MHz,$CDCl_3$)δ8.12(s,1H),8.00(d,J=3.1Hz,1H),7.70-7.63(m,2H),7.60(d,J=3.1Hz,1H),7.58-7.51(m,3H),4.63(d,J=13.2Hz,1H),4.48(d,J=13.2Hz,1H),3.09(hept,J=6.9Hz,1H),1.42(d,J=10.5Hz,3H),1.39(d,J=10.5Hz,3H).ESI-MS(m/z):399.9。

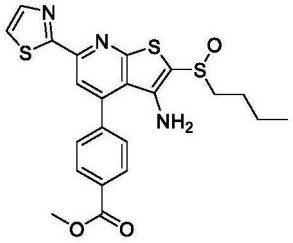
[0476] 

[0477] SW208780.2-(异丙基(11-氧基)-13-巯基)-4-苯基-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-3-胺。将t-BuOK(2.5mg,0.023mmol)加入2-(((异丙基(11-氧基)-13-巯基)甲基)硫代)-4-苯基-6-(噻唑-2-基)烟腈(15mg,0.038mmol)在DMF(148μL)中形成的溶液中,并在35℃下搅拌40分钟。使用EtOAc稀释反应混合物,并使用10%AcOH洗涤,然后使用H_2O多次洗涤。将有机层在$NaSO_4$上干燥,过滤并在减压下浓缩。使用快速色谱法纯化粗产物,从而以75%产率给出产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.05(s,1H),7.91(d,J=3.2Hz,1H),7.57-7.42(m,6H),4.68(s,2H),3.47-3.33(m,1H),1.44(d,J=6.8Hz,3H),1.27(d,J=6.8Hz,3H).ESI-MS(m/z):399.9。

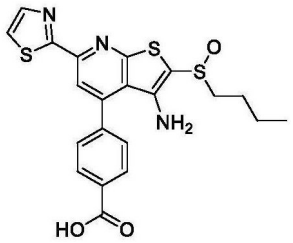
[0478] 

[0479] 甲基4-(2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡

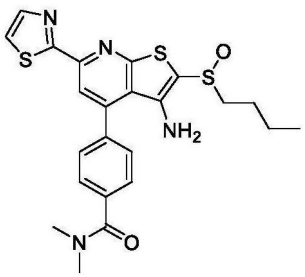
啶-4-基)安息香酸酯。根据标准的氧化过程,使用甲基4-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯作为起始材料,从而以98%分离产率给出白色固体。^{1}H NMR(400MHz,$CDCl_3$)δ8.15(d,J=8.3Hz,2H),8.05(s,1H),7.95(d,J=3.1Hz,1H),7.68(d,J=8.3Hz,2H),7.57(d,J=3.1Hz,1H),4.68(d,J=13.1Hz,1H),4.42(d,J=13.1Hz,1H),3.91(s,3H),3.01-2.86(m,1H),2.87-2.74(m,1H),1.88-1.72(m,2H),1.55-1.35(m,2H),0.91(t,J=7.3Hz,3H).ESI-MS(m/z):472.1$[M+H]^+$。

[0480] 

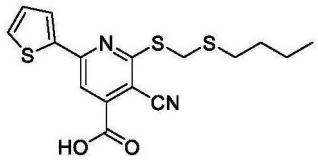
[0481] SW209127.甲基4-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)安息香酸酯。将t-BuOK(21.8mg,0.194mmol)加入处于DMF(1.30mL)中的甲基4-(2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)安息香酸酯(152.8mg,0.3239mmol)中,并将溶液在35℃下搅拌40分钟。使用EtOAc稀释反应混合物,并使用10%AcOH洗涤,在使用H_2O多次洗涤。分离有机层,在Na_2SO_4上干燥,过滤并在减压下浓缩。使用自动化快速色谱法纯化粗产物,从而以66%分离产率给出亮绿色产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.19(d,J=7.5Hz,2H),8.04(s,1H),7.91(d,J=3.2Hz,1H),7.67-7.54(m,2H),7.50(d,J=3.2Hz,1H),3.97(s,3H),3.27(ddd,J=12.8,8.9,6.2Hz,1H),3.10(ddd,J=12.8,9.0,6.8Hz,1H),1.81-1.63(m,2H),1.54-1.39(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):472.1$[M+H]^+$。

[0482] 

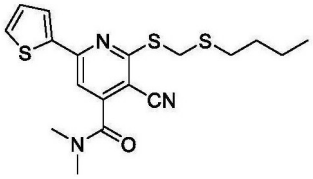
[0483] SW209281.4-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯甲酸。根据标准的水解过程,使用SW209127作为起始材料,从而以84%分离产率给出亮绿色固体。^{1}H NMR(400MHz,$CDCl_3$)δ8.16(d,J=8.4Hz,2H),8.05(s,1H),7.95(d,J=3.2Hz,1H),7.68-7.55(m,2H),7.52(d,J=3.2Hz,1H),3.40-3.24(m,1H),3.24-3.04(m,1H),1.83-1.65(m,2H),1.55-1.37(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):458.1$[M+H]^+$。

[0484] 

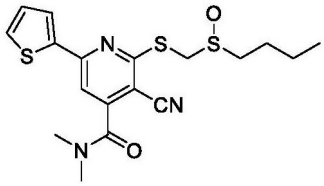
[0485] SW209282.4-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)-N,N-二甲基苯甲酰胺。根据标准的酰胺键偶联过程,使用SW209281作为起始材料,并使用二甲基胺盐酸盐作为偶联试剂。使用自动化快速色谱法(20%己烷,80%EtOAc)纯化产物,从而以59%分离产率给出亮绿色固体。^{1}H NMR(400MHz,$CDCl_3$)δ8.03(s,1H),7.91(d,J=3.2Hz,1H),7.66-7.44(m,5H),3.36-3.21(m,1H),3.14(s,3H),3.13-3.06(m,1H),3.02(s,3H),1.81-1.64(m,2H),1.55-1.41(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):485.1$[M+H]^+$。

[0486] 

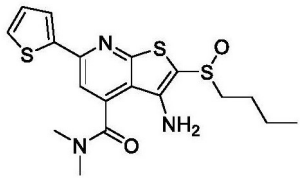
[0487] 2-(((丁基硫代)甲基)硫代)-3-氰基-6-(苯硫-2-基)异烟酸。根据标准的水解过程,使用乙基2-(((丁基硫代)甲基)硫代)-3-氰基-6-(苯硫-2-基)异烟酸酯作为起始材料,从而以94%产率给出分离产物。^{1}H NMR(400MHz,$CDCl_3$)δ10.65(s,1H),7.95(s,1H),7.76(dd,J=3.8,1.1Hz,1H),7.57(dd,J=5.0,1.0Hz,1H),7.17(dd,J=5.0,3.7Hz,1H),4.46(s,2H),2.72(t,J=7.2Hz,2H),1.67-1.55(m,2H),1.40(h,J=7.4Hz,2H),0.90(t,J=7.3Hz,3H).ESI-MS(m/z):365.0$[M+H]^+$。

[0488] 

[0489] 2-(((丁基硫代)甲基)硫代)-3-氰基-N,N-二甲基-6-(苯硫-2-基)异烟酰胺。根据标准的酰胺键偶联过程,使用作为起始材料,并使用二甲基胺作为偶联试剂。使用自动化快速色谱法(20%EtOAc,80%己烷)纯化粗材料,从而以53%分离产率给出产物。^{1}H NMR(400MHz,氯仿-d)δ7.67(d,J=3.8Hz,1H),7.54(d,J=5.0Hz,1H),7.34(s,1H),7.15(t,J=4.8,3.9,0.7Hz,1H),4.49(s,2H),3.16(s,3H),2.98(s,3H),2.72(t,2H),1.62(p,J=7.7Hz,2H),1.41(h,J=7.3Hz,2H),0.90(t,J=7.7,7.0Hz,3H).ESI-MS(m/z):392.1$[M+H]^+$。

[0490] 

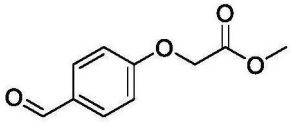
[0491] 2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-N,N-二甲基-6-(苯硫-2-基)异烟酰胺。根据标准的氧化过程,使用2-(((丁基硫代)甲基)硫代)-3-氰基-N,N-二甲基-6-(苯硫-2-基)异烟酰胺作为起始材料,从而以85%分离产率给出固体产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.67(d,J=3.8Hz,1H),7.54(d,J=5.0Hz,1H),7.34(s,1H),7.20-7.06(m,1H),4.49(s,2H),3.16(s,3H),2.98(s,3H),2.72(t,2H),1.62(p,J=7.7Hz,2H),1.41(h,J=7.3Hz,2H),0.90(t,J=7.7,7.0Hz,3H).ESI-MS(m/z):408.1$[M+H]^+$。

[0492] 

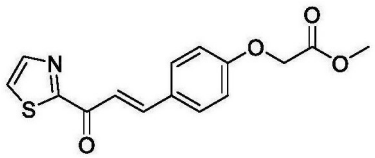
[0493] SW209283.3-氨基-2-(丁基(11-氧基)-13-巯基)-N,N-二甲基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-4-甲酰胺。将t-BuOK(6.5mg,0.058mmol)加入2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-N,N-二甲基-6-(苯硫-2-基)异烟酰胺(39.2mg,0.962mmol)在DMF(380μL)中形成的溶液中,并将溶液在35℃下加热40分钟。使用EtOAc稀释反应混合物,并使用10%AcOH洗涤,然后使用H_2O多次洗涤。分离有机层,在Na_2SO_4上干燥,过滤并在减压下浓缩。使用自动化快速色谱法(20%已烷,80%EtOAc)分离粗材料,从而以20%分离产率给出最终产物。^1H NMR(400MHz,氯仿-d)δ7.66(dd,J=3.8,1.1Hz,1H),7.52-7.42(m,2H),7.13(dd,J=5.0,3.7Hz,1H),3.34-3.23(m,1H),3.21(s,3H),3.15-3.02(m,1H),2.96(s,3H),1.79-1.62(m,2H),1.55-1.36(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):408.1$[M+H]^+$。

[0494] 

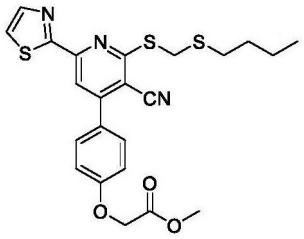
[0495] SW212366.4-(3-氨基-2-(丁基亚磺酰基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苄基二甲基甘氨酸酯。将N,N-二甲基甘氨酸(3.5mg,0.034mmol),1-乙基-3-(3-二甲基氨基丙基)碳二亚胺(6.5mg,0.034mmol),和DMAP(4.1mg,0.0334mmol)加入SW209510(10mg,0.023mmol)中,并使其溶解于DMF(270μL)中。将反应混合物在室温过夜搅拌,然后使用1M NaOH中和,并使用H_2O洗涤,再使用EtOAc萃取。将有机层在Na_2SO_4上干燥,过滤并在减压下浓缩。使用快速色谱法(7%MeOH,93%DCM)纯化粗产物,从而给出定量产率的绿色固体产物。^1H NMR(400MHz,$CDCl_3$)δ8.02(s,1H),7.90(d,J=3.2Hz,1H),7.56-7.43(m,5H),5.25(s,2H),4.61(s,2H),3.35-3.27(m,1H),3.26(s,2H),3.16-3.04(m,1H),2.37(s,6H),1.78-1.63(m,2H),1.55-1.39(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):529.1$[M+H]^+$。

[0496] 

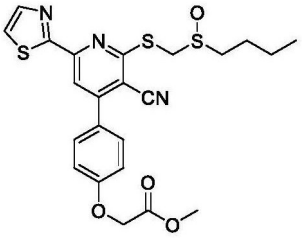
[0497] 甲基2-(4-甲酰基苯氧基)乙酸酯。向4-羟基安息香醛(3.0g,25mmol)在丙酮(61.4mL)中形成的溶液中,加入K_2CO_3(5.43g,39.3mmol),并将混合物强力搅拌。加入甲基硫代乙酸酯(2.8mL,29mmol),并将混合物在室温下搅拌3.5小时。在减压下浓缩反应混合物,然后使用H_2O洗涤,并使用EtOAc萃取。分离有机层,在Na_2SO_4上干燥,过滤并浓缩,从而给出在真空下固化的82%分离产率的无色油。^1H NMR(400MHz,$CDCl_3$)δ9.87(s,1H),7.82(d,J=8.8Hz,2H),6.98(d,J=8.7Hz,2H),4.70(s,2H),3.79(s,3H).ESI-MS(m/z):195.1$[M+H]^+$。

[0498] 

甲基(E)-2-(4-(3-氧代-3-(噻唑-2-基)丙-1-烯-1-基)苯氧基)乙酸酯。在N_2下,将2-乙酰基噻唑(534μL,5.15mmol)加入甲基2-(4-甲酰基苯氧基)乙酸酯(1.0g,5.2mmol)在MeOH(11mL)中形成的溶液中。最后加入NaOMe(279mg,5.15mmol),并将反应混合物在室温下过夜搅拌。过滤反应混合物,并使用少量MeOH洗涤沉淀物,然后使用DCM稀释,并使用H_2O洗涤。分离有机相,在Na_2SO_4上干燥,过滤并在减压下浓缩。这给出21%分离产率的固体产物。^1H NMR(400MHz,氯仿-d)δ8.03(d,J=3.0Hz,1H),7.95(d,J=15.9Hz,1H),7.82(d,J=16.0Hz,1H),7.70-7.61(m,3H),6.92(d,J=8.8Hz,2H),4.67(s,2H),3.80(s,3H).ESI-MS(m/z):304.1$[M+H]^+$。

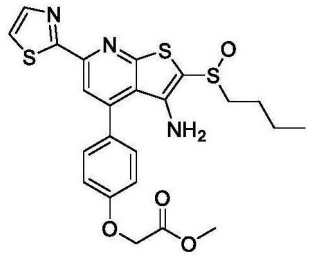
[0499] 

[0500] 甲基2-(4-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)苯氧基)乙酸酯。将EtOH(495μL)加入2-氰基硫代乙酰胺(49.5mg,0.494mmol)和甲基(E)-2-(4-(3-氧代-3-(噻唑-2-基)丙-1-烯-1-基)苯氧基)乙酸酯(50mg,0.16mmol)中,然后加入1滴哌啶。将反应混合物在80℃下加热4小时,然后在减压下浓缩,并使粗品进入下一步骤中。根据标准的烷基化过程,使用甲基2-(4-(3-氰基-6-(噻唑-2-基)-2-硫代-1,2-二氢吡啶-4-基)苯氧基)乙酸酯作为起始材料,并使用丁基(氯代甲基)硫烷作为烷基化试剂。使用自动化快速色谱法(20%EtOAc,80%己烷)纯化粗产物,从而以70%分离产率给出固体产物。^1H NMR(400MHz,$CDCl_3$)δ7.96(s,1H),7.95(d,J=3.1Hz,1H),7.62(d,J=8.8Hz,2H),7.54(d,J=3.1Hz,1H),7.02(d,J=8.8Hz,2H),4.69(s,2H),4.49(s,2H),3.81(s,3H),2.73(t,J=7.3Hz,2H),1.68-1.56(m,2H),1.46-1.34(m,2H),0.89(t,J=7.3Hz,3H).ESI-MS(m/z):486.1$[M+H]^+$。

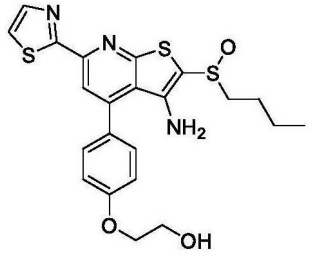
[0501] 

[0502] 甲基2-(4-(2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)苯氧基)乙酸酯。根据标准的氧化过程,使用甲基2-(4-(2-(((丁基硫代)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)苯氧基)乙酸酯作为起始材料。使用自动化快速色谱法(50%EtOAc,50%己烷)纯化粗产物。^1H NMR(400MHz,$CDCl_3$)δ7.97(s,1H),7.90(d,J=3.1Hz,1H),7.57(d,J=8.8Hz,2H),7.52(d,J=3.1Hz,1H),6.98(d,J=8.8Hz,2H),4.65(s,2H),4.62(d,J=13.1Hz,1H),4.37(d,J=13.1Hz,1H),3.75(s,3H),2.96-2.84(m,1H),

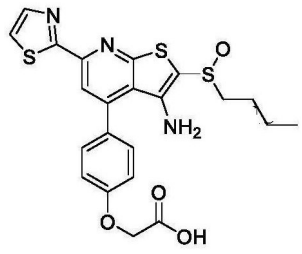
2.81-2.71(m,1H),1.76(p,J=7.6Hz,2H),1.51-1.33(m,2H),0.88(t,J=7.3Hz,3H).ESI-MS(m/z):502.1[M+H]$^+$。

[0503] 

[0504] SW212365.甲基2-(4-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯氧基)乙酸酯。将甲基2-(4-(2-(((丁基(11-氧基)-13-巯基)甲基)硫代)-3-氰基-6-(噻唑-2-基)吡啶-4-基)苯氧基)乙酸酯(80mg,0.16mmol)和t-BuOK(10.7mg,0.0954mmol)合并在小瓶中,该小瓶3次排空气体并回充N_2,然后加入DMF(627μL),并将N_2鼓泡通过溶液。将反应混合物在室温下搅拌大约10分钟,然后使用EtOAc稀释,并使用10%AcOH洗涤。使用水多次洗涤有机层,在Na_2SO_4上干燥,过滤并浓缩。使用自动化快速色谱法(30%EtOAc,70%己烷)纯化粗产物,从而以56%分离产率给出绿色固体。^{1}H NMR(400MHz,$CDCl_3$)δ7.97(s,1H),7.89-7.86(m,1H),7.47(d,J=3.1Hz,1H),7.46-7.37(m,2H),7.02(d,J=8.5Hz,2H),4.70(s,2H),4.66(s,2H),3.82(s,3H),3.34-3.18(m,1H),3.16-3.01(m,1H),1.77-1.64(m,2H),1.51-1.38(m,2H),0.92(t,J=7.3Hz,3H).ESI-MS(m/z):502.1[M+H]$^+$。

[0505] 

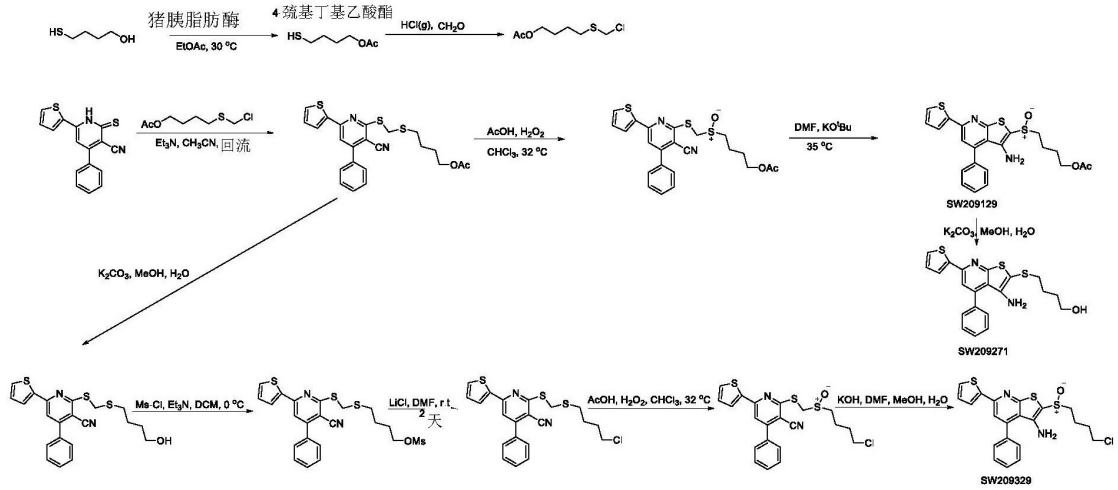
SW212364.2-(4-(3-氨基-2-(丁基(I1-氧基)-I3-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯氧基)乙-1-醇。根据用于2-(((丁基硫代)甲基)硫代)-4-(4-(羟甲基)苯基)-6-(噻唑-2-基)烟腈的相同的过程,使用SW212365作为起始材料,从而给出定量产率的所需的产物。^{1}H NMR(400MHz,$CDCl_3$)δ8.01(s,1H),7.90(d,J=3.2Hz,1H),7.48(d,J=3.1Hz,1H),7.46-7.35(m,2H),7.07-6.99(m,2H),4.69(s,2H),4.18-4.11(m,2H),4.04-3.96(m,2H),3.34-3.23(m,1H),3.17-3.04(m,1H),1.80-1.61(m,2H),1.53-1.40(m,2H),0.93(t,J=7.3Hz,3H).ESI-MS(m/z):474.1[M+H]$^+$。

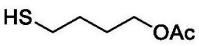
[0506] 

[0507] SW212363.2-(4-(3-氨基-2-(丁基(11-氧基)-13-巯基)-6-(噻唑-2-基)噻吩并[2,3-b]吡啶-4-基)苯氧基)乙酸。根据标准的水解过程,使用SW212365作为起始材料,从而

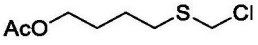
给出定量产率。^{1}H NMR(400MHz,MeOD)δ7.98(s,1H),7.94(d,J=3.2Hz,1H),7.74(d,J=3.2Hz,1H),7.46(d,J=8.4Hz,2H),7.14(d,J=8.9Hz,2H),4.67(s,2H),3.35-3.24(m,1H),3.16-3.04(m,1H),1.78-1.57(m,2H),1.55-1.43(m,2H),0.95(t,J=7.3Hz,3H).ESI-MS(m/z):488.1[M+H]$^+$。

[0508] 氯代甲基硫代醚的合成

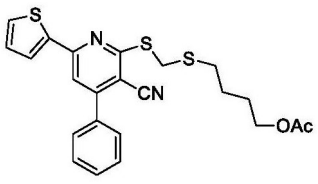
[0509] 



[0510] 4-巯基丁基乙酸酯。将猪胰脂肪酶(2.35g)加入4-巯基-1-丁醇(2.45g,23.10mmol)在乙基乙酸酯(42.0ml)中形成的溶液中。将反应物在30℃下加热6天。尽管不完全转化,但是过滤混合物并浓缩。在自动化快速色谱法系统上,在100%DCM中实施纯化,从而给出84%产率的油。^{1}H NMR(400MHz,$CHCl_3$)δ4.08(t,J=6.2Hz,2H),2.57(q,J=7.1Hz,2H),2.05(s,3H),1.85-1.59(m,4H),1.36(t,J=7.9Hz,1H)。

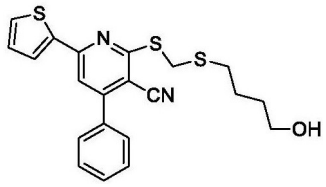
[0511] 

[0512] 4-((氯代甲基)硫代)丁基乙酸酯。在40分钟内,将氯化氢气体鼓泡至4-巯基丁基乙酸酯(2.84g,19.2mmol)中,将其在干冰/丙酮浴中冷却,直至内部温度稳定,然后使用固体加入漏斗缓慢加入多聚甲醛(0.815g,27.17mmol)。将反应物搅拌在冷的条件下搅拌3小时,在该过程中持续氯化氢鼓泡,然后当反应物温和地温暖至环境温度时终止鼓泡,并过夜搅拌。使用少量DCM稀释混合物粗品。除去水相,并使用生理盐水洗涤有机层,在Na_2SO_4上干燥,过滤并浓缩,从而给出62%产率的油。^{1}H NMR(400MHz,$CHCl_3$)4.75(s,2H),4.10(t,J=6.0Hz,2H),2.95-2.66(m,2H),2.06(s,3H),1.85-1.67(m,4H)。

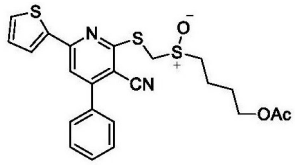
[0513] 

[0514] 4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丁基乙酸酯。将4-((氯代甲基)硫代)丁基乙酸酯(602.3mg,3.1mmol),4-苯基-6-(苯硫-2-基)-2-硫代-1,2-二氢吡啶-3-腈(352.2mg,1.2mmol)和三乙基胺(250ml,1.8mmol)在乙腈(1.2ml)中形

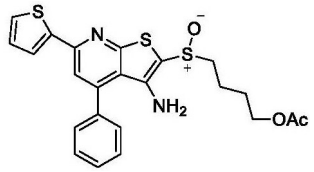
成的混合物回流3小时。然后浓缩混合物粗品，并在自动化快速色谱法系统上在0-40％EtOAc/己烷中纯化。在自动化快速色谱法上在0-30％EtOAc/己烷中进一步纯化包含所需产物的级份，从而给出41％产率的澄清的油。^{1}H NMR(400MHz,$CHCl_3$)δ7.72(dd,J＝3.7,1.1Hz,1H),7.64-7.59(m,2H),7.55(dt,J＝5.6,2.3Hz,4H),7.44(s,1H),7.17(dd,J＝5.0,3.8Hz,1H),4.55(s,2H),4.11-4.02(m,2H),2.86-2.63(m,2H),2.05(s,3H),1.77(t,J＝3.4Hz,4H).ESI-MS(m/z):455.1$[M+H]^+$。

[0515] 

[0516] 2-((((4-羟基丁基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。将K_2CO_3(157.7mg,1.14mmol)加入4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丁基乙酸酯(245.4mg,0.54mmol)在甲醇(8.0ml)和水(2.0ml)中形成的溶液中，并将反应物搅拌2小时。干燥混合物，然后使用EtOAc稀释，并使用水、接着使用生理盐水2次洗涤。将有机层在Na_2SO_4上干燥，过滤并在减压下浓缩，从而给出71％产率的所需的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.72(dd,J＝3.7,1.1Hz,1H),7.61(dd,J＝6.6,3.0Hz,2H),7.54(dd,J＝5.1,2.2Hz,4H),7.43(s,1H),7.16(dd,J＝5.0,3.8Hz,1H),4.55(s,2H),3.67(t,J＝6.2Hz,2H),2.80(t,J＝7.1Hz,2H),1.84-1.63(m,4H).ESI-MS(m/z):413.1$[M+H]^+$。

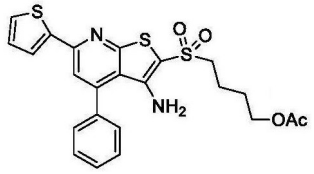
[0517] 

[0518] 4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)亚磺酰基)丁基乙酸酯。将乙酸(370μl)和过氧化氢(29μl,在水中的30％溶液)加入4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丁基乙酸酯(85.2mg,0.19mmol)在氯仿(370μl)中形成的溶液中。将反应混合物在32℃下搅拌90min。一旦反应结束，便使用氯仿稀释反应物，并使用饱和的$NaHCO_3$溶液洗涤，再使用氯仿萃取3次。将合并的有机层在Na_2SO_4上干燥，过滤并在减压下浓缩，从而给出94％产率的所设计的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.77(d,J＝3.8Hz,1H),7.62(dd,J＝4.1,2.3Hz,2H),7.60-7.54(m,4H),7.51(s,1H),7.19(dd,J＝5.0,3.8Hz,1H),4.78(d,J＝13.0Hz,1H),4.44(d,J＝13.0Hz,1H),4.11(t,J＝6.4Hz,2H),3.03(dt,J＝12.9,8.0Hz,1H),2.87(dt,J＝12.8,7.3Hz,1H),2.05(s,3H),2.03-1.77(m,4H).ESI-MS(m/z):471.1$[M+H]^+$。

[0519] 

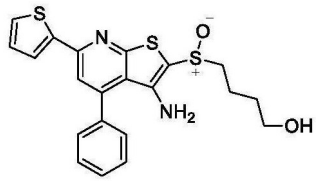
[0520] SW209129.4-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丁基乙酸酯。将叔丁醇钾(9.7mg,0.086mmol)加入4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)亚磺酰基)丁基乙酸酯(58.2mg,0.12mmol)在DMF(490μl)中形成

的溶液中。将反应混合物在35℃下搅拌45分钟，然后使用EtOAc稀释，并使用水多次洗涤。还将水层反萃取。使用生理盐水洗涤合并的有机层，在Na_2SO_4上干燥，过滤并在减压下浓缩。使用自动化快速色谱法，在0-90％EtOAc/己烷中进行纯化，从而给出44％产率的所需的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.63-7.49(m,5H),7.45(dd,J＝4.9,1.1Hz,2H),7.41(s,1H),7.10(dd,J＝5.0,3.7Hz,1H),4.59(bs,2H),4.08(t,J＝5.8Hz,2H),3.39-3.23(m,1H),3.10(ddd,J＝12.8,8.4,6.2Hz,1H),2.03(s,3H),1.96-1.72(m,4H).ESI-MS(m/z):471.1[M+H]$^+$。

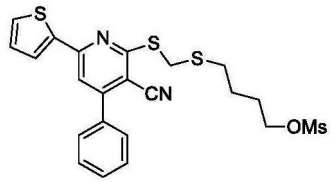
[0521] 

[0522] SW209128.4-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丁基乙酸酯。由4-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丁基乙酸酯以13.5％产率分离过氧化产物。

[0523] ^{1}H NMR(400MHz,$CDCl_3$)δ7.71(dd,J＝3.7,1.1Hz,1H),7.61-7.55(m,3H),7.53-7.44(m,4H),7.15(dd,J＝5.0,3.7Hz,1H),5.10(s,2H),4.06(t,J＝6.3Hz,2H),3.32-3.18(m,2H),2.02(s,3H),1.98-1.87(m,2H),1.77(dt,J＝8.6,6.4Hz,2H).ESI-MS(m/z):487.1[M+H]$^+$。

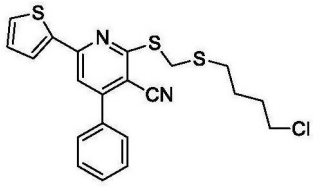
[0524] 

[0525] SW209271.4-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丁-1-醇。将K_2CO_3(12.5mg,0.09mmol)加入SW209129(18.7mg,0.04mmol)在甲醇(470μl)和水(100μl)中形成的溶液中，并将反应物搅拌2.5小时。然后使用EtOAc稀释混合物，并使用水、接着使用生理盐水2次洗涤混合物。将有机层在Na_2SO_4上干燥，过滤并在减压下浓缩，从而给予80％产率的所需的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.62(d,J＝1.1Hz,1H),7.60-7.50(m,4H),7.49-7.41(m,3H),7.11(dd,J＝5.0,3.7Hz,1H),4.68-4.44(s,2H),3.67(t,J＝6.1Hz,2H),3.42-3.27(m,1H),3.13(ddd,J＝12.9,8.4,6.9Hz,1H),1.93-1.65(m,4H).ESI-MS(m/z):429.0[M+H]$^+$。

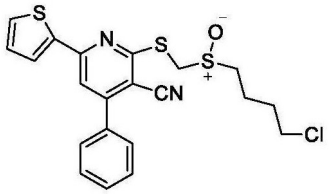
[0526] 

[0527] 4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丁基甲磺酸酯。将三乙基胺(38μl,0.28mmol)在无水DCM(1.0ml)中形成的溶液在冰浴中冷却，然后加入2-((((4-羟基丁基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈(40.6mg,0.098mmol)，再滴加甲磺酰氯(17.5μl,0.23mmol)。在30分钟后，使用生理盐水洗涤混合物粗品，并在Na_2SO_4上干燥，过滤并浓缩，从而给出98％产率的所需的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.74

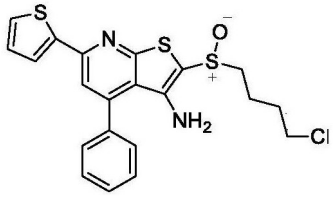
(dd,J＝3.9,1.1Hz,1H),7.64-7.50(m,7H),7.17(dd,J＝5.1,3.8Hz,1H),5.46(s,2H),4.01-3.78(m,2H),2.65(ddd,J＝10.1,5.3,1.9Hz,2H),2.52-2.37(m,4H).ESI-MS(m/z):491.1[M+H]$^+$。

[0528] 

[0529] 2-((((4-氯代丁基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。将氯化锂(32.0mg,0.75mmol)加入4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丁基甲磺酸酯(21.8mg,0.044mmol)在DMF(0.4ml)中形成的溶液中。反应在2天内结束。使用EtOAc稀释混合物,并使用水、接着使用生理盐水多次洗涤。将有机层在Na_2SO_4上干燥,过滤并浓缩。在自动化色谱系统上在0-40％EtOAc/己烷中进行纯化,并给出76％产率的所需的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.72(dd,J＝3.7,1.1Hz,1H),7.62(dd,J＝6.5,3.0Hz,2H),7.59-7.52(m,4H),7.44(s,1H),7.17(dd,J＝5.0,3.8Hz,1H),4.56(s,2H),3.56(t,J＝6.3Hz,2H),2.80(t,J＝7.0Hz,2H),1.95-1.79(m,4H).ESI-MS(m/z):431.0[M+H]$^+$。

[0530] 

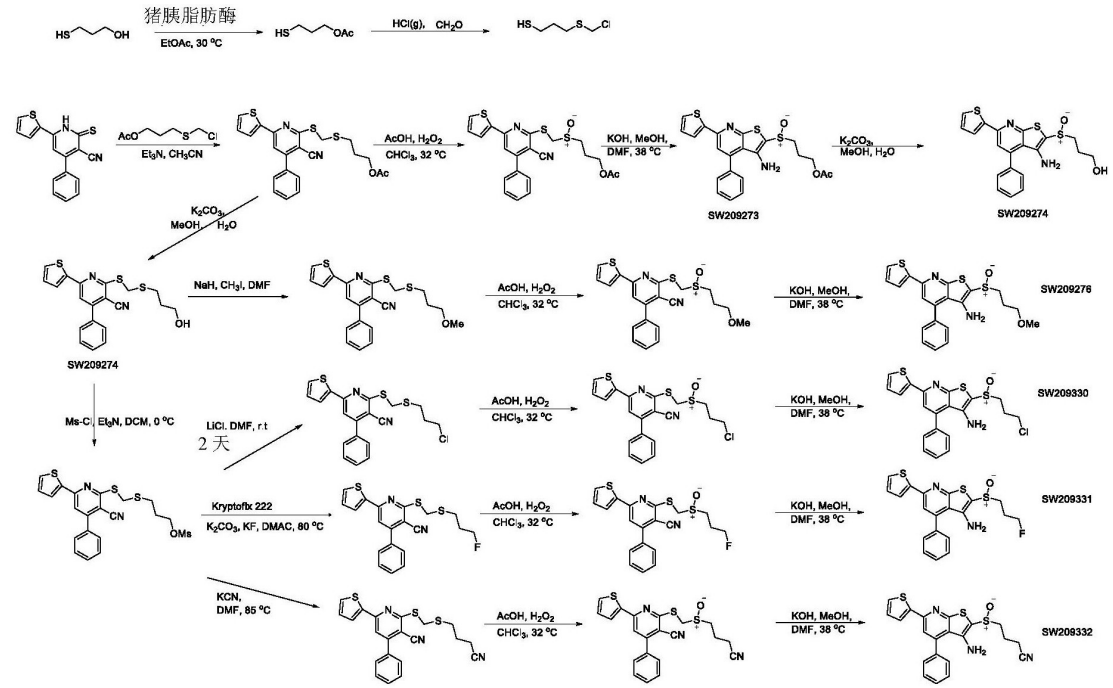
[0531] 2-((((4-氯代丁基)亚磺酰基)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。将乙酸(70μl)和过氧化氢(5.2μl,在水中的30％溶液)加入2-((((4-氯代丁基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈(14.6mg,0.034mmol)在氯仿(70μl)中形成的溶液中。将反应混合物在32℃下搅拌40min,然后使用氯仿稀释并使用饱和的$NaHCO_3$溶液洗涤,接着使用氯仿3次萃取。将合并的有机层在Na_2SO_4上干燥,过滤并在减压下浓缩,从而给出所设计的产物。^{1}H NMR(400MHz,$CDCl_3$)δ7.77(d,J＝3.8Hz,1H),7.62(dd,J＝6.6,2.9Hz,2H),7.57(q,J＝4.5,3.1Hz,4H),7.51(s,1H),7.19(t,J＝4.4Hz,1H),4.77(d,J＝13.0Hz,1H),4.47(d,J＝13.0Hz,1H),3.58(t,J＝6.2Hz,2H),3.03(dt,J＝13.2,7.7Hz,1H),2.87(dt,J＝13.4,7.0Hz,1H),2.16-1.87(m,4H).ESI-MS(m/z):447.1[M+H]$^+$。

[0532] 

[0533] SW209329.2-((4-氯代丁基)亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺。将碱性甲醇溶液(1.0mg,0.018mmol氢氧化钾,处于12.0μl水和57.5μl甲醇中)转移至小瓶中,该瓶中包含2-((((4-氯代丁基)亚磺酰基)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈(12.4mg,0.028mmol)在二甲基甲酰胺(91.5μl)中形成的溶液。将反应物在38℃下加热30分钟,然后冷却,使用EtOAc稀释,并使用水、然后使用生理衍生多次洗涤。将有机层在Na_2SO_4上干燥,过滤并浓缩。使用自动化色谱系统在0-60％EtOAc/己烷中纯化混合物粗

品。分离产率＝65％。^{1}H NMR(400MHz,$CDCl_3$)δ7.64(d,J＝3.7Hz,1H),7.61-7.50(m,4H),7.50-7.43(m,3H),7.12(t,J＝4.4Hz,1H),4.59(s,2H),3.66-3.47(m,2H),3.40-3.24(m,1H),3.20-3.06(m,1H),1.95(q,J＝5.6Hz,4H).ESI-MS(m/z):447.0$[M+H]^+$。

[0534]

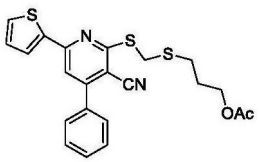




[0535] 3-巯基丙基乙酸酯。将猪胰脂肪酶(5.52g)加入3-巯基-1-丙醇(5.03g,54.6mmol)在乙基乙酸酯(70ml)中形成的溶液中。将反应物在28℃下加热12天。尽管不完全转化,但是过滤并浓缩混合物。在自动化快速色谱法系统上在100％DCM中进行纯化,从而给出66％产率的油。^{1}H NMR(400MHz,$CHCl_3$)δ4.17(t,J＝6.2Hz,2H),2.60(q,J＝7.4Hz,2H),2.05(s,3H),1.93(p,J＝6.6Hz,2H),1.39(t,J＝8.1Hz,2H)。

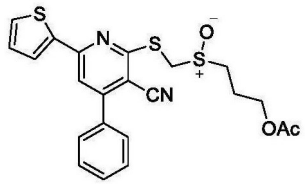
[0536] 

[0537] 3-((氯代甲基)硫代)丙烷-1-硫醇。在60分钟内将氯化氢气体鼓泡至3-((氯代甲基)硫代)丙烷-1-硫醇(4.80g,35.7mmol)中,将其在干冰/丙酮浴中冷却,直至内部温度稳定,然后使用固体加入漏斗缓慢加入多聚甲醛(1.59g,53.3mmol)。将反应物在冷的条件下搅拌1.5小时,在该过程中持续氯化氢鼓泡,然后当反应物温和地温暖至环境温度时终止鼓泡,并过夜搅拌。使用少量DCM稀释混合物粗品。除去水相,并使用生理盐水洗涤有机层,在Na_2SO_4上干燥,过滤并浓缩,从而给出80％产率的油(所需的单体氯化物与二乙酸酯二聚体为2.4:1的混合物)。^{1}H NMR(400MHz,$CHCl_3$)δ4.74(s,2H),4.17(t,J＝6.4Hz,2H),2.91-2.77(m,2H),2.06(d,J＝1.0Hz,3H),2.03-1.94(m,2H)。

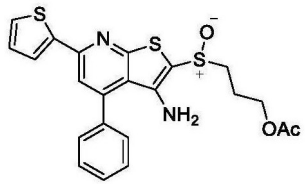
[0538] 

[0539] 3-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丙基乙酸酯。

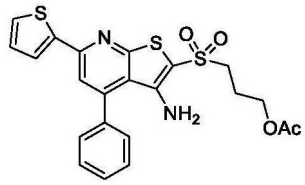
与26%产率(分离的)的4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丁基乙酸酯的制备过程类似。^{1}H NMR(400MHz,$CHCl_3$)δ7.72(dd,J=3.8,1.1Hz,1H),7.66-7.58(m,2H),7.54(dd,J=4.2,2.9Hz,4H),7.44(d,J=1.3Hz,1H),7.17(dd,J=5.0,3.8Hz,1H),4.55(s,2H),4.18(t,J=6.3Hz,2H),2.84(t,J=7.3Hz,2H),2.05(s,3H),2.05-1.97(m,2H).ESI-MS(m/z):441.0$[M+H]^+$。

[0540] 

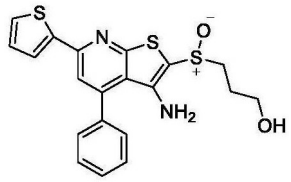
[0541] 3-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)亚磺酰基)丙基乙酸酯。与90%产率的4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)亚磺酰基)丁基乙酸酯的制备过程类似。^{1}H NMR(400MHz,$CHCl_3$)δ7.77(dd,J=3.7,1.1Hz,1H),7.68-7.60(m,2H),7.57(ddd,J=6.9,4.5,2.0Hz,4H),7.51(s,1H),7.19(dd,J=5.0,3.8Hz,1H),4.81(d,J=13.1Hz,1H),4.44(d,J=13.1Hz,1H),4.22(td,J=6.3,1.3Hz,2H),3.09(dt,J=13.0,8.1Hz,1H),2.89(dt,J=13.1,7.1Hz,1H),2.28-2.17(m,2H),2.04(s,3H).ESI-MS(m/z):457.1$[M+H]^+$。

[0542] 

[0543] SW209273.3-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丙基乙酸酯。与37%产率的4-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丁基乙酸酯的制备过程类似。^{1}H NMR(400MHz,$CHCl_3$)δ7.62-7.52(m,5H),7.45(dd,J=5.0,1.1Hz,2H),7.41(s,1H),7.10(dd,J=5.0,3.7Hz,1H),4.65-4.56(s,2H),4.27-4.14(m,2H),3.42-3.25(m,1H),3.15(dt,J=12.9,7.7Hz,1H),2.09(ddd,J=7.5,6.2,1.3Hz,2H),2.05(s,3H).ESI-MS(m/z):457.1$[M+H]^+$。

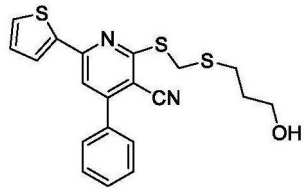
[0544] 

[0545] SW209272.3-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丙基乙酸酯。由3-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丙基乙酸酯以7%产率分离过氧化产物。^{1}HNMR(400MHz,$CHCl_3$)δ7.72(d,J=3.8Hz,1H),7.62-7.53(m,3H),7.54-7.45(m,4H),7.15(dd,J=5.0,3.8Hz,1H),5.12(s,2H),4.15(t,J=6.2Hz,2H),3.39-3.19(m,2H),2.25-2.12(m,2H),2.03(s,3H).ESI-MS(m/z):457.1$[M+H]^+$。

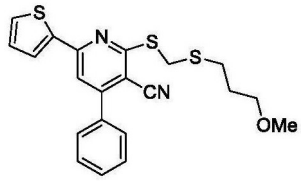
[0546] 

[0547] SW209274.3-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丙-1-醇。与84%产率的SW209271.4-((3-氨基-4-苯基

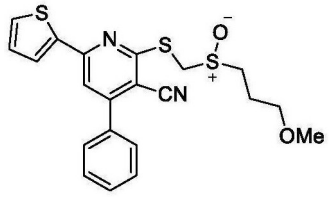
[0548] -6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丁-1-醇的制备过程类似。^{1}H NMR(400MHz,$CHCl_3$)δ7.63(dd,J=3.7,1.1Hz,1H),7.55(p,J=4.6,3.2Hz,4H),7.46(dd,J=5.0,1.1Hz,2H),7.43(s,1H),7.11(dd,J=5.0,3.7Hz,1H),4.60(s,2H),3.77(t,J=5.8Hz,2H),3.49-3.33(m,1H),3.21(dt,J=13.5,6.9Hz,1H),2.13-1.98(m,2H).ESI-MS(m/z):415.1$[M+H]^+$。

[0549] 

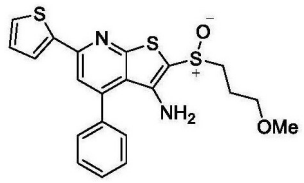
[0550] 2-((((3-羟基丙基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。与98%产率的2-((((4-羟基丁基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈的制备过程类似。^{1}H NMR(400MHz,$CHCl_3$)7.71(dd,J=3.8,1.1Hz,1H),7.63-7.57(m,2H),7.55-7.50(m,4H),7.41(s,1H),7.15(dd,J=5.0,3.8Hz,1H),4.54(s,2H),3.76(t,J=6.1Hz,2H),2.88(t,J=7.1Hz,2H),1.93(ddd,J=13.2,7.1,6.1Hz,2H),1.88-1.80(m,1H).ESI-MS(m/z):399.1$[M+H]^+$。

[0551] 

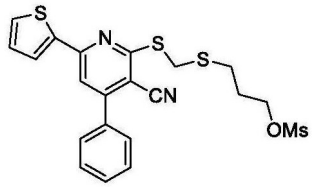
[0552] 2-((((3-甲氧基丙基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。氢化钠(微型刮铲)加入2-((((3-羟基丙基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈(41.6mg,0.10mmol)在DMF(1.0ml)中形成的冰冷的溶液中。将混合物在冷的条件下搅拌15分钟,然后加入甲基碘化物(34ml,0.55mmol)。将混合物在融化冰浴(melting ice-bath)中在冷的条件下搅拌2小时,然后使用EtOAc稀释,并使用水、接着使用生理盐水多次洗涤。在Na_2SO_4上干燥有机层,过滤并浓缩。在自动化快速色谱法系统上,在0-40%EtOAc/己烷中以分离产率56%进行纯化。^{1}H NMR(400MHz,$CHCl_3$)δ7.72(dd,J=3.8,1.1Hz,1H),7.61(dd,J=6.6,3.1Hz,2H),7.57-7.51(m,4H),7.43(s,1H),7.17(dd,J=5.0,3.8Hz,1H),4.55(s,2H),3.49(t,J=6.1Hz,2H),3.34(s,3H),2.85(t,J=7.3Hz,2H),1.95(ddd,J=13.4,7.3,6.1Hz,2H).ESI-MS(m/z):413.1$[M+H]^+$。

[0553] 

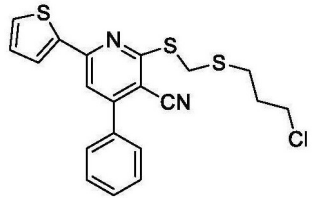
[0554] 2-((((3-甲氧基丙基)亚磺酰基)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。与71％产率的4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)亚磺酰基)丁基乙酸酯的制备过程类似。^{1}H NMR(400MHz,$CHCl_3$)δ7.76(dd,J＝3.8,1.1Hz,1H),7.65-7.58(m,2H),7.56(td,J＝4.6,2.0Hz,4H),7.49(s,1H),7.18(dd,J＝5.0,3.8Hz,1H),4.73(d,J＝13.1Hz,1H),4.47(d,J＝13.0Hz,1H),3.54(qt,J＝9.5,5.8Hz,2H),3.34(s,3H),3.14(dt,J＝13.1,7.9Hz,1H),2.89(ddd,J＝13.1,8.0,6.4Hz,1H),2.20-2.08(m,2H).ESI-MS(m/z):429.1$[M+H]^+$。

[0555] 

[0556] SW209276.2-((3-甲氧基丙基)亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺。与SW209329.2-((4-氯代丁基)亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺的制备过程类似。分离产率＝48％。^{1}H NMR(400MHz,$CHCl_3$)δ7.64(ddd,J＝7.2,3.8,1.7Hz,2H),7.58-7.52(m,4H),7.48-7.42(m,2H),7.12(qd,J＝3.7,1.8Hz,1H),4.57(s,2H),3.50(td,J＝6.1,1.6Hz,2H),3.40-3.29(m,4H),3.26-3.13(m,1H),2.09-1.95(m,2H).ESI-MS(m/z):429.1$[M+H]^+$。

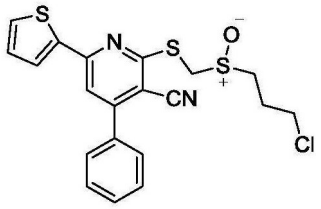
[0557] 

[0558] 3-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丙基甲磺酸酯。与定量产率的4-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丁基甲磺酸酯的制备过程类似。^{1}H NMR(400MHz,$CHCl_3$)δ7.69(t,J＝3.3Hz,1H),7.63-7.55(m,2H),7.52(p,J＝3.6,3.0Hz,4H),7.41(q,J＝2.6,2.2Hz,1H),7.14(p,J＝3.4,2.5Hz,1H),4.52(q,J＝2.2Hz,2H),4.40-4.22(m,2H),2.99(s,3H),2.86(td,J＝7.2,4.8Hz,2H),2.10(qt,J＝6.4,2.3Hz,2H).ESI-MS(m/z):477.0$[M+H]^+$。

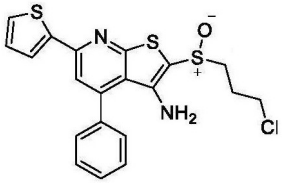
[0559] 

[0560] 2-((((3-氯代丙基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。与2-((((4-氯代丁基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈的制备过程类似。使用自动化快速色谱法系统,在0-50％EtOAc/己烷中以分离产率69％进行纯化。^{1}H NMR(400MHz,$CHCl_3$)δ

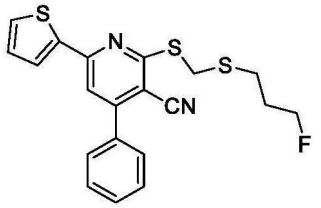
7.72(dd,J＝3.7,1.1Hz,1H),7.64-7.59(m,2H),7.57-7.53(m,4H),7.44(s,1H),7.17(dd,J＝5.0,3.8Hz,1H),4.56(s,2H),3.68(t,J＝6.3Hz,2H),2.93(t,J＝7.0Hz,2H),2.15(p,J＝6.7Hz,2H).ESI-MS(m/z):417.0[M+H]$^+$。

[0561] 

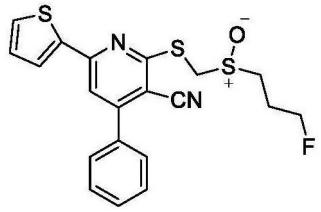
[0562] 2-((((3-氯代丙基)亚磺酰基)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。与90％产率的2-((((4-氯代丁基)亚磺酰基)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈的制备过程类似。^{1}H NMR(400MHz,$CHCl_3$)δ7.76(dd,J＝3.8,1.1Hz,1H),7.62(dq,J＝7.1,2.6,2.2Hz,2H),7.59-7.53(m,4H),7.51(s,1H),7.18(dd,J＝5.0,3.8Hz,1H),4.74(d,J＝13.1Hz,1H),4.51(d,J＝13.1Hz,1H),3.79-3.63(m,2H),3.28-3.16(m,1H),3.04-2.88(m,1H),2.43-2.31(m,2H).ESI-MS(m/z):433.0[M+H]$^+$。

[0563] 

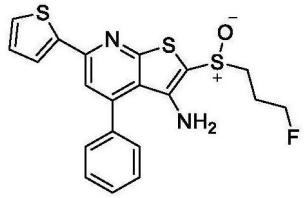
[0564] SW209330.2-((3-氯代丙基)亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺。与SW209329的制备过程类似。在自动化色谱系统上在0-60％EtOAc/己烷中进行的纯化给出所需的88％产率。^{1}H NMR(400MHz,$CHCl_3$)δ7.57(h,J＝5.7,5.3Hz,1H),7.45(t,J＝6.0Hz,0H),7.40(s,0H),7.09(t,J＝4.4Hz,0H),4.61(s,0H),3.67(td,J＝6.4,3.2Hz,0H),3.40(dt,J＝14.1,7.3Hz,0H),3.24(dt,J＝13.1,7.6Hz,0H),2.25(p,J＝7.0Hz,0H).ESI-MS(m/z):433.0[M+H]$^+$。

[0565] 

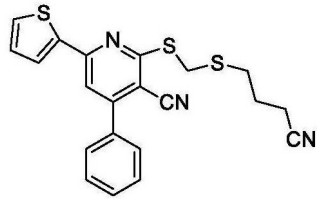
[0566] 2-((((3-氟代丙基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。将Kryptofix 222(44.4mg,0.012mmol),KF(6.1mg,0.10mmol)和K_2CO_3(3.0mg,0.022mmol)装入装有3-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丙基甲磺酸酯(54.2mg,0.11mmol)的小瓶中。加入DMF(1.1ml),并将反应物在85℃下加热65分钟。使用EtOAc稀释冷却的混合物,并使用水、接着使用生理盐水多次洗涤。将有机层在Na_2SO_4上干燥,过滤并浓缩。产率＝96％。使粗产物进入下一步骤。^{1}H NMR(400MHz,$CHCl_3$)δ7.72(dd,J＝3.7,1.1Hz,1H),7.64-7.59(m,2H),7.54(dd,J＝4.9,2.2Hz,4H),7.43(s,1H),7.17(dd,J＝5.1,3.7Hz,1H),4.63(t,J＝5.7Hz,1H),4.55(s,2H),4.51(t,J＝5.8Hz,1H),3.67(t,J＝6.3Hz,2H),2.91(dt,J＝11.2,7.1Hz,1H),2.14(p,J＝6.7Hz,1H).ESI-MS(m/z):401.1[M+H]$^+$。

[0567] 

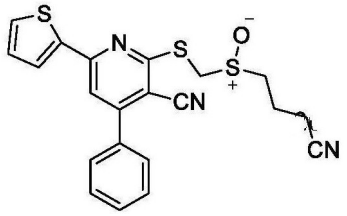
[0568] 2-((((3-氟代丙基)亚磺酰基)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。将乙酸(215μl)和过氧化氢(16.75μl,在水中的30%溶液)加入2-((((3-氟代丙基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈(43.3mg,0.034mmol)在氯仿(215μl)中形成的溶液中。将反应混合物在32℃下搅拌50min,然后使用氯仿稀释,并使用饱和的$NaHCO_3$溶液洗涤,再使用氯仿萃取3次。将合并的有机层在Na_2SO_4上干燥,过滤并在减压天浓缩,产率为94%。ESI-MS(m/z):417.1$[M+H]^+$。

[0569] 

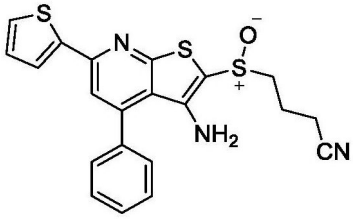
[0570] SW209331.2-((3-氟代丙基)亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺。与SW209329.2-((4-氯代丁基)亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺的制备过程类似。在4%MeOH/DCM中以制备方式纯化混合物粗品。分离产率=32%。^1H NMR(400MHz,$CHCl_3$)δ7.68(dd,J=3.8,1.1Hz,1H),7.56(q,J=2.7Hz,4H),7.53-7.44(m,3H),7.14(dd,J=5.1,3.7Hz,1H),4.65(td,J=5.8,3.2Hz,1H),4.60(s,2H),4.53(td,J=5.8,3.1Hz,1H),3.40(dt,J=13.0,7.3Hz,1H),3.24(dt,J=13.1,7.6Hz,1H),2.19(dtt,J=26.4,7.5,5.7Hz,2H).ESI-MS(m/z):417.1$[M+H]^+$。

[0571] 

[0572] 2-((((3-氰基丙基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。将3-((((3-氰基-4-苯基-6-(苯硫-2-基)吡啶-2-基)硫代)甲基)硫代)丙基甲磺酸酯(54.6mg,0.11mmol)和KCN(76.9mg,1.18mmol)在DMF(1.14ml)中形成的溶液在85℃下加热4小时。使用EtOAc稀释冷却的混合物,并使用水、接着使用生理盐水多次洗涤。将有机相在Na_2SO_4上干燥,过滤并浓缩。产率=89%。^1H NMR(400MHz,$CHCl_3$)δ7.71(d,J=3.5Hz,1H),7.60(dt,J=6.4,2.0Hz,3H),7.54(qt,J=5.6,2.5Hz,4H),7.44(d,J=1.4Hz,1H),7.16(ddd,J=5.2,3.8,1.5Hz,1H),4.53(d,J=1.7Hz,2H),2.93-2.82(m,2H),2.52(td,J=7.1,1.4Hz,2H),2.09-1.92(m,2H).ESI-MS(m/z):408.1$[M+H]^+$。

[0573] 

[0574] 2-((((3-氰基丙基)亚磺酰基)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈。将乙酸(205μl)和过氧化氢(15.6μl,在水中的30％溶液)加入2-((((3-氰基丙基)硫代)甲基)硫代)-4-苯基-6-(苯硫-2-基)烟腈(41.1mg,0.10mmol)在氯仿(205μl)中形成的溶液中。将反应混合物在32℃搅拌70min,然后使用氯仿稀释,并使用饱和的$NaHCO_3$溶液洗涤,再使用氯仿3次萃取。将合并的有机层在Na_2SO_4上干燥,过滤并在减压下浓缩,产率为91％。ESI-MS(m/z):424.1$[M+H]^+$。

[0575] 

[0576] SW209332.4-((3-氨基-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-2-基)亚磺酰基)丁腈。与SW209329.2-((4-氯代丁基)亚磺酰基)-4-苯基-6-(苯硫-2-基)噻吩并[2,3-b]吡啶-3-胺的制备过程类似。在4％MeOH/DCM中以制备方式纯化混合物粗品。分离产率＝45％。^1H NMR(400MHz,$CHCl_3$)δ7.65(d,J＝3.7Hz,1H),7.60-7.51(m,4H),7.51-7.44(m,3H),7.13(t,J＝4.4Hz,1H),4.64(s,2H),3.41(dt,J＝14.0,7.3Hz,1H),3.19(dt,J＝13.3,7.5Hz,1H),2.59(t,J＝7.1Hz,2H),2.20(p,J＝7.3Hz,2H).ESI-MS(m/z):424.0$[M+H]^+$。

[0577] 实施例2

[0578] 方法

[0579] 小鼠

[0580] 8周龄的雌性C57/BL6J小鼠购自Jackson Labs(货号#000664)。所有小鼠的研究均经过Case Western Reserve University的动物护理和使用机构委员会(the institutional animal care and use committee)的批准。

[0581] 博来霉素灌注

[0582] 为了诱导疾病发作,使用氯胺酮/甲苯噻嗪麻醉小鼠,并通过宫颈切除术暴露气管。将博来霉素硫酸盐(Enzo-BML-AP302-0010)溶解于H_2O中,并以单一剂量为2mg/kg/50μl溶液/动物于气管内给予。

[0583] IP注射

[0584] 在博来霉素灌注后,在35天内每日2次向小鼠的腹膜内腔中注射媒介物(10％EtOH,5％Cremaphor,D5H2O)或5.0mg/kg SW033291(+)。

[0585] 动物死亡率和体重

[0586] 在研究过程中每日观察死亡率。在灌注前测量体重,并且在博来霉素灌注后每周2次测量体重。

[0587] 羟基脯氨酸测试

[0588] 羟基脯氨酸(Sigma-MAK008-1KT)用于测量小鼠肺中胶原的内部的含量。简言之，处死小鼠，并切除右肺用于胶原蛋白定量。根据制造商的方案进行试验。将10mg总肺称重，在无菌水中均化，并在120℃微量恒温仪上在12N HCl中水解3h。将水解的样品与4-(二甲基氨基)安息香醛(DMAB)在60℃下温育90min，并在560nm下测量氧化的羟基脯氨酸的吸光率。

[0589] 基因表达研究

[0590] 为了在博来霉素灌注后第35天时炎性细胞因子的表达，处死小鼠，并切除左肺用于RNA分离。将组织样品在冰上均化，并使用RNAqueous试剂盒(Ambion-AM1912)分离总RNA。合成cDNA(Invitrogen Superscript III-18080044)，并使用以下Taqman引物(Applied Biosystems)进行实时PCR：

[0591] 小鼠B2M(内部对照)-Mm00437762_m1

[0592] 小鼠CCL4-Mm00443111_m1

[0593] 小鼠TNF-Mm00443258_m1

[0594] 小鼠TGFB-Mm01178820_m1

[0595] 小鼠IFNG-Mm01168134_m1

[0596] 小鼠IL2-Mm99999222_m1

[0597] 小鼠CCL3-Mm00441259_g1

[0598] 图1示出在特发性肺纤维症的小鼠模型中用于测量SW033291对体重保持和生存的作用的测试示意图。

[0599] 图2(A-B)示出显示媒介物和SW033291处理的特发性肺纤维症小鼠模型的(A)体重变化和(B)生存的图。与媒介物处理小鼠相比，SW033291处理的小鼠显示增强的体重保持和改善的生存。

[0600] 图3示出在特发性肺纤维症的小鼠模型中用于测量SW033291对胶原蛋白沉积的作用的测试示意图。

[0601] 图4示出显示媒介物和SW033291处理的特发性肺纤维症小鼠模型的胶原蛋白沉积的图。与媒介物处理小鼠相比，SW033291处理的小鼠显示减少的胶原蛋白沉积，其是通过组织羟基脯氨酸含量测定的。

[0602] 图5示出在特发性肺纤维症的小鼠模型中用于测量SW033291对炎性细胞因子表达的作用的测试示意图。

[0603] 图6(A-B)示出显示媒介物和SW033291处理的特发性肺纤维症小鼠模型的炎性细胞因子表达的图。

[0604] 实施例3

[0605] 为了建立由慢性结肠炎引起肠纤维症模型，使8周龄的雄性FVB/N小鼠经历3轮无菌饮用水中的硫酸葡聚糖钠盐(DSS;2％w/v)。每轮由7天DSS、然后10天无DSS的恢复组成。为了研究15-PGDH抑制对肠纤维症的作用，在第三次DSS暴露(第41天)结束开始，在总计28天中，对小鼠给予每天2次(+)SW033291 5mg/kg IP注射或媒介物注射。在第69天时，由小鼠收获结肠，纵向切开并包埋于琼脂中用于取向，并在福尔马林中过夜固定。根据标准的过程，由石蜡包埋的福尔马林固定的样品制备载玻片。通过Masson's Trichrome染色，比较在2组小鼠结肠中纤维症的程度。使用ImageJ软件按照以下方式定量阳性三色染色的强度。在20x下，由各小鼠的各降结肠(third of the colon)捕获10个均匀间距的图像。(图7(A-D))

在图像捕获过程中，排除在载玻片上所见的明显的淋巴管室或肠外解读组织附着。由图像分开RGB通道，并由各个图像得到的蓝色通道除以红色通道。在所得的图像中在生成所有像素的强度柱状图后，针对高于1.3(蓝色/红色)临界值的强度，计算曲线下面积(AUC)。通过结肠长度归一化AUC的总和(总的三色强度)。图8示出结肠纤维症(+)SW033291处理的小鼠比媒介物处理的小鼠大幅减少。

[0606] 尽管参照本发明的优选的实施方案特定示出并描述本发明，但是本领域那些技术人员将理解的是，在不脱离所附权利要求书涵盖的本发明的范围的情况下，可以由这些实施方案形成多种形式和细节的变化。在上述说明书中引用的所有专利、公开和参考文献均以引用方式全文并入本文。

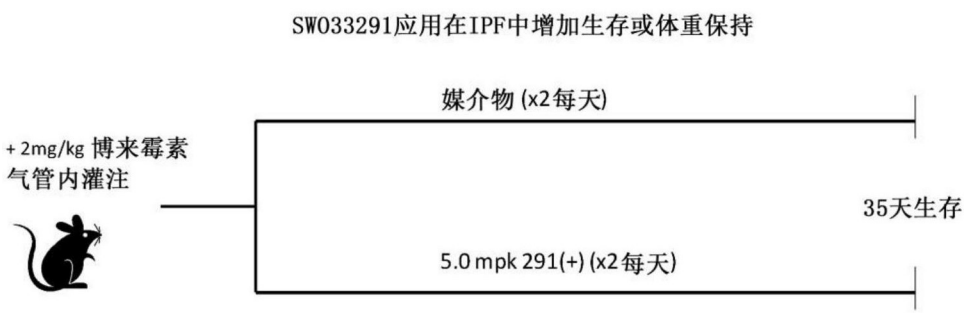
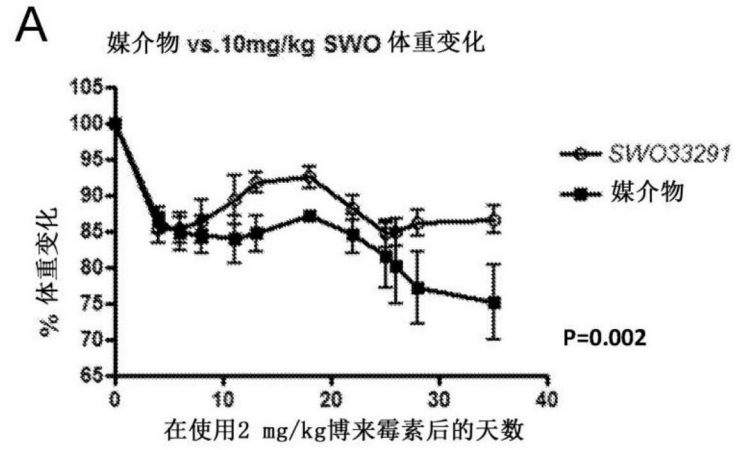
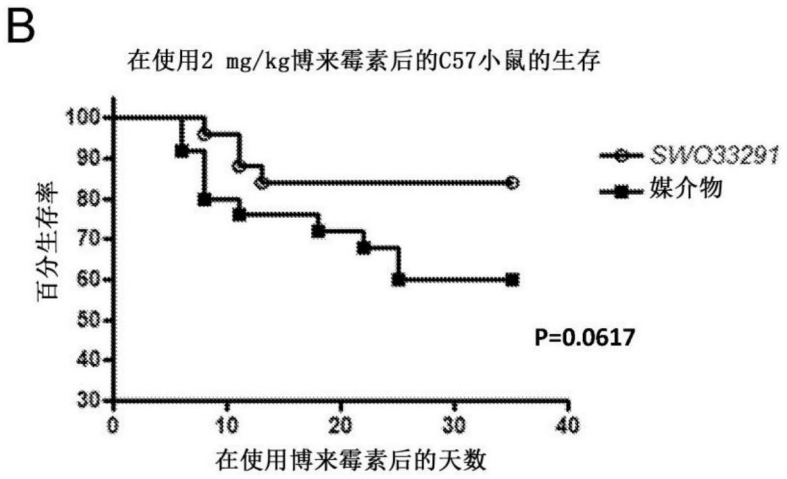


图1



N= 10 小鼠 /组

图2A



N= 25 小鼠 /组

图2B

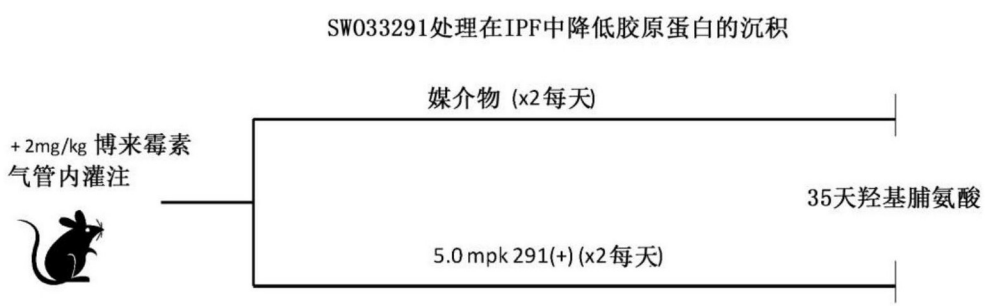

SWO33291处理在IPF中降低胶原蛋白的沉积
媒介物 (x2每天)
+2mg/kg 博来霉素
气管内灌注
35天羟基脯氨酸
5.0 mpk 291(+) (x2每天)

图3

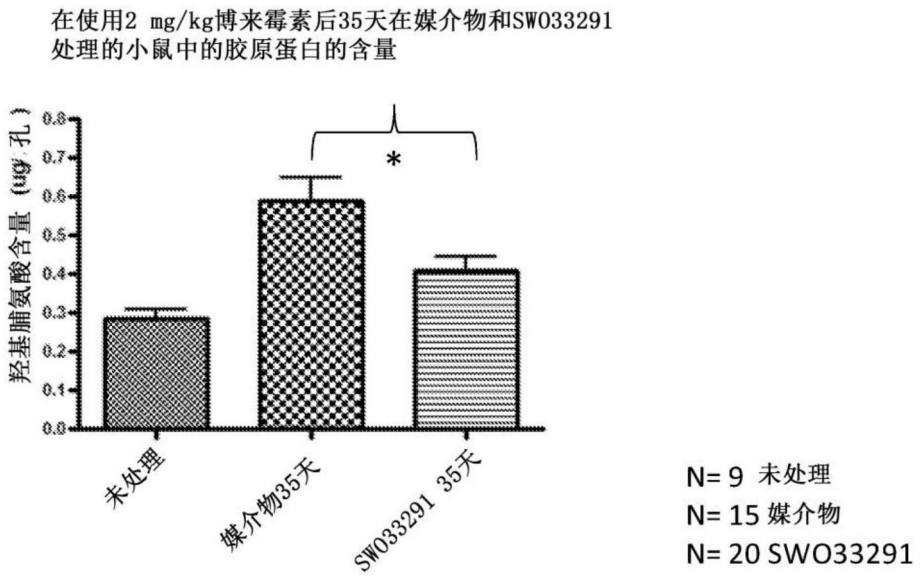

在使用2 mg/kg博来霉素后35天在媒介物和SWO33291
处理的小鼠中的胶原蛋白的含量
羟基脯氨酸含量 (ug/孔)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
*
未处理
媒介物35天
SWO33291 35天
N= 9 未处理
N= 15 媒介物
N= 20 SWO33291

图4

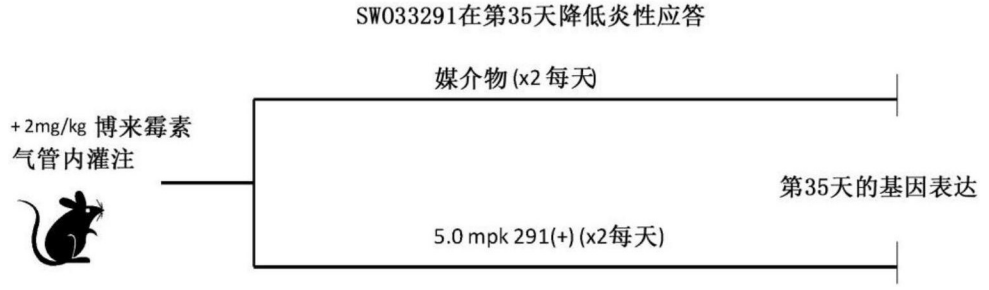

SWO33291在第35天降低炎性应答
媒介物 (x2 每天)
+2mg/kg 博来霉素
气管内灌注
第35天的基因表达
5.0 mpk 291(+) (x2每天)

图5

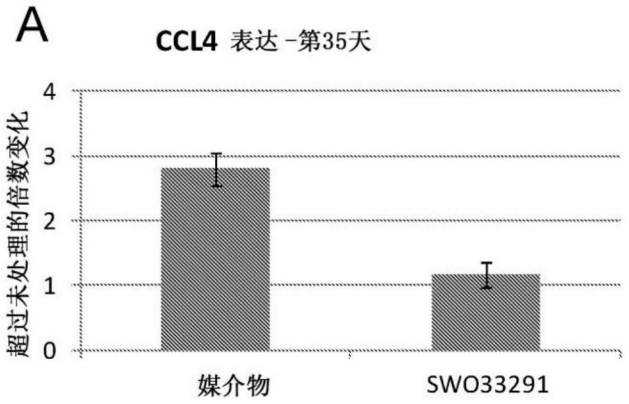


图6A

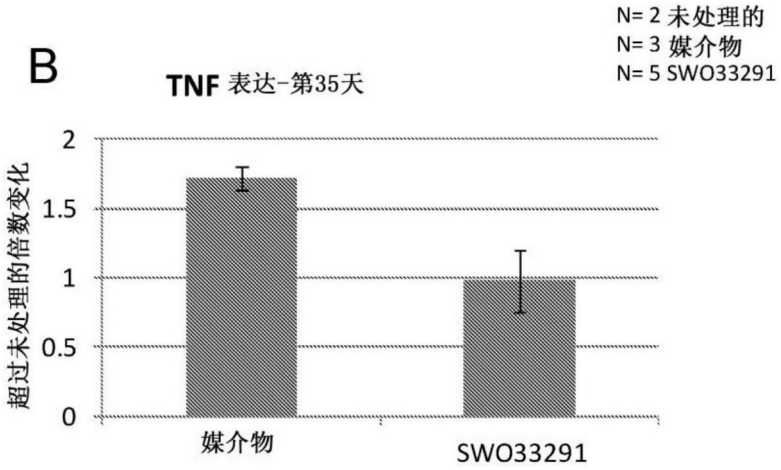


图6B

SWO33291在第35天降低炎性应答

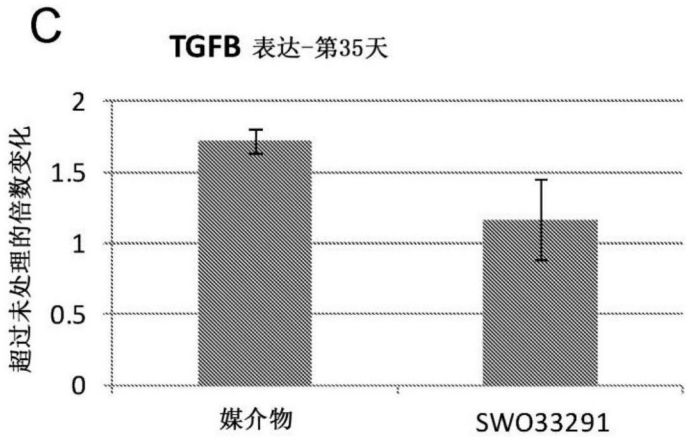


图6C

N= 2 未处理的
N= 3 媒介物
N= 5 SWO33291

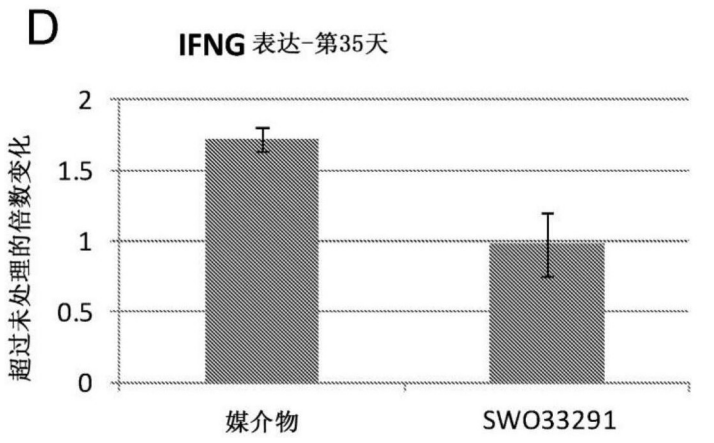


图6D

SWO33291在第35天降低炎性应答

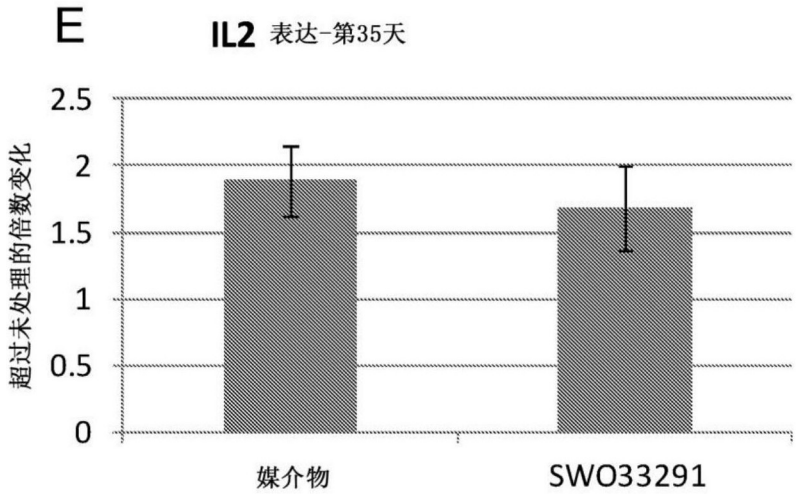


图6E

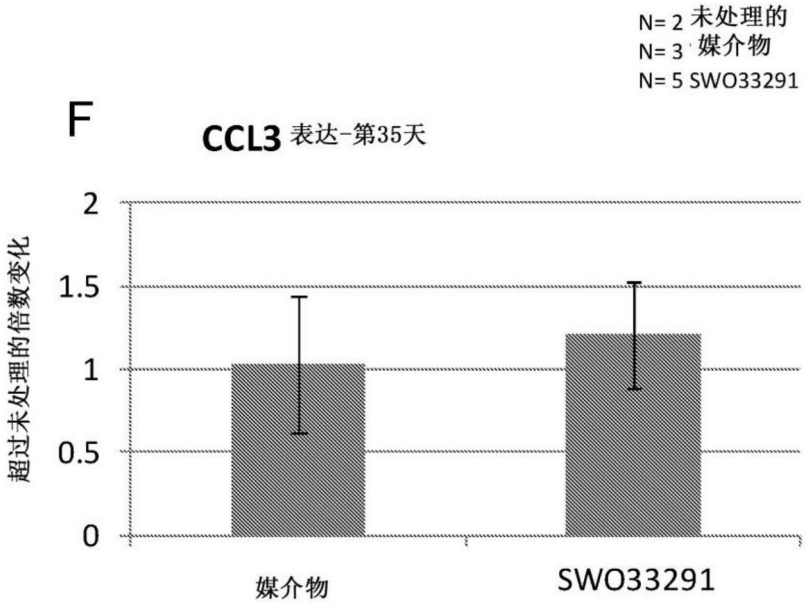

N= 2 未处理的
N= 3 媒介物
N= 5 SWO33291
F
CCL3 表达-第35天
超过未处理的倍数变化
2
1.5
1
0.5
0
媒介物
SWO33291

图6F

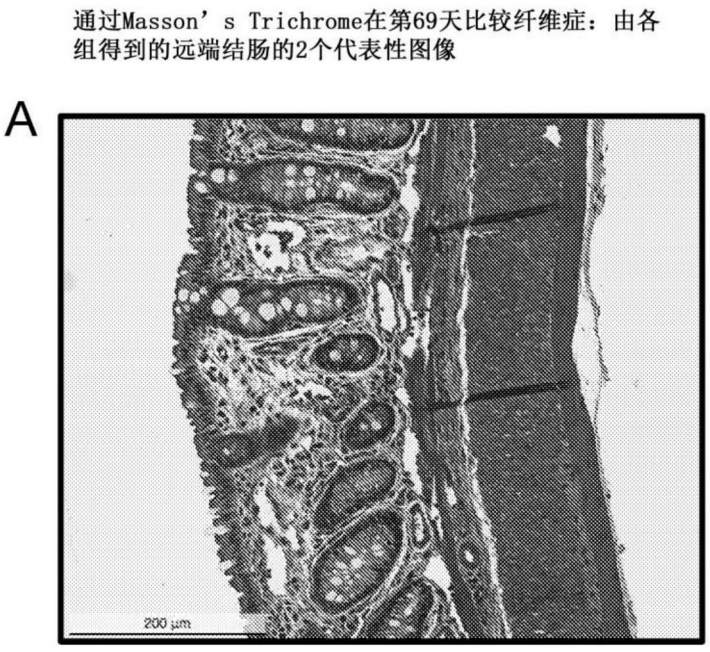

通过Masson’s Trichrome在第69天比较纤维症：由各组得到的远端结肠的2个代表性图像
A
200 µm

图7A

B

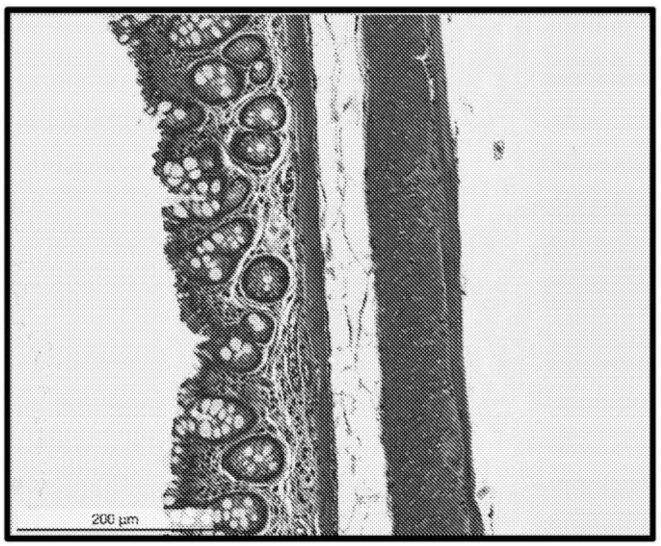


图7B

通过Masson’ s Trichrome在第69天比较纤维症：由各组得到的远端结肠的2个代表性图像

C

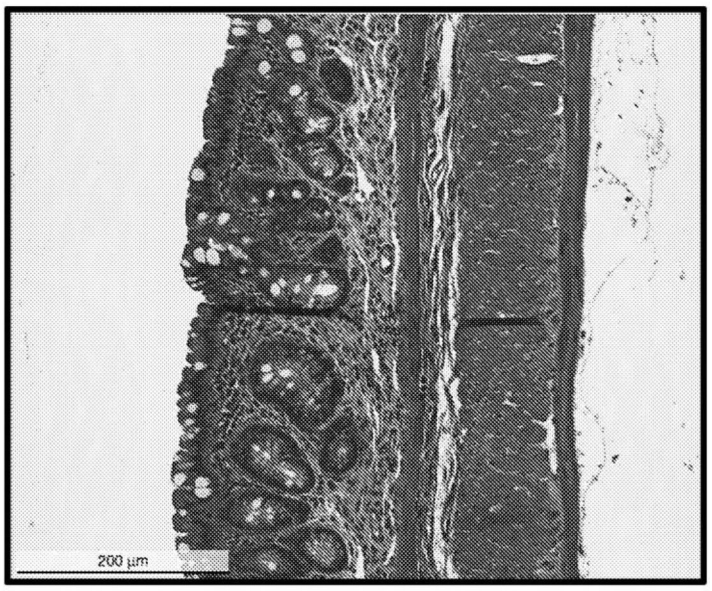


图7C

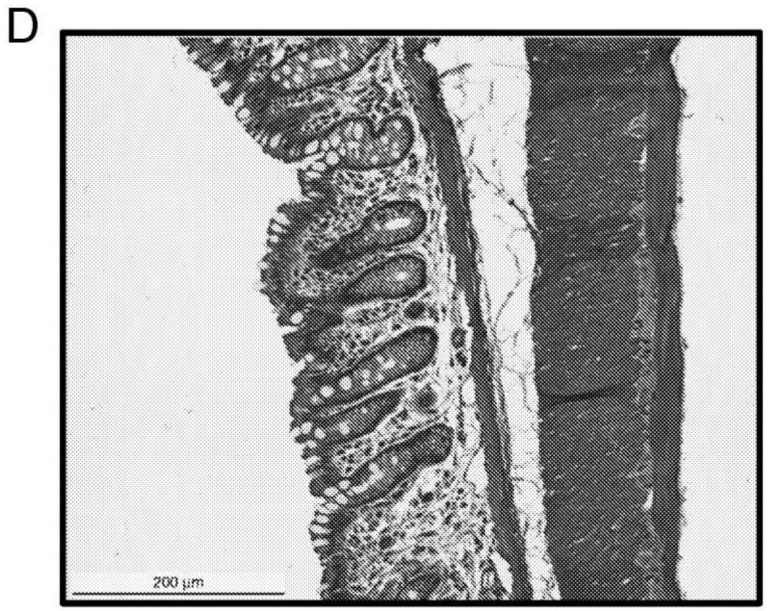

D
200 µm

图7D

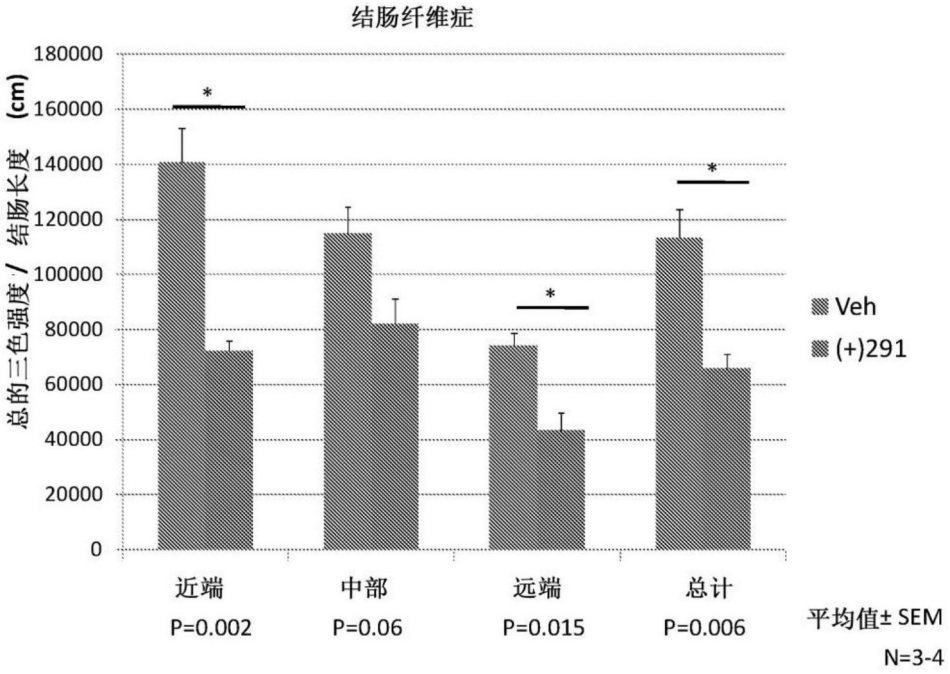

结肠纤维症
总的三色强度 / 结肠长度 (cm)
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
*
*
*
Veh
(+)291
近端
中部
远端
总计
P=0.002
P=0.06
P=0.015
P=0.006
平均值± SEM
N=3-4

图8